A Practical Manual of Diabetes in Pregnancy

A Practical Manual of Diabetes in Pregnancy

Second Edition

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Foreword

I am pleased and very honoured to write the foreword for the second edition of the *Practical Manual of Diabetes in Pregnancy*.

The foreword of the first edition was written by Professor David Hadden, a founding member of the European Diabetic Pregnancy Study Group (DPSG). David was a charming, highly intellectual, and stimulating person, respected by so many clinicians, researchers, health authorities, and certainly by people living with diabetes.

This second edition is also edited by David R. McCance, Michael Maresh, and David A. Sacks. All three are members of the DPSG.

Certainly, important progress has been made in the understanding and management of diabetes in pregnancy since the discovery of insulin nearly 100 years ago. But major problems are not yet well understood and not yet under efficient control. Therefore, this book is welcomed.

This second edition highlights the whole spectrum of diabetes in pregnancy and finds inspiration in achievements in the past, the present knowledge, and perspectives for the future. An important point remains efficient screening for gestational diabetes mellitus (GDM). It is necessary to obtain a consensus on GDM screening in Europe and worldwide. This book underlines this universal and uniform screening. The DPSG and the European Board and College of Obstetrics and Gynaecology (EBCOG) are collaborating to achieve this consensus in Europe, and the International Federation of Gynecology and Obstetrics (FIGO) is elaborating on a global consensus.

It is also clear that the epidemic of obesity has an effect on the occurrence and manifestation of diabetes in pregnancy. The challenges are clearly expressed in this edition.

The most important message is certainly that diabetes in pregnancy remains a high-risk situation for the mother, the unborn and newborn child, and also the next generations. Progress in this field should be achieved. A multidisciplinary team, including research and with a central role of the pregnant diabetic and her environment, must put all the efforts in line, including new available knowledge and technology.

Andre Van Assche, MD, PhD, FRCOG, FEBCOG

Preface

The second edition of any book presents new challenges. While it may be comforting for the editors to know that its predecessor was favorably received, and sufficient faith has been placed by the publisher to commission a second edition, the editorial dilemma and responsibility are to ensure that a new edition contains sufficiently new material and in the most appropriate format, given the rapidly changing methods of learning and communication. We concluded that a succinct, handheld, evidence-based, practical guide to the management of diabetes during pregnancy is still needed. This edition has been extensively revised and contains many new chapters, but it deliberately retains the successful chapter format of a short illustrative case history, with a number of questions being posed and then answered in the text, along with practice points, illustrative diagrams and tables, and relevant bibliography.

There is certainly no shortage of new material. Since publication of the first edition in 2010, the global increase in diabetes and obesity during pregnancy has become even more acute, with all its preventive and logistical implications. Pre-pregnancy planning, with the emphasis on continuing contraception until optimal control has been achieved, clearly reduces the adverse effects of pregestational diabetes, but substantially more women need to embrace it – and how do we make that happen? Long-acting reversible contraceptive methods have contributed to a recent decline in unplanned pregnancies in many parts of the world, and we as healthcare professionals need to provide immediate access to these devices and medications. The chapter about family planning highlights these issues and discusses currently available contraceptive methods. Many more women with type 1 diabetes are now carbohydrate counting, and some are using a continuous subcutaneous insulin infusion/continuous glucose-monitoring system (CSII/CGMS). This requires upskilling of the whole diabetes team from the pre-pregnancy planning clinic to the delivery suite, and each consultation now takes more time. The evidence clearly shows that outcomes of women with type 2 diabetes during pregnancy are similarly poor to those with type 1, and urgent innovation is needed to educate the primary care providers who frequently now care for these women. Following the World Health Organization (WHO) endorsement in 2013 of the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) criteria for the diagnosis of gestational diabetes mellitus, we are nudging toward a global consensus on these thresholds, but more individual population and cost economic data are needed. An evolving question is whether we should be diagnosing diabetes much earlier in pregnancy than late second trimester. The final chapter speculates on the role of the microbiome, proteomics, and metabolomics – and these developments even now are on our doorstep.

However, in all of this activity, the patient must remain central. While the combination

of diabetes and pregnancy unfortunately is still a high-risk situation, pregnancy should be a pleasurable experience, and as healthcare professionals we can easily forget this. The multidisciplinary team is pivotal to communication, coordination of care, and assessment of risk. Enabling technology can go a long way toward helping, and remote transmission of glucose-monitoring results (even a screenshot of a diary page with a mobile telephone) is now commonplace, and should help to reduce the frequency of review, especially for women with gestational diabetes mellitus.

Finally, since the first edition, it is with great sadness that we, as editors, note the passing of our esteemed colleague, mentor. and friend David Hadden.[1] His interest in and passion for this field were legendary, and his legacy lives on. In writing the Foreword to the first edition, he highlighted that this book was for the whole diabetes team. We echo his words for this new edition and dedicate it to him. Our hope is that it will prove useful and will be widely used, as a point of reference and practical example.

David R. McCance
Michael Maresh
David A. Sacks
December 2017

[1] McCance DR. David Hadden commentary. *Diabetic Med*. 2014 Jun;31(6):637–638.

Section I

Introduction

1

Epidemiology of Diabetes in Pregnancy

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PRACTICE POINTS

- The World Health Organization (WHO) (3) has recommended that hyperglycemia first detected at any time during pregnancy should be classified as either:
  - diabetes mellitus in pregnancy (DIP), or
  - gestational diabetes mellitus (GDM).
- Pre-gestational diabetes is diabetes that had been diagnosed before pregnancy.
- The prevalence of pre-gestational diabetes has been increasing across the world over >40 years and has a prevalence of 1–5%. Approximately 0.3–0.8% of pregnancies are complicated by type 1 diabetes; the rest are type 2 diabetes, and a small fraction have rare forms of diabetes.
- DIP has a prevalence of 0.2–0.4%, mostly type 2 diabetes postpartum.
- WHO (3) criteria for GDM have now changed, involving a much lower fasting criterion (≥5.1 mmol/l), the introduction of a 1 h value after a 75 g oral load (≥10.0 mmol/l), and an increased diagnostic cutoff 2 h post load (≥8.5 mmol/l). These criteria substantially increase the prevalence of GDM, in some populations to over 35%.
- Non-European ethnicity and obesity are the major risk factors for hyperglycemia in pregnancy; others such as a family history of diabetes, previous GDM, polycystic ovarian syndrome, age, and previous stillbirth or macrosomic infant are important.
- Pre-gestational diabetes and DIP contribute significantly to malformations.
- Total hyperglycemia in pregnancy contributes to adverse pregnancy outcomes on a population level, particularly shoulder dystocia.
- GDM is a precursor of up to 34% of type 2 diabetes in women.
- There is an association between maternal hyperglycemia in pregnancy and obesity, diabetes, and metabolic syndrome in the offspring.

Case History

A 32-year-old woman, G3P2, with no significant past medical history and no family history of diabetes, had a random glucose of 7.8 mmol/l at 8 weeks gestation with a normal oral glucose tolerance test (OGTT) (4.3, 7.6, and 7.4 mmol/l) at 11 weeks (1). Her pre-pregnancy BMI was 19.9 kg/m^2. At 28 weeks, she presented acutely, afebrile but with severe general fatigue. A random plasma glucose was 27.2 mmol/l, blood pressure was 110/84 mmHg, and heart rate 106 beats/min. Ketones were 3+, arterial pH was 7.45, bicarbonate 12.1 mmol/l, and base excess −9.8 mmol/l (i.e., compensated metabolic acidosis). HbA1c was 125 mmol/mol (13.6%). Anti-glutamic acid decarboxylase (GAD) antibody was 25.0 (reference range 1–5). She was diagnosed

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as having type 1 diabetes and commenced insulin therapy. The rest of the pregnancy was uneventful, although total weight gain was only 3 kg and birth weight was 3006 g.

Questions to be answered in this chapter:

- What proportion of pregnancies are complicated by type 1 diabetes, type 2 diabetes, monogenic diabetes, or other rare forms of diabetes?
- What proportion of pregnancies are complicated by GDM?
- What type of patient develops hyperglycemia first detected in pregnancy?
- What is the public health impact of hyperglycemia in pregnancy?

Prevalence of Total Hyperglycemia in Pregnancy

Diabetes in pregnancy (DIP) and gestational diabetes mellitus (GDM) have been terms used in clinical medicine for over 100 years. In 2010 and 2013, respectively, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) (2) and the World Health Organization (WHO) (3) reclassified hyperglycemia in pregnancy into three groups to incorporate all aspects of the range of raised glucose that can increase pregnancy complications:

Known pre-gestational diabetes	(Overt) diabetes in pregnancy (DIP)	Gestational diabetes mellitus (GDM)
Known diabetes	Diagnosed first time in pregnancy and expected to continue postnatally	Diagnosed first time in pregnancy and no permanent diabetes expected postnatally
For example: type 1 diabetes, type 2 diabetes, and rare forms of diabetes (e.g., monogenic diabetes)	Usually type 2 diabetes; occasionally, rare forms or type 1 diabetes	

The global prevalence of total hyperglycemia in pregnancy has recently been estimated to have been 16.9%, or 21.4 million, live births (women aged 20–49 years) in 2013 (4). The highest prevalence was in Southeast Asia at 25.0%, with 10.4% in North America and the Caribbean Region. Low- and middle-income countries are estimated to be responsible for 90% of cases.

Prevalence of Known Pre-Gestational Diabetes in Pregnancy

The prevalence of both type 1 and type 2 diabetes among reproductive-aged women has been increasing globally (5). In the USA, the incidence of type 1 and type 2 diabetes among those aged under 20 years is projected to triple and quadruple by 2050, respectively (5). An example of the growth in pre-gestational diabetes between 1999 and 2005 is shown for Southern California in Figure 1.1 (by age group), where age- and ethnicity-adjusted rates increased from 8.1/1000 in 1999 to 18.2/1000 by 2005 (6).

There are significant ethnic differences in prevalence. For example, in 2007–2010 among women aged 20–44 years across the USA, prevalence ranged from 2.7% (1.8–4.1%) among non-Hispanic whites, to 3.7% (2.2–6.2%) among Hispanic women, to 4.6% (3.3–6.4%) among non-Hispanic blacks (7). Prevalence rates are higher in other populations (4).

Prevalence of Type 1 Diabetes in Pregnancy

The prevalence of type 1 diabetes in pregnancy is less than in the nonpregnant population in view of the lower standard fertility ratio (SFR) (fertility rate in comparison with the wider population). The SFR in type 1

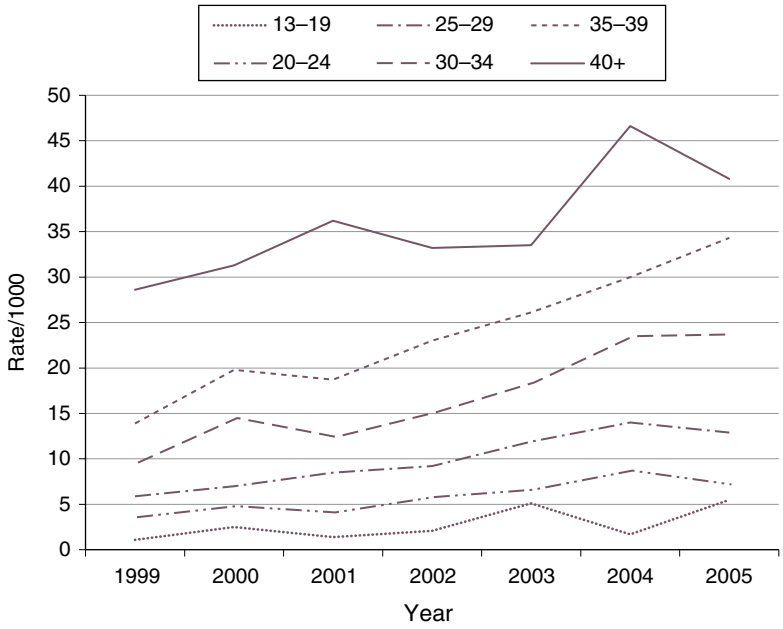

Figure 1.1 Pregnancies complicated by pre-gestational diabetes, 1999–2005 (per 1000), by age.

diabetes is 0.80 (95% CI: 0.77–0.82), and is particularly low among women with retinopathy, nephropathy, neuropathy, or cardiovascular complications (0.63, 0.54, 0.50, and 0.34, respectively) (8). The gap in fertility between women with and without type 1 diabetes has closed considerably over time, and it appears to be greatest for women who were diagnosed as a child, rather than as an adult (9).

The prevalence of type 1 diabetes in pregnancy increases with age, as shown in Table 1.1 for Norway (1999–2004) (10) and Ontario, Canada (2005–2006) (11).

Besides women with preexisting type 1 diabetes, a small proportion of women with diabetes first diagnosed during pregnancy are found to have type 1 diabetes (see, e.g., the Case History for this chapter). In New Zealand in 1986–2005, 11/325 (3.4%) of women with new diabetes diagnosed postpartum had type 1 diabetes (12). Other women with GDM have autoimmune markers (islet cell antibody

Table 1.1 Prevalence (per 1000) of type 1 and type 2 diabetes in pregnancy, by age.

Norway 1999–2004		**Ontario 2005–2006**		
Type of diabetes	1	Type of diabetes	1	2
Overall	4.5	Overall	7.5	4.3
By age		By age		
≤20 years	2.9	≤20 years	2.0	0.2
20–34	4.5	20–29	5.7	2.9
35–39	5.0	30–34	8.3	4.9
40+	4.7	35+	11.5	7.3

[ICA], GAD antibody [GADA], or tyrosine phosphatase antibody [IA-2A]) without necessarily overt DIP. Overall, the prevalence of such autoimmune markers ranges between 1 and 10%, and it is greatest in populations where the prevalence of type 1 diabetes is higher (13). In a Swedish study, 50% women with antibody positivity had developed type 1 diabetes, compared with none among the GDM control subjects (14).

Prevalence of Type 2 Diabetes in Pregnancy

While fertility rates in type 2 diabetes have not been reported, they would be expected to be low (particularly in view of the associated obesity, polycystic ovarian syndrome [PCOS], and vascular disease) (15). Nevertheless, the rates of type 2 DIP are increasing more rapidly than those of type 1 diabetes in pregnancy (16).

In addition to the increasing age-standardized prevalence and lowering of the age at onset of type 2 diabetes (driven by the obesity epidemic), demographic changes (e.g., ethnicity) may partly explain the changes in prevalence over time in individual locations. For example, in Birmingham, UK, in 1990–1998, the ratio of type 1 to type 2 diabetes was 1:2 in South Asians but 11:1 in Europeans (17). In the north of England in 1996–2008, the prevalence rates of type 1 and type 2 diabetes in pregnancy were 0.3% and 0.1%, respectively (18), but while 97% of women with type 1 diabetes were European, 21% of women with type 2 diabetes were non-European. Table 1.1 also shows the increasing proportion of women in Ontario having type 2 diabetes in pregnancy as age increases (11).

Prevalence of other Forms of Pre-Gestational Diabetes in Pregnancy

There are few reports of the prevalence of monogenetic forms of diabetes or secondary diabetes in pregnancy. Glucokinase mutations are present in up to 5–6% of women with GDM and up to 80% of women with persisting fasting hyperglycemia outside pregnancy combined with a small glucose increment during the OGTT, and a family history of diabetes (19).

Cystic fibrosis is associated with a doubling in the prevalence of diabetes outside of pregnancy, with a further increase during pregnancy (e.g., from 9.3% at baseline to 20.6% during pregnancy, and 14.4% at follow-up) (20).

PITFALL

A significant proportion of younger women with diabetes in pregnancy have rare forms of diabetes, which often remain undiagnosed.

Prevalence of Hyperglycemia First Detected in Pregnancy

The prevalence of hyperglycemia first detected in pregnancy globally was examined in 1998 by King *et al.* (21). However, such an epidemiologic comparison between studies was difficult to interpret for the reasons shown in Figure 1.2 and discussed more fully in Chapters 4 and 5. Key issues are the diagnostic criteria and screening approaches used. In addition, screening too early (before 24 weeks) could result in fewer cases with hyperglycemia in pregnancy being detected. In some women, the diagnosis of GDM is only made later in pregnancy, and they will have had a normal test on conventional screening between 24 and 28 weeks.

Overweight, obesity, and extreme obesity (BMI 35+) are significant contributors to the development of GDM and DIP. Recently, the respective population attributable fractions (PAFs) in South Carolina, USA, have been calculated to be 9.1%, 11.8%, and 15.5% (i.e., a total of 36.4% of GDM is attributable to excess weight) (22). This did vary marginally between ethnic groups (e.g., 18.1% [16.0–20.2%] American blacks vs. 14.0% [12.8–15.3%] non-Hispanic whites vs. 9.6% [7.3–12.0%] Hispanics of all GDM was attributable to extreme obesity).

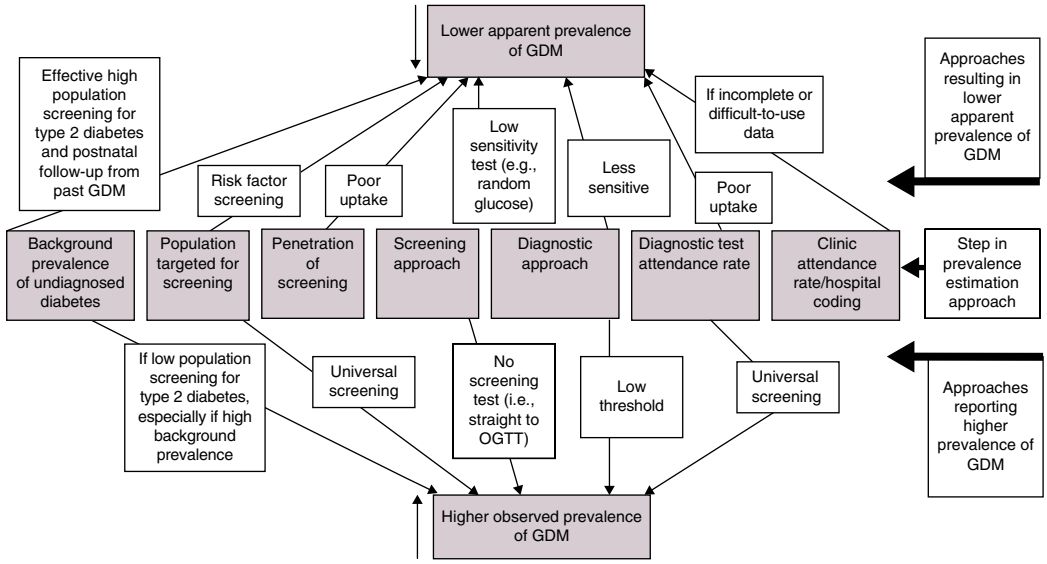

Figure 1.2 Difficulties in comparing prevalence data in gestational diabetes mellitus (GDM) with different approaches. OGMM = Oral glucose tolerance test.

Diagnosis of diabetes in Pregnancy and Gestational Diabetes Mellitus

The diagnoses of DIP and GDM are discussed in detail in Chapter 5. Few other areas in medicine have been associated with such confusion and controversy, while the differing criteria for diagnosis have, until recently, made epidemiological comparison problematic. Adoption of the new WHO (IADPSG) criteria in 2013 (2,3) has, for the first time, brought uniformity to this confused field, although they have not been accepted universally. These criteria were based upon epidemiologic data generated by the HAPO study (23) rather than either consensus or risk of future maternal diabetes. HAPO also highlighted the relevance of hyperglycemia to maternal fetal outcome, independent of maternal obesity. A further important observation was the comparable relationship between hyperglycemia and maternal/fetal outcome between all participating ethnic groups. One caveat is that some ethnic groups, such as Polynesians, were not included in HAPO, and evidence from New Zealand suggests that hyperglycemia may increase their birthweight more than among Europeans (24) after adjusting for maternal weight.

While obesity, ethnicity, maternal age, and a family history of diabetes are the major risk factors for GDM/DIP, others also exist (e.g., previous large baby, previous stillbirth, multiple pregnancy, and physical inactivity), and these form the basis of screening strategies (25) (see also Chapter 4). There is also clear evidence of the importance of PCOS as a risk factor for GDM/DIP (26). Another important group of women at increased risk of GDM are those with a previous history of GDM (27), particularly in association with excess weight or with weight gain between pregnancies and where previous GDM was diagnosed early in pregnancy and required treatment with insulin (28).

Prevalence of Diabetes in Pregnancy

Few studies have reported the prevalence of DIP as defined by the new WHO 2013 criteria (3): fasting glucose ≥7.0 mmol/l, HbA1c ≥6.5% (47 mmol/mol), random glucose ≥11.1 mmol/l, and confirmed with another test. A number of

studies have previously reported the prevalence of diabetes immediately after a pregnancy complicated by GDM, such as in New Zealand where 21% of Polynesians and 4% of Europeans had diabetes postpartum (29). However, these studies were before the IADPSG/WHO criteria for DIP and DIP is often not associated with diabetes postpartum. For example, in one Australian cohort study, only 21% had diabetes postpartum (41% returned to normal) (30).

PRACTICE POINT

DIP does not always imply permanent diabetes postpartum.

Of the 133 patients with overt diabetes in pregnancy who attended a follow-up oral glucose tolerance test (OGTT) at 6–8 weeks postpartum, 21% had diabetes, 37.6% had impaired fasting glucose or impaired glucose tolerance, whilst 41.4% returned to normal glucose tolerance.

Few papers to date describe the characteristics of women with DIP. The Japan Diabetes and Pregnancy Study Group reported that compared with women with GDM, women with DIP had higher pre-gestational Body Mass Index (BMI: 24.9 ± 5.7 vs. 26.2 ± 6.1 kg, $P < 0.05$), earlier gestational age at delivery (38.19 ± 2.1 vs. 37.89 ± 2.5 weeks, $P < 0.05$), more retinopathy (0% vs. 1.2%, $P < 0.05$), and more pregnancy-induced hypertension (6.1% vs. 10.1%, $P < 0.05$) (31). Others have also found women with DIP to have a greater BMI and more adverse pregnancy outcomes (30).

Prevalence of Gestational Diabetes

There are major differences in the prevalence of GDM between ethnic groups, reflecting both the background prevalence of type 2 diabetes and its age at onset (32). All populations apart from those of European descent (and even including some European populations) are now considered at high risk. The prevalence has also generally increased over time (33,34). While this most likely reflects the epidemics of obesity and type 2 diabetes in the nonpregnant state, an additional feature is likely to be the increasing age at which pregnancy occurs, and for some total populations, the immigration of high-risk ethnic groups. Prevalence rates vary within the same ethnic group in different locations, with migrant populations generally having a higher prevalence than those remaining in traditional rural areas, probably relating to lifestyle change (a higher energy diet and less physical activity) and greater adiposity. Such data need careful scrutiny to recognize these factors and to ensure that no change in ascertainment (e.g., screening approaches) or diagnostic criteria have occurred.

Many studies describing prevalence of GDM include different screening approaches that underreport the true prevalence.

The prevalence of GDM using the WHO 2013 criteria is now being increasingly reported from different sites, allowing a more global picture to be obtained beyond the original HAPO sites as shown in Table 1.2. The prevalence is substantially more than using the older criteria, and this is discussed more in Chapter 5.

No data using the WHO 2013 criteria have yet been published from Africa, although women of African descent have been shown to have a high prevalence of GDM in, for example, Oslo (33). The IDF Atlas (4) cites a prevalence of hyperglycemia in pregnancy in Africa at 16.0% (4.6 million affected births in 2013), the region with the greatest number of cases. This prevalence is more than in Europe (15.2%), North America (13.2%), South/Central America (13.2%), or the Western Pacific (11.8%), but less than in the Middle East/North African (22.3%) or South/Eastern Asia (23.1%).

The risk of hyperglycemia in pregnancy is associated with lower socioeconomic status on a population basis. In an Australian study, women living in the three lowest socioeconomic quartiles had higher adjusted odds

Table 1.2 Prevalence of GDM using WHO 2013/IADPSG criteria in complete populations and in the HAPO study for comparison.

Location	Year	Prevalence: WHO (2013) (%)	Other criteria used	Prevalence: other criteria
Europe				
Belgium (35)	2014	23	NDDG	8
Norway-Western European (36)	2012	24	WHO (1999)	11
Norway-ethnic minorities (36)	2012	37	WHO (1999)	15
Spain (37)	2010	35.5	NDDG	10.6
UK-Belfast-HAPO (2)	2010	17.05	WHO (1999)	1.5%
UK-Manchester-HAPO (38)	2010	24.28		
Ireland (39)	2011	12.4	WHO (1999)	9.4
Hungary (40)	2011	16.6	WHO (1999)	8.7
Middle East				
Petah-Tiqva, Israel-HAPO (38)	2010	10.06		
Beersheba, Israel-HAPO (38)	2010	9.25		
UAE (41)	2010	37.7%	ADA	12.9%
North America				
Barbados-HAPO (38)	2010	11.9		
Canada (42)	2014	10.3	CDA (2008)	7.3
Canada-Toronto-HAPO (38)	2010	15.53		
California-USA-HAPO (38)	2012	25.5		
Ohio-USA-HAPO (38)	2012	25.0		
Chicago-USA-HAPO (38)	2012	17.3		
Rhode Is-USA-HAPO (38)	2012	15.5		
Central/South America				
Mexico (43)	2011	30.1	NDDG	10.3
Asia				
India (44)	2012	14.6	DIPSI	13.4
Hong Kong-HAPO (38)	2010	14.39		
Singapore-HAPO (38)	2010	25.13		
Thailand-HAPO (38)	2010	22.97		
Japan (45)	2011	6.6	JSOG	2.4
China (46)	2014	18.9	NDDG	8.4
Vietnam (47)	2012	20.36	ADA	6.07
Pacific				
Newcastle-Australia-HAPO (38)	2012	15.3		
Brisbane-Australia-HAPO (38)	2012	12.4		
Wollongong-Australia (48)	2011	13.0	ADIPS	9.6

ratios (ORs) for GDM compared with women in the highest quartile, who had an OR of 1 versus 1.54 (1.50–1.59), 1.74 (1.69–1.8), and 1.65 (1.60–1.70) for decreasing socioeconomic status quartiles (49).

Another key finding from the HAPO study has been the different patterns of hyperglycemia in different ethnic groups, with 55% of women diagnosed on the fasting glucose, 33% on the 1 h, and 12% on the 2 h. This has major implications for decisions over whether to drop the fasting, 1 h, or 2 h time point during the OGTT. The proportion diagnosed on the fasting ranged from 74% in Barbados to 26% in Hong Kong and 24% in Thailand (38). This naturally shifted the diagnostic "time point," such that in Thailand and Barbados, 64% and 9% were diagnosed at the 1 h time point and in Hong Kong 29% were diagnosed at the 2 h time. The greater likelihood of diagnosis on the 2 h glucose among Asians was predictable from studies outside of pregnancy (50).

Public Health Impact of Hyperglycemia in Pregnancy

The public health impact of hyperglycemia in pregnancy relates to the numbers affected as described here, impact on quality of life, additional resource utilization, and potentially intergenerational transmission. The additional resources required for mitigating the harm from hyperglycemia in pregnancy and potential savings from intervention are shown in Table 1.3.

Table 1.3 Interventions for hyperglycemia in pregnancy and potential savings from intervention.

	Interventions	Potential savings
Type 1 and type 2 diabetes		
Preconception	Optimization of metabolic control, folate therapy, medication optimization	Malformations Fetal loss sequelae
Antenatal management	Optimization of metabolic control including blood pressure control	Neonatal, maternal birth complications
	Optimization of obstetric management	Offspring risk of diabetes, obesity
Retinal management	Retinal screening, laser if needed	Vitreous surgery, cesarean section
Other complication management	Renal replacement therapy, hospitalization for cardiac event, autonomic neuropathy	
Gestational diabetes mellitus (GDM) and diabetes in pregnancy (DIP)		
Diagnosis of GDM	Screening and diagnosis program	
Antenatal management	Optimization of metabolic control, including blood pressure control	Neonatal, maternal birth complications
	Optimization of obstetric management	Offspring risk of diabetes, obesity
Retinal management	Retinal screening if likely undiagnosed type 2 diabetes, laser if needed	cesarean section (rare)
Postnatal screening and intervention	Screening	Prevention of permanent diabetes
	Primary prevention (lifestyle, drugs)	Prevention of undiagnosed type 2 diabetes in pregnancy

Public Health Impact of Pregnancy Among Women with Known Preexisting Diabetes

Pre-gestational diabetes is a major risk factor for congenital malformations, particularly congenital heart defects (51). Type 1 and type 2 diabetes probably have a comparable teratogenic effect (52). Relative to type 1 diabetes, type 2 diabetes in pregnancy has been associated with higher perinatal mortality (OR: 1.50; CI: 1.15–1.96) and fewer cesarean sections (OR: 0.80; 95% CI: 0.59–0.94), but similar rates of stillbirth, neonatal mortality, miscarriage, preterm birth, small and large for gestational age infants, neonatal hypoglycemia, jaundice, and respiratory distress (53).

In the USA, the PAF of congenital heart defects among those with pre-gestational diabetes was estimated to be 8% (7), although the PAF rises to approximately one-quarter for atrioventricular septal defects (Table 1.4) (7). Besides death in 2–3%, others require surgery and long-term risks of reoperation, arrhythmia, endocarditis, heart failure, and pulmonary hypertension.

Population impact depends on the implementation of pre-pregnancy care, which is associated with a risk ratio (RR) of 0.25 (95% CI: 0.16–0.37) and number needed to treat (NNT) of 19 (95% CI: 14–24), for congenital malformations and a RR of 0.34 (95% CI: 0.15–0.75) and NNT of 46 (95% CI: 28–115) for perinatal mortality (54).

Public Health Impact From GDM/DIP

Although the costs of GDM/DIP have been difficult to estimate with the variation in criteria across the world, the increasing adoption of the WHO 2013 criteria has made health economic analyses more achievable. Previous estimates of the population impact of GDM/DIP suggested that 2.8% of perinatal mortality, 2.5% of malformations, 5.9% of cesarean sections, 9.9% of babies ≥4.5 kg, and 23.5% of cases of shoulder dystocia occurred in women with diabetes in pregnancy of some sort (55). However, these estimates were prior to the new criteria and new screening approaches, and hence many women with potentially preventable adverse outcomes were considered "normal" without the opportunity of GDM/DIP treatment.

Naturally, the extent of ascertainment, and therefore achievability of the benefits from treating GDM/DIP, are dependent on the approaches used for its identification (e.g., universal screening vs. risk factor–based screening). Other important determinants are not only the degree to which treatment is implemented, but the extent to which treatment goals are reached. For example, in one study, 24.8% of the women achieving 0% of fasting test results >5.3 mmol/l experienced an adverse pregnancy outcome, compared with 57.9% of women whose fasting glucose was >5.3 mmol/l on over 30% of occasions (56).

Table 1.4 Population attributable fraction of congenital heart disease from pregestational diabetes (7).

Congenital heart defect	Summary odds ratio (95% CI)	Population attributable fraction, % (95% CI)
All congenital heart defects	3.8 (3.0–4.9)	8.3 (6.6–11.8)
Atrioventricular defects	10.6 (4.7–20.9)	23.4 (10.6–40.0)
Co-arctation of the aorta	3.7 (1.7–7.4)	7.9 (2.1–17.6)
Hypoplastic left heart syndrome	3.7 (1.5–8.9)	8.0 (1.6–20.4)
Tetralogy of Fallot	6.5 (3.3–11.8)	14.8 (6.6–26.3)
Transposition of the great arteries	4.8 (2.7–8.3)	10.9 (5.1–19.8)

Source: Simeone *et al.* (2015) (7). Reproduced with permission of Elsevier.

Health economic analyses often omit benefits from improvements in quality of life (QoL) and potential to prevent diabetes in mother and offspring. In the ACHOIS study (based on the older WHO 1999 criteria), there was a significant improvement in QoL with GDM diagnosis and treatment and in health economic modeling; this was associated with significant gains on a population basis (57). The first attempt at modeling the intergenerational and intragenerational effects of GDM on type 2 diabetes, from the Saskatchewan database, has suggested that among the high-risk First Nations population, prior GDM may be responsible for 19% to 30% of type 2 diabetes. However, GDM was responsible for only approximately 6% of cases among other persons (58).

Also excluded to date in health economic analyses has been the importance of diagnosing pre-gestational diabetes after a pregnancy complicated by GDM and any subsequent pregnancies. There is evidence of a greater risk of permanent diabetes in mothers with increasing numbers of pregnancies complicated by GDM (59). Identification of GDM also provides an opportunity to manage this risk through timely use of reliable contraception.

Even with these caveats, a number of modeling studies have examined the cost of GDM and the costs–benefits of treatment. Reports from a number of countries have shown a high cost of GDM (e.g., the USA in 2011 dollars, $831,622,028 per 100,000 women) and cost-effectiveness of treatment (e.g., the USA, Israel, and India (60,61)).

Health economic analyses should include estimates of the benefits of identifying and intervening among women at risk of progressing to type 2 diabetes.

FUTURE NEEDS

More studies using the WHO criteria for GDM and DIP with universal screening
Studies in many more populations on the interplay and independent effects of obesity and GDM
Studies looking at the criteria required for GDM in early pregnancy
More studies looking at monogenic diabetes and other rare forms of diabetes
More studies from Africa
More studies looking at population impact of intergenerational effects of maternal diabetes, including GDM
More studies looking at the epidemiology of diabetes in pregnancy
More studies looking at the health economic impact of total hyperglycemia in pregnancy in different economies

Multiple-Choice Questions

One or more answers are correct.

1 The WHO 2013 criteria for gestational diabetes are based upon:
- **A** long-term risk of diabetes in the mother.
- **B** long-term risk of obesity in the offspring.
- **C** 100% greater risk of a pregnancy complication versus "normal" women.
- **D** 75% greater risk of a pregnancy complication versus "normal" women.
- **E** 50% greater risk of a pregnancy complication versus "normal" women.

Correct answer: D.

2 The risk of GDM is greater if:
- **A** a woman has normal weight.
- **B** a woman has polycystic ovarian syndrome.
- **C** a woman has had a stillbirth in the past.
- **D** a woman has had a major antepartum hemorrhage in the past.
- **E** a woman has been inactive both before and during pregnancy.

Correct answer: B, C, E.

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2

Pathophysiology of Diabetes in Pregnancy

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PRACTICE POINTS

- Insulin resistance and compensatory hyperinsulinemia are adaptations to normal pregnancy.
- The etiology of insulin resistance in pregnancy is multifactorial and likely to include placental factors, such as human placental growth hormone and tumor necrosis factor-alpha (TNFα), as well as body composition changes and nutrient excess.
- Glucose intolerance and gestational diabetes result when pancreatic β-cell function fails to compensate adequately for the degree of insulin resistance in pregnancy.
- Metabolic plasticity during pregnancy allows for protection of the fetus during periods of limited maternal resources.

Maternal Metabolic Adaptation to Pregnancy

Pregnancy is a period of significant maternal metabolic adaptations. Teleologically, the changes in maternal anatomy and physiology are thought to occur to support the growth and development of the fetus and prepare the mother for the physiological demands of pregnancy and lactation. The composite of changes is dynamic and evolves throughout the pregnancy.

Normal Metabolic Homeostasis

Metabolic fuels are derived from carbohydrates, fats, and proteins in the diet. All cells require a constant supply of fuel to provide energy for the production of adenosine triphosphate (ATP) and cellular maintenance. After a meal, dietary components (glucose, free fatty acids, and amino acids) are delivered to tissues, taken up by cells, and oxidized to produce energy. Any dietary fuel that exceeds the immediate needs of the body is stored, mainly as triglycerides in adipose tissue; as glycogen in the liver, muscle, and other cells; or, to a lesser extent, as protein in muscle. Between meals, substrates are drawn from stores and used as needed to provide energy. The regulation of body fuels is a complex interaction of nutrients and hormones that ensures a continuous supply of energy substrates with intermittent refueling or feeding.

Insulin and glucagon are the two major hormones that regulate fuel mobilization and storage. Insulin is a polypeptide synthesized as proinsulin in β cells of the pancreatic islets and cleaved into insulin and C-peptide. Its primary role is to orchestrate the metabolism of not only glucose but also lipids and

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amino acids. Insulin has anabolic and anticatabolic properties. In the liver, insulin promotes glycogen and fat synthesis, while suppressing glycogenolysis and ketogenesis. In adipose tissue, it promotes fat storage and glycerol synthesis, and suppresses lipolysis. In muscle, insulin promotes glycolysis and glycogen and protein synthesis, and suppresses proteolysis. Glucagon, synthesized in the α cells of the pancreas, is a major counterregulatory hormone of insulin. When plasma glucose levels are low, glucagon secretion promotes glucose production through glycogenolysis and gluconeogenesis.

Post-absorptive State

In the post-absorptive or fasting state, glucose-dependent tissues, like the brain, renal medulla, and certain blood cells, continually oxidize glucose as the primary fuel source. Because glucose is the preferred substrate for the brain, the maintenance of an adequate plasma glucose level is a physiologic priority. Low insulin levels result in a decrease in peripheral glucose uptake in tissues, such as adipose tissue and muscle. Initially, liver glycogen is degraded to provide glucose for glucose-dependent tissues. Approximately 70 g of glycogen is stored in the liver (1), while the total basal consumption of glucose is 200–250 g/day (2), well in excess of stored hepatic glycogen. When the limited stores of glycogen are depleted, the liver uses carbon from lactate, glycerol, and amino acids to synthesize glucose through gluconeogenesis. Decreased insulin levels promote gluconeogenesis, and glucagon plays an additional role in the maintenance of continuous endogenous glucose supply. Glycogenolysis and gluconeogenesis increase to match the basal need for glucose for glucose-dependent tissues during fasting (Figure 2.1a).

Insulin levels affect the availability of all nutrients, including amino acids and fatty acids, during periods of fasting. Low insulin levels allow for the increase in proteolysis and the augmentation of the release of amino acids from skeletal muscle, the primary reservoir of protein stores. The net flux of amino acids is from the muscle to the liver, with the gluconeogenic precursors, alanine and glutamine, accounting for the largest proportion of amino acids released (3). In adipose tissue, insulin inhibits hormone-sensitive lipase, which catalyzes the hydrolysis of stored triglycerides to free glycerol and free fatty acids. The consumption of free fatty acids in skeletal muscle is an important factor in limiting muscle glycolysis and glucose oxidation.

Post-absorptive State in Pregnancy

Pregnant women have an added burden of supplying the growing fetus with energy substrates during periods of fasting. Glucose is the primary energy source for the fetus, and the fetus is obligated to obtain most of the glucose it utilizes from maternal plasma due to the absence of significant gluconeogenesis (4). A carrier-mediated transport system in the placenta (GLUT1) (5) meets the high fetal demand with rapid transfer of glucose from the maternal compartment to the fetus. Maternal plasma glucose concentration and uterine/placental blood flow determine glucose supply, making transfer across the placental barrier a relatively rapid process that has been described as a *flow-limited process* (6).

Fasting in pregnancy is more metabolically challenging for the mother due to the growing fetal demand for glucose as an energy substrate. After the first trimester, maternal fasting plasma glucose levels decrease progressively with increasing gestational age (7). With short intervals of fasting, human pregnancy is marked by increased fasting plasma insulin levels and increased basal hepatic glucose production compared with nonpregnant levels (8,9). A reduced insulin-induced suppression of hepatic glucose production may provide increased endogenous glucose production and therefore augment the supply of glucose for the mother and fetus between meals. In 1970, Felig *et al.* (3) reported on studies of healthy women who were scheduled to undergo termination of

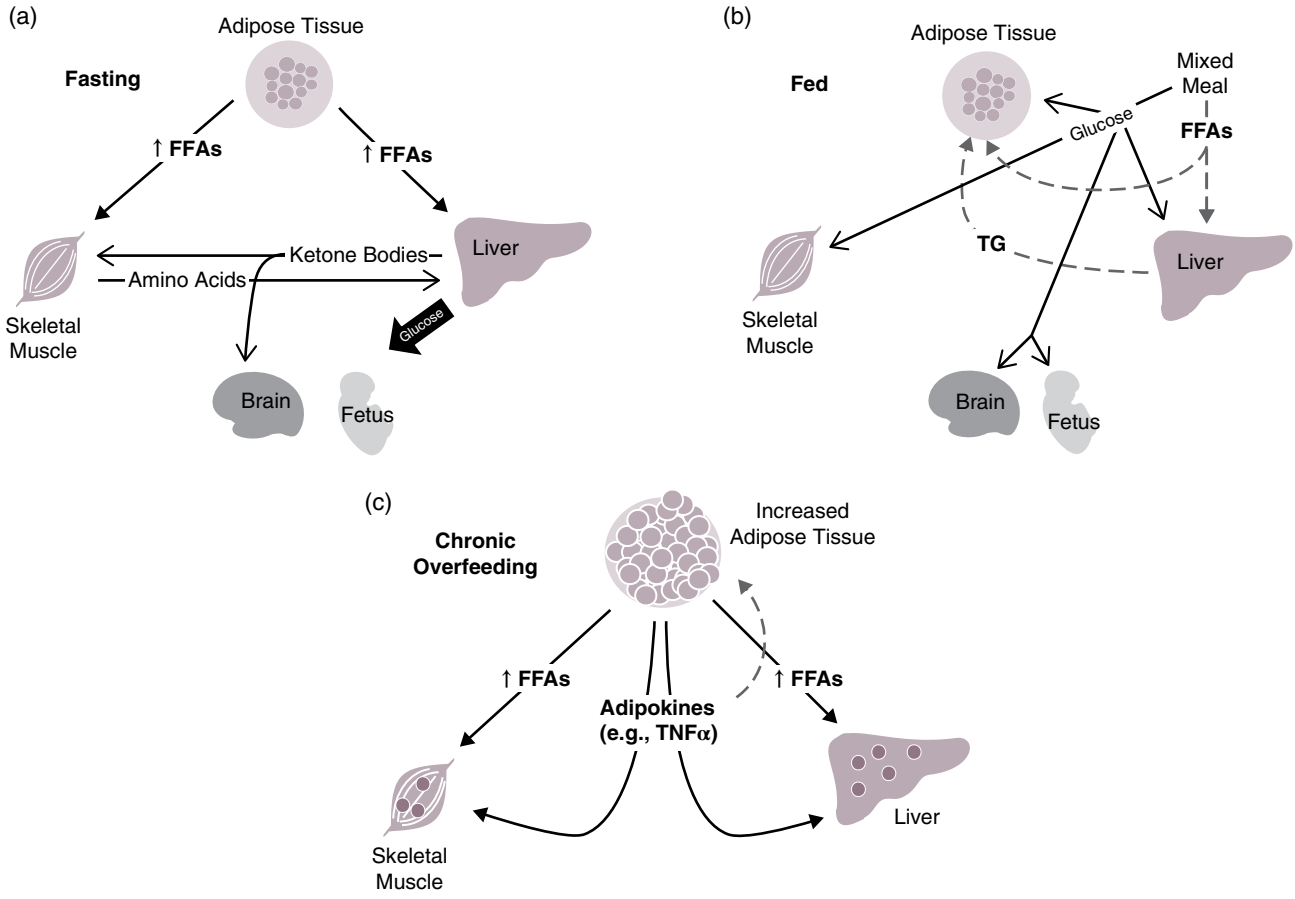

Figure 2.1 (a) In the fasting state, glucose for dependent tissues, like the brain and the fetus, is derived from the breakdown of hepatic glycogen stores. Once this reserve is depleted, glucose is produce *de novo* from amino acids released from protein stores in muscle. Free fatty acids (FFAs) are released from adipose tissue, converted to ketone bodies in the liver, and used to prevent excessive glycolysis in non-glucose-dependent tissues. (b) Fed state. After the ingestion of a mixed meal, carbohydrates are broken down into glucose and other monosaccharides and taken up by all tissues. Any glucose that is not needed immediately for glycolysis is converted to glycogen or triacylglyerol and stored in liver, muscle, and adipose tissue for later use. Lipids are hydrolyzed to fatty acids, resynthesized to triacylglyerol (TG), and stored in adipose tissue. (c) Chronic overfeeding. Chronic overnutrition and obesity can lead to adipocyte dysfunction and cellular inflammation. The release of various adipokines, including tumor necrosis factor-α (TNFα), results in insulin resistance in adipose tissue, skeletal muscle, and liver. Insulin resistance in adipose tissue leads to lipolysis and increased FFA release, even in the presence of relatively increased insulin levels. With continued nutrient excess, adipocyte storage capacity is exceeded and lipid "overflows" to other tissues, such as muscle and liver, worsening insulin resistance and resulting in lipotoxicity and metabolic inflexibility.

pregnancy in the second trimester and healthy nonpregnant controls during a prolonged 84 h fast. The fasted pregnant women had lower concentrations of plasma glucose and insulin, and greater ketone concentrations, compared to the nonpregnant women. Felig's work led to the concept of "accelerated starvation" in pregnancy. The higher plasma ketones found in the fasted pregnant women were seen only in the presence of decreased insulin levels and presumably resulted from increased lipolysis.

Why are fasting glucose levels lower in pregnancy despite increased endogenous glucose production? The mechanism for this is not well understood. Decreased fasting glucose does not appear to be a result of decreased maternal protein catabolism based on urinary nitrogen excretion in pregnant compared to nonpregnant women (3). Maternal plasma alanine levels are decreased in fasted pregnant women compared to nonpregnant women and may represent the fetal siphoning of glucogenic precursors. Although protein catabolism is increased in pregnancy, increased utilization by the placenta and fetus is likely to cause a decrease in circulating gluconeogenic precursors (10). Some have suggested that the suppression of hepatic glucose production is not impaired in late pregnancy, but rather that the set point for plasma glucose levels is decreased (11).

Postprandial State, Nonpregnant

The changes in response to ingestion of a mixed macronutrient meal are based on homeostatic mechanisms that allow immediate usage or storage of fuel in expectation of periods of fasting (Figure 2.1b). Incretin peptides, such as glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP1), are secreted from the gastrointestinal tract into the circulation in response to the ingestion of a meal, which enhances glucose-stimulated insulin secretion. Insulin release in the first phase acts predominately in the liver to decrease or shut down hepatic glucose production (12). Glucose uptake in the splanchnic bed is largely a result of increases in glucose availability, most of which will pass through the liver (13). Subsequently, increased insulin levels mediate peripheral glucose uptake, mainly in the muscle and adipose tissue (14). Larger amounts of insulin are required to effect peripheral glucose uptake than are needed to suppress hepatic glucose production (12). The repletion of muscle nitrogen depends on the net uptake of amino acids in muscle following a meal. In addition to its other functions, insulin acts to suppress proteolysis and accelerates the uptake of free fatty acids, promoting fat synthesis and triglyceride storage in adipose tissue and the liver. Postprandial increases in insulin levels promote the storage of all nutrients (glucose, amino acids, and lipids) for later use.

Postprandial State in Pregnancy

In addition to the short-term (hour-to-hour) management of fuels, pregnant women have to regulate long-term energy balance that occurs with the changing metabolic demands of the mother and fetus throughout the pregnancy and during lactation. Early pregnancy is marked by storage of nutrients (anabolic state) in preparation for the later use of stored resources in the third trimester and during lactation when energy requirements increase (catabolic state). The energy balance adaptations in early to mid-pregnancy probably result from large increases in estrogen, progesterone, and lactogens (human placental lactogen and prolactin) (reviewed by Freemark (15)). Lactogens and progesterone increase appetite and induce hyperphagia, resulting in a 10–15% increase in food intake. Progesterone facilitates fat storage, and the decline in pituitary growth hormone plays a permissive role in the deposition of body fat. The roles of lactogens and estrogen in lipogenesis are less clear, and studies have been conflicting (15). Human placental lactogen stimulates hyperplasia and hypertrophy of β islet cells. The resulting enhanced insulin secretion with normal peripheral and hepatic insulin sensitivity in early pregnancy promotes the storage of energy substrates

through the inhibition of lipolysis, proteolysis, and glycogenolysis.

Overall, after the first trimester, insulin sensitivity decreases progressively during the remainder of the pregnancy. Early and late pregnancy changes differ significantly. Although some debate exists about insulin action in early pregnancy, Catalano *et al.* found no change in peripheral and hepatic insulin sensitivities in early pregnancy using the hyperinsulinemic–euglycemic clamp technique and glucose tracer, but glucose tolerance was improved (7,8,16). In early pregnancy, insulin secretion increases, while insulin action is variable and, therefore, glucose tolerance may increase in some women.

Insulin resistance and a compensatory hyperinsulinemia are hallmarks of late pregnancy. Insulin-induced peripheral glucose uptake decreases 56% by the third trimester compared to the pre-pregnancy period, and insulin secretion increases 3–3.5-fold (8). Some animal (17,18) and human studies (19,20) have shown a reduction in insulin-induced suppression of hepatic glucose production in pregnancy, while others have not (11,21). Methodological differences during insulin clamps are the likely explanation for the discrepancy, but the weight of evidence suggests that insulin's ability to suppress hepatic glucose production is impaired in late pregnancy. Obese women with normal glucose tolerance have an impaired insulin-induced decrease in hepatic glucose production compared with their lean counterparts (20). In pregnant rodents, the accumulation of visceral fat contributes to the development of hepatic insulin resistance, an effect that may be mediated through the accumulation of hepatic triglycerides (22).

Insulin Resistance in Pregnancy

The etiology of insulin resistance in pregnancy is not completely understood and is likely to be multifactorial. Historically, placental hormones have been implicated for many reasons. The extent of insulin resistance in pregnancy corresponds to the growth of the placenta, and many placental hormones induce insulin resistance when given to nonpregnant individuals, including human placental lactogen (hPL) (23,24), human placental growth hormone (hPGH) (25), and progesterone (26,27). hPGH induces insulin resistance by inhibiting key regulators in the insulin signaling cascade in adipose tissue (28). Placental factors clearly have a role in the development of insulin resistance in pregnancy. Some hormones, such as hPGH, may directly affect insulin action; other factors may contribute indirectly to the insulin resistance through increased food intake and the promotion of lipogenesis.

Normal pregnancy shares many common features with the metabolic syndrome, including increased adiposity, insulin resistance, hyperinsulinemia, and hyperlipidemia. Maternal body fat increases on average more than 3 kg (29) over a relatively short time interval. Epidemiologic (30,31) and animal (22) studies suggest that visceral fat in particular increases in pregnancy, although descriptions of human body composition changes are limited due to increases in total body water and the restrictions of measurement modalities that can be used during pregnancy (32–35). Adipose tissue plays a role in regulating food intake, energy balance, and metabolic homeostasis through the production of fat-derived peptides. Several of these biologically active peptides (adipokines) affect energy homeostasis, such as leptin, which is expressed and secreted primarily by adipocytes. Leptin signals the adequacy of adipose stores to the hypothalamus, providing the afferent limb in energy homeostasis (36,37). In addition to maternal fat as a source of leptin, the human placenta produces and secretes leptin into both maternal and fetal circulation (38), and the concentrations of leptin are elevated in pregnancy compared to the nonpregnant state, irrespective of Body Mass Index (39), which may seem paradoxical because food intake is increased. This phenomenon is termed

leptin resistance, and pregnancy is a *leptin-resistant* state. Emerging evidence supports the presence of a central cellular resistance to leptin in pregnancy (40–42). As in obesity, cellular leptin resistance allows for a new equilibrium for food intake through limited leptin action and greater requirements for suppressing food intake.

Although adipocyte production of adipokines has a critical role in metabolic homeostasis, some adipokines may mediate the harmful biologic effects of increased adiposity. For example, TNFα is associated with decreased insulin sensitivity in a number of conditions outside of pregnancy, including obesity (43) and aging (44). In pregnancy, TNFα plasma concentration is more predictive of insulin resistance than cortisol, human chorionic gonadotropin (hCG), estradiol, hPL, and prolactin (45). Other adipokines (resistin, interleukin-1 [IL1], and IL6) have also been implicated as mediators of insulin resistance (46).

Nutrient Excess and Metabolic Dysfunction

The expansion of adipose tissue due to chronic overnutrition and obesity can lead to adipocyte dysfunction, cellular inflammation, and insulin resistance (Figure 2.1c). In addition to the metabolic dysfunction caused by excess adipose tissue, the process of accumulating excess adipose tissue leads to metabolic dysregulation. Gregor and Hotamisligil (47) have proposed that a pathologic excess of nutrients and excessive lipid storage in the adipocyte lead to loss of mitochondrial function, an increase in endoplasmic reticular stress, and adipocyte dysfunction, all of which result in insulin resistance. Additionally, when continued nutrient excess exceeds adipocyte storage capacity, lipid then "overflows" into other tissues (48). The oversupply of lipids into the liver, skeletal muscle, and pancreatic islets results in a tissue-specific insulin resistance and impaired insulin secretion, generally termed *lipotoxicity* (48). In 1963, Randle *et al.* (49) proposed that increased fatty acid oxidation inhibits glucose oxidation, and later, McGarry *et al.* (50) showed that hyperglycemia inhibits fatty acid oxidation. As a result of these two concepts, the concept of *metabolic inflexibility* has arisen, which proposes that in the setting of chronic overnutrition, muscle tissue is unable to select the appropriate substrate for oxidation (glucose vs. fatty acids) in response to the current nutrient supply (51), resulting in metabolic dysregulation in skeletal muscle, the primary tissue for peripheral glucose uptake in the nonpregnant state. This theory applied to pregnancy, a state of hyperphagia and rapid increases in maternal body fat, may have important implications, including greater peripheral insulin resistance.

Insulin Resistance and Glucose Intolerance

The terms *insulin resistance* and *glucose intolerance* are often erroneously used interchangeably and should be differentiated. *Insulin resistance* refers to the reduced ability of insulin to act on target tissues. In the most basic terms, insulin is less effective in suppressing hepatic glucose production, and greater amounts of insulin are needed to induce peripheral glucose uptake in the muscle and adipose tissue. In insulin-resistant states, more insulin is required to maintain glucose homeostasis. *Glucose-intolerant states* generally include some degree of insulin resistance and hyperinsulinemia, but the secretion of insulin is relatively inadequate for the degree of insulin resistance, and the result is elevations in fasting and/or postprandial plasma glucose levels.

In normal pregnancy, despite a well-demonstrated insulin resistance, in normal-weight women, the large compensatory increase in insulin secretion maintains maternal plasma glucose levels within a relatively narrow margin (19). Continuous

glucose monitoring demonstrates that normal-weight, glucose-tolerant women at around 29 weeks of gestation had a mean fasting glucose level of 4.0 ± 0.7 mmol/L (72.1 ± 13 mg/dL) and a peak postprandial level of 5.9 ± 0.9 mmol/L (106.2 ± 16 mg/dL) (52). Women who are unable to compensate with increased insulin secretion become glucose intolerant. Although glucose tolerance has a continuous distribution, pregnant women are labeled categorically as glucose tolerant or intolerant. The detection of gestational diabetes is aimed at identifying pregnancies at risk for adverse maternal–fetal outcomes and, to some extent, identifying women at risk for type 2 diabetes later in life. The threshold for maternal glycemia at which the risks for the fetus are increased is currently being debated (see Chapters 6 and 7).

The relationship between insulin sensitivity and insulin secretion is reciprocal and nonlinear in nature (Figure 2.2). In order to maintain normal glucose tolerance, changes in insulin sensitivity must be matched by a proportionate yet opposite change in circulating insulin levels. With decreasing insulin sensitivity, as is seen in pregnancy, insulin secretion must increase for glucose concentrations to remain unchanged. Failure to secrete adequate amounts of insulin for the degree of insulin resistance results in a shift of the curve to the left and impaired glucose tolerance. This process underlies the development of diabetes.

Increasing insulin resistance and a compensatory hyperinsulinemia are progressive throughout the pregnancy. If insulin secretion cannot compensate for increased insulin resistance, glucose intolerance ensues. Much of our current understanding of insulin sensitivity and secretion in pregnancy comes from work by Catalano and colleagues in the 1980s (53) and 1990s (54,55). Based on hyperinsulinemic–euglycemic clamp studies, nonpregnant women with a history of gestational diabetes were found to have reduced insulin sensitivity compared to women with a history of normal glucose tolerance (53). All pregnant women seem to have a consistent 50–60% decrease in insulin sensitivity by the third trimester compared to pre-pregnancy, and differences in insulin sensitivity in late pregnancy among women largely represent pre-pregnancy differences. Changes in insulin sensitivity in early pregnancy can be variable and correlate inversely with changes in maternal body fat mass. To compensate for insulin resistance in

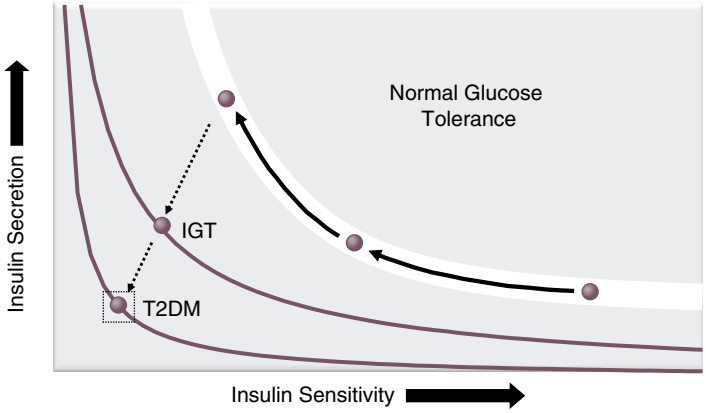

Figure 2.2 To maintain normal glucose tolerance, insulin secretion must increase to compensate for decreasing insulin sensitivity during pregnancy (solid arrows). Failure to secrete adequate amounts of insulin for the degree of insulin resistance results in a shift of the curve to the left and impaired glucose tolerance (dotted arrows). This process underlies the development of diabetes (both gestational [IGT] and type 2 [T2DM]). (Adapted from Kahn *et al.* Nature 2006;444:840–846 (63), with permission.)

pregnancy, insulin secretion is increased. Lean women with normal glucose tolerance have significant increases in first-phase insulin response, whereas women with gestational diabetes have greater increases in second-phase insulin response. Obese women show increases in both first- and second-phase response (54,55). These findings suggest that obese women with gestational diabetes would be at greatest risk for β-cell stress and later development of type 2 diabetes.

Metabolic Plasticity in Pregnancy

Maternal metabolic plasticity during pregnancy may allow for protection of the fetus during periods of limited resources. While the complex factors that determine the balance between the competing needs of the mother and fetus are incompletely understood, the study of a unique population of women in the resource-poor country of Gambia has offered some insight. Poppitt and colleagues (56) performed a longitudinal study using whole-body calorimetry in a cohort of Gambian women who had limited resources. The women were lean but not underweight, they had mean weight gain during pregnancy below the US Institute of Medicine recommendations, and yet the mean birthweight was 3.02 kg at term, normal in this small cohort. From the beginning of pregnancy, the Gambian women had a decrease in basal metabolic rate, and when corrected for lean body mass, the women maintained a basal metabolic rate below their pre-pregnancy rate, even late in the third trimester. This study demonstrated that in an environment in which food intake cannot be increased, pregnant women have "metabolic plasticity" and adapt in order to conserve energy, perhaps through changes in energy expenditure for the developing fetus.

In an environment with ample resources, an increase in nutrient intake results in a positive energy balance throughout the pregnancy. In sharp contrast to the women in Gambia, women in more affluent countries maintain an increased basal metabolic rate throughout pregnancy (57). These findings suggest that the increased energy demands of pregnancy can be met through many means, such as increased intake, decreased activity, and deceased fat storage. Furthermore, the total energy costs of pregnancy (fetus, fat deposition, and maintenance) in women from affluent and poor countries are strongly correlated with pre-pregnancy body fat and weight gain (57). Metabolic plasticity in women who are unable to increase food intake may be protective for the fetus. Therefore, recommendations for the adequacy of caloric intake are variable and largely dependent on the resources available and the nutritional status of the mother at the start of pregnancy.

Pre-gestational Diabetes

Type 1 diabetes mellitus is an immune-mediated process of pancreatic β-cell destruction. The gradual loss of β cells over time leads to an impaired ability to secrete insulin, and it begins long before the clinical onset of disease. The etiology of T1DM is thought to include inherited susceptibility and exposure to environmental triggers that have not yet been identified (58). Risk alleles have been linked to HLA-DQ, but susceptibility has been associated with over 40 genetic factors (59). The presence of antibodies to insulin, GAD65, IA2, and ZnT8 transporter are clinical markers of autoimmunity (60), and the level of risk and interval to clinical detection of disease are related to the number of autoantibodies to β-cell proteins present (61).

Insulin resistance and β-cell dysfunction are the two key pathophysiological factors leading to type 2 diabetes mellitus. Nutrient excess (e.g., hyperglycemia and hyperlipidemia) and obesity lead to high metabolic load, insulin resistance, and chronic inflammation.

The cellular response of β cells to these environmental changes and chronic stress is variable based on the genetic susceptibility of the individual. The distinct gene–environment interaction leads to variable temporal sequences of events and clinical manifestations (62).

Summary and Future Directions for Research

The physiologic adaptations that occur in pregnancy provide adequate energy and substrates for the growing fetus and prepare the mother for the increased burden of pregnancy and lactation. Insulin resistance is progressive throughout gestation, and a compensatory increase in insulin secretion maintains plasma glucose levels within a relatively narrow window. Placental factors contribute to insulin resistance directly (e.g., hPGH and TNFα) and indirectly through the increase in appetite and weight gain. A chronic positive energy balance results in adipose tissue accretion that may be used later for increased fetal demands in late pregnancy and lactation. However, excessive amounts of adiposity before pregnancy or excessive weight gain during pregnancy may have deleterious effects on insulin action and glucose tolerance. Definitions of a healthy amount of adiposity, ideal weight gain, or the necessary degree of insulin resistance required for normal fetal growth are unclear and should be the focus of future research.

Multiple-Choice Questions

1 Insulin has all of the following metabolic regulatory properties EXCEPT:
- A Glycogen synthesis
- B Suppression of lipolysis
- C Glycogenolysis
- D Protein synthesis

The correct answer is C. Insulin promotes glycogen synthesis in the liver and protein synthesis in muscle, and it suppresses lipolysis. The counterregulatory hormone, glucagon, promotes glycogenolysis in the fasting state.

2 Which of the following statements is true?
- A Insulin resistance decreases in late pregnancy compared to early pregnancy.
- B Glucose tolerance may be variable in the first trimester.
- C Inability to secrete adequate amounts of insulin results in insulin resistance in pregnancy.
- D The relationship between insulin secretion and insulin sensitivity is always linear.

The correct answer is B. Insulin secretion increases in the first trimester, but insulin sensitivity may vary in different women, making glucose tolerance variable in early pregnancy.

3 Which of the following do NOT contribute to insulin resistance in pregnancy?
- A Human placental growth factor
- B TNFα
- C Excess nutrients
- D GLP1

The correct answer is D. Placental hormones, adipokines, and excess nutrients may all contribute to the development of insulin resistance in pregnancy. GLP1 is secreted by the gastrointestinal tract after a meal and enhances insulin secretion from the pancreas.

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3

The Placenta in a Diabetic Pregnancy

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PRACTICE POINTS

- The distinct placental changes associated with diabetes mellitus depend on the gestational period during which the diabetic insult occurs, and, thus, on the type of diabetes.
- Early placental development may be altered by insulin and tumor necrosis factor-α (TNFα)-induced changes in matrix metalloproteinases that degrade extracellular matrix.
- The placenta is often heavier in women with diabetes, with an increase in maternal (i.e., syncytiotrophoblast) and fetal (i.e., endothelial) surface area.
- Trophoblast proliferation is regulated by maternal insulin; hypervascularization is the collective result of fetal hypoxia.
- Glucose from the maternal to fetal circulation is unaltered in gestational diabetes mellitus (GDM). The higher flux results from the steeper maternal-to-fetal concentration gradient. Amino acid transport may be altered.
- Fetal insulin and insulin-like growth factors directly influence fetal growth, but additionally promote maternal-to-fetal amino acid transport that will sustain fetal growth.
- Leptin shares parts of its signaling pathways with insulin. It is highly expressed by the placenta and secreted into the maternal and fetal circulation. It may contribute to developmental changes in diabetes.
- Fetal sex is likely to modulate the effect of GDM on placental and fetal development and function.
- The diabetic environment of GDM alters DNA methylation profiles and, thus, affects the offspring in the long term.

Normal Development

The placenta is a complex organ essential for fetal growth and development. It fulfills a wide spectrum of functions, among which the transport of maternal fuels to the fetus and the synthesis of various hormones and growth factors are foremost examples. Its development and function are tightly regulated by a range of hormones, cytokines, growth factors, and substrates present in the maternal and fetal circulations. Placenta-derived factors affect the maternal adaptation to pregnancy as well as fetal growth and development.

After blastocyst implantation into the decidual surface, the placenta continuously develops by the differentiation and proliferation of trophoblast cells eventually leading to placental villi of varying degrees of maturation (1), most of which float freely in the intervillous space (i.e., the area between the placental villi) (Figure 3.1). Highly proliferative villous cytotrophoblasts fuse to form the syncytiotrophoblast that represents the outermost interface of the placenta that contacts

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the maternal circulation. The microvillous membrane of this syncytium is in contact with the maternal blood and is richly endowed with receptors (2), enzymes (3), and transporters (4). Maternal blood emanating from remodeled and opened spiral arteries bathes the villi.

Some villi physically anchor the placenta to the uterus, thus establishing a connection between the fetus and the maternal decidua (Figure 3.1). These anchoring villi are formed by proliferation, differentiation, and invasion by cytotrophoblasts of the maternal lining of the decidual cavity. Extravillous cytotrophoblasts also invade the decidual spiral arteries and remodel them into low-resistance arteries. The resulting increase of maternal blood flow into the intervillous space ensures adequate maternal nutrient supply to the fetus (1). Trophoblast invasion is tightly regulated in time and space by invasion-promoting and invasion-inhibiting factors originating from the maternal decidua or the placenta. The decidua derives from the maternal endometrium after decidualization before implantation of the embryo. Decidualization produces a dense extracellular matrix and a cytokine milieu that reduces trophoblast invasion (5). Levels of these factors are altered in various pregnancy-associated pathologies and diabetes mellitus (Table 3.1).

During villous development, vasculogenesis and angiogenesis result in the formation of placental vessels, a process that again is controlled by various growth factors, cytokines, and oxygen (Table 3.2), and thus can be dysregulated in diabetes.

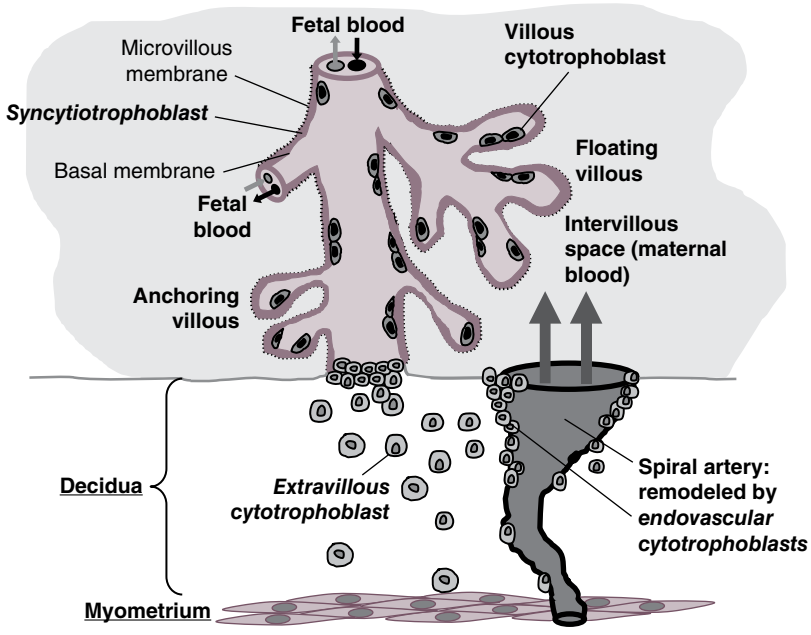

Figure 3.1 Organization of placental villi after week 20 of gestation. The syncytiotrophoblast represents the outermost surface of the placenta and is in contact with the maternal blood via its microvillous membrane that is richly endowed with receptors, enzymes, and transport molecules. The syncytium regenerates and expands by proliferation and fusion of cytotrophoblasts lying underneath. Some cytotrophoblasts at the tips of floating villi invade into the decidua, thereby anchoring the villi. A proportion of these extravillous cytotrophoblasts further invade the uterine spiral arteries, which leads to their remodeling into low-resistance vessels. For discrimination between maternal and placental cells and tissues, maternal structures are dotted and their labeling is underlined.

Table 3.1 Alterations in maternal levels of trophoblast invasion-inhibiting and invasion-promoting factors in GDM and T1DM.

Invasion inhibiting		Invasion promoting				
TNFα		**VEGF**	**Leptin**	**IGF1**	**IGF2**	**Insulin**
GDM	↑ (84)	↑ (38)	↑ (85)	↑ (86) NC (87)	↑ (87) NC (37,86)	↑ (45) insulin treated ↑ (88)
T1DM	↑ (36)		NC (89)	↓ (37) NC (87)	↑ (87) NC (37)	↑ (45)

Note: TNFα inhibits trophoblast invasion, whereas VEGF, leptin, and insulin-like growth factor-1 and -2 (IGF1 and IGF2) promote trophoblast invasion.
GDM = Gestational diabetes mellitus; IGF1 = insulin-like growth factor-1; NC = no change; T1DM = type 1 diabetes mellitus; TNFα = tumor necrosis factor alpha; VEGF = vascular endothelial growth factor.

Table 3.2 Alterations in fetal levels of pro- or anti-angiogenic factors in pregnancy with GDM and T1DM.

Anti-angiogenic		Pro-angiogenic							Other
TNFα		**VEGF**	**FGF2**	**PGF**	**Leptin**	**IGF1**	**IGF2**	**Hypoxia**	**Insulin**
GDM	↓ (84)	NC (90)	↑ (38)	↓ (90) NC (91)	↑ (92) NC (93,94)	↑ (90)	↑ (87) NC (90)	↑ (95)	↑ (96)
T1DM		↓ (97)	↑ (98)	↓ (90) NC (91)	↑ (92)	↑ (37,52) NC (90)	↑ (52,87)	↑ (99)	↑ (45)

Note: Both types of diabetes are characterized by enhanced vascularization.
FGF2: Fibroblast-specific growth factor-2; GDM = gestational diabetes mellitus; IGF1 and IGF2: insulin like growth factor-1 and -2; NC: no change; TNFα: tumor necrosis factor-alpha; PGF: placental growth factor; VEGF: vascular endothelial growth factor.

The Placenta in Diabetes

Because of the presence of receptors and enzymes on both placental surfaces (i.e., the microvillous syncytiotrophoblast membrane as well as the basal membrane of the syncytiotrophoblast and the placental endothelial cells), the diabetic environment may have profound effects on placental development and function. We recently proposed that these specific effects will critically depend on the time period in gestation when the insult of the diabetic environment acts upon the placenta (6).

As glucose can stimulate and repress gene expression (12), maternal and fetal hyperglycemia are likely to affect the production of various placental proteins, but a detailed analysis is pending. Moreover, maternal and fetal hyperinsulinemia also affect placental metabolism, growth, and development (3,13,14). However, the changes in the diabetic environment extend beyond glucose and insulin (Tables 3.1 and 3.2). Those in the mother can induce modifications in the placenta, including altered synthesis of cytokines and growth factors, which in turn may act locally in an autocrine or paracrine manner. Altered cytokines and growth factors along with metabolites can be secreted into both the maternal and the fetal circulation and thus affect both mother and fetus (Figure 3.2).

Despite the improvement in maternal glycemic control over the last few decades (15), structural and functional changes of the diabetic placenta at term may occur independent

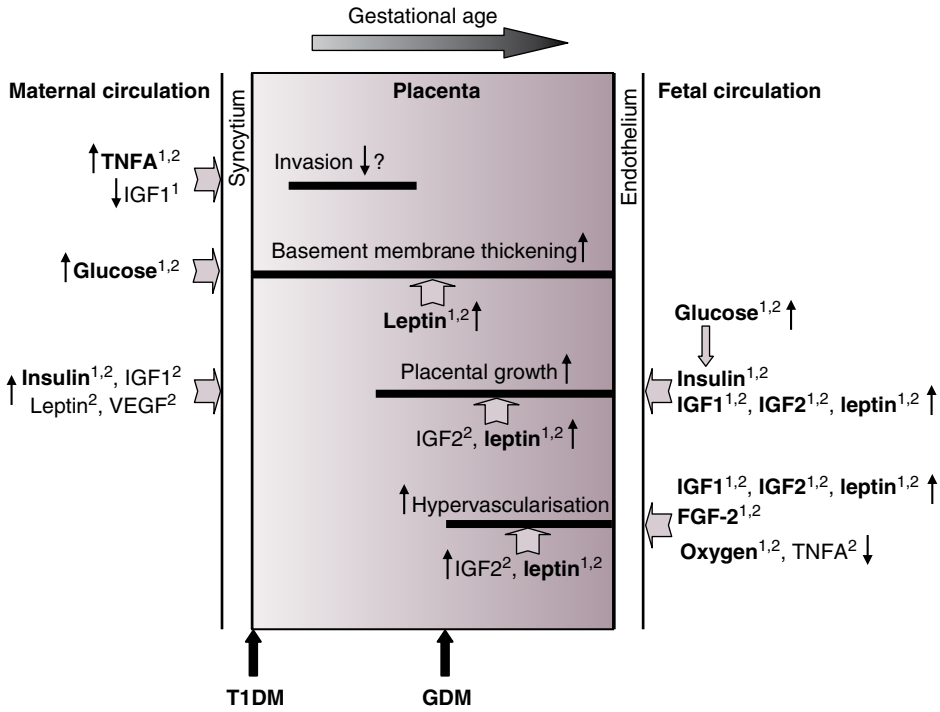

Figure 3.2 Hypothetical model for diabetes-induced alterations in human placenta. Elevated maternal TNFα and reduced IGF1 levels in T1DM may inhibit placental invasion, paralleling a higher incidence of early pregnancy loss in diabetes. Maternal hyperglycemia induces thickening of the placental basement membrane, hence reducing oxygen transport. Increased levels of placental leptin may even further contribute to the excessive extracellular matrix (ECM) synthesis. Various factors elevated in the placental (IGF2, leptin), maternal (insulin, VEGF), or fetal (insulin, IGF1, IGF2, leptin) circulations in diabetes promote proliferation and placental growth. Placental hypervascularization may be supported by elevated levels of placental IGF2 and leptin; by increased fetal IGF1, IGF2, leptin, and FGF2; and by reduced fetal TNFα as well as by fetal hypoxia. These derangements in the feto-placental compartment are characteristic of GDM, overt diabetes, or both.
Note: Factors in bold denote similar dysregulation in T1DM and GDM.
[1] Changed in T1DM.
[2] Changed in GDM.

of the type of diabetes (16). Similar to fetal weight, placental weight tends to be heavier in diabetic pregnancies, but the weight gain is more pronounced in the placenta than in the fetus, which is reflected in a higher placental-to-fetal weight ratio than in normal gestation (17,18). It has remained an unresolved question whether placental overweight is the cause or consequence of fetal overgrowth in diabetes.

Intuitively, possible changes in placental transport in diabetes may be implicated. Maternal-to-fetal transport of glucose has been intensively studied in gestational diabetes mellitus (GDM) pregnancies. GLUT1 is the major glucose transporter (GLUT) in the human placenta, where it is found on all cell types at all stages in pregnancy (7). In addition, the high-affinity glucose transporter GLUT3 is predominantly found on the feto-placental endothelium. The insulin-regulatable GLUT4 is located on the syncytiotrophoblast in early human pregnancy (8), whereas at the end of pregnancy it is predominantly located in the stroma of placental villi (9). The interplay between these placental glucose transporters, and their relative contribution to

placental glucose metabolism and transplacental glucose flux, is unknown. These transporters can be regulated by a wide range of hormonal and metabolic stimuli, including ambient glucose levels (10,19,20). As a result, the glucose transporter levels are modified in the human placenta in GDM and overt forms of maternal diabetes mellitus (11,21). Despite these molecular changes, perfusion experiments have demonstrated an unchanged if not reduced transplacental glucose transport in GDM (22) even on a total placenta weight basis. Studies that also integrate potential structural changes argue strongly for the steeper maternal-to-fetal glucose concentration gradient as the major if not only reason for increased glucose fluxes across the placenta in diabetes. This conclusion is also supported by unchanged concentration differences for glucose in umbilical arteries and veins in GDM (23).

Syncytiotrophoblast amino acid transport systems may be altered in diabetes (4,24). However, even for transport systems that are unaltered, when expressed per unit protein or tissue weight, an increase in total placental weight will result in increased nutrient transport. It is unclear if this will stimulate fetal growth or just serve to cover the increased fetal nutrient requirements when its overgrowth is driven by other factors.

In all types of diabetes, gross placental structure may be altered. In particular, the surface and exchange areas are enlarged (25) as a result of hyperproliferation and hypervascularization. The underlying mechanisms for the villous surface increase are not clear. Maternal hyperinsulinemia early in gestation is a candidate (13), but other maternal growth factors may also contribute.

The greater placental capillary surfaces may result from feto-placental counterregulatory mechanisms to fetal hypoxia, which can be inferred from the elevated fetal erythropoietin levels, polycythemia, and increased nucleated red cells often observed in fetuses of diabetic women (26). Materno-placental oxygen supply may be reduced in diabetes because of:

- decreased maternal arterial oxygen saturation and increased proportion of glycosylated hemoglobin, which has a higher affinity for oxygen than non-glycosylated hemoglobin (27);
- thickening of the trophoblast basement membrane (28), although this was not uniformly found (29); and
- under certain instances, reduced uteroplacental blood flow (30) as a result of increased flow impedance in the uterine and umbilical arteries (31,32).

In addition to impaired oxygen supply, fetal oxygen demand is increased because aerobic metabolism is stimulated by fetal hyperinsulinemia. The resulting low fetal oxygen levels ultimately upregulate the transcriptional synthesis of pro-angiogenic factors in the feto-placental compartment. Established examples include fibroblast growth factor-2 (FGF2), vascular endothelial growth factor (VEGF), and leptin (33–35). Higher levels of these factors promote placental endothelial cell proliferation, a key process in angiogenesis. The increase in placental vascular exchange area against a background of fetal hypoxia appears paradoxical in a situation of maternal nutritional oversupply and may underline the overriding importance of adequate oxygen delivery to the fetus.

Little is known about the placental changes in the first trimester, when the developing placenta is exposed to the maternal diabetic environment, such as hyperglycemia, hyperinsulinemia resulting from the relatively excessive insulin doses needed to maintain strict metabolic control, increased expression of tumor necrosis factor-α (TNFα) (36), reduced insulin-like growth factor-1 (IGF1) (37), and elevated FGF2 (38). It seems reasonable to assume that the diabetic milieu will have an influence on placental development and function during this critical period when placental structures are formed and the placenta is likely to be most sensitive to environmental derangements. Placental growth and development sometimes appear to be

retarded in the first gestational weeks, probably because of a reduction of trophoblast proliferation resulting from hyperglycemia (39,40). A higher incidence of spontaneous abortions (41) and pregnancy pathologies such as preeclampsia and intrauterine growth restriction (IUGR) suggests impaired trophoblast invasion, which would result in inadequate placental anchoring and opening of the maternal spiral arteries (42). This is further supported by the reduced uteroplacental blood flow as observed occasionally (30), although not uniformly (43,44).

Matrix metalloproteinases MMP14 and MMP15 are involved in tissue-remodeling processes associated with invasion, angiogenesis, and proliferation. Both metalloproteinases are elevated in type 1 diabetes (3) induced by elevated maternal insulin and TNFα (36,45). MMP14 and MMP15 possess a remarkably wide spectrum of substrates, including components of the extracellular matrix (46). In addition, mature and immature cytokines may become activated or inactivated, thus further contributing to the alterations in diabetes. In particular, the active form of placental MMP14, which is generated by cleavage by the protease furin, is elevated in diabetes. Furin contains a hypoxia-inducible factor-1-α (HIF1α) promoter binding site. This makes it tempting to hypothesize that hypoxic conditions in the villous placental structure in diabetes may be implicated as a cause of increased MMP14 activity. These results demonstrate the sensitivity of early placental development to changes in growth factor and cytokine levels. However, reduced trophoblast invasion in maternal diabetes still remains speculative.

The Role of the Insulin/LGF System and Leptin on the Placenta in Diabetes

Maternal and fetal hyperleptinemia, as well as increased placental leptin expression, are well established in diabetes and obesity. However, recent reports did not support higher fetal leptin levels in GDM (Tables 3.1 and 3.2). Both insulin and leptin fulfill versatile roles beyond the regulation of metabolism, including stimulating growth factor activity and potency, which in turn stimulates expression of various target genes (14,47). Resistance to insulin and leptin occurs often coincidentally in human obesity, because of the considerable overlap between their signaling pathways (48). The extensive cross-talk between their signaling cascades may represent a major contributing factor to the diabetes-induced placental changes, especially in the first trimester of obese pregnancy.

Insulin, IGF1, and IGF2

The insulin/insulin-like growth factor system is thought to have a central role in the control of fetal and placental growth and development (49). The insulin receptor and the highly related IGF1 receptor (IGF1R) both essentially signal through two main intracellular pathways (50): the ERK1/2 pathway stimulating proliferation, and the PI3K–AKT pathway mainly modulating metabolic function.

The feto-placental expression of insulin, IGF1, IGF2, and their receptors is developmentally regulated in a tissue-specific manner and can be affected by nutritional and endocrine conditions (49). Placental expression of insulin receptors undergoes a developmental shift from the trophoblasts in the first trimester to the placental endothelial cells in the third trimester (14,51). The placental IGF1R is mainly expressed on the basal membrane of the syncytiotrophoblast. Hence, it is predominantly accessible for fetal IGF1 and IGF2 (2). The specific roles of these growth factors for the human placenta have not been investigated in great detail. Targeted disruption of the fetal IGF1, IGF2, or IGF1R gene in mice resulted in retardation of fetal growth, whereas IGF2 overexpression enhanced fetal growth. IGF1 stimulates fetal growth dependent on the nutrient supply, whereas placental IGF2 is a key regulator of placental growth and nutrient

transfer, thereby allowing enhancement of fetal growth (49).

IGF1 and IGF2 effects can be attenuated or amplified by soluble insulin-like growth factor-binding proteins (IGFBPs) that influence their bioavailability. In humans, the most prevalent IGFBPs in fetal plasma and tissue are IGFBP1–IGFBP4. Fetal cord blood data suggest that these binding proteins may be dysregulated in diabetic pregnancies (52). A decrease in IGFBPs would result in higher bioavailability of IGFs and, thus, indirectly might contribute to fetal overgrowth in diabetes.

The endocrine interaction between mother, fetus, and placenta is exemplified by the effect of maternal and fetal insulin on the placenta. Maternal insulin affects placental development (3) via receptors expressed on the microvillous membrane of the syncytiotrophoblast. In turn, the placenta affects the mother by secretion of hormones, cytokines, and metabolic waste products. For instance, maternal insulin upregulates leptin production in trophoblast cells (53), and after secretion into the maternal circulation increased leptin levels may enhance maternal insulin resistance. Both leptin and insulin suppress secretion of placental growth hormone (PGH) in trophoblast cells (54). PGH can cause maternal insulin resistance (55). Thus, as a speculation, a reduction of PGH secretion by insulin and leptin may represent a maternal-placental forward feedback mechanism ultimately alleviating maternal insulin resistance.

Fetal insulin affects gene expression in endothelial cells from placental arteries and veins (14), which will directly or indirectly affect placental and fetal development. The change of insulin receptor expression from the trophoblast in the first trimester to the endothelium at term thus enables maternal insulin to regulate placental function at the beginning of gestation, whereas as gestation advances, the fetus takes over control of placental insulin effects (Figure 3.3) (14).

IGF1 and IGF2 stimulate trophoblast invasion (56) by upregulation of the metalloproteinases MMP2 and MMP9 that degrade gelatin and collagen, components of the extracellular matrix. Lower maternal IGF1 levels in type 1 diabetes mellitus may thus contribute to impaired trophoblast invasion. Insulin and IGFs stimulate nutrient transport through the syncytiotrophoblast, in particular the transport of a broad range of neutral amino acids by upregulation of amino acid transporter system A (57–59). Hence, in GDM, transplacental amino acid transport and thereby fetal growth may be promoted by the diabetes-associated increase in maternal concentrations of growth factors (Table 3.1).

Changes can also be seen in the fetal circulation (Table 3.2). However, the consequences of these changes for the fetus, apart from the well-known insulin-stimulated fat accretion, remain unclear.

Leptin

Leptin is a central hormone in metabolic control indirectly promoting insulin resistance (60). In humans, leptin levels correlate highly with adiposity. However, the hormone has various functions beyond metabolic control, such as stimulation of angiogenesis, regulation of hematopoiesis, and the inflammatory response (61). The main source of leptin is adipose tissue, but it is also expressed in various organs of the feto-placental unit. During gestation, maternal leptin concentrations rise by 30%, and the placenta becomes an additional source of leptin.

The predominant expression site of the leptin receptor in the placenta is the syncytiotrophoblast. Leptin induces human chorionic gonadotropin (hCG) production, enhances mitogenesis, stimulates amino acid uptake, and increases the synthesis of extracellular matrix proteins and metalloproteinases (61), the latter implying a role for the hormone in the regulation of placental growth. Moreover, one might further hypothesize a contribution of hyperleptinemia to other placental changes in diabetes (e.g., basement membrane thickening), owing to its ability to alter collagen synthesis (62). In addition, the pro-angiogenic effect of leptin

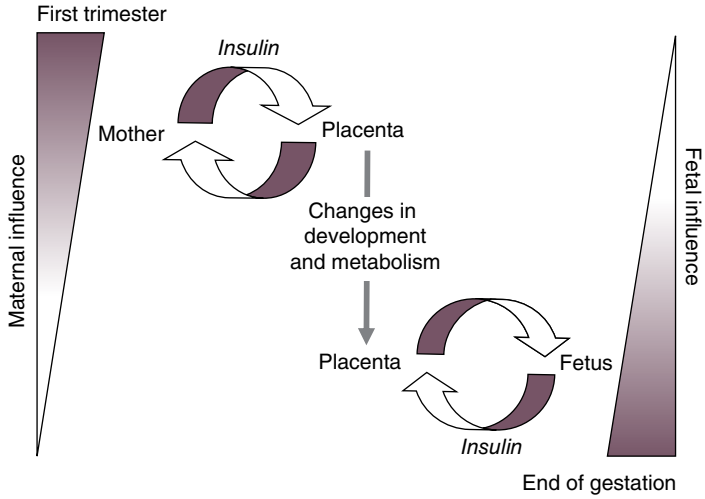

Figure 3.3 Spatiotemporal change of insulin receptor expression in the placenta allows a shift in control of insulin regulation from mother to fetus. Insulin receptor expression shifts from the trophoblast in first trimester to the endothelial cells in third trimester. In the first trimester, maternal insulin influences the placenta by interaction with trophoblast insulin receptors. These may in turn affect the mother by secretion of cytokines, hormones, or metabolic waste products. Later in gestation, the fetus takes over control of insulin-dependent placental processes by fetal insulin interacting with placental endothelial cells. The effects on placental development and metabolism induced at the beginning of pregnancy by maternal insulin along with the effects of fetal insulin on the placenta later in gestation may have repercussions on fetal development and metabolism. Copyright © 2001 American Diabetes Association from (6). Reprinted with permission from The American Diabetes Association.

suggests a contributing role to the diabetes-associated placental hypervascularization (Figure 3.2).

Influence of Fetal Sex on Placental Function in GDM

It has long been recognized that pregnancy outcome is different for both fetal sexes (63). Even the incidence of GDM as a maternal disease is affected by fetal sex: the mother's risk for developing GDM is higher with a male fetus (63,64). The placenta is one of the main drivers for the adaptation of maternal metabolism to pregnancy and thus may be causally involved in sex-dependent aspects of pregnancy disorders. In fact, the placenta of male and female fetuses is molecularly and functionally different. It expresses different levels of a wide range of transcripts (65,66), and these differences not only are found in total placental tissue, but are distinct for different cell types in the placenta (66). The functional consequences are unclear so far, but may relate to different growth strategies of male and female fetuses (67).

In addition to these sex-dependent molecular differences in male and female placentas, the response to environmental factors is also different: dietary interventions in pregnancy result in sex-specific changes in the placental transcriptome, which are more pronounced in female fetuses. Furthermore, female fetuses also seem to respond stronger to intrauterine changes associated with GDM such as hyperinsulinemia, because they are insulin resistant at birth (68,69). These data may reflect female fetuses being more flexible to environmental challenges than males (70). So far, no sex dimorphism in placental

adaptations to GDM has been described. However, given the plasticity of the female placenta and fetus, one can expect that such changes will be found (71,72).

Placental Methylation

The long-term consequences of the intrauterine environment for offspring's health have led to the concept of early-life exposures to "program" fetal tissues such that they remember the intrauterine events in later periods of life. Epigenetic changes, predominantly methylation of DNA regions rich in cytosine–guanosine dinucleotides (CpGs), have been established as molecular representation of this memory effect. Since the placenta is an easily accessible fetal tissue, its methylation changes associated with GDM have recently become the focus of several studies.

Several GDM-associated methylation changes have been found in the placenta (73–77), which are distinct from changes that derive from other pregnancy pathologies such as preeclampsia (75). Interestingly, placental methylation of the genes encoding adiponectin and leptin, both involved in the regulation of insulin sensitivity and resistance, respectively, is altered in GDM in a manner related to maternal metabolic status before and during pregnancy (78). Reduced methylation of the maternally imprinted MEST gene, a member of the alpha/beta hydrolase superfamily, was found not only in GDM-exposed placentas at birth, but also in blood cells of adults with morbid obesity (73). Also, circulating cells in cord blood of GDM-exposed offspring show methylation changes in their DNA (73,74,77). Among these changes, the methylation of a distinct CpG locus in the retinoic acid receptor promoter was associated with childhood fat mass at the age of 9 years in two independent cohorts (79,80). All together, these results indicate that the long-term consequences for the offspring of intrauterine exposure to the GDM environment are in part mediated through methylation changes (i.e., alterations in the offspring's epigenome).

DNA methylation is highly cell specific. The studies described here have been carried out in total placenta tissue. Thus, it cannot be ruled out that the methylation changes are a mere reflection of the changes in cell composition often associated with GDM. Therefore, such studies may lead to the identification of biomarkers for offspring disease risk in later life rather than provide mechanistic insights into how the intrauterine GDM environment influences disease risk.

Summary

Placental structure and function can be changed as a result of maternal diabetes. The specific nature and extent of these changes depend on the gestational period of the diabetic insult and, by inference, on the type of diabetes. Some alterations (81,82) continue to occur despite improvements in maternal glycemic control over recent decades, thus indicating that hyperglycemia is not the only causal factor. However, various changes in villous morphology may improve if diabetes is well controlled (16,83). Maternal and fetal concentrations of several growth factors, cytokines, and hormones are also altered in diabetes and may affect fetal and placental growth and development. Fetal sex was recently identified to modulate the impact of the maternal metabolic status, and hence likely also of GDM, on placental function. The altered intrauterine environment of GDM will not only affect placental and fetal development, but also cause persistent changes by altering DNA methylation profiles. Current research in this area is trying to identify the specific biological effects and the detailed mechanisms underlying them.

Questions

1 How can insulin alter early placental development?

At least through altering matrix metalloproteinase expression, such as MMP14, which can play multiple roles in regulating placental growth and development, including invasion and angiogenesis.

2 What is the main driver for enhanced transplacental glucose flux in diabetes?

The concentration gradient between mother and fetus is the main driver late in gestation. Utero-placental and feto-placental blood flow may also contribute to regulating glucose flux. The regulators of glucose flux early in diabetes are unknown.

3 Is placental leptin secreted? If so, into which circulation(s)?

Yes; it is secreted into the maternal and fetal circulation.

4 Does placental function depend on fetal sex?

Yes, although there is not yet much evidence; but, collectively, gene expression is different between male and female placentas in a cell-type-specific manner. This would very likely also entail sex-specific differences in placental function.

5 Does GDM modify methylation profiles of placental genes?

Yes, there is good evidence that the methylation profile of placental genes is altered by GDM. However, it is unclear because of lack of data whether this is a real change or just a reflection of an altered cellular composition of the placenta in GDM versus controls, since methylation is very cell-type specific.

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Section II

Gestational Diabetes

4

Screening for Gestational Diabetes

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PRACTICE POINTS

- In many populations, women who have gestational diabetes (GDM) will not have historical risk factors. Thus, determining which patients should or should not be tested for GDM based on the presence of risk factors alone may not identify a large number of women who have the disease.
- Results of the 50 g glucose screening test (GST) vary with time of day and time since the last meal, and are poorly reproducible.
- GST results ≥200 mg/dl (11.1 mmol/l) are not diagnostic of gestational diabetes and should be followed by a fasting plasma glucose test.
- The fasting plasma glucose has poor sensitivity and specificity when used as a screening test for GDM.
- Using hemoglobin A1c in lieu of conventional second- or third-trimester screening tests for GDM is not advised because of the wide range of sensitivities and specificities reported for glycated hemoglobin.

Case History

A 26-year-old woman, G5P2Sab2, whose two spontaneous abortions occurred in first trimester, was discovered to have GDM during her second pregnancy and was begun on oral hypoglycemics during the eighth month of that pregnancy. Her youngest child is 5 years old. She has gained 6 kg since her delivery, and has not had any glucose testing since that delivery. She presents now at 13 weeks of gestation in her fifth pregnancy and is found to be hypertensive, with glycosuria and a BMI of 37 kg/m^2.

- Should she be tested for GDM now or not until 24–28 weeks?
- If tested now, is it best done with a 50 g GST, a fasting plasma glucose, a complete 75 g or 100 g glucose tolerance test (GTT), hemoglobin A1c, or a combination of these tests? Alternately, should treatment for diabetes be given empirically?
- If she has a 50 g GST result lower than the threshold used to indicate a GTT, should she have some confirmatory blood test of her glycemic status?

Introduction

The term *gestational diabetes* was first coined in a 1957 study of 621 pregnant women who were tested for glucose intolerance with the 100 g, 3 h glucose tolerance test (GTT) (1). Although this label was reserved for women who had the highest level of glucose intolerance, the term was subsequently generalized to identify pregnant women who had any

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degree of glucose intolerance with onset or first recognition during pregnancy (2). In the USA, the concept of screening for gestational diabetes mellitus (GDM) was popularized following the publications of O'Sullivan *et al.* (3,4). In this chapter, the definition, methods, risks, benefits, and costs of screening for GDM will be discussed. It is hoped that from this discussion, the reader may decide whether screening should be incorporated in the diagnosis of GDM, and, if so, which approach is more suitable for his or her practice.

Definition

The terms *diagnosis* and *screening* are frequently used interchangeably in medical parlance. Within the context of gestational diabetes, a screening test should be used to identify those at higher risk of disease (i.e., those within an unselected population who are more likely, when tested with the diagnostic test, to have GDM). The major benefit of preceding the definitive test with some screening procedure is that fewer patients have to be given that definitive (and, for most women, unpleasant) and more expensive test. Thus, two important characteristics of a screening test are that its threshold be set low enough to include the overwhelming majority of women who have the disease (sensitivity) but that the test threshold value be set high enough to exclude the majority of women who do not have the disease from receiving the diagnostic test (specificity). The dilemma of determining the appropriate balance between sensitivity and specificity for a screening test is illustrated in Figure 4.1.

Should we Screen for Gestational Diabetes?

Whether or not GDM merits any kind of screening test has been a subject of debate for several years (5). To be a candidate for screening, a disease should have certain characteristics:

- The disease should be prevalent.
- The disease should be causally associated with selected adverse outcomes.
- The disease should have an asymptomatic phase during which detection is possible.
- Treatment should be available to ameliorate the effects of the disease.

With a worldwide prevalence of from 1.7 to 25% (6,7), data indicating a positive relationship between levels of maternal glycemia on a GTT and adverse pregnancy outcomes (8), the lack of symptoms accompanying GDM, and evidence from two randomized controlled trials that treatment will ameliorate some of the associated morbidities (9,10),

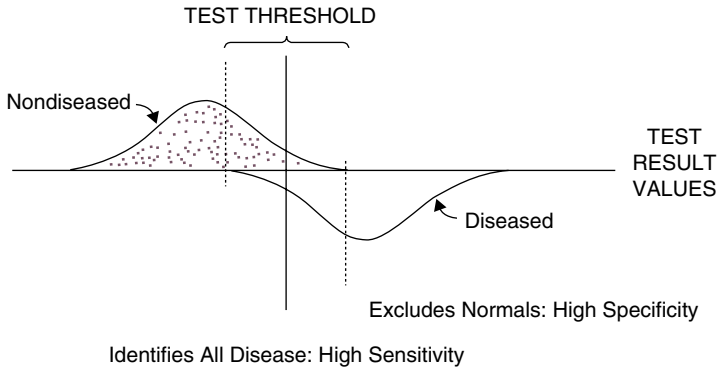

Figure 4.1 Relationship of sensitivity, specificity, and screening test threshold value. (*Source*: Carpenter & Coustan 1982 (11). Reproduced with permission of Elsevier.)

currently available information suggests that gestational diabetes is eminently suited for screening.

Screening Methods

Before discussing the different tests and strategies available for screening for GDM, it is important to address the parameters used in evaluating the utility of a screening test. As mentioned in this chapter, the ideal screening test is one that is highly sensitive and also has a satisfactory degree of specificity. It must be noted that in order to calculate these two measures, the entire population under study must be tested with both the definitive (diagnostic) test as well as the screening tool. As we shall see, most studies identify women as being at a sufficiently increased risk of meriting definitive testing for GDM by virtue of having a positive screening test, and then administer the definitive test only to those meeting the selected threshold value on the screening test. While this allows calculation of the predictive value of a positive test (positive predictive value [PPV]), it does not allow calculation of the sensitivity of the test. To calculate the latter statistic, one must also know the number of women whose screening test results fell below the screening test threshold but who did have the disease (false negatives). To calculate the specificity of the screening test, one must also know the number of women who tested negative on the screening test and who did not have the disease (true negatives) as well as those who tested positive on the screening test but did not have the disease (false positives). Again, for both determinations, the entire population must be tested with both the screening and the diagnostic test, as is illustrated in Figure 4.1 (11).

Screening with Risk Factors

Women who have one or more historical risk factors are, as a rule, at greater risk of developing GDM than women who do not have these factors. Among these factors are maternal age above a selected threshold (e.g., 30 years), belonging to certain ethnic groups (e.g., from Latin America, Africa, Pacific Islands, Southeast Asia, and the Asian subcontinent), increased parity, overweight and obesity, a personal history of GDM in a previous pregnancy, a prior macrosomic baby, and a first-degree relative with a history of diabetes (12). Determining the proportion of GDM that will be detected by screening only those with risk factors is a function of a number of factors. Certain risk factors (e.g., antecedent GDM) have a greater PPV for GDM than do others. The greater the number of risk factors that the individual has, the greater the PPV for GDM (13). Some factors may be identified only in women who have had prior pregnancies (e.g., prior GDM, prior macrosomia), creating a bias for parous women to be at increased risk for GDM (13,14). Finally, regardless of how risk is defined or how many risk factors are present, in every population there will be those women who have no risk factors but who, if universally tested, will be found to have GDM (13,15).

The 50 g Glucose Screening Test

Overview

Variously referred to as the glucose challenge test (GCT) or the glucose screening test (GST), administering a 50 g glucose load to pregnant women and drawing their blood glucose 1 h later to determine whether they are at high enough risk to merit definitive testing with a GTT has been used in several venues, and is currently endorsed as either the method of choice (16) or one of two valid methods of testing for GDM (17) by authoritative bodies in the USA. Because until the publication of the International Association of Diabetes in Pregnancy Groups' (IADPSG) recommendation for universal, one-step testing for GDM (18) it had been so widely used, and because of the persistent controversy about the two-step method versus the one-step method of screening and testing for

GDM, details regarding its application will now be discussed in detail.

Sensitivity and Specificity

In O'Sullivan's original study, the 50 g, 1 h GST was administered to 752 unselected pregnant women on the afternoon of their registration for prenatal care (3). Three percent of these women were in first, 45% in second, and 52% in third trimester. A whole blood glucose threshold value of 130 mg/dl (7.2 mmol/l) was selected for the GST. It must be noted that O'Sullivan's assay method (Somogyi–Nelson) assayed for all reducing substances (e.g., glutathione, glucuronic acid) in addition to glucose. In addition, whole blood, which has a lower glucose concentration than plasma, was the medium assayed. Using contemporary laboratory enzyme methods on serum or plasma, the rough equivalent of O'Sullivan's 130 mg/dl (7.2 mmol/l) glucose value is 140 mg/dl (7.8 mmol/l). The resulting sensitivity and specificity for GDM were 79% and 87%, respectively. Fourteen percent of those women who had a positive GST also had GDM. GDM was diagnosed with a 100 g, 3 h GTT. In clinical terms, had only those women whose GST result was ≥130 mg/dl (7.2 mmol/l) been administered a GTT, 79% of women with GDM would have been identified and 21% would have been missed, but 87% of those women who did not have GDM would have avoided having a GTT (4).

It must be noted that there were only 19 women found to have GDM in O'Sullivan's study. Since that initial publication, a number of other studies have addressed issues concerning sensitivity and specificity of this screening test. A review of 26 studies examining the 50 g, 1 h GST reported that, not surprisingly, the lower the threshold value on this test, the greater the sensitivity and the lower the specificity. Women who were selected for glucose tolerance testing based on the presence of risk factors at a test threshold of 140 mg/dl (7.8 mmol/l) had a sensitivity for GDM that was not significantly different from that of women universally screened at the same test threshold. However, at that threshold, the women with risk factors had a lower specificity than those universally screened (77% vs. 85%, respectively); that is, the addition of risk factors as a criterion for definitive testing for GDM did not increase the detection of women who had GDM, but it did increase the proportion of women who did not have GDM who were tested with a GTT (19).

Timing of Screening Relative to Gestational Age

Both early- and late-pregnancy insulin sensitivity progressively decrease, but at a given gestational age, sensitivity to insulin is greater in women who do not have GDM than in those who do. With advancing pregnancy, beta cell function (insulin secretion in response to a glucose load) is progressively and proportionately less in women with GDM (20). Thus, it would seem reasonable to assume that, while some women with GDM would have elevated GST results early in pregnancy, women who have elevated GSTs as well as women with GDM are more likely to be discovered later in pregnancy. This assumption was confirmed in a study in which all women exceeding a 150 mg/dl threshold in first trimester were tested with a GTT in second trimester. Those not found to have GDM were given another GTT in third trimester. A greater proportion of women were found to have GDM on the test performed later in pregnancy (21). In another study, women were given both a GST and a GTT at 6–14 weeks. Except for those found to have GDM on the first set of tests, the same women were again tested at 20–30 weeks. Absolute glucose concentrations were significantly greater for both the GST and the GTT on the examinations conducted later in pregnancy. Of the 85 women who were found to have GDM, 68% were discovered on the test performed later in pregnancy (22). While fetal benefits of early screening have yet to be established, screening women early in pregnancy may be of value in populations that have a high prevalence of type 2 diabetes to

better identify those women who have not been recently tested and whose glucose intolerance likely antedated their pregnancies.

Timing of Screening Relative to a Meal

In O'Sullivan's pioneering work, all 752 women received the 1 h, 50 g GST on the afternoon of registration for prenatal care. No mention was made of the temporal relationship between the time since the last meal and the GST result, nor were data generated regarding testing at other times of day. Cross-sectional data of another population found that the longer the time after the last meal that the 50 g GST was administered, the higher was the maternal glycemic result (23). Two more studies compared administering the 50 g glucose load on different days to the same patients after overnight fasting on one day and 1 h after a standard breakfast on a second day (24,25). While no difference was noted for the test results in women who did not have GDM, those who did had significantly higher glucose concentrations when tested after an overnight fast (24). This apparent increased glucose disposal after successive glucose loads (Staub–Traugott effect) does not appear to be mediated by increased insulin secretion (25).

Time of day of Test Administration

Whether the time of day of administration of the GST affects glucose results and/or diagnosis of GDM has been explored. In women who had GDM and who served as their own controls, glucose concentrations after the morning meal were significantly greater at 1 h, were not different at 2 h, and were significantly lower from 3 through 9 h postprandial than those at corresponding times after the evening meal. The early-morning hyperglycemia in women with GDM was associated with the morning increase in cortisol (26). Elevated morning glucose has also been associated with chronic hypertension, perhaps attributable to sympathetic overactivity (27). In another study, GTTs were administered in the morning and afternoon to 12 women who had GDM. Although no difference was found in fasting glucose results, the respective 1, 2, and 3 h results after a 100 g glucose load were significantly greater following the afternoon glucose load than following that in the morning (28). Cumulatively, these studies do suggest diurnal variation in GST and GTT results, but the direction of difference appears inconsistent.

What is the Ideal Threshold Value of the GST?

The ideal screening test for any disease provides a high level of sensitivity and specificity. Sensitivity and specificity, in turn, are dependent on the threshold values selected for the screening test. In O'Sullivan's study, 15 of the 19 women found to have GDM equaled or exceeded the 130 mg/dl (7.2 mmol/l) threshold, producing a sensitivity of 79% with a corresponding specificity of 87%. Given the small number of women with GDM, a small change in the GST value may have resulted in a large shift in sensitivity and specificity. A subsequent study of 704 women of whom 90 had GDM employed receiver–operator characteristic curves and the Youden index ([sensitivity + specificity] – 1) (29) to determine the point at which the best balance of sensitivity and specificity could be achieved (30). The GST threshold identified 141 mg/dl (7.8 mmol/L) as that threshold producing a sensitivity of 90% and a specificity of 74%. From these data, it seems that a reasonable balance of sensitivity and specificity may be achieved at a GST threshold near 140 mg/dl. It must be borne in mind, however, that this threshold will leave undetected a proportion of pregnant women who do meet criteria for GDM.

Is the Glucose Screening Test Ever Diagnostic?

Most but not all women with GST ≥200 mg/dl (11.1 mmol/l) have GDM (Table 4.1). It remains unclear what proportion of women whose GST is ≥200 mg/dl (11.1 mmol/l) and have normal GTTs have pregnancies exhibiting adverse outcomes ascribed to GDM (31–35).

Table 4.1 GDM following a 50 g GST result ≥200 mg/dl (11.1 mmol/l).

Author	GTT	*n* with GST ≥200 mg/dl (11.1 mmol/L)	*n* (%) with GST ≥200 (11.1 mmol/L) and GDM	mg/dl Highest GST result with no GDM
Sacks (31)	2nd IWC (60)	15	8 (53%)	225 mg/dl (12.5 mmol/L)
Bobrowski (32)	NDDG (61)	27	18 (67%)	216 mg/dl (12.0 mmol/L)
Landy (33)	NDDG (61)	51	46 (90%)	NS
Shivvers (34)	NDDG (61)	59	48 (81%)	256 mg/dl (14.2 mmol/L)
Wong (35)	ADIPS (62)	528*	465 (88%)	216 mg/dl (12.0 mmol/L)

* GST ≥198 mg/dl (11.0 mmol/l). Test performed before noon.
2nd IWC = Second International Workshop-Conference on Gestational Diabetes; ADIPS = Australasian Diabetes in Pregnancy Society; GDM = gestational diabetes mellitus; GST = glucose screening test; GTT = glucose tolerance test; NDDG = National Diabetes Data Group; NS = not stated.

A realistic concern is giving a GTT to a woman with a markedly elevated GST result who may have undiscovered overt diabetes. Perhaps the safest strategy is to follow a markedly elevated GST with a fasting plasma glucose. If the result of the latter test is below the threshold defining GDM, the risk of performing a complete GTT would appear to be minimal. It also seems reasonable to continue closely monitoring a woman who has the combination of a normal GTT after a GST result ≥200 mg/dl (11.1 mmol/l) as her pregnancy advances.

Reproducibility of the 50 g, 1 h Glucose Screening Test

Precision, or the ability to reach the same test result on repeat testing, is an important characteristic of a screening test. A GST result for the same individual that on one day exceeds the threshold for definitive testing while on another day falls below that threshold obviously may lead to failure to diagnose GDM for that individual. To test the reproducibility of a GST, one must control for confounding. Therefore, the second test should be performed within close temporal proximity of the first, at the same time of day, following the same time interval after a prior meal, and by the same analytical method on the same blood component. Two studies of similar design presented pregnant women not known to have GDM with 50 g, 1 h GSTs. In the first, all subjects were tested in the morning with varying sequences of fasting and feeding preceding the test. Half of the subjects were tested at 12–24 weeks, and half at 24–28 weeks. In the early group, 43% exceeded the 140 mg/dl (7.8 mmol/l) threshold on both days, whereas that number rose to 83% for those tested late in pregnancy (36). In the second study, women were tested within 1 h of the time of testing on the first day and requested to reproduce their activities and meals at similar times on the next (i.e., the second day of testing). Of the 30 women with GDM who participated, three had GST results below the 135 mg/dl (7.5 mmol/l) threshold on both days, and another 10 had an elevated GST on only one of the two days (i.e., as a result of the GST on any given day, 27% of women with GDM might not have received the diagnostic test) (37). Using the same diagnostic thresholds to define GDM, two other studies looked at the reproducibility of the 100 g GTT given a week apart during pregnancy, and reported respectively that 22% (38) and 24% (39) of women had a test result indicating GDM during only one of the two weeks. Combining the data within the last two citations, because of poor postchallenge reproducibility up to 45% (27% + [73% × 24%]) of women who have GDM may be missed by requiring

that a screening test glycemic threshold be met prior to definitive glucose tolerance testing in pregnancy.

The Fasting Plasma Glucose Screening Test

Fasting plasma glucose (FPG) concentrations reach a nadir at about the 12th week of gestation and then stay relatively constant throughout the rest of pregnancy (40). The FPG seems an attractive alternative for screening for GDM because it is easy to administer, well-tolerated, reproducible (41), and inexpensive (42). The ideal protocol for determining the sensitivity, specificity, and positive and negative predictive values of the FPG would be to administer the FPG and GTT within close temporal proximity. Unfortunately, most studies of the FPG screening test exhibited selection bias by testing only patients with risk factors (including elevated 50 g GSTs). All use the FPG of the GTT as the screening test value. While this approach may enhance sensitivity, it assumes 100% reproducibility for the FPG, which is not likely to be the case. Publications evaluating the FPG screening test also differ with regard to glucose loads, numerical criteria, and number of glycemic thresholds to be equaled or exceeded to define the presence of GDM, all of which potentially affect the interpretation of the test results (43). In two studies, one using the Carpenter–Coustan and the other the WHO criteria to define GDM, similar sensitivities (respectively, 81% (44) and 88% (45)) and specificities (76% (44) and 72% (45)) were found at an FPG threshold of 86 mg/dl (4.8 mmol/l). In contrast, two studies both of which defined GDM by the IADPSG criteria (18) reported respective sensitivities of 92.5% (46) and 74% (47) at an FPG of 85 mg/dl (4.7 mmol/l). Studies of the first-trimester FPG as a screening test for GDM when the latter was diagnosed in early third trimester by IADPSG criteria (18) have been reported. At a FPG threshold of 92 mg/dl (5.1 mmol/l) sensitivities were 27% (48) and 26% (49), while respective specificities were 95% (48) and 90% (49). Perhaps due to the physiologic decline in FPG at the end of first trimester and despite the fact that a first-trimester FPG of 92 mg/dl (5.1 mmol/l) defines a woman as having GDM, the false positive rate for the first-trimester FPG by a third-trimester GTT was over 50% in both studies. Particularly when screening is performed in first trimester, until data are available comparing fasting glucose performed independently of the GTT, it seems prudent to not rely on the FPG to determine the necessity for a GTT.

Hemoglobin A1c as a Screening Test

Glucose binds to the N-terminal valine in the beta chain of hemoglobin by a non-enzymatic irreversible reaction. The concentration of the resulting glycated hemoglobin (of which hemoglobin A1c [HbA1c] is the subtype most frequently assayed) within the red cell varies directly with the duration of exposure to glucose and with the lifespan of the red blood cell (120 days). Thus, HbA1c best reflects average glucose concentration over the previous 4 months (50). In analyses of its use as a screening test for GDM it is clear that, regardless of when during pregnancy the test is done, the higher the HbA1c, the more likely the diagnosis of GDM (51–55). However, because of the marked overlap between values for women with GDM and those without, the value of HbA1c as a screening test for GDM is quite limited (53). Among four studies in which all subjects received diagnostic testing for GDM using a threshold HbA1c of 5.45–5.7%, sensitivities varied from 26% to 86% and specificities from 21% to 92% (52–55). A large ($n = 8497$) study of HbA1c as a screening test early in pregnancy addressed the issues of screening test thresholds and when to perform the GTT. All women were screened with an HbA1c at their first prenatal visit (median: 47 days) and were requested to have a follow-up GTT. GDM was defined by the IADPSG criteria. Of the 692 found to have GDM, 82% had HbA1c results <5.9%. Twenty-three

percent of GDM was found in women tested prior to 20 weeks; the remaining 77% of GDM was discovered either on initial or repeat GTT after 20 weeks. Of note is that only 55% of the 8497 women who underwent HbA1c screening proceeded to undertake the GTT (56).

Costs of Screening

In an age of limited medical resources, attention must be paid to costs of delivery of healthcare. With specific regard to gestational diabetes, assessing the risks and benefits of a screening test should consider the costs and benefits of treatment to those identified as having GDM and the costs and risks to those who have GDM but who are not identified because of having a low screening test result. Cost models differ depending on input. For example, cost analyses limited to improvement in maternal and perinatal outcome will differ greatly from those including diagnosis and treatment of diabetes following the index pregnancy. Using QALYs (quality-adjusted life years) over a lifetime, one analysis determined that no screening for populations in which the risk of GDM is <1% is the most cost-effective approach, while for those with a risk >4.2% universal testing with a GTT is the most cost-effective (57). Another study that was premised on the uniform use of a 75 g GTT and that used the costs of reduction in DALYs (disability-adjusted life-years) as the endpoint determined that universal testing for GDM was cost-effective.

Whether the two-step (GST followed by a GTT for those women who equal or exceed the selected threshold) or one-step testing protocol is most cost-effective has been analyzed. While two studies concluded that testing with the new IADPSG criteria is expensive but cost-effective (58,59), one reported that cost-effectiveness could be demonstrated only if postdelivery care was accomplished (59).

Conclusions

While the debate over the benefits of treatment for gestational diabetes has been largely laid to rest by the results of the ACHOIS (10) and MFMU (9) trials, determining the best testing strategy for GDM remains an elusive goal. Current screening strategies save costs in the short run, but may prove costlier to the individual and society when the failure to identify women and their infants at risk for GDM-related morbidity and mortality is considered. Because of ethical constraints, resolution of this issue will not likely be achieved by randomized controlled trials but rather by large cohort studies.

Multiple-Choice Question

1 Which of the following statement(s) is/are true about the 50 g glucose screening test?

- **A** Its sensitivity is over 75% when follow-up testing is performed with the 75 g glucose tolerance test using the IADPSG criteria.
- **B** It may be administered without regard to time of day or time of the last meal without substantially affecting test results.
- **C** Results of the test may differ substantially when given on two successive days at the same time of day to the same woman.
- **D** The lower the threshold used to indicate a follow-up glucose tolerance test, the greater the likelihood of identifying women who have gestational diabetes.

Answer: C and D.

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5

Diagnostic Criteria for Hyperglycemia in Pregnancy

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PRACTICE POINT

- Controversy surrounds the most appropriate criteria for diagnosing gestational diabetes.

Case History

Ms Smith is a 28-year-old G1P1. Other than her grandmother, who was diagnosed with type 2 diabetes at aged 55 years, there is no family history of diabetes. A booking HBA1c, measured in light of an elevated BMI (32 kg/m^2), a recognized risk factor for hyperglycemia in pregnancy, was 47 mmol/mol (6.4%; normal: 20–42 mmol/mol [4.0–6.0%]). No further action was taken until a 75 g oral glucose tolerance test at 24 weeks of pregnancy showed a fasting glucose of 5.2 mmol/l (94 mg/dl), a 1 hour value of 9.6 mmol/l (173 mg/dl) and a 2 h value of 7.8 mmol/l (140 mg/dl). She was diagnosed with gestational diabetes and offered dietary advice and home blood glucose monitoring. At 30 weeks of pregnancy, she exceeded local glycemic targets (5.5 mmol/l [99 mg/dl] fasting and 7.0 mmol/l [126 mg/dl] 2 h postprandial) and was started on metformin. At 38 weeks, labor was induced and she subsequently had an emergency cesarean section because of fetal distress.

- What is the scientific evidence for diagnostic thresholds for gestational diabetes?
- What is the benefit of detecting and treating gestational diabetes?

Introduction

In Chapter 4, methods of screening for gestational diabetes mellitus (GDM) were discussed. In this chapter, we consider the diagnostic criteria that are currently used to define GDM or hyperglycemia in pregnancy. This remains a controversial area, and there is still no international consensus on either diagnostic thresholds or even whether these should be underpinned by purely clinical outcomes or, as has been recently proposed, by health economic analyses.

Gestational Diabetes: Historical Development

Early clinical recognition of the importance of hyperglycemia in pregnancy was dominated by often dismal pregnancy outcomes in women with preexisting diabetes (1).

A Practical Manual of Diabetes in Pregnancy, Second Edition. Edited by David R. McCance, Michael Maresh and David A. Sacks.

Prior to the discovery of insulin in 1922, outcomes were very poor, with high maternal and fetal mortality and high rates of ketoacidosis (1). While the advent of insulin improved these outcomes considerably, rates of perinatal mortality and stillbirth have remained several times higher than those of the background population (2). Hadden suggested that the first documented case of GDM was recorded as early as 1823 in a woman with new-onset thirst and glycosuria during a pregnancy; it resulted in delivery of a dead macrosomic baby (1).

It was only in the 1950s that the first major prospective studies of carbohydrate metabolism in pregnancy were carried out (3,4). In a seminal study in 1964, O'Sullivan and Mahan measured glucose tolerance in 752 women during pregnancy and defined a normal range for glucose values in the fasting state and at 1, 2, and 3 h following a 100 g glucose load (5). They further proposed that the presence of two or more values greater than 2 standard deviations above the mean at each of these times might be considered abnormal (5). They based this on follow-up of an older cohort of 1013 women at the same hospital, showing that the 2% of women with two or more values above these thresholds had an increased risk of diabetes up to 8 years later (5). In additional studies, they showed that the defined group had a fourfold increase in perinatal mortality (6) and an increase in maternal diabetes up to 16 years later (7).

These findings, with various later modifications for the assay techniques used, were to form the basis of diagnosis of GDM, at least in the USA, for over 40 years, and in some cases to the present day. Notably, criteria were largely based on subsequent risk of type 2 diabetes in the mother.

At the end of the 1960s, the term *gestational diabetes* was used by Pedersen and others (1), but it was only toward the end of the 1970s that there was a move to formalize diagnostic criteria for GDM (coincidentally with the diagnosis of diabetes outside of pregnancy) by the US National Diabetes Data Group (NDDG) and internationally under the World Health Organization (WHO) (8). The work of the NDDG was also influenced by an International Workshop Conference on Gestational Diabetes Mellitus held in Chicago in 1979 (9), the first of a series of such consensus workshops that were held intermittently over the next 20 years. It was agreed that *gestational diabetes* should be defined as "glucose intolerance with first recognition of onset during pregnancy." In the published consensus document in 1980, it was also stated that women should be universally screened in pregnancy and that all women should have a measure of plasma glucose after the 24th week of pregnancy (if not already known to have diabetes). Consensus was reached, at the conference at least, on the use of a 100 g glucose load and a 3 h oral glucose tolerance test (OGTT) interpreted by O'Sullivan criteria. Internationally, however, there was no agreement on the glucose load to be used, its timing during pregnancy, or the type of blood sample for screening.

The reports of the US NDDG in 1979 and WHO in 1980 led to largely concordant definitions of diabetes outside of pregnancy; however, no such consensus was achieved in pregnancy. The WHO criteria, which were simply extrapolated from the nondiabetic context, recommended that women with either diabetes or impaired glucose tolerance (IGT; ≥7.8 mmol/l fasting and ≥7.8 mmol at 2 h after the OGTT*) receive "careful surveillance." In contrast, the US NDDG (in line with the first GDM Consensus Conference recommendations) supported universal screening with a 50 g glucose challenge test, followed by a 100 g OGTT and criteria based on those of O'Sullivan (5). These differing approaches are of more than mere historical interest as, while in the intervening years there have been subsequent modifications to both sets of criteria (including the diagnosis of diabetes outside pregnancy), these differing

* The WHO report in fact suggested 8.0 mmol/l for both of these values, but this represented a rounding to the nearest mmol. It was later clarified to 7.8 mmol/l in the 1985 report, in agreement with NDDG.

approaches to the diagnosis of GDM have continued to the present day. Indeed, the two influential randomized clinical trials of the treatment of "mild" GDM diagnosis by Crowther in Australia (10) and Landon (11) in the United States published in 2005 and 2009, respectively, used criteria and approaches descended from this broad division (v.i.).

Subsequent international GDM workshops in 1984, 1990, and 1998 made incremental changes to the diagnosis of GDM. The second conference consensus formalized adoption of the 50 g oral glucose challenge for screening and endorsed the use of a post-challenge venous plasma cutoff of 140 mg/dl (7.8 mmol/l) as a criterion for progression to OGTT (12). In addition, it was recognized that the definition of GDM included those women who were likely to have had unrecognized diabetes before the index pregnancy. The third conference noted other factors likely to influence outcome, including maternal obesity, ethnicity, past obstetric experience, and family history.

In 1998, the WHO refined their definition of GDM to "carbohydrate intolerance resulting in hyperglycemia of variable severity with onset or first recognition during pregnancy" (13). Again, this overtly included the important group of women with probable preexisting diabetes. At this time, the diagnostic criteria for diabetes outside of pregnancy were revised to a venous plasma glucose ≥7.0 mmol/l (126 mg/dl) fasting or ≥11.1 mmol/l (200 mg/dl) at 2 h after OGTT; and, for IGT, to ≥7.8 mmol/l (140 mg/dl) but <11.1 mmol/l at 2 h after OGTT (13). The WHO thresholds for GDM, as a combination of those used for diabetes and IGT outside of pregnancy, were retained, albeit with the new diagnostic levels. The WHO also effectively supported a risk factor–based approach rather than universal screening. It was recommended that a 75 g OGTT should be confined to women at *high risk for gestational diabetes*, namely those with a "history of large for gestational age babies, women from certain high-risk ethnic groups, and any pregnant woman with an elevated fasting, or random blood glucose."

Finally, it should be noted that other national guideline groups adopted their own modifications of these two broad approaches. For example, in the southern hemisphere, the Australian Diabetes in Pregnancy Society recommended plasma glucose thresholds of ≥5.5 mmol/l (99 mg/dl) fasting and ≥9 mmol/l (162 mg/dl) at 2 h, although even here, a lower 2 h value was used in New Zealand (≥8 mmol/l [144 mg/dl]) (14).

This web of different definitions and screening policies has caused much confusion. There was skepticism among several screening and obstetric groups about the virtue of diagnosis of GDM (e.g., in Canada (15) and the UK (16)), and no agreement over the best means of both screening and diagnosis. A number of factors led to a revision of these earlier opinions (17). Data from large-scale trials of diagnosis and treatment of GDM began to define the benefits of treatment (10,11). The multinational observational Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, involving 23,316 women across nine countries, allowed a more precise drawing of the relationship of maternal glucose to adverse pregnancy (19) outcomes.

These lines of evidence resulted in an international workshop, which resulted in the publication of agreed diagnostic thresholds by the International Association of Diabetes in Pregnancy Study Groups (IADPSG) in 2010 (18). The recommended plasma glucose thresholds (discussed further in this chapter) were based on the average values at which there was a 1.75-fold increase in the odds of birthweight, cord C-peptide, and neonatal skinfolds being greater than the population 90th percentile. Since publication, the IADPSG recommendations have continued to excite debate, being variously adopted in some countries. The global reaction to the proposed criteria, however, is a measure of the influence and importance of the HAPO data and IADPSG initiative. The American College of Obstetrics and

Gynecology (ACOG) opted for retention of the two-stage process involving a 50 g glucose challenge followed by a 100 g OGTT (19). By contrast, the American Diabetes Association (20) allowed for either the IADPSG or two-stage method. The choice of a 1.75-fold increase in the combined HAPO complication has also aroused controversy – with some suggesting (21,22) that a twofold increase would be more appropriate, which in turn would lead to diagnostic thresholds closer to previous ACOG guidance. By contrast, in 2013 the WHO generally accepted the broad approach of the IADPSG (23).

Most recently, a separate diagnostic approach was recommended by the National Institute for Clinical Excellence (NICE) in England, Wales, and Northern Ireland. This body, arrived at thresholds based almost exclusively on a health economic analysis with a cost of screening and treatment meeting criteria of £30,000 per quality-adjusted life year (QALY). The preferred thresholds differed markedly from those advocated by the IADPSG – with fasting ≥5.6 mmol/l (101 mg/dl) and 2 h ≥7.8 mmol/l (140 mg/dl) (24). Other groups have based their analyses on the IADPSG 1.75-fold increased risk, but suggested that these thresholds should be lower and that different criteria would possibly be appropriate for different ethnic groups (25).

Most recently, the International Federation of Gynecology and Obstetrics (FIGO) (26) have also attempted to develop screening and diagnostic criteria with close scrutiny of how these might have to be adapted for various healthcare systems around the world. It was noted that screening and diagnostic criteria would need to be modified depending on various factors, including underlying biology (essentially relating to the propensity of different populations to either have undiagnosed diabetes or develop GDM) but also pragmatic issues of access to laboratory measures of glucose and the potential quality of measures of glucose or HbA1c (26). Nevertheless, FIGO adopted the overall recommendations of WHO and IADPSG – in particular, universal screening with a biochemical test rather than risk factor–based screening, and the diagnostic criteria proposed by these bodies (26).

Importance of Overt Diabetes in Pregnancy

In addition to revision of the diagnostic criteria for GDM, the international bodies (IADPSG (18), WHO (23), and later FIGO (26)) distinguished GDM from "overt diabetes in pregnancy" or "diabetes mellitus in pregnancy." The latter category conforms to the definition of diabetes outside pregnancy (i.e., fasting ≥7.0 mmol/l [126 mg/dl] or 2 h ≥11.1 mmol/l [200 mg/dl]) and appears to be clinically useful as a means of identifying women who are likely not only to require more intensive management, but also to be at increased risk of microvascular complications of diabetes and more severe complications of diabetes and pregnancy, most importantly congenital anomaly, as a reflection of more severe degrees of hyperglycemia preceding pregnancy (18).

The implication of this classification is that many women with preexisting but undiagnosed diabetes may be included in the category of overt diabetes rather than gestational diabetes. It should also be noted that women with overt diabetes, together with women diagnosed with GDM but with higher levels of glucose, were not included in the HAPO study and the large-scale intervention trials for ethical reasons. For example, in the HAPO study, women were excluded if fasting glucose was ≥5.8 mmol/l (104 mg/dl) or 2 h glucose was ≥11.1 mmol/l (200 mg/dl) during the OGTT at an average of 28 weeks gestation. This resulted in exclusion of 1.7% of women because of a raised fasting or 2 h value at baseline. A further 1.2% of women were omitted from the study due to raised random glucose (above 8.9 mmol/l; 160 mg/dl) later in pregnancy.

Therefore, while this observational study is invaluable for describing the relationship of maternal glucose to the various pregnancy outcomes, around 2.9% of the population not previously diagnosed with diabetes, but with the highest glucose levels during pregnancy, were excluded from the observational study, potentially (and appropriately) reducing some of the adverse outcomes. Similarly, various exclusion criteria were also similarly applied to the two large intervention studies, which were overtly designed as randomized studies of "mild" GDM and excluded women with the highest levels of glucose during pregnancy (10,11).

Rationale for Diagnosing Maternal Hyperglycemia During Pregnancy

Review of the historical background to the diagnosis of hyperglycemia during pregnancy clearly shows that the controversy, at least partially, relates to disagreement over what outcomes should define the diagnosis of GDM. Outside of pregnancy, the rationale for diagnosis is more straightforward, and whether by fasting glucose, post-challenge glucose, or HbA1c, a level is sought that is predictive of increased risk of microvascular complications in the population (13). It is possible to identify thresholds above which there is an increased risk of development of microvascular complications, such as diabetic retinopathy and nephropathy, and above which the prevalence of the complication increases considerably. This approach forms the logical basis for classification of a part of the population as having diabetes and, critically, who would be expected to benefit from a screening program to detect such microvascular complications. While people with diabetes are also at increased risk of macrovascular disease, no such glucose thresholds exist as for microvascular disease, and in addition, this endpoint is not unique to people with diabetes.

One of the seminal contributions of the HAPO analysis is the clear demonstration of maternal hyperglycemia, short of diabetes, as a predictor of adverse pregnancy outcomes (27). It was also immediately apparent from the data that there was no clear threshold above which these outcomes increase markedly. This continuous graded relationship of a risk factor to a clinical outcome is thus more analogous to the association of cholesterol or blood pressure with ischemic heart disease, than to nonpregnancy definitions of diabetes. Equally, and again analogous to cholesterol and heart disease, maternal glucose might be conceived as one of several risk factors, and the rationale for detection and treatment might differ depending on the presence of these other risk factors. This again is familiar territory in cholesterol management, where we are comfortable with different treatment thresholds depending on other risk factors such as age, hypertension, and indeed diabetes. Notably, at the time of this writing, such a pattern of different diagnostic or treatment thresholds based on other risk factors has not been adopted for GDM – although such an approach has been suggested at least for South Asian women (25).

These considerations also raise questions regarding nomenclature. For an individual, the diagnostic label of diabetes may be unhelpful, and alternative terminology such as *hyperglycemia in pregnancy* may be more useful and would allow maternal glucose to be considered as one of a number of risk factors (28). The difference may be more than semantic, as it has been long argued that labeling a patient as having GDM increases the likelihood of operative delivery and may have negative connotations for the mother, even if this is not entirely borne out in more recent literature (10,11).

We next consider the specific outcomes that might underpin the diagnosis and, critically, whether it has been demonstrated that intervention reduces risk of those outcomes.

Basing Treatment on Improving Outcomes

Maternal hyperglycemia in pregnancy is clearly associated with an increased risk of certain key outcomes for both mother and child. For the mother, outcomes can be divided into those present in the pregnancy and immediate postpartum period (e.g., risk of preeclampsia or instrumental delivery) versus longer term implications, most notably risk of later type 2 diabetes for the mother. Similarly, for the child, the risks may be present in pregnancy and delivery, including macrosomia (with a potentially traumatic delivery) and neonatal hypoglycemia, but also in the longer term including programming of obesity and type 2 diabetes.

The HAPO study has demonstrated a continuous graded relationship with likelihood of macrosomia, cord insulin >90th percentile, clinical neonatal hypoglycemia, and cesarean section (27) but also neonatal adiposity (29) and weaker relationships with neonatal glycemia (30). Of the secondary outcomes in HAPO, shoulder dystocia and preeclampsia were positively associated with maternal fasting and post-challenge blood glucose, while preterm delivery, hyperbilirubinemia, and intensive neonatal care were related to post-challenge but not fasting glucose (27). The HAPO data were largely in keeping with previous smaller studies in the literature, most notably that of Sacks (31). The HAPO study was not powered for, and did not show, any significant relationship with perinatal mortality – perhaps reflecting the exclusion of mothers at the highest level of blood glucose, as discussed in the "Importance of overt diabetes in pregnancy" section (27). More broadly, it is worth highlighting that the literature has not convincingly demonstrated an association between GDM and stillbirth or perinatal mortality, with only a few studies suggesting such a relationship (32,33).

Critically, however, it is important not only that key outcomes are associated with the diagnosis but also that intervention improves those outcomes. To that end, the two landmark intervention studies of mild GDM have shown a clear reduction in fetal growth (average birthweight and rates of large-for-gestational-age [LGA] offspring) (Table 5.1) (10,11). Reduction in fetal growth with glucose

Table 5.1 Relative risk for adverse outcomes in ACHOIS and MFMU trials.

	ACHOIS	MFMU
Primary outcome*	↓ 0.33 (0.14–0.75) ($P = 0.01$)	↔ 0.87 (0.72–1.07) NS
Large for gestational age	↓ 0.62 (0.47–0.81) ($P < 0.001$)	↓ 0.49 (32–0.76) ($P < 0.001$)
Macrosomia: birthweight >4 kg	↓ 0.47 (0.34–0.64) ($P < 0.001$)	↓ 0.41 (0.26–0.66) ($P < 0.001$)
Neonatal fat mass	–	↓ ($P = 0.003$)
NICU admission	↑ 1.13 (1.03–1.23) ($P = 0.04$)	↔ 0.77 (0.51–1.18) (P = NS)
Shoulder dystocia	↔ 0.46 (0.19–1.10) (P = NS)	↓ 0.37 (0.14–0.97) ($P = 0.02$)
Induction of labor	↑ 1.36 (1.15–1.62) ($P < 0.001$)	↔ 1.02 (0.81–1.29) (P = NS)
Preeclampsia	↓ 0.70 (0.51–0.95) ($P = 0.02$)	↓ 0.46 (0.22–0.97) ($P = 0.02$)
Cesarean section	↔ 0.97 (0.81–1.16) (P = NS)	↓ 0.79 (0.64–0.99) ($P = 0.02$)

* The primary outcome in ACHOIS was a composite of death, shoulder dystocia, bone fracture, and nerve palsy. The primary outcome in MFMU was a composite of stillbirth, neonatal death, neonatal hypoglycemia, hyperbilirubinemia, hyperinsulinemia, and birth trauma.

Note: All figures are given as the relative risk (95% confidence intervals) in the intervention vs. control arms of the respective studies.

ACHOIS = Australian Carbohydrate Intolerance Study in Pregnant Women; MFMU = Maternal and Fetal Medicine Unit Network; NICU = neonatal intensive care unit; NS = not significant.

lowering may also occur even at levels of glucose below thresholds for GDM, although the number and size of studies are small (34).

Does treatment of hyperglycemia during pregnancy reduce more severe maternal and neonatal outcomes? There is a consistent reduction in risk of preeclampsia (Table 5.1) to around 50–70% of the untreated groups' rate (10,11). Rates of shoulder dystocia also appear reduced, although the low rates of this complication and difficulty in clinically defining this outcome make this a controversial result (10). The Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) and Maternal and Fetal Medicine Unit Network (MFMU) studies are, however, discordant for other outcomes that may be dependent on medical behaviors. Thus, while cesarean section rates were reduced in the MFMU study and neonatal intensive care admission and induction rates were unchanged, cesarean section was unchanged and the other two outcomes increased in ACHOIS (10,11). This is in part a reassuring result given long-term concern that labeling women as having GDM might serve to paradoxically increase C-section rates (35), but it remains unclear whether treatment will definitively reduce some of these outcomes.

At the most severe end of the spectrum of complications, maternal type 1 and type 2 diabetes are associated with an increased rate of perinatal mortality, with increases in both stillbirth and early neonatal death (36). Meta-analyses have shown no significant increase in perinatal mortality in GDM (32). It should be noted that some national surveys have shown an increase (33), perhaps explained by the effects of undiagnosed pregestational diabetes. In the ACHOIS study, there was a significant reduction in the primary outcome of the study – which included death (Table 5.1) – although rates of all of these outcomes were low (10). By contrast, in the MFMU study, the primary outcome was not significantly reduced (11). Notably, there were no stillbirths in the MFMU study population – likely reflecting the exclusion of those with higher levels of glucose (11). Taken together, it would not appear that treatment of mild GDM will result in improvement in perinatal mortality. At the same time, these benefits may emerge where women with higher degrees of hyperglycemia are detected in screening programs, particularly in populations with a high rate of undiagnosed type 2 diabetes.

Maternal diabetes has also been suggested to increase the risk of obesity and type 2 diabetes in their offspring (37,38). These late-life effects are usually suggested to reflect *in utero* "programming" by aspects of the intrauterine environment, most likely hyperglycemia. This is an important area, as while effects are best described in mothers with pre-gestational diabetes, such an influence in GDM would, because of the greater numbers involved, have a much larger public health impact. As described in early studies in the Pima Indian population, it appears clear that offspring of mothers with type 2 diabetes have an increase in adiposity and altered glucose tolerance (37,38), and similar effects are observed in offspring of mothers with type 1 diabetes (39,40), supporting the notion that programming effects are occurring. Data for offspring of mothers with GDM are less clear – in part, because the glycemic programming effect might be expected to be more modest. As yet, longer term follow-up of both children born to mothers in the HAPO study (41) and intervention studies does not suggest an improvement in longer term child health dependent on treatment (42,43), but further studies are in progress.

As a further development, it is suggested not only that clinical outcomes should be improved by detection and treatment of gestational diabetes, but also that diagnostic and intervention programs should be shown to be cost-effective (24). Based on clinical outcomes felt to be most important to mother and baby (shoulder dystocia, cesarean section, neonatal jaundice, preeclampsia, induction of labor, and neonatal intensive care unit admission) and analysis based on the costs of screening and treatment of these outcomes, NICE have suggested a separate set of

thresholds with a fasting glucose ≥5.6 mmol/l and 2 h value of ≥7.8 mmol/l representing the optimal cutoff for costs of screening. By contrast, other groups have suggested that the IADPSG cutoffs can be supported in health economic terms (44), although the models used are in turn disputed (45).

Diagnosis in the First Trimester

A further important area is the potential for diagnosis of hyperglycemic states in early pregnancy. Traditionally, due to the development of insulin resistance in the second and third trimesters, screening for GDM has been targeted to 24–28 weeks of pregnancy, the exception being testing in earlier pregnancy in women with previous GDM. The IADPSG consensus noted a lack of evidence for interpretation of OGTT results in early pregnancy and did not recommend routinely performing OGTT before 24–28 weeks (18). It was, however, suggested that fasting plasma glucose ≥5.1 mmol/l (92 mg/dl) be classified as GDM (18). Systematic review of the literature around the same time (2008) found no randomized controlled trials of screening and treatment earlier than 24 weeks (46).

Broadly, higher glucose by a variety of measures would appear predictive of adverse outcomes. In observational studies, first-trimester fasting glucose is predictive of later GDM, LGA, and cesarean section (studied in a "normal" range up to 5.8 mmol/l [105 mg/dl]) (47). Women who have GDM diagnosed in the first trimester (by Carpenter–Coustan criteria in this study) have an increase in complications including hypertension and preeclampsia compared to those diagnosed later (48), with a suggestion of increases in neonatal hypoglycemia and perinatal mortality although based on very small numbers (48). Comparison of successive observational cohorts of women undergoing either screening at 24–28 weeks or with additional early screening suggested a potential reduction in some outcomes (hydramnios, and preterm deliveries) but no overall difference in birthweight in those screened earlier (49). Similarly, in women with GDM, while higher HbA1c (41–49 mmol/l [5.9–6.6%]) at diagnosis was a marker of increased risk of adverse outcomes (preeclampsia and preterm birth), women in this subgroup who were diagnosed and treated before 24 weeks had a reduction in preeclampsia compared to those who began treatment later (50). Taken together, these data give a sense that earlier treatment may be advantageous, but they are far from determining what the best marker (glucose or HbA1c) or threshold might be and have all of the caveats usually applied to observational data. In particular, much of the data do not address the controversies of treatment of "mild" GDM from early pregnancy. It is clear that further randomized controlled trials will be key.

An important exception to this will be those groups who, while diagnosed in pregnancy, are likely to have preexisting GDM. Thus, where HbA1c is clearly raised in early pregnancy (greater than 6–6.5%), it would be expected that existing data from women with type 1 and type 2 diabetes regarding early risk of congenital anomaly and miscarriage, along with management plans and counseling for pre-gestational diabetes, would be appropriate.

Conclusions

There is still no universally agreed definition of GDM. However, substantial progress has been made since publication of the IADPSG/WHO criteria, and there is a major thrust toward a global consensus. The dramatic secular increase in type 2 diabetes and obesity should not be forgotten, and it seems clear that it will be necessary to define a group of women with very high glucose who are at particularly high risk of adverse maternal fetal outcomes and who require particular

supervision. This group currently most closely conforms to the category of *overt diabetes in pregnancy* and reflect diabetes not detected before pregnancy. Below this category is a much larger group of women who benefit in terms of fetal growth from the detection and management of hyperglycemia in later pregnancy. The exact lower boundaries of this group are clearly still disputed, as is whether the goal will be purely clinical or governed by health economics. This will be refined and may become different in different healthcare settings (26). Particularly for those with the mildest abnormalities of glucose tolerance, there are legitimate concerns over the potential for "medicalizing" pregnancy (51), but the beneficial effects on fetal growth and indeed preeclampsia from a fairly unintrusive healthcare intervention in many women should also be emphasized. The great majority (80–90%) of women in these studies of mild GDM could be managed by dietary intervention alone (10,11). As others have written, the term *gestational diabetes* is possibly unhelpful (28) if these women are viewed not as having a defined disease in pregnancy but rather as a group with one of several risk factors.

Multiple-Choice Questions

1 *Overt diabetes in pregnancy* or *diabetes mellitus in pregnancy* can be diagnosed at or above a fasting plasma glucose level of:
   A 5.1 mmol/l.
   B 5.3 mmol/l.
   C 5.6 mmol/l.
   D 7.0 mmol/l.

Answer: D.

2 In the second trimester, HbA1c at or above the following is an accepted diagnostic criterion (World Health Organization) for gestational diabetes.
   A 5.8%
   B 6.5%
   C 7.0%
   D None of the above

Answer: D.

Abbreviations

FIGO	International Federation of Gynecology and Obstetrics
GDM	gestational diabetes mellitus
HAPO	Hyperglycemia and Pregnancy Outcomes (study)
HbA1c	hemoglobin A1c
IADPSG	International Association of Diabetes and Pregnancy Study Groups
IGT	impaired glucose tolerance
NDDG	National Diabetes Data Group
NICE	National Institute for Clinical Effectiveness
OGCT	oral glucose challenge test
OGTT	oral glucose tolerance test
SIGN	Scottish Intercollegiate Guidelines Network
WHO	World Health Organization

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6

Lifestyle Treatment

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PRACTICE POINTS

- Maternal obesity is recognized as one of the largest contributors to compromised health during pregnancy.
- Overweight and obesity affect about 50% of women entering pregnancy in developed countries.
- Obesity increases the risk of gestational diabetes, preeclampsia, preterm birth, stillbirth, and macrosomia.
- Lifestyle intervention trials in pregnancy have been shown to reduce gestational weight gain and improve quality of diet.
- Lifestyle intervention trials have only had a limited impact on clinical pregnancy and neonatal outcomes.
- Results from ongoing subgroup analyses from an Individual Patient Data (IPD) meta-analysis are awaited to see if any populations might benefit from specific interventions.
- Follow-up in the offspring of mothers participating in lifestyle intervention trials in pregnancy are important to demonstrate impact and safety on long-term outcomes.
- Early maternal metabolic conditions program placenta function and gene expression from the time of conception.
- Future intervention trials in pre-pregnant obese women are needed to examine the effect on maternal and neonatal outcomes in a subsequent pregnancy.

Case History

Linda is a 29-year-old primipara with a pre-gestational Body Mass Index (BMI) of 31. She goes through her first pregnancy without any complications. At gestational week 28, an oral glucose tolerance test is performed with a 2 h glucose level of 8.4 mmol/l, just below the threshold for gestational diabetes. She gains 18 kg during pregnancy. At delivery, there is 4 min of shoulder dystocia, but the baby recovers after a few minutes with continuous positive airway pressure (CPAP). Birthweight is 4300 g. Breastfeeding is never successfully initiated afterward. After 20 months, Linda gets pregnant again. She never lost all the weight she gained in the first pregnancy and now enters pregnancy with a BMI of 34. Due to glucosuria, an oral glucose tolerance test is done at gestational week 24, and Linda is now diagnosed with gestational diabetes and referred to a program with a diabetes nurse, a dietician, obstetricians, and endocrinologists. By the time of diagnosis, she has gained 5 kg, and with the intervention initiated she restricts the total gestational weight gain to 8 kg. From gestational week 35, insulin treatment is added, and the delivery is induced 4 weeks later due to rapid increase in abdominal circumference of the baby. Birthweight is 4650 g, and the delivery is complicated with a grade 3 anal sphincter injury.

A Practical Manual of Diabetes in Pregnancy, Second Edition. Edited by David R. McCance, Michael Maresh and David A. Sacks.

Introduction

Maternal obesity has been identified as an important clinical issue in contemporary obstetric practice. Both developed and developing countries have experienced a rapid increase in the prevalence of obesity (1), and this global epidemic poses a significant burden to public health and clinical practice (2,3). Among women in the USA, 20 to 39 years of age, the prevalence of obesity (Body Mass Index [BMI] ≥30 kg/m^2) has reached 36% (4), and in England, about 16% of pregnant women are obese (5).

The condition has profound effects on glucose metabolism both within and outside pregnancy, and is associated with type 2 diabetes, polycystic ovary syndrome, and gestational diabetes mellitus (GDM). Studies have shown that potentially modifiable maternal factors such as pre-pregnancy BMI, gestational weight gain (GWG), and various degrees of glucose intolerance are associated with adverse pregnancy outcomes (6). Most importantly, an unfavorable intrauterine environment is predictive of macrosomia at birth, GDM in future pregnancies, and obesity, diabetes, and other metabolic problems in the offspring, creating an intergenerational vicious circle.

Pregnancy has been considered "a window of opportunity" in terms of changing behavior and improving awareness of healthy living. Furthermore, pregnant women are easily reached because of frequent contacts with healthcare professionals during pregnancy. Despite a large number of recent clinical trials on lifestyle interventions during pregnancy, evidence of their clinical impact is limited, especially with regard to GDM. This chapter highlights different lifestyle intervention trials in obese women and discusses reasons why targeting pregnancy as a time to treat obesity is challenging.

Lifestyle Intervention in Obese Pregnant Women

Pregnancy offers the opportunity to manage or prevent obesity as many women are concerned with the health of their babies during pregnancy and also are in frequent contact with their healthcare professionals. In 2009, the US Institute of Medicine (IOM) recommended obese women to gain 5–9 kg during pregnancy. For overweight and normal-weight women, the recommended weight gain was 7–11.5 kg and 11.5–16 kg, respectively (7). Lifestyle intervention has the potential to improve feto-maternal outcomes by limiting GWG and improving maternal glucose metabolism and insulin sensitivity. Excessive GWG is associated with increased risk of maternal and fetal complications as well as postpartum weight retention. A large proportion of obese women exceed the recommended GWG. Thus, in the Danish National Birth Cohort, 58% of obese women exceeded a weight gain of 10 kg with total mean GWG of 10.5 ± 8.3 kg (8). A recent meta-analysis found that excessive GWG, even in normal-weight women, influences offspring obesity over the short and long term (9).

A number of clinical trials of lifestyle intervention in overweight or obese women at increased risk of GDM have been published. The majority of these have focused on changing dietary habits, physical activity, or a combination of both, and many have used GWG as the primary outcome and/or whether women gained below, within, or above the IOM recommendations for GWG (7). A few studies have also looked at maternal metabolic parameters such as hyperglycemia, insulin, and lipid profile (10,11). Only one study so far has published detailed childhood follow-up data in the offspring (12). Some of the most recent studies have been sufficiently powered to examine the clinical, maternal, and neonatal outcomes, including GDM and macrosomia (11,13–15).

The Australian LIMIT study is so far the largest published trial (a randomized controlled trial [RCT]) and included 2212 overweight or obese nondiabetic pregnant women who were randomized to either lifestyle intervention or standard antenatal care. Participants were included between 10 and 20 weeks gestation (16). Lifestyle intervention comprised dietary advice, individual diet plans, and encouragement to exercise.

The behavioral strategies were provided by a research dietician during a face-to-face visit after inclusion and in gestational weeks 28 and 36, and followed up by three personal phone calls at 22, 24, and 32 weeks gestation. The study did not significantly reduce the risk of infants born large for gestational age (LGA) in the lifestyle group compared to standard care (19% vs. 21%, $p = 0.24$), which was the primary outcome. Furthermore, there was no significant reduction in GWG between groups: the intervention group gained 9.39 kg versus 9.44 kg in controls, $p = 0.89$. The risk of having a baby with birthweight above 4.5 kg was decreased; however, this measure did not take gestational age into consideration. Follow-up in the offspring is ongoing.

In UPBEAT (the UK Pregnancies Better Eating and Activity Trial), 1555 obese pregnant women (BMI ≥30 kg/m^2) with multiethnic backgrounds were randomized between 15 and 18 + 6 weeks of gestation either to behavioral intervention targeting diet and physical activity or to standard antenatal care (11). Women allocated to the intervention group had an individual interview with a health trainer, followed by weekly sessions for 8 weeks (control theory and elements of social cognitive therapy). The primary outcomes, GDM and LGA, were similar in the two groups (25% vs. 26% and 8% vs. 9%, respectively), as were a number of other obstetric complications. Women in the intervention group gained less weight in pregnancy than controls (7.19 vs. 7.76 kg; $p = 0.04$), and they obtained goals of reduced dietary glycemic load and higher physical activity (11).

In the ROLO study (Randomized cOntrol trial of LOw glycemic index diet to prevent macrosomia in euglycemic women) in Ireland, 800 euglycemic pregnant women in all BMI categories with a prior macrosomic baby (birthweight >4000 g) were randomized to receive low-glycemic-index and healthy-eating dietary advice in a group session before 22 weeks of gestation, or to a standard control group (17). Based on a 3-day food diary during each trimester, the intervention group had a significantly lower energy intake and a reduced intake of food with high glycemic index. The intervention group had significantly lower GWG (kg) compared to the control group (mean 11.5 ± 4.2 vs. 12.6 ± 4.4 kg; $p = 0.003$), and a lower percentage of women in the intervention group exceeded the IOM recommendations on GWG. No differences in birthweight (primary outcome), length, or neonatal abdominal circumference were seen.

In the Danish LiP (Lifestyle in Pregnancy) study, a total of 360 obese pregnant women (BMI ≥30 kg/m^2) were randomized to intervention or control groups before 14 weeks gestational age (18). Women in the intervention group received four individual diet-counseling sessions during pregnancy and an exercise program consisting of aerobic classes (1 h weekly), free fitness club membership during pregnancy, and exercise-motivating initiatives. The intervention group had significantly lower GWG (kg) compared to the control group (median [interquartile {IQ} range]: 7.0 [4.7–10.6] vs. 8.6 [5.7–11.5]; $p = 0.01$). No significant differences were found for risk of preeclampsia, pregnancy-induced hypertension, gestational diabetes, cesarean section, having a LGA infant, or admission to the neonatal intensive care unit. The study measured a number of metabolic outcomes throughout pregnancy and found that the lifestyle intervention resulted in attenuation of the physiologic pregnancy-induced insulin resistance (10). The intervention had no effect on duration of breastfeeding or postpartum weight retention (19). The study is the first pregnancy intervention trial to publish detailed follow-up in the offspring, showing no anthropometric or metabolic effects at 2.5 to 3 years of age (12,20).

The TOP study (Treating Obesity in Pregnancy) was a Danish RCT with 425 obese pregnant women (BMI ≥30 kg/m^2) randomized to two intervention arms of either physical activity (PA) with pedometers, physical activity and dietary counseling (dietician every second week) (PA + D), or a control group (21). Median values of GWG (ranges) were lower in each of the intervention groups

(PA + D: 8.6 [−9.6 to 34.1] kg; PA: 9.4 [−3.4 to 28.2] kg) compared with the control group (10.9 [−4.4 to 28.7] kg: [PA + D vs. C; $P = 0.01$] and [PA vs. C; $P = 0.042$]). The authors found no differences in any of the obstetric or neonatal outcomes.

The DALI (Diabetes and Pregnancy Vitamin D And Lifestyle Intervention) study was a European multicenter study in obese pregnant women (BMI ≥29 kg/m^2). DALI aimed to prevent GDM in obese women by lifestyle interventions (motivational interviewing) and/or vitamin D supplementation (22). In the DALI Lifestyle Study, obese, glucose-tolerant women were enrolled in early pregnancy and randomized to one of four intervention arms: Healthy Eating (HE) (113 women), Physical Activity (PA) (110), HE + PA (108), and a control group who received usual care (105). In the HE + PA group, but not HE or PA alone, women achieved substantially less GWG than did the controls by 35 to 37 weeks (−2.02; 95% confidence interval [CI]: −3.58 to −0.46 kg). Despite this reduction, no improvements were seen in fasting or post-load glucose levels, insulin concentrations, or homeostatic model assessment of insulin resistance (HOMA-IR). The birthweights and large and small for gestational age rates were similar (14).

The Finnish Gestational Diabetes Prevention Study (RADIEL) included 293 pregnant women with BMI ≥30 kg/m^2 and/or prior GDM enrolled before 20 weeks of gestation (23). The women were randomized to individual counseling on diet and physical activity or to standard antenatal care. The incidence of GDM was lower in the intervention group compared with controls (13.9% vs. 21.6%, $p = 0.097$ unadjusted, and $p = 0.044$ after adjustment for baseline data). Thus, the finding was significant only after adjustment for baseline data. In addition, the intervention had favorable effects on diet quality and physical activity.

A number of other RCT studies have focused on GWG and found different results. The "Fit for Delivery Study" by Phelan *et al.* (24) was a low-intensity behavioral intervention with 410 normal and overweight to obese women in the USA randomized at 10–16 weeks gestation to intervention or standard care. They found that the intervention significantly decreased the percentage of normal-weight women who exceeded the IOM recommendations on GWG, but did not significantly affect GWG in overweight and obese women. Luoto *et al.* found a significant reduction in birthweight after individual counseling on diet and exercise among patients with at least one risk factor for GDM in the Finnish NELLI study (28). In a Belgian RCT with low-intensive lifestyle education by nutritionists, they did not significantly affect GWG (29); however, a later Belgian RCT found a significant reduction in GWG in the intervention group receiving antenatal lifestyle intervention focusing on mental and physical health (30). Results from main studies within the last 5 years are listed in Table 6.1 (11,14,16,18,21,23–28,30–32).

Systematic Reviews on Intervention Trials

A number of systematic reviews and meta-analyses have been performed during recent years (33–36). From these, it can be concluded that despite the recognition of obesity as a severe clinical problem and considerable efforts to prevent complications, no specific evidence-based lifestyle intervention has yet been identified. This knowledge gap is important to address in future studies. The latest systematic reviews consistently conclude that antenatal intervention is associated with restricted GWG, and it seems that dietary interventions are associated with the greatest reduction in GWG. As mentioned, this was not the finding in the large LIMIT trial that was published later on. Furthermore, it is concluded that existing studies are of low to moderate quality, and results should be interpreted with caution. A Cochrane Review

Table 6.1 Lifestyle intervention trials.

Author (year) Study	Design	Population (*n*)	Intervention	Results
Simmons (2017) (14) DALI	RCT 3 groups: Healthy Eating (HE), Physical Activity (PA), and HE + PA	BMI ≥29 9 European countries (*n* = 436)	5 face-to-face and 4 optional telephone coaching sessions, based on the principles of motivational interviewing	HE women had significantly lower GWG (−2.02 kg [95% CI −3,58, −0.46]). Fasting glucose and insulin resistance were comparable. No significant differences between HE + PA and the other groups were observed. GDM prevalence was similar in all intervention groups.
Koivusalo (2015) (23) RADIEL	RCT Intervention/ control	BMI ≥30 Finland (*n* = 293)	Individualized counseling on diet, physical activity, and weight control from study nurses and one group meeting with a dietitian	The incidence of GDM was 13.9% in the intervention group and 21.6% in the control group (95% CI: 0.40–0.98%; *P* = 0.044), after adjustment for baseline characteristics. Significant reduction in GWG: −0.58 kg (95% CI: −1.12 to −0.04); adjusted *p* = 0.037.
Poston (2015) (11) UPBEAT	RCT Intervention/ control	BMI ≥30 UK (*n* = 1555)	Behavioral intervention with 8 weekly health trainer–led sessions in groups, or individualized	No difference in GDM between intervention and controls: 25% vs. 26%, *p* = 0.68. No difference in LGA: 9% vs. 8%, *p* = 0.40. Significant reduction in GWG: 7.19 kg vs. 7.76 kg, *p* = 0.041.
Dodd (2014) (13) LIMIT	RCT Intervention/ control	BMI ≥25 Australia (*n* = 2212)	Dietary, exercise, and behavioral strategies delivered by dieticians and assistants at two face-to face visits followed up by 3 personal phone calls	No reduction in LGA between intervention and control: 19% vs. 21%, *p* = 0.24. Significantly lower rate of macrosomic infants (>4000 g): 15% vs. 19%, *p* = 0.04. No difference in GWG: 9.39 vs. 9.44kg, *p* = 0.89.
Renault (2014) (21) TOP	RCT 3 groups: Physical Activity (PA) + Diet (D), PA, and control	BMI ≥30 Denmark (*n* = 425)	Dietary advice by dieticians every 2 weeks (face-to-face and phone calls). PA included pedometer with encouragement to obtain 11,000 steps daily.	Significant reduction in GWG in both intervention groups compared to controls: 8.6 vs. 9.4 vs. 10.9 kg, *p* = 0.01. No effect on birthweight, LGA, or GDM.

(*Continued*)

Table 6.1 (*Continued*)

Author (year) Study	Design	Population (*n*)	Intervention	Results
Bogaerts (2013) (30)	RCT 3 groups: Lifestyle, brochure, and control	BMI ≥29 Belgium (*n* = 205)	The brochure group received written information on healthy lifestyle. The lifestyle group had 4 antenatal intervention sessions with midwifes trained in motivational interviewing.	Significant reduction in GWG in both intervention groups compared to control: 9.5 vs. 10.6 vs. 13.5 kg, $p = 0.007$. Significantly lower level of anxiety in the active lifestyle group only. No effect on birthweight or GDM.
Walsh (2012) (32) ROLO	RCT Intervention/ control	Second pregnancy, prior delivered infant >4000 g Ireland (*n* = 800)	Low-glycemic-index diet from early pregnancy (1 group session with dieticians), follow-up with written material, and two sessions with reinforcement	No significant difference in birthweight or macrosomia. Significant reduction in GWG: −1.3 kg (95% CI: −2.4 to −0.2 kg), $p = 0.01$.
Vinter (2011) (18) LiP	RCT Intervention/ control	BMI ≥30 Denmark (*n* = 360)	4 individual face-to-face visits with dieticians, weekly training sessions in groups with physiotherapists, pedometer, and free fitness club membership	Significant reduction in GWG: n7.0 vs. 8.6 kg, $p = 0.01$ No effect on birthweight, LGA, or GDM.
Luoto (2011) (28) NELLI	Cluster-RCT Intervention/ control	All BMI groups, euglycemic but at least 1 GDM risk factor Finland (*n* = 399)	5 face-to-face antenatal visits with nurses, with individual dietary and exercise counseling	No effect on GWG: 13.8 vs. 14.2 kg, $p = 0.52$. Significantly lower birthweight in intervention group vs. control: 3532 vs. 3659 g, $p = 0.008$; and significant reduction in birthweight/week and LGA. No effect on GDM or macrosomia.
Phelan (2011) (24) Fit for Delivery	RCT Intervention/ control	BMI 19.8 – 40 USA (*n* = 401)	Low-intensity behavioral intervention, with one face-to-face contact with interventionist at study entry and 3 brief supportive phone calls	Significant reduction in exceeding 1990 IOM criteria for GWG: 40.2% vs 52.1%, $p = 0.003$ (normal weight only). No significant effect on GWG in overweight/ obese.

BMI = Body Mass Index; GDM = gestational diabetes mellitus; GWG = gestational weight gain; IOM = US Institute of Medicine; LGA = large for gestational age; RCT = randomized controlled trial.

from 2015 also assessed the effects of combined diet and exercise interventions for preventing GDM specifically (37). The review included 13 RCTs in the study involving 4983 women and their babies. When comparing pregnant women receiving diet and exercise intervention versus controls, there was no significant difference in the risk of developing GDM. The review concluded that given the variable quality of these trials, the characteristics of interventions and populations, as well as outcome definitions, it was not possible to draw any definitive conclusions. Thus, based on the data currently available, there is no conclusive evidence available that lifestyle intervention is able to prevent the development of GDM.

Is It Possible that Intervention Might Be Harmful?

It is important that the beneficial effects of any lifestyle interventions are balanced against potential adverse outcomes, such as small for gestational age (SGA), low birthweight, preterm birth, and stillbirth. Based on results from observational studies, the IOM recommendations on GWG in 2009 suggested a minimum weight gain of 5 kg. So far, no published RCT study has reported any adverse effects of the intervention programs, not even among pregnant women gaining less than 5 kg. Hinkle *et al.* examined associations between GWG and fetal growth according to obesity class in more than 122,000 obese women (38). For obesity class I, gestational weight *loss* was associated with significantly increased risk of SGA infants compared to GWG of 5–9 kg. Gestational weight gain of 0.1–4.9 kg in obesity class I and GWG of –4.9 to +4.9 kg in obesity class II and III were not associated with increased risk of SGA, but decreased risk of macrosomia. In another study, Blomberg *et al.* evaluated maternal and neonatal outcomes in 46,000 deliveries among obese women in Sweden, according to GWG below the IOM recommendations (39). It was reported that women in obesity class II and III who lost weight during pregnancy had decreased risk of cesarean delivery and LGA and no significant increased risk of preeclampsia, low Apgar score, and fetal distress compared to obese women with GWG within the recommendations. There was a twofold increased risk of SGA infants, but the risk in obese women was low (3.7%). The increased risk of SGA disappeared if the obesity class III women had a low weight gain (0–4.9 kg). The results from these studies suggest that GWG below the IOM criteria is reasonably safe for women in obesity class II and III. Still, these conclusions are based on observational data, and we have no information on long-term consequences for these infants. In a later observational study from Catalano *et al.*, it was observed that GWG below 5 kg in obese women was associated with a significantly lower birthweight, lean body mass, fat mass, and length compared with neonates of obese women gaining above 5 kg (40). These preliminary findings need to be confirmed or rejected in future trials, as interventions must do no harm in relation to both short- and long-term outcomes in mothers and offspring.

Ongoing Studies and Meta-Analyses

Well-powered and comprehensive intervention trials are ongoing, and results are pending. The Australian SPRING study (the Study of Probiotics IN the prevention of Gestational diabetes) is an RCT of probiotics in the prevention of GDM in 540 overweight and obese pregnant women (41). Probiotics are microorganisms that are believed to provide health benefits by changing the gut microbiome species composition. In a recent RCT, the use of probiotics among normal-weight pregnant women was shown to reduce the rate of GDM (42). An International Weight Management

in Pregnancy (iWIP) Collaborative Network is currently overseeing an ongoing IPD meta-analysis involving pooled data from 36 collaborators (43). Results from more than 9000 women participating in RCTs of weight management in pregnancy will be included. The primary outcome of the study is GWG, but a number of secondary outcomes will also be analyzed. The IPD meta-analysis will allow identification and subsequent targeting of the intervention to those groups that may benefit from interventions in pregnancy in the largest powered sample size to date. Finally, the iWIP collaboration is also planning to extend the study to encompass follow-up data in children from these studies.

Comparison of Studies

Lifestyle interventions in obese pregnant women may have the potential to limit GWG, which is important for reducing postpartum weight retention and limiting pre-gestational weight in a subsequent pregnancy. Moreover, a limited GWG may have a positive impact on the future weight trajectory. The RCTs referenced in this chapter used different lifestyle interventions during pregnancy, and they provided different combinations of behavioral changes, dietary habits, and physical activities that ranged from low-intensity behavioral studies to more intensive interventions involving repeated individual counseling and exercise sessions. The inconsistencies in study setting, BMI, design of intervention, and intensity make comparisons difficult. Another limitation of the intervention studies is the inability of the investigators to consistently and properly monitor compliance with diet and/or physical activity requirements. Other reasons for lack of clinical effect may relate to the fact that intervention trials attract the healthiest women who are not representative of the background population of overweight and obese pregnant women. Blinding of the intervention is not possible, and as controls are motivated and aware of the ongoing intervention, they may improve their pregnancy behaviors, which in turn may reduce fasting glucose and GWG (14). The discrepancy between results of intervention studies might be partly due to differences in inclusion criteria according to metabolic status at study entry (BMI class, exclusion of women with GDM after inclusion, etc.). This should be addressed in future studies. Still, it is promising that it was possible to prevent GDM by lifestyle intervention in the Finnish RADIEL study, where the women were at high risk of GDM and about 30% of them had previous GDM (23). Most studies, however, have not been successful in reducing clinical, maternal, and neonatal outcomes such as GDM, preeclampsia, macrosomia, and preterm birth. These complications may all be associated with an unfavorable metabolic milieu in early gestation, and thus interventions beginning in the second trimester might be too late and of insufficient duration to overcome the negative impact of an early dysmetabolic condition. It has been shown that pre-gestational BMI is a stronger predictor of maternal and neonatal pregnancy outcomes than GWG (44). Women with pre-gestational obesity are more insulin resistant and have higher circulating plasma triglycerides from the beginning of pregnancy compared with lean women (45). It has been suggested that early maternal metabolic conditions program placenta function and gene expression, both factors that may influence later fetal growth. Several observational studies have shown that interpregnancy weight change is important for the risk of complications in the next pregnancy (46–48). Even a minor interpregnancy weight gain increases the risk of GDM, preeclampsia, and macrosomia in the subsequent pregnancy in both overweight and obese women, but in normal-weight women as well (46,49).

A mild to moderate interpregnancy weight loss in obese women has been shown to significantly reduce the risk of subsequent LGA infants in observational studies, without an

increased risk of SGA infants (48). All together, these findings underline the importance of optimizing maternal pre-gestational body weight and the metabolic conditions before conception. The interpregnancy interval may be a crucial period for targeting weight loss in obese women in future studies.

Future Directions

Paradoxically, at a time where obesity in pregnancy presents a massive burden to public health and clinical practice, with huge health issues and maternal and neonatal complications, we have a knowledge gap in terms of how to handle the problems efficiently. To address the clinical issues, there is a need to understand better the underlying metabolic, physiological, and behavioral and psychological mechanisms. We have a vicious cycle of obesity from generation to generation, but exactly where and how to intervene in this circle are yet to be clarified. Follow-up of the offspring after lifestyle intervention in the mothers during pregnancy is very important to provide further insight into the importance of the intrauterine environment and any later impact on the children's metabolism and long-term health issues. Results from detailed follow-up of the offspring of large intervention studies such as the LIMIT and UPBEAT trials are in progress. With the limited impact of behavioral interventions during pregnancy on maternal and neonatal complications, we now face the reality that a pre-conceptional intervention may well be needed to optimize the metabolic status before pregnancy. Such studies are much more challenging to carry out because nonpregnant women are not as readily accessible, and a large proportion of pregnancies are unplanned. Large-scale studies have not yet been published. Based on existing knowledge, it is obvious that to make substantive improvements to the health of the mother and future generations, the approach needs to be expanded beyond the gestational period.

As a minimum, and until any evidence-based regimen on dietary health and physical activity exists, healthcare professionals should encourage (overweight or obese) pregnant women to avoid excess GWG; eat a healthy, varied diet; and be physically active, and they should support women in breastfeeding and weight loss after pregnancy.

Multiple-Choice Questions

1 A number of lifestyle intervention studies have been performed in obese women. Which one of the following statements is true?
   - **A** Lifestyle intervention has consistently shown a reduction in the risk of macrosomia.
   - **B** Lifestyle intervention can reduce gestational weight gain.
   - **C** Lifestyle intervention has consistently shown a reduction in the risk of GDM.
   - **D** Intervention does not affect gestational weight gain.

The correct answer is B.

2 What could be a good strategy for further research in this field?
   - **A** Prospective meta-analyses pooling clinical data to define the subgroups that benefit from different interventions
   - **B** More large RCTs with diet and exercise intervention in obese pregnant women
   - **C** Intervention with exercise only
   - **D** None of the above

The correct answer is A.

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7

Obesity and Diabetes in Pregnancy

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PRACTICE POINTS

- Both gestational diabetes mellitus (GDM) and obesity are independently associated with an increased risk of pregnancy complications and deserve clinical attention.
- Beware of excessive dietary restriction in GDM, sometimes adopted by a woman with GDM to avoid insulin therapy. A weight "plateau" is frequently observed for 2–3 weeks after GDM diagnosis. If ongoing weight loss occurs, the urine should be tested for ketonuria and the diet closely reviewed.
- Avoid oral glucose tolerance tests (OGTTs) within 2–3 days of administration of antenatal glucocorticoid therapy for fetal lung maturation as results are likely to be falsely elevated.

Case History

Suzie, a 38-year-old chef, Gravid 3, Para 1, Miscarriages 2, consults you for preconception care. She has recently remarried. Her new husband is aged 25 years, and the couple wishes to have a child. Her past obstetric history includes a pregnancy 15 years ago previously complicated by GDM and preeclampsia, and which resulted in the birth of a baby girl by cesarean section at 36 weeks gestation weighing 3980 g. Suzie has had two early miscarriages since that time. She has been overweight/obese since childhood and was diagnosed with polycystic ovarian syndrome at age 18 years. Since age 23, she has gained 25 kg to a current weight of 105 kg (height: 168 cm; Body Mass Index [BMI]: 37.2 kg/m^2). Five years ago, she was diagnosed with type 2 diabetes, for which she is taking a combination of metformin 2 g at night and linagliptin 5 mg in the morning. Her most recent HbA1c was 7.0% (53 mmol/mol). She also has a 3-year history of essential hypertension, hypercholesterolemia, and microalbuminuria (800 mg/24 h) and is taking irbesartan 300 mg/day. Her most recent lipid profile was satisfactory on rosuvastatin 10 mg/day. She smokes 30 cigarettes/day. In the past, she gained 10 kg in weight when trying to stop smoking but is currently once again trying to reduce her intake with the use of nicotine transdermal patches. She is using no contraception. Her menses are regular, and a recent luteal phase

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progesterone suggested ovulation. On examination she is obese, BP 140/90 mmHg, with acanthosis nigricans affecting the axillary and neck skinfolds.

- List the issues that increase Suzie's risk of adverse pregnancy outcomes.
- Is pregnancy advisable at this stage, or should she commence reliable contraception pending treatment of her medical problems? If so, what form of contraception would you recommend?
- Which medical problems should receive priority?
- Is her current level of glycemic control satisfactory for a planned pregnancy?
- What alterations would you make to her diabetes treatment regimen?
- Which of her current medications should be stopped in preparation for pregnancy, and which alternative medications would you recommend?
- Which additional potential complications of obesity and diabetes should be specifically considered, and what further testing is required?
- What are the potential advantages and disadvantages of bariatric surgery in this clinical context?

Introduction

Diabetes and obesity are both becoming more common on a worldwide basis, with increased prevalence in high-, middle-, and lower-income countries (1). Compounding these "twin epidemics," women are choosing to have children at later ages, particularly in many developed countries. These factors have led to an increasing prevalence of gestational and preexisting diabetes mellitus in pregnancy (2). Maternal diabetes and maternal obesity are both associated with a similar range of pregnancy complications (3). This chapter aims to consider these risks both separately and in combination to outline their epidemiology, prevalence, and contribution to overall risk of adverse pregnancy outcomes from several perspectives: (1) a clinical case discussion; (2) underlying physiology and pathophysiology; (3) epidemiology; (4) the current evidence base for treatments, emphasizing the results of randomized controlled trials; and (5) the importance of these pregnancy factors for later offspring health.

Definitions

The definition of gestational diabetes mellitus (GDM) has been controversial since the term was first coined by Carrington (4). It is widely recognized that the hormonal changes of pregnancy can convert some normoglycemic women to varying degrees of hyperglycemia. From the very beginnings of the study of GDM, it has also been recognized that women identified with GDM in pregnancy carry a substantial long-term risk of permanent (generally type 2) diabetes (T2DM) (5).

In the modern context, the worldwide population prevalence of T2DM and lesser forms of dysglycemia including impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) have increased dramatically among women of childbearing age (6). Therefore, especially in countries with high T2DM prevalence, many of the cases previously described as GDM (defined as "any form of hyperglycemia first identified in pregnancy" (7)) probably had abnormal glucose metabolism antedating but only identified by testing during pregnancy. Women with pre-pregnancy undiagnosed T2DM have a much higher risk of severe complications in pregnancy (8) and arguably deserve separate classification and urgent medical care.

For this chapter, we have adopted the recently developed International Association of Diabetes and Pregnancy Study Groups (IADPSG) (9) and World Health Organization (WHO) (10) definitions of GDM, which distinguish GDM from those women with oral glucose tolerance test (OGTT) thresholds consistent with diabetes if

Table 7.1 Definitions of gestational diabetes and (overt) diabetes in pregnancy.

Category	IADPSG (mmol/L)	WHO (mmol/L)
"Overt diabetes" (IADPSG) *or* "diabetes in pregnancy" (WHO)	Fasting plasma glucose ≥7.0 Random plasma glucose ≥11.1 (with confirmation) *or* HbA1c ≥ 6.5%/48 mmol/mol	Fasting plasma glucose ≥7.0 2 h plasma glucose ≥11.1 after 75 g glucose load Random plasma glucose ≥11.1 mmol/L with symptoms
Gestational diabetes*	Fasting plasma glucose 5.1–6.9 1 h plasma glucose ≥10.0 2 h plasma glucose ≥8.5	Fasting plasma glucose 5.1–6.9 1 h plasma glucose ≥10.0 2 h plasma glucose 8.5–11.0

Note: WHO uses the collective term *hyperglycemia in pregnancy* to describe the sum of diabetes in pregnancy and gestational diabetes, as defined by their criteria.
* Values obtained with a 75 g oral glucose tolerance test (OGTT).
IADPSG = International Association of Diabetes in Pregnancy Study Groups; HbA1c = glycosylated hemoglobin; mmol/L = millimoles per liter; WHO = World Health Organization.

noted outside pregnancy. The latter category is described as "overt diabetes" (IADPSG) or simply "diabetes in pregnancy" (WHO). The relevant thresholds for glycemic measures defining GDM are shown in Table 7.1.

The definition of obesity is less controversial, with most authorities recognizing the WHO classification (11), while acknowledging both the imperfect precision of Body Mass Index (BMI) as a measure of underlying adiposity and the fact that identical BMI thresholds are not uniformly applicable across all ethnic groups.

Physiology and Pathophysiology

In early pregnancy, maternal metabolism is anabolic and results in maternal fat deposition. In healthy pregnancy, maternal insulin resistance increases throughout the second trimester with a peak in the third trimester due to secretion of placental hormones. In normal women, insulin sensitivity decreases by 50 to 60% from pre-pregnancy to late pregnancy (12). This decrease in insulin sensitivity (or increase in insulin resistance) is usually overcome by increased insulin secretion, ensuring relative normoglycemia.

Increasing insulin resistance shifts maternal metabolism from an anabolic to a catabolic state. In the catabolic state, maternal metabolism becomes more reliant on lipids and ketones. This ensures adequate nutrient supply to the developing fetus. Insulin sensitivity is inversely correlated to maternal plasma free fatty acid levels (13). In addition to an increase in free fatty acid levels, other aspects of maternal lipid metabolism are also altered during pregnancy. Fat oxidation is significantly higher, and a marked hyperlipidemia occurs in late gestation. This includes an increase in the triglyceride content of very-low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL). Maternal plasma cholesterol also rises. The metabolic adaptations of healthy pregnancy are further altered in pregnancies affected by GDM and/or maternal obesity (14).

Glucose Metabolism in GDM and Obesity

In women with pre-pregnancy obesity, the pregnancy-associated rise in insulin resistance further exacerbates preexisting insulin resistance due to obesity. For many obese women, the additional rise in insulin resistance can be counterbalanced by increased insulin secretion. However, when the pancreatic beta cells cannot meet this compensatory

increase in insulin secretion, hyperglycemia ensues and GDM is diagnosed. Pregnancy-induced insulin resistance increases throughout the second trimester, reaching a high steady state at the end of the second trimester coinciding with the recommended time point for GDM testing.

GDM is more prevalent in women with an increased pre-pregnancy BMI. Other women with a reduced insulin secretory potential, for example those with a genetic predisposition to glucose intolerance (e.g., a strong family history of type 2 diabetes), are also at increased risk of developing GDM (15). This is especially true for lean women who develop GDM: these women show a minimal increase in the insulin resistance index (homeostatic model assessment [HOMA]-IR) in GDM compared to non-GDM women, while the index of insulin secretion (HOMA-B) is significantly decreased (16,17). In lean women, family history and plasma triglyceride levels are associated with GDM (16). There are also ethnic differences in the predisposition to the development of GDM, with South Asians having higher HOMA-IR and HOMA-B indices at the start of second trimester and postpartum than Western Europeans independent of their BMI (18).

Even without accompanying GDM, obese women undergoing continuous glucose monitoring demonstrate mild hyperglycemia (19).

Lipid and Adipose Tissue Metabolism in GDM and Obese Pregnancies

Decreased insulin sensitivity leads to increased availability not only of glucose but also of lipids. Obese normoglycemic women and women with GDM have higher triglycerides, higher VLDL-cholesterol, and lower HDL-cholesterol levels than normal-weight normoglycemic women from early pregnancy onward (20,21). Subcutaneous adipose tissue of women with GDM shows lower protein expression for the insulin receptor substrate 1 compared with pregnant women without GDM, whereas levels of insulin receptor substrate 2 are increased in fasting pregnant women compared with nonpregnant women independent of their glucose tolerance (13). The transduction of insulin signaling, especially in mediating the metabolic effects in its target tissues, is critically dependent on the insulin receptor substrates, with insulin receptor substrate 1 being the main substrate in skeletal muscle and adipose tissue and insulin receptor substrate 2 in the liver (22). While the substrates have overlapping functions, they also regulate specific processes and therefore cannot fully compensate for each other (22). Furthermore, in adipose tissue from obese women with and without GDM, gene expression of many genes involved in fatty acid metabolism is decreased (23). This included genes encoding proteins involved in fatty acid uptake and intracellular transport, triglyceride synthesis, lipogenesis, and lipolysis. In late pregnancy, inhibition of lipolysis by insulin through inhibition of hormone-sensitive lipase is less effective. Gene expression for transcription factors that regulate lipid metabolism, including PPARγ, is also reduced in obese pregnant women with GDM (13,23). These alterations in insulin signaling in adipose tissue in women with GDM contribute to the excess insulin resistance seen in GDM. Lower expression of PPARγ in adipose tissue in pregnancy may be a reflection of the "accelerated starvation" with fasting late in pregnancy (13). (See also Chapter 2.)

Inflammation in Obesity and GDM in Pregnancy

The placenta is an active endocrine organ that contributes to the regulation of metabolism in both the mother and the developing fetus. The placenta synthesizes and secretes a large array of hormones, cytokines, and metabolic signaling molecules. Microarray studies of placentas from overweight women with GDM have shown increased expression of genes involved with inflammation and

lipid metabolism but not glucose metabolism (24). In obese pregnancy, the placenta and the adipose tissue both regulate maternal metabolism, although their regulation is not coordinated.

White adipose tissue is not only a repository for lipids but also an active endocrine organ, secreting a wide variety of adipokines and cytokines. In obese pregnancy, there is increased release of inflammatory markers such as interleukin-6 (IL6) and tumor necrosis factor-α (TNFα) from the adipose tissue, which may contribute to the increased levels of insulin resistance present in obese GDM (25). Pre-pregnancy BMI is a determinant of which metabolic fuels are oxidized in pregnancy. In lean women with or without GDM, there is a 55–80% increase in basal carbohydrate oxidation but no change in fat oxidation, whereas obese pregnant women have increased fat rather than carbohydrate oxidation (25). Thus, in obese GDM, lipids may provide additional substrates for fetal lipid synthesis (26), which may potentiate fetal growth and increase the risk of macrosomia.

Pregnancy is also a state of low-grade "meta"-inflammation with the expression of pro-inflammatory cytokines from the placenta and the uterine epithelium (27). The triggers for this inflammatory response are not well understood, but placental debris in the form of microparticles known as syncytiotrophoblast membrane microparticles (STBMs) (28) or exosomes (29) as well as placental-derived signaling molecules may be implicated. As normal pregnancy progresses, the balance between pro-inflammatory and anti-inflammatory cytokines shifts toward the anti-inflammatory cytokines (30). In normal-weight women with GDM, levels of TNFα but not IL6 (both pro-inflammatory cytokines) are increased when compared to matched controls (31). Furthermore, increased leukocyte counts in early pregnancy are predictive of the development of GDM, independent of maternal BMI status (32). However, obesity itself is a state of low-grade inflammation, and obese pregnant women have higher circulating IL6 levels than non-obese women, independent of GDM status (33). The combination of obesity and GDM exacerbates the inflammatory profile in some but not all studies (33), and this may reflect timing of sampling and heterogeneous populations. The inflammatory profile is further complicated by the fact that the placenta can express and secrete cytokines as well; however, it may serve as a buffer to limit fetal exposure to maternal inflammation in response to obesity and GDM (33).

GDM and Obesity – Interrelationships and Common and Divergent Mechanisms

Insulin Resistance

Obesity in pregnancy increases the risk for developing GDM by a factor of 3.0 for moderately obese and by 5.6 for morbidly obese women (34). The prevalence of GDM increases by 0.92% for each 1 kg/m^2 increase in BMI (34). Insulin resistance is a hallmark of both obesity and GDM. Skeletal muscle insulin receptor phosphorylation is reduced by one-third in GDM, but there is no change in receptor number in lean women, whereas in obese women both insulin receptor number and phosphorylation are decreased. All pregnant women have reduced amount and phosphorylation of skeletal muscle insulin receptor (IRS1), the most important and abundant insulin receptor substrate in skeletal muscle, indicating a lower capacity for insulin signaling in pregnancy (35).

Insulin Secretion

In women with preexisting insulin resistance, as seen in obesity, the physiological rise in insulin resistance of pregnancy cannot always be compensated for by increased insulin secretion, predisposing some obese women to develop GDM. This decrease in insulin secretory capacity can be measured by calculating the HOMA-B index or more direct measures such as the intravenous glucose tolerance test.

Epidemiology of GDM and Obesity

Many reports have attempted to dissect the relative clinical and population health importance of GDM and obesity in terms of their effects on pregnancy outcomes and later maternal and infant health. Separation of their associations is difficult, especially as the two conditions frequently coexist and obesity commonly lies on the causal pathway toward hyperglycemia. Furthermore, heterogeneity in study population, screening, treatment, and analysis complicates the interpretation of studies.

Fortunately, these problems were largely addressed by the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study (3,36), in which the caregivers were blinded to the results of a 75 g OGTT performed on average at 28 weeks gestation unless the glucose levels rose above predefined thresholds, leading to the participants being excluded from the study. In addition, no specific intervention was provided for obese women. The HAPO study showed that the associations of increasing maternal BMI and hyperglycemia with pregnancy outcomes were similar. Both were associated with increased rates of the primary outcomes (large for gestational age [LGA] babies, primary cesarean section, clinical neonatal hypoglycemia, and neonatal hyperinsulinemia) and important secondary outcomes including fetal adiposity and preeclampsia. In general, the associations of maternal BMI with these outcomes tended to "plateau" in the highest categories, whereas those of glucose did not show this trend (36). It is important to remember that, for ethical and safety reasons, women were unblinded from the HAPO study if their glucose levels exceeded predefined thresholds, whereas no such limits were enforced for BMI.

The combined associations of BMI and GDM with adverse pregnancy outcomes were also reported (Figure 7.1) (3). Across the HAPO study, obesity was present in 13.7% and GDM by IADPSG criteria (9) in 16.1% of those who remained blinded. Only 25% of the women with GDM were obese. Compared to women with neither GDM nor obesity, the adjusted odds ratios (ORs) for most pregnancy complications were increased both in women with obesity alone and in those with GDM alone. Preeclampsia appeared to be more prevalent in the "obesity alone group," while excess fetal growth and fetal hyperinsulinemia were slightly more common in the "GDM alone group" than in the "obesity alone group." The combination of GDM and obesity was clearly associated with a marked increase in the risk of pregnancy complications (Figure 7.2). The HAPO study was also examined by categorization of BMI into *normal & underweight*, *overweight*, and *obese*, and similar categorization of the composite OGTT *z* scores into *normal*, *intermediate*, and *GDM*. The definition of intermediate glycemia was selected to approximate the frequency of overweight in the HAPO participants.

Some other studies also help to separate the contributions of obesity and GDM to adverse pregnancy outcomes. In a case–control cohort from the USA, untreated lean women with essentially untreated GDM (women with very little to no prenatal care who were diagnosed with GDM at >37 weeks gestation) had a twofold higher risk of the composite outcome of stillbirth; neonatal macrosomia (LGA); neonatal hypoglycemia, erythrocytosis, and hyperbilirubinemia; and a sevenfold increase in metabolic complications (37). These increases in adverse outcomes were similar to those in obese women without GDM. Untreated lean women with GDM also had higher rates of induction of labor and delivery by cesarean section than lean women without GDM. For obese untreated women with GDM, these risks were increased by tenfold for the composite outcome, threefold for an LGA infant, fivefold for metabolic complications, fourfold for induction of labor, and ninefold for delivery by cesarean section. These results suggest that obesity and GDM individually are associated with adverse outcomes but that their combined occurrence significantly increases

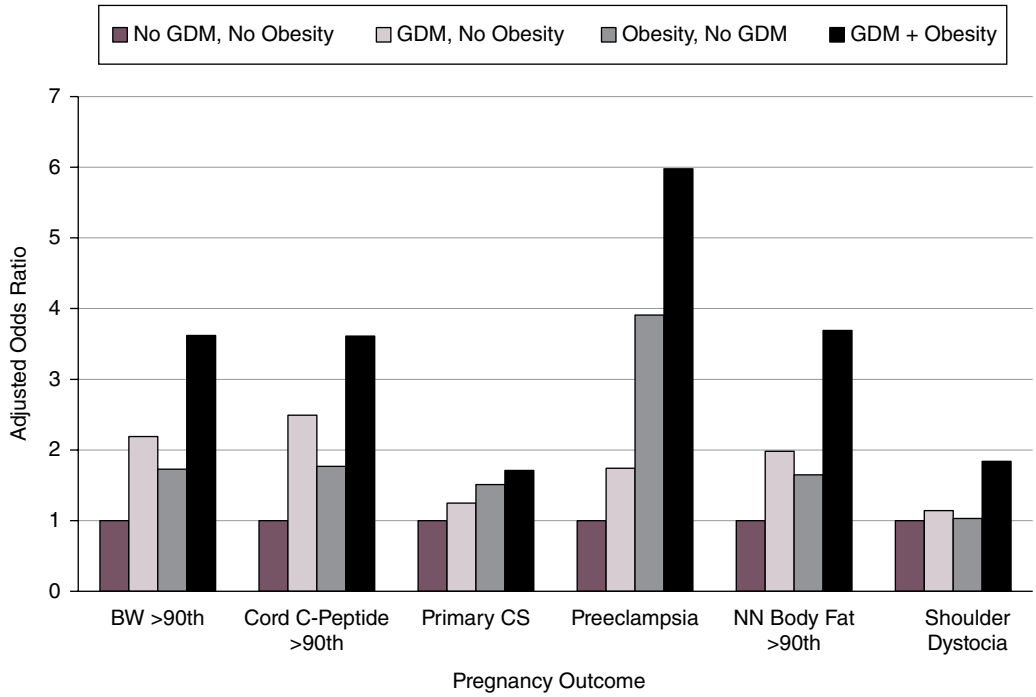

Figure 7.1 Odds ratios for pregnancy complications by obesity and GDM status.
Note: Fully adjusted odds ratios for selected pregnancy complications in the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study (3). The "No GDM, No Obesity" category served as the referent group for all comparisons. The other categories, as labeled, refer to GDM alone, Obesity alone, and the combination of both factors. Odds ratios refer to "Model II" as explained in detail in the source publication, with full adjustment for potential confounders.
GDM = Gestational diabetes mellitus.

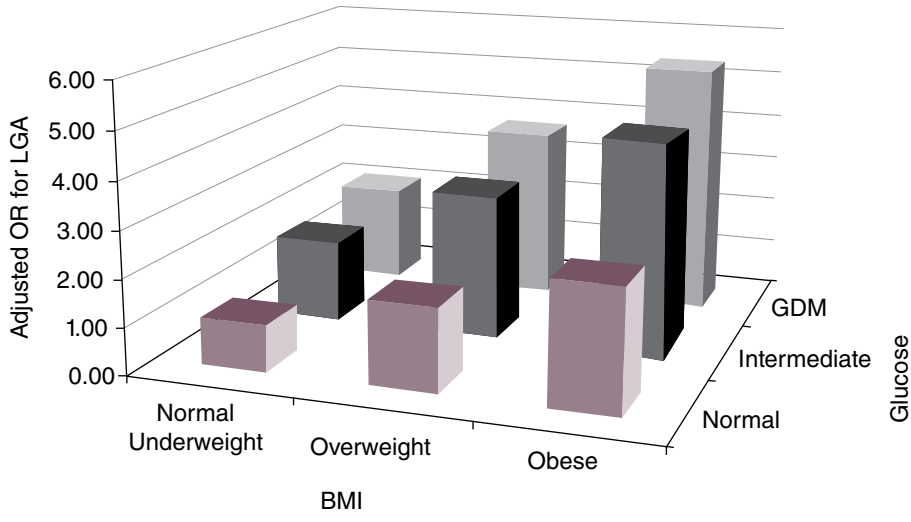

Figure 7.2 Odds ratios for LGA infant divided by three category classifications of glycemia and BMI.
Note: Fully adjusted odds ratios for delivery of an LGA infant, characterized as Birthweight >90th centile in HAPO study participants (3). The group with normal glucose levels and normal- or underweight-range BMI served as the referent group. The intermediate glucose group were defined according to their mean standard deviation (*z*) scores for the fasting, 1 h, and 2 h glucose levels during the diagnostic OGTT. The values used to define this category were chosen to achieve a frequency of intermediate glucose equivalent to the frequency of overweight in the HAPO study cohort (3). BMI was measured at the time of the diagnostic OGTT and converted to equivalent WHO categories by regression analysis.
BMI = Body Mass Index; GDM = gestational diabetes mellitus; HAPO = Hyperglycemia and Adverse Pregnancy Outcome; LGA = large for gestational age; OGTT = oral glucose tolerance test; Uweight = underweight; WHO = World Health Organization.

the risks. However, when treated for GDM, the risks for adverse pregnancy outcomes were reported not to be higher for obese women in general (38) or obese women treated with insulin but not diet (39).

In summary, there is evidence to demonstrate that maternal BMI and glycemia have independent and essentially additive associations with adverse pregnancy outcomes. In view of this, the relative "importance" of these factors is heavily influenced by the potential costs and benefits of preventative or treatment strategies.

Population Risks and Prevention

Another consideration in addressing obesity and GDM is their relative importance across the entire population of pregnant women. A number of studies have attempted to address this issue, but ascertainment bias regarding glycemia in pregnancy and treatment confounding due to active intervention for GDM remain major issues.

A study (40) regarding 9835 women from Southern California with a high prevalence of overweight (32%) and obesity (28%) reported that, on a population basis, overweight and obesity accounted for 21.6% of LGA infants in women without and 23.3% in women with GDM. In their cohort, 75% of women who developed GDM were overweight or obese. This study also emphasized the importance of gestational weight gain as a determinant of LGA, which has also been reported by others and is a potentially modifiable factor (41,42). These conclusions depend heavily on the background population. In the global HAPO study cohort, the prevalence of overweight (22%) and obesity (14%) was much lower (43).

In summary, it is clear that, especially in populations with a high prevalence of overweight and obesity, these factors constitute a large fraction of the population risk of LGA. However, therapeutic strategies for addressing obesity in pregnancy have proved disappointing, in contrast to the positive results noted for "glucocentric" treatment of GDM. (See Chapter 12.)

Evidence Base for Treatment of GDM and Obesity

Two well-designed large prospective randomized controlled studies confirm that diagnosis and treatment of gestational diabetes have short-term benefits for both mother and baby (44,45). Women in the Australian (Crowther) study had early-pregnancy BMIs ranging from 22.9 to 31.2 kg/m^2, and women in the intervention arm of the study had lower weight gain during pregnancy, with less macrosomia, less LGA, and lower rates of preeclampsia (44) than those in the untreated group. In the USA (Landon) study, the BMI at recruitment of women in the treatment arm was 30.1 +/– 5 kg, and in the control arm it was 30.2 +/– 5.1 kg. Once again, in this study, women in the intervention arm had lower weight gain, there were lower rates of LGA and macrosomia in infants, and women had lower rates of preeclampsia than in untreated controls (45).

There are now two large trials sufficiently powered to examine maternal and perinatal outcomes after a lifestyle intervention in overweight and obese women – the LIMIT study (46) and the UPBEAT study (47). The results of both of these trials were disappointing. Essentially, these studies aimed to limit weight gain in overweight and obese pregnant women through lifestyle intervention. Neither study found a difference in rates of GDM or infants born LGA, although the LIMIT study did report a reduction in infants weighing over 4000 g. In addition, the EMPOWaR study of the use of metformin in obese women from early pregnancy, powered to examine changes in birthweight centile, found no difference in birthweight centile or measures of maternal glucose or lipid metabolism (48). Another recent randomized controlled trial of metformin in obese pregnant women demonstrated reduced gestational weight gain and reduced preeclampsia in the treated group, but there was no reduction in the primary outcome of birthweight, nor in the prevalence of GDM (49).

There have been numerous small randomized controlled trials of (usually intensive) lifestyle and other interventions in overweight and obese women that have demonstrated reduced weight gain in pregnancy, and some have demonstrated reduced neonatal weight. These studies have been summarized in meta-analyses (50,51). To date, the benefits seen in these small studies were not replicated when translated in practical interventions that are affordable at a population level (46).

At present, it would appear that diagnosing and treating gestational diabetes in overweight and obese women have the best evidence with regard to limiting weight gain, preventing maternal adverse outcomes, and preventing neonatal adverse outcomes. However, it is important to note that the long-term impacts of any of these interventions on the health of adult offspring are as yet unproven and will need to be carefully examined.

In Utero Exposure to Obesity and GDM, and Later Offspring Health

Birthweight and Body Composition

The Pedersen hypothesis, first proposed in 1952, states that macrosomia (excess fetal growth and adiposity) results from fetal hyperglycemia and hyperinsulinemia due to hypertrophy of fetal islets in response to maternal hyperglycemia (52). Macrosomia can occur even when maternal glucose control appears satisfactory and may be due to increased maternal triglycerides and other lipids (14,20). Maternal obesity is a predictor for higher fetal fat mass (53) and is associated with fetal insulin resistance (54). These results suggest that maternal obesity specifically affects fetal adiposity rather than overall fetal growth. GDM in the absence of obesity is also associated with fetal adiposity (55). Birthweight and fetal fat-free mass are both correlated with maternal insulin sensitivity in late gestation (12).

Longer Term Consequences

Maternal obesity doubles the risk for childhood obesity (56,57) and is associated with metabolic syndrome in the offspring (58). Similarly, children born LGA also have increased risks of developing metabolic syndrome independent of maternal GDM (58,59). In glucose-tolerant Pima Indian mothers who are genetically predisposed to developing type 2 diabetes, maternal glucose levels in the third trimester were strongly associated with increased risk of type 2 diabetes in the offspring (60).

These increased risks in the offspring may largely be determined by a genetic background predisposing to obesity as well as by the postnatal environment related to the family lifestyle. However, some of the increase in risk may result from an altered intrauterine environment "programming" the offspring for later disease, as encapsulated by the Developmental Origins of Health and Disease (DOHaD) theory. Animal models have demonstrated altered epigenetic regulation in many regulatory and metabolic organs in the offspring, including brain, liver, pancreas (61), and adrenals, in response to maternal obesity and hyperglycemia in pregnancy and lactation. In humans, long-term effects of the intrauterine environment have been reported with maternal undernutrition in the Dutch hunger winter study (62). The intrauterine environment may therefore affect the health of the offspring long beyond the immediate perinatal period.

For the mother, GDM is associated with higher risks of future hypertension, impaired glucose tolerance, and hyperlipidemia, which are all components of metabolic syndrome (59). These increased risks are especially pronounced in women who were obese prior to pregnancy (59).

Other Effects on Offspring

Beyond excessive intrauterine growth, other significant complications may affect infants born to women with diabetes mellitus and women with obesity. There are similarities

and differences in these risks, and the maternal conditions of diabetes mellitus and obesity are synergistic in their effects on the infant.

Infant of Diabetic Mother

Congenital Malformations

The association of maternal pre-gestational diabetes with increased rates of congenital malformations has long been recognized. This risk is clearly related to glycemic control around the time of conception and during organogenesis. In meta-analysis, the relative risk of major congenital malformations is increased in women with pre-gestational diabetes mellitus by 2.7-fold (63). Recent population registry studies show persistent increased rates of congenital malformations in women with type 1 diabetes, which are increased further in women with type 2 diabetes (64).

Infant of Obese Mother

Congenital Malformations

Maternal obesity is itself associated with increased rates of congenital malformations. A recent systematic review demonstrated a positive association between increasing maternal obesity and congenital heart defects. The relation was similar for moderate and severe obesity with increases by 1.15 and 1.39, respectively, independent of diabetes mellitus status. However, for women who were overweight, there was an association (OR: 1.08) but only when women with diabetes were included in the analysis (65). An analysis of the Florida Birth Defects Registry showed an increase in prevalence of birth defects in live-born infants, increasing from 3.9% in underweight women to 5.3% in obese women with BMI >40 (66). Studies have shown a positive dose–response relationship for most birth defects with maternal obesity, with the exception of gastroschisis (66). Additionally, maternal obesity decreases the chance of detecting congenital anomalies antenatally by 23% in obese women (67).

Effects on Neonatal Complications

In addition to excess adiposity, offspring of obese women have been found to be more metabolically unhealthy at birth, with greater HOMA-IR, leptin, and IL6 measured in cord blood (54). Adiposity assessment using anthropometric measures and total body electrical conductivity demonstrated a marginal increase in birthweight, no change in lean body mass, but a significant increase in percent body fat from 9.7 to 11.6% in neonates born to overweight or obese women (53). The risk of LGA infants is increased with increasing maternal weight gain in obesity (68). When adjusted for weight gain in pregnancy, the odds for LGA was increased for normal-weight women with GDM by 1.96, by 2.63 for only obese women, and by 5.47 for obese women with GDM when compared to normal-weight, euglycemic women (69).

Infants born to obese and morbidly obese women are at increased risk of neonatal hypoglycemia, and infants of morbidly obese women are also at increased risk of premature delivery, admission to intensive care, and jaundice (70).

Combined Exposures – Infants of Mothers with Both Diabetes and Obesity

The effects of maternal diabetes mellitus and maternal obesity are both additive and independent. Treating maternal diabetes and minimizing maternal weight gain may ameliorate the impact of both on the infant.

Effects on Body Composition and Size

In the setting of GDM, maternal weight and fasting glucose at OGTT are independently associated with birthweight, and only maternal weight at delivery significantly and independently predicted LGA (71). In women with type 1 diabetes, maternal BMI is not associated with a change in prevalence of LGA, but women with type 2 diabetes, overweight women, and obese women are more likely to have an LGA infant (72). However, maternal gestational weight gain influences the risk of

LGA in women with type 1 diabetes, with each 450 g per week increase being associated with a 4% increase in odds of an LGA infant (72). In women with type 1 diabetes, infant birthweight rose with increasing maternal weight gain even after adjusting for maternal BMI, HbA1c at 36 weeks, smoking, parity, and ethnicity (73). A similar study in women with type 2 diabetes showed infant birthweight 0.5 kg higher in women with excessive gestational weight gain than in those with recommended gestational weight gain (74).

Summary and Future Research

GDM and maternal obesity are associated with a similar spectrum of adverse pregnancy outcomes, especially those related to excessive fetal growth and adiposity and to hypertensive complications. GDM and obesity commonly, but not inevitably, coexist, and the development of common preventative and therapeutic strategies seems an attractive prospect.

Despite data showing associations of GDM and obesity with adverse pregnancy outcomes, our understanding of the mechanisms underlying these associations remains limited. The Pedersen hypothesis has served as a useful framework for considering the pathogenesis of hyperglycemia in pregnancy (21), but even our most energetic approaches to achieving normoglycemia have not normalized pregnancy outcomes, particularly with the addition of obesity as a comorbid condition. Specific therapy targeting pregnancy dyslipidemia in GDM and obesity seems attractive, but it is difficult in practice due to safety concerns (14). The exploration of metabolic inflammation and its consequences in pregnancy may also improve our mechanistic understanding (26,75,76), but again the current therapeutic options appear to be limited.

Interventions commenced during pregnancy appear to have limited efficacy in preventing the complications of obesity. This aligns with the observation that, in obese women (in contrast to women of normal weight), pre-pregnancy weight is more closely associated with neonatal adiposity than weight gain during pregnancy (77). Thus, preventative and therapeutic measures may need to be initiated preconception to reap positive benefits.

By contrast, the efficacy of therapy for GDM is well demonstrated. Effective implementation of GDM diagnostic and therapeutic strategies (78–80) currently appears to have the greatest potential for overall benefit.

Future research should concentrate on the delineation of the pathogenesis of obesity and GDM through basic and clinical studies; the development of effective strategies to target both conditions before, during, and after pregnancy; and the effective implementation of treatments that are known to be effective but are currently underutilized.

Multiple-Choice Questions

1 Which of the following measurements is (on average) lower in obese than in lean pregnant women?
   - **A** Serum leptin
   - **B** Body Mass Index
   - **C** Serum adiponectin
   - **D** Fasting serum insulin
   - **E** Homeostasis model assessment–insulin resistance (HOMA-IR)

Answer: Serum adiponectin (option C). This cytokine is associated with a "healthy" metabolic profile, and lower serum concentrations are found in obesity both during and outside pregnancy.

2 Which of the following statements regarding oral glucose tolerance testing (OGTT) in pregnancy is correct?

A Excess carbohydrate intake must be avoided for 5 days prior to the OGTT.
B The OGTT clearly identifies all women with LGA infants.
C All OGTT values (fasting, 1 h, 2 h, and 3 h) are generally tightly correlated.
D OGTT results are highly reproducible.
E Use of glucose polymer produces less nausea and vomiting than use of glucose monomer.

Answer: E is correct, although glucose monomer was used in the HAPO study and is more widely available.

3 Regarding obesity and GDM, which of the following statements is correct?
A Obesity is not associated with pregnancy complications in the absence of GDM.
B GDM is not associated with pregnancy complications in the absence of obesity.
C Obesity and GDM generally have additive effects in terms of the risk of pregnancy complications.
D On a population basis, GDM contributes more to the risk of large-for-gestational-age (LGA) babies than obesity.
E Highly effective treatments are available for obesity in pregnancy.

Answer: C is correct. Both obesity and GDM are associated with increased pregnancy complications, and their effects are generally additive (rather than synergistic or multiplicative). In most populations, obesity contributes more to population LGA risk than GDM.

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8

Metabolic Abnormalities in Gestational Diabetes

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PRACTICE POINTS

- Women who develop gestational diabetes mellitus (GDM) have an elevated risk of developing both type 2 diabetes and cardiovascular disease in the future.
- Compared to their peers, women who develop GDM are at increased risk of multiple metabolic abnormalities beyond pre-diabetes or diabetes. These abnormalities include metabolic syndrome, dyslipidemia, hypertension, subclinical inflammation, and dysregulation of adipokines.
- In a woman with a history of GDM, it is important to consider her modifiable cardiometabolic risk factors, such blood pressure, lipids, and weight control.

Case History

A 41-year-old woman is seeing her new family doctor for an initial consultation. She has no acute medical concerns currently. She is currently on no medications. Her past medical history is significant only for gestational diabetes mellitus (GDM) in her only pregnancy, which was 3 years ago. There is a family history of type 2 diabetes mellitus (T2DM) in her mother. The patient is married with one child, and works as a banker. On examination, weight was 70 kg with Body Mass Index 26.3 kg/m^2. Blood pressure was 130/80 mmHg with heart rate 72 beats per minute. Her exam was otherwise unremarkable.

The patient is very proactive toward her healthcare and recognizes that it is important to inform her new family doctor of her history of GDM. The patient understands that, based on her history of GDM, she is at risk for the development of T2DM in the future. Indeed, she appropriately underwent postpartum glucose tolerance testing after her pregnancy, which showed normal glucose tolerance at the time. The question she poses today is whether or not her history of GDM indicates that she could be at risk for other metabolic disorders besides T2DM.

Gestational Diabetes Mellitus: A Chronic Metabolic Disorder

Although it is diagnosed on the basis of hyperglycemia in pregnancy, gestational diabetes mellitus (GDM) identifies a population of women with multiple metabolic abnormalities beyond dysglycemia alone (1). Importantly, many of these metabolic defects are present during pregnancy and may persist thereafter. Indeed, the differences in metabolic function between women with a history of GDM and their peers are often

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more readily apparent after the pregnancy than during gestation. Furthermore, there is a growing body of evidence pointing to clinical and metabolic differences *prior to* gestation in women who will go on to develop GDM when they are pregnant, as compared to women who will maintain normal glucose tolerance in pregnancy (2). Accordingly, it is now emerging that GDM is likely a chronic metabolic disorder that presents clinically in pregnancy but is characterized by metabolic dysfunction that continues long after gestation and likely precedes it. The prototypical example of this pathology is the chronic beta-cell dysfunction and insulin resistance that contribute to both the development of GDM and the subsequent risk of postpartum progression to type 2 diabetes mellitus (T2DM) (reviewed in Chapters 9 and 27) (3–5). In this chapter, we will review current understanding of the other metabolic abnormalities associated with GDM, besides beta-cell dysfunction and insulin resistance.

Metabolic Syndrome in Women with GDM

The metabolic syndrome is a construct that describes the concomitant clustering of specific cardiometabolic risk factors in an individual. Although various definitions of the metabolic syndrome have been proposed by different organizations, the component risk factors generally include central obesity, glucose intolerance, hypertension, hypertriglyceridemia, and low levels of high-density-lipoprotein (HDL) cholesterol (6). Since its introduction, the metabolic syndrome has been a touchstone for controversy and debate regarding its diagnostic criteria, pathophysiologic basis, clinical utility, and even its very existence (6). These issues notwithstanding, it is nevertheless clear that the patient population identified by this syndrome is at high risk of developing T2DM and cardiovascular disease (6). Thus, there exists a resemblance to GDM, which itself identifies a population of women at risk of ultimately developing both of these conditions (7–10). As such, it follows that the relationship between GDM and metabolic syndrome warrants consideration.

Several studies have consistently shown an increased prevalence of metabolic syndrome in women with a history of GDM (11–14). For example, in Danish women at a median 9.8 years postpartum, the prevalence of metabolic syndrome (as defined by World Health Organization criteria (6)) was reported to be 38.4% in those with a history of GDM, as compared to 13.4% in their peers who had not had GDM (11). The age- and Body Mass Index (BMI)-adjusted odds ratio for having the metabolic syndrome was 3.4 (95% confidence interval [CI]: 2.5–4.8) for the women with previous GDM versus controls (11). Similarly, in a US study population at 11 years postpartum, the prevalence of metabolic syndrome (as defined by National Cholesterol Education Program–Adult Treatment Panel III criteria (6)) was 27.2% in women with previous GDM, compared to 8.2% in comparators (12). Overall, a recent meta-analysis of 17 studies involving 5832 women confirmed a significantly higher risk of metabolic syndrome after a pregnancy complicated by GDM (odds ratio: 3.96; 95% CI: 2.99 to 5.26) (13).

Importantly, this increased risk of metabolic syndrome is evident as early as 3 months after delivery, with prevalence rates of 20% (by International Diabetes Federation criteria) and 16.8% (by American Heart Association/National Heart Lung and Blood Institute criteria) reported at that time (14). This increased risk of metabolic syndrome in women with a history of GDM exists after adjustment for covariates, including BMI (14). Its presence so early in the postpartum period thus raises the question of whether this disorder afflicts women with GDM during pregnancy as well. The absence of established criteria for diagnosing metabolic syndrome in the gravid state precludes direct evaluation of this possibility. Nevertheless, a cross-sectional study by Clark *et al.* showed that, at the time of antepartum glucose tolerance testing, women who are diagnosed with

GDM do indeed exhibit features of metabolic dysfunction, including low HDL cholesterol and elevated triglycerides (15).

Collectively, these data have led to the hypothesis that GDM may represent a latent metabolic syndrome (2,15). Accordingly, the relationships between GDM and the individual components of the syndrome are of interest. While the risks of central obesity and dysglycemia in women with GDM are discussed elsewhere in Chapters 9 and 27, the ensuing sections of the current chapter will focus on dyslipidemia and hypertension, in addition to emerging nontraditional markers of metabolic dysfunction, namely subclinical inflammation and adipokine dysregulation.

Lipid Profiles in Women with GDM

Owing to the need for cholesterol and essential fatty acids in fetal development, there is a physiologic upregulation of lipoprotein fractions in pregnancy. The resultant hyperlipidemia occurs in response to the hormonal milieu of pregnancy (particularly estrogen) and supports the delivery of lipids to the placenta and fetus (16). Accordingly, serum triglycerides and low-density-lipoprotein (LDL) cholesterol are elevated in pregnancy, while HDL peaks in mid-gestation and declines thereafter (16). In this context, previous studies have reported varying findings with respect to the impact of GDM on lipid profile in pregnancy, although it is generally found that triglycerides are higher and HDL cholesterol is lower in women with GDM than in their peers (16–18). The fetal implications of these differences, however, remain uncertain. Some investigators have reported an association between higher maternal triglyceride concentration and increased fetal fat mass or birthweight, but this has not been consistently observed in all studies (16,19,20). In this context, comparisons between studies have been limited by differences in glucose tolerance criteria/strata, modest sample sizes, and varying degrees of covariate adjustment.

While the physiologic adaptations to the gravid state may obscure differences in lipid profile between women with and without GDM during pregnancy, such differences are apparent in the years after pregnancy. These differences included lower HDL and higher levels of LDL cholesterol, triglycerides, and liver fat content (14,18,21,22). Furthermore, as with the metabolic syndrome, lipid differences between women with and without GDM are readily detectable by as early as 3 months postpartum (18). Indeed, in a study of 482 women reflecting the full spectrum of gestational glucose tolerance who were assessed both in pregnancy and at 3 months postpartum, there was little difference in the lipid profile between gestational glucose tolerance groups (ranging from normal to GDM) in the late second and early third trimesters, whereas clear gradients were apparent postpartum (18). Most notably, on multiple linear regression analyses, GDM emerged as an independent predictor of postpartum total cholesterol, LDL, triglycerides, total cholesterol–to-HDL ratio, and apolipoprotein B (apoB), and an inverse predictor of HDL cholesterol. While hypertriglyceridemia and low HDL are typical features of the dyslipidemia seen in T2DM and hence might be anticipated in women with GDM (i.e., given its pathophysiologic and clinical relationship with T2DM), the findings of increased LDL and apoB are particularly noteworthy. Specifically, these observations (detectable even in the early postpartum period) raise the possibility that women with GDM may have a chronic atherogenic dyslipidemia that may be a factor contributing to their elevated risk of cardiovascular disease, which has been shown to manifest by 11–12 years after the index pregnancy (9,10).

Other elements of lipid physiology in GDM may support this hypothesis. First, as compared to their peers, women with GDM have (1) lower mean LDL particle size; (2) a preponderance of small, dense LDL particles;

and (3) an altered distribution of LDL subspecies characterized by an increased proportion of the very small LDL IVA and LDL IVB subclasses (23,24). Small dense LDL is known to be susceptible to oxidation and thereby contributes to endothelial dysfunction and atherosclerosis. Accordingly, it is notable that women with GDM have been shown to have an increased susceptibility of LDL to oxidation across all three trimesters of pregnancy (25). While absolute LDL concentrations may not appear to be markedly elevated, the model potentially emerging from these data is that chronic exposure over many years to the combination of higher LDL levels and enhanced oxidative susceptibility may contribute to increased long-term cardiovascular risk in women with a history of GDM (18).

Blood Pressure in Women with GDM

Hypertensive disorders of pregnancy can be classified into four groups: (1) chronic hypertension, (2) gestational hypertension, (3) preeclampsia or eclampsia, and (4) preeclampsia superimposed on chronic hypertension (26,27). There are several associations between GDM and these disorders. First, GDM and hypertensive disorders of pregnancy share several common risk factors, including major clinical determinants of diabetic risk such as increased maternal age, obesity, ethnicity, and family history (26). Second, GDM itself has been associated with an increased risk of hypertension in pregnancy (27). Third, elevated blood pressure in early pregnancy can predict an increased risk of subsequent GDM after adjustment for covariates, including age, ethnicity, BMI, and parity (28). While the etiologic basis of relationship between GDM and hypertension is not certain, insulin resistance has been proposed as a factor that could contribute to the pathophysiology of both conditions (29).

In the years after delivery, several studies have reported higher blood pressure in women with previous GDM, compared with those without such a history (14,30,31). Again, as with metabolic syndrome and dyslipidemia, this difference can be detected as early as 3 months postpartum (14). Furthermore, like GDM, hypertensive disorders of pregnancy predict an increased future risk of both T2DM and cardiovascular disease in the mother in the years after pregnancy (32). Thus, taken together, these data support a chronic link between GDM and hypertension both during and after pregnancy, with the presence of these metabolic abnormalities identifying a population of women at elevated lifetime risk of cardiometabolic disease.

Inflammation in Women with GDM

Chronic low-grade inflammation is a pathologic effect of central obesity (particularly the expansion of visceral fat mass) that is characterized by elevated circulating concentrations of inflammatory biomarkers such as C-reactive protein (CRP). This subclinical systemic inflammatory response has been shown to predict the future development of T2DM and cardiovascular disease (33). Accordingly, there has been interest as to the relevance of the inflammatory biomarker profile of women to the future cardiometabolic risk of this patient population.

In prospective nested case–control studies, increased CRP concentrations in the first trimester were associated with an increased risk for the subsequent development of GDM (34,35). This relationship is not significant after adjustment for BMI, similar to the attenuation that has been observed in studies linking subclinical inflammation with T2DM outside of pregnancy (34). Later in pregnancy, women with GDM have been reported to exhibit increased CRP concentrations in some but not all cross-sectional studies (36,37).

While the basis for these conflicting findings is not certain, it has been suggested that they may relate to maternal obesity, which appears to be the dominant determinant of subclinical inflammation in pregnancy. In this context, it should be noted that CRP concentrations in pregnancy are independently associated with fasting insulin (an indirect measure of hepatic insulin resistance), after adjustment for covariates, including BMI (37). Taken together, these data potentially suggest that maternal obesity mediates a chronic low-grade inflammatory response, which in turn contributes to adverse metabolic sequelae such as increased insulin resistance and glucose intolerance in pregnancy (37).

Several studies have now reported that, in the years after the index pregnancy, women with a history of GDM exhibit elevated circulating levels of inflammatory biomarkers, including CRP, sialic acid, and plasminogen activator inhibitor-1 (38–41). These studies have also consistently noted the relationship between CRP and central obesity. For example, in the Third National Health and Nutrition Survey Examination, differences in CRP between women with and without a history of GDM were not significant upon adjustment for waist circumference (38). Thus, while subclinical inflammation appears to be a chronic feature of women with GDM, it remains unclear whether this finding is entirely due to visceral fat and central obesity.

Adipokine Dysregulation in Women with GDM

Another known pathologic effect of obesity in the general population is dysregulation of fat-derived proteins or adipokines. Analogous to the dominant role of CRP in inflammation, the best studied adipokine is adiponectin, a collagen-like protein that circulates at high concentrations and has putative insulin-sensitizing, anti-atherogenic, and anti-inflammatory properties (42). Weight gain and increased visceral fat mass can contribute to (or are associated with) a reduction in circulating adiponectin levels, the significance of which is demonstrated by longitudinal studies consistently showing that baseline hypoadiponectinemia can predict the development of T2DM (42). Low circulating adiponectin levels have been consistently reported in women with GDM, as compared to those without GDM (42–46). Furthermore, several lines of evidence have raised the possibility that hypoadiponectinemia may play a pathologic role in GDM. First, low adiponectin in pregnancy has been independently associated with both beta-cell dysfunction and insulin resistance (43,44). Second, these effects have been specifically linked to the high-molecular-weight (HMW) form of adiponectin in women with GDM (i.e., the circulating multimeric form of adiponectin that is believed to mediate the putative antidiabetic effects that have been attributed to this adipokine) (45). Third, hypoadiponectinemia in the first trimester independently predicts the development of GDM later in pregnancy, after adjustment for known GDM risk factors (46).

As with other metabolic features of GDM, the presence of adipokine dysregulation may also extend beyond pregnancy. Women who had GDM have lower levels of adiponectin than their peers in the first year postpartum (39). Moreover, hypoadiponectinemia (i.e., low circulating adiponectin in women with GDM) has been linked to postpartum elevations in plasma glucose, insulin resistance, and beta-cell dysfunction, after adjustment for covariates (including obesity) (47). Most importantly, low adiponectin is reported to be an independent predictor of deterioration of beta-cell function in the years following a pregnancy complicated by GDM (48). Accordingly, hypoadiponectinemia may be an independent factor in the progression to T2DM in this patient population.

Metabolic Abnormalities Before Pregnancy and in Early Gestation Prior to the Diagnosis of GDM

A recurring theme that has emerged in recent years is that metabolic abnormalities are readily apparent in women with GDM within the first year after delivery, raising the possibility that they reflect long-standing metabolic dysfunction that may precede the clinical diagnosis of GDM in this patient population. This concept is supported by a growing body of evidence of metabolic perturbations early in pregnancy in women who will go on to later develop GDM. Indeed, at 15 weeks gestation, the amniotic fluid of women who will go on to develop GDM exhibits altered levels of amniotic fluid glucose, insulin, and insulin-like growth factor-binding protein-1 (49). Furthermore, in the first trimester, serum levels of various biomarkers have been reported to predict the subsequent development of GDM later in pregnancy. These factors have included lipids (increased triglycerides and low HDL), CRP, hypoadiponectinemia, and elevated tissue plasminogen activator antigen (17,28,34,35,46,50). Accordingly, there has recently been considerable interest in metabolic features prior to pregnancy that may identify women who are likely to develop GDM during pregnancy. To date, the following pre-gravid metabolic and clinical factors have been reported to predict GDM after varying degrees of covariate adjustment: elevated fasting glucose, fasting insulin, BMI, triglycerides, blood pressure, gamma-glutamyl transferase, and lower concentrations of adiponectin as well as low levels of HMW adiponectin (28,51–56). Taken together, these data support the concept that a phenotype of metabolic dysfunction is present well before pregnancy in women who will go on to develop GDM (2). This metabolic phenotype before, during, and after pregnancy is summarized in Table 8.1.

Future Perspectives

There are themes arising from the recognition of the chronic nature of metabolic dysfunction in women with GDM that will have implications for future research in coming years. First, it is anticipated that an area of future research interest will be the metabolomic and proteomic characterization of this patient population. Second, careful study design will be needed to identify the metabolic implications attributable to GDM per se, independent of potentially confounding conditions, particularly obesity/overweight and prediabetes/diabetes (57). Third, this research is likely to reveal new determinants of metabolic

Table 8.1 Summary of metabolic abnormalities that have been demonstrated in women with GDM with respect to their timing before, during, and after the index pregnancy.

Metabolic abnormalities	Before pregnancy	During pregnancy	After pregnancy
Metabolic syndrome			+
Elevated LDL cholesterol			+
Low HDL cholesterol		+	+
Elevated triglycerides	+	+	+
Hypertension	+	+	+
Obesity/overweight	+	+	+
Subclinical inflammation (CRP)		+	+
Hypoadiponectinemia	+	+	+

function, such as the recent emergence of fetal sex as a previously unrecognized factor affecting maternal glucose metabolism in pregnancy (58–60). Ultimately, the detailed longitudinal characterization of women with GDM is likely to yield novel insights into the pathophysiology of metabolic and vascular disease that may inform strategies for the modification of metabolic risk in this population. Furthermore, in clinical practice, recognition of the metabolic abnormalities that may be present in women with a history of GDM underscores the importance of screening for cardiovascular risk factors and encouraging healthy lifestyle practices in this high-risk patient population.

Multiple-Choice Questions

1 If they could be tested longitudinally, at which of the following timepoints would women who develop GDM generally be found to have metabolic abnormalities?
   - **A** Only when pregnant
   - **B** Only after pregnancy
   - **C** Before and during pregnancy
   - **D** Before, during, and after pregnancy

Answer: D.

2 As compared to their peers, lipid abnormalities that have been demonstrated in women with a history of GDM in the years after the index pregnancy include:
   - **A** Elevated triglycerides and low HDL cholesterol
   - **B** Higher LDL cholesterol
   - **C** Higher apolipoprotein-B
   - **D** All of the above

Answer: D.

3 In the years after the index pregnancy, women with a history of GDM exhibit an increased incidence of which of the following?
   - **A** Type 2 diabetes
   - **B** Cardiovascular disease
   - **C** Metabolic syndrome
   - **D** All of the above

Answer: D.

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9

Maternal Risk After the Gestational Diabetes Mellitus Pregnancy

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PRACTICE POINTS

- Women with gestational diabetes mellitus (GDM) have an increased risk for GDM in future pregnancies as well as subsequent type 1 and type 2 diabetes.
- Postpartum glucose testing should be performed soon after delivery. While traditionally performed at approximately 6 weeks postpartum to coincide with the postpartum visit, earlier testing may be appropriate if it is unlikely a woman will attend the visit.
- Recommendations on the optimal postpartum glucose test vary, reflecting concerns regarding sensitivity, compliance, and cost. Women who were diagnosed with GDM on the basis of an elevated post-challenge glucose level may benefit from postpartum testing that includes a post-challenge glucose.
- Postpartum weight reduction through increased physical activity and improved dietary quality may reduce postpartum glucose levels.
- Family planning choices and breastfeeding behavior may alter a woman's postpartum risk of recurrent GDM and subsequent type 2 diabetes.

Pitfalls

- Women with GDM need to be informed that they have an increased risk of diabetes after delivery.
- While hemoglobin A1c (HbA1c) is often used to detect diabetes early in pregnancy, HbA1c may have reduced sensitivity for diabetes detection in the weeks following delivery.
- Lifestyle change immediately postpartum has not yet been shown to reduce subsequent diabetes risk. However, weight reduction through increased physical activity and healthy eating should be encouraged due to the strong associations between postpartum weight and diabetes risk.
- Progestin-only contraception is often prescribed postpartum due to concerns regarding impact of the combined pill on breast milk production, but this form of contraception may increase diabetes risk in women with lactational amenorrhea.

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Case History

A 34-year-old white gravida 2 para 2 presents for postpartum care 8 weeks after delivery. Prior to this pregnancy, she had a Body Mass Index (BMI) of 28 kg/m^2 (i.e., overweight according to Institute of Medicine [IOM] guidelines (1)) but her medical history was otherwise unremarkable. The pregnancy was complicated by GDM, which was diagnosed on a routine screening, using a 75 g oral glucose tolerance test (OGTT) at 25 weeks gestation. Fasting plasma glucose (FPG) was 4.8 mmol/l (86 mg/dl), 1 h glucose was 10.5 mmol/l (189 mg/dl), and 2 h glucose was 8.3 mmol/l (149 mg/dl). During the remainder of pregnancy, her self-monitored capillary blood glucose levels remained within target with diet and physical activity. Due to prior cesarean section, the infant was delivered by planned cesarean section at 38 weeks.

At the postpartum visit, her BMI was 31 kg/m^2 (i.e., obese according to IOM (1) guidelines). She reported difficulty with breastfeeding after her cesarean section, but was able to use a breast pump successfully. She was not able to exercise due to discomfort from the surgery. She and her partner had not yet engaged in sexual intercourse, but she was interested in using another form of contraception that would not require condoms. She volunteered that she would like to conceive again in about a year.

- For which complications is she at risk due to her GDM diagnosis?
- What type of postpartum contraception would you recommend?
- What postpartum glucose testing would you recommend?
- What postpartum lifestyle modifications would you recommend?

Introduction

After delivery, GDM is associated with adverse health outcomes for the mother. These outcomes include GDM in future pregnancies, type 1 and type 2 diabetes, abnormal cardiovascular risk factors, and cardiovascular events. Thus, screening for glucose intolerance postpartum and lifestyle modification are recommended. However, the optimal ways to implement these practices are not clear. In this chapter, we summarize the risks of metabolic abnormalities after the GDM delivery, recommendations for glucose testing, and the scientific literature regarding benefits of lifestyle change.

Maternal Sequelae of GDM After Delivery

Women with a GDM pregnancy are at risk for GDM in their future pregnancies (2). In one study of approximately 65,000 women (3), the prevalence of GDM in the second pregnancy was 41% versus 4% in women with and without GDM in their first pregnancy.

Type 2 diabetes comprises the major type of diabetes diagnosed in postpartum GDM women. In a meta-analysis (4), women with previous GDM had a sevenfold increased risk of diabetes compared to women without GDM. The risk may be particularly marked in the first 5 years postpartum (5), reflecting in part women who had unrecognized diabetes prior to pregnancy. Women with a greater number of elevated fasting or post-challenge values prenatally are at greater risk for diabetes (6,7), as are nonwhite women (particularly Asians) (3,8) and women who require insulin therapy during pregnancy (9). Women with a history of GDM also have elevations in other cardiovascular risk factors including blood pressure (6,10–13) and unfavorable changes in lipid levels (6,10–14). GDM is also associated with increased risk of future cardiovascular events (15–17), although the risk appears to be primarily among women who progress to diabetes.

After delivery, women with GDM pregnancies are also at increased risk for type 1

diabetes, the prevalence of which reflects the prevalence of type 1 diabetes in their racial/ethnic group (18). Thus, type 1 diabetes is most often reported in northern European women (19). For example, in a cohort of Finnish women followed for 6 years after delivery, 5% developed type 1 diabetes and 5% developed type 2 diabetes (19). Type 1 diabetes risk is particularly elevated among women with detectable serum islet-cell autoantibodies during pregnancy (20,21) and 1–2 years after delivery (22), suggesting it is a defect in insulin secretion rather than the insulin resistance that characterizes type 2 diabetes (22).

Recommendations for Postpartum Glucose Screening

Due to the increased risk of impaired glucose regulation, women with previous GDM should undergo glucose testing postpartum. Recommended tests include an FPG only versus a 75 g OGTT versus an HbA1c or a combination of these tests (23–27), with variations reflecting a balance between the greater convenience and precision of the fasting glucose versus the greater sensitivity of the OGTT. These strategies have not been compared regarding their ability to distinguish between women who have subsequent adverse outcomes postpartum: the OGTT will diagnose a greater proportion of women with diabetes due to detection of women who have isolated post-challenge hyperglycemia, but it is not known whether these women, once identified and treated, will then have lower risks of microvascular and macrovascular complications, as well as complications in future pregnancies.

Since the postpartum visit occurs at approximately 6 weeks, recommendations for glucose screening largely focus on this visit with periodic screening thereafter. Of note, however, is the fact that postpartum attendance rates are reportedly poor, and at least one report suggests that testing prior to 6 weeks results in similar glucose values (28). While adherence would be expected to be higher for an FPG rather than an OGTT due to the need for only a single blood draw and the absence of a glucose challenge, this has not been demonstrated. Currently, the American Diabetes Association does not recommend the use of hemoglobin A1c (HbA1c) at the 6-week postpartum visit due to its weak correlation with concurrent blood glucose levels and hypothetical confounding by prenatal therapies, fluid shifts, and alterations in maternal red cell turnover (29). Moreover, in one report, HbA1c did not improve sensitivity and specificity of FPG compared with a single 75 g OGTT at 1-year postpartum (30). In contrast, the National Institute for Health and Care Excellence (NICE) recommends either an HbA1c or a fasting glucose, noting that the HbA1c measurement requires no fasting and therefore compliance might be improved (27).

It is unknown how the 2 h 75 g OGTT compared to the 3 h 100 g OGTT would affect the prevalence rates of postpartum glucose tolerance. One might anticipate that lower glucose thresholds required for GDM diagnosis during pregnancy would result in lower risk for the diagnosis of diabetes using routine WHO criteria after pregnancy, thus minimizing the benefit of more intensive testing postpartum. This principle is illustrated by one report (31) that compared the prevalence of postpartum impaired glucose regulation among women diagnosed with GDM using the Carpenter and Coustan criteria compared with the National Diabetes Data Group criteria, the latter of which identifies fewer women as having GDM. While the prevalence of GDM increased by approximately 50%, the additional populations tended to be low risk, with the increases in prevalence observed in women aged <25 years (70%) and in whites (58%). Since the 2013 WHO criteria for hyperglycemia during pregnancy identify more women with GDM than other historical criteria (32), the prevalence of postpartum diabetes may be even lower.

Recommendations for Behavior Modification

Breastfeeding

Observational studies suggest that breastfeeding reduces future diabetes risk (33–35). Women with a history of GDM who breastfed had a median time to diabetes of 12.3 years, compared with 2.3 years among women who did not breastfeed (20). Increased duration of breastfeeding led to greater reductions in diabetes risk (20). This reduction in risk did not seem to be mediated entirely through postpartum weight (20). Studies in nonwhite populations are currently lacking.

In contrast to the above findings, lactational amenorrhea associated with exclusive breastfeeding when combined with progestin-only contraceptive medication may increase risk of diabetes in certain racial/ethnic populations (36). Lactation may introduce a relatively progestogenic state that, when combined with progestin-only contraception, results in elevated glucose. Such risk has been observed with both oral and injectable progestins in Latinas (Hispanics) and Native American tribes including Navajos, and it occurs through and apart from weight changes (14,36,37). Of note, contraceptive type (progestin-only vs. combined estrogen–progestin pills) does not seem to be associated with differences in breast milk production in recent reports (38). Thus, breastfeeding should be encouraged, but progestin-only contraception in the setting of lactational amenorrhea may not be the best choice in women who are at high risk for diabetes due to their ethnicity.

Postpartum Weight Loss

Higher preconception maternal weight increases diabetes risk postpartum (9). However, few studies have examined the impact of weight loss interventions in postpartum GDM women. A recent systematic review identified 11 randomized controlled trials of lifestyle interventions conducted among women with a history of GDM (summarized in Table 9.1). Each of the trials addressed both dietary intake and physical activity with the exception of a single trial that focused on dietary modification only (39). The physical activity goals in the trials were modest, primarily targeting 150 minutes per week (40–45), or 10,000 pedometer steps per day for 5 days a week (40,46). Dietary modification goals were similarly modest, targeting decreased intake of dietary fat, usually under 30% of total caloric intake (35,42,45). The majority of the trials were pilot studies that were not sufficiently powered to detect the impact of the intervention on the outcome of incident postpartum diabetes, and only one trial found a protective effect of their intervention on this outcome (45). However, three of the trials demonstrated that lifestyle intervention could lower glucose and/or insulin levels when implemented sooner after delivery (42,44,47).

The single successful trial was a secondary analysis of the Diabetes Prevention Program, a multicenter randomized trial of an intensive lifestyle intervention conducted among a population of adults who had elevated fasting and post-load plasma glucose concentrations. The trial was not specifically designed to target women with GDM but, rather, glucose-intolerant adults overall. Thus, women with GDM were approximately 12 years from their pregnancies, and the highest risk women (i.e., those who converted before 12 years had elapsed) were not included (45). Women randomized to lifestyle change had a 53% reduced risk of diabetes compared to women randomized to placebo ($p = 0.002$), and women randomized to metformin had a 50% reduced risk of diabetes compared to women randomized to placebo ($p = 0.006$).

The trials in Table 9.1 also examined the impact of the interventions on postpartum weight loss; postpartum women may undergo rapid weight loss immediately postpartum. Lifestyle modification led to significant weight reductions in five of these trials (42,44,47–49), while four trials found no impact of the intervention on postpartum weight loss

Table 9.1 Randomized trials of lifestyle interventions to reduce risk of type 2 diabetes among women with gestational diabetes mellitus (GDM); study designs.

Author (year)	Length of follow-up	Population	Intervention	Mode	Impact on diabetes	Impact on glucose	Impact on weight	Impact on physical activity	Impact on diet
Cheung *et al.* (2011) (40)	12 months	43 women with previous GDM <4 y previously; Australia	Exercise intervention vs. usual care control	Individualized in-person; telephone; mailings	NA	NA	BMI (kg/m^2): 28 (95% CI: 23.9, 34.3) vs. 25.5 (95% CI: 22.5, 28.7), $p = 0.14$	Steps (% achieving goal): 30.8 vs. 17.6 $p = 0.34$; PA (% achieving goal): 70.0 vs. 57.9, $p = 0.51$	NA
Ferrara *et al.* (2011) (41,52)	12 months	197 women with current GDM; California	Lifestyle intervention (diet, exercise, breastfeeding) vs. usual care control	individualized in-person; telephone	NA	NA	Weight (% achieving goal): 37.5% vs. 21.4%, $p = 0.07$	PA (difference in mean change in min/week): 25.3, $p = 0.91$	Fat (% difference in mean change) −3.6, $p = 0.002$
Hu *et al.* (2012) (42)	12 months	404 women with previous GDM from 05-09; China	Lifestyle intervention (diet and exercise) vs. usual care control	Individualized in-person	NA	FG (change in mmol/l): −0.09 + .52 vs. −0.09 + 0.6, $p = 0.97$	Weight change: −1.4 + 3.44 kg vs. −0.21 + 3.52 kg (0.3%), $p = 0.001$; BMI change: −0.50 + 1.41 kg/m^2 vs. −0.09 + 1.37 kg/m^2, $p = 0.004$	LTPA (% increased): 59.4% vs. 26.9%, $p < 0.001$	Fat (% decrease): 77.1 vs. 68.9, $p = 0.064$; fiber (% increase) 59.5 vs. 47.4, $p = 0.012$
Kim *et al.* (2012) (46)	13 weeks	49 women with previous GDM within past 3 years; Michigan	Exercise intervention vs. usual care control	Web based	NA	FG (change in mmol/l): −0.046 vs. 0.038, $p = 0.65$; 2 hr. glucose on 75 g OGTT (change in mmol/l): −0.48 vs. −0.42, $p = 0.91$	Weight (change in kg): −0.14 kg vs. −1.5 kg, $p = 0.13$	PA (% moderate-intensity): 58 vs. 47, $p = 0.51$	NA

(*Continued*)

Table 9.1 (Continued)

Author (year)	Length of follow-up	Population	Intervention	Mode	Impact on diabetes	Impact on glucose	Impact on weight	Impact on physical activity	Impact on diet
McIntyre *et al.* (2012) (43)	12 weeks	28 women with previous GDM 6 weeks postpartum; Australia	Exercise intervention vs. usual care control	individualized in-person; telephone	NA	FG (change in mmol/L): 0.25 + .56 vs. 0.12 + 0.42, NS	Change in weight (kg): 0.97 + 3.7 vs. 0.22 + 4.2, NS	PA (median [range] increase in planned PA minutes/week): 60 (0–540) vs. 0 (0–580); $p = 0.234$; walking: NS	NA
Nicklas *et al.* (2014) (49)	12 months	75 women with previous GDM 6 weeks postpartum; US	Lifestyle intervention vs. usual care control	individualized web-based intervention	NA	NA	Weight change: −2.6 (−4.4, −0.8) vs. 1.4 (−0.4, 3.1), $p = 0.003$	NA	NA
Peacock *et al.* (2015) (47)	12 weeks	Women with previous GDM 6–24 months postpartum; Australia	Lifestyle intervention (diet and exercise) vs. wait-list control	Individualized web-based intervention; nutrition workshop	NA	FG (change in mmol/L): 0.3 + .5 vs. −0.1 + 0.6, $p = 0.052$	Change in weight (kg): −2.5 + 1.4 vs. 0.0 + 2.3 $p = 0.002$	PA (difference between arms): 135 minutes/week in intervention minus control, NS	Total fat (change in g/day) 0.2 + 0.4 vs. 0.2 + 0.5, NS
Ratner *et al.* (2008) (45)	2.8 years	350 women with previous GDM and current elevated glucose levels from the DPP; US	Lifestyle intervention (diet and exercise) vs. placebo	Individualized in person; group sessions	Diabetes: 53% risk reduction vs. placebo, $p = 0.002$	NA	Weight (change in kg): −5.13 + 0.43 vs. approx. 0 in placebo at 6 mos. $p < 0.01$; −1.6 + 0.80 vs. approx. 0 in placebo at 3 y, $p = 0.021$	PA (change in h/week): 1.5 h/week 1 year after randomization, $p < 0.01$ and 0.5 h/week 3 years after randomization, NS	NA
Reinhardt *et al.* (2012) (48)	6 months	38 women following GDM diagnosis; Australia	Lifestyle intervention (diet and exercise) vs. usual care control	Telephone; mailings	NA	NA	BMI (difference in change in kg/m^2): −1.5 (95% CI: −2.8, −0.1), $p < 0.05$; weight (difference in change in kg): −4.0 (95% CI: −7.6, −0.5), $p < 0.05$	LTPA (change in min/day): 11 (95% CI: 1, 22)	Total fat (change in g/day): −19 (95% CI: −37, −1), $p < 0.05$; GL (unit change) −26 (95% CI: −48, −4), $p < 0.05$

Shyam *et al.* (2013) (44)	6 months	77 women with previous GDM within 2 mos.; Malaysia	Low GI diet vs. usual care control	In person, text messaging, emails	NA	Glucose: 2 h post 75 g OGTT (median mmol/l, IQR): −0.2 (2.8) vs. 0.8 (2.0), $p = 0.025$	Weight (% achieving goal): 33% vs. 8%, $p = 0.01$	PA (median MET-min/week, IQR): 933 (1403) vs. 965 (857), $p = 0.908$	Fat (g): 58 + 18 vs. 53 + 16, $p = 0.695$ for difference in change; fiber (g): 17 + 4 vs. 13 + 4, $p = 0.02$ for difference in change; GI: 57 + 5 vs. 64 + 6, $p = 0.033$ for difference in change
Wein *et al.* (1999) (39)	796 person-years (median 51 months)	200 women with previous GDM from 89-91 and subsequent IGT	Diet intervention vs. control	telephone; mailings	Diabetes (annual IR): 6.1% vs. 7.3% (IRR = 0.83, 95% CI: 0.47, 1.48), $p = 0.50$	NA	NA	NA	NA

FG = fasting glucose; FU = follow-up; GDM = gestational diabetes mellitus; GI = glycemic index; IGT = impaired glucose tolerance; LTPA = leisure time physical activity; PA = physical activity; RCT = randomized clinical trial.

(Table 9.1). While these trials are promising, it remains unclear whether diabetes can be averted through lifestyle change in the years immediately after delivery. Several larger studies are now underway that may help determine the optimal delivery mode and intensity of behavior change needed to prevent the development of diabetes (50–54).

Summary

While it has been established that women with GDM constitute a group at high risk for glucose intolerance after pregnancy, it remains less clear how to reduce this risk. The DPP demonstrated that women with a history of GDM can change their behavior even when interventions are implemented a decade after delivery, but studies in the immediate postpartum period in reproductive-aged women have been less effective. In the meantime, the standard of care for postpartum women with GDM consists of informing women about: the risks of postpartum glucose dysregulation associated with their GDM diagnosis, the importance of weight reduction achieved through increased physical activity and reduced percent calories from fat, the need for regular glucose screening tailored to specific metabolic derangements during pregnancy, and discussion of family-planning methods. Women should undergo glucose testing prior to planned conceptions, with subsequent referral for close monitoring during pregnancies, as well as repeat screening at 1–3-year intervals.

Future Directions

Ongoing trials are testing several risk reduction strategies that should provide guidance on best practices to assist women in postpartum risk reduction. Ongoing studies are also examining whether weight management interventions during the pregnancy may lead to lower weight in the postpartum period without compromising pregnancy outcomes. Future research should also include comparison of postpartum screening strategies to determine whether specific strategies impact outcomes for future pregnancies and maternal health.

Multiple-Choice Questions

1 Women with GDM have an increased risk for all but which of the following conditions?
- **A** Recurrent GDM
- **B** Type 1 diabetes mellitus
- **C** Cardiovascular disease
- **D** Hypothyroidism

The correct answer is D. Women with GDM have increased risk for recurrence, type 1 as well as type 2 diabetes, and cardiovascular abnormalities.

2 Which of the following is NOT associated with reduced risk of glucose intolerance after a GDM pregnancy?
- **A** Breastfeeding
- **B** Progestin-based contraception
- **C** Weight loss
- **D** Increased physical activity

The correct answer is B. Progestin-based contraception, combined with lactational amenorrhea, may actually increase risk of diabetes after a GDM pregnancy.

3 Which test is NOT recommended for glucose testing at the routine postpartum visit?
- **A** Fasting glucose only
- **B** 2-hour glucose tolerance test
- **C** Hemoglobin A1c

The correct answer is C. Hemoglobin A1c at the postpartum visit may reflect prenatal glycemic control, as well as iron deficiency, anemia, and other factors that may confound postpartum glycemic levels. Both A and B are recommended by different medical organizations.

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Section III

Diabetes Preceding Pregnancy

10

Pre-Pregnancy Care in Type 1 and Type 2 Diabetes

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PRACTICE POINTS

- Pre-pregnancy care (PPC) is the additional support needed to prepare a woman with diabetes for pregnancy. A principle goal is to advise and support the woman to achieve optimization of glycemic control before conception.
- PPC in women with type 1 diabetes is associated with improved glycemic control in early pregnancy and a threefold reduction in risk of major congenital malformation in the offspring.
- PPC includes commencement of folic acid 5 mg daily preconception; discontinuation of potentially teratogenic medications, such as statins, ACE inhibitors, and certain hypoglycemic agents; and smoking cessation. Dietary input is important to encourage a healthy weight before pregnancy and to optimize glycemic control.
- Pregnancy outcomes for women with type 2 diabetes are the same or worse as those for women with type 1 diabetes. However, women with type 2 diabetes are less likely to receive formal PPC.
- Preconception counseling, as opposed to PPC, should take place at regular intervals throughout the reproductive years. It includes a discussion with the patient about future plans for pregnancy, contraceptive advice, education about the increased risks associated with unplanned pregnancies and how they may be minimized, and advice on how to access PPC.

Case History

Mary, a 25-year-old, was delighted to find she was expecting a second baby. Her first pregnancy had been complicated by gestational diabetes treated with diet. Despite advice to lose weight, she had become depressed following the pregnancy and gained 9 kg. Two years later, she had been diagnosed with type 2 diabetes. She found it difficult to keep to the recommended diet and required metformin and a sulphonylurea for glycemic control. Recently, she had been started on an ACE inhibitor to control her blood pressure. She was about 8 weeks pregnant. Her family doctor referred her urgently to the diabetes antenatal clinic, where she was shocked to discover she would need insulin treatment during her pregnancy as her HbA1c at booking was 68 mmol/mol (8.4%). She later explained that she had not been counseled at any time previously, either about possible risks to a future pregnancy or that she would need to discontinue her oral hypoglycemics and commence insulin. She commenced twice-daily insulin injections and discontinued her oral hypoglycemics. Her ACE inhibitor was discontinued, and she was started on labetalol and prescribed folic acid tablets. Her 20-week anomaly scan showed a ventricular septal defect.

A Practical Manual of Diabetes in Pregnancy, Second Edition. Edited by David R. McCance, Michael Maresh and David A. Sacks.

After 20 weeks, her diabetes became more difficult to control, requiring four insulin injections daily. An additional blood pressure tablet was commenced at 28 weeks. Development of preeclampsia led to an emergency cesarean section at 35 weeks. The baby was admitted to the neonatal care unit for treatment of hypoglycemia, which led to difficulties establishing breastfeeding. The baby will require cardiac surgery later.

- How effective is PPC care in reducing pregnancy complications in women with pre-gestational type 1 and type 2 diabetes?
- What are the essential components of PPC for women with type 1 and type 2 diabetes?
- What are the aims of tight glycemic control?
- Why do women not access PPC?
- What is preconception counseling, and what should it include?

Background

Pre-pregnancy care (PPC) for women with diabetes was introduced 40 years ago and is associated with improved pregnancy outcomes. However, only one-third of women access PPC, and pregnancy outcomes remain poor. Worldwide, type 2 diabetes is the most common type of diabetes to complicate pregnancy; women with type 2 diabetes are more likely to enter pregnancy with obesity and take potentially teratogenic medications, and less likely to access PPC than women with type 1 diabetes. All healthcare professionals delivering diabetes care should understand the importance of PPC and be skilled to provide preconception counseling, including contraceptive advice.

History of Pre-Pregnancy Care

Molsted-Pedersen first described the high incidence of congenital malformations in women with diabetes in 1964, with 6.4% of infants of their diabetic mothers showing a malformation compared to 2.1% of women without diabetes (1). Hyperglycemia was proposed as a possible mechanism, with both animal and human studies supporting this hypothesis (2,3). However, the concept of PPC for women with diabetes was only developed after Pedersen observed the relationship between glucose control and malformations and described how "the occurrence of hypoglycemic reactions and insulin coma during the first trimester was low in mothers with malformed infants," indicating a positive relationship between maternal hyperglycemia in early pregnancy and the development of fetal malformations (4).

Is Pre-Pregnancy Care Effective?

Congenital Malformations

The neural tube closes at 6 weeks of gestation. The fetal heart is formed by 8 weeks of gestation. Hence, for an improvement in glycemic control to influence these events, the improvement must occur prior to pregnancy.

Fuhrmann's study in 1983 of 420 women with type 1 diabetes showed preconception optimization of maternal blood glucose was associated with a significant reduction in congenital malformations, with a malformation rate of 0.8% in the glycemic group that had established preconception compared to 7.5% in the control group (5). By the early 1980s, pre-pregnancy clinics were becoming part of routine care in some centers, such as Steel's in Edinburgh (6). Studies have confirmed the effectiveness of PPC, showing improved glycemia in early pregnancy and a reduction in the risk of malformations (Table 10.1) (5–15). However, these studies have all been prospective or retrospective cohort studies, and only five include data on glycosylated hemoglobin.

Table 10.1 Pre-pregnancy care and congenital malformations in type 1 diabetes.

Author	Year	PPC number	PPC % malformation	No PPC number	% Malformation	*P* value
Fuhrmann (5)	1983	128	0.8	292	7.5	0.01
Steel (6)	1994	196	1.5	117	12.0	<0.005
Goldman (7)	1986	44	0	31	9.7	NS
Mills (8)	1988	347	4.9	279	9.0	0.03
Kitzmiller (9)	1991	84	1.2	110	10.9	0.01
Rosenn (10)	1991	28	0	71	1.4	NS
Cousins (11)	1991	27	0	347	6.6	NS
Drury (12)	1992	100	1.0	244	4.1	NS
Willhoitte (13)	1993	62	1.6	123	6.5	NS
Temple (14)	2006	110	1.8	180	6.1	0.07
Murphy (15)	2010	107	0.9	230	5.7	0.02

Data from references (5–15).

Two meta-analyses of studies of PPC, one including over 2500 pregnancies (16) and one with 12 cohort studies (17), showed that the absence of PPC was associated with a three- to fourfold increase in risk of major congenital malformation and that PPC was associated with a reduction in glycosylated hemoglobin (HbA1c) in the first trimester of pregnancy by an average of 1.9%.

Perinatal Mortality

In a meta-analysis of five cohort studies, PPC was associated with a reduction in risk of perinatal mortality (risk ratio: 0.35; 95% CI: 0.15–0.82) (17). However, it is well recognized that perinatal deaths may be associated with a malformation. This was especially true in earlier studies, carried out prior to the development of detailed anomaly scans.

Spontaneous Abortions

It is difficult to assess the effect of PPC on spontaneous abortions, since there is likely to be an underrecording of spontaneous abortions in women without PPC and early diagnosis of pregnancy, and hence recognition of miscarriage in women with PPC. Several studies have suggested risk of spontaneous abortion is increased three- to fourfold in women with poor glycemic control in early pregnancy (18,19). One early study suggested PPC is associated with a reduced risk of spontaneous abortion (8.4% compared to 28%) (19). However, a meta-analysis of seven studies of PPC and spontaneous abortions found no effect of PPC on spontaneous abortions (20).

Perinatal Morbidity

There are few studies on the effect of PPC on perinatal morbidity or obstetric complications. One study in 290 women with type 1 diabetes showed PPC was associated with a significant reduction in delivery before 34 weeks gestation (5.0% vs. 14.2%) (14). A recent meta-analysis of studies of PPC has also shown PPC is effective in reducing risk of premature delivery (defined as delivery before 37 weeks), with a risk ratio of 0.70 (95% CI: 0.55–0.90) (21). In contrast, studies have shown no relationship between PPC and risk of macrosomia, preeclampsia, small-for-gestational-age babies, or cesarean delivery, suggesting that these complications may be more related to glycemic control in later rather than early pregnancy (Table 10.2) (14,22–25).

Table 10.2 Pre-pregnancy care and pregnancy outcomes in women with type 1 diabetes (14).

	Pre-pregnancy care	No pre-pregnancy care	*P* value
Number	110	180	
Pregnancy complications			
Delivery <34 weeks (%)	5.0	14.2	0.02
Macrosomia (%)	44.0	43.4	NS
Preeclampsia (%)	13.1	12.7	NS
Pregnancy outcome			
Spontaneous abortion (%)	5.7	14.0	0.056
Malformation (*n*)	2	11	0.065
Adverse outcome* (%)	2.9	10.2	0.026

* Adverse outcomes include congenital malformations, stillbirths, and neonatal deaths.

Effectiveness of Pre-Pregnancy Care in Type 2 Diabetes

Many studies of preconception care were carried out when there were few women of reproductive age with type 2 diabetes. Consequently, the majority of studies have included only women with type 1 diabetes. To date, there have been no studies of PPC in only women with type 2 diabetes.

A regional pregnancy program in the East of England reported on 680 pregnancies, including 274 (40.2%) in women with type 2 diabetes (15). Only 27% of women accessed PPC (31% with T1 diabetes and 20% in women with T2 diabetes). Within the whole cohort, PPC was associated with a highly significant reduction in risk of malformation (0.7 vs. 5.6%, $p = 0.02$) and risk of adverse outcome (a composite of malformation or perinatal death) (1.3 vs. 7.8%, $p = 0.0009$). In women with T2 diabetes, there were no adverse outcomes in women with PPC compared to 6.8% adverse outcomes in women without PPC, but these results were nonsignificant.

Why Do Women not Attend Pre-Pregnancy Care?

There is increasing awareness of the reasons why women may choose not to access PCC. Women who do not access PPC are more likely to have type 2 diabetes, and to be younger, heavier, from a lower social class, from an ethnic minority group (25,26), and also less likely to have had preconception counseling (Table 10.3) (15).

Recent studies have explored the complex issues in non-attendance for PPC by interviewing women. In a study of 29 pregnant women who did not attend PPC, knowledge concerning the risks of pregnancy (90%) or past preconception counseling (38%) did not encourage women to attend PPC, and neither did personal experience of miscarriage, malformation, or stillbirth in women with previous poor pregnancy outcome (41%). Barriers to attendance included conceiving faster than anticipated (45%), fertility concerns (31%), negative experiences with health professionals (21%), desire for a "normal" pregnancy (17%) and the logistics of attending (10%) (27). Results of a study, in 15 women with 40 pregnancies, suggest that "the dichotomy between planned and unplanned pregnancies is problematic" (28). There appeared to be a challenge for women between "mastering or becoming enslaved" to glucose levels. One woman reported experiencing fear after a preconception clinic and said "it was a very, very negative experience." In a further study of 14 women, most with type 1 diabetes, women cited fear, and worry about being lectured as reasons for non-attendance (29).

Table 10.3 Characteristics of women with type 1 and type 2 diabetes and attendance of PPC (15).

	PPC	No PPC	*P* value
Number	181	499	
Age (years)	33	31	0.002
Ethnicity (% white)	91.7	77.6	0.0005
Deprivation: quintiles 4 and 5 (%)*	41.2	55.1	0.01
BMI	26.1	27.9	0.005
Preconception counseling (%)	82.1	31.7	<0.0001
Nonsmoker (%)	83.9	71.4	0.0002

* Quintiles of deprivation were derived from the postcode of residence according to the East of England Index of Multiple Deprivations (IMD) scores.

Components of a Pre-Pregnancy Service

There are two separate components to education about reproductive health. First is *preconception counseling*, which should be a part of education of the woman on reproductive health and take part at regular intervals throughout her reproductive years. It should include advice on contraceptive use, the importance of planning any pregnancy. Second is *pre-pregnancy care*, which is the focused care needed when a woman with diabetes wishes to become pregnant in the near future so that any risks can be minimized.

Preconception Counseling

Preconception counseling is the education of, and the discussion with, women of reproductive age about pregnancy and contraception. It is an essential component of every consultation in primary and/or specialist care.

Preconception counseling should be given regularly throughout the reproductive years. It includes:

- Discussion about future pregnancy plans.
- Documentation about use of contraception and advice about it, with assessment of risks including diabetes complications, smoking status, and weight.
- Education on increased risks of poor pregnancy outcome associated with poor glycemic control.
- Education about what PPC is and how this can improve pregnancy outcomes.
- Advice how to access PPC, including contact details for self-referral.
- Education of women with type 2 diabetes about discontinuing potentially teratogenic oral hypoglycemic agents, such as a sulfonylurea or dipeptidyl peptidase-4 inhibitor.
- Education about folic acid supplements before and during early pregnancy.
- Advice on avoidance of statins and ACE inhibitors during pregnancy.
- Education on risks of smoking in pregnancy.
- Education on risks of poor pregnancy outcome with obesity and diabetes, both individually and collectively.
- Information on how to self-refer if unplanned pregnancy occurs.
- Documentation in the records of any discussion and education.

Pre-Pregnancy Care

PPC is the additional care needed to prepare a woman with diabetes for pregnancy and involves a close partnership between the woman and healthcare professionals. It includes optimization of glucose control,

prescribing folic acid supplements, avoidance of potentially teratogenic medications, weight management, smoking cessation advice, assessment for any diabetes-related complications such as eye or renal complications, and discussion of pregnancy risk.

PPC should ideally begin at least 6 months before a woman with diabetes embarks on a pregnancy. A summary of what it should include is shown in Table 10.4.

It is preferable for PPC to be delivered by the multidisciplinary team who will care for the woman during her pregnancy so that her relationships with members of the team can be developed before the pregnancy begins.

Glycemic Targets

Optimizing glycemic control reduces the risk of congenital abnormalities, and women

Table 10.4 Aims of pre-pregnancy care for women with type 1 or type 2 diabetes.

Contraception

1) Document use of effective contraception.
2) Continue contraception until optimum HbA1c achieved.

Optimize glucose control

1) Aim HbA1c as close to normal range as possible without significant hypoglycemia.
2) Advise blood glucose monitoring before and 1 h postprandial, and occasionally during night.
   - Pre-meal glucose <5.8 mmol/L.
   - Post meals (1 h) <7.8 mmol/L.
3) Stop oral hypoglycemic agents and initiate insulin if suboptimal glucose control.
4) Consider metformin if improved glycemia outweighs potential risks.
5) Advise on management of hypoglycemia.

Diet, exercise, and structured education

6) Refer to dietician for education on regular, but small to moderate portions of low-glycemic-index carbohydrates.
7) Education about weight loss if BMI >27.
8) Encourage regular exercise.
9) Provide smoking and alcohol cessation advice.

Prescribe folic acid supplements

Supplemental dose: 5 mg daily (lower dose in some countries)

Review other medication

10) Stop ACE inhibitors (ACE-Is), angiotensin receptor antagonists, statins, or diuretics.
11) Treat hypertension with methyldopa or labetalol.

Screen for diabetic complications

12) Assess for retinopathy at initial visit (unless it has been assessed in previous 6 months) and then annually. If retinopathy is present, consider referral to ophthalmologist.
13) If proteinuria or reduced GFR is present, refer to nephrologist.
14) Assess cardiac status and consider referral to cardiologist.

Screen for rubella immunity

Counsel on risks of pregnancy with diabetes and obesity

15) To fetus: miscarriage, malformation, stillbirth, neonatal death, macrosomia
16) To pregnancy: eclampsia, premature delivery, cesarean section
17) Progression of diabetic complications

Consider referral to obstetrician or diabetes specialist midwife

18) Assessment of obstetric risk
19) Further education and support

should be encouraged and supported to reduce their HbA1c prior to pregnancy. However, this should always be balanced against the risk of severe hypoglycemia for the mother. In agreeing a target HbA1c, women should be advised that any reduction in HbA1c reduces malformation risk to her baby. A recent study (31) demonstrates the risk of malformation is around 10% with a peri-conceptual HbA1C above 90 mmol/mol (10.4%), and drops in an almost linear fashion to around 3% with an HbA1c below 45 mmol/mol (6.3%). Reduction of HbA1c by 11 mmol/mol (1%) resulted in a 30% reduction in risk (30). A meta-analysis of studies of glycosylated hemoglobin and congenital malformation also showed a stepwise fall in risk with fall in HbA1c, with a 12% risk of malformation for an HbA1c of 108 mmol/mol (12%), a 6% risk for an HbA1c of 75 mmol/mol (9.0%), and a 3% risk for an HbA1c of 42 mmol/mol (6.0%) (31). However, women should also be aware that the risk of congenital abnormality in the general population without diabetes is around 3%.

- In the UK, the National Institute for Clinical Excellence guidelines, published in 2015, recommend a target HbA1c of 48 mmol/mol (6.5%) prior to pregnancy, if this is achievable without problematic hypoglycemia (32).
- In contrast, the American Diabetes Association recommends an HbA1c below 53 mmol/mol (7.0%) preconceptionally (33).

For women with longstanding type 1 diabetes, a target HbA1c below 48 mmol/mol may not be achievable without the risk of severe hypoglycemia. For these women in particular, the choice of words when expressing risk is important in order to give more meaningful information about an uncommon, albeit serious, outcome. Women may find the concept of individual risk ratios more helpful, in particular when these are related to women with and without diabetes. So, for example, in women without diabetes 1 in 33 pregnancies may have a malformation, while in women with diabetes, the odds are 1 in 33 with an HbA1c of less than 48 mmol/mol (6.5%), 1 in 26 for an HbA1c of greater than 53 mmol/mol (7.0%), 1 in 20 for an HbA1c of greater than 58 mmol/mol (7.5%), and 1 in 9 for an HbA1c of greater than 86 mmol/mol (10%) (30).

Although it is important to discuss risk of malformation with the patient, the healthcare professional must be aware that giving "impossible" HbA1c targets can discourage women from attending PPC (27–29). In order to achieve these targets, women should be encouraged to test intensively, with daily fasting, pre- and postprandial blood glucose measurements, and recording results in a home blood glucose-monitoring diary or with a memory meter. Downloading glucose meters at clinic visits or remotely is helpful to verify glucose monitoring. Blood ketones should be checked if glucose is high or the woman is unwell. Continuous glucose-monitoring systems can be extremely helpful in some patients, particularly for identifying erratic overnight or high postprandial blood glucose levels, or for identifying high postprandial glucose levels in women with suboptimal HbA1c values.

Hypoglycemia

All women, but especially those with type 1 diabetes, must be advised that they may lose their usual warning signs of hypoglycemia or these may be reduced. Women should always test their blood glucose before driving and should be advised to discontinue driving if there is loss of hypoglycemic awareness. Family members should be instructed in the use of glucagon. Although there is no human evidence to show hypoglycemia is damaging to the fetus, it is potentially harmful to the mother and can often limit her success in achieving optimum glycemic control.

Studies have shown risk of severe hypoglycemia is most common in early pregnancy. Evers and colleagues showed risk of severe hypoglycemia is increased in women with lower HbA1c and increased duration of diabetes (34). A recent study showed no increase

in the risk of severe hypoglycemia with PPC, despite women with PPC having a lower HbA1c at booking (14).

Diabetic Complications

Generally, women can be reassured that pregnancy is not associated with an increased risk of microvascular complications (35). Risk of progression of retinopathy is increased by both pregnancy and intensification of glycemic control. It is important that retinal imaging is performed before pregnancy and that any retinopathy is assessed and treated, if necessary, before initiation of tight glycemic control and conception (see Chapter 21). Women with longer duration diabetes or retinopathy present in early pregnancy are most at risk of deterioration in retinopathy during pregnancy (36).

Pregnancy outcome in women with mild renal disease should be optimized by optimum control of glycemia and blood pressure, but women need to be advised they are at increased risk of preeclampsia or deterioration of their nephropathy, and premature delivery. These risks can probably be reduced with early and aggressive antihypertensive treatment (37). All women should have an assessment of albumin and creatinine excretion before conception. Women with ischemic heart disease should be referred for assessment by a cardiologist.

Factors Other than Blood Glucose Control

Women with diabetes have an increased incidence of having a baby with congenital abnormalities, particularly congenital heart defects and neural tube defects. Preconceptual folic acid reduces this risk, and in the UK it is recommended that all women with type 1 or 2 diabetes should take 5 mg folic acid prior to pregnancy (32). All drug therapy should be reviewed. Potentially teratogenic drugs (including statins and ACE inhibitors) should be discontinued, and if necessary, blood pressure treatment should be changed to a drug suitable for use in pregnancy. Smoking cessation programs should be offered, and weight management advice given if the woman's BMI is greater than 27 kg/m^2.

Additional Factors with Pre-Pregnancy Care in Women with Type 2 Diabetes

The specific issues contributing to poor outcomes in type 2 diabetes are complex and include other medical comorbidities, obesity, suboptimal glucose control, potentially teratogenic drugs, older age, greater socioeconomic deprivation, and ethnicity. Many of these can be addressed with PPC (see Table 10.4). In particular, tight glycemic control can usually be more easily achieved in women with type 2 diabetes than in women who have type 1. Obesity must be addressed with intensive dietary support to encourage an optimum BMI (<27) before pregnancy. Women must be advised of the wide-ranging increased risks of pregnancy with obesity, including congenital malformations, perinatal mortality, preeclampsia, prematurity, cesarean section, and thrombo-embolic disorders.

Future Research

The effectiveness of PPC on improving pregnancy outcomes, particularly reducing risk of malformation, in pre-gestational diabetes is well documented; but many questions remain. We need to increase our understanding of why so few women still access PPC. This requires studies in different populations and will also probably require in-depth interviews to deepen our understanding of this problem. With the rapid rise in type 2 diabetes, compounded by obesity, there is an urgent need to study ways of increasing PPC for these women (many of whom are managed exclusively in primary care) and determining whether PPC in type 2 diabetes is as effective as in type 1 diabetes.

Multiple-Choice Questions

1 Pre-pregnancy care should be offered to all women with diabetes who are planning a pregnancy. Women should be advised that pre-pregnancy care will reduce their risk of which of the following pregnancy complications?
- **A** Progression of retinopathy
- **B** Preeclampsia
- **C** Congenital malformation
- **D** Macrosomia
- **E** Intrauterine growth retardation

The correct answer is C. To date, studies have shown no relationship between pre-pregnancy care and any of the other complications.

2 Women with diabetes who do NOT have pre-pregnancy care are more likely to have which of the following characteristics?
- **A** From higher socioeconomic class
- **B** Have a history of retinopathy
- **C** Older
- **D** To be from an ethnic minority group
- **E** To be an ex-smoker

The correct answer is D. Several studies have shown women from an ethnic minority group are less likely to access pre-pregnancy care. Women who have pre-pregnancy care are usually from a higher socioeconomic group, older, and nonsmokers.

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11

Malformations

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PRACTICE POINTS

- Regularly ask diabetic women of childbearing age as to their pregnancy intention, and provide counseling regarding the relationship between maternal glycemia at the time of conception and the incidence of congenital malformations (CMs), the importance of contraception until glycemia is optimized, and so on.
- Advise on initiation of folic acid supplementation before pregnancy.
- Remember that risk of CMs is similar in women with type 2 and type 1 diabetes.
- Do not stop sulfonylureas or metformin in the first trimester without ensuring good glycemic control.
- Make sure that diabetic women are offered appropriate detection of CMs and corresponding advice.

Case History

A 32-year-old woman with type 1 diabetes mellitus (T1DM) consulted with an unintended pregnancy. She had been diagnosed with T1DM when she was 12, she used insulin analogs in a basal-bolus schema, and her HbA1c usually ranged between 7 and 8% (53–63.9 mmol/mol). She had diabetic retinopathy and overt diabetic nephropathy; she had undergone laser therapy and currently was on enalapril 20 mg/day. At her first consultation, her gestational age was 12^{+2} weeks and HbA1c 7.5% (58.5 mmol/mol); enalapril was stopped, methyldopa initiated, and diabetes treatment intensified. A first scan confirmed the dates, a fundoscopy showed stable diabetic retinopathy, and a high-resolution ultrasound at 18 weeks suggested a cardiac malformation (single ventricle). The patient was scheduled for fetal echocardiography one week later, and at that time there was no heartbeat. Labor was induced, and necropsy confirmed the heart defect. Contraception options were discussed, and the patient was asked about her pregnancy intention. As she expressed her wish to become pregnant again, she was referred for pre-pregnancy care.

A Practical Manual of Diabetes in Pregnancy, Second Edition. Edited by David R. McCance, Michael Maresh and David A. Sacks.

Congenital malformations (CMs) continue to be a serious problem in diabetic pregnancy, despite clinical practice guidelines and improvements in diabetes management and obstetric surveillance.

Epidemiology

Prevalence

An increased risk of CMs in infants of diabetic mothers was clearly established in the 1960s (1) with reported odds ratios (ORs) compared to the reference group of up to 7.9.

In population-based studies published in the twenty-first century, summary statistics of CMs in diabetic women continue to depict an increased risk (2,3). Most articles addressing time trends have not observed significant differences, with the exception of Feig (4) who reported a 23% reduction in relative risk (RR) from 1996 to 2010.

Although information on CMs in DM initially came from T1DM, in the last 10 years several authors have also reported a high CM risk in women with type 2 diabetes mellitus (T2DM). A meta-analysis published in 2009 (5) concluded that the risk of CMs in women with T2DM was similar to that in T1DM (RR: 1.19), even when first-trimester HbA1c was lower in the former.

Types

CMs in offspring of diabetic women are not specific either for DM per se or for diabetes types. Some CMs are more frequent, while others are more characteristic (6).

The most frequent CM in offspring of diabetic women are cardiac defects (CDs), and these represent about 40% of all anomalies. Neural tube defects (NTDs), musculoskeletal CMs, and genitourinary CMs follow in prevalence, although the specific sequence can differ depending on the series. Multiple CMs are present in up to 20% of malformed infants.

Large studies comparing risk of CMs in infants of pre-gestational diabetic women versus nondiabetic mothers are presented in Table 11.1. Caudal regression is rarely seen, but the risk in DM is greatly increased compared with nondiabetic pregnancies (RR: 26), so that it is the most characteristic CM in DM. Multiple CMs are also characteristic of diabetes, with RR up to 12 compared with nondiabetic women. RRs for heart and central nervous system defects are about twofold higher, although with some exceptions. For other anomalies, RRs are more heterogeneous.

Using a developmental approach, Mills inferred that anomalies in infants of diabetic mothers occurred before the eighth week of gestation (12). The fact that these infants have more blastogenic and midline anomalies supports this conclusion, since blastocyst development takes place from the fifth to ninth postconception days (6).

Pathogenesis

Hyperglycemia

In the present era, the role of maternal hyperglycemia in the pathogenesis of CMs is undisputed. After early data suggested a role, more definitive evidence came with the advent of $HbA_{1c.}$ In 2007, a meta-analysis of seven cohort studies relating periconceptional HbA1c and CM reported an exponential association: for each 1% increase in HbA1c, the OR of a CM increases by 1.71 (13).

In vivo and *in vitro* experimental animal studies clearly demonstrate the teratogenic potential of hyperglycemia in early pregnancy. Underlying mechanisms are described in the "Mediators" section.

Hypoglycemia

The possibility of hypoglycemia being a pathogenic factor for CMs was suggested by reports of insulin shock therapy (induced insulin coma as a form of psychiatric treatment) in early pregnancy of nondiabetic women (14). Information in diabetic mothers does not support this possibility. For example, Rowland reported that the frequency of hypoglycemia during pregnancy was lower in

Table 11.1 Major congenital malformations in offspring of women with pre-gestational diabetes: prevalence of specific types in population-based studies published in the twenty-first century.

		Australia (7)	USA (8)	EUROCAT (9)	UK (10)	Canada (11)
System	Type	RR (CI 95)	RR (CI 95)	OR (CI 95)	PR* (CI 95)	RR (CI 95)
Central nervous system		3.16 (1.02–9.85)	8.38 (3.99–17.64)	1.23 (0.96–1.57)	2.7 (1.5–4.4)	2.65 (0.64–10.9)
Cardiac		2.84 (1.89–4.26)	8.43 (3.49–20.4)	2.20 (1.88–2.58)	3.4 (2.5–4.6)	1.32 (0.59–2.98)
Musculoskeletal / connective tissue	Limb	1.34 (0.85–2.12)	0.77 (0.11–5.53)	0.61 (0.49–0.77)	1.4** (0.8–2.1)	1.33 (0.50–3.59)
	Omphalocele			2.28 (1.13–3.97)		
	Other musculoskeletal			1.5 (1.11–2.02)		
Caudal regression				26.4 (8.98–77.64)		
Genitourinary tract	Renal agenesis / obstructive defects	2.34 (1.64–3.33)	9.47 (3.02–29.7)	0.88 (0.70–1.11)	1.2 (0.6–2.2)	0.56 (0.08–4.01)
	Hypospadias			0.73 (0.50–1.07)	1.5 (0.5–3.4)	
Gastrointestinal		0.98 (0.37–2.61)	6.15 (2.30–16.45)	0.8 (0.59–1.08)	0.8 (0.2–2.5)	3.27 (0.79–13.56)
Multiple			12.4 (6.86–22.5)	13.6 vs. 6.1% ***	21 vs. 6.1%***	

* Based on EUROCAT 2002.
** For all types of musculoskeletal/connective tissue malformations.
*** Reference is a random sample of nondiabetic cases from EUROCAT.
PR: Prevalence ratio; OR: odds ratio; RR: risk ratio.

diabetic mothers of infants born with CDs than in those without (15). Also, the frequent mild hypoglycemic episodes that occur when optimization of blood glucose is undertaken are not associated with CMs (16).

The above information appears to be *at odds* with animal experimental data showing that hypoglycemia in early pregnancy is teratogenic (17). Human and animal data can be reconciled by taking into account that hypoglycemic exposure in animal models (1–48 h) corresponds to human equivalents (14 h–28 days) that are not observed in clinical practice.

Ketones

In women with T1DM, first-trimester B-hydroxybutyrate is higher than in those without diabetes, but is not associated with CMs (18). This can be reconciled with animal studies demonstrating a causal association between ketone bodies and CMs because teratogenic concentrations of B-hydroxybutyrate are 20-fold higher. The concentrations of B-hydroxybutyrate associated with CMs in animal models (>8 mmol/l) can be found in diabetic ketoacidosis, but are not reached in starvation ketosis.

Insulin

In animal studies, both excess and lack of insulin can induce CMs (19,20). Insulin/pro-insulin levels are finely regulated during development, since excess interferes with morphogenesis, reducing naturally occurring apoptosis. A teratogenic role for insulin in human pregnancy is therefore possible (21).

In the absence of specific antibodies, the human placenta is usually impermeable to insulin, but it is unclear whether insulin crosses the placenta in early pregnancy. Interestingly, a case–control study identified obesity and hyperinsulinemia as risk factors for NTDs; the risk associated with hyperinsulinemia was only slightly reduced when corrected for obesity (22).

Obesity

There is a positive association between increasing Body Mass Index (BMI) and CMs in the general population. In a meta-analysis that examined the risk of NTDs, there was evidence of a dose–response relationship with BMI (OR 1.20 in overweight and 1.87 in obesity, both of them significant) (23). In a meta-analysis addressing CDs, the risk also displayed a dose–response relationship with BMI: OR 1.08 in overweight, 1.23 in obesity, and 1.39 in severe obesity, all of them significant (24). Proposed mechanisms by which obesity induces CMs include increased nutrient availability, hyperinsulinemia, and low folate availability.

In women with T1DM, there is an interaction between DM and BMI categories (25). In women without diabetes, the observed RR for CMs was 1.00 for normal weight (reference category), 1.10 in overweight, and 1.15 in obesity. Corresponding figures for women with T1DM were 2.28, 2.34, and 4.11 in the normal-weight, overweight, and obese categories, respectively.

Mediators

In *in vitro* models, the serum of animals with diabetes is teratogenic. Among the serum components, excess glucose was the first fuel to be tested and shown to be a teratogen, later followed by ketones and amino acids. A dose-dependent effect has been demonstrated, and the effect of different fuels is synergistic (26).

One of the final steps in the induction of diabetic embryopathy is excess *apoptosis*, which is an important event in embryogenesis (27). Excess fuels lead to excess apoptosis through *oxidative stress*, which modifies the signaling of several pathways: activation of protein kinase C, which leads to apoptosis both directly and through lipid peroxidation and arachidonic acid alterations; mitogen-activated protein kinase signaling, which suppresses cell proliferation and induces mitochondrial dysfunction; activation of Jun N-terminal kinases, which induce endoplasmic reticulum stress; and activation of apoptosis signal-regulating kinase 1. *Inositol depletion* can also contribute to teratogens through protein kinase C signaling. Hyperglycemia-induced *hypoxia* can contribute to CMs through increased oxidative stress.

Drugs

Angiotensin Converting Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs)

ACEIs and ARBs are frequently used in women with pre-gestational DM, for both hypertension and diabetic nephropathy. They are contraindicated in the second and third trimesters of pregnancy because *in utero* exposure during this period is associated with severe impairment of renal development and function, oligohydramnios, limb contractures, lung hypoplasia, intrauterine growth retardation, and death – the ACEI/ARB fetopathy (28,29).

An increase of CMs in women without diabetes treated with ACEI in the first trimester was reported in a cohort study (RR 2.71 vs. women not receiving antihypertensive medication), while this was not observed in women receiving other drugs (30). However, a meta-analysis has concluded that the increased risk of CMs observed with ACEI versus healthy controls (RR: 1.78) was similar to that of other antihypertensive drugs (RR: 1.45) (31). In fact, maternal hypertension itself is associated with a significant increase risk of CMs, even without treatment (ORs: 1.20) (32). Therefore, the use of ACEI limited to the first trimester of pregnancy does not seem to be associated with a risk of CMs additional to that of hypertension itself or other antihypertensive drugs.

Statins

Statins are considered as potential teratogens, and their use is contraindicated in pregnancy. Cholesterol acts as an activator of the sonic Hedgehog proteins, which are essential for morphogenesis in vertebrates. In animal models, statins with high affinity for lipid tissues reach the embryo and downregulate cholesterol biosynthesis with reduction of sonic Hedgehog signal transduction, leading to abnormal morphogenesis (33). In an uncontrolled case series including all FDA reports of statin exposure during pregnancy, the rate of major CMs was 31.4% in exposed pregnancies, all of them in women taking lipophilic statins at the beginning of pregnancy. A specific pattern was described, including unusual anomalies such as holopresencephaly, limb deficiencies, and VACTERL association, a pattern that has been reported by some but not all studies. However, a recent meta-analysis concluded that the prevalence of CMs is not increased in pregnancies exposed to statins (RR: 1.15), although the results are limited by studies being of poor quality, of small sample size, and without adjustment for confounding factors (34). These studies were not, however, confined to women with diabetes.

With the available information, it seems prudent to advise women to discontinue statins before pregnancy. However, their inadvertent use at the beginning of pregnancy should not be a reason for termination of pregnancy.

Oral Agents

A study in women with T2DM exposed to oral agents in the first trimester of pregnancy (mainly first-generation sulfonylureas) reported a prevalence of 50% of CMs (both major and minor) versus 15% in women with similar glycemic control treated with insulin (35). However, additional studies including a greater number of women did not report an increased rate of CMs in offspring exposed to sulfonylureas during embryogenesis (36).

Although phenformin was reported to induce CM in mouse embryos in culture, metformin was not teratogenic. In humans, most information comes from studies in women with polycystic ovarian syndrome given metformin in the first trimester, and this is also reassuring. In a recent meta-analysis, women exposed to metformin had a nonsignificantly lower ratio of CMs (37). In women with T2DM, information is very limited, but metformin does not seem to be associated with CMs (35,38).

The ADA 2015 diabetes guidelines do not mention the use of either glyburide or metformin in women with preexisting DM (39). Rather, the recommendation is that women becoming pregnant while taking oral medications should start insulin as soon as possible, but metformin and glyburide can be continued until insulin is started in order to avoid severe hyperglycemia, a known teratogen. NICE 2015 considers the use of metformin in the preconception period and during pregnancy, when the likely benefits from improved glycemic control outweigh the potential for harm (informed consent is required since the summary product characteristics indicate that women pregnant or planning pregnancy should not be treated with metformin) (40).

Insulin and Insulin Analogs

The question of insulin per se as a teratogen has been addressed under pathophysiology. At present, there is no clear evidence relating insulin doses or type with CMs.

Even when evidence on improved pregnancy outcomes with insulin analogs is lacking, recent guidelines suggest preferential use of US Food and Drug Administration (FDA) and European Medicines Agency (EMEA)-approved short-acting analogs (lispro and aspart) over regular insulin (41,42) because they are more likely to reduce postprandial glucose excursions. In the aspart trial, postprandial glucose increments at the end of first and third trimesters were significantly lower with aspart than with regular insulin. Information on lispro comes essentially from post-marketing surveillance.

In the case of long-acting analogs, the detemir trial demonstrated lower fasting glucose at 24 and 36 weeks of gestation with

detemir (FDA and EMEA approved) than with NPH insulin, but pregnancy outcomes did not differ. For insulin glargine, no clinical data on exposed pregnancies from controlled clinical trials are available, but data from exposed pregnancies reported as post-marketing surveillance indicate no adverse effects. The recommendation is that women with diabetes successfully treated with these long-acting analogs preconceptionally continue with this therapy (41).

Prevention

Pre-Pregnancy Care (PPC)

As CMs associated with DM occur very early in pregnancy, when women may not even know that they are pregnant, it is essential that preventive measures begin before pregnancy. PPC is associated with a reduced CM rate, with attendants having about one-third the risk of non-attendants (43). Randomized clinical trials have not been performed and probably will never be, because the data supporting a beneficial effect of PPC render this trial unethical. Essentially, preventive measures are: (1) optimization of glycemic control prior to and early in pregnancy, (2) avoidance of teratogenic drugs, and (3) folic acid (FA) supplementation. Optimization of BMI should also be included. These preventive measures imply that women with pre-gestational diabetes should plan their pregnancies and use effective contraception methods until they are in the best possible condition for pregnancy.

Folic Acid Supplementation

FA supplementation in the periconceptional period to prevent CMs has been used since the 1990s. It prevents the occurrence of NTDs (overall RR: 0.28), and a preventive effect on other CMs has been suggested but not confirmed (44). As the recommendation of initiating FA supplementation preconceptionally is not followed in a large number of pregnancies, a good number of countries over the world have initiated mandatory food fortification with FA. These programs have achieved large reductions in NTDs without evidence of untoward effects.

Despite pregnancy in women with diabetes not being a folate-deficient state (45), most guidelines for pregnancy care of women with diabetes in the last two decades have included specific recommendations on FA supplementation (Table 11.2). With few exceptions (39), guidelines advise periconceptional supplementation of high doses of FA (4–5 mg/day). The rationale for this is the high risk of CMs including NTDs, supportive animal studies (51), and a mathematical model addressing both the impact of FA supplementation on maternal FA concentration and the association of the FA concentrations with NTDs (52). However, the wordings of the recommendations are cautious, and the strength of the recommendations is heterogeneous.

Data on the effect of FA supplementation on the risk of CMs in women with preexisting DM are limited to observational data, including fewer than 700 pregnancies, and are not conclusive.

As FA's tolerable upper intake level after nutritional guidelines is 1 mg/day (53), the aforementioned recommendations should be considered to be in the pharmacological range and with potential side effects. *Masking of vitamin B_{12} deficiency* was among the first concerns, but the 2009 US Preventive Services Task Force did not find any evidence to support or refute this (54). The potential increase of *cancer* (overall or specific types) was not confirmed in a recent meta-analysis, although most studies used doses <1 mg/day and exposures <5 years (55). The suggested association of FA supplementation with twinning disappeared after adjustment for *in vitro* fertilization (54). As to the possible association between FA supplementation and *asthma and allergic disease,* a systematic review concluded that most studies reported no association, and those supporting a positive relationship found a small increase in risk associated

Table 11.2 Recommendations of folic acid supplementation for women with pre-gestational diabetes.

Society	Recommended dose or evidence level and/or strength of recommendations	Period
Australian Diabetes in Pregnancy Society 2005 (46)	• "5 mg/day … should be" • Strength of recommendation not given	"Should be commenced before conception"
Endocrine Society 2013 (41)	• "We suggest … 5 mg/day" • Evidence 2++; less strong recommendation	"Beginning 3 months before withdrawing contraceptive measures or … trying to conceive … at 12 weeks gestation the dose of folic acid reduced to 0.4–1.0 mg/d"
Canadian Diabetes Association 2013 (42)	• 5 mg/day • Grade D, the best evidence was … consensus or other than clinical trials or cohort studies	"At least 3 months pre and continuing until at least 12 w postconception"
American College of Obstetricians and Gynecologists 2005 on Pregestational Diabetes (47)	• "at least 400 μg … Higher doses of folic acid may be beneficial in some cases, especially in the presence of other risk factors for neural tube defects" • Strength of recommendation not given	"Should be given to all women contemplating pregnancy"
American College of Obstetricians and Gynecologists 2003/2013 on Neural Tube Defects (48)	• "For women at high risk of NTDs … folic acid supplementation of 4 mg per day is recommended" • Level A, based on good and consistent scientific evidence	"Periconceptional"
Royal College of Obstetricians and Gynaecologists 2014 (49)	• "you may be advised… 5 mg/day" • Strength of recommendation not given	"Start taking extra folic acid before … and continue … until … 13th week"
Society of Obstetricians and Gynaecologists of Canada 2015 (50)	• "… require a diet of folate-rich foods and daily oral supplementation with a multivitamin containing 1.0 mg folic acid … Measurement of red blood cell folate levels could be part of the pre-conception evaluation to determine the multivitamin and folic acid supplementation dose strategy (1.0 mg with RBC folate < 906 nmol/L and 0.4 to 0.6 mg with RBC folate > 906) with a multivitamin" • A; there is good evidence to recommend the clinical preventive action	"Beginning at least 3 months before conception … until 12 weeks"
American Diabetes Association 2008/2016 (39)	• At least 400 ug/day • Strength of recommendation not given	"In the periconception and prenatal periods"
National Institute for Health and Care Excellence 2015 (40)	• "advise women … to take folic acid (5 mg/day) … " • Evidence level 3–4 (nonanalytical studies/expert opinion)	"Since planning … until 12 weeks"

with supplementation in late pregnancy and generally confined to early childhood (56). Finally, in a population with a high prevalence of vitamin B_{12} deficiency and receiving a high FA supplementation, high maternal concentrations of folate predicted *insulin resistance and obesity* in the offspring (57).

Proposed mechanisms are speculative and include epigenetic modifications and a reduction in lean body mass accompanying increased lipogenesis. The reduction of protein synthesis is due to the deficiency of vitamin B_{12} preventing the synthesis of methionine from homocysteine, an effect that would be boosted by the increased levels of 5-methyltetrahydrofolate. In parallel, the deficiency of vitamin B_{12} blocks methylmalonyl-CoA mutase, and the increased levels of methylmalonyl-CoA would block beta-oxidation of fatty acids and facilitate lipogenesis.

Detection and Management

Screening for CMs gives the opportunity to the mother and family to be prepared for unexpected events, allowing antenatal counseling, treatment, and appropriate obstetric management according to maternal decisions.

Once pregnancy is confirmed, the woman should contact the obstetrician to confirm both viability and dates. The risk of chromosomal abnormalities is not increased in DM, and women with diabetes should be offered screening for aneuploidy just as women without diabetes. However, for first-trimester biochemical screening, it has to be taken into account that maternal DM may affect the concentrations of alfa-feto-protein (decreased), unconjugated estriol (decreased), beta-HCG (decreased in some studies), and pregnancy-associated plasma protein-A (decreased). Other parameters such as nuchal translucency do not seem to be affected by DM (40). Thus, aneuploidy screening results by either alfa-feto-protein + estriol + beta-HCG or pregnancy-associated plasma protein-A + beta-HCG + nuchal translucency need adjustment by maternal DM to allow advice on risk category. Indications for placental biopsy or amniocentesis do not differ from the general population.

The ultrasound scan performed for aneuploidy screening can detect an important percentage of major anomalies (30–70%). However, between 18 and 22 weeks, a high-resolution ultrasound scan should be offered to all pregnant women and particularly those with DM. The aim is to detect structural abnormalities that could not be identified earlier in pregnancy, but women should be warned of the limitations of the screening, particularly in the presence of obesity. The organs and structures of the fetal body and in particular central nervous system should be described, and NTDs ruled out (Figure 11.1). Ultrasound scan is the best test to detect cardiac CMs, fetal echocardiography should use the four-chamber view, and the outflow tracts need to be visualized and described. The cost-effectiveness of this approach has been described as robust in sensitivity analysis. If there are doubts or abnormal findings, the ultrasound examination should be repeated in a few weeks together with a pediatric cardiologist to advise the woman about the importance of the abnormality.

If a severe CM is diagnosed, a decision is needed with respect to termination or continuation of pregnancy. Counseling and support for mother and family are a necessity and should be done ensuring that the mother does not feel guilty. If the decision is to terminate pregnancy, this can be done with prostaglandin induction and epidural anesthesia; contraceptive advice should be given, and future pregnancy intentions evaluated with appropriate pre-conception advice. If the decision is to continue pregnancy, advice should be given regarding the prognosis for the baby and the need for surgery after birth; this should be planned with a multidisciplinary approach in a tertiary and well-equipped center.

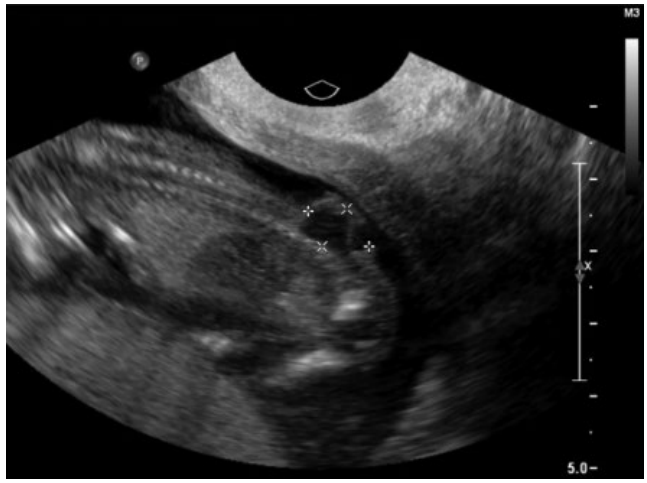

Figure 11.1 Ultrasound scan of a diabetic woman at 13 weeks of gestational age showing a lumbar myelomeningocele.

Multiple-Choice Questions

1 One of the following statements regarding CMs in humans is not true:
- **A** Prevalence is similar in women with type 1 and type 2 DM.
- **B** Cardiac anomalies are the most frequent type.
- **C** Hypoglycemia is a potent teratogen.
- **D** High body mass index is teratogenic.

The correct answer is C. Even when hypoglycemia is a potent teratogen in animal models, its role in human diabetic pregnancy is not clear; the most likely reason is that exposure time in human pregnancy is not equivalent to that in animal models.

It is true that prevalence of CMs is similar in women with T1DM and T2DM, that cardiac anomalies are the most frequent type, and that high body mass index is teratogenic.

2 One of the following statements regarding folic acid supplementation in pregnancy is not true:
- **A** 1 mg/day of folic acid is the upper tolerable intake level in adults.
- **B** In animal models, folic acid prevents hyperglycemia-induced malformations.
- **C** Diabetic pregnancy is a folate-deficient state.
- **D** Evidence on folic acid supplementation in human diabetic pregnancy is scarce.

The correct answer is C; diabetic pregnancy is not a folate-deficient state.

It is true that 1 mg/day is the upper tolerable intake level of dietary folic acid in adults, that folic acid prevents hyperglycemia-induced malformations in animal models, and that evidence on folic acid supplementation in human diabetic pregnancy is scarce.

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12

Provision of Pregnancy Care

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PRACTICE POINTS

- There is a lack of international consensus regarding the management of diabetes in pregnancy, particularly gestational diabetes.
- A UK survey in 2002–2003 indicated that pregnancy outcomes for women with preexisting diabetes are suboptimal, and recent surveys in England and Wales suggest no significant improvement.
- Across the UK, the quality of care for women with diabetes is variable, and preconception care is frequently lacking. In the USA, lack of uniformity in the availability of healthcare services is an additional barrier.
- A single international guideline, along with improvements in preconception care and the universal adoption of a multidisciplinary team approach, could transform the quality of care provided to these women.

Case History

Emma is a 32-year-old primigravida who developed type 1 diabetes at the age of 5. Background retinopathy and proteinuria were first noted in her mid-20s. She smokes 20 cigarettes daily. She and her long-term partner are thinking about starting a family, but have not discussed this with the diabetes care team. When she attended her diabetes center for annual review, her Body Mass Index (BMI) was 28 kg/m^2 and HbA1c 78 mmol/mol (9.3%). Her diabetes physician routinely reminded her of the importance of pregnancy planning, glycemic targets, and the potential fetal complications should conception occur in association with poor glycemic control. She was also advised of the need to stop her lisinopril once the pregnancy was confirmed and simvastatin prior to conception, to commence high-dose folic acid (5 mg), and of the importance of contraception. She subsequently met a diabetes specialist midwife who discussed the likely outcomes and risks of pregnancy, and the pros and cons of optimal glycemic control. She also met a specialist dietician. She was also given the telephone number of the pregnancy team so that she could make rapid contact if she thought she was pregnant.

Emma saw her diabetes specialist nurse and dietician regularly over the next 6 months. When her HbA1c was below 53 mmol/mol (7%) and with no significant hypoglycemia, she was advised

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that she could stop using contraception. Two months later, a pregnancy test was positive and she immediately contacted the joint diabetes antenatal team. Emma was advised to commence aspirin 75 mg once daily to reduce the risk of pre-eclampsia.

During pregnancy, she was reviewed every 1 – 3 weeks at this clinic by the team, with phone call support with regard to her diabetes control between visits. She achieved good glycemic control, with her HbA1c decreasing to 42 mmol/mol (6%) without significant hypoglycemia. Regular ultrasound scans showed a normal growth profile. Retinal assessment showed no deterioration. Her blood pressure and proteinuria remained stable until 35 weeks, when Emma developed significant hypertension and proteinuria. This progressed in severity over the following weeks, requiring induction of labor at 37 weeks. After successful management of her diabetes during labor using a glucose insulin infusion according to a standard protocol, she delivered a healthy baby weighing 3.3 kg who did not require admission to the neonatal unit.

Immediately following delivery, her subcutaneous insulin dose was reduced to below her pre-pregnancy insulin regime, and continued at the lower doses as she was breastfeeding. At her 6-week postnatal review, she received contraceptive advice and an intrauterine contraceptive device was inserted. Her angiotensin-converting enzyme inhibitor (ACE-I) and statin were restarted after she stopped breastfeeding, and she was referred back to her diabetes center for ongoing care.

- What are the specific objectives of antenatal care for women with diabetes?
- What are the key components of antenatal care?
- What makes up a successful multidisciplinary team?
- What are the barriers to effective pregnancy care?
- What are the key components of postnatal care?

Background

A multidisciplinary team operating in a secondary- or tertiary-care setting is a commonly adopted model for the provision of pregnancy care to women with diabetes (1). Our own clinic started in the 1960s, and our practice has evolved over the years in response to changes in patient population, clinical evidence, and local resources. It mirrors practice elsewhere in the UK. Here, we offer simple practical advice on how to provide a diabetes-in-pregnancy service meeting the standards recommended in the UK National Institute for Health and Care Excellence (NICE) guidelines (2).

Guidelines for the Provision of Care

In a review of 12 international guidelines for the care of women with diabetes in pregnancy published in 2006 (3), the guidelines for preconception care for women with pregestational diabetes were similar apart from folic acid doses varying between 0.4 and 5 mg daily. The guidelines for antenatal care rarely distinguished patients with type 1 or type 2 diabetes, and there were significant differences in glycemic targets during pregnancy, frequency of antenatal appointments, ultrasound scans, and gestational age at induction or caesarean section. However, recommendations for labor and postnatal management were similar.

For gestational diabetes mellitus (GDM), there was even greater variation within and between countries in the selection process for screening; the screening methodology; oral glucose tolerance testing (OGTT), including the number of samples taken; and the diagnostic criteria. For example, the selection criteria for screening vary from none, to selected groups only, to all women. Screening includes: a 50 g nonfasting OGTT performed between 24 and 28 weeks, a random plasma glucose at 28 weeks, and a 75 g OGTT. Diagnostic thresholds include fasting glucose values ranging from 5.1 to 6.0 mmol/L (95–126 mg/dL) and/or 2 h

glucose from 7.8 to 11.1 mmol/L (140 – 200 mg/dL) following a 75 g oral glucose load (4–6).

In the management of GDM, areas of disagreement involve capillary glucose targets fasting (<5.3 – 6.0 mmol/L [95–108 mg/dL]), post-prandially (1 h: <7.0 or 2 h: <8.0 mmol/L [126 – 144 mg/dL]), timing of delivery (38–41 weeks), and timing and type of postnatal testing (fasting glucose, OGTT, or HbA1c) at 4–26 weeks, but usually 6 weeks for glucose testing and after 12 weeks for HbA1c (4).

There is therefore no international consensus on the management of women with diabetes in pregnancy, particularly for the diagnosis and management of GDM. However, attempts have been made by the World Health Organization (WHO) and the International Federation of Gynecology and Obstetrics (FIGO) to address some of these issues related to GDM (see Chapters 4 and 5).

Aims of Multidisciplinary Joint Antenatal Diabetes Care

The overall aims are to allow the mother to have a good experience of pregnancy, excellent glycemic control, and a normal delivery of a healthy baby.

Pre-Pregnancy Care

The reader is referred to Chapter 10. The barriers to achieving these aims are discussed in detail in the "Special needs" section.

Pregnancy Care

The aims of care for women with diabetes during pregnancy are:

- Rapid referral (self or via a health professional) to a combined (diabetes and obstetric) antenatal clinic when pregnancy is suspected
- Maintenance of near-normal blood glucose levels throughout pregnancy if this can be achieved safely
  - Premeal capillary glucose levels: 4.0–5.3 mmol/L (72–95 mg/dL)
  - 1 h postprandial capillary glucose levels: less than 7.8 mmol/L (140 mg/dL) (2)
  - 2 h postprandial capillary glucose levels: less than 6.4 mmol/L (115 mg/dL) (2)
- Cessation of any potentially teratogenic medication
  - Patients are often prescribed statins and drugs affecting the renin angiotensin system prior to pregnancy.
- Prescription of folic acid 5 mg daily during the first trimester
- Measurement of HbA1c to assess risk of fetal abnormalities
- Detection, monitoring, and appropriate management of any diabetes-related complications, including rapid referral for retinal assessment (see Chapter 21)
- Accurate pregnancy dating by ultrasound
- Provision of routine antenatal screening/testing (e.g., blood group antibodies)
- Ultrasound detection of fetal abnormalities by approximately 20 weeks or earlier
- Assessment of fetal well-being with regular ultrasound in late second and third trimesters
- Assessment of risk by measurement of HbA1c in late second or early third trimester
- Determination of the most appropriate time and mode of delivery
- In women at high risk of delivery at less than 34 weeks, in-hospital administration of steroids with careful capillary glucose monitoring and intensified insulin therapy (see also Chapter 23)
- An individualized written plan for management of blood glucose levels post-delivery agreed by 36 weeks gestation at the latest
- Provision of patient-centered care and support appropriate to the patient's educational, cultural, religious, and social background.

Major factors limiting the standard of care include:

- Late referral due to poor primary care services or delayed pregnancy diagnosis

- Late and poor attendance associated with maternal deprivation or other socioeconomic factors
- Severe hypoglycemia and hypoglycemia unawareness:
  - Major risk factors for women with type 1 diabetes, particularly in the first trimester
  - Aggravation by nausea, vomiting, and/or autonomic neuropathy.

Postnatal Care

The aims for postnatal care are to:

- Revise glucose-lowering regime post-delivery with regular glucose monitoring, on the understanding that the regime may need changing depending on clinical circumstances.
- Encourage skin-to-skin contact and breastfeeding within an hour of birth.
- Enable all babies to remain with their mothers unless there are neonatal complications.
- Encourage early feeding after delivery with monitoring of neonatal blood glucose as indicated (see Chapter 24).
- Maintain acceptable maternal blood glucose control:
  - Target 4 – 7 mmol/L (72 – 126 mg/dL) pre-meals as nonpregnant goal, but important to consider running blood glucose levels somewhat higher to prevent hypoglycemia, especially in women who are breastfeeding. Avoid pre-breakfast values less than 5 mmol/L (<90 mg/dL) for 4 – 6 weeks.
  - Close monitoring of blood glucose if breastfeeding.
- Discuss and provide contraception (e.g., oral or injectable, or arrange e.g. intrauterine contraceptive device [IUCD] insertion) by 5 – 6 weeks postpartum (see Chapter 25).
- Arrange a 6-week follow-up clinic visit.
- Offer women with GDM:
  - A 6-week fasting glucose or 75 g OGTT or, if not seen until after 12 weeks, an HbA1c test
  - Advice on weight management, diet, and exercise
  - An annual screening visit for diabetes with an HbA1c performed in the community
  - Glycemic assessment prior to discontinuation of contraception when future pregnancy is desired.

Organization: Members of the Multidisciplinary Team

The composition of the clinical team will vary according to local circumstances. Essential members of the team include an obstetrician and a diabetes physician supported by a diabetes-trained midwife, a diabetes nurse, and a dedicated dietician. In US centers, other members may include a perinatologist and social worker. On the basis of clinical experience, we suggest that important characteristics of a multidisciplinary team should include:

- Inclusion of motivated individuals with good interpersonal skills and a high affinity for team working, and ideally possessing training in motivational interviewing and behavior change. The team members should meet regularly to discuss organization of the service, protocols, national standards, adverse events, audit, research, and education.

Team members have some specific roles and some shared and/or exchangeable roles. Good communication between team members, and clearly defined team goals, facilitate task sharing. The role of each team member as developed from our own clinical experience is summarized in Table 12.1.

The diabetes specialist midwives and diabetes specialist nurses provide telephone support, sometimes on a daily basis, to optimize glycemic control. The obstetricians and physicians have an on-call system providing continuous cover for emergencies.

The organization of clinics will vary according to local circumstances. In our practice, we have seven clinic rooms to enable individual

Table 12.1 Roles of multidisciplinary team members.

Team member	Roles
Team leader	Chair monthly team meetings. Liaise with primary care physicians. Coordinate regional policies and procedures. Have responsibility for clinical governance, including auditing adverse outcomes.
Obstetrician	Counsel women on risks to mother and baby associated with diabetes. Educate all women about screening and diagnostic tests for Down's syndrome. Assess fetal well-being, including anomaly and growth scans. Decide on timing and mode of delivery and intrapartum management. Counsel parents and staff regarding adverse events. Take a lead role in audit and research with the diabetes physician.
Diabetes physician	Identify women of childbearing age for preconception care. Give preconception advice, including medication review. Optimize glycemic control before, during, and after pregnancy. Manage and/or refer to appropriate subspecialists for treatment of complications, such as retinopathy or nephropathy. Manage insulin: prescription, education, and dose adjustment. Educate patient, and partner/friend/support person, about diagnosis and treatment of hypoglycemia, including the use of glucagon. Offer emergency advice (e.g., on recognition of hypoglycemia and ketoacidosis).
Diabetes specialist midwife (equivalent to certified diabetes educator in the USA, who is frequently a registered nurse)	Provide educational support during preconception, antenatal, and postnatal stages. Explain potential risks to mother and baby. Offer advice on blood glucose monitoring, insulin use, hypoglycemia, hyperglycemia, ketoacidosis, and sickness. Optimize glycemic control. Liaise with partner/family, and offer telephone support between clinics. Give advice to delivery suite staff on management of diabetes in labor. Give advice on feeding of the neonate.
Diabetes specialist nurse	Provide educational support during preconception, antenatal, and postnatal stages. Offer advice on blood glucose monitoring, insulin use, hypoglycemia, hyperglycemia, ketoacidosis, and sickness. Optimize glycemic control. Provide specialist advice with regard to insulin pumps and sensors. Liaise with partner/family, including telephone support.
Dietician	Give dietary advice in the preconception, antenatal, and postnatal phases. Give advice about a healthy balanced diet, carbohydrate counting, folic acid, weight management, and strategies for coping with illness. Optimize glycemic control. Promote and encourage breastfeeding.
Primary care team	Identify women with diabetes of childbearing age for preconception care. Inform about contraception and pre-pregnancy management. Refer to a specialist multidisciplinary team in a timely fashion.
General ward staff	Provide high-quality diabetes and obstetric care to inpatients. Optimize glycemic control (e.g., with a glucose–insulin infusion) during labor.

(one-to-one) consultations with review of women by individual members of the team based on clinical need. This is determined by the week of gestation and the previous visit assessment (Figure 12.1). At the end of each clinic visit, the investigations required at the next clinic visit are agreed, based on a standard template with individual variation as indicated, thus reducing phlebotomy and ultrasound scanning waiting time.

Date	Type of diabetes
Name	Date of diagnosis
Hospital number	Date GTT
	Results: fasting 2 h
DOB	Age
Obstetric history	Parity
BMI pre-pregnancy	Gestation at first visit
Past medical history	Medication, incl. folic acid 5 mg
Social/family history/smoking	Allergies
Pre-con diabetes treatment	Diabetes complications
Hypoglycemia (frequency/severity/awareness)	
Pre-con care: Y/N – why?	Folic acid 5 mg od R'xd Y/N
Fundi: dates and findings	1. 2. 3.
Glucagon prescribed Y/N	Ketostix prescribed Y/N
High risk: Y/N – why?	Date Action
Diabetes management: For spontaneous labor, induction of labor or C-section, and postnatally. Refer to local guidelines. Specific instructions:	
Management of the neonate: Refer to local guidelines. Specific instructions:	

Figure 12.1 Diabetes in pregnancy proforma.

Name Hospital number

Glucose targets: premeal, 4.0–5.3 mmol/L (70–95 mg/dL); 1 h post meal, <7.8 mmol/L (<140 mg/dL); and 2 h post meal, <6.5 mmol/L (<117 mg/dL).

Week	Special visit	Weight (kg)	HbA1c	Glucose: pre/post-meal representative results				Insulin dose: current/new. Circle long-acting dose. Write name above column.				
				Breakfast	Lunch	Eve meal	Before bed					
4	Booking Bloods			/	/	/	/	/	/	/	/	/
5	Scan 7–8 wk			/	/	/	/	/	/	/	/	/
6	Folic acid			/	/	/	/	/	/	/	/	/
7	Hb, U&E			/	/	/	/	/	/	/	/	/
8	LFT, TFT			/	/	/	/	/	/	/	/	/
9	HbA1c			/	/	/	/	/	/	/	/	/
10	Retinal screening (if not done in last 3 months for pre-gestational diabetes)			/	/	/	/	/	/	/	/	/
11	Glucagon			/	/	/	/	/	/	/	/	/
12	Ketostix. Down screen			/	/	/	/	/	/	/	/	/
13				/	/	/	/	/	/	/	/	/
14				/	/	/	/	/	/	/	/	/
15				/	/	/	/	/	/	/	/	/
16				/	/	/	/	/	/	/	/	/
17	Retinal screening if first screening abnormal			/	/	/	/	/	/	/	/	/
18				/	/	/	/	/	/	/	/	/
19				/	/	/	/	/	/	/	/	/
20	Anomaly scan			/	/	/	/	/	/	/	/	/
21				/	/	/	/	/	/	/	/	/
22				/	/	/	/	/	/	/	/	/
23				/	/	/	/	/	/	/	/	/
24	Scan			/	/	/	/	/	/	/	/	/
25				/	/	/	/	/	/	/	/	/
26				/	/	/	/	/	/	/	/	/
27				/	/	/	/	/	/	/	/	/
28	Anti-D, scan Retinal screen			/	/	/	/	/	/	/	/	/
29				/	/	/	/	/	/	/	/	/
30				/	/	/	/	/	/	/	/	/
31				/	/	/	/	/	/	/	/	/
32	Scan			/	/	/	/	/	/	/	/	/
33				/	/	/	/	/	/	/	/	/
34				/	/	/	/	/	/	/	/	/
35				/	/	/	/	/	/	/	/	/
36	Scan			/	/	/	/	/	/	/	/	/
37				/	/	/	/	/	/	/	/	/
38				/	/	/	/	/	/	/	/	/
39				/	/	/	/	/	/	/	/	/
40				/	/	/	/	/	/	/	/	/

Figure 12.1 (Continued)

Standardization of Schedules and Documentation

National guidance is particularly useful when quality of care is variable and the standard is often suboptimal (7). Here, we describe our local practice that is in line with the recommendations of NICE 2015 guidelines (2).

Preconception Care Tools

These will depend on the specific needs of the population served and local resources. In a clinic such as ours, where women come

from a multiethnic inner-city population, there are several potential strategies that could improve access to care:

- Recruitment of specialist members of the team relevant to the ethnic groups who need targeting
- Creation of educational posters to be displayed in diabetes clinics in primary and secondary care
- Production of an educational DVD to be sent by physicians or specialist nurses caring for women with diabetes with childbearing potential (8,9)
- Production of an educational leaflet to be mailed annually to all women with diabetes with childbearing potential
- Annual educational text messaging and email reminders to all women with diabetes with childbearing potential from their physician or specialist nurse caring for their diabetes
- Development of diabetes support smartphone apps to aid optimization of preconception care.

Provision of Care for Women with Pre-gestational Diabetes

Referral

We facilitate early clinic attendance once conception is confirmed (e.g., about 5 weeks gestation) by encouraging phone call referrals from the women themselves or any healthcare professional. In our service, it is our diabetes specialist midwives who make immediate telephone contact with the woman, although in other centers it may the diabetes specialist nurse. Advice given includes: home blood glucose monitoring with testing a minimum of seven times a day (pre- and post-prandial and before bed); blood glucose targets and the rationale for excellent glycemic control; folic acid usage; stopping potentially teratogenic medication; and providing contact numbers for future support. Women with a history of GDM during a previous pregnancy are also encouraged to be referred directly to our diabetes specialist midwife at booking (<12 weeks of gestation) and are given similar advice.

First Visit Following Conception

This first review is offered within 1 week of referral (usually with the diabetes specialist midwife) in accord with 2016 NICE Quality Standards (10). This first visit is an opportunity to obtain a detailed history of the woman's diabetes, assess her understanding and management of her condition, and discuss management changes associated with improved glycemic control in pregnancy. This allows the woman to be offered an educational package tailored to her individual needs.

This might include:

1) Diabetes treatment, including insulin regime, technique, and injection sites
2) Training and/or review of blood glucose and blood ketone meters and sensors, often encouraging more frequent testing to improve overall diabetes control
3) Educating women and family members about hypoglycemia, how and when to treat, and warning signs; also, teaching family members how to use glucagon
4) Sick day rules and when to come into hospital
5) Importance of eye screening during pregnancy.

This consultation is time-consuming but helps to prepare the woman for the rest of the pregnancy. This initial contact is followed by a clinic appointment, which includes a review by all members of the multidisciplinary team and an ultrasound scan to confirm pregnancy and for dating if the pregnancy is sufficiently advanced.

Dietician Review

At the initial visit, which ideally should have occurred pre-pregnancy, we review diet and lifestyle and provide dietary advice to improve nutritional quality if necessary. Women with type 2 diabetes may wish to reduce weight or minimize weight gain during pregnancy. Carbohydrate awareness is important for women with type 2 diabetes, for example whether in conjunction with recently commenced insulin therapy or in conjunction with metformin,

both in an effort to optimize glycemic control. The knowledge and skills of women with type 1 diabetes in self-management and capability to perform carbohydrate counting are assessed on an individual basis. Emphasis is placed on low-glycemic-index food choices, and guidance is provided where needed.

Planning Care for Pregnancy

All women are provided with a care plan from onset of pregnancy to 6 weeks postdelivery (Figure 12.1). This document includes blood glucose targets, retinal and renal screening and follow-up, fetal surveillance including anomaly and serial growth scans, and plans for delivery and diabetes management after delivery. The care plan is part of a woman's medical records and is used by all team members.

At the first visit, women are screened for the presence of all diabetes-related complications. In England, there is a National Retinal Screening Programme that has replaced the need for fundoscopy being performed by the diabetes physician in clinic. Arrangement should be made for it to be done as soon as possible (unless performed in the immediate 3 months prior to conception) and then, if any abnormalities are noted, repeated again between 16 and 20 weeks gestation. All women should have a further assessment at about 28 weeks gestation. Women with pre-proliferative or proliferative retinopathy are referred to an ophthalmologist. Renal function is assessed by baseline screening for proteinuria, and quantified using a protein–creatinine ratio (PCR) with a threshold of 30 mg/mmol. If the urinary protein–creatinine ratio is greater than 30 mg/mmol or total protein excretion exceeds 0.5 g/day, or if the serum creatinine is abnormal (120 mmol/L or more), referral to a nephrologist should be considered. Women with nephrotic-range proteinuria (≥300 mg/mmol), evidence of significant renal impairment, or uncontrolled hypertension are referred to a nephrologist for further evaluation and treatment. They will also be advised to have thromboprophylaxis.

Follow-up

For women with type 1 or 2 diabetes, clinic attendance should be weekly initially until glycemic control is satisfactory. For the remainder of the pregnancy, women are usually seen at least every 1 – 3 weeks until 36 weeks, and then weekly until delivery. Current national guidance suggests that there should be contact, which can be by phone in appropriate cases, every 1–2 weeks (2). It is also often possible to review glycemic control remotely by downloading the data from home meters, thus reducing the need for such frequent hospital visits.

For those women in whom good glycemic control is not being achieved despite dietary and therapy review, and those with an early pregnancy HbA1C of >85 mmol/mol, we consider admission to hospital for supplementary intravenous sliding-scale insulin (with no glucose infused) and hourly blood glucose measurements to determine an appropriate insulin regime (11). Alternatively, we sometimes use a glucose sensor for 1–2 weeks to facilitate the improvement of glycemic control.

All women are offered screening for fetal abnormalities with a detailed fetal anomaly ultrasound scan by 20 weeks gestation, which includes a cardiac four-chamber view and visualization of outflow tracts in accordance with UK national recommendations (7). Serial ultrasound scans for growth, liquor volume, and umbilical artery Doppler continue until delivery. If glycemic control is satisfactory and the growth profile is not showing growth acceleration, then we follow NICE guidance of four weekly scans (2). If there are concerns about deviation of fetal growth or concerns regarding maternal condition, particularly glycemic status, then scans are performed more frequently. If there is concern about a reduction in fetal growth rate, increased surveillance with additional tests of fetal wellbeing (middle cerebral artery and ductus venosus Doppler) are offered as appropriate, as for women without diabetes.

If preterm delivery before 35 weeks is anticipated, then admission to hospital for corticosteroid therapy to enhance fetal lung maturity is advised, and we favor using a

supplementary intravenous sliding-scale insulin regime continued for 24 h after the second dose of steroid (see Chapter 23).

Pregnancies in which the fetus is estimated to be macrosomic have a clear management plan that includes fetal surveillance and the timing and mode of delivery.

In the final weeks of pregnancy, the timing and mode of delivery are discussed, along with the management of diabetes, and if necessary an anesthetic assessment is arranged. In uncomplicated pregnancies, we aim for a spontaneous vaginal delivery by no later than 40 weeks of gestation, with almost all being delivered before 39 weeks in keeping with current NICE guidance (2). Postnatal management, including the plan to reduce or stop insulin depending on diabetes type, supervision of the neonate, and the initiation of breastfeeding and evaluation of its effect on glycemic control, is explained.

Delivery

Continuous electronic fetal monitoring is offered to all women in established labor (see Chapter 22). Hourly blood glucose monitoring is carried out in established labor, and in the presence of excursions in blood glucose concentrations, sliding-scale intravenous dextrose–insulin is used to maintain maternal normoglycemia (see Chapter 23). Increasing numbers of women are using continuous subcutaneous insulin infusion (CSII) pumps during pregnancy with regular self-adjustment and often wish to continue their use in labor. Women are advised that as long as they (or their birthing partner) are able to make the necessary adjustments to the pump to maintain normoglycemia, then it is acceptable to continue the pump in labor with documented discussion in advance about regime changes (see Chapter 17). Similarly, for women having a planned cesarean section, careful planning of the basal rates around the time of the operation have allowed many to avoid a sliding scale and maintain normoglycemia before, during, and after delivery.

Postnatal Care

Glycemic targets, glucose management, and contraception are discussed prior to hospital discharge. All women with preexisting diabetes are reviewed postnatally and at around 6 weeks after delivery or earlier if there have been anxieties with regard to control. Here, they receive further advice on contraception and preconception care for future pregnancies. Contraception is prescribed or supplied at this visit if not already provided at hospital discharge. Women are advised not to discontinue contraception when a future pregnancy is desired until maternal glucose concentrations are at a level that provides minimal risk of diabetes-related birth defects. Women are then referred back to their pre-pregnancy care providers.

Provision of Care for Women with Gestational Diabetes

Women are usually referred to the joint clinic at the time of diagnosis of GDM. We currently perform diagnostic glucose tolerance tests at 26 weeks gestation and, if positive, offer appointments within 1 week of the test (10). Women are taught how to perform blood glucose monitoring and are reviewed within 1 week of diagnosis to assess their response to dietary advice from our dietician. Women whose readings are persistently above target despite dietary advice are prescribed metformin in the first instance. However, if glucose values are significantly raised (e.g., pre-prandial >6.5 mmol/l [117 mg/dL] or post-prandial >11.0 mmol/l [198 mg/dL]), then insulin is commenced immediately in conjunction with metformin therapy. Subsequent management is the same as for women with preexisting diabetes (as discussed in this chapter). Women are reminded at around 36 weeks gestation that their blood glucose–lowering therapy will be stopped at delivery. They are also advised regarding lifestyle, given the increased risk of type 2 diabetes in later life.

Postnatally, prior to discharge, previous advice is reinforced with regard to weight

management, diet, and exercise. Women with GDM are offered an assessment of glucose tolerance in the postnatal period. Previously, we offered a full 75 g OGTT around 6 weeks postpartum, but now in concordance with 2015 NICE guidance (2), we offer a fasting venous plasma glucose in primary care, although this will miss a very small number of women with a post–glucose load test diagnostic of diabetes. If women are delayed in returning for their 6-week check, then an HbA1c can be measured as an alternative. Women should also be offered annual checks of HbA1c in primary care in accordance with National Guidelines. If in pregnancy a woman had an OGTT fulfilling the criteria for the diagnosis of diabetes, then after pregnancy an OGTT should still be advised.

Special Needs

Several barriers limit the provision of good-quality diabetes care in pregnancy. These include external factors such as socioeconomic status, the healthcare system, the availability of and access to healthcare personnel, and the attitudes of healthcare professionals. Psychosocial factors include group pressure, prejudice, family and work demands, communication difficulties, and lack of support. Psychological factors include cultural, religious, and health beliefs; poor motivation; low self-efficacy; difficulty setting priorities; being in the pre-contemplative stage of change; and emotional issues, including anxiety and depression.

Social Deprivation

Social deprivation contributes to diabetes through dietary factors, higher levels of obesity and psychological stress, and lower levels of physical activity, education, and employment. Those who develop diabetes in poor communities often experience lower quality diabetes care. People from socially deprived communities have been shown to be less compliant with diabetes interventions and have lower levels of diabetes knowledge compared to more affluent individuals (12). This is of particular relevance to type 2 diabetes, where there is a high prevalence of deprivation; 66% of women are in the fourth or fifth quintiles of deprivation (13), and this is discussed further in Chapter 14.

Ethnicity

Type 2 diabetes and GDM are more common in ethnic minority groups compared to whites. In the UK and Europe, there are large numbers of high-risk women from South Asia and the Middle East. In the USA, while there are also many South Asians, Latinas, particularly those of Mexican and Central American provenance, comprise a high-risk group for GDM.

People from different ethnic groups may not speak or understand the local language, and they may have different cultural and health beliefs. For example, Bangladeshi immigrants have been found to have very different healthcare beliefs about diabetes, and particularly about diet and exercise, compared to whites.

British South Asians report lower levels of physical activity than the general population, particularly among women and older people (14). Social rules and cultural expectations, such as restrictions on women leaving the home to socialize and take part in other outdoor activities, could partly explain this.

Members of ethnic minorities tend to report more knowledge gaps about diabetes than the native population. Patients who do not speak English may also have poor literacy skills in their own language. The production of culturally appropriate patient information in the language understandable by the patient can be helpful. The provision of DVDs and internet resources may be more appropriate, particularly for those with poor literacy skills.

Problems with Provision of Maternity Care and Clinical Governance

The 2002–2003 UK CEMACH survey reported alarmingly poor outcomes for women with either type 1 or type 2 diabetes when compared to women without diabetes (7). Fewer than one in five of NHS Hospital Trusts had any kind of preconception service. A survey of births in England and Wales in 2014 (13) demonstrated minimal improvement, with only 55% of women with type 1 diabetes and 33% of women with type 2 diabetes taking folic acid in the preconception period. Glycemic control prior to pregnancy, as assessed by first-trimester HbA1c, was also poor, with only 8% of women with type 1 diabetes and 22% with type 2 diabetes having an HbA1c <43 mmol/mol (6.1%). All of these factors are dependent on the delivery of, and access to, high-quality pre-pregnancy care.

Despite multidisciplinary secondary care for women with type 1 diabetes, there still remain high rates of preterm delivery (43%) and cesarean section (67%). Stillbirth rates remain higher than in the background population. However, admission to special care baby units has declined, with now only 33% of babies being separated from their mothers at birth.

The Way Forward

The most urgent problem relates to the availability of high-quality pre-pregnancy care, which, despite recommendations in England and other countries, is frequently not occurring. For women with type 2 diabetes, whose management is often in primary care, it is essential that the healthcare professionals routinely offer advice about pregnancy risks and recommend appropriate preparation for pregnancy to all women in the reproductive age group. In areas of high deprivation and large numbers of ethnic minority women, innovative approaches may be required. However, even for women with type 1 diabetes who have the majority of their care in a secondary care setting, the data suggest that similar approaches are still required.

In order to maintain and improve the standard of pregnancy care, there is the need for regular, simple standard audits conducted at local, regional, and national levels. The ability of individual hospitals and care providers to be able to benchmark against regional/national performance is very useful in driving improvements in care, particularly as a method of securing additional resources. Sufficient knowledge is now available to inform best practice. The universal implementation of this best practice could transform the outcomes for women with diabetes in pregnancy. Our challenge is to deliver this quality of care to all women with diabetes.

Editor's Note: A Us Perspective

It is important to first note the similarities in provision of healthcare to women who have diabetes on both sides of the Atlantic. Preconception care, glycemic control, the administration of folic acid preconceptionally and prenatally, assessment of maternal retinal status and renal function, control of maternal glycemia, and assessment of fetal well-being are but a few shared goals in delivering care to women with diabetes. It must also be noted that healthcare policy in the USA is formulated by a number of nongovernmental agencies, and that these authorities do not always agree on certain aspects of patient care. Examples of the latter include the definition of gestational diabetes and the target glucose values recommended for care of women who have diabetes (15,16).

Since the publication of the first edition of this text, there have been significant changes in the delivery of healthcare in the USA. Following inauguration of provisions of the Affordable Care Act (ACA) in 2010, the number of American adults with healthcare insurance increased by 16 million (17), decreasing the proportion of adults without healthcare insurance from 18% in the third quarter of 2013 to 11% in the first quarter of 2016. Maternity and newborn care is

included as one category of *essential health benefits* prescribed by this law. Preconception care is stipulated as a benefit under the rubric of maternity care. The provision of contraception information, medication, devices, and procedures is also mandated by the law. Groups that view provision of contraception as a burden to their religious beliefs are, however, exempt from the contraception requirement. Assessing the impact of these changes on the care of women with diabetes is an ongoing effort. It must be noted that, particularly in rural areas, the persistent ability of some pharmacists to legally refuse to provide contraception (including emergency postcoital contraception) and some states setting barriers to the availability of medical and surgical abortions make activation of some provisions of the ACA problematic. It is of more than passing interest that in the UK, where most of these barriers are either minimal or nonexistent, problems in healthcare delivery mostly pertaining to patient education and compliance remain. There is a universal need for us to learn how to improve compliance with elements of preconception and prenatal care for diabetic women that have been shown to be effective.

Multiple-Choice Questions

1 Which of the following is true?

- **A** Women with type 1 diabetes should aim for pre-meal glucose values of 3.5–5.0 mmol/l (57–90 mg/ml) as soon as they are pregnant.
- **B** Social deprivation is not a factor associated with late presentation for antenatal care.
- **C** Retinal screening should be performed early in pregnancy, even if also performed about 2 months prior to conception.
- **D** Family members (e.g., the partner or mother) of a woman with type 1 diabetes should be advised on when and how to administer glucagon to her.
- **E** Dietary advice should include instructions on how to avoid low-glycemic-index foods.

Answer: D.

2 Which of the following are true? (Choose as many as apply.)

- **A** Fetal cardiac outflow tract scanning is not generally recommended as a component of fetal anomaly scanning in women with diabetes.
- **B** Nephrotic-range proteinuria is generally considered to be an indicator for thromboprophylaxis.
- **C** With appropriate pre-delivery preparation, many women using insulin pumps (CSII) should be able to use them for glycemic control for labor and delivery.
- **D** Similar glycemic targets as in pregnancy should be advised post-delivery, particularly in breastfeeding mothers.
- **E** Women who have had gestational diabetes should be tested for glucose intolerance every 1–3 years if their initial postpartum test is normal in order to try to reduce future health risks.

Answer: B, C, and E.

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Problems Encountered More Frequently in Women with Type 1 Diabetes

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PRACTICE POINTS

- Maternal hypoglycemia remains a major challenge to the achievement of near-normal blood glucose levels during pregnancy for both patient and clinician.
- Hypoglycemia unawareness, which can be pregnancy related or as a manifestation of autonomic neuropathy, is of particular concern to the clinician. Management may necessitate newer technologies, including continuous subcutaneous insulin infusion (CSII) and glucose sensing with alarm devices.
- Diabetic gastroparesis, as a manifestation of autonomic neuropathy, should be suspected in the context of other diabetes microvascular complications and poorly controlled or fluctuating blood glucose levels, especially when routinely recommended treatments for hyperemesis are ineffective. These patients present considerable management difficulties.
- Diabetic ketoacidosis in pregnancy is associated with significant fetal mortality; education of mothers regarding sick day rules and 24 h helplines are pivotal to prevention.
- Stillbirth is still reported to occur three times more frequently in pregnant women with type 1 diabetes than the general maternity population, and it is likely to be multifactorial.
- More women are now using carbohydrate counting to guide insulin dosing in pregnancy; further studies are needed to assess the impact of structured patient education on maternal fetal outcomes.

Introduction

The focus of this chapter is on problems that are encountered more frequently in women with type 1 diabetes mellitus (T1DM) than type 2 diabetes mellitus (T2DM). While hypoglycemia is included in this chapter, obviously this complication is also encountered in women with T2DM who are on insulin. In addition, cases of diabetic ketoacidosis (DKA), while typically associated with T1DM, have been reported with T2DM and even gestational diabetes mellitus.

Hypoglycemia

Hypoglycemia (blood glucose <4.0 mmol/l) is a major challenge for women with T1DM striving to achieve optimal glycemic control during pregnancy. It is classified as either mild (treated by the patient) or severe (requiring assistance from another party), with both categories occurring more frequently during pregnancy. In a study of 108 mothers with T1DM, 45% of women had a severe hypoglycemic event at some stage in pregnancy, with incidence rates of 5.3, 2.4,

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and 0.5 events/patient year in the first, second, and third trimesters of pregnancy, respectively, compared with 1.1 events/patient year in the year preceding pregnancy (1). Mild hypoglycemia is also more common in early pregnancy and is often attributed to pregnancy-induced nausea and vomiting alongside a declining insulin requirement in the late first trimester of pregnancy (1). Predictors of severe hypoglycemia include impaired hypoglycemia awareness, a past history of severe hypoglycemia, a long duration of diabetes, low HbA1c in early pregnancy, fluctuating glucose levels, and excessive use of supplementary insulin between meals (2).

To date, there are no known long-term consequences of maternal hypoglycemia on the offspring followed up to 5 years of age (3). Conversely, the maternal consequences of severe hypoglycemia are significant and include loss of consciousness, seizure, and hospital admission (2). In many countries, severe hypoglycemia is a contraindication to driving for up to 12 months. Women with T1DM during pregnancy have a significantly increased mortality rate, with a Finnish study reporting a 100-fold increased death rate versus pregnant women without T1DM (0.51% vs. 0.0047%) (4). Two out of the five reported maternal deaths in this cohort were attributed to hypoglycemia (the remaining three deaths were due to DKA, brain stem infarction, and hemorrhage) (4). A more recent review of maternal deaths in the UK from 2009 to 2012 identified five women with T1DM who died during pregnancy, one of whom had not known she was pregnant and died of pancreatitis (5). The remaining women died of drowning as a result of hypoglycemia (1 woman), DKA (2 women), and diabetic "dead in a bed syndrome" (1 woman). These four women had been attending a diabetes antenatal service and had been experiencing hypoglycemic episodes during attempts to optimize control (5). This highlights the continuing challenges of optimizing glycemic control during pregnancy for both patient and clinician and the importance of hypoglycemia avoidance. This is achieved through close capillary glucose self-monitoring, together with dedicated education on the risk of hypoglycemia and its management during pregnancy by the diabetes specialist team. If hypoglycemia persists, consideration should be given to the use of available technologies such as insulin pump therapy or glucose-monitoring sensors with hypoglycemia alarm features.

Guidelines recommend that symptomatic hypoglycemia is treated with 15–20 g of quick-acting carbohydrate (e.g., 150 ml pure fruit juice) followed by long-acting carbohydrate (e.g., a slice of bread,) with repeat doses of quick-acting carbohydrate until capillary glucose returns to normal (6). Treatment also involves insulin dose adjustment to avoid future hypoglycemia if recurrent episodes are reported.

Hypoglycemic Unawareness

Hypoglycemic unawareness is of major concern to the clinician trying to optimize glycemic control in pregnancy. One possible explanation for loss of warning symptoms is autonomic neuropathy that may attenuate the catecholamine response to hypoglycemia. Studies in pregnancy are limited, but there is evidence to suggest that pregnancy itself is associated with loss of a counterregulatory response to hypoglycemia, and this effect is accentuated in pregnant women with diabetes (7). However, in the Airaksinen studies, there was no significant increase in hypoglycemic accidents in pregnant women with cardiovascular autonomic neuropathy compared to those without, despite comparable glycemic control (8). Management of hypoglycemia in the acute setting is identical regardless of whether hypoglycemic unawareness is the result of autonomic neuropathy. The availability of glucose-monitoring sensors with alarm features for hypoglycemia may be useful for these challenging patients (see Chapter 16).

Autonomic Neuropathy

Autonomic neuropathy is one of the longer term complications of diabetes, occurring particularly if glycemic control has been suboptimal. While it can occur in pregnant women with T2DM, it is more commonly encountered in T1DM. It may affect a number of organ systems, including the cardiovascular, gastrointestinal, urinary, and visual systems. In addition, hypoglycemic awareness may be impaired. Outside of pregnancy, there is uncertainty about prevalence, which is partly related to variation in the diagnostic criteria. However, it has been estimated that approximately 50% of people with longstanding diabetes, particular in the context of other microvascular complications, have delayed gastric emptying (gastroparesis). The symptoms of autonomic neuropathy can all be present in pregnant women without neuropathy, making the diagnosis difficult. Accordingly, the prevalence of the condition in pregnancy remains uncertain, but almost certainly it is underdiagnosed. The literature on the subject is (out of practical necessity) largely confined to small studies or occasional case reports.

Gastrointestinal Effects

The most commonly suspected manifestation of autonomic neuropathy is delayed gastric emptying, caused by damage to the vagus nerve. Symptoms include early satiety, nausea, vomiting, epigastric discomfort, and bloating. Nausea and vomiting are common in early pregnancy, usually disappearing by early in the second trimester. Continuation of these symptoms, or their appearance or reappearance later in pregnancy, should raise the possibility of underlying autonomic neuropathy. Standard anti-emetic treatments are the first line of management but are rarely effective. Metoclopramide, a pro-kinetic agent, and other pro-kinetic drugs such as domperidone or erythromycin may also be considered. Erythromycin is possibly more effective when given intravenously rather than orally. The literature on the subject is predominantly confined to case reports, often with poor outcomes (9,10). Steroid therapy (e.g., prednisolone 30 mg/day) is also reported to be beneficial (11), although this usually disrupts glycemic control, which frequently is already significantly disturbed through variable nutrient absorption due to altered gastrointestinal transit, compounded by nausea and vomiting. Severe cases of gastroparesis may cause nutritional depletion and dehydration, requiring inpatient admission for rehydration and blood glucose stabilization. In severe cases, parenteral nutrition may be needed and has been associated with symptomatic improvement, although this could be partly psychological (10). The major fluctuations in maternal metabolism increase the risk of fetal death *in utero*, hence the need for a high index of suspicion and remedial action with probable cases of gastroparesis.

Other less serious gastrointestinal symptoms, although still troubling to the woman, which may be caused by autonomic neuropathy include constipation and diarrhea. If standard measures fail to help constipation, then a pro-kinetic agent (as discussed here) should be tried. Sometimes, constipation and diarrhea alternate, and antibiotics such as metronidazole may help as it is possible that bowel stasis has allowed bacterial overgrowth.

Cardiovascular Effects

Damage to the autonomic nerves to the heart and blood vessels may affect heart rate control, resulting in tachycardia, and blood pressure control, causing postural hypotension or hypertension. Again, these problems are common in normal pregnancy, causing diagnostic confusion. These cardiovascular changes may limit exercise tolerance and increase the risk of adverse cardiovascular events during exercise. As thermoregulation may also be affected, particular care is needed to avoid strenuous exercise in any extremes of temperature. It is considered that the normal hemodynamic changes of pregnancy are impaired due to subclinical autonomic

impairment. In a longitudinal pregnancy study, Airaksinen *et al*. showed that the normal physiological increase in the maternal heart rate was less in women with T1DM compared to pregnant women without diabetes, resulting in decreased cardiac output (12). However, in another study, no cardiovascular function changes were demonstrated (13). Another study (8) showed an increase in adverse pregnancy events in women with objective evidence of autonomic neuropathy affecting the cardiovascular system compared to women without such evidence. A case report noted that a woman with postural hypotension secondary to autonomic neuropathy had an improvement during pregnancy, possibly secondary to increased blood volume, with immediate regression post-delivery (14). Cases of maternal death secondary to cardiovascular autonomic neuropathy have been reported (9). If cardiovascular symptoms and signs are suggestive of autonomic neuropathy, evaluation includes electrocardiograph, postural blood pressure measurement, and determination of beat-to-beat heart rate variation with respiration (although this test has not been validated for use in pregnancy). Management should be based on explanation with symptomatic treatment.

Diabetic Ketoacidosis

DKA is defined as the biochemical triad of ketonemia, hyperglycemia, and acidemia. Historically, DKA during pregnancy is reported in 1 to 2% of mothers with diabetes (15,16). With more intensive glycemic control and follow-up, it is likely that present rates are lower. Although DKA is typically associated with T1DM, it also occurs in women with T2DM and has been reported in gestational diabetes. It is also important to note that when women present with DKA during pregnancy, glucose is often lower than anticipated due to utilization of maternal glucose by the fetus and placenta (17,18). Therefore, DKA should be considered in women with all types of diabetes who present unwell during pregnancy, even if blood glucose is normal or low (18–21).

DKA occurs in the setting of absolute or relative insulin deficiency. Insulin deficiency leads to hyperglycemia and a rise in plasma glucagon, which in turn stimulates hepatic gluconeogenesis and lipolysis with subsequent ketogenesis (see Figure 13.1). The physiological changes that occur during pregnancy can increase the risk of ketosis and subsequent acidosis. Human placental lactogen (hPL), which is synthesized by the

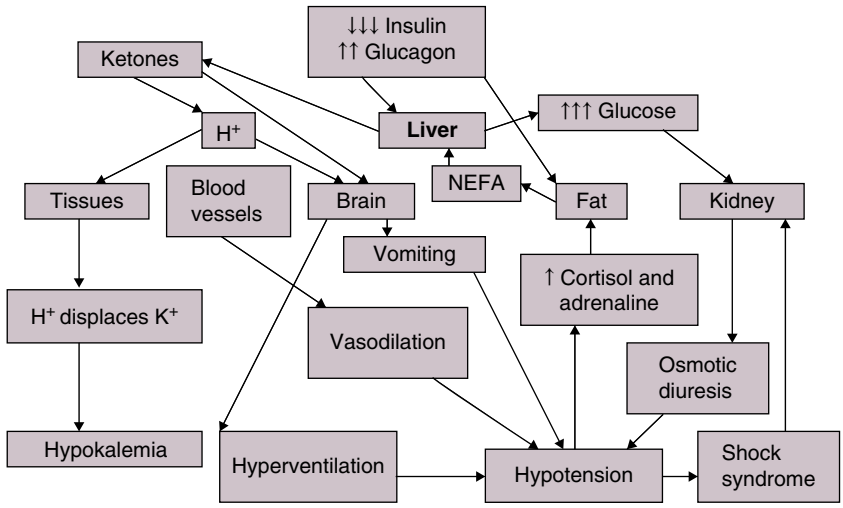

Figure 13.1 Pathogenesis of diabetic ketoacidosis (DKA).

trophoblast and released into maternal blood, reduces maternal insulin sensitivity, increasing post-prandial glucose level. The pregnant woman is also more susceptible to the effects of fasting, particularly in the second and third trimesters. In late pregnancy, the placenta and fetus use up large amounts of glucose as a major source of energy, resulting in reduced maternal fasting glucose. This results in the release of fatty acids for use as a maternal alternative fuel, with subsequent synthesis of ketones. Finally, the respiratory alkalosis that occurs in later pregnancy, due to increased respiratory rate, results in an increased renal excretion of bicarbonate and thus reduced buffering capacity to ketoacids. Women with T1DM can therefore develop ketoacidosis if control is suboptimal and they are exposed to a precipitating factor. Precipitants for DKA during pregnancy are similar to those outside of pregnancy and include infection, systemic illness, emesis, dehydration, and insulin omission. Medications given during complications of pregnancy, namely corticosteroids and tocolytics, are also associated with precipitating ketoacidosis (18–20).

DKA is a medical emergency. In the past 20 years, maternal mortality has fallen from 7.96% to 0.67%, reflecting improved treatment protocols and attention to preventing complications of DKA (22). Protocols vary between centers, but all involve initial assessment of the patient for level of consciousness, hemodynamic status, and possible precipitating illness. An example of a protocol is outlined in Figure 13.2. Management thereafter focuses on five key areas:

1) *Fluids*: In the setting of hyperglycemia, initial choice of fluid is 0.9% saline (0.45% saline if the patient is also hypernatremic). Rate of delivery is typically high at the start in view of the low-volume status of the patient, reducing to maintenance rates over the first few hours of admission.
2) *Insulin*: Current guidelines recommend a fixed, weight-adjusted intravenous (IV) insulin infusion rate (i.e., 0.1 unit/kg/h) (23). This is started alongside IV fluids and continued until capillary ketones are normal. To achieve this, an additional infusion of 10% dextrose is often required to avoid hypoglycemia. Patients continue to take their usual long-acting subcutaneous insulin alongside IV insulin. This is important in enabling patients to transfer promptly to regular subcutaneous insulin upon resolution of ketoacidosis. Once ketones are absent, a variable-rate insulin infusion, or insulin and dextrose infusion, is commenced to maintain euglycemia until the patient is able to eat when subcutaneous insulin is substituted.
3) *Potassium*: Significant hypokalemia is the most common life-threatening electrolyte derangement that occurs during the treatment of DKA (24). An essential part of DKA management is proactive potassium replacement, even with normal serum concentrations (23). To ensure adequate potassium replacement, serum potassium is measured 2–4 hourly as per protocol.
4) *Precipitants*: Underlying causes need to be identified and treated (see the precipitants discussed earlier in this section).
5) *Prevention of complications*: Complications of DKA include hyper/hypokalemia (also discussed in this section), cerebral and pulmonary edema, and thromboembolic disease. Cerebral edema is attributed to cerebral hypoperfusion followed by reperfusion (25). Although rare in adults, it accounts for 70–80% of deaths in children presenting with DKA (26). Pulmonary edema is also a rare complication of DKA associated with rapid infusion of fluids over a short period (27). Strict adherence to the fluid protocol, regular assessment of fluid balance and patient level of consciousness, and use of an adapted fluid protocol for patients under 18 years of age are essential to avoid these complications (28). Thromboembolism risk is increased in both pregnancy and DKA, and consequently prophylaxis with heparin or low-molecular-weight heparin, in a weight-adjusted dosage, is necessary in all patients presenting in DKA (29).

Investigations

Baseline	Capillary glucose and ketones Laboratory glucose, urea, and electrolytes Venous blood gas Serum osmolarity if hyperosmolar hyperglycemia suspected Glasgow Coma Scale (GCS)
Monitoring regimen	Regular observations Hourly capillary glucose and ketones Venous bicarbonate and potassium at 0, 1, 2 hours, and 2 hourly thereafter until ketones cleared GCS: hourly
Other investigations	Full blood count, blood culture, urine culture, ECG, and CXR

Intravenous fluids

0.9% sodium chloride:

1000 ml	Over first hour
2000 ml	Over next 4 h
2000 ml	Over next 8 h
1000 ml	Every 6 h subsequently as needed

If initial systolic blood pressure is less than 90 mmHg, give 500 ml of 0.9% sodium chloride over 10–15 min. Repeat as necessary, and consider other causes such as heart failure or sepsis. If sodium >155 mmol/l, consider initial use of 0.45% sodium chloride.

Insulin

Commence a fixed IV insulin infusion (50 units of soluble insulin in 50 ml sodium chloride 0.9%) at 0.1 unit/kg/h (based on patient's estimated weight). If there is a delay in starting IV insulin, then 20 units of soluble insulin intramuscularly can be administered initially. If patient normally takes a long-acting insulin, continue this at the usual time and dose.

Potassium

Commence potassium at the time of first insulin as shown here:

Potassium level	Potassium replacement
>5.5 mmol/l	None
3.5–5.5 mmol/l	40 mmol per liter of 0.9% sodium chloride
<3.5 mmol/l	Stop insulin temporarily. Immediate senior consultation as additional potassium is needed.

Additional measures

- A nasogastric tube must be passed if the patient is obtunded or persistently vomiting.
- Consider urinary catheterization if incontinent or anuric at 1 h.
- Prescribe thromboprophylaxis with low-molecular-weight heparin as appropriate.
- Consider the precipitating cause of DKA.
- Capillary ketones should fall by 0.5 mmol/l/h, and capillary glucose by at least 3 mmol/l/h. If not, consider increasing the insulin infusion rate by 1 unit/h.

Resolution phase

- When capillary glucose <14 mmol/l: Add 10% glucose at 125 ml/h and adjust as necessary, aiming for glucose 5–10 mmol/l. IV insulin and 0.9% sodium chloride with potassium should be continued.
- When capillary ketones <0.3 mmol: Stop IV insulin by syringe and 10% glucose solution. Until ready to eat, commence 5% glucose 500 ml IV with 8 units soluble insulin over 6 h, adjusted as necessary to maintain glucose at 5–10 mmol/l. Continue 0.9% sodium chloride if necessary.
  Convert to subcutaneous insulin, and commence feeding when clinical condition permits. Continue IV glucose/insulin until at least 30 min after first subcutaneous insulin administered.

Figure 13.2 Belfast Protocol for diabetic ketoacidosis in adults.

Fetal Consequences of Diabetic Ketoacidosis

Studies dating back over 20 years report fetal mortality rates of 9–35% among women presenting in DKA, with the greatest loss occurring if diagnosis and treatment are delayed (15,16,30). These figures are likely to have improved in the intervening years with improved antenatal care. After treatment of DKA is in progress, and the mother begins to improve clinically and biochemically, fetal assessment is necessary by ultrasound and cardiotocography (CTG). Assessment of fetal well-being is delayed until the mother is in the recovery phase, regardless of fetal status, as no action can be taken until the mother's condition has stabilized. In addition to fetal demise, there is some evidence that increasing intrauterine exposure to ketones is associated adversely with behavioral and intellectual development in the offspring (3). This further reinforces the importance of avoidance of DKA in pregnancy.

Prevention of Diabetic Ketoacidosis

DKA is preventable with frequent blood glucose monitoring, proactive insulin adjustment, and the use of insulin titration algorithms in such settings as antenatal steroid administration. Mothers with T1DM must be instructed how to monitor urinary or capillary ketones and reminded constantly of "sick-day rules," including the need for supplementary insulin as guided by intensive glucose monitoring (see Figure 13.3). Integral to this is the availability of 24 h access to the diabetes team.

Stillbirth

Antenatal death *in utero* remains the most feared of all outcomes for women with T1DM and the clinicians who care for them. Most women with T1DM are aware of this increased risk, and it is the duty of the supervising clinician to ensure the mother is adequately informed. The risk is typically about three times that of the background population, affecting 1 in 100 pregnancies in the UK between 2009 and 2011 (31). Thus, an average large maternity unit might expect to have a stillbirth every 1–2 years. Small units are likely to have fewer stillbirths numerically and so may be unaware that they have a relatively high rate. Such high rates are unacceptable today, although unfortunately UK rates were reported to have changed little over the last 10 years (32,33). There has been a longstanding tendency to deliver women early to try to reduce the risk of death *in utero*, and current recommendations are to deliver from 37 + 0 weeks or even earlier if there appears to be specific maternal or fetal risks (34). However, studies have shown that the increased risk of stillbirth for women with diabetes preceding pregnancy occurs from as early as 32 weeks gestation (35).

Illness and diabetes

When you are ill, your blood glucose will rise even if you do not eat. Controlling your blood glucose is more difficult, and you should contact your Diabetes Center for help and advice.

What should you do?

- Never stop taking your insulin.
- Monitor your blood glucose frequently.
- Check for blood ketones frequently – if present, contact your Diabetes Center immediately.
- If you have repeated vomiting and/or increasing ketones, go to hospital as soon as possible.
- Increase the amount of fluid that you drink.
- If you don't feel like eating, replace solid foods with a still sweet drink, such as fruit juice. Milky drinks, ordinary fruit yogurt, and ice cream also provide carbohydrates.

If in doubt, contact your Diabetic Center (24 h contact numbers should be provided to each patient).

Figure 13.3 Sick day rules.

While modifiable risk factors for stillbirth have been explored in the general population (36), it is more difficult to identify causes specifically associated with T1DM, as numerically these pregnancies are relatively uncommon and death is fortunately rare. While fetal death in T1DM is likely to be multifactorial in origin, there are a number of factors that place some women at increased risk, including problems with vascular supply to the placenta in association with the increased risk of preeclampsia, and renal and macrovascular disease. This may also result in poor first-trimester placentation, which may present at varying stages of pregnancy with fetal growth restriction. Furthermore, a depressingly high number of women with diabetes still smoke, 19% in one study (37), which may also reduce placental oxygen supply. Maternal hyperglycemia, as assessed by third-trimester HbA1c, is associated with an increased risk of stillbirth and adverse pregnancy outcomes (38,39), and it seems likely that levels below 6.0% (42 mmol/mol) are required to minimize these risks to a significant degree. Maternal hyperglycemia is associated with increasing fetal acidemia (40). Amniotic erythropoietin is elevated in women with diabetes compared with controls, suggesting preceding hypoxia, and amniotic fluid erythropoietin correlates positively with maternal HbA1c and negatively with umbilical artery pH (41); this may be partly as a result of impaired 2,3-DPG activity. If the fetus is macrosomic, it is likely to have myocardial hypertrophy and an increased oxygen demand. It may also be susceptible to dysrhythmias. The increasing uterine contractility found in the third trimester will cause transient hypoxic episodes, which a normal fetus is able to withstand without difficulty. However, a fetus with an increased oxygen requirement, already mildly acidemic, and with a borderline placental vascular supply may not. A controlled postmortem study in women with diabetes reported lower placental weights and an increased incidence of thymic changes in the offspring, which may be attributable to critical subacute metabolic disturbances (42).

In conclusion, smoking cessation, meticulous ultrasound monitoring of fetal growth, consideration of second-trimester uterine artery Doppler measurements, and strenuous efforts to achieve near-normal blood glucose levels by a multidisciplinary team, aware of the specific risk factors, should reduce the risk of these tragedies occurring in women and their families, who have almost always invested so much in time and effort into the pregnancy. Whether centralization of care improves these outcomes remains uncertain.

Carbohydrate Counting and Type 1 Diabetes

It is recommended that all patients with T1DM should be offered structured education in carbohydrate counting (43). The UK Dose Adjustment for Normal Eating (DAFNE) course is a structured education program of proven benefit in which patients with T1DM are empowered to adjust insulin based on the carbohydrate content of their meals or snacks (see, e.g., Figure 13.4) (44).

Lunch
1 slice of bread: 15 g carbohydrate
1 boiled egg: 0 g carbohydrate
1 glass of milk: 15 g carbohydrate
Total: 30 g carbohydrate

10 g carbohydrate = 1 carbohydrate point

Therefore, this meal is 3 carbohydrate points. If the patient has an insulin-to-carbohydrate ratio of 1:1, they will take 3 units of insulin.

Figure 13.4 Insulin adjustment for carbohydrate content of a meal.

Bolus insulin doses are therefore calculated using individualized insulin-to-carbohydrate ratios. Increasingly, women with T1DM in pregnancy will have been trained in carbohydrate counting. Diabetologists caring for these women will be familiar with the need for regular adjustment of insulin-to-carbohydrate ratios during pregnancy. Published studies on carbohydrate-counting experience among women with type 1 diabetes during pregnancy are scarce. In Belfast, a small study of 28 women with T1DM (14 trained in DAFNE) found that the DAFNE-trained women had better pre-pregnancy glycemic control, and were more likely to attend pre-pregnancy counseling and take an appropriate dose of folic acid (unpublished data). This is likely to reflect the enhanced education around pregnancy planning incorporated into the structured education program. Our study was not powered to evaluate pregnancy outcomes. Further larger studies evaluating the impact of structured education on maternal and fetal outcomes are needed.

Multiple-Choice Questions

1 Regarding hypoglycemia in type 1 diabetes in pregnancy (*choose as many as apply*):

- **A** It remains a significant cause of maternal death.
- **B** Current UK NICE guidelines advise aiming for glucose ≥3.5 mmol/l.
- **C** Hypoglycemic awareness may be worsened by autonomic awareness.
- **D** Severe hypoglycemic events are reduced when the woman is pregnant.
- **E** Treatment of hypoglycemic events should include both short- and long-acting carbohydrates.

Answer: A, C, and E are correct.

2 Regarding diabetic ketoacidosis (DKA):

- **A** DKA is associated with an over 40% risk of fetal death *in utero*.
- **B** When presenting with DKA, if the cardiotocograph (CTG) is pathological, a cesarean should be performed rapidly.
- **C** DKA should not be diagnosed if there is normoglycemia.
- **D** DKA may occur both in T2DM and gestational diabetes.
- **E** The normal respiratory alkalosis of late pregnancy partially mitigates against the development of DKA.

Answer: D is correct.

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14

Problems Encountered More Frequently in Women with Type 2 Diabetes

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PRACTICE POINTS

- Type 2 diabetes has similar pregnancy outcomes compared to type 1 diabetes.
- Type 2 diabetes may be complicated by hypertension, nephropathy, and/or retinopathy. Women with type 2 diabetes should be evaluated for these complications regardless of length of time since diagnosis.
- Women with type 2 diabetes may be managed with oral agents outside of pregnancy. Most of these agents have little to no data on safety and efficacy during pregnancy. Insulin is the preferred medication to achieve glycemic control during pregnancy.

Case History

A 33-year-old woman with type 2 diabetes and no prior pregnancies presents for preconception counseling. She was diagnosed with type 2 diabetes and hypertension at age 31. She has not seen her primary physician in almost one year. She is currently taking metformin and an ACE inhibitor. Your evaluation includes a hemoglobin A1c of 53 mmol/mol (7.0%), a urine protein–creatinine ratio of 0.3, and a blood pressure of 145/93. Referral to an ophthalmologist demonstrates benign proliferative retinopathy.

- What is the recommended HbA1c prior to pregnancy, and how is that best achieved in someone attempting to conceive?
- How does the presence of nephropathy affect her pregnancy outcomes?
- What are her blood pressure goals, and what medications are recommended to achieve these goals?
- What are the recommendations for retinopathy screening during pregnancy? How does the presence of retinopathy impact her outcomes?

Prevalence of Type 2 Diabetes

In 2013, the International Diabetes Federation estimated that 8.3% of adults, or 382 million people, had diabetes (1). Of these, 90% have type 2 diabetes. When restricted to reproductive ages (20–44), prevalence estimates range from 2% (for 20–24-year-olds) up to 7% (for 40–44-year-olds) (1). Alarmingly, 45% of all cases are undiagnosed, and younger adults of reproductive age are the most likely

A Practical Manual of Diabetes in Pregnancy, Second Edition. Edited by David R. McCance, Michael Maresh and David A. Sacks.

group of subjects with diabetes to go undiagnosed (2).

Historically, type 1 diabetes was more frequently encountered during pregnancy due to the younger age at diagnosis. However, as the prevalence of obesity, and in particular childhood obesity, increases, type 2 diabetes is being diagnosed at younger ages. For example, Dabalea *et al*. reported a 30% increase in the prevalence of type 2 diabetes in 10–19-year-olds over a 10-year period (3). Simultaneously, women are choosing to delay pregnancy, resulting in older maternal ages during pregnancy and an increased risk of type 2 diabetes at the time of pregnancy (4). As a result, the proportions of women with type 1 versus type 2 diabetes during pregnancy are changing. In the UK in 2002–2003, type 2 diabetes accounted for 27% of pre-gestational diabetes (5); in 2014, this increased to 47% (6).

Compared to women with type 1 diabetes in pregnancy, women with type 2 diabetes tend to be older: in the UK, 79% were 30 years old or more, compared to only 50% of women with type 1 diabetes. Women with type 2 diabetes were also less likely to be white and more likely to be either Asian or black. Type 2 diabetes was also strongly associated with lower socioeconomic status (6).

Due to the ever-increasing prevalence of type 2 diabetes, and of type 2 diabetes in pregnancy, the practicing obstetrician must be familiar with the problems unique to type 2 versus type 1 diabetes. Differences in the routine management of type 2 diabetes, comorbid conditions, and patient attitudes present distinct challenges in the management of these women during pregnancy.

Preconception Counseling with Type 2 Diabetes

Preconception counseling should focus on glycemic control, assessing for comorbid conditions, and modifying medications to avoid teratogenic exposures. Preconception counseling is beneficial and cost-effective in diabetic women (7–14).

Although most studies have focused on type 1 diabetes, pre-pregnancy counseling is equally important for women with type 2 diabetes. However, the reality is that women with type 2 diabetes are less likely to seek pre-pregnancy care. Despite the fact that women with type 2 diabetes have lower glycated hemoglobin values at conception (5,6,15), one recent study examining the risk of birth defects in maternal diabetes found the greatest increase in women with type 2 diabetes (16). Although the reason for this is unclear (undiagnosed diabetes leading to poor glycemic control, lack of folic acid intake, obesity, or teratogenic exposure), it is clear that type 2 diabetes remains a high-risk group and efforts should be made to diagnose and optimize control prior to pregnancy.

Diabetic Complications in Type 2 Diabetes

Pregnancies complicated by diabetic microvascular complications have significantly worse outcomes compared to diabetic pregnancies without complications. Therefore, a key component of the preconception and initial obstetric visits is screening for these conditions. Although microvascular complications (nephropathy or retinopathy) are due in large part to long-standing poor diabetic control, and therefore more frequently diagnosed in type 1 diabetes, screening for these conditions must still occur in women with type 2 diabetes. At diagnosis, 6–7% of women with type 2 diabetes have microalbuminuria, likely due to the time from onset of diabetes to clinical diagnosis (17,18). In type 2 diabetes, progression from no nephropathy to microalbuminuria, from microalbuminuria to macroalbuminuria, and from macroalbuminuria to elevated creatinine occurs at a rate of 2–3% per year. Given these facts, all women with type 2 diabetes should be screened for nephropathy at their initial pregnancy visit.

Up to 20% of women with type 2 diabetes have retinopathy at the time of diabetes diagnosis (19). Over a 4-year period, 26% of patients with no retinopathy at the beginning of the study developed retinopathy, the majority of which was background retinopathy, although maculopathy and proliferative retinopathy occurred (20). Significantly, the vast majority (91%) of patients did not undergo annual screening for retinopathy; therefore, pregnancy represents an opportune moment for screening for retinopathy. All women with type 2 diabetes should be screened for retinopathy at the beginning of pregnancy and then be monitored as indicated by the initial exam (21).

Common Comorbidities Associated with Type 2 Diabetes

Hypertension

At the time of diabetes diagnosis, hypertension is present in about one-third of patients, in large part due to the metabolic syndrome associated with type 2 diabetes (18,22). Both systolic and diastolic hypertension are closely linked to the progression of nephropathy and retinopathy, thus blood pressure control is critical to the health of women with type 2 diabetes. The American Diabetes Association recommends treating to a blood pressure of <140/90 mmHg, and consideration of a lower target of <130/80 mmHg for younger patients (23). Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blocker (ARB) therapy are frequently used as first-line agents for hypertension in diabetes due to their protective effect on the kidneys. Both ACE inhibitors and ARBs are contraindicated in pregnancy, however, due to their associations with fetal death, heart defects, renal tubular dysgenesis, and pulmonary hypoplasia (24–28). Therefore, in reproductive-age women, ACE inhibitors and ARBs should be used with caution. For women with type 2 diabetes attempting to conceive, adequate blood pressure control should be achieved with non-teratogenic anti-hypertensives: calcium channel blockers, beta blockers, and hydralazine are frequent choices in pregnancy. For women exposed to ACE inhibitors or ARBs during pregnancy, the agent should be discontinued immediately, the patient counseled, the need for alternative medication reviewed, and a detailed ultrasound advised at the appropriate gestational age to examine for anomalies.

The presence of hypertension significantly increases the risk of preeclampsia, fetal growth restriction, preterm delivery, and adverse neonatal outcomes regardless of diabetes type (29). Recognition of hypertension can aid in counseling patients regarding their risks and in distinguishing chronic hypertension from preeclampsia. It is unclear if blood pressure control alters the risk of adverse pregnancy outcomes.

Dyslipidemia

Up to 70% of patients with type 2 diabetes exhibit dyslipidemia (30), with a characteristic pattern of elevated triglycerides and decreased high-density lipoprotein (HDL) cholesterol (31). In the nonpregnant state, statin therapy is recommended for women with elevated triglycerides (≥150 mg/dL or 1.7 mmol/L) or low HDL (<50 mg/dL or 1.3 mmol/L). However, statin therapy is currently contraindicated during pregnancy. Statins function by inhibiting production of cholesterol, which is essential for fetal development. Although human studies have not shown teratogenic effects to date (32,33), statins should be discontinued in women attempting to conceive and in those who are currently pregnant. Patients should be counseled on lifestyle recommendations to reduce cardiovascular risk factors and lower low-density lipoprotein (LDL) cholesterol. Because pregnancy causes alterations to the lipid profile, lipids need not be routinely monitored during pregnancy.

Cardiovascular Disease

Type 2 diabetes is a significant risk factor for cardiovascular events, although screening asymptomatic patients is not recommended (23). Fortunately, heart disease remains rare

in reproductive-age women with type 2 diabetes. Low-dose aspirin is often recommended in women with diabetes, which may be continued throughout pregnancy.

Depression

Depression and type 2 diabetes frequently coexist (34–36). Women with type 2 diabetes should be screened for depression. Depression is associated with adverse pregnancy outcomes (preterm delivery, preeclampsia, and growth restriction) and should be treated during pregnancy, either with psychosocial therapy or with approved medications (37–42).

Obesity

Up to 80% of patients with type 2 diabetes are obese (43). Obesity is associated with significant pregnancy complications, including stillbirth, cesarean, preeclampsia, macrosomia, shoulder dystocia, and preterm delivery (44–48). If seen prior to conception, women should be counseled to attempt to achieve a normal body mass index prior to pregnancy. If seen during pregnancy, women should be advised to follow a healthy diet and 30 min of moderate exercise daily. Although weight loss is not advised during pregnancy, obese women should be counseled regarding the Institute of Medicine's (IOM) guidelines for weight gain of 10–20 pounds. Gaining more than the IOM recommendations has been associated with adverse outcomes in diabetic women (49–51). Although no increase in the risk of small-for-gestational-age infants was found with weight gain less than the IOM recommendations, these studies were too small to recommend women with diabetes gaining less than the IOM recommendations at this time.

Obstructive Sleep Apnea/Sleep-Disordered Breathing

Sleep disturbances, characterized by sleep-disordered breathing or obstructive sleep apnea, may be more prevalent in those with type 2 diabetes (52,53). This is likely related to the relationship of obesity with type 2 diabetes and obstructive sleep apnea rather than an independent association of type 2 diabetes with obstructive sleep apnea. Sleep-disordered breathing is a risk factor for hypertensive disorders of pregnancy and severe maternal and neonatal morbidity (54–56). Consideration should be given to screening women with type 2 diabetes and obesity for sleep-disordered breathing prior to conception or the initial prenatal visit. However, it remains to be determined if treatment for sleep-disordered breathing will improve pregnancy outcomes.

Cancer

Type 2 diabetes is associated with an increased risk of cancers of the liver, pancreas, colon, breast, bladder, and endometrium (57). Providers should recommend women with type 2 diabetes to undergo age-appropriate screening either prior to conception or postpartum (58).

Fatty Liver Disease

Type 2 diabetes may be associated with unexplained elevations of hepatic transaminases. This is likely part of the metabolic syndrome frequently associated with type 2 diabetes, consisting of obesity, increased waist circumference, elevated triglycerides and fasting insulin, and lower HDL cholesterol. Treatment of hyperglycemia and dyslipidemia, and weight loss, are frequently beneficial for non-alcoholic fatty liver disease (59,60). Care should be taken not to confuse non-alcoholic fatty liver disease with acute fatty liver disease.

Pregnancy Complications

Regardless of type, diabetes increases the risk of a multitude of pregnancy complications: stillbirth, perinatal death, small for gestational age, large for gestational age, macrosomia, shoulder dystocia, preterm delivery, preeclampsia, and cesarean. Vascular complications of diabetes (nephropathy, retinopathy, and heart disease) are more closely associated with the risk of adverse outcomes than is the type of diabetes (29). In a cohort of 468 women with diabetes, the risk

of adverse outcomes was similar between type 1 and type 2 diabetic subjects without vasculopathy, whereas the risk of adverse outcomes (except for fetal overgrowth and shoulder dystocia) sharply increased for both types of diabetes complicated by vasculopathy (Table 14.1). However, the risk of fetal overgrowth and shoulder dystocia was decreased in those with vasculopathy. In spite of the decreased risk of fetal overgrowth, the risk of cesarean remained high in those with vasculopathy, suggesting that cephalopelvic disproportion is not the only reason for cesarean in this group.

Postpartum Management

Postpartum, most women may revert to their pre-pregnancy medications. If a woman was on oral medications before, these can typically be restarted, particularly if she had evidence of good glycemic control prior to pregnancy. Women who were diagnosed early in pregnancy may be given a trial of metformin, the first-line agent for treating diabetes. Glycemic control is particularly important in those who had a cesarean delivery as hyperglycemia may hinder wound healing and places patients at risk for wound infection. Attention should be paid to comorbidities (as listed in this chapter), with prescription of appropriate medications and referral to an appropriate managing physician as necessary. The postpartum period is an excellent time point for contraceptive counseling as many women will be highly motivated to use contraception at this time.

Unless other contraindications exist, women with type 2 diabetes should be encouraged to breastfeed their infants. In women with a history of gestational diabetes, those who exclusively breastfeed their infants have improved glycemic profiles compared to those who formula feed (61,62). Similar improvements in the glycemic profile can be expected in those with type 2 diabetes as well. Most oral hypoglycemic agents and insulin are not contraindications to breastfeeding (see Chapters 15 and 26).

Table 14.1 Risk of pregnancy complications by type of diabetes, with and without vasculopathy.

	No vasculopathy		Vasculopathy (nephropathy, retinopathy, heart disease)	
	Type 1 ***n*** **= 107**	**Type 2** ***n*** **= 297**	**Type 1** ***n*** **= 40**	**Type 2** ***n*** **= 24**
Neonatal/fetal complications				
Composite neonatal outcome	11%	13%	21%	25%
Stillbirth	2.8%	7.1%	10.0%	8.3%
Small for gestational age (<10th percentile)	4.7%	5.4%	10.0%	29.0%
Large for gestational age (>90th percentile)	35.0%	25.0%	7.5%	4.2%
Macrosomia	28.0%	19.0%	2.5%	4.2%
Shoulder dystocia	7.5%	5.1%	2.5%	0
Preterm delivery	51.0%	38.0%	65.0%	71.0%
Maternal complications				
Preeclampsia	36.0%	25.0%	63.0%	79.0%
Cesarean delivery	55.0%	58.0%	65.0%	75.0%

Note: Composite neonatal outcome: stillbirth, neonatal death, shoulder dystocia, birth injury, neonatal seizures, blood pressure support, or CPR or intubation in the delivery room (29).

Multiple-Choice Questions

1 The preferred treatment for type 2 diabetes during pregnancy is:
- A Metformin
- B Glyburide
- C Insulin
- D All of the above

The correct answer is C. Although metformin is the first-line therapy outside of pregnancy and glyburide is also frequently used, once a woman is pregnant, treatment is typically converted to insulin which has the most safety and efficacy data. Research is ongoing regarding the use of metformin and glyburide for type 2 diabetes during pregnancy, although many now use them as the first-line agents for gestational diabetes.

2 Preconception counseling for type 2 diabetics should focus on:
- A Glycemic control
- B Optimizing the medication regimen to avoid teratogenic agents
- C Assessing for diabetic nephropathy and retinopathy
- D All of the above

The correct answer is D.

3 Type of diabetes is more important than the presence of vasculopathy for pregnancy outcomes.
- A True
- B False

This statement is false. Type 1 and type 2 diabetics have very similar outcomes; however, the presence of a vasculopathy (nephropathy, retinopathy) significantly increases the risk of adverse outcomes.

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15

Advances in Oral Anti-Diabetes Drugs in Pregnancy

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PRACTICE POINTS

- Metformin and glibenclamide (glyburide) cross the placenta but are unlikely to be teratogenic.
- Metformin use during pregnancy for gestational diabetes (GDM) is efficacious and has good short-term safety data. Some international guidelines recommend metformin as first-line treatment in women with gestational diabetes who do not achieve optimal glycemic control with lifestyle modifications, while others suggest metformin can be used as second-line treatment after insulin.
- Evidence suggests that glibenclamide is inferior to insulin and metformin when used during pregnancy for the treatment of GDM, but may be considered as third-line treatment in women with inadequate glycemic control who are intolerant of metformin and/or who refuse insulin. Among women with type 2 diabetes, glibenclamide should be preferentially switched to insulin or metformin during pregnancy.
- Insulin remains the mainstay of treatment for women with GDM who fail treatment with lifestyle modifications (and metformin in some guidelines) and/or for women who are intolerant of metformin or find it unacceptable (see guidelines by international bodies below).
- Acarbose has been used in very small studies in pregnancy with limited safety data, and tolerability is likely to be an issue.
- PPARγ agonists (thiazolidinediones) cross the placenta and should be avoided in pregnancy until more safety data are available.
- Metformin and glibenclamide are secreted into breastmilk, but short-term safety data suggest they can be considered for use among breastfeeding mothers.
- The use of DPP4 inhibitors, GLP1 agonists, or SGLT2 inhibitors during pregnancy and breastfeeding is not recommended as there are no human studies to date.
- There is a paucity of long-term follow-up data on children exposed to oral anti-diabetes drugs (OADs) *in utero* and during breastfeeding.

Case History 1

A 32-year-old woman gravida 2, para 0, and spontaneous abortion 1 (G2P0SA1) with type 2 diabetes for 3 years presents at 9 weeks of gestation with an unplanned pregnancy. Her HbA1c is 9% while on metformin 1 g twice daily and glibenclamide 10 mg twice daily. What do you advise her?

Case History 2

A 30-year-old woman G1P0 is diagnosed with GDM at 28 weeks of gestation. She has implemented lifestyle modifications and is on an appropriate diabetic diet, but her blood sugars remain above target. She is afraid of needles and asks if she can take pills. What do you advise her?

A Practical Manual of Diabetes in Pregnancy, Second Edition. Edited by David R. McCance, Michael Maresh and David A. Sacks.

Background

Diabetes in pregnancy is associated with adverse pregnancy outcomes if glycemic control is inadequate during pregnancy (1). Traditionally, women with gestational diabetes mellitus (GDM) and type 2 diabetes in pregnancy managed with lifestyle modifications including diet and physical activity, with the addition of insulin when blood sugar targets are not achieved. However, with rising prevalence of diabetes among women of reproductive age (2), an increasing number of women are conceiving while taking oral anti-diabetic drugs (OADs). In cases where women may be non-adherent, decline to take multiple daily injections of insulin, or lack access to store insulin appropriately, the need to prescribe OADs in pregnancy may be necessary to improve glycemic control. Although there are potential safety concerns with OADs, there is now a growing body of literature on the use of OADs in pregnancy, and many countries recommend certain OADs as first-line therapy in women with GDM if lifestyle modifications fail to achieve optimal glycemic control. In this chapter, we examine the evidence for the safety and efficacy of OADs in women with GDM, polycystic ovarian syndrome (PCOS), and type 2 diabetes in pregnancy.

Sulfonylureas and Meglitinides

Sulfonylureas and meglitinides are "insulin secretagogues" that bind to pancreatic beta-cell receptors (not at identical sites) and stimulate insulin secretion. Examples of sulfonylureas include the first-generation sulfonylureas, such as tolbutamide, chlopropramide, and tolazamide, and the second-generation sulfonylureas, such as glibenclamide (glyburide), glipizide, and glimeperide. First-generation sulfonylureas are rarely used due to a high incidence of adverse reactions. Second-generation sulfonylureas possess better safety profiles and are more potent than the first-generation agents (3). The meglitinides include nateglinide and repaglinide. Meglitinides have a more rapid anti-hyperglycemic action with a shorter duration of action than sulfonylureas, thus providing better post-prandial hyperglycemia control and lower risk of late hypoglycemia (4,5).

Placental Transfer

The human cotyledon perfusion model has been used to explore the mechanism of action of sulfonylureas given the concern for neonatal hypoglycemia should it cross the placenta. This involves the placenta being obtained from a healthy mother at delivery and testing the relevant drug with perfusion and transfer studies. Studies have found that first-generation sulfonylureas crossed the placenta in moderate amounts (tolbutamide 21.5%, and chlorpropramide 11%), while second-generation sulfonylureas crossed less (glipizide 6.6%, and glibenclamide 3.9%) (6). In two more recent studies, however, among mothers using glibenclamide (7,8), drug concentrations in cord blood were on average 50–70% of maternal concentration; the transfer of the drug was quite variable, with some infants showing even higher levels than their mother (7,8). Glibenclamide efflux is assisted by various placental transporters (9), and differences in levels have been postulated to be due to variability in their function (8). The only study examining placental transfer of meglitinides noted the maternal-to-fetal transfer of repaglinide at 1.5% but higher fetal-to-maternal transfer of 6.7% (10). In summary, placental transfer of repaglinide appears to be low but has only been evaluated in one study, while several studies have found that glibenclamide crosses readily.

Clinical Experience with Sulfonylureas

Congenital Anomalies

Women with Type 2 Diabetes

Analyzing the potential teratogenicity of any drug in pregnancy complicated by diabetes is confounded by the fact that maternal

hyperglycemia during first trimester is itself a potential teratogen. The majority of studies examining the use of sulfonylureas in the first trimester have not demonstrated an increased rate of congenital anomalies (11–14). Only two small studies have noted an increased rate of congenital anomalies ($n = 20$ and $n = 43$, respectively); however, glycemic control was either not ideal (15) or not described (16). In a large retrospective cohort study ($n = 342$), congenital anomalies were associated with poor glycemic control rather than the specific OAD used (glibenclamide or metformin) (11). A meta-analysis of 471 women exposed to OADs (sulfonlyureas and/or biguanides) in the first trimester, compared with 1344 women not exposed, noted no significant differences in the rates of major malformations (17). In summary, sulfonylureas are unlikely to be teratogenic.

There are limited data on congenital anomalies with meglitinide use, but two case reports of three women exposed to repaglinide during the first trimester of pregnancy did not note any congenital malformations (18,19).

Perinatal Outcomes

Women with Type 2 Diabetes

In a retrospective cohort study in South Africa of 379 pregnancies, the use of OADs *throughout* pregnancy (glibenclamide alone or in combination with metformin) was associated with an increased rate of perinatal mortality (11) compared to those who were switched to insulin at the beginning of pregnancy or who were treated with insulin alone. However, there was no increased risk of perinatal deaths in infants of women taking metformin exclusively. This could not be explained by differences in glycemic control, maternal age, Body Mass Index (BMI), parity, gestational age, or comorbidities between groups. The reason for this increased rate of perinatal mortality is unclear. However, a meta-analysis (10 studies on 471 exposed women to sulfonylureas and biguanides in first trimester) found no significant difference in the rate of major malformations or neonatal death among women with first-trimester exposure to OADs compared with women who were not exposed (17).

Women with Gestational Diabetes Mellitus

In 2000, Langer and colleagues conducted a landmark trial involving 404 women with GDM who failed to meet glycemic targets with lifestyle modifications and randomized them at 11–33 weeks of gestation to receive either insulin or glibenclamide therapy (starting at 2.5 mg in the morning and titrated to 20 mg/day when necessary) (20). There were no significant differences in glycemic control or neonatal outcomes [large for gestational age (LGA), macrosomia, birthweight, neonatal hypoglycemia, pulmonary complications, admission to the neonatal intensive care unit (NICU), congenital anomalies, or perinatal mortality] between each treatment arm. Eight patients (4%) in the glibenclamide group needed insulin. While this study was groundbreaking to support the use of glibenclamide among women with GDM, one of the main criticisms was that it was underpowered to assess neonatal outcomes.

In a large retrospective cohort study of over 9000 women with GDM that compared glibenclamide versus insulin, newborns of women treated with glibenclamide were at increased risk for NICU admission, respiratory distress, hypoglycemia, birth injury, and LGA compared with those treated with insulin (21). In a recent meta-analysis of randomized controlled trials examining perinatal outcomes among GDM women that compared OADs versus insulin, those mothers treated with glibenclamide had infants with higher birth weight, more macrosomia, and more neonatal hypoglycemia compared to those treated with insulin (22). Maternal hypoglycemia was reported in two studies; one study reported a lower incidence of maternal hypoglycemia in women taking glibenclamide compared to insulin (20), while another found a similar incidence (23). The average treatment failure among the glibenclamide group was 6.4%.

In the meta-analysis referenced above, two studies compared glibenclamide to metformin directly. Metformin was associated with less maternal weight gain, lower birth weight, less macrosomia, and fewer LGA newborns. The average treatment failure among these studies was 26.8% with metformin versus 23.5% with glibenclamide (22).

There are no data on the use of meglitinides in pregnancy among women with GDM.

Use of Sulfonylureas During Pregnancy: Summary

Glibenclamide crosses the placenta but does not appear to be teratogenic. In women with GDM, glibenclamide is associated with good glycemic control in the majority, with average treatment failure rates of 6–24%. However, evidence supports a higher risk of macrosomia and neonatal hypoglycemia with glibenclamide use compared with insulin and a higher risk of increased birth weight, LGA, macrosomia, and maternal weight gain with glibenclamide use compared with metformin among women with GDM. Therefore, both metformin and insulin are preferable to glibenclamide among women with GDM. There are little data on the use of sulfonylureas in pregnant women with type 2 diabetes. Based on a single retrospective study, there is some concern regarding increased perinatal mortality with continued use of glibenclamide throughout pregnancy, but this has not been reproduced in other studies. In light of this and the data among women with GDM, until further data are available, women with type 2 diabetes on glibenclamide should consider switching to insulin or metformin during pregnancy.

Metformin

Metformin is a widely used biguanide that acts by reducing hepatic glucose output, increasing peripheral glucose uptake in skeletal muscle and adipocytes, and reducing intestinal glucose absorption leading to improved insulin sensitivity. It does not cause insulin secretion and hence does not cause hypoglycemia or weight gain (24), but it can be associated with gastrointestinal intolerance (25).

Placental Transfer

Metformin freely crosses the placenta as demonstrated in a placental transfer study among women with GDM (26). Two studies throughout pregnancy found metformin levels were 50–100% as high in cord blood as maternal blood concentrations, and in some infants the level was even higher (27,28).

Clinical Experience with Metformin

Ovulation Induction, Pregnancy, and Live Birth Rates

Women with Polycystic Ovarian Syndrome

Metformin has been widely used in women with PCOS during the preconception phase in the setting of subfertility to improve ovulation, and during pregnancy to reduce complications (29,30).

Observational trials have suggested that metformin may decrease the rate of spontaneous abortion in the first trimester (31,32), but this has not been confirmed in a meta-analysis of 17 randomized controlled trials of metformin use in the preconception period, where metformin was discontinued in the first trimester (33). There is conflicting evidence regarding the benefits of metformin to improve pregnancy and live birth rates compared with clomiphene (29,34). A Cochrane Review of 38 randomized controlled trials of 3495 women noted that metformin, used alone or in combination with clomiphene, was effective in improving ovulation and pregnancy rates in women with PCOS but did not result in significant improvements in live birth rates (35). Among women with PCOS, the role of metformin to improve live birth rates appears to be limited, but needs to be further explored.

Congenital Anomalies

Women with Type 2 Diabetes

The majority of studies using metformin alone or with sulfonlyureas during pregnancy

have not found an increased rate of congenital malformations (11–13,17,36,37).

Women with Polycystic Ovary Syndrome

While hyperglycemia is a major confounding factor in studies that have examined congenital anomalies in women with type 2 diabetes exposed to OADs in the first trimester, this issue does not arise in women with PCOS, where blood sugar levels are usually within normal limits unless there is a history of glucose intolerance. In a systematic review and meta-analysis of eight randomized controlled studies among women affected by PCOS, there was no significant increase in the rate of major birth defects among infants born with first-trimester metformin exposure compared with the disease-matched control group (38).

Other Morbidity and Mortality

Women with Type 2 Diabetes

A retrospective study in South Africa noted that while perinatal mortality was higher in women taking glibenclamide alone or in combination with metformin, there was no increase found with metformin alone compared to insulin (11). A recent randomized, open-label study of 206 women not previously on insulin with type 2 diabetes in pregnancy compared metformin versus insulin, where insulin could be added to metformin if required; women in the metformin-treated group had less maternal weight gain, fewer hypoglycemic episodes, and less pregnancy-induced hypertension (39). However, 84.9% patients in the metformin group required add-on insulin therapy at a mean gestational age of 26 weeks, and small-for-gestational-age babies were more common in the metformin group (39). Some limitations include the open-label design, lack of intention-to-treat analysis, and small sample size. In another open-label randomized trial of 90 women with GDM or type 2 diabetes, a reduction of neonatal hypoglycemia and NICU admissions was noted when metformin was added to insulin, although small sample size, late randomization (up to 34 weeks of gestation), and lack of intention-to-treat analysis make the results less reliable (40). A large multicenter randomized, placebo-controlled trial is underway to determine if the addition of metformin to insulin will benefit mothers with type 2 diabetes and their infants (MiTy Trial and MiTy Kids).

Women with Gestational Diabetes Mellitus

The metformin in GDM (MiG) trial was a large randomized controlled trial in which 751 women with GDM and inadequate glycemic control on diet therapy were randomized to receive either metformin (starting at 500 mg once or twice daily, and titrated to a maximum of 2500 mg as necessary) or insulin (41). The rate of the primary composite outcome of neonatal morbidity, which included neonatal hypoglycemia, respiratory distress, need for phototherapy, birth trauma, a 5 min Apgar score less than 7, and prematurity, was not significantly different in women assigned to metformin and those assigned to insulin. Severe neonatal hypoglycemia (<1.6 mmol/L [<28.8 mg/dL]) was decreased in the metformin group, but preterm birth was more common in the metformin group (12.1% vs. 7.6%; $p = 0.04$). There was no significant difference in glycemic control between the groups, although 46.3% of women in the metformin group required supplemental insulin to maintain glycemic control. Of note, 1.9% of women had to discontinue metformin due to gastrointestinal side effects, and 8.8% required a dose reduction of metformin due to gastrointestinal side effects. Total fat mass and percentage body fat assessed by bioimpedance and DEXA were not different in the two arms of the study. The authors speculated that metformin may be responsible for increased peripheral fat deposition relative to visceral fat distribution, the latter of which is responsible for insulin resistance and the production

of inflammatory cytokines, but this needs to be further elucidated (42).

In a systematic review and meta-analysis of six open-label studies comparing metformin versus insulin for GDM, metformin was associated with less maternal weight gain, lower gestational age at delivery, and more preterm birth (22). Of note, treatment failure was 33.8% with metformin use.

As stated previously, in a pooled analysis of two studies comparing glibenclamide to metformin, metformin was associated with lower birth weight, fewer LGA infants, less macrosomia, and less maternal weight gain (22).

Women with Polycystic Ovary Syndrome

Observational and cohort studies among women with PCOS have noted no adverse maternal or fetal outcomes with metformin use, and possibly some potential benefits, such as decreased rates of gestational diabetes when metformin is given throughout pregnancy (30,43). However, in a large randomized placebo-controlled trial among pregnant women with PCOS, metformin treatment started in the first trimester did not result in lower rates of preeclampsia, gestational diabetes, preterm delivery, or a composite of the three outcomes (44). In summary, there appears to be limited benefit of metformin use in pregnancy among women with PCOS with normal glucose tolerance.

Use of Metformin in Pregnancy: Summary

Metformin freely crosses the placenta, but does not appear to be teratogenic. Metformin improves ovulation rates, although it does not improve live birth rates or decrease preeclampsia, GDM, or preterm delivery in women with PCOS. Metformin appears to be efficacious and safe for use in women with GDM, but additional insulin use due to treatment failure is often required and gastrointestinal side effects may limit tolerability. Metformin use in women with type 2 diabetes in pregnancy appears to be safe, and early data appear promising; however, results from adequately powered and blinded randomized trials are awaited, and studies of longer duration are indicated to assess possible effects on children.

Alpha-Glucosidase Inhibitors

The alpha-glucosidase inhibitors, acarbose and voglibose, slow carbohydrate absorption and reduce postprandial glucose levels by inhibiting the alpha-glucosidase enzymes present on the brush border of the small intestine. These drugs are not absorbed into the bloodstream in any significant amount. Only acarbose has been studied in pregnancy. In one case series, six women with GDM not well controlled on diet alone were given acarbose three times a day before meals. In all six, the fasting and postprandial glucose values normalized, and infants were healthy (45). Acarbose, however, was associated with intestinal discomfort that persisted throughout the pregnancy. A small study among women with GDM who were insufficiently controlled on diet therapy and randomized to either insulin ($n = 27$), glibenclamide ($n = 24$), or acarbose ($n = 19$) noted no differences in glycemic control, rate of LGA, or birthweight among the three groups. Tolerability of acarbose was not mentioned (46). Larger randomized controlled trials are needed to elucidate the benefits of acarbose in pregnancy and to further explore tolerability in pregnancy.

Pparγ Agonists

The peroxisome proliferator-activated receptor-γ (PPARγ) agonists, also known as thiazolidinediones, include rosiglitazone, pioglitazone, and troglitazone (no longer available because of hepatic toxicity). They bind to the nuclear transcription factor

PPARγ, which modulates gene expression in adipose tissue, skeletal muscle, and the liver, leading to changes in several metabolic pathways that involve glucose transport, lipoprotein lipase, and insulin signaling. They are known as *insulin sensitizers* as they enhance insulin action at these sites. They are used in patients with type 2 diabetes and do not cause hypoglycemia, although they have been associated with weight gain, fluid retention, and heart failure. There is evidence to suggest rosiglitazone crosses the placenta based on human and placental transfer studies (47,48). However, based on limited clinical data, there is no evidence that it is associated with congenital anomalies or obstetrical complications (49–52). Given cardiovascular safety concerns with rosiglitazone use, it is no longer recommended for ovulation induction among women with PCOS.

In summary, PPARγ agonists cross the placenta, and with limited data on the safety of these drugs in pregnancy, they are not recommended.

Dipeptidyl Peptidase-4 (DPP4) Inhibitors

DPP4 is an enzyme that degrades the incretin hormones glucagon-like peptide-1 (GLP1) and glucose-dependent insulinotropic polypeptide (GIP). GLP1 and GIP increase insulin biosynthesis and secretion from pancreatic beta cells. No adverse events have been noted in animal reproductive studies (53); however, they have not been studied in pregnant women to date and thus are not recommended for use in pregnancy.

GLP1 Receptor Agonists

GLP1 receptor agonists are incretin mimetics that are agonists of the GLP1 receptor. In *ex-vivo* studies using the human placental cotyledon model, there was negligible crossing of exenatide (54). In animal reproductive studies, there have been some adverse events noted (53), and given there are no studies in pregnant women to date, the use of GLP1 receptor agonists during pregnancy is not recommended.

Sodium-Glucose Co-Transporter-2 (SGLT2) Inhibitors

SGLT2 is a glucose transporter located in the proximal tubule of kidneys that promotes renal tubular reabsorption of glucose. Inhibition of SGLT2 leads to the decrease in blood glucose levels due to an increase in renal glucose excretion. SGLT2 inhibitors are associated with a small increased risk for urinary tract infection (UTI) due to glucosuria (55). Among women with diabetes, UTI during pregnancy can be associated with pyelonephritis and sepsis and potential long-term effects on the neonate (56). There have been some adverse events noted in animal reproductive studies, including adverse effects on renal development when SGLT2 inhibitors are used in the second and third trimesters, although there are no human data available (53). The use of SGLT2 inhibitors during pregnancy is not recommended.

Breastfeeding

Women with type 2 diabetes are often on OADs prior to pregnancy, and after delivery, the question of when these drugs can safely be restarted arises. The main issue is whether OADs are secreted into breast milk, which can potentially pose a risk to infants.

Sulfonylureas

The first-generation sulfonylureas cross into breast milk in significant amounts (57). In a study that examined the transfer of second-generation sulfonylureas (glibenclamide or glipizide) into breast milk among women with type 2 diabetes noted that neither agent was detected in breast milk among eight women who received a single

oral dose of 5 or 10 mg of glibenclamide or among five women given 5 mg of glibenclamide or glipizide daily from the first day postpartum (58). Blood glucose was normal in three infants (one glibenclamide and two glipizide) who were exclusively breastfed. Binding of glibenclamide and glipizide to plasma proteins has been postulated as the reason for their observed limited transfer into breast milk. Maternal use of second-generation sulfonylureas seems unlikely to exert any clinically significant pharmacologic action on breastfed infants.

Metformin

Three studies that examined the transfer of metformin into breast milk noted that metformin crosses into breast milk, albeit in very small quantities (59–61). The mean estimated infant dose as a percentage of the mother's weight-adjusted dose was 0.65%. In addition, blood glucose levels taken from three infants of nursing mothers on metformin were normal (60). At 6 months of age, the weight, height, and motor–social development of infants of mothers taking 1.5 to 2.5 g of metformin while breastfeeding did not differ from those of formula-fed infants (62). In summary, metformin is excreted into breast milk, but it is not associated with adverse outcomes in limited studies.

Other OADs and Breastfeeding

There are no data on PPARγ agonists, alpha-glucosidase inhibitors, DPP4 inhibitors, GLP1 agonists, and SGLT2 inhibitors and breastfeeding, and the use of these drugs is not recommended during the lactation period.

OADs and Breastfeeding Summary

Glibenclamide, glipizide, and metformin can be considered for use during breastfeeding, but further long-term safety studies are required.

Multiple-Choice Questions

1 Which one of these OADs has not been studied in placental-transfer studies?
   - **A** Repaglitinide
   - **B** Metformin
   - **C** Glibenclamide
   - **D** Sitagliptin

Answer: D. Both metformin and glibenclamide cross the placenta. There has been only one study examining placental transfer of meglitinides that noted maternal-to-fetal transfer of repaglinide of 1.5% (10). No placental transfer studies have conducted for sitagliptin.

2 Which one of these OADs has been studied with breastfeeding and has not been associated with adverse safety concerns?
   - **A** Metformin
   - **B** DPP4 inhibitor
   - **C** Alpha-glucosidase inhibitor
   - **D** PPARγ agonist

Answer: A. Metformin is excreted into breast milk, but at low levels. Short-term studies are encouraging regarding neonatal developmental outcomes, but long-term data are unavailable.

Answers to Case Histories 1 and 2

Case History 1

In this 32-year-old woman with type 2 diabetes and PCOS, metformin and glibenclamide are unlikely to be teratogenic; however, with an elevated HbA1c, there is an increased risk of congenital malformations. This should be assessed with an anatomy ultrasound at 18–20 weeks of gestation. For better glycemic control, glibenclamide should be discontinued and insulin initiated. Some international bodies suggest the continuation of metformin in women with type 2 diabetes needing insulin (63), while in others insulin alone remains the mainstay treatment (64,65). Research is underway to determine the benefit of using metformin in women with type 2 diabetes in pregnancy. While there is some evidence that continuation of metformin up to the first

trimester, or throughout pregnancy, may reduce the risk of spontaneous abortions in women with PCOS, more recent data from randomized trials and meta-analyses suggest that this is not the case.

Case History 2

Both glibenclamide and metformin cross the placenta. Randomized trial evidence suggests that metformin has good short-term safety data and may have benefits over insulin in terms of reduced maternal weight gain. However, further data are indicated regarding long-term effects on offspring. In addition, insulin needs to be added nearly 34% of the time to achieve adequate glycemic control. Recent data from a meta-analysis suggest that glibenclamide is inferior to both metformin and insulin among women with GDM and that it may result in higher rates of macrosomia and neonatal hypoglycemia compared with insulin, and higher birth weight and maternal weight gain with higher rates of large-for-gestational-age offspring and macrosomia when compared to metformin. Metformin should be offered first, with glibenclamide second, with appropriate discussion of the risks and benefits for both and with consideration of local professional guidelines.

Appendix Current International Guideline Recommendations of OADs in Diabetes Management

Guideline recommendations for OADs use	UK NICE guidelines (63)	ADA guidelines (64)	CDA guidelines (65)
Type 2 diabetes during pregnancy	• Metformin can be used. • Other OADs should be discontinued.	• No comment	• Insulin is preferred. • Glibenclamide or metformin can be continued until insulin can be initiated in pregnancy.
GDM during pregnancy	• Metformin can be used as first-line therapy following lifestyle modifications.* • Insulin can be offered if metformin is contraindicated, is unacceptable, or provides inadequate control, and if fasting blood sugar is ≥7 mmol/L (126 mg/dl) or between 6.0–6.9 mmol/L (108 mg/dl-124 mg/dl), with pregnancy complications such as macrosomia or polyhydramnios • Glibenclamide can be considered as third line in those whose targets are not achieved with metformin and who decline insulin; can also be used if metformin is not tolerated.	• Insulin and metformin are preferred since glibenclamide is associated with higher rates of neonatal hypoglycemia and macrosomia. • Patients should be informed that both metformin and glibenclamide cross the placenta and that long-term data are lacking.	• Glibenclamide or metformin may be used as alternatives to insulin in those who are non-adherent or refuse insulin, but they are considered off-label.
Breastfeeding	Metformin and glibenclamide can be continued or resumed postpartum.	No comment.	Metformin and glibenclamide may be used during breastfeeding.

* Metformin does not have UK marketing authorization for this indication; it is recommended that the prescriber follow relevant professional guidance, take responsibility for the decision, and obtain informed consent from the patient.

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Advances in Insulin Therapy

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PRACTICE POINTS

- It is difficult to predict which patients will respond well to new diabetes technologies. These technologies should be more rigorously evaluated and made available to women with suboptimal glucose control.
- The costs of new technologies are substantial (approx. £3500 for a sensor-augmented pump therapy pregnancy compared to £150 for an MDI pregnancy). However, a single neonatal intensive care unit (NICU) admission also costs approximately £3500, so any improvement in maternal and infant morbidity may offset the additional costs of treatment.
- Diabetes technologies are developing rapidly, with new devices released every 2 to 3 years. Clinical trials take 3 to 5 years, and as a result, diabetes pregnancy research often lags behind clinical practice. We should not make assumptions about current technology based on trials of superseded devices or on trials of nonpregnant patients.
- Little is known about how and why pregnant women and/or their healthcare professionals make decisions about switching to using new technologies in pregnancy.

Introduction

Maternal hyperglycemia plays a pivotal role in the development of diabetes-related pregnancy complications (1). Hence, the main goal of insulin therapy is to safely achieve euglycemia during preconception, pregnancy, labor, and delivery (2). However, due to gestational changes in insulin sensitivity, the limitations of subcutaneous insulin administration, and the very tight glucose targets required for optimal pregnancy outcome, most women with type 1 diabetes struggle to maintain glycemic levels within the recommended range (3). Longitudinal data from continuous glucose monitoring studies confirm the widespread prevalence of both hyper- and hypoglycemic excursions.

The main hazard of intensified/very tight glycemic control is the development of maternal hypoglycemia, which can be very serious and in the worst scenario result in maternal coma, seizure, and even death (4–6).

Unfortunately, in view of these challenges, the frequency of pregnancy complications associated with diabetes remains high. Recent advances in therapeutic and monitoring tools have been driven by the aim of achieving very strict glycemic control while avoiding hypoglycemia. New technologies include continuous subcutaneous insulin

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infusion (CSII; insulin pumps), continuous glucose monitoring (CGM), and closed-loop "artificial pancreas" systems.

Continuous Subcutaneous Insulin Infusion

Insulin pumps deliver a continuous infusion of short-acting insulin via a fine tube placed subcutaneously; larger boluses are given with meals (7). This pattern of glucose administration aims to mimic normal physiology and allows far more customization of insulin delivery than is possible with traditional treatment using multiple daily injections of insulin (MDIs).

Pumps have improved dramatically since their introduction in the 1970s. Modern insulin pumps are small, lightweight, and battery operated, and they hold several days' insulin supply. The main advantage of insulin pumps is that they facilitate a variable basal rate of insulin. In nonpregnant populations, this can help improve glycemic control with decreased HbA1c levels and glycemic variability without increasing hypoglycemia (7). In pregnancy, when insulin requirements are constantly changing and risk of hypoglycemia is high, insulin pumps have the potential to offer substantial benefit.

The UK National Institute for Health and Care Excellence (NICE) recommends that pregnant women with diabetes who cannot obtain adequate glucose control without significant disabling hypoglycemia using MDIs should be offered CSII (8). The 2015 American Diabetes Association (ADA) guidelines recommend even tighter glucose control targets (fasting, pre-meal, bedtime, and overnight: 3.3–5.4 mmol/l; peak postmeal: 5.4–7.1; and HbA1c <6%) but do not specify whether these can be more safely achieved by MDIs or CSII (9).

However, literature comparing the use of CSII with MDIs in pregnant women is limited and outdated. The randomized studies were conducted one to two decades ago, prior to the introduction of rapid-acting insulin analogs and with less user-friendly pumps. Additionally, most recent studies are retrospective and observational, have small sample sizes, and lack statistical power to detect differences in maternal and fetal outcomes.

Observational studies have shown that CSII provides comparable outcomes to MDIs in terms of maternal and fetal outcomes (10,11) and that both can be used in pregnancy (10–18). Some studies comparing CSII with MDIs have demonstrated better glycemic control (12,14,18,20) and pregnancy outcome (12) with similar (13) or decreased insulin requirements (10,12,20) and decreased hypoglycemia (10).

However, there is also potential concern about increased maternal weight gain, ketoacidosis, and adverse neonatal outcomes associated with CSII (16,21,22). Given the observational nature of these studies, the patient populations are often highly selective, and many confounders may contribute to these results. Patients on CSII tend to be older, have a longer duration of diabetes, and are more likely to have microvascular complications (11,12,18,20,21). It may be that outcomes observed in these patients reflect a more severe glycemic disturbance and are unrelated to mode of insulin delivery.

A 2011 Cochrane Review (19) identified five prospective randomized trials comparing CSII with MDIs in pregnant women with type 1 diabetes, including overall 153 pregnant women and 154 pregnancies. This meta-analysis showed no difference between MDIs and pump therapy in terms of maternal hyperglycemia, maternal hypoglycemia, operative (i.e., caesarean) birth, perinatal mortality, macrosomia, and small-for-gestational age infants. Borderline significant difference was noted with respect to increased birthweight associated with CSII ($p = 0.05$). For other neonatal outcomes, including rates of neonatal hypoglycemia, there were no apparent differences (19% vs. 15%) between MDIs and CSII. However, the authors noted that the negative results of this meta-analysis may reflect the limited number of trials and the small numbers of women in each trial.

There was some historical concern about changing women from MDIs to insulin pump therapy during the first trimester (2) because of the potential for hyperglycemia associated with the change in therapy. Although commencing CSII before pregnancy is preferred, women can be safely transitioned to insulin pumps during pregnancy with appropriate input and support. As organogenesis is largely completed shortly after a viable pregnancy is confirmed (6 weeks gestation), there is no medical reason to delay pump therapy. Furthermore, while some clinicians previously advised NPH insulin before bed to avoid diabetic ketoacidosis (DKA) in the event of a pump failure (2), this approach is rarely used except in patients with repeated DKA admissions and/or compliance issues. Current-generation pumps have sensitive occlusion alarms that alert the user to any interruption of insulin delivery. For selected patients with type 2 diabetes, using pump therapy for basal insulin with pre-meal boluses by subcutaneous injection is sometimes applicable.

Overall, the evidence suggests that pumps are safe in pregnancy and as effective as MDIs. Technological advances are making CSII more precise and user-friendly, but they are more expensive and require more advanced diabetes management skills from both the patient and antenatal healthcare team. New, larger, randomized trials of contemporary insulin pumps compared to contemporary insulin analog MDI regimens are needed to better understand the impact of CSII on maternal and fetal outcomes.

Continuous Glucose Monitoring

Glucose monitoring is of fundamental importance to ensure adequate insulin dosing and avoid hyper- and hypoglycemia and associated complications. Currently, the gold standard for glucose monitoring is self-monitoring of blood glucose (SMBG) with intermittent capillary finger stick tests. Recent advances in technology have led to the development of CGM systems.

CGM systems are composed of a subcutaneous glucose-sensing device that measures interstitial glucose every 10 s, providing an average value every 5 min and around 288 blood glucose readings every day. The main benefit of CGM is that it provides detailed information about glucose excursions that would be missed by intermittent finger stick testing. CGM was first introduced into clinical practice in 1999 (23). Originally, it was only able to store data retrospectively and provide blood glucose levels retrospectively (blinded CGM). Blinded CGMs are worn for up to 7 days; the stored data are then downloaded, and glucose patterns can be analyzed retrospectively with insulin therapy amended accordingly.

More recently, real-time continuous glucose monitoring (RT-CGM) has become available. In addition to the subcutaneous sensor – which in this case transmits rather than stores data – patients carry a receiver, which provides continuous information on trends in glycemic levels, including magnitude, frequency, and duration of excursions, in real time. Additionally, alarms can be set to predict episodes of hypo- and hyperglycemia, allowing patients to intervene proactively to minimize glycemic excursions (24,25).

CGM is relatively without side effects. Main issues include skin irritation, sensor inaccuracy, and user discomfort. As interstitial glucose lags slightly behind blood glucose, CGM requires calibration with SMBG and is not very accurate during periods of glucose fluctuations. When first introduced, RT-CGM was reserved for selected motivated patients who were thought unlikely to be overwhelmed by the large quantity of RT-CGM data (24–26). Currently, RT-CGM is used for a wider range of patients, with the UK NICE guidelines recommending CGM for any pregnant woman who has suboptimal glucose control (27). Given that pregnant women with type 1 diabetes spend an average of 12 h a day with suboptimal glucose levels (3), if fully implemented, RT-CGM would be indicated for almost all pregnant women.

In nonpregnant cohorts, including children and adults with both type 1 and type 2 diabetes, RT-CGM has been shown to improve glycemic control, decreasing duration of hyperglycemia without increasing hypoglycemia, reducing glucose fluctuations, and improving HbA1c levels (24,25,28,29). A meta-analysis of 449 patients from six randomized trials found only modest impact on overall HbA1c levels (0.3% reduction), with benefits most apparent (up to 0.9%) in patients with increased sensor use (29,31,34) and higher baseline HbA1c levels (29,32). Median exposure to hypoglycemia was reduced by 23% during CGM use (25).

Sensor-Augmented Pump (SAP) Therapy

Further advances in technology have led to the development of SAP therapy. A RT-CGM and insulin pump are worn simultaneously, and the glucose readings provided by the CGM are entered into the pump – either manually or automatically. Using specific inbuilt calculators, the pump then recommends adequate insulin boluses or doses. SAP therapy has been shown to be beneficial in the treatment of type 1 diabetes outside pregnancy. When compared to pump therapy alone or MDIs, SAP can improve glycemic control and reduce both HbA1c and frequency of hypoglycemic episodes (30–34). Low-glucose suspend (LGS) pumps can automatically suspend insulin delivery during hypoglycemia. This is particularly helpful for providing an additional layer of safety for patients at increased risk of hypoglycemia during sleep, with one study of high-risk individuals showing that duration of nocturnal hypoglycemia (<2.2 mmol/l) was reduced from over 45 to under 2 min (35). Data are awaited from trials of currently available sensor-augmented pumps that suspend insulin when hypoglycemia is predicted, which may further reduce the risk of hypoglycemia.

In theory, CGM and SAP therapy may be useful for treating diabetes during pregnancy when achieving good glycemic control while avoiding hypoglycemia is difficult. However, the literature evaluating CGM and SAP therapy in pregnancy is very limited and lags behind current clinical practice.

In pregnancy, blinded CGM has been shown to be accurate (36) and can help with delivering more targeted insulin doses in women with both type 1 and type 2 diabetes (37,38). A prospective, open-label, randomized trial in 46 women with type 1 diabetes and 25 women with type 2 diabetes has shown that blinded CGM was associated with improved glycemic control in the third trimester (0.6% reduction), lower birthweight standard deviation (SD) scores (0.7 SD lower), and 60% reduced risk of macrosomia (39).

RT-CGM is also useful and well tolerated in women with both type 1 and type 2 diabetes in pregnancy (40). When initiated in early pregnancy, RT-CGM may help to decrease the rate of severe hypoglycemic events in particularly high-risk women (41). As in nonpregnant populations, RT-CGM is less accurate during periods of high glycemic fluctuations, such as during exercise (42).

To date, there is only one randomized clinical trial investigating the role of *intermittent* RT-CGM in pregnancy. In 123 women with type 1 diabetes and 31 women with type 2 diabetes, there was no improvement in glycemic control or pregnancy outcome (43). This could be because RT-CGM was only worn intermittently and baseline HbA1c values were below 7%, making it hard to achieve significant reduction. Current literature suggests that the benefits of RT-CGM are most apparent in patients with higher HbA1c levels and that daily rather than intermittent use of RT-CGM is required (24). A recent Cochrane Review concluded that further evidence from large well-designed trials is needed to evaluate the impact of CGM on maternal and infant health outcomes (44).

CONCEPTT (i.e., the Continuous Glucose Monitoring in Women with Type 1 Diabetes

during Pregnancy Trial; ClinicalTrials.gov NCT01788527) is an international, randomized trial currently underway. It will evaluate the effectiveness of *continuous* RT-CGM in 110 pre-pregnant and 224 pregnant women with type 1 diabetes (total: 334 women) from Canada, the UK, the USA, Spain, Ireland, and Italy. The primary outcome is maternal glycemic control (change in HbA1c from baseline to 34 weeks gestation in pregnant women and from baseline to 24 weeks in the pre-pregnant cohort). Secondary maternal outcomes include CGM time in target, rates of hypoglycemia, gestational hypertension/preeclampsia, gestational weight gain, and delivery by caesarean section. Secondary infant outcomes include miscarriage, stillbirth, neonatal death, birthweight, birth injury, neonatal hypoglycemia, hyperbilirubinemia, respiratory distress, and neonatal intensive care unit admissions. A Dutch multicenter randomized trial of retrospective CGM (using CGM for 5–7 days every 6 weeks) in 300 pregnant women with diabetes (type 1, type 2, or insulin-treated gestational diabetes), GlucoMOMS (TrialRegister.nl NTR2996), is now nearing completion. The primary outcome for this trial is macrosomia (defined as birthweight >90th percentile), with secondary outcomes including glycemic control, maternal and infant morbidity, and measures of cost-effectiveness, which will be important for publicly funded healthcare systems.

Closed-Loop Insulin Delivery Systems

Despite advances in pump therapy and RT-CGM and intensive effort from clinicians, pregnant women with type 1 diabetes still spend up to half of the day with abnormal glucose levels. In an attempt to improve glucose control, quality of life, and longer term health outcomes, closed-loop insulin delivery or the "artificial pancreas" is being developed. A closed-loop artificial pancreas differs from LGS and/or threshold suspend systems by responding to *both* hyperglycemia and hypoglycemia. Earlier sensor-augmented pumps stop insulin in response to hypoglycemia but do not increase insulin delivery to minimize hyperglycemic excursions.

Closed-loop systems are formed of three components – a RT-CGM, a control algorithm device, and an insulin pump. During closed-loop, glucose is measured continuously via CGM and transmitted to a computer that houses an algorithm. The algorithm uses glucose information from the individual to calculate insulin doses at 12–15 min intervals. This provides much more precision in insulin delivery than is available with conventional or sensor-augmented pump therapy, and it removes the need for patients to adjust their basal insulin. The algorithm is based on predicted changes in post-prandial hyperglycemia and on the pharmacokinetics of subcutaneous fast-acting insulin analogs during pregnancy. These physiological studies that underpin the algorithm highlight the challenges of optimizing post-prandial glucose control. The duration of post-prandial hypoglycemia increases as pregnancy advances due to both delayed glucose uptake into skeletal muscle and delayed absorption of subcutaneous insulin (45). The time to peak plasma concentration of aspart is up to 90 min in late gestation, with very substantial inter-occasion variability, confirming patients' experiences that every day is different (46).

Low-Glucose Suspend

The simplest form of automated insulin delivery is LGS. LGS systems are designed to reduce hypoglycemia by automatically suspending insulin delivery when hypoglycemia is present.

In 2009, the first commercially available LGS system was launched (Paradigm Veo and MiniMed 530G with Enlite; Medtronic Diabetes, Northridge, CA, USA). In periods of hypoglycemia, but not predicted hypoglycemia, this system automatically suspends insulin delivery for 2 h. It has been shown to

reduce hypoglycemia without significantly increasing hyperglycemia in high-risk populations (47–49).

In 2015, Medtronic Diabetes launched a more advanced threshold suspend system (MiniMed 640G system with Enhanced Enlite sensor). This suspends insulin delivery when hypoglycemia is predicted, and automatically resumes insulin delivery once glucose levels recover. Neither LGS nor threshold suspend systems have been evaluated in pregnancy. Although the LGS and Medtronic 640G devices will be used by the CONCEPTT trial participants, it is expected that the numbers will be too small to permit meaningful subgroup analyses.

Overnight Closed-Loop

Approximately one-half of severe hypoglycemic episodes occur overnight. In pregnancy, the risk of severe hypoglycemia is increased two- to threefold (5), and this can have devastating consequences including loss of consciousness, seizures, and death. A logical initial application of closed-loop technology is overnight, when concern regarding severe hypoglycemia is high.

Preliminary feasibility studies have demonstrated that closed-loop systems are safe and can effectively control glucose overnight in both inpatient (50–54) and home settings (55,56). Participants using closed-loop had improved glucose control with less exposure to hypoglycemia. Additionally, the closed-loop system was able to cope well after alcohol and high-carbohydrate meals.

Two small inpatient studies have shown that overnight closed-loop can achieve near-euglycemia without increasing hypoglycemia in early and late pregnancy (57,58). The first outpatient study of closed-loop in pregnancy (the Closed-Loop in Pregnancy Overnight Home Feasibility Study; CLIP_03, ISRCTN71510001) is nearing completion. This will be the first home closed-loop study addressing human pregnancy, which, if feasibility is demonstrated, will pave the way for longer duration day-and-night closed-loop systems in pregnancy.

Day-and-Night (24 H) Closed-Loop System

The ultimate aim of closed-loop insulin delivery is to develop a system that controls glucose without human intervention, including during meal and exercise times. Small proof-of-concept studies have demonstrated that closed-loop systems can control glucose effectively with low rates of hypoglycemia (59–61). However, in fully automated closed-loop systems, the algorithm relies on detecting changes in glucose levels from meals or exercise before it can react and change insulin doses. This creates an inherent delay and is in contrast to conventional therapy in which meal boluses are given proactively. Unsurprisingly, initial studies of fully automated systems showed that 24 h closed-loop resulted in prolonged post-prandial hyperglycemia and frequent post-prandial hypoglycemia (62).

A 24 h closed-loop system in which users input the timing and/or carbohydrate quantity of meals is an important step toward a fully automated system. Some studies use closed-loop to control basal insulin and rely on the user to administer meal boluses, with good effect (63,64).

In pregnant women, 24 h closed-loop with manual bolusing and standardized meals and exercise achieved near normoglycemia with reduced frequency of hypoglycemia (58).

Limitations and Challenges for Closed-Loop Systems

Closed-loop systems rely on interstitial glucose measured using subcutaneous sensors. While sensor accuracy is improving, there is an inherent lag between blood and interstitial glucose measurements (65). This error is considered in closed-loop algorithms, but inaccurate CGM still limits the effectiveness of currently available closed-loop systems.

In addition, absorption of insulin delivered subcutaneously takes time, with up to 90 min for rapid-acting insulin analogs to reach their peak activity (66). Insulin absorption and pharmacokinetics also differ between patients and within the same patient on different days.

In pregnancy, insulin absorption becomes slower with advancing gestation (46).

Further challenges include meal times and exercise, when glucose levels fluctuate (67). Fully automated closed-loop systems rely on CGM to detect glucose changes, and so are inherently reactive rather than proactive at these times. The most feasible way forward is a hybrid system where basal insulin is automated via closed-loop and meal boluses are given manually. This is particularly likely to be necessary in pregnancy, when glucose targets are tighter and, as a result of slower absorption of insulin, boluses can be required up to 30–60 min before food.

Conclusions and Future Directions

Advances in diabetes-related technology have the potential to improve clinical outcomes and quality of life for women with diabetes in pregnancy and their offspring. Continuous glucose monitors provide more information about glucose excursions than have ever been previously available. Ongoing trials will demonstrate if this additional information is translated into improved glycemic control and clinical outcomes. Insulin pumps are being increasingly used in routine clinical practice and allow more individualization of insulin doses; however, robust data are lacking to support their use before and during pregnancy. A randomized trial of contemporary pumps with detailed economic evaluation of the equipment and specialist staff costs required to support intensive therapy is needed. Closed-loop insulin delivery has the potential to revolutionize treatment of type 1 diabetes and may be particularly beneficial in pregnancy when tight glucose control is important, but insulin doses are constantly changing and challenging to predict. If clinical effectiveness is achieved, a closed-loop system would cost no more than standard sensor-augmented pump therapy and could be implemented without dedicated personnel and expensive staffing costs. Currently, it is only applicable in type 1 diabetes pregnancy, but trials of early closed-loop in hospital patients with type 2 diabetes are underway and could lead to more widespread use.

Multiple-Choice Questions

1 Which of the following statements is correct?
   - **A** There is clear evidence to support the use of continuous glucose monitors in pregnancy.
   - **B** It is safe to start insulin pump therapy in pregnancy.
   - **C** Closed-loop systems reduce hyperglycemia but in doing so often increase hypoglycemia.
   - **D** A trial of low-glucose suspend systems is currently underway, after which these systems may become commercially available.

Answer: The correct answer is B. At present, there is no evidence to support the routine use of continuous glucose monitors in pregnancy, although two large trials are nearing completion. Closed-loop insulin delivery systems have been demonstrated to reduce hyperglycemia without increasing hypoglycemia. Low-glucose suspend systems are already commercially available. It is safe to transfer women from multiple daily injections to insulin pump therapy in pregnancy.

2 Which of the following statements is correct?
   - **A** Continuous glucose monitors have developed rapidly over recent years and are now more accurate than finger stick blood glucose measurements.

B Continuous glucose monitors should be restricted to educated, highly motivated patients who are unlikely to be overwhelmed by the large amount of data the device provides.

C Continuous glucose monitoring is most likely to provide benefit for people with lower HbA1c results, as it allows them to "fine-tune" their glycemic control.

D Continuous glucose monitors are less accurate during periods of rapid glucose fluctuation.

Answer: The correct answer is D. Continuous glucose monitoring (CGM) provides additional information about glycemia, but it is less accurate than finger stick blood glucose measurements, which should be relied upon for insulin dosing. It is difficult to predict which patients will benefit the most from CGM, and the UK NICE Guidelines currently recommend CGM for pregnant women who have suboptimal glucose control. As with most interventions, CGM is likely to provide the greatest benefit for people with poorer control. Continuous glucose monitors are less accurate during hypoglycemia and periods of rapid glucose fluctuation.

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17

Putting Pregnant Women with Diabetes on the Pump

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PRACTICE POINTS

1) Where there is an indication for using insulin pump therapy in pregnancy, it is preferable to start preconceptually, if possible.
2) When starting pump therapy during pregnancy, the initial total daily dose (TDD) of insulin for the pump should usually be 85% of the TDD on multiple daily insulin injections (MDIs).
3) If HbA1c is >8.5% (70 mmol/mol) when starting pump therapy during pregnancy, use an initial pump TDD equivalent to the MDI TDD; if the indication for starting pump therapy during pregnancy is problematic hypoglycemia, then use an initial pump TDD that is 75% of the MDI TDD.
4) By the late third trimester, expect basal insulin infusion rates to have increased by approximately 50%, and bolus insulin doses to have increased about fourfold.
5) In later pregnancy, if post-prandial hyperglycemia is problematic, consider giving meal insulin boluses 45–60 min pre-meals and using a super-bolus with large carbohydrate meals.
6) Change insulin infusion sets at least every 48 h during pregnancy to reduce the risk of hyperglycemia and ketosis if sets start to become blocked.
7) If there are problems with infusion sites, consider using an alternative site to the abdomen and/or different infusion sets.
8) Consider continuing insulin pump therapy if steroids are administered to promote fetal lung maturation, and during labor and delivery, rather than routinely switching to intravenous insulin infusion.
9) Ensure there are labor ward guidelines for managing women on insulin pump therapy during the peripartum period.
10) If unsure about postpartum insulin dosing, use a basal rate of 0.3 units/kg body weight, reducing to 0.2 units/kg body weight if breastfeeding.

Pitfalls

- Do not delay starting insulin pump therapy because of misplaced concerns that glycemic control will deteriorate when switching from multiple daily injections.
- Ensure that women do not adjust insulin infusion rates and bolus ratios too conservatively as pregnancy progresses.
- When initiating pump therapy preconceptionally or during early pregnancy, consider that large volumes of insulin may be required in later pregnancy and choose a pump with an appropriate capacity insulin reservoir.
- When women are breastfeeding, ensure that insulin doses are reduced by approximately one-third to protect against the increased risk of hypoglycemia.

A Practical Manual of Diabetes in Pregnancy, Second Edition. Edited by David R. McCance, Michael Maresh and David A. Sacks.

Case History

Kate has had type 1 diabetes since aged 11, and also suffers from hypothyroidism. She had her first pregnancy aged 28. This was a planned pregnancy, and she conceived with an HbA1c of 46 mmol/mol (6.3%) on twice-daily isophane insulin (insulatard) and insulin lispro (Humalog) with meals. She had frequent episodes of severe hypoglycemia in the first trimester complicated by seizures and a car crash. She maintained similarly good glycemic control throughout the pregnancy, but developed severe polyhydramnios so was transferred to the regional center where a macrosomic baby was delivered at 34 weeks gestation.

A second pregnancy 2 years later on the same insulin regimen followed a similar pattern: she again had hypoglycemic seizures during the first trimester, but despite glycemic control remaining close to target she again developed polyhydramnios and delivered a macrosomic baby at 36 weeks.

Her third pregnancy, on the same insulin regimen, was unplanned. Her HbA1c was 60 mmol/mol (7.7%) at conception, but by the time she found she was pregnant at 8 weeks she was experiencing worsening episodes of hypoglycemia. She was therefore immediately converted to insulin pump therapy, with a starting pump total daily dose 75% of her previous total daily dose. She had no further episodes of severe hypoglycemia, with only infrequent mild episodes for the remainder of the pregnancy. Blood glucose levels were better controlled from the start of pump therapy, and her HbA1c at 30 weeks gestation was 29 mmol/mol (4.8%). There was a slight increase in amniotic fluid volume but no significant polyhydramnios. She had a normal baby delivered by cesarean section at 38 weeks gestation.

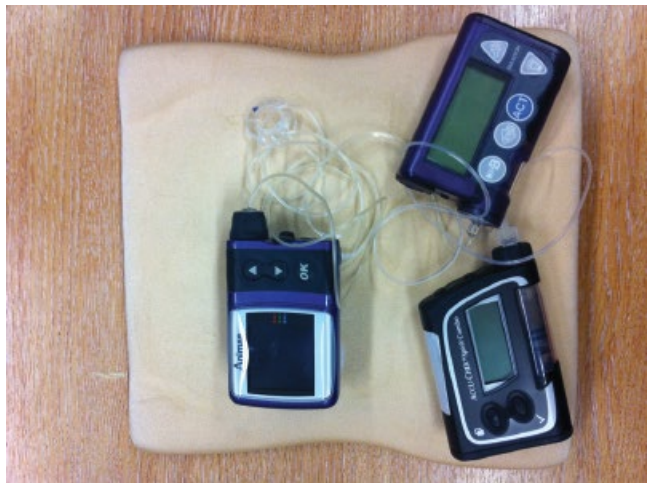
This case illustrates the benefit of insulin pump therapy in helping to achieve tight glycemic control while reducing the risk of hypoglycemia. It also supports the consideration that pump therapy should be offered to women who have had previous pregnancy problems while on a multiple daily injection regimen. Certainly, women who have tried both regimens in pregnancy usually report greater satisfaction with pump therapy, citing improved control, greater flexibility, easier insulin delivery, and better diet manageability (10).

Introduction

Insulin pump therapy offers potential advantages over multiple daily injections (MDIs) as a method of delivering intensive insulin therapy. Insulin can be delivered more flexibly via the pump. In particular, this includes a variable rate of basal insulin delivery, different types of bolus insulin profiles, and an ease of giving bolus doses that favors more frequent use of correction boluses.

The main components of an insulin pump are a reservoir containing soluble insulin, usually in the form of a rapid-acting analog such as insulin aspart or lispro; a pumping mechanism for driving insulin from the reservoir at a defined rate; and an infusion set that delivers the insulin from the pump into the subcutaneous tissue. Conventional insulin pumps (Figure 17.1a) are described as tethered, with infusion sets comprising a significant length of tubing attached to a plastic or metal cannula sited in the subcutaneous tissue. Conventional pumps may be controlled by a remote device, or directly via buttons and menus integral to the pump. More recently, "patch" pumps (Figure 17.1b) have become available, which are smaller devices applied directly to the skin, with either no tubing and the delivery system sitting directly under the pump, or with a very short length of tubing, such that the infusion site sits adjacent to the site where the pump is applied. These patch pumps have more limited reservoir volumes, and do not have any in-built software for controlling the insulin delivery, depending instead on signaling from a handheld remote control. Infusion sets are generally sited into the abdominal wall, but alternative sites include the flanks,

(a)



(b)

Figure 17.1 Insulin pumps: (a) conventional pump, and (b) "patch" pump.

thighs, and tops of buttocks; patch pumps can be sited on the upper arms.

Insulin pumps are able to deliver basal insulin at a rate that can be adjusted every 30–60 min depending on the device. Although described as continuous, in reality small boluses are infused every few minutes to deliver the defined cumulative dose. Pumps can deliver bolus insulin in a variety of ways. Pump users find it easier to give a bolus for snacks or to correct hyperglycemia as they do not have to give an additional subcutaneous injection. However, as well as delivering a standard bolus, which has a profile similar to the bolus delivered by a conventional insulin injection, an extended bolus can be delivered by the pump in which the insulin is infused over a prespecified period, which can be several hours long; or a dual-wave bolus; or a hybrid of a standard and extended bolus, with the user determining the proportion of the bolus given in each form. The pump software includes a bolus calculator, sometimes referred to as a *wizard*. This is based on a mathematical algorithm that varies with the device, but provides similar information to the user. This facility automatically suggests a bolus dose for a given blood glucose level and

carbohydrate intake, taking into account any residual insulin that is likely to be "active" from a previous insulin bolus.

In nonpregnant individuals, insulin pump therapy has been shown to be superior to MDIs, with improved glycemic control, as measured by HbA1c, and associated with a lower risk of hypoglycemia (1). Although the evidence base for superiority of pump therapy over MDIs in pregnancy, particularly in terms of maternal/fetal rather than glycemic outcomes (see Chapter 16), is lacking, pump therapy can be a valuable option for the individual woman with type 1 or type 2 diabetes who is attempting to optimize glycemic control preconceptionally or during pregnancy. This is especially so when efforts to optimize glycemic control using MDIs are limited by hypoglycemia, as reflected by NICE guidance on insulin pump therapy for pregnancy (2). However, there are certain practical issues about using pump therapy that are particular to pregnancy, and these will be addressed in this chapter.

Initiating Insulin Pump Therapy

Ideally, pump therapy should be commenced preconceptionally. This is definitely the preferred option when a woman fails to meet preconceptional glycemic targets with an optimized MDI regimen, or is struggling to maintain tight glycemic control because of problematic hypoglycemia. As preconceptional targets should mirror the targets for pregnancy, any problem is likely to persist into the crucial early stages of pregnancy. Starting pump therapy preconceptionally may also be considered for women who have achieved desired levels of glycemic control, but had problems in a previous pregnancy either maintaining that level of control or where pregnancy was associated with adverse pregnancy outcomes that might have been related to suboptimal glycemic control (see Case History, this chapter).

The majority of women with diabetes still present once pregnant rather than for preconceptional care, so when necessary pump therapy can be started during pregnancy, and this may happen for a variety of reasons. The most common indication is failure to achieve glycemic targets with optimized MDIs and/or hypoglycemic problems, particularly during the first trimester. However, other reasons for initiation include managing hyperemesis, where the ability to give frequent small boluses can help to achieve more stable blood glucose levels, which in our experience often reduces the severity of the nausea. In addition, later in pregnancy, pump therapy may be considered to control hyperglycemia caused by a more marked dawn phenomenon as insulin resistance increases, and where the basal rate of insulin delivery can be increased from the early hours of the morning if needed. There are reports of insulin pump therapy being used in gestational diabetes mellitus (GDM) (3); however, given the fact that this diagnosis is usually made relatively late in pregnancy, and the time taken to institute an intensive insulin regimen, the indication for pump therapy in GDM seems remote.

Starting insulin pump therapy preconceptionally should follow the standard practice for nonpregnant women. One approach is to take the total daily dose (TDD) of MDIs, and reduce this by 25% (pump TDD). Fifty percent of the resulting dose should then be delivered as the total daily basal insulin dose. Either this can be started as a flat basal rate, the number of units/hour being equivalent to 1/24th of the total daily basal dose (see Worked Example 17.1), or alternatively the total basal dose can be delivered over 24 h in a small number of different rates, usually no more than four, based on the individual's typical diurnal glucose profile. In these situations, the results from continuous glucose monitoring may help to confirm the profile, or a bespoke algorithm for a typical adult basal insulin profile can be used, such as that provided with the Accu-Chek pump range. It is not uncommon for those on insulin MDI

regimens to require quite large basal insulin doses, so a useful check is that the starting total daily basal insulin pump dose should be approximately 0.3 units/kg/day for a woman with type 1 diabetes – this is an alternative method for determining the starting total daily basal dose.

Preferably, bolus doses for meals should be based on carbohydrate counting, and the bolus calculator on the pump can be pre-programmed with the insulin-to-carbohydrate (IC) ratio (grams of carbohydrate covered by 1 unit insulin), which can be varied according to the time of day if appropriate. A useful rule of thumb for the IC ratio is the *500 rule*, which states that the IC ratio should approximate to 500/pump TDD. Similarly, the insulin sensitivity factor, which estimates by how much glucose will be reduced by 1 unit insulin, can be calculated by the *100 rule*, with 1 unit reducing blood glucose measured in mmol/l by 100/pump TDD (see Worked Example 17.1).

Insulin pump therapy during pregnancy can be started at any gestational age. There is no evidence that control is likely to deteriorate when pump therapy is started, and therefore no reason to defer starting insulin pump therapy until after 12 weeks. This is particularly important for women troubled by severe hypoglycemia or hyperemesis in the first trimester, where prompt initiation of pump therapy may be of great symptomatic benefit to the woman. Initiation of pump therapy should follow similar principles to those described in this chapter, although our policy is to use a starting pump TDD of 85% MDI TDD, unless there are problems with severe hypoglycemia in which case it is reduced to 75% MDI TDD. Equally, if control is particularly poor (HbA1c >8.5%, 70 mmol/mol), 100% MDI TDD would be a more appropriate starting pump TDD. The resulting basal infusion rate can be checked against the requirement of approximately 0.35 units insulin/kg/day.

Although a single basal insulin rate may be perfectly adequate across the 24 h, some authorities suggest a starting basal rate profile based on three or four blocks (4,5). One example is:

- 0.1 × pump total daily basal dose (TDBD) over 4 h from 00.00–04.00 h
- 0.2 × TDBD over 4 h from 04.00–08.00 h
- 0.3 × TDBD over 8 h from 08.00–16.00 h
- 0.4 × TDBD from 16.00–00.00 h (5).

Changing Insulin Requirements During Pregnancy

The change in insulin requirements during pregnancy as women become increasingly insulin resistant is well recognized and has implications for the changes that are needed to insulin infusion rates and bolus doses during pregnancy.

The most striking change as pregnancy progresses is the increased need for meal-related bolus insulin. A recent Danish study suggested that while basal insulin infusion rates increased by one-third to one-half from early to late pregnancy, with the greatest increase being seen at 05.00 h compared to 17.00 h, on average there was a fourfold increase in mealtime bolus (IC) ratios from early to late pregnancy, with the average IC ratio increasing from 1 unit:12 g carbohydrate to 1 unit:3 g carbohydrate (6). Closed-loop studies confirm the relatively small change in basal insulin requirements through pregnancy (7), consistent with the negligible change in fasting glucose after the first trimester.

In order to assess adequacy of insulin dosage during pregnancy, the expected TDD for a woman with type 1 diabetes at various stages of pregnancy is approximately:

- 0.7 units/kg/day during the first trimester,
- 0.8 units/kg/day in the second trimester, and
- 0.9 units/kg/day in the third trimester (4).

In early pregnancy, the expectation is that the proportion of the TDD delivered as basal insulin will be just under 50%, but by late pregnancy this proportion will have dropped to around 35%.

The biggest barrier to escalation in insulin doses is conservatism in incrementing bolus ratios and basal rates. Increments in bolus ratios need to be bold. For some women, ratios of 4:1 or 6:1 are not unusual, and there is likely to be a greater need for different bolus ratios at different times of day. In particular, due to the increased insulin resistance through the morning, more bolus insulin will often be needed at breakfast for a given carbohydrate intake than at other times of day. It is not uncommon for the IC ratio to be several-fold greater at breakfast than at lunch and evening meal (e.g., a 2:1 ratio at breakfast and 1:5 ratio for lunch and evening meal). Similarly, although the increase in basal rates is likely to be less marked, women established on insulin pump therapy for some time will be used to increasing basal rates in 0.1 unit/h increments, and this may be inadequate in later pregnancy. The pregnant woman needs to be prepared either to make such small changes more frequently, probably once or twice a week, from around 24 weeks gestation onward, or to make bigger incremental changes, of the order of 0.2 to 0.4 units/h. Regular review of uploaded pump data either remotely or at the joint diabetes antenatal clinic is necessary to advise women regarding these changing insulin needs.

Another consideration with regard to bolus delivery relates to evidence that insulin absorption is delayed in later pregnancy, and so bolus doses may need to be given as much as 1 h before meals (8). We advise women to give bolus doses 15–20 min pre-meals in the first trimester, 30 min pre-meals in the second trimester, and 45–60 min pre-meals in the third trimester when possible.

One of the challenges, particularly later in pregnancy, is controlling the peak in blood glucose levels after breakfast. Although changes to dietary composition can help with this, another option for pump users is a basal-to-bolus switch, also termed the *superbolus*. In this maneuver, the usual bolus dose is topped up and this extra top-up is taken from basal insulin delivery over the next few hours (see Worked Example 17.2).

Finally, some women experience delayed gastric emptying in late pregnancy and therefore find it helpful to use more complex bolus waveforms, usually a dual-wave bolus in which a proportion of insulin bolus is delivered over 4 to 6 h, and in some more extreme cases it may be appropriate to use an extended insulin bolus alone.

The insulin sensitivity factor (ISF) will need adjusting in parallel with the bolus ratio, so that by the end of pregnancy there will be a three- to fourfold reduction in the ISF. Therefore, if in early pregnancy 1 unit of insulin is expected to reduce blood glucose by 3 mmol/l, by late pregnancy 1 unit of insulin may be required to reduce blood glucose by 1 mmol/l.

The other factor included in bolus calculators is the active insulin duration. This is often a somewhat arbitrary figure, usually 3 or 4 h, although it can be assessed by determining how long it takes for blood glucose levels to return to baseline when there is certainty that an accurate insulin bolus has been administered. In later pregnancy, as insulin absorption slows, the active insulin time is likely to be extended, and if women find that the bolus calculator is overestimating the insulin dose needed in late pregnancy, then the active insulin duration can be increased to 5 to 6 h.

Steroids for Fetal Lung Maturation

Women with diabetes may receive steroids. Those being treated for autoimmune disease (e.g., systemic lupus) will usually be maintained on a fixed dose of prednisone or similar medication. However, on occasion the patient's clinical situation may require preterm delivery (e.g., in cases of severe preeclampsia or preterm labor), and steroids are given to promote fetal lung maturation. A number of regimens are used for delivering steroids in this situation. Our local practice for such women involves the administration of betamethasone in two doses, 12 h apart.

Steroids may have a significant hyperglycemic effect, and it is wise to admit women for more intensive monitoring and management (see Chapter 23). We have found that the effects of steroids for many women can be effectively managed on the insulin pump, and, having previously followed a complex schedule of temporary basal rate increases over 72 h after the first steroid dose, use a simple 50% temporary basal rate increase (150% of usual basal insulin infusion rate) and a 50% increase in bolus doses for approximately 24 h, starting 6 h after the first steroid dose has been given. Women are usually still admitted overnight, and when not in hospital should be encouraged to keep in close telephone contact with healthcare professionals and to monitor more frequently until blood glucose levels have stabilized again on their standard insulin regimen. This can usually be reinstated after 24–48 h of using the increased doses. Some women do have significantly greater increases in insulin requirements, by as much as 100% of their usual doses. Judicious use of correction boluses can help maintain control for such women, but there is a need to avoid bolus stacking. Women should be reminded that, for the duration of increased insulin requirement, their bolus calculator will underestimate their bolus need, so manual bolus delivery will be required.

Other Considerations Specific to Pregnancy

Insulin pump infusion sets are usually sited on the abdominal wall, although patch pumps are often sited on the upper arm as an alternative. As pregnancy progresses, women often find the abdominal wall site difficult to use, particularly if the skin becomes taut. In the latter scenario, plastic infusion cannulae are prone to bending, hampering insulin delivery. To overcome these issues, alternative sites can be considered, including the flanks, thighs, buttocks, and even breasts, which are easier to use given pregnancy-related changes; or a different infusion set can be used with a stainless-steel cannula, which is less likely to buckle.

Given that the accelerated ketosis of pregnancy predisposes to diabetic ketoacidosis should insulin delivery fail, pump users need to be constantly alert to the possibility of infusion set occlusions or other malfunctions. Some authorities suggest that a long-acting basal insulin injection (analog or isophane) should replace a proportion of pump basal insulin overnight to protect against the possibility of pump failure during this time, but this is not a commonly used strategy. We stress to our pump users the importance of changing insulin infusion sets frequently, at most once every 48 h, to reduce the risk of occlusions or slowing of the infusion rate. We also advise checking blood ketone levels at any time if blood glucose levels are above 10 mmol/l.

Insulin doses escalate through pregnancy, and this has implications given the volume of insulin that the pump reservoir can hold. Those pumps with a smaller reservoir (1.5–1.8 ml) may need to have the reservoir filled each day. Therefore, consideration should be given to changing to a pump with a larger (≥3 ml) reservoir before the second half of pregnancy, and this should also be taken into account when deciding which pump to use if initiation takes place before or during pregnancy.

The Peripartum Period

There is no reason why pump therapy cannot be continued throughout pregnancy, including during the peripartum period, irrespective of the mode of delivery. This does, however, require education of and close liaison between the diabetes, midwifery, obstetric, and anesthetic teams. Provided clearly established guidelines are in place, it is usually not necessary for women using insulin pumps routinely to revert to intravenous insulin infusion for delivery, although this option should always be available if pump therapy proves ineffective at maintaining optimal glycemic control.

From an international perspective, there is no consistency as to the use of pump therapy during labor, with many centers in the UK and USA preferring to manage all women, whatever their insulin regimen, with a variable-rate insulin infusion (VRII) according to protocol to maintain good glycemic control at this time. In this situation, at the time of substitution of a VRII protocol for the pump when in labor, women are advised to preprogram their pump basal insulin rates to 50% of those used pre-pregnancy and similarly reduce their insulin carbohydrate ratios to those used around conception. These settings will then be immediately available when they restart the pump on resumption of eating and drinking shortly after delivery. If women elect to use pump therapy during labor and delivery, then all the obstetric and other medical staff involved in labor ward care need to be familiar with pump therapy, labor ward guidelines for pump therapy should be in place, and women need to be advised about what they will need to facilitate management of their diabetes on the labor ward and what preparations are necessary.

We provide women using a pump with a checklist of items to bring into hospital at the time of delivery:

- Spare sets of batteries × 2
- Reservoirs/cartridges × 2
- Vial of rapid-acting insulin × 1
- Infusion sets (including lines) × 5 and inserter device (if using)
- Insulin syringes × 10
- Vial of long-acting insulin
- Hypo treatment of their choice (e.g., Glucotabs/Glucogel/Lucosade)
- Carbohydrate snacks

We then provide them with further advice as to what to check at the onset of labor:

- New batteries are put into the pump.
- Fill a new reservoir/cartridge with insulin for the pump.
- Put in a new infusion set (including a new line).
- Locate the infusion set below your rib cage and toward the back, so that it is out of the way in case emergency intervention is required.
- Check that you have written down or have inputted your pre-pregnancy basal rates as a second basal rate. This needs to be programmed so that you can change to this immediately after the baby is delivered. If you were not on a pump prior to this pregnancy, then the Diabetes Team will have advised you on what to reduce your basal rates to at a previous appointment. If not, then use a temporary basal rate of 50% immediately following delivery until you have seen a member of the Diabetes Team.

The siting of the infusion set well away from any possible operative field is particularly important in case an emergency cesarean section is required.

In general, once labor is established, or when a cesarean section is planned, women are able to maintain stable blood glucose levels within the target range by continuing on their established basal rate. We provide an algorithm for correcting blood glucose levels if they are outside the target range.

Our recommendation for intraoperative insulin adjustment is:

- If blood glucose >7 mmol/l, give a correction bolus aiming for a blood glucose of 5 mmol/l, using 1 unit insulin to lower blood glucose by 2.5 mmol/l unless the Diabetes Team have documented otherwise – as mentioned above, at this stage of pregnancy some women may need 1 unit to reduce the glucose level by only 1 mmol/l and so will be advised to use a larger correction dose.
- If this correction bolus is ineffective after 1 h, then give a further correction bolus.
- If after a further half hour blood glucose is between 7 and 10 mmol/l, then give a third correction bolus; if > 10 mmol/l, switch to intravenous insulin.
- If a third bolus is given, repeat blood glucose after another half hour, and if >7 mmol/l switch to intravenous insulin.
- If the blood glucose levels at any time are causing concern, switch to intravenous insulin.

- In the event of hypoglycemia (blood glucose <4 mmol/l), treat according to the hospital protocol.
- If the woman has recurrent hypoglycemia, advise her to adopt a 50% temporary basal rate reduction and to continue with this until the baby is delivered.

As soon as feasible, once the baby is delivered the woman or one of her support team should switch to a reduced basal infusion rate to match the expected fall in insulin requirements. Ideally, the woman should have preprogrammed a basal rate to switch to after delivery. There are a number of ways of working out what this rate should be. The simplest approach for the woman who has been on pump therapy at conception is to use this basal rate after delivery. If she is planning to breastfeed, then these rates should all be reduced by one-third. Alternatively, the total daily basal rate can be calculated on the basis of 0.3 u/kg body weight, and this should be reduced to 0.2 u/kg body weight if breastfeeding (9).

Breastfeeding and the Postpartum Period

In the immediate postpartum period, insulin requirements can be very low and women should be advised to use temporary basal rate reductions as needed if blood glucose levels continue to drop. If they are requiring much reduced basal rates, then they should be cautious with bolus dosing, and consider giving frequent small boluses to cover meals.

When breastfeeding, there is often a dip in blood glucose levels overnight as glucose is utilized in breast milk production. The basal rate profile may need adjusting to compensate for this.

Glycemic control tends to worsen in the postpartum period, but generally women on pumps find it easier to maintain control during this time (10), as the pump provides greater flexibility in the administration of correction doses when blood glucose levels are elevated. This also compensates for the fact that women are able to focus less on their diabetes care while looking after a newborn.

Future Directions

Insulin pump therapy can be combined with continuous glucose monitoring (see Chapter 16) as sensor-augmented pump therapy, and this enhanced technology may also assist pregnant women in optimizing glycemic control. The latest technology offers a low-glucose suspend option that can automatically turn off insulin delivery when hypoglycemia is likely to occur, and restart it once glucose levels start to rise again. In the near future, treat-to-range systems are likely to deliver small bolus doses to correct blood glucose levels above target range; and in the more distant future, closed-loop insulin delivery systems will provide the option of automating all basal and bolus insulin delivery to maintain normal blood glucose levels.

Multiple-Choice Questions

1 Which of the following statements is correct?
   - **A** The percentage of the pump's total daily insulin dose delivered as basal insulin increases as pregnancy progresses.
   - **B** Bolus doses should be administered at greater intervals pre-prandially as pregnancy progresses.
   - **C** One way of managing the increased insulin demand with breakfast in later pregnancy is to perform a bolus-to-basal switch.
   - **D** When breastfeeding, the basal rate should be based on 0.3 u/kg body weight/day.
   - **E** Pump therapy should not be used in the peripartum period.

Answer: B is correct: boluses are ideally given 15–20 minutes pre-prandially outside of pregnancy, but up to 60 min pre-prandially toward the end of the third trimester. A is incorrect; the percentage of total daily dose made up of bolus insulin increases through pregnancy, from about 50% preconception to about 65% in the late third trimester. C is incorrect: a basal-to-bolus switch allows a bigger bolus to be administered without increasing the risk of hypoglycemia in the late morning. D is incorrect: a lower basal insulin rate is needed when breastfeeding due to carbohydrate uptake into breast milk. Finally, E is incorrect: pump therapy can safely and effectively be used in the peripartum period, but individual units have to decide if this is appropriate for them, and if so ensure the correct protocols and procedures are in place.

2 Insulin pump therapy offers which of the following advantages over multiple daily insulin injections? (*Choose as many as apply.*)
- **A** Basal insulin infusion rates can be varied every 15 min.
- **B** A reduced risk of hypoglycemia for a given level of glycemic control
- **C** An automated correction bolus when blood glucose levels are greater than 10 mmol/l
- **D** Bolus doses can be given over an extended interval.
- **E** Bolus calculators take into account active insulin from previous bolus doses.

Answer: B, D, and E are correct. For B, there is a substantial body of evidence from randomized controlled trials and meta-analyses that this is the case. For D, curr ently available pumps can deliver extended (square wave) boluses delivered over several hours (typically, 1–6), which can also be used in combination with a conventional bolus to give a dual-wave bolus. And for E, bolus calculators have in-built algorithms that adjust for previous insulin doses based either on assessment of active insulin dependent on the user's estimate of active insulin duration or on the difference between actual and expected capillary blood glucose values. A is incorrect, because currently available insulin pumps allow changes in basal rates at 30 or 60 min intervals. C is incorrect because the only automated feature on currently available pumps is an insulin suspend on the Medtronic Veo and 640G systems to protect against hypoglycemia; in future, treat-to-range systems will offer automated bolus correction for hyperglycemia.

Worked example 17.1 Switching from MDIs to pump therapy pre-pregnancy

A 25-year-old woman, weighing 70 kg, is taking insulin detemir 16 units twice daily and using an IC ratio of 1 unit:10 g carbohydrate, taking approximately a total of 32 units of bolus insulin each day. Her HbA1c is 58 mmol/mol (7.4%). She has been trying to tighten blood glucose control but is struggling with increasing numbers of hypoglycemia episodes and decreased hypoglycemia awareness.

Total daily insulin dose (TDD) = 64 units
75% TDD = 48 units
Starting basal insulin infusion = 24 units/day = 1 unit/h
(Basal rate check: expected basal rate @ 0.3 units/kg/day = 21 units/day)
Insulin–carbohydrate ratio (ICR) = 500/48 = 10.4 (i.e., 1 unit per 10.4 g carbohydrate)
Insulin sensitivity factor (ISF) = 100/48 = 2.08 (i.e., 1 unit reduces blood glucose by 2.08 mmol/l)

Worked example 17.2 Basal-to-bolus switch

A 32-year-old woman is at 28 weeks gestation and is struggling with post-breakfast hyperglycemia with blood glucose levels usually between 9 and 12 mmol/l 1 h after breakfast. She is using an IC ratio of 1:3 (1 unit for 3 g carbohydrate) and has been trying to limit her carbohydrate intake. If she tries giving 2–3 units more insulin with her pre-breakfast bolus at 08.00, then she will be hypoglycemic around 11.00–12.00.

She is advised to try a basal-to-bolus switch. She usually gives her insulin bolus at 08.00. Her basal insulin infusion rate from 08.00–13.00 is 1.6 u/h. If she has a breakfast containing 30 g carbohydrate, then she would normally give 10 units. Instead, she should give 12 units, deducting 2 units from her basal rate over the next 5 h, so her basal infusion rate from 08.00–13.00 will be 1.2 u/h. This can be achieved by setting a temporary basal rate of 75% for this 5-hour period.

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Pregnancy, Perinatal, and Fertility Outcomes Following Bariatric Surgery

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PRACTICE POINTS

- A history of bariatric surgery is not an independent indication for cesarean delivery.
- Perform a comprehensive screen for micronutrient deficiencies, including iron, vitamins B_{12}, A, D, E, and K, folate, calcium, and protein, as routine prenatal practice.
- Children born to post-bariatric women are at decreased risk for LGA and increased risk for SGA and other growth abnormalities.
- Post-bariatric status is correlated with decreased risk of hypertensive disorders of pregnancy.
- Infertility may improve during the post-bariatric period; however, more studies are necessary.

Pitfalls to Avoid

- A history of bariatric surgery is never an independent indication for cesarean delivery.

Case History

A 25-year-old G2P1 woman with a lifelong history of obesity and a 3-year history of diabetes and hypertension presents at 6 weeks gestation in her second pregnancy. She has a history of bariatric surgery one year prior, after which her BMI fell from 44 kg/m^2 to that currently of 36 kg/m^2. On examination, her blood pressure (125/85 mmHg) and HbA1c (6.3% mmol/l) have improved compared with pre-bariatric values of 156/92 mmHg and 7.6% mmol/l. She reports that since her surgery, she has stopped taking her blood pressure medicine and is only taking metformin. Her first pregnancy, which resulted in a transverse cesarean delivery at 35 weeks 4 days because of fetal distress, was complicated by a 36 kg weight gain and mild preeclampsia. The baby weighed 3500 g (above the 90th percentile), and Apgars on delivery were 7 and 9 at 1 and 5 min. The current pregnancy is desired, but the patient has concerns about the outcome following bariatric surgery.

- Is the patient's post-bariatric surgery status an indication for cesarean section?
- Is the woman at an increased risk of pre-term delivery because of her post-bariatric status?

A Practical Manual of Diabetes in Pregnancy, Second Edition. Edited by David R. McCance, Michael Maresh and David A. Sacks.

- Does the patient have a decreased risk of gestational hypertension because of her post-bariatric status?
- Will the patient's child be at an increased risk of fetal malformations or weight-related abnormalities because of post-bariatric status?

These are a few of the questions that many providers may have when dealing with the post-bariatric obstetric patient. This chapter examines these questions and serves as a guide and reference for the clinician.

Introduction

Obesity is present in up to 30% of the US population and is an increasingly prevalent problem among women of reproductive age (1–3). Obesity is defined as a BMI above 30 and is associated with a number of reproductive health issues, such as infertility, miscarriage, gestational hypertension, gestational diabetes mellitus (GDM), preeclampsia, and cesarean delivery (4–11).

Obesity Classification based on BMI

Obese: BMI >30

Obese Class I: BMI 30–34.9

Obese Class II: BMI 35–39.9

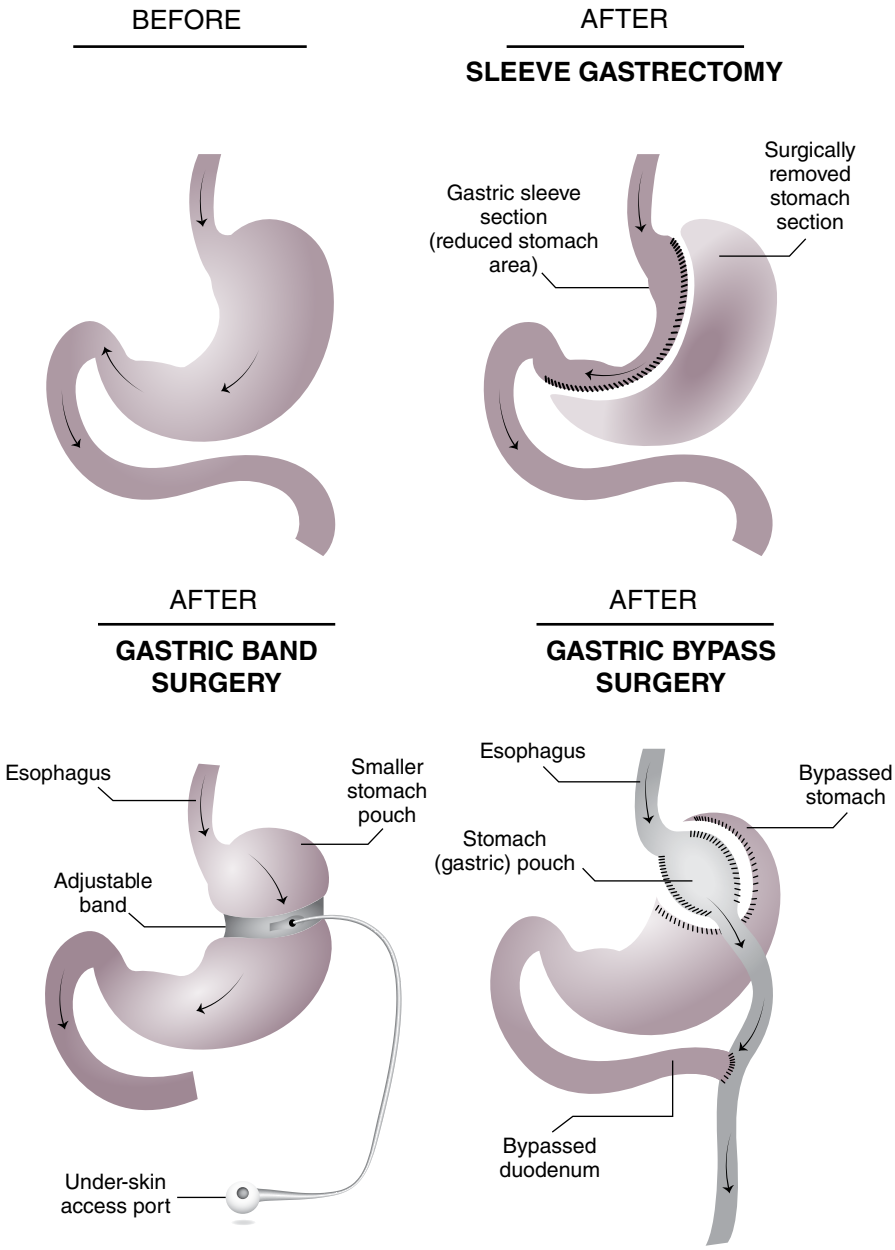
Obese Class III: BMI > 40

World Health Organization (3) National Institutes of Health (4)

In addition, it is difficult to examine the obese patient, which may make management of an already high-risk pregnancy more difficult. For example, the increased occurrence of oligo/anovulation in obese women may confound attempts to establish an accurate last menstrual period (LMP) for determination of gestational age. Furthermore, reduced visualization of the fetus in the obese mother during diagnostic ultrasound hampers efforts to obtain an accurate assessment of the intrauterine environment (12), highlighting the importance of early transvaginal ultrasound (TVUS) in the obese patient (13). Bariatric surgery is one means to attain significant weight loss and as such may lessen the risks of comorbidities associated with obesity in pregnancy (14–16). This chapter examines and summarizes the documented outcomes in pregnancy following bariatric surgery and provides a guide for the clinician who is involved with the postoperative care of these women with regard to reproductive health.

Classifications of Bariatric Surgery

The mechanisms by which bariatric surgery promotes weight loss include restriction, malabsorption, and/or neuroendocrine changes. These mechanisms occur to various degrees depending on the type of procedure performed. The most common procedures currently employed are laparoscopic standard Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG), laparoscopic adjustable gastric banding (LAGB), and biliopancreatic diversion/duodenal switch (BPD/DS) (see illustration) (17). There has been a shift in the trends of bariatric procedures performed in the last 10 years. RYGB is still a very popular procedure at 45% as of 2013, down slightly from 49% in 2008. SG represents the second most frequently performed procedure, and rates have increased considerably from 5.3% in 2008 to 37% in 2013 (17–19). However, rates of procedures such as adjustable gastric banding (AGB) and BPD/DS have dropped significantly. The rates of AGB procedures performed have dropped from an estimate of 42.3% in 2008 to 10% in 2013, and BPD/DS procedure rates have slowed from 4.9% in 2008 down to 1.5% in 2013. A summary of the types of procedures is reviewed in this section.



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Roux-en-Y Gastric Bypass and Biliopancreatic Diversion/ Duodenal Switch

The RYGB procedure involves the creation of a stomach pouch via stapling so that the lateral borders of the pouch are made up of the lesser curvature and the cut portion of the stomach, respectively. The jejunum is severed approximately 50–100 cm from the pylorus, and the distal end is connected directly to the pouch effectively bypassing the duodenum. The greater portion of the

stomach, including the greater curvature, the pylorus, and the proximal portion of duodenum and jejunum, are anastomosed distally to create a roux limb length approximately 100–150 cm in length (20). Rates of weight loss range from 56.2 ± 29.3% of excess BMI (long-term outcome) to 88.0 ± 29.6% of excess BMI (2 years out from surgery) (21). RYGB is associated with an increased risk of micronutrient deficiencies, the most common being iron, calcium, vitamin B_{12}, and vitamin D. Other deficiencies include the fat-soluble vitamins (A, E, and K), folate, and thiamine (22).

The BPD/DS procedure starts with an incision distal to the pylorus. A French bougie is inserted into the incision, placed parallel to the lesser curvature of the stomach, and a sleeve gastrectomy is created with several applications of the linear stapler. This new gastric pouch is connected to the distal ileum to form the alimentary limb. The duodenum, jejunum, and proximal ileum remain intact and make up the biliopancreatic limb, which is connected to the distal 100 cm portion of the alimentary limb to form the common channel (23). Similar micronutrient deficiencies are seen following BPD/DS as compared to RYGB (24). Other postoperative issues associated with BPD/DS include increased incidence of hypoalbuminemia secondary to protein malabsorption and malnutrition, with the possibility of the need for short periods of parenteral nutrition for nutritional support (25). Longer limb lengths have been shown to increase the incidence of protein malabsorption but are associated with improved weight loss outcomes (26,27). One study reported the need for parenteral nutrition during pregnancy following BPD/DS as high as 20%, although the frequency in the literature is variable (14,28,29). It is therefore recommended that patients undergoing RYGB and BPD/DS procedures be supplemented with calcium, folate, iron, and vitamins B_{12} and D (21,30,31). Importantly, the RYGB procedure is found to reduce rates of type 2 diabetes mellitus (32). This improvement seems to occur even before weight loss is achieved and is thought to be caused by two major mechanisms. The first is improved hepatic insulin sensitivity influenced by caloric restriction, and the second is improved beta-cell functioning associated with altered transit of nutrients bypassing the duodenum, leading to increased secretion of GLP1 (33). In terms of gestational complications, BPD/DS and RYGB rarely may lead to intrauterine growth restriction (IUGR), small-for-gestational-age (SGA) fetus, and fetal malformations (34–36). However, consensus on this issue has not been reached within the documented literature. The rates at which IUGR, SGA, and fetal malformations arise in the postsurgical cohort have been documented to be similar to the rates in the general population (29). In fact, studies suggest that the risks for pregnancies following RYGB and BPD/DS procedures are rather low. In a retrospective study of post-RYGB pregnancies, Wittgrove *et al.* (37) found decreased rates of large-for-gestational-age (LGA) infants, diabetes mellitus, and hypertensive disorders as compared to patients' own pre-surgery pregnancies. Another study done by Wax *et al.* (38) found no significant variance in birthweight or rates of IUGR between post-RYGB cases and the general population. In a recent Swedish study, in which nearly 98% of the bariatric surgery procedures were gastric bypass, pregnancies after bariatric surgery (as compared with matched pregnancies in women who had not undergone bariatric surgery) were associated with a higher rate of SGA infants (15.6% vs. 7.6%; odds ratio: 2.20; 95% confidence interval [CI]: 1.64 to 2.95; $P < 0.001$) and an increased risk for stillbirth or neonatal death (1.7% vs. 0.7%; odds ratio: 2.39; 95% CI: 0.98 to 5.85; $P = 0.06$) (39). The same study found no increased rates of fetal malformations, and decreased rates of LGA infants and GDM. In a retrospective study by Sheiner *et al.* (40) comparing outcomes between different types of bariatric procedures, the authors reported no difference in rates of low-birthweight

babies or LGA babies between different types of bariatric procedures. Collectively, the body of evidence suggests that outcomes for post-RYGB and post-BPD/DS patients may be better than pregnancy outcomes in an obese cohort but worse than in the general population.

Adjustable Gastric Banding

AGB is a restrictive procedure with less favorable weight loss outcomes than RYGB and BD. It is not usually associated with nutritional deficiencies or hypoalbuminemia (41,42). One study found an excess weight loss (EWL) outcome in AGB of 57 ± 15% EWL at 72 months (43). The complications associated with AGB during pregnancy include discomfort related to band tightness, uncommon but potentially fatal complications due to band slippage, and rarely a deficiency of vitamin K resulting in cerebral hemorrhage (44,45). Babies born to women with post-LAGB status have fetal birthweights similar to those of a non-obese cohort and lower than those of severely or morbidly obese controls (46,47). Incidence rates for GDM, low birthweight, preeclampsia, and LGA infants are found to be less for the patients with LAGB than for obese controls (48–50).

Band adjustment during pregnancy is performed in cases of severe nausea or vomiting, or if there is inappropriate weight loss or gain (51–53). Distinct guidelines have not been established as to whether band adjustment should be considered routinely, especially as the risks of weight gain resulting from premature band deflation during pregnancy may outweigh the risks associated with band adjustment on an as-needed basis. Additionally, it has not been determined whether children born to mothers with regular adjustment can expect improved outcomes. As such, it is imperative that these patients be monitored carefully for signs of excessive nausea, vomiting, and abdominal discomfort. If these signs develop, it is advisable that the pregnancy is managed in appropriate consultation with a qualified bariatric surgeon specializing in LAGB. Healthcare providers should be cognizant of the possibility that post-AGB pregnant patients may need band adjustment for excessive nausea and vomiting or if weight fluctuations are inappropriate.

Sleeve Gastrectomy

SG was initially performed as a modification to the BPD/DS in 1990. It gained popularity as a stand-alone procedure when it was realized that patients experienced weight loss after SG alone. The procedure is performed by vertically transecting the stomach using multiple applications of a linear stapler over a 38 French bougie (54). The major advantages of SG are the technical simplicity of the surgical procedure, the appreciable weight loss results, lower risks of malabsorption, and avoidance of intestinal surgery and associated complications. One study, that followed patients 5 years out from SG, found an excess weight loss of 55 +/– 6.8% (55). It is believed that the major mechanism of weight loss is related to neuroendocrine changes with the excision of the ghrelin-producing stomach portion. Ghrelin is a neuroendocrine peptide hormone that acts centrally to increase hunger signals, gastrointestinal motility, and gastric acid secretions, all of which behaviorally reinforce the desire to eat (56–58). Ghrelin shares the same central receptor as leptin, a peptide important in satiety signaling, and ghrelin is believed to block the ability of the body to feel satiated when it is bound to the receptor (59). The excision of the ghrelin-producing portion of the stomach during SG may account for the appreciable weight loss results and long-term weight loss maintenance (60). Recent studies indicate that the results of SG are promising. Several studies have been done examining maternal and fetal outcomes following SG; however, the data are not sufficient at this time to draw clear conclusions (61,62). Further studies are required to determine the reproductive health outcomes following SG (63).

Fertility

It is well established that obesity is linked to higher rates of oligo/amenorrhea and infertility (64,65). Additionally, it is known that weight loss is instrumental in helping to restore fertility (66). Various studies have endeavored to establish whether the weight loss associated with bariatric surgery might also help restore fertility (66–69). However, this issue is confounded by multiple factors such as the increased rate of infertility among women undergoing bariatric-surgery, which has been found to be as high as 41.9% preoperatively (69), and the increased weights of the post-bariatric patient population as compared to the average obstetric population. It is clear that more extensive prospective studies must be performed before a definitive conclusion can be made as to whether bariatric surgery will exacerbate or improve infertility, especially as compared to obese comparison cohorts and community rates.

Contraception

There is evidence that the effectiveness of oral contraceptives may be affected by post-bariatric status, as effectiveness of oral contraceptives relies on sufficient absorption (70,71). In one systematic review examining drug absorption following bariatric surgery, conflicting evidence was found with regard to the effect of post-bariatric surgery status on absorption of oral contraceptives. The theoretical mechanism of reduced absorption is related to the metabolism of oral contraceptives, including reduced drug disintegration and dissolution; delayed gastric emptying; bypass of large portions of the small intestines, which may be important for drug absorption; and the reliance of oral contraceptives on first-pass metabolism and enterohepatic recirculation (72). If patients would like to postpone or avoid pregnancy, the ACOG generally advises that healthcare providers should encourage the use of an appropriate non-oral contraceptive (73,74).

Surgery-to-Conception Interval

Considering the favorable improvement in fertility status among post-bariatric patients, there is substantial interest in determining an ideal time for conception following surgery. Currently, the American College of Obstetrics and Gynecologists (ACOG) recommends patients wait 12–24 months after bariatric surgery before attempting to become pregnant (75). This advice is related to concerns over potential micronutrient deficiencies and adverse perinatal outcomes associated with rapid weight loss. However, several studies have shown that these concerns may be unfounded. In one large population-based study, rates of SGA or preterm births were not found to differ based on interval from surgery to delivery (76). In another study of 104 women that conceived within one year of surgery and 385 that conceived after the first year following surgery, a shortened surgery-to-conception interval was not correlated with adverse events in pregnancy (77). Furthermore, in a study comparing 158 post-RYGB women who conceived within the first year of surgery and 128 who conceived sometime after the first year, no significant difference was found with regard to risks of preeclampsia, GDM, preterm birth (before 37 weeks), labor induction, cesarean section, postpartum hemorrhage (>500 ml), birthweight, SGA, LGA, Apgar score (5 min) below 7, or the need of neonatal intensive care (78). These studies, along with a growing body of evidence, suggest that the ideal surgery-to-conception interval may not be as critical as previously thought (79). Nevertheless, although patients who conceive during the first postoperative year have comparable short-term perinatal outcomes compared with patients who conceive after the first postoperative year, it seems reasonable to advise women to delay pregnancy for one year until consensus is reached within the obstetric community. If a pregnancy, however, occurs in a shorter interval, the existing

data should help the caregiver in advising these patients. Following bariatric surgery, practitioners should provide patients with the relevant information and tailor an appropriate reproductive timeline suited to their needs.

Miscarriage

No studies have comprehensively evaluated the relationship between bariatric surgery and miscarriage. In one large retrospective survey study, miscarriage rates were unaffected by pre- or post-BD status, indicating that BD may not influence rates of miscarriage (29). Another study found decreased miscarriage rates among post-bariatric patients; however, the study was underpowered (80). Collectively, these studies suggest that the prevalence of miscarriage may have more to do with a patient's preoperative rather than postoperative status. Additionally, it is important to recognize that patients who come to bariatric surgery may do so in an attempt to restore fecundity following multiple miscarriages. However, since the number of studies is insufficient and the sample sizes are small, definitive conclusions may not be drawn.

Preterm Labor

Obesity is associated with an increased risk for preterm delivery. Reducing the rate of preterm deliveries is a key component of reducing maternal/fetal risks, and as such it is of interest to examine the impact of bariatric surgery on this outcome. In one large Swedish cohort, pregnancies of patients following bariatric surgery were associated with shorter gestation (273.0 vs. 277.5 days; mean difference: −4.5 days; 95% CI: −2.9 to −6.0; $P < 0.001$), as compared to pregnancies from the general population who did not undergo bariatric surgery and were matched for a variety of factors, including BMI; of note, the preterm birth rate was not significantly different (10.0% vs. 7.5%; odds ratio: 1.28; 95% CI: 0.92 to 1.78; $P = 0.15$) (39). Overall, the evidence to date is inconclusive as to whether the prevalence of preterm labor is appreciably different following bariatric surgery (39,81–83).

Hypertensive Disorders of Pregnancy

Obesity has long been associated with increased rates of hypertension and hypertensive disorders of pregnancy (5), which pose risks for the fetus and the mother during pregnancy (65,84). As such, it is imperative to determine whether the weight loss associated with bariatric procedures lowers the likelihood of hypertensive disorders in pregnancy.

On the whole, post-bariatric status seems to be associated with a lower risk of developing hypertensive disorders during pregnancy; this decrease in risk is found both when patients are compared with their own preoperative status and as compared to an obese cohort (15,50,52,84). One retrospective cohort study by Bennett *et al.* (85) compared rates of chronic hypertension affecting pregnancy and gestational hypertension in women before and after bariatric surgery and identified a lower rate of these disorders after surgery. Some studies have not found any significant difference in the rates of hypertension among post-bariatric surgery patients and obese cohorts (86,87). Others have found an increased rate of hypertension among post-bariatric surgery patients as compared to a normal-BMI cohort, but lower rates as compared to an obese cohort (88).

Several studies have focused on determining the risk of preeclampsia following bariatric surgery. One study found that following RYGB, there was no associated increased incidence of preeclampsia compared with a normal-BMI cohort (87) but an increased risk of preeclampsia in the obese control cohort, indicating that there may be a benefit linked to post-bariatric status with regard to

preeclampsia. Other studies found similar reductions in risk of preeclampsia after bariatric surgery both for RYGB and for AGB procedures, compared with obese women who did not have surgery (10,84,89).

Gestational Diabetes Mellitus

GDM is strongly associated with maternal obesity and can lead to a variety of adverse pregnancy outcomes, including LGA babies, shoulder dystocia, and hypoglycemia in infants (90–92). Even when obese patients manage to attain adequate glycemic control, there is still a two- to threefold increased risk of pregnancy complications as compared to the non-obese cohort (93). Existing evidence suggests that weight loss could have a positive impact on GDM rates (93). Initial studies have pointed toward a potential benefit from bariatric surgery, not only due to the resulting weight loss, but also because of potential associated neuroendocrine changes (94). In one large population-based study by Sheiner *et al.* (67), higher crude rates of GDM were found in women who had undergone bariatric surgery when compared to pregnancies in the general population. However, after accounting for confounding factors such as BMI, there was no appreciable increase in risk of GDM in postoperative mothers (67). In fact, decreased rates of GDM (17.3% vs 11.0; $P = 0.009$) are found when post-bariatric surgery patients are compared to their obese counterparts (15,50); yet, the evidence is less straightforward when postoperative rates of GDM are compared to patients' own preoperative rates of GDM or the general population (52,68,95). In another recent study, including parturients from the Swedish Medical Birth Register, 670 singleton pregnancies occurred in women who had previously undergone bariatric surgery and for whom pre-surgery weight was documented. Pregnancies of patients following bariatric surgery were associated with lower risks of GDM (1.9% vs. 6.8%; odds ratio: 0.25; 95% CI: 0.13 to 0.47; $P < 0.001$) and LGA infants (8.6% vs. 22.4%; odds ratio: 0.33; 95% CI: 0.24 to 0.44; $P < 0.001$) as compared to matched controls from the general population (matched for BMI, among other variables) (39). Thus, it would appear that rates of GDM in post-bariatric surgery patients are lower than those found in a comparative obese cohort, although they may never normalize to those found in the general population.

Cesarean Section

Some studies have found that the rate of cesarean section is no higher than community rates (37), while others have documented higher rates of cesarean section following bariatric surgery (15,67).

Despite a higher crude rate of cesarean section among post-bariatric patients, several factors may confound this rate, including provider bias, history of prior C-section, and postsurgical BMI. For example, one large prospective study recently found that rates of prior C-section are high among patients who elect for bariatric surgery, highlighting the role that history of prior C-section may play in confounding postoperative rates (88). This same study found that rates of emergent C-section were lower among postoperative patients compared to controls (88). Additionally, studies have largely compared C-section rates between post-bariatric patients and community rates, making it difficult to account for BMI in analysis of data. Furthermore, it is difficult to know whether crude rates of cesarean section have been influenced by provider bias toward the patient's post-bariatric status. According to the ACOG guidelines on pregnancy after bariatric surgery, post-bariatric status is not an indication for cesarean delivery. Healthcare providers should be careful to scrutinize the indications for operation when considering referral for cesarean section and not be influenced by a patient's post-bariatric status (74).

Fetal Outcomes

Given the favorable obstetric risk profile in post-bariatric patients as compared to their obese counterparts, it is logical to reflect on whether post-bariatric patients can also expect improved perinatal and fetal outcomes. In one report by Sheiner *et al.* (67) on 159,210 pregnancies, there were no significant differences in perinatal outcomes in the 298 post-bariatric deliveries compared to deliveries in the general population. Specifically, no meaningful variations in rates of perinatal complications such as perinatal mortality, meconium-stained amniotic fluid, and low Apgar scores at 1 and 5 minutes were reported between the groups.

In another study comparing rates of perinatal complications between post-bariatric surgery pregnancies and those of non-operated obese patients, no significant differences were found, even though both had higher rates of complications as compared to non-obese counterparts (79). Therefore, after accounting for BMI, the rate of perinatal risks seems to be unaffected by post-bariatric status.

Birthweight

Maternal obesity increases the risk of LGA infants (96,97). Following bariatric surgery, the risk of LGA is decreased, an effect that is most likely associated with the change in maternal BMI (15,50,52,82). However, it is important to note that following bariatric surgery, women still have increased risks of LGA infants when compared to the general population (39,67).

Despite the reduced risk of LGA babies born to post-bariatric patients (as compared to an obese comparison cohort), there are still increased crude rates of weight-related abnormalities in the fetus, particularly SGA infants and IUGR (98). However, these associations often did not persist in multivariable analysis, and no significant differences in rates of SGA were found compared to the general community. One large retrospective study documented decreased rates of LGA and higher rates of SGA infants in post-bariatric surgery patients as compared to both normal-BMI and obese controls (88). The main long-term risks related to SGA are reduced cognitive and educational achievement; however, several studies, one of which followed patients up to 26 years of age, found that these children attained similar rates of employment, marital status, and satisfaction with life (99).

Fetal Malformations

Another priority for the medical community is establishing whether bariatric surgery is linked to an increase in fetal malformation or other congenital defects. The theoretical reason for concern is related to possible maternal micronutrient deficiencies and the resulting effect on the intrauterine environment (100). In a recent prospective, population-based study by Josefsson *et al.* (101) of 270,805 firstborns, 341 of which were delivered to a post-bariatric mother, post-bariatric status did not alter the risk for congenital malformations as compared to the general obstetric population. In another large study by Weintraub *et al.* (15), there were increased crude rates of fetal malformations in 507 post-bariatric surgery deliveries as compared to 301 deliveries to women before bariatric surgery; yet, the relationship did not persist after controlling for preterm delivery and maternal age. Importantly, the multivariate analysis performed in said study did not control for maternal BMI, a known risk factor for increased congenital malformations. In a study of 159,210 pregnancies by Sheiner *et al.* (67), no association between fetal malformations and bariatric surgery was documented, a conclusion that is supported by other studies (39,102).

Even with the strong body of evidence, healthcare providers should continue to check for maternal micronutrient deficiencies and fetal malformations and provide medically appropriate treatments. This is especially vital in postoperative patients whose obesity persists following surgery, since obesity is an independent risk factor for

neural tube defects (100). ACOG guidelines currently advise a comprehensive screen for micronutrient deficiencies, including iron, vitamins B_{12} and D, folate, calcium, and protein, with follow-up screening every trimester (74).

Summary

Given the large body of evidence documented in the literature so far, several general conclusions can be made about the impact of bariatric surgery on reproductive health outcomes. The first is that fertility may improve following bariatric surgery, but further studies are needed. Following bariatric surgery, patients are advised to wait one year before conception, although large, population-based studies have not found significant differences between pregnancies within or after the one-year period. Therefore, if patients wish to postpone or prevent pregnancy, clinicians should recommend a non-oral contraceptive as there is a theoretical risk of decreased absorption and effectiveness of oral contraceptives, and no conclusive studies have been performed. There is evidence that post-bariatric procedure patients are at decreased risk of hypertensive disorders of pregnancy and GDM. Additionally, children born to post-bariatric mothers are at lower risk of LGA but higher risk of SGA. Women should be monitored for micronutrient deficiencies throughout pregnancy. Finally, post-bariatric patients may develop surgical complications during pregnancy, and should be monitored by a bariatric surgeon in addition to a women's healthcare provider if complications arise.

Future Directions

Further studies are needed to determine the effects, if any, of bariatric surgery on rates of pre-term delivery and miscarriage. Additionally, studies examining the efficacy of oral contraceptives following bariatric surgery are imperative to establish appropriate contraceptive guidelines. Since SG is increasing in popularity among bariatric surgeons, more studies are necessary to clarify whether post-SG patients can expect similar maternal and fetal outcomes as patients who have undergone other bariatric procedures. Finally, additional large population-based trials and randomized controlled trials should address the possible ramifications of micronutrient deficiencies on the developing fetus.

Multiple-Choice Questions

1 A G3P2 woman comes to your office in her first trimester. She underwent bariatric surgery three years ago and is concerned about problems she may have during pregnancy because of the bariatric surgery. Her first two children were delivered by cesarean section. Other than the prior cesarean sections, her obstetric history is unremarkable. Which of the following is true?

A Due to her post-bariatric status, this woman is at an extremely high risk of preterm labor. She should have postponed her bariatric surgery until she was sure she no longer wanted to have children.

B This woman has a very high risk of miscarriage due to her history of bariatric surgery.

C The healthcare provider should consider the need for a cesarean section delivery solely because of her post-bariatric status, irrespective of the patient's history of prior caesarean section delivery.

D None of the above

Answer: D.

2 A woman in her early twenties comes to your office and tells you that she is considering bariatric surgery. She has a few questions about reproductive health. Which of the following is true?
   - **A** In order to ensure the best maternal and fetal outcome, the best time for this woman to become pregnant is in the first year following bariatric surgery.
   - **B** After bariatric surgery, oral contraceptives are the most effective form of birth control and are preferred over other birth control methods.
   - **C** Bariatric surgery is a leading cause of infertility.
   - **D** The effectiveness of oral contraceptives is questionable following bariatric surgery, especially in the setting of rapid weight loss. An alternative form of birth control should be prescribed.

Answer: D.

3 A woman missed her menstrual period 3 weeks ago and had a positive home pregnancy test. She has come to your office in order to confirm the test and is very excited about this much-wanted pregnancy. She underwent bariatric surgery 9 months ago in order to restore fertility, and her BMI has gone from 39 to 28.5 in that time. Which of the following statements is true?
   - **A** This woman's child has a higher risk of being LGA despite the patient's large weight loss following bariatric surgery.
   - **B** There is a reduced risk of intrauterine growth restriction (IUGR) in the fetus due to the patient's dramatic weight loss following the bariatric surgery.
   - **C** The risk of gestational diabetes and pregnancy-induced hypertension is elevated in this patient because of the recent timing of the bariatric surgery.
   - **D** According to the recent ACOG bulletin, it is indicated to follow the levels of iron, vitamin B_{12} and D, calcium, folate, and protein for deficiencies within the first trimester.

Answer: D.

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19

Fetal Surveillance

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PRACTICE POINTS

- Pregnancy in women with diabetes is associated with increased perinatal morbidity and mortality.
- The mechanism of fetal compromise in fetuses with normal or accelerated growth is not well understood and is likely to be multifactorial.
- Fetal compromise in women with diabetes with vasculopathy or preeclampsia is likely related to placental vascular disease.
- No currently available fetal surveillance technique has been proven to predict fetuses at risk or to prevent poor outcome in pregnant women with diabetes.
- Serial growth scans in the second half of pregnancy are recommended to detect accelerated fetal growth and/or polyhydramnios or growth restriction.
- Surveillance methods are of proven value only in pregnancies with vascular complications of diabetes, preeclampsia, or fetal growth restriction, or if the pregnancy is continued beyond 38 weeks gestation.

Case History

A 22-year-old nulliparous woman with type 1 diabetes was booked at antenatal clinic at 7 weeks of gestation. She subsequently had a normal anomaly scan at 20 weeks gestation. Serial growth scans were commenced from 28 weeks of gestation, which showed accelerated fetal growth with an abdominal circumference above the 95th centile, polyhydramnios, and normal umbilical artery Doppler flow. Ultrasound scanning for liquor volume and umbilical artery Dopplers were performed weekly, and biometry on alternate weeks. Although the polyhydramnios remained stable, acceleration of fetal growth continued with an estimated fetal weight of 3900 g at 35 weeks.

Labor was induced at 38 weeks gestation because of suspected macrosomia. She delivered a healthy female baby vaginally weighing 4200 g, which was complicated with shoulder dystocia. The baby was admitted to the neonatal unit for 5 days because of persistent neonatal hypoglycemia and jaundice. Mother and baby were discharged home after 8 days but with follow-up due to concerns regarding a possible brachial plexus injury in the baby.

- How does the pattern of fetal growth differ in women with diabetes from those having a normal pregnancy?
- How do we define macrosomia?

A Practical Manual of Diabetes in Pregnancy, Second Edition. Edited by David R. McCance, Michael Maresh and David A. Sacks.

- Why is diabetes associated with an increased risk of stillbirth, and when is stillbirth most likely to occur?
- What is the optimal fetal surveillance in women with diabetes with a suspected macrosomic fetus?
- Is assessment of fetal lung maturation justified before delivery? If so, what are the methods for doing this?

Background

Pregnancy in women with diabetes is associated with high rates of perinatal morbidity and mortality. The fetal and neonatal complications include increased risk of the following:

Fetal

- Miscarriage
- Congenital malformations
  - Cardiac anomalies
  - Neural tube defects
  - Microcephaly
  - Renal anomalies
  - Sacral agenesis
- Polyhydramnios
- Preterm delivery
- Stillbirth
- Macrosomia
- Intrauterine growth restriction (IUGR): particularly in women with vascular complications as a result of placental insufficiency

Neonatal

- Birth trauma: shoulder dystocia, fractures, brachial plexus injury, and asphyxia
- Cardiomyopathy
- Respiratory distress syndrome
- Metabolic derangements
  - Hypoglycemia
  - Hypocalcemia
  - Hypomagnesemia
- Hypothermia
- Polycythemia
- Jaundice

During the last few decades, improved diabetes care and preconception counseling have led to a reduction in perinatal mortality (PNM) (1). However, unfortunately, more recent studies demonstrate that the goal of the 1989 St. Vincent Declaration has not yet been achieved (2,3). In England and Wales, the rate of stillbirth and neonatal death in women with diabetes remained unchanged over the next 10 years (3), with a stillbirth rate of 12.8/1000 live and a stillbirths and neonatal death rate of 7.6/1000 live births, compared to a national rate of 4.9 and 2.8, respectively, in 2012. However, there had been a significant improvement in the number of babies who did not require admissions to neonatal intensive care units when compared with the CEMACH survey 10 years previously (70.3% vs 33.3%) (3,4). Perinatal mortality in European countries and other UK regional studies is comparable, and ranges from 28 to 48 per 1000 live births.

Fetal surveillance includes monitoring of fetal growth and assessment of fetal well-being to identify the fetuses at risk, in order to intervene in a timely and appropriate fashion and reduce perinatal morbidity and mortality. This chapter focuses on the currently available tools and the future directions for fetal surveillance in the third trimester in pregnancies complicated by diabetes.

Pathophysiology of Fetal Compromise in Diabetes in Pregnancy

The pathophysiology of fetal compromise, where the fetus is normally grown or large for gestational dates, is likely to be multifactorial. It is probable that the majority of unexplained stillbirths result from chronic

fetal hypoxia and/or fetal acidemia secondary to maternal/fetal hyperglycemia and fetal hyperinsulinemia (5). This can be explained by the Pedersen hypothesis (6), which states that maternal hyperglycemia and resultant fetal hyperglycemia cause marked fetal hyperinsulinemia via fetal pancreatic beta-cell overstimulation. This in turn causes accelerated fetal growth, excess subcutaneous fat deposition, and increased hepatic glycogen storage. The increased fetal metabolism associated with hyperglycemia may lead to relative fetal hypoxia and metabolic derangements. This hypothesis is now generally accepted and has driven the clinical management of diabetes in pregnancy, with the belief that better glycemic control in the mother can reduce fetal growth and hence perinatal morbidity and mortality.

There are several postulated mechanisms of fetal damage associated independently and collectively with maternal hyperglycemia, hyperinsulinemia, and the placental changes found in pregnancies complicated by diabetes. The first mechanism relates to tissue hypoxia. Fetal erythropoietin (EPO) levels in amniotic fluid are usually raised in the presence of fetal hypoxia in women with diabetes (5). Maternal hemoglobin A1c (HbA1c) concentrations in the third trimester correlate with fetal umbilical venous EPO at delivery (7), suggesting that antepartum maternal hyperglycemia is a significant factor associated with fetal hypoxia. In addition, fetal amniotic fluid insulin levels correlate significantly with fetal plasma EPO levels independently of maternal glycemia, suggesting that insulin exerts an effect on fetal oxygenation beyond that of maternal and fetal glycemia (7). Strong relationships between fetal weight, umbilical cord plasma insulin (8), and amniotic fluid EPO levels (5) suggest that the larger the fetus, the greater is the risk of fetal hypoxia. Extramedullary hematopoiesis is found more often in stillborn infants of mothers with diabetes (9). Postmortem reports in matched pairs of stillbirths in women with and without diabetes found a "starry sky" appearance in the fetal thymus on histology, indicative of critical subacute metabolic disturbance, in more than 50% of stillbirths in women with diabetes (10). In addition, thickening of the basement membrane of chorionic villi has been described in placentae of women with diabetes (11), which potentially could reduce oxygen transfer.

An alternative mechanism advocates that fetal cardiac dysfunction may be a cause of stillbirths in pregnancies complicated by diabetes (12). Maternal/fetal hyperglycemia, fetal hyperinsulinemia, and increased concentrations of EPO may have negative effects on the fetal heart *in utero* (13). High levels of B-type natriuretic peptide (BNP), proBNP, and Troponin T, markers of acute myocardial damage, are found in offspring of mothers with poor glycemic control during early pregnancy (14). Additionally, hypertrophic cardiomyopathy is found in 40% of infants of diabetic mothers, the cause of which remains unclear (15–17). These changes are transient and usually disappear within the first 6 months of life, but they can also lead to severe morbidity and even mortality (17).

A systematic review of four studies of adverse pregnancy outcome in types 1 and 2 diabetes found increased perinatal mortality associated with poor glycemic control (pooled OR: 3.23; 95% CI: 1.87–4.92) (18), although the studies had methodological limitations. Marked oscillations in maternal glycemic control may explain accelerated fetal growth and fetal compromise seen in some pregnancies with apparently excellent diabetes control (19). Maternal hypoglycemia does not seem to impact the fetus significantly; however, there are few studies addressing this issue.

When fetal death occurs, it is usually after 32 weeks of pregnancy (3,4) and is frequently in the context of poor glycemic control, polyhydramnios, and/or accelerated fetal growth (20). In contrast, women with diabetes and vasculopathy and/or preeclampsia may develop IUGR and fetal demise as early as the second trimester, probably related to placental vascular disease. However, 50% of

stillbirths remain unexplained, that is, no obvious cause can be identified by clinical examination or standard postmortem (12).

Accelerated Fetal Growth

Various definitions of accelerated fetal growth are in use, including birthweight over 4000 or 4500 g, or birthweight over the 90th centile or two standard deviations above the mean weight for gestational age and sex. The latter is preferred, as it allows premature newborns with excessive fetal growth to be identified, but even this does not characterize the selective organomegaly seen in the infant of the woman with diabetes. Macrosomia in newborns of mothers with diabetes is characterized by an excess in body fat, an increase in muscle mass, and organomegaly without increased brain size. There is a linear and continuous relationship between percentage body fat in newborns, maternal glycemia, and fetal insulin levels (21). The CEMACH survey (4) reported that 21% of singleton babies of women with diabetes weighed over 4000 kg compared with 11% in the general population.

Growth acceleration may start as early as 18 weeks of gestation (22). However, the growth potential of fetuses seems to be determined by prevailing maternal glycemia before then, and excessive growth can continue despite optimum glycemic control in later pregnancy (23).

One of the major challenges in managing pregnancies with suspected fetal macrosomia is how to minimize shoulder dystocia, brachial plexus injury, and other major birth trauma in babies with suspected accelerated growth. Shoulder dystocia is more common in larger babies, ranging from 1% in babies less than 2500 g to 43% in babies over 4500 g. In addition, it has been reported that babies born to women with diabetes have a three- to sevenfold greater risk for shoulder dystocia at each given weight category compared with women without diabetes (24). This can be explained by anthropometric differences between babies of mothers with and without diabetes (25). With pre-gestational diabetes, an incidence of brachial plexus injury of 4.5 per 1000 births was reported, which is tenfold greater than for the general population (4).

Nonetheless, optimal glycemic control during pregnancy is associated with a reduced incidence of accelerated fetal growth (26) and therefore with improved perinatal outcome.

Fetal Surveillance in Pre-gestational Diabetes (Type 1 or Type 2) and Gestational Diabetes Mellitus (GDM)

Although much data assessing fetal risk and antepartum surveillance pertain to type 1 diabetes, evolving evidence suggests that outcomes in type 2 diabetes are similarly poor (4). In fact, the risk of accelerated fetal growth and perinatal morbidity/mortality may be greater in type 2 diabetes given the frequent occurrence of other risk factors for poor obstetric outcome, such as advanced maternal age, raised maternal body mass index (BMI), non-Caucasian ethnicity, social deprivation, and poor pregnancy preparation (see Chapter 14). Also, perinatal death in type 2 diabetes is mainly due to stillbirth, chorioamnionitis, and birth asphyxia, whereas a single-center New Zealand study showed that over a 20-year period, 75% of such deaths in type 1 diabetes are secondary to congenital malformations or complications of prematurity (26a).

The issue of fetal surveillance is even more controversial in GDM than preexisting diabetes. There are few data in the literature to support or refute antenatal fetal surveillance in GDM. The optimal method, timing, and frequency of fetal surveillance in GDM remain unclear and will only be resolved by prospective, randomized controlled trials. It would seem reasonable, however, that women with poorly controlled GDM, whose babies have accelerated growth and who

require insulin or have other risk factors such as hypertension or adverse obstetric history, should have fetal surveillance similar to women with preexisting diabetes (27). Ultrasound measurement of abdominal circumference may also serve to guide the clinician as to the need for insulin therapy in conjunction with the results from home blood glucose monitoring (27).

Standard Fetal Surveillance Methods

Given the multifactorial nature of the etiology and the timing of fetal demise in pregnancies with diabetes, it is difficult to know which forms of monitoring, if any, are appropriate. It is generally accepted that standard clinical assessment needs to be supplemented by other methods of surveillance, although two reviews in pregnancy complicated by diabetes (9,28) show that no currently available technique has been proven to predict the fetuses at risk or to prevent poor outcome. Standard fetal surveillance methods include:

- Antenatal cardiotocograph (CTG)
- Two-dimensional ultrasound (2D USS) assessment of fetal growth
- Ultrasound assessment of amniotic fluid volume
- Umbilical artery Doppler velocimetry
- Biophysical profile
- Amniocentesis – assessment of fetal lung maturity and fetal insulin.

Antenatal Cardiotocography

There are no randomized controlled trials assessing the value of antenatal CTG for fetal surveillance in pregnant women with diabetes. Nonrandomized studies indicate that the tool is a poor predictor of fetal compromise in diabetes, with fetal demise being reported hours after a normal trace (29). This is not surprising considering the probable pathogenesis of fetal demise in diabetes in pregnancy. A review of seven studies of antepartum CTGs found that within 7 days of a normal CTG, there was a stillbirth rate of 1.4% in pregnancies with diabetes, similar to that of pregnancies complicated by IUGR (2%) (30).

A systematic review comparing the use of computerized CTG to traditional CTG found a significant reduction in perinatal mortality with computerized CTG (RR: 0.20; 95% CI: 0.04 to 0.88) (29). However, the sample size was small ($n = 496$) and included all high-risk women. Further studies are required, both in high-risk pregnancy overall and in pregnancy in women with diabetes.

In conclusion, available evidence does not support the routine use of antenatal CTG in pregnancies with diabetes outside the usual indications, including reduced fetal movements, fetal growth restriction, preeclampsia, or antepartum hemorrhage (31).

Two-Dimensional Ultrasound Estimation of Fetal Growth

Prediction of fetal weight in pregnancy in diabetes using 2D USS biometry is inaccurate, and one should interpret the results with caution. This is because diabetes influences the abdominal circumference (AC), but not bony measurements, via its effect on insulin-sensitive tissues such as the liver (glycogen storage) and abdominal wall adipose tissue. Accordingly, USS measurements will predict IUGR but are less reliable for the detection of accelerated fetal growth and therefore cannot be expected to accurately predict trauma at delivery for these babies (24). Nonetheless, biometric measurements are incorporated in standard recommendations for management of women with diabetes (31–33).

A systematic review (34) of nearly 20,000 pregnancies concluded that there was no difference in accuracy between ultrasonographic estimated fetal weight (EFW) and AC in the prediction of birthweight over 4000 g. These studies, however, were in women without diabetes and therefore cannot be extrapolated directly to women with diabetes, but it is likely that accuracy would be even lower in the latter. This systematic review has recently been updated to include comparison of 2D USS with 3D USS and

magnetic resonance imaging (MRI) (35); the sensitivity of 2D USS AC (>35 cm) alone (0.80 [95% CI; 0.69–0.87]) was significantly superior to 2D estimated fetal weight (0.56 [95% CI: 0.49–0.62]), but significantly less specific, suggesting more false-positive results with the use of AC measurement alone ($p = 0.012$). Only about 300 women had MRI fetal weight estimations, but there was high sensitivity (0.93 [95% CI: 0.76–0.98]) and specificity (0.95 [95% CI: 0.92–0.97]) for macrosomia. However, larger studies are required before this technique can be applied in clinical practice. Assessment of the diagnostic accuracy assessment of 3D USS for macrosomia was not possible in this meta-analysis.

In conclusion, serial growth scans in pregnancy with diabetes can be helpful for identifying growth restriction. If USS suggests accelerated fetal growth, the precise risks to the fetus either antenatally or at delivery are uncertain, and therefore the information is of limited value. Accelerated growth may indicate poor glycemic control and so may be useful for intensifying glycemic control measures and lifestyle advice.

Ultrasound Assessment of the Amniotic Fluid Index

There are two methods of quantifying the amniotic fluid: the amniotic fluid index (AFI) and maximal pool depth (PD). The AFI is calculated as the sum of the deepest vertical pools of amniotic fluid (in centimeters), free of the umbilical cord and fetal parts, in each quadrant of the uterus. Maximal PD simply measures the single largest vertical pool of liquor. There is no consensus as to which method is best practice to determine amniotic fluid abnormalities. AFI is more time-consuming, and MPD is equally as effective for determining oligohydromnois and polyhydramnios. Between 27 and 42 weeks, AFI measurements are greater in pregnancies with diabetes than without diabetes (36). This probably reflects fetal polyuria secondary to hyperglycemia-induced osmotic diuresis. There have been no prospective studies looking at the value of AFI measurements in predicting fetal outcome in structurally normal, term pregnancies with diabetes. A raised AFI on its own does not seem to help in predicting antenatal fetal compromise, although it may suggest the need to intensify glycemic control.

Umbilical Artery Doppler Velocimetry

Umbilical artery (UA) Doppler velocimetry is an indirect measure of placental flow resistance. A Cochrane Systematic Review found a significant reduction in perinatal deaths (RR: 0.71; 95% CI: 0.52–0.98) and less obstetric interventions with the use of fetal and UA Doppler USS in high-risk pregnancies (including diabetes) thought to be at risk of placental insufficiency (37).

In diabetes, however, the fetal hemodynamic and metabolic response to maternal hyperglycemia is complex and dependent on the duration of insult. The fetus increases its oxidative metabolism, becoming more hypoxemic. Perfusion of the brain and kidneys increases even in the absence of any changes in the feto-placental perfusion. In maternal diabetes, UA Doppler velocimetry may therefore remain unchanged despite fetal hypoxemia (unless there is also vasculopathy or placental insufficiency and fetal growth restriction), and the presence of normal Doppler indices does not exclude fetal compromise (38,39). UA Doppler velocimetry should be reserved for pregnant women with diabetes who are at risk of developing IUGR (31,32).

Biophysical Profile

The biophysical profile (BPP) involves four ultrasound assessments (fetal breathing, fetal tone, fetal body movements, and AFI) and CTG analysis. It was originally validated for growth-restricted pregnancies in the absence of a major congenital anomaly. However, BPP in pregnancies complicated by diabetes is a poor predictor of adverse pregnancy outcome (40), as there are a number of problems in interpreting the results; maternal hyperglycemia can be associated with an increased

AFI and increased fetal breathing, and thereby diabetes itself can influence two of the five parameters. A normal test result, however, is usually thought to be reassuring of fetal well-being (41). The role of BPP in pregnancy with diabetes remains controversial; it is not routinely advocated in the UK (31), but forms a part of standard care for all pregnant women with diabetes in the USA (32,33).

Amniocentesis and Assessment of Fetal Lung Maturity

Historically, assessment of fetal lung maturity (FLM) in pregnancy with diabetes helped obstetricians plan when to deliver preterm fetuses, aiming both to minimize the risk of respiratory distress syndrome (RDS) and to avoid late stillbirth. Various amniotic fluid analyses have been used to assess FLM, such as the lecithin-to-sphingomyelin (L:S) ratio, presence of phosphatidylglycerol (PG), surfactant-to-albumin ratio, lamellar body counts (LBCs), foam stability index (FSI), and optical density (42).

In recent years, amniocentesis for FLM has been used less frequently as the usefulness of these tests is greatest when the test result is consistent with fetal lung maturity, but not when the result is consistent with immaturity (43,44). The latter may result in unnecessary administration of steroids, which risks iatrogenic hyperglycemia, or unnecessary postponement of an indicated delivery, in the instance where the test result falsely predicts the absence of fetal pulmonary maturation.

Amniocentesis for Prediction of Macrosomia and Assessment of Glycemic Control by Measuring Amniotic Fluid Insulin

High fetal insulin levels in the third trimester have been implicated in accelerated fetal growth, as well as fetal acidemia (45). Conceptually, identification of the hyperinsulinemic fetus before delivery might allow the intensification of maternal insulin therapy, leading to a reduction in the incidence and severity of diabetes-related fetopathy (46). However, there are not enough data yet to warrant measuring antenatal levels of amniotic fluid insulin in routine clinical practice.

Fetal Surveillance Methods: What is the Future?

Three-Dimensional Ultrasound Estimation of Fetal Weight and Organ Volumes

3D USS allows volumetric assessments of fetal weight and organ volumes (e.g., liver). It has been hypothesized that EFW calculated with volumetry would be more reliable, as the ideal biometric view could be optimized within the volume and fetal subcutaneous fat assessment could be included. However, studies so far have failed to demonstrate improved sensitivity in the detection of macrosomia in women with diabetes (47), and the technique is time-consuming (48) and not easy to perform unless experienced. More research is needed before its incorporation into routine clinical practice.

Ductus Venosus Velocimetry

The ductus venosus (DV) (Figure 19.1) is an important fetal vessel through which oxygenated blood is directed from the umbilical vein toward the foramen ovale. Approximately 20–30% of the umbilical venous blood flow bypasses the hepatic circulation through the DV (49). Abnormal blood flow through the DV is noted in conditions associated with fetal acidosis and declining forward cardiac function. Assessment of the peak velocity index for veins (PVIV) has been demonstrated as a reliable and useful venous Doppler index (50).

Fetuses of mother with pre-gestational diabetes are at increased risk of developing congenital heart disease, myocardial hypertrophy, and fetal acidemia, resulting in impaired cardiac function. Furthermore, right heart function may deteriorate more

Figure 19.1 Typical wave form of Doppler for ductus venosus.

significantly in cases of poorly controlled diabetes (51). Studies (52) have found a raised DV-PVIV in fetuses of women with diabetes and statistically significant correlation with HbA1c values, but sensitivity and specificity in predicting adverse fetal outcome are inadequate.

Assessment of Fetal Cardiac Function

A number of studies have used the myocardial performance index (or Tei index), which is a predictor of global cardiac function. The majority suggest that maternal diabetes is associated with variable degrees of impairment in cardiac function, with diastolic dysfunction being the most common finding. However, the largest study (a retrospective review) involving fetal echocardiography of 2000 cases, including 140 with maternal diabetes, found no difference in the results of the diabetes group compared to other subjects (53). There is very little research relating this cardiac dysfunction to fetal outcomes, and this investigation currently remains a research tool and requires a high degree of skill to perform.

Amniotic Fluid Erythropoietin, and Oxidative and Nitrosative Stress Biomarkers

Tissue hypoxia is the major stimulus for EPO synthesis, and high amniotic fluid EPO levels are a surrogate marker for chronic fetal hypoxia. EPO neither crosses the placenta nor is stored. Fetal plasma and amniotic fluid levels are therefore indicative of fetal EPO synthesis and elimination. Repeated amniotic fluid EPO measurements reveal exponential increases during fetal hypoxia in pregnancies with diabetes and other high-risk pregnancies (54). It is possible that weekly measurements of amniotic fluid EPO from 37 weeks, with delivery if levels are rising toward a threshold, could be the way forward in the management of these complex high-risk pregnancies with diabetes, but this remains a theory that requires confirmation in clinical trials.

MRI Studies

Fetal Adiposity

Babies born to mothers with diabetes tend to be larger with increased subcutaneous fat deposition. The measurement of fetal

adiposity using MRI is in its early phase of development and shows promise in quantifying subcutaneous fat and demonstrating a difference in body composition between women with pre-gestational diabetes and controls in the third trimester of pregnancy (55).

Prediction of Fetal Lung Maturity

Whilst amniocentesis has been used for the determination of FLM in women where delivery is contemplated near term, research is being conducted in an attempt to noninvasively gain similar information. Two techniques have been described: first, MRI spectroscopy that measures a variety of compounds, including choline and lecithin; and, second, the lung-to–liver signal intensity ratio compares the ratio of fluid in the lung to that of the liver and is thought to reflect the cell number, phospholipid content, and development of epithelial and interstitial tissue in the lung. Both techniques are challenging and in the early phase of development, and neither have yet been applied to a population of pregnant women with diabetes.

Practical Approaches to Fetal Surveillance

Given the lack of an ideal fetal monitoring test, the limitations of the available tests, and lack of rigorous scientific trials, including randomized controlled trials, all protocols used for fetal surveillance are empiric, rather than evidence based, and all have limitations (Table 19.1). The financial impact on health resources, the maternal anxiety generated, and the lack of evidence regarding the efficacy of the tests must all be considered when local protocols are developed.

Table 19.1 Summary of usefulness of available tests for fetal well-being in the third trimester in clinical practice in the context of a pregnancy with diabetes.

Fetal surveillance test	Recommendation
Serial growth scans using 2D ultrasound (USS)	Recommended routinely
Umbilical artery Doppler velocimetry	Recommended in specific cases such as IUGR, preeclampsia, reduced FM
Antenatal CTGs	Recommended twice weekly in women with pre-gestational DM in USA, but in UK for specific cases such as IUGR, preeclampsia, reduced FM
Biophysical profile	Routinely recommended in women with pre-gestational DM in USA, but in UK for specific cases such as IUGR, preeclampsia, reduced FM
Amniocentesis and assessment of fetal lung maturity	For selective use
Amniotic fluid insulin	Not recommended in routine clinical practice
3D ultrasound estimation of fetal weight and organ Volumes*	Not recommended in routine clinical practice
Ductus venosus velocimetry*	Not recommended in routine clinical practice
Assessment of fetal cardiac structure and function*	Not recommended in routine clinical practice
Amniotic fluid erythropoietin*	Not recommended in routine clinical practice
MRI studies*	Not recommended in routine clinical practice

* Potentially useful test, but more research needed before being incorporated into routine clinical practice.
CTG, Cardiotocograph; FM, fetal movements; IUGR; intrauterine growth restriction; MRI, magnetic resonance imaging.

In the UK, the NICE guideline (31) recommends:

- Ultrasound monitoring of fetal growth and liquor volume every 4 weeks from 28 to 36 weeks gestation.
- Additional monitoring for fetal well-being (using methods such as fetal umbilical artery Doppler recording, CTG, and BPP testing) is needed only for pregnancies with risk factors for IUGR. The frequency will be determined by the severity of the underlying comorbidity.
- Weekly tests for fetal well-being, if the pregnancy is continued beyond 38 weeks.

In contrast, the ACOG guideline states periodic ultrasound examination of fetal growth along with twice-weekly CTG and BPP at appropriate intervals starting at 32–34 weeks gestation is a valuable approach in monitoring the fetus in women with preexisting DM. Doppler velocimetry of the umbilical artery should be reserved for pregnancy with vascular complications and poor fetal growth (32). Fetal surveillance may be beneficial in women with GDM with poor glycemic control – the method and frequency of the test will depend on local practice (33).

Research Directions

- Understanding the mechanism of fetal demise in pregnancy with diabetes.
- The use of 3D ultrasound and MRI for determination of fetal fat, body composition, and weight in utero.
- The role for 3D power Doppler for evaluation of placental volume, vascularization, blood flow, and structure.
- Randomized controlled trials of amniotic fluid EPO to detect the "at-risk" fetus.
- Noninvasive methods to assess FLM and fetal compromise.
- The most appropriate management strategy following detection of accelerated fetal growth antenatally.
- Randomized controlled trials to determine the optimal surveillance tests and the frequency of testing.

Multiple-Choice Questions

1 The following feature was found on postmortem in the majority of the stillbirths in women with diabetes:
   - **A** Large placenta
   - **B** Retroplacental hemorrhage
   - **C** "Starry sky" appearance in the fetal thymus
   - **D** Thymic hypertrophy

Correct answer is C (see also (12)).

2 Which of the following is not associated with accelerated fetal growth in pregnancies complicated with maternal diabetes?
   - **A** Acute fetal hypoxia
   - **B** Brachial plexus injury
   - **C** Intrauterine fetal death
   - **D** Shoulder dystocia

Correct answer is A. Accelerated fetal growth in women with diabetes usually leads to chronic fetal hypoxia rather than acute.

3 The following test is currently recommended in routine clinical practice for fetal surveillance in woman with diabetes:
   - **A** Ductus venosus velocimetry
   - **B** Placental ultrasound assessment
   - **C** Serial growth scans using 2D ultrasound
   - **D** 3D ultrasound estimation of fetal weight and organ volumes

Correct answer is C (see also (37–39)).

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20

Complications in Pregnancy: Hypertension and Diabetic Nephropathy in Diabetes in Pregnancy

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PRACTICE POINTS

- Prevalence rates of chronic hypertension, gestational hypertension, preeclampsia, and superimposed preeclampsia are all more frequent in diabetic pregnancy compared to normal pregnancy.
- The presence of chronic hypertension, microalbuminuria, or diabetic nephropathy in early pregnancy should be evaluated.
- It is important to obtain and maintain strict glycemic control and closely monitor for development of preeclampsia in all pregnant women with diabetes.
- Blood pressure (BP) should be measured at booking and at each visit at approximately 1–2 weekly intervals.
- The goal for antihypertensive treatment in pregnant women with diabetes and chronic hypertension is 110–139 mmHg for systolic BP and 65–89 mmHg for diastolic BP. Some centers strive for values below 135/85 mmHg or even below 130/80 mmHg. Strict antihypertensive treatment is important when microalbuminuria or diabetic nephropathy is present.
- BP medications that are safe for pregnancy should be added sequentially until target BP level is achieved.
- Methyldopa, beta-adrenergic blockers (e.g. labetalol), and slow-release calcium blockers may be used during pregnancy.
- Angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) are contraindicated in pregnancy and should be substituted with drugs that are safe in pregnancy before or, at the latest, in early pregnancy.
- Methyldopa, labetalol, captopril, and enalapril can be used during lactation.
- Most of the literature on this topic is from women with type 1 diabetes, but since the clinical findings are similar in women with type 2 diabetes, the clinical recommendations given here are applicable to both type 1 and type 2 diabetes and probably also to women with gestational diabetes.

Case History

A 28-year-old woman with a 23-year history of type 1 diabetes and a 2-year history of diabetic nephropathy presented at 10 weeks in her first pregnancy. She was being treated with an ACE inhibitor and furosemide twice daily. On examination, her blood pressure was 114/75 mmHg; serum creatinine was normal, but urinary albumin excretion was elevated at 941 mg/24 h (normal <30 mg/24 h). She was changed from the ACE inhibitor to methyldopa 250 mg twice daily, while diuretic treatment with furosemide 40 mg twice daily was continued. When her blood pressure exceeded 140/90 mmHg at 29 weeks, methyldopa was gradually increased to 500 mg four times daily. Unfortunately, she developed preeclampsia with severe hypertension and

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proteinuria. Following a 2-day course of betamethasone for fetal lung maturation, she was delivered by caesarean section at 32 weeks. The baby's birthweight was 1800 g.

A few years later, she became pregnant again. By this time, her serum creatinine level had increased to 120 µmol/L (1.36 mg/dL) and the urinary albumin excretion to 3000 mg/24 h. Her blood pressure (108/68 mmHg) was well controlled with ACE inhibition and diuretics. The ACE inhibition was again stopped, but in this pregnancy she was treated with a more intensive antihypertensive strategy aiming for a blood pressure below 135/85 mmHg and urinary albumin excretion below 300 mg/24 h. By 16 weeks, she was on the maximal dose of methyldopa (2000 mg daily), unchanged diuretic therapy, together with labetalol that had been initiated and gradually increased to maximum dose. Her urinary albumin excretion remained in the nephrotic range (>2000 mg/24 h), but BP remained below 130/80 mm/Hg. At 36 weeks, she had no symptoms of preeclampsia and was delivered due to increasing serum creatinine levels. The baby's birthweight was 2584 g.
Questions from this case:

- Does the presence of proteinuria early in pregnancy affect pregnancy outcome?
- Why was the pregnancy outcome better in the second pregnancy?
- What type of antihypertensive drugs can be used during pregnancy?
- What is the treatment goal for hypertension during pregnancy?
- What type of antihypertensive drugs can be used during lactation?

Hypertension in the Nonpregnant Diabetic Population

Outside of pregnancy, hypertension is more common in women with diabetes compared with the background population. The prevalence of hypertension, defined as blood pressure (BP) greater than 140/90 mmHg, was reported as 12% and 22% in nonpregnant women with type 1 diabetes aged 15–30 and 30–44 years, respectively – representing an increased prevalence even in patients without kidney involvement (1,2). Both the prevalence and severity of hypertension increase in the presence of microalbuminuria or diabetic nephropathy (2). Among women with type 2 diabetes, the prevalence of hypertension is comparable to, or probably even higher than, that of type 1 diabetes (1,3).

The diagnostic cutoff level for hypertension in patients with diabetes is 140/90 mmHg, but a treatment goal of 135/85 mmHg with normal kidney function and even of 130/80 mmHg when kidney involvement is present to prevent deterioration of kidney function is now widely accepted (4). See the Fact Box for general guidelines for treatment.

Fact Box

Treatment of women with preexisting diabetes and microalbuminuria or diabetic nephropathy during pregnancy

- Aim for strict glycemic control with HbA1c below 42 mmol/mol (6.0%).
- Supplementation with folic acid during the first 12 weeks.
- Low-dose aspirin from 10–12 weeks until one week before delivery.
- Target for antihypertensive treatment is tight (i.e., blood pressure <135/85 mmHg and urinary albumin excretion <300 mg/24 h).
- Use antihypertensive agents approved for use in pregnancy.
- Review the medication list for drugs contraindicated in pregnancy (e.g., cholesterol-lowering agents).
- Conduct close obstetric surveillance.
- Screen for sight-threatening diabetic retinopathy.
- During breastfeeding, several ACE inhibitors are considered safe.

The development of hypertension in patients with diabetes may be associated with a slight increase in urinary albumin excretion – microalbuminuria – or even frank proteinuria. Microalbuminuria is defined as a spot urinary albumin-to-creatinine ratio of 30–300 µg/mg and overt diabetic nephropathy as an albumin-to-creatinine ratio exceeding 300 µg/mg without signs of other kidney or urinary tract diseases. At least two urine samples are necessary for the diagnosis. Diabetic nephropathy is characterized by development of proteinuria, hypertension, edema, and decline in kidney function leading to end-stage renal disease.

In nonpregnant subjects with type 1 diabetes, hypertension is closely associated with an increased risk of cardiovascular disease. Reduction of BP with antihypertensive drugs, particularly those affecting the renin angiotensin system, in subjects with diabetes and microalbuminuria or diabetic nephropathy is of utmost importance to prevent the progression of kidney disease, reduce cardiovascular morbidity, and improve survival (4–6). Treatment with these drugs is indicated even in normotensive nonpregnant subjects with diabetes and microalbuminuria, the forerunner of overt diabetic nephropathy (7).

Hypertensive Disorders in Pregnancy

Hypertension is reported to complicate one in 10 pregnancies (8). The prevalence is even higher in women with diabetes, where up to 40% have been reported to have BP exceeding 140/90 mmHg during pregnancy (1,9). Hypertension is reported not only in women with type 1 and type 2 diabetes, but also in women developing GDM. There are four major hypertensive disorders in pregnancy: (1) chronic hypertension, (2) gestational hypertension, (3) preeclampsia, and (4) preeclampsia superimposed on hypertension or diabetic nephropathy (10). Each of these conditions has unique pathophysiologic features that have implications for antihypertensive therapy (Table 20.1). All categories are more common in women with diabetes compared to women without diabetes (1). The general diagnostic criteria for hypertension

Table 20.1 Hypertensive disorders in pregnancy.

Chronic hypertension	BP ≥140 mmHg systolic or ≥90 mmHg diastolic prior to pregnancy or before 20 weeks of gestation; or hypertension diagnosed for the first time during pregnancy that does not resolve postpartum (1). However, in diabetic women, BP >135/85 or even BP >130/80 mmHg is considered an indication for antihypertensive treatment in some centers (1,9).
Gestational hypertension	BP ≥140 mmHg systolic or ≥90 mmHg diastolic first detected after 20 weeks of gestation without proteinuria. If increased BP returns to normal by 12 weeks postpartum, the diagnosis is retrospectively made as transient hypertension of pregnancy. If it persists, a diagnosis of chronic hypertension applies (8).
Preeclampsia	BP ≥140 mmHg systolic or ≥90 mmHg diastolic and proteinuria (≥1+ on a sterile urine dipstick or ≥300 mg/24 h) after 20 weeks of gestation (8).
Chronic hypertension with superimposed preeclampsia	In women with hypertension early in pregnancy, developing new-onset proteinuria fulfills the criteria for preeclampsia. In women with diabetic nephropathy with proteinuria in early pregnancy, development of preeclampsia is defined as above if accompanied by a sudden increase of ≥15% in systolic or diastolic BP (7). A sudden 2–3-fold increase in proteinuria and/or thrombocytopenia (platelets < 100 000) and/or an increase in aspartate aminotransferase or alanine aminotransferase above normal levels also indicates preeclampsia (1).

BP = Blood pressure.

in pregnant women with diabetes follow those of the normal population (≥140/90 mmHg): however, as in the nonpregnant diabetic population, lower levels for treatment of chronic hypertension have been suggested (1,9). In Copenhagen, a treatment level of chronic hypertension in pregnancy of 135/85 mm/Hg has been used (9), and even lower treatment levels of 130/80 mmHg for chronic hypertension in diabetic pregnant women are suggested by Kitzmiller and colleagues (1).

Chronic hypertension (i.e., present before pregnancy or documented before 20 weeks) is associated with an increased risk of fetal loss, superimposed preeclampsia, preterm birth, intrauterine fetal growth restriction, and neonatal morbidity (11). In addition, women with chronic hypertension are at risk of developing severe hypertension (≥160/110 mmHg) and stroke during pregnancy.

Gestational hypertension is the development of hypertension after 20 weeks and is not associated with pregnancy complications in mild cases. However, it may progress to preeclampsia in a substantial proportion of cases (10–50%) or to severe hypertension (≥160/110 mmHg) with a comparable risk of severe pregnancy complications as in women with preeclampsia (11).

Preeclampsia is classically defined as development of hypertension later than 20 weeks accompanied by proteinuria greater than or equal to 1+ on a sterile urinary dipstick or ≥300 mg/24 h. Recently, more inclusive definitions have been introduced that define preeclampsia as hypertension with proteinuria and/or either a maternal end-organ complication (thrombocytopenia, elevated liver transaminases, elevated serum creatinine, headaches or visual symptoms, pulmonary edema) or fetal involvement (10,12). Preeclampsia is associated with a substantial risk of severe maternal and fetal complications, such as placental abruption, cerebral catastrophe, eclampsia, coagulation abnormalities, abnormal liver function, and even maternal death. Termination of pregnancy is the most effective treatment; therefore, preeclampsia often leads to preterm delivery with all its consequences. Preeclampsia complicates 7–20% of pregnancies in women with type 1 diabetes, approximately a fivefold higher risk compared to healthy women (1). In patients with chronic hypertension, superimposed preeclampsia often develops earlier in pregnancy and with a more severe clinical presentation.

Normal Blood Pressure in Pregnant Women with Diabetes

Knowledge of normal BP is relevant to setting targets for treatment of pregnant diabetic women with hypertension. Even in normotensive normo-albuminuric women, diabetes is associated with a slightly higher BP in pregnancy, but still well within the normal range, as can be seen in Table 20.2 (9,13).

Practical Aspects of Detecting Hypertension in Pregnancy

At the first visit in pregnancy, BP and urinary albumin excretion should be measured, and a history of hypertension, microalbuminuria

Table 20.2 Blood pressure (mmHg) in pregnancy in healthy controls and in women with type 1 diabetes.

	Number	First trimester	Second trimester	Third trimester	Average
Napoli *et al.* (13)	48 controls,	114/68	117/69	114/69	
	71 type 1 diabetes	118/71	116/72	115/72	
Nielsen *et al.* (9)	25 controls				117 /70
	86 type 1 diabetes				120/72

or diabetic nephropathy, and antihypertensive treatment should be recorded. The patient can thereafter be classified as having hypertension, microalbuminuria, diabetic nephropathy, or none of these. Thereafter, BP should be recorded at each prenatal visit. Home BP measurements might be useful in women with hypertension in pregnancy, but 24 h BP monitoring is generally not useful. Normotensive women with normoalbuminuria should be tested for the presence of proteinuria by dipsticks at each visit, while progression of urinary albumin excretion in women with hypertension, microalbuminuria, or diabetic nephropathy can be monitored at each prenatal visit by estimation of the albumin-to-creatinine ratio or the protein-to-creatinine ratio in a spot urine sample.

Glycemic Control and Hypertension

Development of preeclampsia is associated with poor glycemic control in both early and late pregnancy (14,15). Tight glycemic control before and during pregnancy might therefore reduce the burden of hypertension in diabetic pregnancy. A target HbA1c below 42 mmol/mol (6.0%) is often recommended (1); the Center for Pregnant Women with Diabetes in Copenhagen recommends below 40 mmol/l (5.8%). Due to the high prevalence of preeclampsia, close monitoring for the development of preeclampsia is recommended in all pregnant women with diabetes.

Principles for Treatment of Hypertension in Pregnancy

Mild to Moderate Hypertension

The benefit of antihypertensive treatment for mild-to-moderate elevation of BP in nondiabetic pregnancy (140–160/90–110 mmHg) with either chronic or pregnancy-induced hypertension has not been demonstrated in clinical trials (16). A recent Cochrane Review showed that antihypertensive treatment appeared to reduce the risk of severe hypertension, but no differences were observed in the rates of preeclampsia, neonatal death, preterm delivery, and small-for-gestational-age infants (17).

International guidelines for treatment of hypertension in pregnancy (8,18,19) vary with respect to threshold for initiating treatment and target BP goals, but all are higher than typical National Committee guidelines (8) for treatment of hypertension outside pregnancy. A treatment goal below 140/90 mmHg in women with diabetes is now widely accepted (3), and our Center recommends BP below 135/85 mmHg (9).

Severe Hypertension

It is generally accepted that severe hypertension in pregnancy, defined as greater than or equal to 160/110 mmHg, requires treatment, because of increased risk of maternal intracerebral hemorrhage, and treatment decreases the risk of maternal death (8,11). In the treatment of hypertension, it is generally important to avoid hypotension, because placental blood flow autoregulation is limited and aggressive lowering of BP may thus cause fetal hypoxia (1).

Diabetic Nephropathy and Hypertension

The prevalence of diabetic nephropathy in pregnant women with diabetes is 3–15%, and in addition 5–11% of women who have diabetes in pregnancy have microalbuminuria (9,20–22). Most of the literature on this topic is from women with type 1 diabetes, but the clinical findings are similar in women with type 2 diabetes (20). Diabetic nephropathy mainly affects the outcome of pregnancy by two mechanisms: (1) development of severe maternal hypertension necessitating termination of the pregnancy and thereby preterm delivery, and (2) impaired placental development leading to fetal growth restriction and risk of stillbirth.

In addition, clinically significant deterioration of maternal kidney function during pregnancy may also occur if serum creatinine is above 176 µmol/l at booking visit (23–25). The prevalence of preeclampsia in type 1 diabetes is 6–10% in women with normal urinary albumin excretion, but is increased to 42% in women with microalbuminuria and 64% in women with diabetic nephropathy present before or in early pregnancy (9). Some clinicians may regard an increase in BP and albumin excretion in women with preexisting microalbuminuria or diabetic nephropathy simply as a deterioration of the kidney disease rather than development of preeclampsia. However, since the majority of these cases lead to other maternal end-organ disease manifestations such as thrombocytopenia (personal observation) or fetal problems leading to preterm delivery, it is important to regard a significant increase in BP as a sign of development of superimposed preeclampsia in these patients (22).

The pathophysiological factors involved in the development of preeclampsia in women with type 1 diabetes and diabetic nephropathy or microalbuminuria include endothelial dysfunction and impaired maximal vasodilatory capacity (26), increased activation of components of the renin angiotensin system (27), cardiac overload (28), and anti-angiogenic factors (29–31). The majority of these factors can be modulated by antihypertensive treatment. To prevent an increase in BP and/or urinary albumin excretion, tight antihypertensive treatment during pregnancy should therefore, theoretically, be beneficial in these women.

Screening for microalbuminuria should ideally be performed in all women with type 1 and type 2 diabetes prior to conception and in early pregnancy to detect microalbuminuria or overt diabetic nephropathy. At least two random urine samples for estimation of albumin-to-creatinine ratio or a 24 h urine collection are needed to diagnose microalbuminuria or diabetic nephropathy. It is important to obtain and maintain strict glycemic control and closely monitor for development of preeclampsia in all pregnant women with diabetes.

In women with underlying renal dysfunction, it may be reasonable to choose a lower threshold for initiation of antihypertensive treatment and to focus on the level of albumin excretion (9,32). Women with either microalbuminuria or diabetic nephropathy prior to pregnancy might even benefit from targeting urinary albumin excretion levels with antihypertensive treatment irrespective of BP level (9,32). Our group aims for urinary albumin excretion levels below 300 mg/24 h and BP below 135/85 mmHg in women with diabetes with evidence of microalbuminuria or diabetic nephropathy before pregnancy (9). In a previous study of women with type 1 diabetes, 14% of women with normal urinary albumin excretion, 50% of women with microalbuminuria, and 100% of women with diabetic nephropathy received antihypertensive treatment during pregnancy (9). Compared to older patient series (21,24,32), this strategy with early and strict antihypertensive treatment appeared to be associated with improved pregnancy outcome and fewer preterm deliveries (9). Very similar results have been observed in women with type 2 diabetes (20).

In general, pregnancy outcome is favorable in women with modest elevations in serum creatinine (below 124 µmol/l [1.4 mg/dl]), with proteinuria less than 1 g/24 h, and with normal BP in early pregnancy when tight antihypertensive treatment is given. There is usually no deterioration in renal function in these women during pregnancy. In contrast, a serum creatinine above 176 µmol/l (2.0 mg/dl), severe hypertension or proteinuria in the nephrotic range (above 3 g/24 h), and/or preexisting cardiovascular disease are associated with a high risk for poor maternal and fetal outcome (33), Furthermore, pregnancy-induced deterioration of maternal kidney function to kidney failure is described in women with serum creatinine above 176 µmol/l in early pregnancy (34–36). However, long-term results are only available in small patient series (34,36).

Obstetric Surveillance in Women with Diabetic Nephropathy

Around 20 gestational weeks, these women should be offered an ultrasound examination to screen for congenital malformations. A reduced flow in maternal uterine artery around 23–24 gestational weeks is associated with increased risk of preeclampsia, and measurement of this flow may be considered. In late pregnancy, close obstetrical surveillance, including frequent ultrasound examinations of fetal growth and non-stress testing, is important to diagnose complications and plan the time and mode of delivery, with focus on preventing stillbirth as well as reducing the prevalence of preterm delivery.

Hypertension and Severe Retinopathy

Hypertension in pregnancy is associated with deterioration of retinopathy (37). Appropriate antihypertensive treatment, aiming for stable BP within the normal range, probably protects the eyes during pregnancy in women with diabetes. However, a sudden large decline in BP may result in a deterioration in retinopathy, and antihypertensive treatment may therefore be gradually intensified. Therefore, in pregnant women with diabetes and hypertension, screening for sight-threatening diabetic retinopathy at least twice, and in selected cases more frequently, is important based on individual evaluation.

Choice of Antihypertensive Drugs for Use Before and During Pregnancy

Angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) are both frequently used to treat hypertension and microalbuminuria in nonpregnant young diabetic women. Teratogenicity and fetotoxicity have been reported with these drugs (19,38,39). The most common malformations are in the cardiovascular or central nervous systems (38). In addition to congenital malformations, fetal and neonatal renal failure and oligohydramnios have been observed in women taking these antihypertensives (19,39). A change from blockers of the renin angiotensin system to other types of antihypertensive drugs prior to a planned pregnancy is therefore recommended (1). However, in women with diabetic nephropathy, it is necessary to consider each case individually. In particular, the benefits of discontinuing drugs that inhibit the renin angiotensin system until pregnancy is confirmed (34,35) must be balanced against the risk of disease progression prior to pregnancy, particularly if conception is delayed, resulting in a protracted period of withdrawal of blockers of the renin angiotensin system.

Diuretics are commonly prescribed in essential hypertension before conception and, given their apparent safety, the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy in the USA concluded that these drugs may be continued throughout gestation with an attempt to lower the dose or when used in combination with other antihypertensive drugs (8). Hypertension in diabetic women with microalbuminuria or diabetic nephropathy is often very salt sensitive. In light of this, it may be more appropriate to continue these drugs to avoid the rebound hypertension associated with their discontinuation (9,32). However, initiating diuretic treatment in women with preeclampsia might reduce placental flow and thereby cause fetal hypoxia (17). The commencement of diuretic treatment in late pregnancy should therefore be avoided, except in carefully selected cases, and with close ultrasound monitoring of fetal growth, amniotic fluid, and Doppler blood flow profiles.

Methyldopa remains one of the most widely used drugs for the treatment of hypertension in pregnancy. It is a centrally acting alpha-adrenergic agonist thought not to be teratogenic based on limited scientific data

and over 40 years of use in pregnancy. It has been assessed in a number of trials in pregnant women compared with placebo and with alternative antihypertensive drugs (17). It does not appear to have an adverse effect on utero-placental or fetal hemodynamics, or on fetal well-being. In a follow-up study of offspring at 7 years of age exposed to methyldopa *in utero*, the children exhibited intelligence and cognitive development similar to control subjects (17).

Beta-blockers have been used extensively in pregnancy with no reports of teratogenicity, but long-term use in pregnancy may result in lower birthweight (36). Intravenous treatment with beta-blockers has also been associated with fetal bradycardia and hypoglycemia in the newborn (36). In addition, beta-blockers reduce the adrenal symptoms of maternal hypoglycemia and might therefore increase the risk of hypoglycemic unawareness and severe hypoglycemia in diabetes in pregnancy. However, labetalol, a nonselective beta-blocker with vascular alpha-receptor blocking capabilities, has been extensively investigated during pregnancy and has also gained wide acceptance for use in pregnant women with diabetes. In the USA, both intravenous hydralazine and labetalol are recommended for treatment of diastolic BP levels of 105–110 mmHg (40).

Calcium channel antagonists are also commonly used to treat chronic hypertension and preeclampsia. Nifedipine, verapamil, or other calcium channel antagonists have not been associated with teratogenicity. Nifedipine, the most extensively investigated calcium channel antagonist during pregnancy, does not seem to cause a detectable decrease in uterine blood flow (41). Short-acting nifedipine should be used with caution because of its potential to induce a steep drop in BP, which has been associated with maternal myocardial infarction and fetal bradycardia and hypoxia. Slow-release nifedipine preparations do not have this side effect and are widely used for hypertensive disorders in pregnancy (12); calcium channel antagonists, and other antihypertensive drugs, can be used together with magnesium sulfate, which is used to prevent seizures during preeclampsia, without increasing the risk of serious side effects (41).

Hydralazine selectively relaxes arteriolar smooth muscle and has been extensively used for oral and parenteral treatment of severe hypertension in late pregnancy, but has been replaced by agents with fewer adverse effects (12,41). However, it may have a place in women resistant to other drugs. The remaining classes of antihypertensive drugs are rarely used in pregnancy.

Cholesterol-lowering drugs such as statins are contraindicated during pregnancy due to their possible effects on brain and nerve development (42).

Low-Dose Aspirin

Low-dose aspirin (75–150 mg) is widely used in nonpregnant women with diabetes to reduce the incidence of cardiovascular events. Initiated before 16 gestational weeks, low-dose aspirin may reduce the prevalence of preeclampsia in high-risk women (43). Although it has been widely used in the first trimester, it is a matter of debate whether low-dose aspirin is associated with a slightly increased risk of malformations (44). Use of low-dose aspirin during organogenesis is therefore not routine and should be based on an individual risk–benefit assessment. If a woman is already on low-dose aspirin treatment before pregnancy due to increased risk of cardiovascular events, continued use during organogenesis may be indicated. We, in general, initiate treatment with low-dose aspirin at 10 gestational weeks. Low-dose aspirin is normally stopped at 36–37 gestational weeks.

Antioxidants

Supplementation with antioxidants (vitamins C and E) does not seem to reduce the prevalence of preeclampsia in women with type 1 diabetes (45) and is thus not generally recommended.

Antihypertensive Drugs During Breastfeeding

Breastfeeding during treatment with methyldopa is generally considered safe. Unlike during pregnancy, methyldopa is, however, not the first choice of antihypertensive therapy during breastfeeding because of adverse effects such as fatigue and exacerbation of postpartum depressive states (46). Nifedepine, labetalol, metopolol, captopril, and enalapril are regarded as safe during breastfeeding (47–49).

Future Directions

Randomized controlled trials determining the treatment goal for BP in pregnant women with diabetes and hypertension are needed with a special focus on patients with chronic hypertension, microalbuminuria, or diabetic nephropathy. Trials comparing the beneficial effects and side effects of different types of antihypertensive drugs (e.g., methyldopa versus calcium blockers) during pregnancy are also required.

Multiple-Choice Questions

1 Which antihypertensive drugs are contraindicated during pregnancy? (Choose two.)
- A Methyldopa
- B Beta-adrenergic blockers (e.g., Labetalol)
- C Angiotensin-converting enzyme inhibitors
- D Angiotensin receptor blockers
- E Calcium blockers (e.g., slow-release nifedipine)
- F None of the above

Answer: C and D.

2 Which of the following is more frequent in diabetic pregnancy compared to normal pregnancy?
- A Gestational hypertension
- B Chronic hypertension
- C Preeclampsia
- D Superimposed preeclampsia
- E All of the above

Answer: E.

3 Which statement is correct?
- A Preeclampsia presents clinically as hypertension accompanied by hyperglycemia later than 20 weeks.
- B Development of preeclampsia is associated with poor glycemic control in pregnancy.
- C With careful clinical observation, preeclampsia rarely leads to preterm delivery.
- D All of the above

Answer: B.

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21

Retinopathy in Diabetic Pregnancy

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PRACTICE POINTS

- Diabetic retinopathy, a microvascular complication of diabetes, remains a leading cause of acquired blindness in young and middle-aged adults.
- Pregnancy, with its hormonal, hemodynamic, metabolic, and immunologic changes, is a risk factor for progression of diabetic retinopathy.
- The etiology of retinopathy acceleration during pregnancy is unknown, although proposed mechanisms involve rapid glycemic control, altered hemodynamic properties, and immuno-inflammatory components.
- Vision loss from diabetic retinopathy aggravated by pregnancy is usually preventable if a patient has optimal systemic and ocular management prior to conception and during pregnancy.
- Dilated ocular examinations should be performed prior to pregnancy and then at least every trimester (or more often at the discretion of the ophthalmologist, depending on the retinopathy status at baseline and history of prior therapies for diabetic retinopathy).

Pitfalls

- Failure to recommend ophthalmic screening to pregnant women with diabetes who do not report any visual symptoms. Progression of diabetic retinopathy can occur despite good visual acuity.
- Failure to recommend pre-conception ophthalmic screening to diabetic women. Stabilization of diabetic retinopathy prior to pregnancy can decrease progression during gestation.

Case History

A 27-year-old woman with a 20-year history of type 1 diabetes presented for ophthalmic monitoring during pregnancy. During the first trimester, she had a visual acuity of 20/20 in both eyes and minimal nonproliferative diabetic retinopathy on dilated examination (Figure 21.1a). Upon institution of tighter metabolic control, her glycosylated hemoglobin (HbA_1C) fell from 8.6% to 7.0% (70 mmol/mol to 53 mmol/mol) during early pregnancy. On second trimester examination, her vision was 20/25 in both eyes, and her retinopathy had progressed to severe nonproliferative diabetic retinopathy (Figure 21.1b). During the third trimester, her vision declined to 20/60 in the right eye and 20/80 in the left eye due to clinically significant macular

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edema (Figure 21.1c). After laser treatment, her macular edema resolved and vision partially recovered to 20/40 in both eyes.
Questions to be answered in this chapter:

- What are the putative mechanisms and risk factors for progression of retinopathy during pregnancy?
- What is the relevance of intensification of glycemic control to retinopathy progression? Is this a transient phenomenon?
- How often should the fundi be examined during pregnancy?
- How should the sight-threatening complications of diabetic retinopathy be treated during pregnancy?

First, we will briefly review diabetic retinopathy in general and then focus on how the unique state of pregnancy affects retinopathy progression.

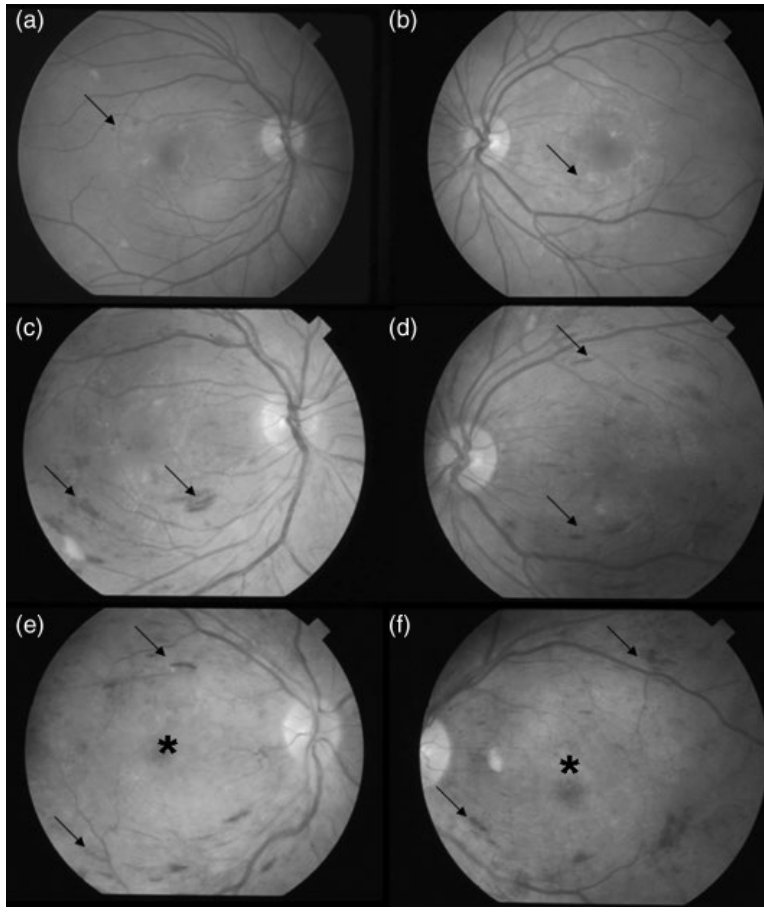

Figure 21.1 During the first trimester, dilated examination of the (a) right and (b) left eye reveals occasional intraretinal hemorrhages (arrows) consistent with minimal nonproliferative diabetic retinopathy. (c and d) After institution of rapid glycemic control, the patient developed increasing intraretinal hemorrhages (arrows) indicative of severe nonproliferative diabetic retinopathy during the second trimester. (e and f) In the third trimester, examination revealed further retinopathy progression (arrows) with the development of clinically significant macular edema (*).

Introduction

Diabetic Retinopathy Prevalence at Baseline

Diabetic retinopathy, a microvascular complication of diabetes, remains a leading cause of acquired blindness in young and middle-aged adults (1). The current estimated general population prevalence rates for retinopathy and vision-threatening retinopathy in the United States are 3.4% (4.1 million persons) and 0.75% (899,000 persons), respectively (2). These pooled data focus almost exclusively on type 2 diabetes (1). An epidemiological study in type 1 diabetes estimated prevalence rates of retinopathy and vision-threatening retinopathy as 1 per 300 persons aged 18 years and older and 1 per 600 persons (3), respectively. Specifically, of the estimated 889,000 persons diagnosed with type 1 diabetes before age 30 years in the United States, 767,000 (86.4%) have some degree of retinopathy and 376,000 (42.1%) have vision-threatening retinopathy (3). These prevalence rates are particularly concerning given the increasing prevalence of diabetes mellitus (1).

Pregnancy as a Risk Factor for Worsening Retinopathy

Pregnancy, with its hormonal, hemodynamic, metabolic, and immunologic changes, is a risk factor for progression of diabetic retinopathy. While the landmark studies focused on worsening retinopathy in pregnant women with type 1 diabetes (4–6), the findings of these studies can be extrapolated to pregnant women with type 2 diabetes as the retinopathy in the two groups is essentially similar. Gestational diabetes, however, is not a risk factor for the development of retinopathy during pregnancy, but may be suggestive of a genetic risk for subsequent diabetes mellitus (7).

Overview of Diabetic Retinopathy Classification

Diabetic retinopathy in both type 1 and type 2 diabetes is broadly classified as either nonproliferative or proliferative (Table 21.1). Nonproliferative diabetic retinopathy (NPDR) occurs when there are only intraretinal microvascular changes, such as microaneurysms and retinal hemorrhages (Figure 21.2). In advanced NPDR, progressive capillary nonperfusion of the retina may develop and lead to increasing ischemia, which results in the more severe proliferative phase. Proliferative diabetic retinopathy (Figure 21.3) is characterized by new vessels on the retinal surface or optic disc that can bleed and result in the visually threatening complications of vitreous hemorrhage, fibrotic scarring, and tractional

Table 21.1 Classification of diabetic retinopathy.

Classification	Lesions present
No retinopathy	No lesions present
Nonproliferative retinopathy	Intraretinal microvasculature changes only
Mild	Mild levels of microaneurysms and intraretinal hemorrhage
Moderate	Moderate levels of microaneurysms and intraretinal hemorrhage
Severe	Presence of one of the following features (4:2:1 rule): • Severe intraretinal hemorrhage in all four quadrants • Venous beading in two or more quadrants • Moderate intraretinal microvascular anomaly (IRMA) in at least one quadrant
Proliferative retinopathy	Neovascularization on the retinal surface

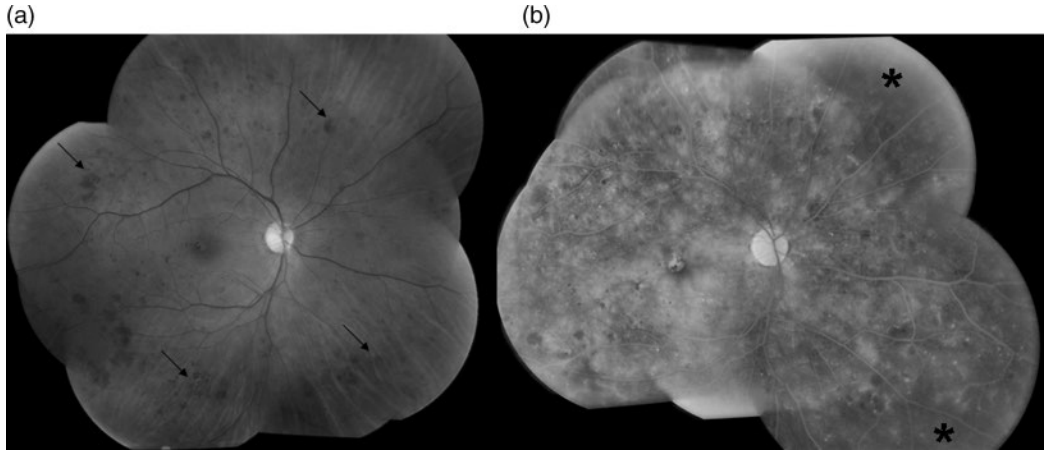

Figure 21.2 (a) Fundus photograph of the right eye reveals dotblot intraretinal hemorrhages in all four quadrants (arrows), consistent with severe nonproliferative diabetic retinopathy. (b) Fluorescein angiograghy shows patches of nonperfusion in the peripheral retina (*), indicative of the severe nature of the nonproliferative retinal changes.

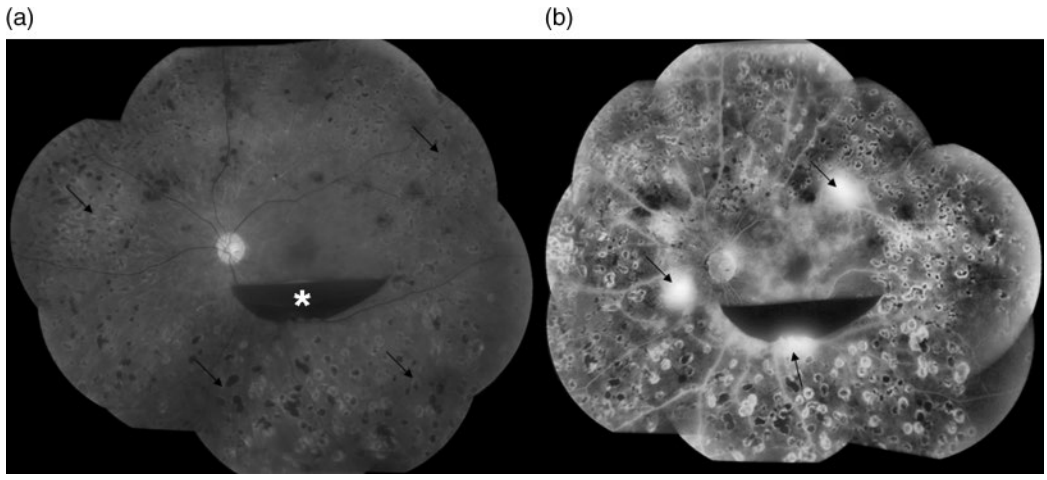

Figure 21.3 (a) Fundus photograph of the left eye shows preretinal hemorrhage overlying the macula (*). The peripheral retina has many laser photocoagulation scars (arrows) indicative of previous treatment for proliferative diabetic retinopathy. (b) Fluorescein angiogram shows patches of bright hyperfluorescence (arrows) corresponding to areas of leaking neovascularization consistent with proliferative diabetic retinopathy.

retinal detachment. In both nonproliferative and proliferative diabetic retinopathy, increased retinal vascular permeability can result in accumulation of fluid in the retinal area serving central vision. This retinal thickening, known as macular edema (Figure 21.4), is a leading cause of visual loss in diabetic patients.

Risk Factors for Progression of Diabetic Retinopathy

Diabetic retinopathy, a microvascular complication, is an end-organ response to a systemic disease. Concomitant systemic issues, therefore, influence the development and progression of diabetic retinopathy (8).

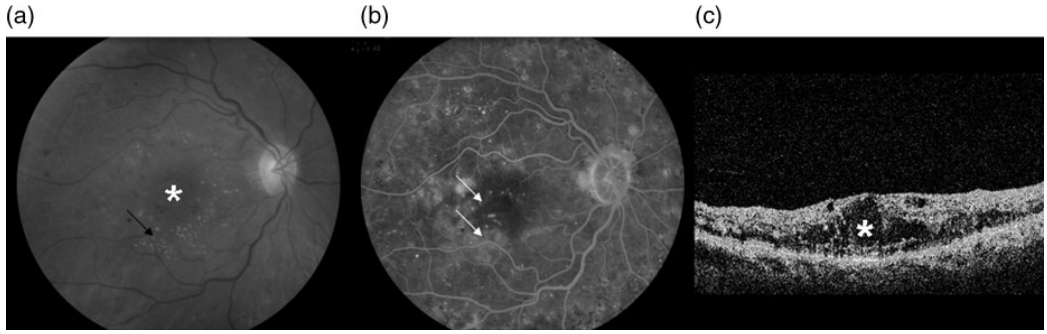

Figure 21.4 (a) Fundus photograph of the right eye shows macular fluid (*) and lipid (arrow) consistent with clinically significant macular edema. (b) Fluorescein angiography reveals multiple leaking microaneurysms (arrows). (c) Optical coherence tomography confirms the presence of cystic fluid changes in the macula (*).

A thorough understanding of diabetic retinopathy is necessary to discuss the specific retinal changes found in the pregnant woman with diabetes. First, studies regarding diabetic retinopathy in general will be examined followed by a review of studies during pregnancy. A number of risk factors have been identified in large epidemiological studies that are relevant to both the pregnant and nonpregnant state, although their role in the dynamic physiological state of pregnancy is unique.

Glycemic Control

Chronic hyperglycemia instigates a cascade of events leading to microvascular complications in diabetes. Both the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated the beneficial effects of intensive glycemic control in reducing the development and progression of retinopathy.

The Diabetes Control and Complications Trial

The DCCT was a randomized, multicenter, prospective trial designed to determine if intensive glucose control, with the goal of near-normal HbA_1C levels, would affect the development and progression of diabetic complications in type 1 diabetes. The 1441 participants were randomly assigned to either conventional or intensive treatment for glucose control and followed for a mean duration of 6.5 years (9–11). The mean HbA_1C was 7.2% in the intensive treatment group and 9.1% in the conventional control cohort. The intensive treatment in the DCCT study resulted in a decreased risk of either the development or progression of diabetic retinopathy in patients with type 1 diabetes. One of the adverse effects of intensive therapy included initial worsening of retinopathy; however, this reversed after 18 months. In patients without any visible retinopathy when enrolled in the DCCT, the 3-year risk of developing retinopathy was reduced by 75% in the intensive treatment group compared with the standard treatment group. The benefit of strict control was also evident in patients with existing retinopathy. There was a 50% reduction in the rate of progression of retinopathy as compared with controls. When the DCCT results were stratified by HbA_1C levels, there was a 35% to 40% reduction in the risk of retinopathy progression for every 10% decrease in HbA_1C (e.g., from 8% to 7.2%).

The United Kingdom Prospective Diabetes Study

UKPDS, the largest and longest study of patients with type 2 diabetes, evaluated the effect of conventional versus intensive glucose management on diabetic complications

in 3867 newly diagnosed patients (12). This study confirmed that the beneficial effect of tight glycemic control on the incidence and progression of diabetic retinopathy also applies in type 2 diabetes. Specifically, UKPDS showed a 25% reduction in the risk of "any diabetes-related microvascular end point," including the need for retinal photocoagulation, in the intensive treatment group compared to the conventional treatment group. For every percentage point decrease in HbA_1C (e.g., 9% to 8%) in UKPDS, there was a 35% reduction in the risk of microvascular complications. Similarly, the Actions to Control Cardiovascular Risk in Diabetes (ACCORD) study of type 2 diabetes showed a 1/3 reduction in the risk of progression of diabetic retinopathy with intensive glycemic control (21).

Concomitant Hypertension

Multiple studies have suggested that diabetic patients with concomitant hypertension are at increased risk for the development and progression of diabetic retinopathy, although conflicting data exist. Hypertension is theorized to exacerbate diabetic retinopathy through mechanical stretching of endothelial cells, resulting in increased vascular endothelial growth factor (VEGF) release (13).

Wisconsin Epidemiology Study of Diabetes Retinopathy (WESDR)

WESDR was a 14-year population-based cohort study assessing the prevalence and risk of diabetic retinopathy among 634 type 1 diabetic subjects diagnosed before age 30 years (14). In addition to higher HbA_1C and greater severity of retinopathy at baseline, the presence of hypertension was demonstrated to be a risk factor for the development of proliferative diabetic retinopathy. Furthermore, participants with the lowest quartile of systolic and diastolic blood pressure had significantly lower rates of progression to proliferative diabetic retinopathy compared with the highest quartile group. These findings were independent of glycosylated hemoglobin (14).

The United Kingdom Prospective Diabetes Study

Of the 3867 type 2 diabetic subjects in the UKPDS, a cohort of 1148 hypertensive subjects were evaluated, with 758 randomly assigned to tight control of blood pressure (either ACE inhibitor or a beta blocker) and 390 to less tight control, with a median follow-up of 8.4 years (12). Tight control was defined as blood pressure less than 150/85. There was a 34% reduction in the two-step progression of retinopathy and a 47% reduction in the risk of moderate vision loss (≥15 letters) in the tight control group as compared to the conventional cohort. The vision data, although not controlled for glycosylated hemoglobin, suggested that tight blood pressure control reduced the risk of diabetic macular edema, the primary cause of visual loss in type 2 diabetes.

Appropriate Blood Pressure Control in Diabetes (ABCD) Trial

The ABCD trial also showed a correlation between tight blood pressure control and decreased risk of retinopathy (15–17). In a normotensive cohort of 480 type 2 diabetic subjects, there were no significant differences in glycosylated hemoglobin levels between the patients randomly allocated to intensive or moderate antihypertensive therapy. For the last 4 years of follow-up, the mean blood pressure was 128/75 in the intensive treatment arm and 137/81 in the moderate group (15). Over a 5-year follow-up period, retinopathy progression occurred in 34% of the intensive group versus 46% of the moderate control group, $p = 0.019$.

Elevated Serum Lipid Levels

An association of elevated serum lipids with diabetic retinopathy was found in both the WESDR and Early Treatment Diabetic Retinopathy Study (ETDRS). Elevated levels of serum lipids were associated with increased severity of retinal hard exudates (18,19). In ETDRS, patients with a total serum cholesterol of 6.21 mmol/L (240 mg/dL) or above were twice as likely to have hard exudates as those with a cholesterol less than

5.17 mmol/L (200 mg/dL). Low-density lipoprotein (LDL) cholesterol levels paralleled the total serum cholesterol results, with almost twice the risk of developing hard exudates among patients with serum LDL levels of 4.14 mmol/L (160 mg/dL) or more compared with those whose levels were less than 3.36 mmol/L (130 mg/dL). Hard exudates are significant because their severity at baseline was associated with decreased visual acuity in the ETDRS, independent of the accompanying macular edema. In fact, the strongest risk factor for the development of vision-threatening subretinal fibrosis in ETDRS patients with diabetic macular edema was the presence of severe hard exudates (20). Of the 264 eyes with multiple hard exudates at baseline or during follow-up, subretinal fibrosis developed in 30.7% of the eyes. In contrast, this complication developed in only 0.05% of the 5498 eyes with clinically significant macular edema but no severe hard exudates (20).

Randomized controlled trials have demonstrated that serum lipids may play an important role in the pathogenesis of diabetic retinopathy, with fenofibrate (which reduces triglyceride levels and increases high-density lipoprotein [HDL] cholesterol) reducing the risk of progression of diabetic retinopathy and the need for laser photocoagulation (21,22). In the ACCORD Study, fenofibrate therapy reduced the rates of diabetic retinopathy progression versus placebo (adjusted odds ratio: 0.60; 95% CI: 0.42–0.87; $p = 0.006$) (21). In the FIELD Study, a composite endpoint including two-step progression of grade of retinopathy, macular edema, or laser treatments, was significantly lower in the fenofibrate group than in the placebo group (hazard ratio: 0.66; 95% CI: 0.47–0.94; $p = 0.022$) (22).

Risk Factors for Diabetic Retinopathy Progression During Pregnancy

Early case–control studies reported that pregnancy is a risk factor for the progression of diabetic retinopathy (23,24), although these changes often regress postpartum (23). Several larger studies have since confirmed the transient progression of diabetic retinopathy during pregnancy without increased long-term risk (5,6).

Progression of retinopathy is more closely associated with type 1 diabetes than type 2 diabetes (25). The mechanism of retinopathy acceleration is unknown, although multiple theories exist related to the hormonal, hemodynamic, metabolic, and immunologic changes associated with pregnancy. Reported risk factors for retinopathy progression in pregnant diabetic patients include glycemic control, hypertension, and hyperlipidemia.

Glycemic Control

The Diabetes in Early Pregnancy (DIEP) Study

The DIEP study was a prospective cohort study of 155 diabetic women followed from the periconceptional period to one month postpartum (4). Development of retinopathy was observed in 10.3% of patients with no retinopathy, while acceleration was observed in 21.1% of those with microaneurysms only and 18.8% of those with mild NPDR. However, the greatest progression was noted in patients with moderate to severe NPDR at baseline, among whom 54.8% experienced worsening retinopathy. Proliferative diabetic retinopathy developed in 6.3% of patients with mild and 29% with moderate to severe baseline retinopathy. Unlike earlier studies (23), the DIEP found that changes in metabolic control were more important than duration of diabetes in predicting acceleration of retinopathy. Those women in this study with the poorest prepregnancy glycemic control and the greatest reduction in HbA_1C during the first trimester were at a higher risk for retinopathy progression. While the DIEP study did not elucidate the mechanism for worsening retinopathy, it did indicate the clinical importance of optimizing metabolic control before conception to reduce the risk of retinopathy progression.

The Diabetes Control and Complications Trial Ancillary Study

An ancillary study of the DCCT evaluated the role of pregnancy in diabetic retinopathy

progression (5). Similar to the DIEP Study, the DCCT emphasized the importance of optimal glycemic control prior to pregnancy. In this study of 680 female diabetic patients, 180 women became pregnant. These pregnant women had a higher risk of retinopathy progression compared with the 500 nonpregnant study participants. Additionally, women in the conventional treatment group who did not have tight control prior to conception had a 2.48-fold greater risk of retinopathy progression during pregnancy compared with nonpregnant counterparts. Women in the intensive therapy arm who had tighter control prior to pregnancy had only a 1.63-fold greater risk (95% CI: 1.01–2.64) of retinopathy progression during pregnancy compared with nonpregnant women. Therefore, tight metabolic control prior to conception is the ideal.

Hypertension

Hypertension during pregnancy is a risk factor for retinopathy progression. A prospective study of 154 diabetic women found that 55% of women with chronic or gestational hypertension had progression of retinopathy compared with 25% of the pregnant diabetic women without hypertension, $p < 0.05$ (26). Another prospective study indicated that elevated diastolic blood pressure was a risk factor for progression of retinopathy, although not as strong a risk factor as glycemic control (24).

Serum Lipids

Although dyslipidemia has been associated with increasing macular exudates that can lead to the visually threatening complication of subretinal fibrosis in general diabetic studies (18,19), the role of increased serum lipids in pregnant diabetic women has not been studied extensively. Nevertheless, because of the general health benefits of lipid control, optimizing cholesterol and lipids prior to pregnancy is recommended as this could reduce the risk of macular exudates.

Possible Mechanisms of Diabetic Retinopathy Progression During Pregnancy

Metabolic Theory

The metabolic theory simply states that the rapid normalization of glycemia during pregnancy promotes acceleration of diabetic retinopathy. Pregnancy is a state where aggressive glycemic control has long been attempted (4,9,26). The concept of rapid glycemic control resulting in a transient deterioration of retinopathy had previously been noted outside of pregnancy (27–29). While some studies suggest that pregnancy itself may be a risk factor for retinopathy progression even after adjusting for HbA_1C levels, the common practice of instituting tight control at the onset of pregnancy confounds our ability to conclude that pregnancy itself is the cause of retinopathy acceleration (24).

Hormonal Theory

Hormonal changes are also suspected of exacerbating diabetic retinopathy. The characteristic progesterone surge of pregnancy may upregulate intraocular VEGF (30) and result in increased retinal capillary leakage and neovascularization. Additionally, placental hormones create a physiologically adaptive insulin-resistant state to ensure that maternal glucose will be adequately supplied to the fetus to optimize intrauterine growth. A key player is human placental growth hormone, which appears to regulate the maternal levels of insulin-like growth factor-1 (IGF1). Like human placental growth factor, IGF1 increases after 20 weeks of pregnancy. Transgenic mice studies have demonstrated that human placental growth hormone can cause an insulin-resistant state, although the precise mechanism is unknown (31). Additionally, increasing serum IGF1 levels may promote retinal neovascularization by supporting VEGF induction of endothelial

cell proliferation (32). In an observational study of 88 women with type 1 diabetes, progression of diabetic retinopathy during pregnancy was associated with a higher pregnancy-induced increase of circulating IGF1 levels (33).

Hemodynamic Theory

Pregnancy is associated with increased blood volume and cardiac output and decreased peripheral vascular resistance (31). This increased blood flow, coupled with an impaired retinal vascular autoregulatory response in diabetes, may result in a hyperdynamic retinal capillary blood flow that exacerbates diabetic retinopathy via increased sheer on the vascular endothelium and a resultant net increase in fluid leaving the capillaries (34). Some studies have demonstrated increased retinal circulation and hyperperfusion in all pregnant diabetic patients as compared with nondiabetic pregnant women (35), while others have shown increased retinal blood flow only in pregnant women with preexisting (34) or progressive diabetic retinopathy (36). Another small study showed a fall in retinal volumetric blood flow and an even more profound decrease in retinal venous diameter in pregnant women with diabetes compared with nondiabetic pregnant controls (37). The contradictory results of these studies may relate to different patient populations or techniques of retinal circulation assessment. Others have postulated that sudden improvement in glycemic control may lead to a decrease in retinal blood flow, secondary hypoxia, and possible worsening of retinopathy (25).

Immuno-Inflammatory Theory

Diabetic retinopathy has been suggested to be a low-grade inflammatory disease, with leukocyte adhesion to the retinal vasculature possibly resulting in retinal vascular dysfunction (38,39). During pregnancy, increased inflammation has been implicated in patients who develop gestational diabetes (40). A prospective study examining the relation of maternal cytokine levels with diabetic retinopathy showed that although the pro-inflammatory factors interleukin-6, C-reactive protein, and vascular cell adhesion molecule-1 were similar in the diabetic pregnant patients and nondiabetic controls, C-reactive protein levels were higher in pregnant women with retinopathy progression and worse glycemic control compared with pregnant women with stable retinopathy and tighter metabolic control. Another study examined glycodelin, an anti-inflammatory serum marker secreted from the endometrial glands during pregnancy, and found that low levels were associated with retinopathy progression in pregnant diabetic women (41).

Clinical Management of Retinopathy Before, During, and After Pregnancy

Preconception systemic and ocular management is essential to reduce the risk of retinopathy progression during pregnancy and in the postpartum period.

Systemic Management

Systemically, optimal metabolic control prior to pregnancy is essential. The gradual institution of tight control prior to pregnancy avoids the rapid drop in HbA_1C during pregnancy associated with retinopathy progression.

Additionally, hypertension and elevated serum lipids should be controlled to reduce the risk of retinal changes. Such management not only reduces risk of retinopathy progression, but also is important for the systemic health of the mother and fetus.

Ocular Management and Scheduling of Dilated Examinations

All diabetic women should have a dilated ophthalmic examination by an ophthalmologist or optometrist experienced in retinal evaluation prior to pregnancy and again during the first trimester of pregnancy. Depending on

individual findings, additional imaging such as retinal photography, optical coherence tomography, and fluorescein angiography may be performed at the discretion of the examiner. The official guidelines for retinal care of pregnant women with type 1 and 2 diabetes established by the American Academy of Ophthalmology are as follows (42):

1) Diabetic patients who plan to become pregnant should undergo an ophthalmologic evaluation before pregnancy.
2) An eye exam should be repeated during the first trimester, with follow-up evaluations timed according to the severity of retinopathy.
   a) *No retinopathy to mild or moderate NPDR*: Follow up every 3–12 months.
   b) *Severe NPDR or worse*: Follow up every 1–3 months.
3) Women diagnosed with gestational diabetes are not at an increased risk for diabetic retinopathy during pregnancy and do not require additional ophthalmic evaluation.

The National Institute for Health and Clinical Excellence (NICE) also set forth guidelines to help guide the ophthalmic management of pregnant diabetic patients, which are as follows (43,44):

1) "Pregnant women with pre-existing diabetes should be offered retinal assessment by digital imaging with mydriasis following their first antenatal clinic appointment and again at 28 weeks if the first assessment is normal."
2) "If any diabetic retinopathy is present, an additional retinal assessment should be performed at 16–20 weeks."
3) "Women who have pre-proliferative diabetic retinopathy diagnosed during pregnancy should have ophthalmological follow-up for at least 6 months following the birth of the baby."
4) "Diabetic retinopathy should not be considered a contraindication to rapid optimization of glycemic control in women who present with a high HbA1c in early pregnancy."
5) "Diabetic retinopathy should not be considered a contraindication to vaginal birth."

These guidelines are merely general recommendations for the pattern of practice and not for the care of the individual patient. Therefore, subsequent follow-up examinations vary depending on the retinal findings but are usually every 3 months during pregnancy. Given the hormonal changes in late pregnancy that can exacerbate or induce retinopathy, a third-trimester examination is important even if no retinopathy was present in the first or second trimester. Sometimes, patients will need a fluorescein angiogram to assess the retinal perfusion status and vasculature pattern. Although fluorescein dye has been used safely during pregnancy (7), it crosses the placenta, and most retinal specialists instead rely on the results of dilated examination and noninvasive imaging/photography to determine the stage of retinopathy to guide their management. For example, clinical findings such as increased hemorrhages, venous abnormalities, and intra-retinal microvascular abnormalities indicate progression to severe NPDR, while frank neovascularization on the retinal surface or optic nerve confirms the presence of the proliferative stage.

The sight-threatening complications of diabetic retinopathy, diabetic macular edema and proliferative diabetic retinopathy, may develop and/or worsen during pregnancy.

If a woman has signs of severe NPDR or proliferative retinopathy prior to pregnancy, scatter or pan-retinal photocoagulation should be instituted according to the Diabetic Retinopathy Study guidelines (45). Similarly, focal laser treatment should be initiated for clinically significant macular edema (46). Stabilization of diabetic retinopathy prior to pregnancy can decrease progression during gestation.

If new retinal changes develop during pregnancy that meet the criteria for laser treatment, this should be performed, as such treatment is equally effective and safe in

pregnant and nonpregnant patients (47). Opinions differ regarding the role of laser photocoagulation, given the possibility of spontaneous regression postpartum. However, despite the recognized regression postpartum in many cases, conservative management may be harmful as vision could be lost during pregnancy due to complications of proliferative changes or severe macular edema. Laser retinal photocoagulation treatment of macular edema and proliferative diabetic retinopathy has not been reported to cause maternal or fetal harm during pregnancy.

Whereas laser photocoagulation was once the first-line treatment for diabetic macular edema and proliferative diabetic retinopathy, now intraocular injection of antibodies against VEGF has become integral to treating these complications of diabetic retinopathy. Numerous trials have demonstrated the benefits of intraocular anti-VEGF for the treatment of diabetic macular edema (48–50), but there are minimal data with regard to its use in pregnancy. When compared to traditional laser treatment for macular edema, anti-VEGF injections have been associated with better visual acuity outcomes and reduced central macular thickness. Multiple injections may be required to achieve and maintain these gains (48–50). Intraocular anti-VEGF also plays a role in treating retinal neovascularization in proliferative diabetic retinopathy (50).

Bevacizumab and ranibizumab are currently the two most common intraocular anti-VEGF agents used in the United States.

A few case series and reports on either inadvertent or deliberate use of intraocular anti-VEGF during pregnancy have surfaced in recent years (51–55). A case report describing the use of a single ranibizumab intravitreal injection, during the third trimester for an idiopathic choroidal neovascular membrane, describes no maternal or fetal harm up to 12 months postpartum (53). A case series of four pregnant patients, who received a total of 13 intravitreal bevacizumab injections over the course of five pregnancies at varying weeks of gestation, reported no maternal or fetal adverse events after a mean follow-up of 14 months (56). Two cases of early spontaneous abortions 1 week after intravitreal bevacizumab injection have been reported, although the naturally occurring high rate of pregnancy loss in the first trimester makes it difficult to establish a causal relationship (52).

It is not known whether the two most commonly used anti-VEGF agents, ranibizumab or bevacimab, are potentially safe in pregnancy. Although most reported cases are reassuring, there are several theoretical concerns with the use of anti-VEGF agents during gestation. Anti-VEGF drugs may have a deleterious effect on fetal vasculogenesis. Preeclampsia has been associated with inadequate angiogenic growth factors and thus could be exacerbated with further iatrogenic VEGF blockage (57). Given that most of the studies on intravitreal anti-VEGF use in pregnancy are retrospective in nature, with a low number of patients and limited follow-up, the risks to maternal and fetal health remain unknown.

In certain cases, surgical intervention is warranted during pregnancy in patients with proliferative retinopathy. The most common indications for surgery are nonclearing vitreous hemorrhage, tractional retinal detachments, and neovascular glaucoma. The literature on intraocular surgery during pregnancy is very limited (25).

Fortunately, sight-threatening progression of diabetic retinopathy during pregnancy is not very common. A detailed discussion of possible risks and benefits of each treatment modality is required. Furthermore, the adverse effects of pregnancy on diabetic retinopathy are reported to persist into the first postpartum year, and thus increased retinal surveillance should continue during this period.

The Way Forward

As systemic and ocular management of diabetes has progressed since the original studies on diabetic retinopathy in pregnancy,

vision loss from diabetic retinopathy aggravated by pregnancy is usually preventable. Optimal systemic management of blood glucose, hypertension, and serum lipids prior to pregnancy is essential. Similarly, timely and appropriate intervention for retinopathy progression prior to or during pregnancy is critical to prevent visual loss. With greater physician and patient awareness of the importance of both systemic and ocular care, the visual outlook for pregnant diabetic women is optimistic.

Multiple-Choice Questions

1 Who does not require ophthalmic screening during pregnancy?
- **A** A patient with a 5-year history of type 1 diabetes
- **B** A patient newly diagnosed with gestational diabetes
- **C** A patient with a 5-year history of type 2 diabetes

Answer: B.

2 Which of the following factor(s) have been linked to the worsening of diabetic retinopathy during pregnancy?
- **A** Poor glycemic control
- **B** Hypertension
- **C** Rapid improvement in HbA1c levels
- **D** All of the above

Answer: D.

3 Which of the following statements is FALSE?
- **A** Progression of diabetic retinopathy during pregnancy is more closely associated with type 1 diabetes than type 2 diabetes.
- **B** Diabetic retinopathy is a contraindication to vaginal delivery.
- **C** Laser photocoagulation can be performed safely during pregnancy.

Answer: B.

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Section IV

Delivery and Postnatal Care

22

Delivery and Postdelivery Care: Obstetric Management of Labor, Delivery, and the Postnatal Period for Women with Type 1, Type 2, or Gestational Diabetes Mellitus

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PRACTICE POINTS

- In women with type 1 or type 2 diabetes mellitus (DM), delivery should take place in an appropriate perinatal environment.
- Timing of delivery:
  - 37–39 weeks of gestation in women with type 1 or type 2 DM
  - No longer than 40 weeks + 6 days in women with gestational DM.
- Mode of delivery will depend on the past obstetric history, suspicion of macrosomia, adequacy of the pelvis, fetal presentation, and local conditions.
- Capillary blood glucose should be maintained between 4 and 7 mmol/l during delivery.
- Intravenous dextrose and insulin infusion should be considered during labor in women with type 1 DM.
- The management of labor follows standard practice.
- Continuous fetal monitoring is recommended during labor.

Case History

A 40-year-old Caucasian woman who is in her second pregnancy and has had one live birth and no abortions is seen for prenatal care at 37 weeks gestation. Her weight is 120 kg, and her blood pressure is 130/80 mmHg. Uterine size is 38 cm. The patient's past obstetric history includes the spontaneous vaginal delivery of a 4.2 kg male infant at 40 weeks gestation, 8 years ago. The patient reports that the child is doing well. Gestational diabetes was diagnosed at 26 weeks of gestation during the present pregnancy (75 g OGTT: fasting, 115 mg/dl (6.4 mmol/l); 1 h, 192 mg/dl (10.7 mmol/l); and 2 h, 163 mg/dl (9.1 mmol/l). Glycemic control was not achieved with diet; insulin was started at 32 weeks of gestation and is now: aspart 10/15/15 and glargine 0/0/20 units per day. The mean capillary blood glucose (42 measurements) during the last week was 125 mg/dl (6.9 mmol/l). The fetus is in vertex position, and the estimated fetal weight is 3950 g. The cervix is closed.

Background

In women with preexisting type 1 or type 2 diabetes mellitus (DM), delivery should take place in an appropriate perinatal environment, and be managed by pre-established protocols for diabetes and anesthesia (see Chapter 23). Delivery is usually recommended at 37–39 weeks of gestation to reduce the risk of stillbirth

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and complications associated with fetal macrosomia (1).

The rate of macrosomia is increased in newborns of women with type 1 DM: 49–63% of newborns are large for gestational age, and 20–25% are macrosomic (i.e., birthweight more than 4000 g) (2–4). The rate of macrosomia is similar in newborns of women with type 2 DM (5). Macrosomia is associated with an increased risk of shoulder dystocia and brachial plexus injury (6).

A population-based study in Canada found that women with preexisting diabetes were significantly more likely to have cesarean section or induced labor than women without diabetes. Pregnancies in women with preexisting diabetes were also more likely to be complicated by obstructed labor and shoulder dystocia (7). Cesarean delivery should eliminate the risk of brachial plexus injury. Accordingly, the rate of cesarean delivery in women with type 1 DM is twofold to fourfold higher than in the general population, ranging from 45% to 73% (2,4,8–10). In a meta-analysis, women with type 2 DM had a lower cesarean rate than those with type 1 DM (OR: 0.80; 95% CI: 0.59–0.94) without differences in other outcomes (5).

Cesarean delivery is associated with increased maternal morbidity (11). Furthermore, a uterine scar contraindicates induction of labor for many obstetricians and places women at increased risk for uterine rupture, placenta previa, accreta, or all of these, and at increased risk of hysterectomy after a second cesarean delivery (12). Thus, avoidance of unnecessary primary cesarean delivery has important implications for future pregnancies.

Timing of Delivery

The timing and mode of birth should be discussed with the pregnant woman during her antenatal appointments, especially during the third trimester.

There are minimal differences between current national guidelines:

- *UK*: NICE guidelines advise that women with type 1 or type 2 DM should be offered elective delivery between 37^{+0} and 38^{+6} weeks of pregnancy (13), assuming no other significant factors have developed before this time; and that birth before 37^{+0} weeks should be considered if there are metabolic or any other maternal or fetal complications. Women with gestational diabetes mellitus (GDM) should give birth no later than 40^{+6} weeks, and before if there are maternal or fetal complications.
- *USA*: The American Diabetes Association guidelines state that "an emerging consensus suggests that well-monitored diabetic women achieving excellent glycemic control without obstetric complications can await spontaneous labor up to 39–40 weeks of gestation" (14).
- *France*: Current French guidelines recommend that in the absence of complications and if diabetes is well controlled, the pregnancy should be allowed to go to 38–39 weeks of gestation (15).

Although there are general guidelines to follow, an individualized approach to the timing and mode of delivery is essential. Many factors need consideration, including glycemic control, diabetes complications, past obstetric history, fetal growth, and the availability of healthcare resources.

Preterm Delivery

The rate of preterm delivery (less than 37 weeks) is high in women with preexisting diabetes. In 12 population-based studies published within the last 10 years (14,099 women with type 1 DM), preterm delivery, spontaneous or indicated, occurred in 25.2% (13.0–41.7) versus 6.0% (4.7–7.1) (RR = 4.2). Early pregnancy HbA1c was positively associated with adverse pregnancy outcomes, including preterm delivery (16). In a national pregnancy in diabetes report for 2014, 42.6% of the pregnancies in women

with type 1 DM were delivered preterm compared to 23.6% with type 2 DM (17).

Previous studies have shown that indicated preterm delivery explained two-thirds of preterm deliveries. Progressions of nephropathy, occurrence of preeclampsia, and poor glycemic control have been significantly associated with indicated preterm delivery (18).

If premature delivery is indicated, and facilities are not available locally, then *in utero* maternal transfer to a maternity unit with these facilities should occur.

Term Delivery

At term, the timing of delivery reflects the obstetrician's opinion of the gestational age at which the risk of possible excessive fetal growth, plus the risk of unexpected stillbirth, is balanced by the risks of induction of labor and/or cesarean section.

In making a decision about the timing of delivery, it is necessary to individualize care, taking into account a number of maternal and fetal factors, including:

- Poor maternal glycemic control – as episodes of maternal hyperglycemia may cause fetal acidemia, the fetus may be at risk of unexpected death *in utero*.
- Progression of maternal diabetic complications – maternal renal impairment, hypertension, neuropathy, or retinopathy may all cause significant concerns about maternal health (see Chapter 20).
- Fetal growth anomalies (restriction or excessive) or compromise – as assessed by ultrasound and other methods of fetal surveillance (see Chapter 19).
- Maternal preference, particularly if there is a poor obstetric history.

Type 1 DM is associated with a threefold to fivefold increased risk for stillbirth during pregnancy. Unexplained stillbirth has been associated with poor glycemic control, diabetic nephropathy, smoking, and a low socioeconomic status (19). There are ongoing efforts to identify fetuses at risk of stillbirth, but as yet no consensus exists. Retrospective studies have reported that frequent non-stress tests can identify fetuses at high risk for stillbirth, and elective delivery of these neonates to decrease the stillbirth rate has been suggested by some (20,21), although this has been questioned by others (22). Many centers apply non-stress testing one to two times weekly from 32 to 34 weeks of gestation until delivery. Current UK guidelines do not recommend routine monitoring of fetal well-being before 38 weeks, unless there is a risk of fetal growth restriction (13). It has been stated that when good glycemic control is achieved, in the absence of nephropathy, preeclampsia, and abnormal fetal growth, fetal compromise is unlikely to occur (22). The main problem is to define poor glycemic control and to decide the optimal gestational age at which the risk of fetal demise is balanced by the risk of birth. In a nested case–control study within a prospective cohort of 479 women with type 1 diabetes and a singleton pregnancy, managed with standardized protocols, the rate of immediate or urgent cesarean delivery for an abnormal non-stress test was 4%. The rate of stillbirth was 2 per 1000. An HbA1C at delivery of 47 mmol/mol (6.4%) or more was the sole factor independently associated with immediate or urgent cesarean delivery for fetal compromise (sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of 70.6%, 66.7%, 2.1, and 0.4, respectively) (23). If diabetes is unstable despite hospitalization and intensification of insulin therapy, indicated preterm delivery has been suggested (24).

Large studies are needed to address the risks and benefits of delivery at 38–39 weeks. The few relevant studies have been composed of either entirely or predominantly women with GDM, and thus their conclusions may not apply to women with type 1 or type 2 DM. A US study (25) randomized 187 women with insulin-requiring GDM and 13 with preexisting diabetes to either intervention at 38 weeks or expectant management. Intervention was associated with a lower rate

of LGA (above the 90th centile for gestational age) (10% vs. 23%; $p = 0.02$) and a trend toward a reduction in shoulder dystocia (0% vs. 3%; not significant). Similarly, a case–control study in insulin-requiring GDM from Israel ($N = 260$) (26) showed a reduced prevalence of shoulder dystocia in women delivered at 38–39 weeks compared to those delivered at or beyond 40 weeks (1.4% vs. 10.2%; $p < 0.05$). While it might be expected that induction by 38–39 weeks will reduce the risk of perinatal mortality, as yet there is no evidence to support this.

Mode of Delivery

The choice of the mode of delivery will depend on the obstetric history (e.g., uterine scar and previous shoulder dystocia), suspicion of macrosomia, adequacy of the pelvis, fetal presentation, and local conditions. The increased cesarean rate in women with diabetes is mainly related to anticipation of an increased risk of shoulder dystocia in fetuses suspected of being macrosomic (27). There is also an increased risk of genital trauma and postpartum hemorrhage, the latter with both cesarean and vaginal delivery.

Shoulder dystocia is a serious complication that occurs in 8.4% to 16.7% of women with diabetes whose infants weigh 4000 to 4500 g compared with 1.4% of comparable births in the background population (6). When birthweight exceeds 4500 g, the rate is 20–50% in diabetic and 9.2–24% in nondiabetic women (28). Furthermore, it has been reported that 84% of infants born to mothers with diabetes who have shoulder dystocia weigh more than 4000 g (29). Thus, avoidance of vaginal delivery of macrosomic fetuses in women with preexisting DM should eliminate most cases of shoulder dystocia. In one study, an estimated weight threshold of 4250 g as an indication for cesarean delivery reduced the rate of shoulder dystocia without increasing the rate of cesarean section (30). In that study, most women had GDM, and no firm conclusion can be drawn for women with type 1 or type 2 DM.

The risk of brachial plexus injury increases with each extraction maneuver necessary in cases of shoulder dystocia. The frequency of brachial plexus injury is 0.5–3 per 1000 births in industrialized countries (31), and 4–40% in cases of shoulder dystocia (28). The vast majority of brachial plexus injuries are transient, however, with a frequency of serious sequelae of 1.5%.

This risk underlines the importance of a prenatal detection of macrosomia, but this remains difficult, and the positive predictive values of physical examination and ultrasounds are poor (32). At full term, the mean error for estimations of fetal weight by ultrasound is around 15% (33). Among diabetic women, the posttest probability of identifying a newborn weighing >4000 g is over 60% (34).

There are no randomized trials that have examined the optimum route of delivery for pregnancies with suspected macrosomia in women with DM. Different sources have varying thresholds, ranging from 4000 to >4500 g, for proceeding with cesarean delivery with estimated fetal overgrowth as the primary indication (13,30,35,36).

In the absence of consensus, pregnant women with diabetes who have an ultrasound-diagnosed macrosomic fetus should be informed about the risks and benefits of vaginal birth, induction of labor, and cesarean section (13).

Previous Cesarean Section

There is a paucity of data regarding vaginal birth after cesarean (VBAC) outcomes for diabetic women. In a secondary analysis of an observational study conducted at 19 centers, VBAC was attempted in about half of women with GDM, success rate was about 60%, and maternal and neonatal complications were rare. Due to the relatively low number of women with preexisting diabetes, the authors were unable to draw strong conclusions (37). Diabetes is not considered itself as a contraindication to attempt VBAC (13). The decision to attempt VBAC should be made jointly with the woman and her physician on a case-by-case basis.

Planned Cesarean Delivery – Practical Issues

Women with diabetes are managed in the same way as women without diabetes other than with regard to insulin regimen (see Chapter 23). As many of these women are obese or have other diabetic complications, a preoperative anesthetic review is normally required. Regional anesthesia is preferred to general anesthesia, as with nondiabetic women. Possible hemodynamic effects and hypotension, which may be associated with regional anesthesia, should be prevented.

Prophylactic antibiotics are recommended for planned as well as emergency cesarean sections. The issue of tubal ligation should be raised beforehand with all women having diabetes complications and in multiparous women.

Induction of Labor – Practical Issues

Management is similar to women without diabetes, apart from a few specific points. Induction should take place in the delivery suite or an alternative well-staffed environment where monitoring of fetal condition can be performed using cardiotocography (CTG). During cervical maturation with prostaglandins, if the woman is not in significant pain and labor has not commenced, she should be permitted to continue her usual insulin regimen, coupled with routine glucose measurements. When labor is established, it is customary to monitor capillary blood glucose hourly; insulin regimes are discussed further in this chapter.

Specific Obstetric Issues in the First Stage of Labor

Progress in Labor and Use of Oxytocin

The management of labor follows standard practice. The major concern is that of unexpected disproportion between fetus and mother, and possible traumatic delivery. Careful monitoring of progress in labor is required, which may be facilitated by the use of a partograph or Friedman curve. While difficulties with delivery may occur after a relatively rapid first stage of labor, slow progress in the active phase of labor (i.e., ≥5 cm cervical dilation) requires careful review by an experienced obstetrician. In the woman having her first labor, stimulation of the uterus with oxytocin may be considered if the contractions have never been very frequent or strong. However, after good progress in labor followed by cessation of cervical dilation, oxytocin must be used with caution. Intrauterine pressure catheters, whilst not widely used, may be helpful in this situation by quantifying the uterine response to oxytocin.

Monitoring Fetal Condition in Labor

The fetus of the diabetic mother is probably at higher risk of developing intrapartum asphyxia than the fetus of the woman without diabetes, hence the recommendation for continuous electronic fetal monitoring in labor (38). In early labor, CTG monitoring may be performed intermittently if there is maternal normoglycemia (between 4 and 7 mmol/L [72–126 mg/dL]); once labor is established, it should be performed continuously. If the CTG shows a suspicious or pathologic pattern, the first steps should include checking maternal blood pressure, changing maternal position, administering oxygen, and checking that the maternal glucose is normal. If hyperglycemia is present, then this should be corrected by supplementary intravenous insulin (see Chapter 23), and the CTG pattern may well improve as a result. If the mother is normoglycemic, or obtaining normoglycemia fails to correct the CTG abnormality, then other methods of assessing fetal condition and/or expedited (e.g., cesarean) delivery should be utilized. A fetal blood sample may be taken if cervical dilation permits.

Analgesia in Labor

There are no contraindications to the use of opioids or epidurals for analgesia. Given the increased risk of cesarean delivery with maternal diabetes, the placement of an epidural in the early phase of labor is usually sufficient for anesthesia (with an appropriate dosage regime) if a cesarean is required.

Blood Glucose Control During Labor and Birth

Capillary blood glucose should be monitored every hour during labor, ensuring that it is maintained between 4 and 7 mmol/L (72–126 mg/dL).

An intravenous dextrose and insulin infusion should be considered for women with type 1 diabetes from the onset of established labor and for other women with diabetes whose blood glucose is not maintained between 4 and 7 mmol/liter (72–126 mg/dL).

Specific Obstetric Issues in the Second Stage of Labor

The main issues in the second stage are similar to those in the first stage, namely concerns about fetal condition and delay. In view of the increased risk of shoulder dystocia among all deliveries of diabetic women, whether birth is spontaneous or by low forceps or vacuum delivery, the attendants must be experienced and prepared for potential shoulder dystocia. Any early signs of shoulder dystocia should be acted upon using standard maneuvers, such as the McRoberts position and suprapubic pressure. If operative delivery (other than low forceps/vacuum) is required, then an experienced obstetrician needs to make an assessment in the operating theater with good anesthesia. A relatively difficult delivery of the fetal head may well be followed by an extreme case of shoulder dystocia. Unless there has been significant descent and rotation of the head during the time required to move the woman into the operating theatre and to obtain effective anesthesia, then serious consideration should be given to recourse to a cesarean delivery.

Specific Issues Postnatally

- Women should be encouraged to breastfeed (Chapter 26). There are some specific issues that require medical input.
- Reduction of insulin and blood glucose control is discussed in detail in Chapter 23.
- Women with preexisting diabetes should be advised of their increased risk of hypoglycemia, especially when breastfeeding, and encouraged to have a meal or snack available before or during feeds.
- Women with type 2 diabetes may revert to oral hypoglycemic agents, such as metformin and glyburide, even if they are breastfeeding (see Chapters 15 and 26).
- Women who have been diagnosed with GDM should discontinue blood glucose-lowering therapy immediately after birth and check capillary blood glucose levels to exclude persisting hyperglycemia (13).
- There may be a need to revise anti-hypertensive regimes, including the recommencement of angiotensin-converting enzyme (ACE) inhibitors. The latter, although contraindicated during pregnancy, may reasonably be used while breastfeeding.
- Attention must be paid to the increased risks of wound infection following a cesarean section.
- Thromboprophylaxis for at least 5 days postnatally is recommended after cesarean delivery.
- Discussion should be commenced prior to discharge about contraception and possible family planning (see Chapter 25).

Follow-Up Arrangements

On discharge from hospital, arrangements must be in place for all women with diabetes during pregnancy (whether preexisting diabetes or GDM) to have a follow-up review, typically at 6 weeks, but earlier if required from a diabetic perspective. For those with preexisting diabetes, this may be either by the specialist diabetes in the pregnancy team or by the woman's usual diabetes physician. Women with type 2 DM are at particular risk of suboptimal care (39). For those women who required detailed ophthalmology or renal input during pregnancy, it is essential that arrangements are in place for continuing review in the postnatal period (Chapter 21). In women with GDM without persisting hyperglycemia, offer lifestyle advice (including weight control, diet, and exercise) and a fasting plasma glucose test at the 6-week postnatal checkup (13).

Remind women with diabetes of the importance of contraception and the need for preconception care when planning future pregnancies.

Conclusions

All women with any form of diabetes should be assessed for timing and mode of delivery, and individualized decisions should be made following discussion between the woman and her clinicians, taking into consideration both maternal and fetal factors. The practice of routine cesarean section for women with diabetes is inappropriate.

In labor, specific care must be taken with regard to monitoring fetal condition, maintaining maternal normoglycemia, and watching for signs of potential disproportion.

Multiple-Choice Questions

1 How should delivery be managed in this chapter's Case History?
- **A** Await spontaneous labor.
- **B** Induce labor around 38 weeks.
- **C** Induce labor if not delivered by term.
- **D** Perform an elective cesarean section around 39 weeks.

Answer: B, in view of a previous spontaneous delivery of a large baby, estimated fetal weight <4.5 kg, and suboptimal glycemic control.

2 Which measures should be used for blood glucose control during labor?
- **A** Maintain insulin therapy.
- **B** Stop insulin therapy.
- **C** Intravenous dextrose and insulin infusion
- **D** Hourly capillary blood glucose monitoring
- **E** Glycemic targets between 4 and 7 mmol/L (72–126 mg/dL)

Answer: B, D, and E.

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23

Diabetic Management in Labor, Delivery, and Postdelivery

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PRACTICE POINTS

- Diabetic management during labor and delivery should be according to a standard protocol.
- Delivery should be in centers with neonatal intensive care facilities.
- Administration of corticosteroids in the event of preterm labor should be covered by supplemental insulin according to a defined protocol.
- Maintenance of maternal euglycemia is essential to prevent neonatal hypoglycemia.
- Unless the neonate is symptomatic, blood glucose testing should be deferred until after the first feed to prevent unnecessary treatment of hypoglycemia or unnecessary admission to the neonatal intensive care unit.
- Following delivery, all mothers should be encouraged to breastfeed and supported appropriately.

Case History

A 32-year-old parous woman with a 20-year history of type 1 diabetes presented to her family doctor at 12 weeks gestation in her second pregnancy. No complications had been noted during her last hospital review 3 months earlier. The current pregnancy was unplanned. Hemoglobin A1c (HbA1c) was elevated at 70.5 mmol/mol (8.6%) at booking. Apart from insulin therapy (soluble ultra-short-acting pre-prandial insulin and isophane [NPH] at bedtime), she was taking no other medication. She was referred urgently to the local joint diabetes antenatal clinic. Despite continuing advice, her attendance at the clinic was erratic, her home capillary glucose readings were frequently above target, and her HbA1c did not fall below 53 mmol/mol (7.0%). She was admitted with vaginal bleeding at 34 weeks gestation, and intramuscular betamethasone (12 mg × 2) was given. Supplemental insulin was given, as per the local protocol, to avoid resultant hyperglycemia. Pregnancy continued until 38 weeks gestation, when labor was induced. Throughout labor, hourly maternal capillary blood glucose levels were maintained between 5.2 and 7.1 mmol/l (93.6 and 127.8 mg/dL) using an intravenous (IV) insulin–dextrose regimen. She delivered a baby boy weighing 4500 g per vaginum. Four hours following delivery, the baby appeared irritable and was slow to feed. Laboratory plasma glucose was 1.9 mmol/l (34 mg/dL), and the baby was admitted to the neonatal intensive care unit for IV dextrose infusion. The baby subsequently required tube feeding for 24 h until normal feeding was established. The baby was exclusively bottle fed. The mother continued on the IV insulin–dextrose infusion until she was able to tolerate food, at which point subcutaneous insulin was resumed.

A Practical Manual of Diabetes in Pregnancy, Second Edition. Edited by David R. McCance, Michael Maresh and David A. Sacks.

- How should blood glucose be controlled in women receiving antenatal corticosteroid therapy?
- What is the relevance of intrapartum glycemic control to neonatal hypoglycemia?
- What is the target maternal blood glucose level during labor?
- How is this achieved in women with type 1 diabetes, type 2 diabetes, and gestational diabetes?
- What are the issues regarding maternal insulin requirements postpartum?
- Should women with type 1 diabetes be encouraged to breastfeed?
- What advice should be given to the breastfeeding mother with diabetes?

Background

The Confidential Enquiry into Maternal and Child Health (CEMACH) found that babies of women with diabetes in the UK have a 3.8-fold increased risk of perinatal mortality (1). Diabetic mothers had a high rate of preterm delivery with spontaneous preterm delivery in 9.4% of mothers (7.4% in general population) and iatrogenic preterm delivery in 26.4% (1). Cesarean section rate was also higher at 67% of deliveries (37.6% emergency, 29.8% elective). This compares to a 22% cesarean section rate in the general population (1). Delivery is therefore a time of heighted risk for both the mother with diabetes and her baby. There needs to be a seamless transition from close antenatal surveillance to coordinated delivery. This is achieved through multidisciplinary input prior to, during, and following delivery. This chapter will focus on the care of the diabetic mother at each of these three stages.

Prior to delivery, the physician must ensure that the mother has a clear plan for glycemic management during labor. This should be through a standardized protocol, although an individualized plan may be needed for more complex patients. Given the increased risk of preterm delivery in this group, it is prudent to begin to discuss delivery plans, in relation to insulin management, early in the third trimester or late second trimester.

During delivery, the priority for the physician caring for the diabetic mother is to maintain euglycemia. This is to avoid ketoacidosis in the mother, acidemia in the fetus, and hypoglycemia in the neonate. In the postnatal period, the physician should continue to provide close supervision to ensure stable glycemic control in the setting of rapidly changing insulin requirements. There is a unique opportunity for the multidisciplinary diabetes team to provide support and education for the diabetic mother that can potentially have a long-lasting influence on her own health and that of her child.

Before Delivery

It is imperative that the medical management of a mother with diabetes is planned in advance of labor. This approach not only ensures that maternal blood glucose is maintained within tight limits in early labor, but also helps to reassure the woman that there are clear plans to manage her diabetes.

Location of Delivery

Early in pregnancy, or as soon as diabetes is diagnosed in the case of gestational diabetes (GDM), it is important to ensure that the mother is being managed at an appropriate center. Women with diabetes should be cared for and delivered in a center with tertiary maternity and neonatal facilities (1,2). Admission to the neonatal unit should be limited to those infants with clear indications such as significant hypoglycemia, thus avoiding unnecessary separation of mother and baby. This is a change from previous UK practice in which nearly one-third of units routinely admitted babies of mothers with diabetes to the neonatal unit (3).

Antenatal Steroids

The UK's National Institute of Clinical Excellence (NICE) recommends all women at risk of preterm birth up to 34^{+6} weeks of gestation to receive antenatal corticosteroids (4). Similarly, the US National Institute of Health advises consideration of steroids for fetal pulmonary maturation between 24^{+0} and 34^{+0} weeks (5). This is typically given in the form of betamethasone 12 mg intramuscularly in two doses, 24 h apart (or on occasion 12 h apart to limit the period of hyperglycemia), or four doses of dexamethasone 6 mg intramuscularly, 12 h apart (4). Antenatal steroids are associated with a significant risk of maternal hyperglycemia and can precipitate diabetic ketoacidosis. This is well recognized in the mother with diabetes preceding pregnancy and has also been occasionally reported in women with GDM (6–8). It is therefore essential that steroid administration is coupled with close monitoring of blood glucose and anticipatory supplemental insulin. Due to the unpredictability of the individual woman's response to steroids, this is typically administered to inpatients.

Diet or Tablet-Controlled Gestational Diabetes

Women with GDM that is maintained with diet or oral hypoglycemic therapy frequently need insulin during steroid therapy, at least temporarily. A small observational study of pregnant women (nine diet-controlled GDM, three nondiabetic) found an elevation in glucose of 33–48% in those with GDM and 16–33% in women without diabetes (9). It is therefore not surprising that up to 50% of women with GDM require initiation of glucose-lowering therapy following steroids (10).

It is difficult to predict which women will require insulin, and therefore all women with diet-controlled GDM should be closely followed with bedside glucose monitoring, at least 2–4 hourly, with prompt addition and titration of insulin if glucose levels rise above target.

Patients on Insulin Therapy

Women on insulin require additional insulin during and immediately following steroids. Several protocols have been proposed to manage blood glucose levels at this time. We have successfully developed an algorithm in which insulin doses are titrated to maintain pre-prandial glucose at <6.0 mmol/l (108 mg/dL) without inducing hypoglycemia (11). This algorithm is administered to inpatients, is used for women with both GDM and pre-GDM, and is outlined here:

Day 1 (the day on which the first dose of steroid is given): Nocturnal insulin is increased by 30%.
Day 2: All insulin doses are increased by 50%.
Day 3: All insulin doses are increased by 50%.
Day 4: All insulin doses are increased by 30%.
Day 5: All insulin doses are increased by 20%.
Days 6 and 7: The insulin dose is gradually reduced to pre-steroid levels.

This is similar to the less aggressive algorithm described by a Scandinavian group and recently endorsed by UK NICE as a management option for women with diabetes receiving steroids during pregnancy (2,12). A number of centers use an IV insulin infusion that starts with the first steroid dose and is supplementary to the patient's usual insulin regimen. In a small study including eight patients with diabetes (three GDM and five pre-gestational), between 1.3 and 3.7 units/h of IV insulin was needed to maintain 75% of glucose measurements between 4 and 10 mmol/l (13).

When insulin is actively titrated upward with the introduction of steroids, there are significantly fewer hyperglycemic episodes compared with an approach in which insulin is titrated in response to hyperglycemia, with no episodes of severe hypoglycemia (12). Therefore, it is clear that regardless of which protocol is used, insulin needs to be actively titrated with steroids.

Patients on Insulin Pump Therapy

The increasing use of insulin pump therapy in type 1 diabetes is being translated into

pregnancy. Guidance for pump therapy following steroids is an extrapolation of the algorithms described in this chapter. It is important to remember that, in addition to titration of the basal rate and bolus ratios, correction ratios for hyperglycemia also need to be titrated. There will be an increased volume of insulin infused, so it is essential to ensure that the reservoir is full before giving steroids. Given the risk of diabetic ketoacidosis associated with steroid therapy, it is also important that a fresh insulin-giving set is used prior to starting steroids and that traditional insulin pens are available should there be any concern regarding pump delivery (see also Chapter 17).

Preterm Labor and Tocolytic Agents

Tocolytic agents may be given to a woman in preterm labor provided there is no contraindication to prolonging the pregnancy (14). Their main benefit is in suppressing labor for long enough to facilitate steroid administration or potential transfer to a site that has a neonatal unit. Potential agents include nifedipine, atosiban, or beta-agonists. Beta-sympathomimetic agents can cause rapid elevations in blood glucose and have been reported to precipitate ketoacidosis (15). They are not recommended for use in mothers with diabetes (2).

During Delivery

The main objective of glycemic control during labor is to avoid maternal hyperglycemia and in turn to minimize the risks of neonatal hypoglycemia and fetal acidemia.

Neonatal Hypoglycemia

Rates of neonatal hypoglycemia vary depending on the definition of hypoglycemia employed, maternal diabetes type, antenatal glycemic control, and infant birthweight (16). In general, 30–50% of infants born to mothers with diabetes will have hypoglycemia during routine testing in the early postnatal period (16–19).

It is difficult to define hypoglycemia in the neonate. In nondiabetic pregnancy, the lower limit of neonatal fetal glucose is 3.0 mmol/l (54 mg/dL), dropping to 2.8 mmol/l (50.4 mg/dL) in the first 2 h of life (20,21). Even in the absence of food intake, blood glucose rises in the first 3 h of life. Pathological hypoglycemia is persistence of hypoglycemia beyond the first few hours of life. To date, there is no consensus as to the numerical value that constitutes clinically significant neonatal hypoglycemia (22). Guidelines recommend screening at-risk infants and maintaining blood glucose at 2.6 mmol/l (47 mg/dL) or above (23). Infants at risk include those born to a mother with diabetes, those small or large for gestational age, and late preterm deliveries (23).

Glucose is the principal energy substrate for the fetus, with fetal blood glucose levels typically corresponding to 60–80% of maternal levels (24). In the diabetic mother, neonatal hypoglycemia is attributed to fetal hyperinsulinemia, which occurs in response to maternal (and subsequently fetal) hyperglycemia during pregnancy (25–27). Delivery of the infant results in an abrupt cessation of maternal glucose supply, which, in the setting of hyperinsulinemia, will result in hypoglycemia. Studies evaluating the impact of maternal glucose at delivery on neonatal hypoglycemia are summarized in Table 23.1.

Fetal Acidemia

Maternal hyperglycemia is associated with an increased risk of fetal acidemia. Two observational studies in women with type 1 diabetes considered the effect of intrapartum blood glucose control on fetal distress. In one study of 149 subjects, perinatal asphyxia was reported in 27% ($n = 40$) (36). Perinatal asphyxia was defined clinically as fetal distress during labor (late decelerations, persistent fetal bradycardia, or both), 1 min Apgar score less than or equal to six, or intrauterine fetal death. The maximum maternal blood glucose during labor was higher in babies with perinatal asphyxia than in those without

Table 23.1 Observational studies examining the relationship between intrapartum capillary blood glucose (CBG) and neonatal hypoglycemia (NH).

Authors (year)	Subjects	Methods/definitions	Findings
Andersen *et al.* (1985) (28)	53 (type 1)	Plasma glucose measured at birth and 2 h later; NH (<1.7 mmol/l) [31 mg/dl]	Maternal BG at birth correlated positively with neonatal BG at birth ($r = 0.82$, $p < 0.001$) and negatively with neonatal BG at 2 h ($r = -0.46$; $p < 0.001$). If maternal BG at birth was ≥7.1 mmol/l [128 mg/dl] (11/30), 37% rate of NH vs. 0% if maternal BG < 7.1 mmol/l.
Miodovnik *et al.* (1987) (29)	122 (type 1)	IV glucose ± insulin infused to maintain CBG 3.9–5.6 mmol/l; NH (<1.7 mmol) [31 mg/dl]	47% babies whose mothers had CBG >5 mmol/l [90 mg/dl] developed NH compared to 14% with CBG <5 mmol/l.
Feldberg *et al.* (1988) (30)	65 (type 1)	Comparison of CSII ($n = 28$) with constant IV insulin infusion ($n = 37$)	8 cases of NH in constant IV insulin group; no cases in CSII group ($p < 0.05$).
Lean *et al.* (1990) (31)	29 insulin-treated mothers	IV 10% dextrose with IV insulin infusion adjusted to maintain CBG of 4–7 mmol/l (72–126 mg/dL); NH–CBG <2.0 mmol/l (36 mg/dL)	NH in 11 babies (37.9%); neonatal CBG correlated negatively with maternal BG at delivery ($r = -0.58$, $p < 0.01$).
Curet *et al.* (1997) (32)	233 insulin-requiring (77 type 1, 156 type 2)	Day of delivery: 10% glucose–fructose infusion; IV insulin at 1–4 U/h to maintain BG 3.3–5.0 mmol/l [59–90 mg/dl]; NH (<1.7 mmol) [31 mg/dl]	Incidence of NH was 16.5%. Mean intrapartum BG level was significantly lower in mothers of babies without hypoglycemia ($p < 0.05$).
Carron Brown *et al.* (1999) (33)	80 women with type 1 diabetes	IV 10% dextrose with variable doses of short-acting insulin added to bag to maintain CBG at 4–7 mmol/l (72–126 mg/dL); NH–CBG <2.2 mmol/l (39.6 mg/dL)	NH in 23.8% of infants (19/80). If maternal glucose is maintained in target range and does not rise above 8 mmol/l (144 mg/dL), no detectable adverse effect on neonates.
Balsells *et al.* (2000) (34)	54 insulin-treated	IV glucose (8.3 g/h); IV insulin infusion via syringe pump	5 babies developed NH; maternal BG in last 2 h of birth was associated with NH.
Rosenberg *et al.* (2006) (35)	35 women with gestational ($n = 28$) and pre-gestational ($n = 7$) diabetes	Insulin infusion or rotating fluids with target CBG 5.6 mmol/l (100 mg/dL). Protocols detailed in Table 23.2. NH–blood glucose < 1.9 mmol/l (<35 mg/dL) in the first 24 h of life.	NH in 5 babies: 1 (6.7%) rotating fluids, 4 (19.0%) insulin drip (NS).

BG = Blood glucose; IV = intravenous.

(9.5 ± 3.7 vs. 7.0 ± 3.0 mmol/l [171 ± 67 vs. 126 ± 54 mg/dL]; $p = <0.0001$) (36). In the second study of 65 subjects, mean blood glucose during labor in women using continuous subcutaneous insulin infusion (CSII) ($n = 28$) was 4.8 ± 0.6 mmol/l (86 ± 11 mg/dL) (range: 3.8–5.8 mmol/l) compared with 7.2 ± 1.1 mmol/l (130 ± 20 mg/dL) (range: 5.6–8.3 mmol/l) ($p < 0.025$) among those using a constant intravenous (IV) insulin infusion ($n = 37$) (30).

Acute fetal distress (defined using fetal scalp pH values) occurred in 27% of the IV infusion group versus 14.3% of the CSII group ($p < 0.001$); cesarean section occurred in 38% versus 25% ($p < 0.05$), respectively (30).

These data suggest that maintenance of maternal blood glucose between 4 and 7 mmol/l (72–126 mg/dL) during labor and delivery reduces the incidence of both neonatal hypoglycemia and "fetal distress" (2).

Glycemic Control During Labor and Delivery

The main objective during labor is to achieve stable glycemic control and avoid maternal hyperglycemia. This is achieved through the use of standardized protocols that are adapted depending on the timing and method of delivery. In addition to variation in method of delivery, variation also exists in diabetes type and treatment method.

Method of Delivery

Elective Cesarean Section

- Women on insulin should be placed first on the operating list and admitted either the previous day or early on the morning of surgery.
- Long-acting insulin is taken as normal prior to a light supper.
- The mother should fast from 22.00 h the evening before surgery and should be first on the operating list the next day; rapid-acting insulin should be withheld.
- 1–2 h prior to surgery, hourly monitoring of blood glucose begins; and a glucose–insulin infusion is commenced, if necessary, to maintain blood glucose between 4 and 7 mmol/l (72–126 mg/dL).
- The insulin dose and/or rate is adjusted in response to maternal capillary glucose.

Induction of Labor

- Women should continue their current insulin regimen until labor is confirmed.
- Often, an early breakfast is consumed with their normal morning insulin dose.
- Once labor is confirmed and mother is fasting, a glucose–insulin infusion is commenced as per protocol, unless delivery is imminent.
- Maternal blood glucose levels should be monitored hourly.
- Blood glucose levels should be maintained between 4 and 7 mmol/l (72–126 mg/dL).
- The insulin dose and/or rate is adjusted in response to maternal blood glucose.

Spontaneous Labor

- Following admission in spontaneous labor, the patient is fasted.
- A blood glucose level should be taken on admission and hourly thereafter.
- Women controlled on diet generally do not require a glucose–insulin infusion, unless the capillary glucose is >7 mmol/l (126 mg/dL) or until labor is confirmed.
- Once labor is confirmed, a glucose–insulin infusion should be commenced as per protocol.
- Capillary blood glucose levels should be maintained between 4 and 7 mmol/l (72–126 mg/dL).
- The insulin dose and/or rate is adjusted according to the local protocol in response to maternal blood glucose.

Diabetes Type

Women with GDM that is managed with diet alone should have capillary blood glucose monitoring every 1–2 h once labor is established, with the aim of maintaining blood glucose <7 mmol/l (126 mg/dL). If this is not achieved, an IV insulin–dextrose infusion should be started as per protocol. Women with GDM who required insulin during their pregnancy should be treated the same as women with diabetes on insulin pre-pregnancy.

Women with type 1 diabetes who use CSII therapy should have the opportunity to discuss glycemic management during labor in advance of delivery with their physician. An individualized plan should be clearly documented in their chart. Data on the effectiveness of CSII during labor are limited to a nonrandomized study in which 65

women with type 1 diabetes were managed with either CSII (28 women) or constant IV insulin infusion (37 women), with a significantly lower mean glucose during labor in women with CSII (4.8 ± 0.6 mmol/l vs. 7.2 ± 1.1 mmol/l; $p < 0.025$) (30). CSII throughout labor is therefore a highly useful and feasible means of controlling blood glucose, particularly if basal adjustments are discussed in advance of labor. It is important to remember that delivery unit staff and anesthetists may be unfamiliar with CSII and require additional medical support and advice during labor, or indeed prefer to revert to IV insulin if glucose levels are out of target. The use of CSII during pregnancy is discussed in more detail in Chapter 17.

Insulin Infusion Regimens

UK NICE guidelines recommend the use of IV dextrose and insulin for women with type 1 diabetes from the onset of labor, and for women with diabetes of all causes, when blood glucose is not maintained between 4 and 7 mmol/l (72–126 mg/dl) (2). It is essential that whatever regimen is used to maintain euglycemia, the physician and midwifery or nursing staff initiating and managing the infusions are familiar with them.

A number of different protocols are available and are often devised through personal experience. Three protocols are outlined in Table 23.2. In Belfast, we have recently changed to use IV dextrose with a variable-rate IV insulin regimen (Protocol 1, Table 23.2). This is a variation of the protocol described by Lepercq *et al.*, in which 229 pregnancies in 174 women with type 1 diabetes were managed with a variable-rate infusion of IV insulin alongside 10% dextrose (Protocol 2, Table 23.2) (37). Using this protocol, the maternal glucose during labor was 6.1 ± 1.6 mmol/l (110 ± 29 mg/dL) with a 13% incidence of neonatal hypoglycemia (37). In a comparative study of "rotating fluids" ($n = 15$) versus "insulin drip" ($n = 20$), maternal glucose was 5.8 ± 0.5 mmol/l (103.9 ± 8.7 mg/dL) in the "rotating fluids" group and 5.7 ± 1.0 mmol/l (103.2 ± 17.9 mg/dL) in the "insulin drip" arm, with no significant difference in rate of neonatal hypoglycemia (6.7% vs. 19.0%; $p = 0.9$) as defined as capillary blood glucose of < 1.9 mmol/l (35 mg/dL) within the first 24 h of life (35). These two protocols are outlined in Table 23.2 (Protocols 3 and 4).

Maternal Glucose Control Postpartum

Insulin sensitivity increases in the immediate postpartum period, normalizing over the following fortnight (38). Once the cord is cut, an insulin infusion should be reduced by 50%, with regular capillary blood glucose measurement and administration of IV fluids until the mother is eating normally. In a cohort study of 36 women with type 1 diabetes, blood glucose values and insulin requirements were significantly lower in the first week postpartum when compared to preconception levels (39). This effect was found in both breastfeeding and non-breastfeeding mothers (39). Therefore, for mothers with type 1 diabetes, regular subcutaneous insulin should resume at a reduced dose – often, 50% of their pre-pregnancy dose. This is with close supervision by the diabetes team and titration as needed.

Mothers with type 2 diabetes have a similar reduction in insulin requirement following delivery. If insulin had been added during pregnancy, it should be withdrawn on delivery with close blood glucose monitoring. For mothers who had been on insulin prior to pregnancy, this should be continued at their pre-pregnancy dose and adjusted throughout the early postnatal period. If oral hypoglycemic agents had been used prior to pregnancy, these can be resumed postnatally if the mother is not breastfeeding. The use of oral hypoglycemic agents with breastfeeding is discussed in detail in Chapter 15.

Table 23.2 Insulin infusion protocols for delivery in mothers with diabetes.

***Protocol 1*: Commence protocol at onset of established labor or before cesarean section.**

Maternal capillary blood glucose (mmol/l)	10% glucose infusion	Insulin infusion rate (ml/h = units/h)	10% glucose infusion rate (h)	10% glucose infusion rate (ml/h)	Glucometer monitoring
<2.0	150 ml	0	10 min	900	Recheck in 15 mins
2.0–3.9	500 ml	0	5 h	100	Recheck in 30 mins
4.0–5.9	500 ml	1.0	6 h	83	Check hourly
6.0–7.9	500 ml	2.0	6 h	83	Check hourly
8.0–9.9	500 ml	2.5	6 h	83	Check hourly
10.0–11.9	500 ml	3.0	6 h	83	Check hourly
>12	500 ml	4.0	6 h	83	Check hourly
>16	**Contact endocrine registrar on call (or, at weekends, consultant on call).**				

***Protocol 2* (Lepercq *et al.*, 2008[37]): Commence protocol on morning of delivery or following admission in spontaneous labor.**

- IV 10% dextrose solution at 80 ml/h
- IV short-acting insulin using an infusion pump, starting at 1 U/h
- Capillary blood glucose (CBG) measured hourly until delivery
- Target CBG at 3.4–7.8 mmol/l (61–140 mg/dL) by adjusting insulin as below:
  - 1 U/h if CBG 3.4–7.8 mmol/l (61–140 mg/dL)
  - 1.5 U/h if CBG 7.8–10 mmol/l (140–180 mg/dL)
  - 2 U/h if CBG 10.0–12.2 mmol/l (180–220 mg/dL)
  - 3 U/h if CBG above 12.2 mmol/l (220 mg/dL)
- In the case of hypoglycemia (CBG ≤3.3 mmol/l, ≤59 mg/dL), stop the insulin infusion for 30 min; if the CBG remains low, give 30% dextrose IV.

***Protocol 3* (Rosenberg *et al.*, 2006[35]): Rotating fluids**

Obtain CBG readings hourly with target CBG 5.6 mmol/l (100 mg/dL):
- CBG <5.6 mmol/l (<100 mg/dL): IV 5% dextrose at 125 ml/h
- CBG 5.6–7.8 mmol/l (101–140 mg/dL): lactated Ringer's solution at 125 ml/h
- CBG >7.8 mmol/l (>140 mg/dL): start adjusted insulin drip (see Protocol 4).

***Protocol 4* (Rosenberg *et al.*, 2006[35]): Insulin drip**

- Women maintained on IV 5% dextrose at 125 ml/h and a continuous insulin infusion.
- Start insulin when CBG >4.5 mmol/l.
- Monitor CBG hourly adjusting insulin as shown here to maintain a target of 5.6 mmol/l (100 mg/dL):

CBG	Rate (units/h)
<4.4 mmol/l (80 mg/dL)	Off
4.5–5.6 mmol/l (81–100 mg/dL)	0.5
5.6–7.8 mmol/l (101–140 mg/dL)	1.0
7.8–10.0 mmol/l (141–180 mg/dL)	1.5
10.0–12.2 mmol/l (181–220 mg/dL)	2.0
>12.2 mmol/l (220 mg/dL)	2.5

Breastfeeding

Mothers with diabetes are advised to take a small snack before breastfeeding to avoid hypoglycemia, which is more common in the first hour following a feed. Insulin requirements may increase during the day due to increased caloric intake, with a fall in nocturnal insulin requirements due to glucose siphoning into the breast milk. Women are therefore often advised to reduce their long-acting insulin when breastfeeding. In a cohort study of 30 women with type 1 diabetes, fasting plasma glucose levels were significantly lower in breastfeeding mothers at 6 weeks compared to those who either had stopped breastfeeding or were exclusively bottle feeding (40). Maternal glucose should be kept as normal as possible to avoid elevations in milk glucose and maternal hypoglycemia. This is achieved through regular snacking and careful insulin adjustment with full support from the diabetes specialist team.

Summary and Future Research Directions

Women with pre-gestational and gestational diabetes should be delivered in centers capable of providing tertiary maternal and neonatal care. The literature is clear that the risks of neonatal hypoglycemia and fetal distress are minimized by optimal maternal glucose control peripartum. Randomized trials comparing CSII with traditional insulin–dextrose infusions should be considered, given the early promise that CSII has shown in pregnancy for women with type 1 diabetes.

Multiple-Choice Questions

1 A 28-year-old primigravida women with type 1 diabetes presents at 37 weeks gestation in established labor with 4–5 cm of cervical dilation. Her usual insulin regimen is insulin aspart with meals and insulin detemir 30 units nocte. Glycemic control has been excellent throughout her pregnancy. How should her diabetes be managed?

- **A** Continue with her usual insulin regimen.
- **B** Continue with detemir 30 units and hold insulin aspart until she is able to eat and drink normally.
- **C** Start an insulin–dextrose infusion, and adjust rate to maintain hourly capillary glucose at 4–7 mmol/l (72–126 mg/dL).
- **D** Monitor capillary glucose hourly, and give additional subcutaneous aspart according to a subcutaneous sliding scale.
- **E** Continue regular subcutaneous insulin, reducing dose of aspart and detemir by 50%.

Answer: C. Start an insulin–dextrose infusion, and adjust rate to maintain hourly capillary glucose at 4–7 mmol/l (72–126 mg/dL).

When a woman presents in established labor and is fasting, she needs to be immediately started on an established insulin–dextrose infusion protocol with hourly monitoring and adjustment of the infusion rate to maintain capillary glucose at 4–7 mmol/l (72–126 mg/dL). Subcutaneous sliding scales and regular subcutaneous aspart are insufficiently flexible to allow for regular adjustments, and are likely to result in maternal hypoglycemia.

2 Following delivery of a healthy baby boy, the patient moves to the postnatal ward at 7:00 p.m. and eats a light meal of two slices of toast. Capillary blood glucose is 6.0 mmol/l (108 mg/dL). Prior to delivery, her insulin regimen was aspart (22 units breakfast, 14 units lunch, and 20 units dinner) and detemir (30 units nocte). Her pre-pregnancy regimen was aspart (8 units breakfast, 6 units lunch, and 8 units dinner) and detemir (16 units

nocte). She plans to breastfeed. How should her diabetes be managed?

A Resume subcutaneous insulin at 50% of her pregnancy regimen (i.e., aspart, 11 units breakfast, 7 units lunch, and 10 units dinner; and detemir, 15 units nocte) with regular glucose monitoring and adjustment as needed.

B Resume subcutaneous insulin at 50% of her pre-pregnancy regimen (i.e., aspart, 4 units breakfast, 3 units lunch, and 4 units dinner; and detemir, 8 units nocte) with regular glucose monitoring and adjustment as needed.

C Start back on regular subcutaneous insulin at her pre-pregnancy dose with regular glucose monitoring and adjustment as needed.

D Continue with subcutaneous insulin using her pregnancy regimen (22 units breakfast, 14 units lunch, and 20 units dinner; and detemir, 30 units nocte) to account for increased caloric intake with breastfeeding. Monitor and adjust regularly.

E Continue with subcutaneous insulin using her mealtime pregnancy regimen (22 units breakfast, 14 units lunch, and 20 units dinner) to account for increased caloric intake with breastfeeding. Reduce nocturnal detemir to 20 units.

Answer: B. Resume subcutaneous insulin at 50% of her pre-pregnancy regimen (i.e., aspart, 4 units breakfast, 3 units lunch, and 4 units dinner; and detemir, 8 units nocte) with regular glucose monitoring and adjustment as needed.

Insulin sensitivity increases in the immediate postpartum period, normalizing over the following fortnight. It is therefore necessary to reduce the insulin dose by up to 50% of the pre-pregnancy dose. Breastfeeding necessitates an increase in maternal caloric intake and may be associated with nocturnal hypoglycemia due to glucose siphoning into the breast milk. The initial focus is avoidance of maternal hypoglycemia. Subsequently close glucose monitoring and insulin adjustment, with the support of the diabetes specialist team, are essential to maintain satisfactory glucose control.

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24

Delivery and Postdelivery Care: Care of the Neonate

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PRACTICE POINTS

- Neonatal mortality rates associated with pre-gestational diabetes are about twice those in the general population.
- Preterm delivery with its associated neonatal morbidity is five times as common with pre-gestational diabetes than in the general population and is often avoidable.
- Major congenital anomalies are between three and five times as common in pregnancies with pre-gestational diabetes than in the general population.
- Other recognized neonatal complications of diabetes in pregnancy include macrosomia, birth injury, hypoxic–ischemic encephalopathy, and hypoglycemia.
- The majority of babies born to mothers with diabetes do not have complications and do not require additional specialist care.
- Separation of babies and mothers and formula feeding should only occur if clinically indicated; such policies should not be "routine."

Pitfalls to be Avoided

- Unexpected cardiorespiratory compromise at birth is more common than in the general population, and delayed attendance by healthcare professionals with advanced newborn life support skills may compromise outcomes.
- The assumption that all babies will experience clinically significant hypoglycemia may result in policies of "routine" separation of mother and baby and formula feeding, which in turn affect breastfeeding.
- Postnatal "catch down" in weight gain (as plotted on centile charts) after macrosomia at birth should not cause unnecessary concern.

A Practical Manual of Diabetes in Pregnancy, Second Edition. Edited by David R. McCance, Michael Maresh and David A. Sacks.

Case History

Mrs AB, aged 26 and expecting her first baby, had type 1 diabetes since her teenage years. She planned her pregnancy and attended a pre-pregnancy clinic to discuss best possible control at this crucial time. She envied her closest friend who was planning a home birth for her own baby, but appreciated that even with good diabetic control there were risk factors for her baby that meant hospital birth was advisable. Early ultrasound scans showed normal growth and normal fetal anatomy.

Mrs AB had threatened preterm labor at 28 weeks. She was admitted to hospital and was given intramuscular betamethasone, to reduce the chances of respiratory distress syndrome if the baby were to be born preterm. During the 36 h following administration of the betamethasone, she required up to 10 units/h of continuous insulin infusion to maintain her glucose concentrations in an acceptable range. Fortunately, contractions settled and the pregnancy continued to near term. A junior obstetrician advised Mrs AB that she would need a cesarean section "because she has diabetes." She asked to speak to the consultant, who considered there were no risk factors and that normal delivery could be anticipated. Mrs AB was relieved as she had read that there is an increased risk of breathing problems if babies are delivered by cesarean.

Baby Tom was born at 38 weeks of gestation by normal delivery. His birthweight was 3.6 kg (91st centile). Tom was placed skin-to-skin on his mother's chest immediately after birth, and within 30 min had been to the breast and was noted to have a good latch and suck. At 4 h of age, he had a blood glucose level measured (using the machine in the neonatal unit laboratory) of 1.5 mmol/L (27 mg/dL). The midwife considered Tom had normal tone, color, and vital signs, and encouraged his mother to feed him again. He fed well, appearing to take colostrum. He remained alert and with normal tone, and from his skin-to-skin position fed intermittently but each time with good latch and suck. At 8 h of age, his blood glucose was 2.2 mmol/L (40 mg/dL), and the midwife again evaluated Tom's condition as normal. As his blood glucose level was increasing and his clinical condition was good, no additional formula milk feeds were given to supplement breastfeeds. Tom continued to feed well, and blood glucose levels remained above 2.0 mmol/L (>36 mg/dL). Blood glucose monitoring was discontinued after 24 h, and Tom went home the next day.

Tom's health visitor was initially concerned at his 6-week check that his weight had fallen to the 50th centile. However, she then recalled the history of diabetes in pregnancy and considered that Tom was showing "catch down" to his natural weight.

- Why was the mother advised against home birth?
- Why did Tom have minimal complications after birth?
- Why did Tom not receive formula milk?
- Why did Tom's weight fall to a lower centile?

Background

Adverse consequences from maternal pre-gestational and gestational diabetes for the fetus and the neonate arise either from the directly harmful metabolic environment, from obstetric interventions required when maternal control is poor, or from inappropriate "routine" practices. Optimizing diabetic control, especially pre-conception, minimizes risks to the mother and fetus, and reduces the risk of the postnatal complications described in this chapter (1–5). Whilst in many cases this is achieved and a healthy mother and baby result, it is important to be aware of the complications that can occur.

As the population of women with type 2 diabetes becomes younger, particularly in some ethnic groups, the proportion of women with pregnancies complicated by pre-gestational type 2 diabetes has risen to approaching half of pregnancies complicated

by pre-gestational diabetes (6,7). Babies born to women with type 2 diabetes have complication rates that are similar or worse compared to those with type 1 diabetes (8–10).

Finally, the fetus and neonate of the mother who develops gestational diabetes are also at risk of complications (11–17). There is evidence that screening for and treating gestational diabetes reduce some perinatal complications (14,18,19). However, the recent International Association of Diabetes and Pregnancy Study Group's recommendations for screening for gestational diabetes (19a), subsequently recommended by the World Health Organization (WHO) (19b), have resulted in controversy regarding cost and clinical effectiveness and variation in practice (14,20–23).

Care of the Healthy Infant After Well-Controlled Diabetes in Pregnancy

For many women, especially those who access prenatal counseling and enhanced diabetes care, with good control during pregnancy, fetal and neonatal complications related to diabetes in pregnancy are unlikely. It is important to recognize that a baby at very low risk of complications should be managed according to normal standards for the healthy newborn baby (24,25). In particular, it is important to avoid unnecessary separation of mother and baby, and to facilitate successful breastfeeding if this is the mother's chosen method of feeding. A recent UK audit demonstrates success in this respect (7). Failure to follow these principles and the resulting iatrogenic complications are also covered here.

Neonatal Complications – Etiology and Management

Despite the aspiration that improved maternal diabetes care will minimize perinatal morbidity and mortality, recent data suggest that insufficient progress has been made (Table 24.1) (6,8,10–12,16,26–33). Some neonatal complications arise from the effects of being born preterm or by cesarean section, and are not specific to diabetes, while others are secondary to intrauterine or intrapartum hypoxia–ischemia or the abnormal diabetic metabolic environment that the fetus may be exposed to during pregnancy. Finally, some neonatal problems are iatrogenic (Table 24.2).

Perinatal Mortality

Data since the 1990s, from cohorts of babies born to mothers with pre-gestational diabetes, have shown perinatal mortality rates (stillbirths and first-week neonatal deaths) 2.3–3.8 times above the background population with no improvement over time (6–8,12,26,28–30,32,33). Data for stillbirths and neonatal deaths separately show the same magnitude of difference and no improvement over time. However, there is no definitive evidence of increased perinatal mortality for women with gestational diabetes (25).

For the cohort of babies from the UK Confidential Enquiry into Maternal and Child Health (CEMACH), the most common causes of death were related to congenital abnormality and intrapartum complications (Table 24.3) (29).

Preterm Delivery

Rates of preterm delivery (<37 weeks gestation), whether spontaneous or induced, are significantly higher than the background rate or compared to women who do not have diabetes (Table 24.1) (7,8,15,16,28,32).

The causes of preterm delivery are covered in Chapter 22. As with other maternal conditions that affect pregnancy, there is always a balance between continuing a pregnancy until term and reducing the time that both fetus and mother are exposed to a harmful environment. However, for women in the UK CEMACH cohort, 19% had preterm delivery that was not spontaneous or explained by maternal or fetal compromise, and thus could have been avoided (8). This would have prevented some 235 admissions to neonatal care over the study period.

Table 24.1 Example outcomes from recent publications, highlighting statistically significant odds ratios (ORs) and relative risks (RRs) versus nondiabetic women or general population (including women with diabetes, after diabetes in pregnancy).

	CEMACH (2005) (8)	**Lai *et al.* (2014) (16)**		**Vinceti *et al.* (2014) (10)**	**Feig *et al.* (2014) (12)**		**Colstrup *et al.* (2013) (28)**	**Dunne *et al.* (2012) (30)**	**Al-Agha *et al.* (2012) (26)**	**Balsells *et al.* (2012) (11)**		**Eidem *et al.* (2010) (31)**
Type DM	**Pre**	**Pre**	**GDM**	**Pre**	**Pre**	**GDM**	**Pre**	**Pre**	**Pre**	**Pre**	**GDM**	
Stillbirth		3.7						5				
Neonatal death	2.6	2										
PNM	3.8				2.3		3.7	3.5	3.7			
Spont PT		4.2	1.7									
Ind PT		3.8	2									
Preterm delivery	5						4.2					
CS		2.5	1.6									
Congenital anomaly	2.6	1.6	1.2	1.8	1.8	1.3	2.4	2		2.7–4.7	1.2–1.4	2.1
Birthweight >90th centile	5.2	2.1	1.3				4.5		1.8			
Shoulder dystocia	2.6	1.5	1.32									
Erb palsy	11											
Apgar <7 at 5 min	3.4											
Admission to NNU	5.6	3.8	1.6									
Term admission to SC	3.3											

CS = Cesarean section; DM = diabetes mellitus; GDM = gestational diabetes mellitus; Ind PT = induced preterm delivery; NNU = neonatal unit; PNM = perinatal mortality; Pre = pre-gestational DM; SC = special care unit; Spont PT = spontaneous preterm delivery.

Table 24.2 Neonatal complications after diabetes in pregnancy.

Directly related to diabetes in pregnancy

- Congenital anomalies
- Intrauterine growth restriction
- Intrapartum hypoxia–ischemia
- Macrosomia, obstructed labor, birth injury
- Neonatal death
- Polycythemia/jaundice
- Hypoketonemic hypoglycemia
- Hypocalcemia, hypomagnesemia
- Hypertrophic cardiomyopathy

Complications of necessary, or unnecessary, obstetric interventions

- Complications of preterm delivery
- Complications of cesarean section – respiratory distress, impact on breastfeeding

Iatrogenic

- Inappropriate separation of mother and baby
- Inappropriate formula supplementation – impact on breastfeeding

If preterm delivery is planned, this must be in a unit that can provide neonatal intensive care, which may require transfer of the mother to an appropriate unit, preferably within a perinatal network system. It is now widely recognized that mothers with diabetes should receive steroid injections if preterm delivery is anticipated and babies of diabetic mothers do not in general have worse respiratory distress than other babies of equivalent gestation. The rationale for giving steroid therapy and subsequent maternal management are discussed elsewhere (Chapter 23).

Preterm babies of diabetic mothers should be managed according to standard protocols. In particular, mothers should be encouraged to express and store breast milk. Additional problems specific to the baby of a diabetic mother may be present and need additional management (see further in this chapter).

Effects of Delivery by Cesarean Section

Cesarean section rates for women who have diabetes in pregnancy are significantly higher than background rates for women who do not have diabetes, including for women with gestational diabetes (8,16,32). In the UK study of pre-gestational diabetes, 9% of cesarean sections were not explained by maternal or fetal compromise, and 4% were "routine for diabetes" or "maternal request" (8). As noted, a number of these "routine" cesarean sections were at a preterm gestation (see also Chapter 22).

Although the baby may be protected from hypoxic–ischemic brain injury by avoiding labor and vaginal delivery, the potential adverse impacts on the baby of unnecessary cesarean section are twofold: delayed and disrupted breastfeeding, and respiratory morbidity (transient tachypnea of the newborn or surfactant deficiency) (34–36). These impacts are worsened if caesarean section is unnecessarily early, and in turn they frequently result in avoidable admission to a neonatal unit and separation of mother and baby.

Table 24.3 Causes of perinatal mortality in the UK[8].

Cause of death*	Number (%) in enquiry ($n = 98$)	Number (%) in general population ($n = 5756$)	p value for difference
Unexplained	58 (59)	2516 (44)	0.002
Congenital anomaly	18 (18)	1087 (19)	0.68
Intrapartum causes	10 (10)	429 (8)	0.30
Prematurity	4 (4)	1027 (18)	<0.001
Infection	1 (1)	252 (4)	0.10

* Extended Wigglesworth classification (56).

Effects of Antenatal and Intrapartum Hypoxia–Ischemia

Hypoxia–ischemia is the combined pathology of impaired oxygenation of the blood and reduced perfusion (secondary to the effect of hypoxia on cardiac function). This is potentially damaging to all organ systems, and particularly the brain. The mechanisms by which intrauterine loss and neonatal complications occur secondary to hypoxia–ischemia are not fully understood (see Chapters 3 and 19). However, it is likely that macrosomia and obstructed labor contribute to intrapartum hypoxia–ischemia and increase the risk of neonatal complications.

Babies of diabetic mothers are more likely to require expert neonatal resuscitation than babies whose mothers do not have diabetes. This is one of the reasons why delivery of babies of diabetic mothers must occur in units where advanced neonatal life support is available. If a neonate has unexpected and severe complications of hypoxia–ischemia, he or she will require transfer to a neonatal unit that provides intensive care, including total body-cooling treatment as appropriate, if this is not available in the hospital of birth.

Relative cellular hypoxia causes increased erythropoietin secretion and in turn increased fetal red cell production (37). The resulting neonatal polycythemia may then cause excessive neonatal jaundice (as the red cell burden is lysed) and occasionally hyperviscosity syndrome. Renal vein thrombosis or thrombosis in other vessels is rare, but occurs more frequently in babies whose mothers have diabetes compared to those who do not.

Clinicians caring for these babies must be alert to these complications and test for them if there are abnormal clinical signs, such as irritability, lethargy, and poor feeding. The effects of polycythemia and hypoglycemia may be additive in terms of reduction of glucose delivery to the brain, and polycythemia associated with clinical signs, such as irritability or lethargy, must be treated with partial exchange transfusion, according to standard neonatal guidance.

Congenital Anomalies

It has long been recognized that there is a high incidence of congenital anomalies in pregnancies complicated by diabetes (38). Since the 1990s, rates have been 1.6–2.7 times higher than background rates and have not changed over time;causative factors include the teratogenic effect of hyperglycemia early in gestation prior to presentation for care (Table 24.1) (7,8,10–12,16,27,28,30–33). Rates in gestational diabetes are lower than with pre-gestational diabetes, but remain above background rates, probably due to cases of undiagnosed maternal type 2 diabetes or the independent effects of obesity on congenital anomaly rates (11,12,16).

The most common anomalies are congenital heart disease and anomalies of limb, the musculoskeletal system, or connective tissue (incidence: 0.7%) (8). Neural tube defects, although numerically rare, are 3.4 times more common than in the general population (8). The possible etiologies of these anomalies and strategies for their prevention are covered in Chapters 10 and 11.

The obstetrician and neonatologist must ensure that there has been adequate counseling of parents, involving the specialist team who will care for the baby postnatally, and ensure that delivery takes place at an appropriate center (dependent on the nature of the anomaly) to enable early access to specialist care. Routine postnatal echocardiography to screen for congenital heart anomalies is not indicated, unless an abnormality has been suspected on antenatal ultrasound scanning or the baby presents with clinical signs of congenital heart disease (25).

Macrosomia – Obstructed Labor, Birth Injury, and Organomegaly

Macrosomia and *large for gestational age* are not interchangeable terms. Strictly speaking, macrosomia (large organs) describes a baby who is heavier than his or her genetically determined birthweight, has the clinical appearance of a baby who has had truncal growth in excess of head growth, and may be

present in a baby of "normal" birthweight. Macrosomia and organomegaly attributed to fetal hyperinsulinemia are well-recognized characteristics of pregnancies complicated by diabetes (13,39). Babies born after diabetes in pregnancy are 1.8–5.2 times more likely than the background population to have a birthweight above the 90th centile (8,16,26,28). Recent UK data suggest some improvement over time (Table 24.1) (7).

The clinical significance of macrosomia pertains to the risk of complications presented by delivery of a large infant, such as shoulder dystocia, obstructed labor, perinatal hypoxia–ischemia, and birth injury (e.g., brachial plexus injury and fractured clavicle or humerus). Some complications, such as fractures, cause no long-term morbidity, but significant long-term neurodevelopmental morbidity may be associated with Erb's palsy and hypoxia–ischemia secondary to obstructed labor.

Parents and health professionals must be prepared for "catch down" in postnatal growth of macrosomic babies, especially when breastfed. This is a normal and healthy adaptation, and provided the baby appears to be feeding well and is healthy, there should be no concern if there is an initial period of slow weight gain such that weight trajectory crosses down the centile lines. Overfeeding and remaining overweight have long-term health consequences (e.g., a later risk of cardiovascular disease and diabetes). This is a further reason to promote and support breastfeeding, which protects against long-term metabolic disturbances (40,41).

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy, characterized by hypertrophied septal muscle that obstructs the left ventricular outflow tract, may be sufficiently severe to cause fetal or neonatal death (37). In less severe cases, the presentation is usually within the first weeks of postnatal life with cardiorespiratory distress and congestive heart failure. The majority of infants need supportive care only, as resolution of the signs can be expected in 2–4 weeks. The septal hypertrophy regresses within 2–12 months. Routine postnatal echocardiography is not required unless there are clinical signs of cardiac dysfunction (25).

Intrauterine Growth Restriction

Intrauterine fetal growth restriction, often associated with severe diabetic vasculopathy, may lead to further problems after birth. The small-for-gestational-age infant of the diabetic mother appears to be at even greater risk of adverse outcome than the baby who is normally grown or macrosomic, especially regarding neurodevelopmental sequelae (42). Often this is compounded by a requirement for preterm delivery. Delivery must be planned at an appropriate unit as specialist neonatal care is likely to be required.

Impaired Postnatal Metabolic Adaptation

With the cessation of placental nutrition at birth, the healthy newborn baby undergoes metabolic adaptation to ensure energy provision to vital organs. The infant of the diabetic mother is at risk of transient hyperinsulinism, which in turn causes a high rate of glucose uptake and conversion to fat, reduced hepatic glucose production, and reduced lipolysis and thus reduced production of ketone bodies, which are alternative fuels to glucose (Figure 24.1) (37,43). In the extreme, this will result in hypoketonemic hypoglycemia with markedly reduced fuel availability for the brain and other vital organs.

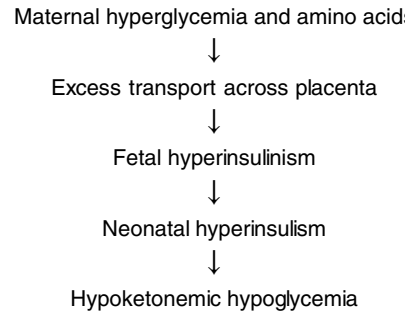

Figure 24.1 Impaired neonatal metabolic adaptation.

The ultimate concern is that of brain injury and long-term neurodevelopmental sequelae. Reviews of a number of published studies have suggested an association between the occurrence of neonatal hypoglycemia and adverse neurodevelopmental outcome, but none has been able to exclude other potentially confounding complications of maternal diabetes, which may also influence outcome (37,43). Although it is clear that untreated hypoglycemia of sufficient severity and duration to cause clinical signs may cause brain injury, there is no evidence that brain injury occurs in the absence of clinical signs (*asymptomatic hypoglycemia*). Clinical signs suggestive of (but not specific to) hypoglycemia are:

- Abnormal tone
- Abnormal level of consciousness
- Poor oral feeding
- Fits that may be atypical (e.g., presenting as apnea).

The purpose of clinical monitoring (see below) is to detect hypoglycemia at an early stage when it becomes clinically significant and to institute appropriate management (25,44).

Fortunately, very few babies develop clinically significant hypoglycemia associated with clinical signs. Reasons for this are likely to include standards of maternal diabetic control during pregnancy and labor (see Chapter 23), such that significant postnatal hyperinsulinism is uncommon due to the transient nature of hyperinsulinism, and early preventive management (discussed further in this chapter).

In the absence of a robust evidence base, recommendations in this chapter, in referenced texts written by clinical experts, and in the UK National Institutes for Health and Clinical Evidence (NICE) guidelines remain empirical, urging clinicians to individualize management for each baby and emphasizing the importance of careful clinical evaluation (Table 24.4) (25,37,43–46).

Table 24.4 Issues in the management of neonatal hypoglycemia.

- Poor maternal blood glucose control, especially prior to delivery, increases risk.
- CEMACH survey – accurate neonatal blood glucose monitoring method in only one-quarter of cases.
- Formula supplementation is likely to suppress metabolic adaptation.
- Formula feeding may increase risk of later obesity and metabolic disturbance.
- Unnecessary separation of mother and baby must be avoided.

Clinical Monitoring

Unless the baby has clinical complications sufficiently severe to require admission to a neonatal unit, mother and baby should remain together (25,47).

Those caring for the baby must regularly monitor the baby for feeding behavior and abnormal neurological signs, and must document their findings. Unless there are risk factors for other complications (e.g., infection) and as long as the baby appears well, it is not necessary to monitor vital signs (temperature, pulse, and respiration rate) or to screen for other potential complications (e.g., polycythemia) (25). If at any stage there are abnormal clinical signs, the blood glucose level must be measured, and an urgent pediatric review arranged.

It is generally accepted that infants of diabetic mothers should have regular blood glucose monitoring (25). Blood glucose monitoring must be by an accurate, laboratory-based method. No reagent strip with meter measurement has been demonstrated to be sufficiently accurate to diagnose or exclude neonatal hypoglycemia (45). The recommended standard is for immediate access to an accurate and quality-assured analyzer (25,29,43–45,48,49). However, UK data indicate that only around 25% of babies have blood glucose monitoring using accurate methods (8).

Blood glucose monitoring should be commenced at around 3–4 h of age. To commence it sooner than this is not informative, as babies experience a physiologic transitional fall in blood glucose level in the first hours after birth, often even in healthy babies,

to levels below 2.0 mmol/L (<36 mg/dL). Therefore, in an otherwise healthy baby, a low blood glucose level in the first 3–4 h after birth does not help to differentiate a baby who has significant but transient hyperinsulinism from a baby who is not affected by hyperinsulinism.

Blood glucose monitoring should be before the feed in order to detect a nadir in blood glucose level. In a baby with no clinical signs, a post-feed glucose level is not helpful and exposes the baby to excessive heel stabs.

If hyperinsulinism occurs, it will usually present in the first 1–2 days postnatally and will be transient, lasting a maximum of a few days. Therefore, if a baby is clinically stable and has shown no evidence of clinically significant hypoglycemia, blood glucose monitoring may be discontinued when laboratory-measured glucose levels are persistently above 2.0 mmol/L (>36 mg/dL), and in these circumstances discharge to community care from 24 h of age is appropriate if all else is well (Table 24.5) (25).

Clearly, babies who are preterm or unwell and admitted to neonatal units will undergo blood glucose monitoring as part of their clinical care.

Feeding

Breastfeeding is the method of choice for all babies (barring notable rare exceptions, e.g., maternal HIV infection). However, in a UK cohort, only 53% of mothers with diabetes intended to breastfeed, and at 28 days only 27% of term babies were breastfed (8). In a Canadian study, mothers with pre-gestational diabetes were 50% less likely to breastfeed in hospital than mothers without diabetes, even after controlling for confounders (50).

Mothers should be encouraged antenatally to consider breastfeeding and receive sufficient information regarding the benefits to make their choice. Immediately after delivery, a healthy baby should be placed skin-to-skin with mother and an early breastfeed offered, with assistance to ensure that the baby achieves an effective latch. Breastfeeds should be offered every 3–4 h (or more frequently if the baby demands), again with support if necessary.

Formula supplements to breastfeeds are required only if there are clinical indications, including intervention for hypoglycemia (see the "Operational thresholds for management" section). Formula supplements often result in reduced frequency of and hunger for breastfeeding, thus reducing breast milk supply and suppressing normal neonatal metabolic adaptation. Therefore, if formula supplementation is required, this must be of the volume required and no more. If a mother elects to formula feed, requirements are not usually in excess of 100 ml/kg/day, but volumes should be adjusted according to clinical monitoring. Finally, the potential long-term metabolic risks of overfeeding and obesity in infancy must be considered.

If a mother and baby are separated, or if the baby requires formula supplements to breastfeeding, the mother should be encouraged to express breast milk, which allows lactation to be sustained and provides breast milk that can be given to the baby.

Table 24.5 Practical aspects of neonatal blood glucose monitoring.

- Use an accurate laboratory-based method.
- Start at 3–4 h after birth.
- Measurements advised: approximately four hourly.
- Intervene if clinical signs (regardless of blood glucose level) or two consecutive glucose levels <2.0 mmol/L (<36 mg/dL).
- Stop monitoring when two consecutive levels >2.0 mmol/L (>36 mg/dL).

Operational Thresholds for Management

A low blood glucose level associated with clinical signs (as discussed in this chpater) must be treated. In the absence of abnormal clinical signs, recommendations for blood glucose thresholds at which to intervene must be pragmatic, and must balance the risks of developing clinically significant

hypoglycemia against the risks of disrupting breastfeeding and separating mother and baby. UK guidance advises that, in the absence of clinical signs, two consecutive (usually 2–4 h apart) blood glucose levels below 2.0 mmol/L (<36 mg/dL) at least 3–4 h after delivery require intervention to aim to raise the blood glucose level (25).

Management of Clinically Significant Hypoglycemia

Management of a low blood glucose level associated with abnormal clinical signs (as discussed here) is a medical emergency necessitating full clinical evaluation and transfer to a neonatal unit. If clinical signs are not severe (e.g., alert baby but poor suck), it is reasonable to assess the effect of tube feeds at an appropriate interval. However, if blood glucose levels do not increase with tube feeds or the baby has serious clinical signs (e.g., reduced level of consciousness or convulsions), intravenous glucose must be given without delay, starting at 5 mg/kg/min (equivalent to 3 ml/kg/h of 10% dextrose), but being aware of the possible need to increase this as necessary if indicated by frequent blood glucose monitoring (51). Intramuscular glucagon (200 µg/kg) is useful if there are clinical signs and a delay in achieving intravenous access, in that glycogen will be broken down to release glucose, but the effect will be transient, lasting less than 1 h.

Hypocalcemia and Hypomagnesemia

Transient neonatal hypocalcemia has been reported following diabetes in pregnancy, and both its incidence and severity appear to be related to maternal diabetes control (37). It is usually associated with hyperphosphatemia and occasionally with hypomagnesemia. The etiology is not entirely clear, but neonatal hypoparathyroidism has been demonstrated and may in part be secondary to maternal magnesium loss. Published studies and clinical experience indicate that hypocalcemia and hypomagnesemia are rarely of clinical significance, unless the baby has other complications (e.g., perinatal hypoxia–ischemia). Therefore, there is no indication to screen for them in the healthy baby. If associated with clinical signs, the deficits must be corrected, as recommended in standard neonatal textbooks.

Iatrogenic Complications

The timing and method of delivery often affect neonatal morbidity. Occasionally decisions are made on fetal grounds, but more often they are related to maternal complications. However, in a number of cases, there are no clear maternal or fetal reasons for preterm delivery or delivery by cesarean section, placing neonatal well-being at risk.

Even if there are no significant maternal or fetal complications and the pregnancy goes to term or near term, the evidence would suggest that the baby is still exposed to potential iatrogenic harm (Table 24.6). The UK CEMACH enquiry demonstrated frequent failings in medical and midwifery care that affected the baby's postnatal course and in particular establishment of feeding (8,29,44). These included:

- "Routine" admission of babies to neonatal units
- "Routine" supplementation or replacement of breastfeeds with formula
- Delayed "skin-to-skin" contact and first feed
- Poor management of temperature control

Table 24.6 Potentially avoidable adverse outcomes for the baby (8,29,44).

- 16% of preterm deliveries – no clear indication for induction or cesarean section
- 30% of preterm babies – no maternal steroids administered
- 5% of babies delivered with no intensive-care/high-dependency-care facility
- 25% of admitted term babies – reason given was "routine"
- 9% of babies who received formula – reason given was "routine"

- Testing of blood glucose with subsequent response to this too soon after delivery.

In addition to the harmful effects of these practices for mother and baby, they represent an avoidable use of neonatal unit resources.

Long-Term Outcomes

Studies of potential long-term neurodevelopmental sequelae in infants born to mothers with poorly controlled diabetes in pregnancy are inconsistent (37,43). However, studies of infants born to mothers with well-controlled diabetes in pregnancy show a favorable neurodevelopmental outcome (15). This is discussed in detail in Chapter 28. The risk of type 1 diabetes developing by the age of 20 years in the offspring of diabetic women is at least seven times that for nondiabetic mothers (lower than the risk if it is the father who has type 1 diabetes) (37). However, there is controversy regarding the etiology of long-term metabolic sequelae of pre-gestational and gestational diabetes (52–55).

Summary – Minimizing Risk

The findings from many published studies have reinforced recommendations for good practice, as these are associated with a reduction in postnatal complications and iatrogenic harm (Table 24.7) (25). All hospitals must have written protocols for the prevention and management of potential neonatal complications and for admission to the neonatal unit to minimize both clinical risk and iatrogenic harm.

Table 24.7 Key points for good practice to prevent neonatal complications.

- Antenatal counseling by experienced clinicians if complications are expected.
- Written policies and guidelines for delivery and postnatal management.
- Avoid unnecessary preterm delivery and/or cesarean section.
- Give maternal steroids if preterm delivery anticipated, anticipating that close observation and management of maternal glycemic control will be required.
- Plan delivery where appropriate neonatal expertise is available.
- Encourage breastfeeding as a method of choice; do not give formula to a breastfed baby unless clinically indicated.
- Offer early feed and skin-to-skin contact.
- Commence blood glucose monitoring, using an accurate method, at 3–4 h after birth.
- Do not treat for hypoglycemia unless two consecutive blood glucose levels are <2.0 mmol/L (<36 mg/dL) or there are clinical signs of hypoglycemia.
- Do not screen for other potential complications unless there are clinical signs.
- Keep mother and baby together unless there is a clinical indication for admission of baby to a neonatal unit.
- Advise mother and primary care health professionals of the normal pattern of "catch-down" growth in a macrosomic baby.

Multiple-Choice Questions

1 Perinatal mortality rates in pregnancy complicated by diabetes (*choose as many as apply*):
   - **A** with improved management of diabetes have fallen to the normal population rate.
   - **B** have not improved, in terms of both stillbirth and neonatal death being higher than the normal population rate.
   - **C** have intrapartum complication as a major underlying cause.
   - **D** have a congenital anomaly as a major underlying cause.
   - **E** can be influenced by pre-conceptional care.

Answer: B, C, D, and E.

2 For the baby born at full term after diabetes in pregnancy (*choose as many as apply*):
- **A** staff skilled in advanced resuscitation of the newborn must be present on site.
- **B** the baby should be admitted to a neonatal unit.
- **C** blood glucose monitoring should be commenced 3–4 h after birth.
- **D** exclusive breastfeeding is contraindicated.
- **E** postnatal echocardiography should be performed.

Answer: A and C.

3 Complications of fetal hypoxia–ischemia include which of the following? (*Choose as many as apply.*)
- **A** Polycythemia
- **B** Macrosomia
- **C** Hypocalcemia
- **D** Encephalopathy
- **E** Stillbirth

Answer: A, D, and E.

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25

Postpartum Contraception for Women with Diabetes

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PRACTICE POINTS

- It is important for women with diabetes to leave suitable time intervals between pregnancies. This approach allows women with gestational diabetes mellitus (GDM) the opportunity to reduce their risk factors for recurrence in subsequent pregnancies. Women with diabetes before pregnancy need time to achieve tight glucose control preconceptionally to reduce risks of congenital anomalies and stillbirth.
- Breastfeeding is beneficial for both the mother and newborn and also facilitates postpartum weight loss. Given that relatively few women continue with breastfeeding for months, it is also important to provide breastfeeding women with the most effective contraceptive methods that will not interfere with lactation.
- Women with pre-gestational diabetes or a history of GDM need safe and effective contraception that has minimal adverse effects on weight, blood pressure, insulin resistance, or lipids. Implants and intrauterine devices (IUDs) are first-choice options because they are the most effective and meet those criteria.
- Both the World Health Organization (WHO) and the US Centers for Disease Control and Prevention (CDC) Medical Eligibility Criteria (MEC) agree that gestational diabetes per se should not influence the choice of contraceptive methods; all methods are rated category 1, except in the immediate postpartum period when estrogen-containing methods should be avoided. The presence of comorbidities (e.g., obesity, hypertension, cardiovascular disease, and depression) needs to be considered when selecting safe options.
- Ovulation usually returns between 25 and 39 days postpartum, and coital activity generally resumes before the traditional 6-week postpartum visit. Immediate postpartum provision of safe and effective contraceptive methods is becoming the gold standard, so contraception must be discussed during prenatal care and reinforced after delivery and before discharge. Among the things women should consider when selecting a delivery hospital, such as the need for neonatal facilities and available labor anesthesia, is the availability of tubal ligation, IUDs, and implants postpartum.

Case History

A 26-year-old woman who is at 33 weeks gestational age was diagnosed with gestational diabetes mellitus (GDM) at 29 weeks. Her pre-pregnancy Body Mass Index (BMI) was 34 kg/m^2; up until this point in her pregnancy, she has gained 35 lbs. Her past obstetric history includes a miscarriage at 7 weeks gestation. Serial ultrasound measurements have suggested the development of fetal macrosomia. She is currently being evaluated for medical therapy since her home capillary glucose readings remain elevated despite diet and exercise.

A Practical Manual of Diabetes in Pregnancy, Second Edition. Edited by David R. McCance, Michael Maresh and David A. Sacks.

She became pregnant once while using oral contraceptives and once while relying on male condoms. She is convinced that she will not have to think about family planning for several months after delivery since she and her husband will be so busy with the new baby.

- When is the best time to provide contraceptive advice to women with diabetes or GDM?
- When is the optimal time to initiate contraception postpartum?
- Are there any contraceptive methods that are contraindicated in the postpartum period?
- Will any of the methods adversely affect follow-up glucose testing at 6 weeks for women with GDM?
- Do some methods work less well in women with BMI >30 kg/m^2?
- Which methods should be avoided in women who are exclusively breastfeeding their babies? How long should those methods be avoided?
- If she has not completed her family, when is the best time for our patient to conceive her next pregnancy?
- What goals should she try to achieve prior to her next pregnancy?
- What (if any) methods might make achieving those goals more difficult?
- Which would be more hazardous to this young woman's health: another pregnancy or any method of contraception for which she is medically eligible?
- What if she had completed her family? Which options would you offer her?
- What contraceptive methods would you recommend if she were found to have had pre-gestational diabetes?

Background

The optimal interval between pregnancies in the general population has traditionally been judged to be 18–24 months (1). However, one-third of all repeat pregnancies in the USA are conceived within 18 months of the prior birth (2). Short interpregnancy intervals may have negative impacts on the growth of both the existing infant and the new fetus. For women with pre-gestational diabetes and gestational diabetes mellitus (GDM), the risks of a short pregnancy interval are even greater. In women with GDM, the GDM recurrence rate may be as high as 85% if the interpregnancy interval is less than 12 months (3).

Unintended pregnancy rates in the USA have continued at high levels in the last two decades despite the introduction of safe and effective contraception; a recent estimate is that 45% of US pregnancies are unintended (4). Rates are highest among women with low income or education and those who are single – most of which are also risk factors for GDM.

Although the remaining 55% of US pregnancies are classified as "intended," that does not mean that they were planned and prepared for, only that at the time those women conceived, they were not opposed to becoming pregnant. Earlier chapters in this volume have demonstrated the importance of tight glucose control prior to conception for women with pre-gestational diabetes and the minimization of risk factors for GDM in women about to conceive. Since 2.2% of US births are to women with pre-gestational diabetes (type 1 or type 2), universal preconception care that includes optimal glycemic control could avert 8397 preterm deliveries, birth defects in 3725 newborns, and 1872 prenatal deaths each year. The discounted lifetime costs avoided would total $4.3 billion (5). The identification of previously undiagnosed diabetes through preconception care would save an additional $1.2 billion (5). In order to prepare for pregnancy, sexually active women must have the ability to control their fertility. Providing effective and safe contraception should be a top priority.

Pregnant women with pre-gestational diabetes and those with GDM share many important considerations that need to be addressed when selecting a method of contraception to be provided postpartum.

- The method should be effective; an accidental pregnancy in this patient population is associated with a several-fold increased risk of adverse maternal and fetal outcomes.

- The contraceptive method should not significantly affect insulin sensitivity or glucose metabolism. Importantly, in the immediate postpartum period, women who have GDM must avoid using anything that might adversely affect postpartum tests of glucose metabolism.
- Contraception should not interfere with breastfeeding or increase the risk of postpartum depressive disorders.
- The method should be convenient to use.
- The method must also be safe to use in the presence of existing comorbidities (e.g., obesity, hypertension, and depression).
- The contraceptive method should not increase long-term cardiovascular risk factors, such as those associated with metabolic syndrome, or diabetic complications.

Important Contraceptive Safety Considerations in Women With Diabetes

The WHO and the US CDC's MEC (see Table 25.1) agree that virtually all methods of contraception can be offered to women with GDM or pre-gestational diabetes (6,7). The main exception is estrogen-containing methods, which should be avoided in women with diabetic complications including retinopathy, nephropathy, or cardiovascular disease. Women with diabetes also need assurance that none of the contraceptive methods being offered will accelerate the development of those conditions (8). For women with GDM, it is also important to consider the impact that a method might have on their progression to overt diabetes.

Often, women with pre-gestational diabetes or GDM have comorbidities, such as obesity, metabolic syndrome, or hypertension, which must be taken into consideration when a contraceptive method is being prescribed (9,10). The preference is to use a method that does not contribute to weight gain or to any of the risks posed by high Body Mass Index (BMI), such as venous or arterial thrombosis. To date, there is no conclusive evidence that combined hormonal contraception (COC) induces any significant metabolic changes in women who have diabetes (11–13). For women who have a history of GDM, a repeat pregnancy is more likely to cause subsequent overt diabetes than is the use of COC (14,18).

Efficacy

The second feature to consider is how important fertility control is to the woman. There are three different measures of contraceptive efficacy: first-year failure rates with correct and consistent method use, total failure rates from clinical trials, and first-year failure rates in typical use (see Table 25.2). In the USA, the estimates of typical-use failure rates are derived from periodic surveys called the National Survey of Family Growth. The gap between the estimates of failure rates with correct and consistent use and those found in typical use (Table 25.2) represents human factors and system barriers blocking access to contraception (15). For example, male condoms should have only a 2% failure rate if used correctly with each act of intercourse, but in the real world, the first-year pregnancy rate is 13%. When counseling women, clinicians should quote the failure rates in typical use, but can try to motivate correct contraceptive use by letting patients know the lower estimate with perfect use. The only reversible methods that reliably provide pregnancy protection equivalent to permanent contraception are IUDs and implants. For women who are confident that their family is complete, it is reasonable to offer permanent contraception (e.g., vasectomy or tubal sterilization with ligation, occlusion, or salpingectomy).

Promotion of Breastfeeding

Breastfeeding has many benefits, including greater loss of maternal weight postpartum and a modest improvement in glucose metabolism (16,17). Some evidence suggests that breastfeeding for at least 3 months reduces the future risk of type 2 diabetes

Table 25.1 2016 US medical eligibility criteria for contraceptive use with diabetes and select comorbidities.

Condition	Subcondition	Cu-IUD	LNG-IUD	Implant	DMPA	POP	CHC
Diabetes	a) History of gestational disease	1	1	1	1	1	1
	b) Nonvascular disease						
	i) Non-insulin dependent	1	2	2	2	2	2
	ii) Insulin dependent	1	2	2	2	2	2
	c) Nephropathy, retinopathy, or neuropathy*	1	2	2	3	2	3/4**
	d) Other vascular disease or diabetes of >20 years' duration*	1	2	2	3	2	3/4**
Hypertension	a) Adequately controlled hypertension	1**	1**	1**	2**	1**	3**
	b) Elevated blood pressure levels (*properly taken measurements*)						
	i) Systolic 140–159 or diastolic 90–99	1**	1**	1**	2**	1**	3**
	ii) Systolic ≥160 or diastolic ≥100*	1**	2**	2**	3**	2**	4**
	c) Vascular disease	1**	2**	2**	3**	2**	4**
Multiple risk factors for atherosclerotic cardiovascular disease	(e.g., older age, smoking, diabetes, hypertension, low HDL, high LDL, or high triglyceride levels)	1	2	2**	3**	2**	
Obesity	a) Body Mass Index (BMI) ≥30 kg/m^2	1	1	1	1	1	2
	b) Menarche to <18 years and BMI ≥30 kg/m^2	1	1	1	2	1	2

1 = No restriction (method can be used); 2 = advantages generally outweigh theoretical or proven risks; 3 = theoretical or proven risks usually outweigh the advantages; 4 = unacceptable health risk (method not to be used); CHC = combined hormonal contraception (pill, patch, and, ring); Cu-IUD = copper-containing intrauterine device; DMPA = depot medroxyprogesterone acetate; LNG-IUD = levonorgestrel-releasing intrauterine device; POP = progestin-only pill.

* Condition that exposes a woman to increased risk as a result of pregnancy.

** See the complete guidance for a clarification to this classification: www.cdc.gov/reproductivehealth/unintendedpregnancy/USMEC.htm. Complete summary available at: https://www.cdc.gov/reproductivehealth/unintendedpregnancy/pdf/legal_summary-chart_english_final_tag508.pdf

Table 25.2 First-year failure rates.

	Women experiencing an unintended pregnancy within the first year of use (%)	
Method	**Perfect use**	**Typical use**
No method	85	85
Spermicides	16	21
Fertility awareness–based methods		15
Withdrawal	4	20
Sponge	12	17
Condom		
Female	5	21
Male	2	13
Diaphragm with spermicide	16	17
Combined pill and progestin-only pill	0.3	7
Evra patch, NuvaRing (assumed)	0.3	7
Depo-Provera (DMPA)	0.2	4
Intrauterine contraceptives		
ParaGard (copper T)	0.6	0.8
Mirena (LNG)	0.5	0.5
ENG implant	0.01	0.01
Female sterilization	0.5	0.5
Male sterilization	0.10	0.15

Adopted from Sundaram A, Vaughan B, Kost K, *et al*. Contraceptive failure in the United States: estimates from the 2006–2010 national survey of family growth. Perspect Sex Reprod Health 2017;49(1):7–16.

among women with GDM (18,19). By itself, lactational amenorrhea provides a good protection against unplanned pregnancies for the first 6 months postpartum (2% failure rate) because bleeding generally precedes resumption of ovulation. After this time, a second method is needed because ovulation returns without warning, generally before the first menses. However, since most women stop breastfeeding within weeks of delivery (20), it is important to provide breastfeeding women with early contraception.

Traditionally, there has been a concern about the use of hormonal methods when the new mother is trying to establish lactation. Since it is the drop in circulating progesterone levels postpartum that stimulates milk production, theoretically, progestin methods given too soon after delivery could reduce milk production. Fortunately, several large-scale studies have provided reassurance about the neutrality of early progestin contraceptive use on breast milk production, breastfeeding continuation, and infant growth (20–23).

Timing of Contraceptive Initiation

The preferred approach promoted by the CDC and WHO is to provide a woman with the most effective method she desires and for which she is eligible on the day she presents, as long as the clinician is reasonably confident that she is not pregnant (24). The same

urgency needs to be applied during the postpartum period. Several factors have led to the growing opinion that the initiation of contraception should occur before the woman is discharged home from the hospital. First is the recognition that resumption of both ovulation and sexual activity occurs much earlier than previously estimated; overall, 25% of women ovulate between 25 and 39 days postpartum (25). Younger women have more rapid return to fertility than older woman (26). Second is the appreciation that many women do not keep their postpartum appointments and even if they do attend, many do not have any access to the most effective methods for a number of financial or systemic reasons. In one study from New Mexico, only 60% of women who requested an IUD actually received one before they left the system; one of the most frequent reasons for not getting an IUD was a repeat pregnancy (27). Immediate postpartum initiation of contraception requires that counseling be provided during prenatal care and all relevant consents can be obtained before onset of labor.

The American Congress of Obstetricians and Gynecologists (ACOG) has noted with some alarm that many women who seek permanent contraception postpartum are not provided with it. Failure to provide permanent contraception results when the delivery hospital does not provide these services. There are also difficulties in obtaining informed consent (28) and in delivering it to the surgeon in the hospital (36). Other failures relate to delays, lack of access to surgical resources, and the lack of priority for what is seen as an elective procedure. In one study, only 45 of 89 women who desired tubal ligation actually received those procedures as planned (29). Women who did not receive the postpartum tubal ligation they had requested were twice as likely to get pregnant within 12 months compared with a control group matched for postpartum visit attendance (46.7% vs. 22.3%) (30). ACOG recommends that postpartum tubal ligation should be considered an urgent surgical procedure (31).

Several studies have demonstrated the safety and efficacy of immediate (within 10 min of delivery of the placenta) postpartum placement of IUDs (32–35). The only conditions that preclude such placement are postpartum hemorrhage, chorioamnionitis/endometritis, or risk factors for such infection (7). Placement following a vaginal delivery requires instruments that can extend into the endometrial cavity, perhaps under ultrasound guidance. Placement of IUDs at the time of cesarean section is more straightforward (36). An additional monofilament suture material should be tied onto the IUD tailstrings to ensure that the tailstrings are available in the vagina should IUD removal be needed at any time (37). Expulsion rates are higher when IUDs are placed immediately following vaginal delivery compared to placement following uterine complete involution about 6–8 weeks postpartum, and range from 3 to 24%, but these rates are lower when placed at the time of elective cesarean delivery (33). Continuation rates at 1 year generally average 75% (33).

The hormonal contraceptive implant is an excellent choice for placement prior to hospital discharge and is technically more straightforward than IUDs. There is no urgency to place the implant immediately at the time of delivery, which means that uncounseled women have additional opportunity to consider this option. Postpartum implant placement does not increase expulsion rates with the implant (as seen with IUDs) or requests for early removal for bleeding (38). First-year continuation rates are over 85% (39) and are highest among women at highest risk for rapid repeat unintended pregnancies (38,40). Breastfeeding women who were randomized to receive etonogestrel implants 3–4 days postpartum had no differences in lactation failure, milk composition, volume, or infant growth compared to women whose implants were placed at 6–8 weeks (23,41).

Contraceptive Options by Method

Permanent Contraception

Vasectomy is the safest and one of the most effective methods of permanent contraception. Worldwide, less than 3% of married women (33 million total) of reproductive age rely on their partner's vasectomy. But there is a wide discrepancy in those rates: 10–15% of married couples in Canada, the US, China, and parts of Europe use vasectomy, but rates are lower in other parts of the world (42,43). In many situations, techniques such as the no-scalpel vasectomy permit the procedure to be easily performed in an office setting under local anesthesia. In a recent summary of published studies, average operational time was reported to be 8–20 min for incisions that were 5.0–8.4 mm long and with complication rates in the range of 0.67–5%, with the most common complications being hematoma and infection (44).

Partners of pregnant women with diabetes will often want to wait until after delivery to undergo vasectomy. Given that couples will not be able to rely on vasectomy for at least 3 months following the procedure, the woman should be offered a short-term bridging method, such as progestin-only injections or progestin-only pills, to use during that time.

On the other hand, permanent contraception for women (either hysterectomy or tubal ligation procedures) is the most common method used by older (>30 years) women in the USA. There are many methods used to interrupt the fallopian tubes. The most common techniques used postpartum involve elevating a section of the fallopian tube with an atraumatic clamp, placing rapidly absorbable sutures around the base, and cutting off the tied portion of the tube. There are variations to this procedure that individually tie off the two cut ends of the tube or place one end of the interrupted tube into a different compartment than the other (retroperitoneal or below the uterine serosa). Tubal ligation can be performed easily at the time of cesarean delivery or through a small infraumbilical incision shortly after a vaginal delivery. Other procedures are performed as interval procedures at a time when the patient is remote from pregnancy. In general, the two different approaches used are categorized by the approach used to reach the fallopian tubes – laparoscopic procedures and hysteroscopic procedures. With laparoscopic procedures, the patient is given regional or general anesthesia; through small abdominal incisions, each of the tubes is interrupted with either sutures or a variety of clamps. Those methods provide contraception immediately, but do carry the risks and costs associated with anesthesia. With the hysteroscopic procedures, patients generally only need intravenous pain medications. Coils filled with irritating polyethylene terephthalate (PET) fluids, which cause an inflammatory response, are placed in the proximal portion of each fallopian tube. With time, the PET fibers induce fibrosis, which osculates the tubes. Until occlusion is complete, the couple needs to use contraception. Generally, a second test (ultrasound or fluoroscopy) is performed at 3 months to document complete tubal occlusion.

With new understanding that the most aggressive form of epithelial ovarian cancer – serous adenocarcinoma – arises from within the fallopian tube, many have suggested that salpingectomy would be preferable to small tubal interruption procedures, particularly for women at risk for ovarian cancer. This recommendation would be easiest to adopt if procedures were to be done at the time of an uncomplicated cesarean delivery. As more evidence about the feasibility, safety, and long-term benefits and risks accumulates, the frequency with which these different techniques are used may change (45,46).

It is important to remember that a significant number of women (>10%) later regret their decision for permanent contraception. Now that the equivalent pregnancy protection can be provided by reversible methods, many

of which offer other important noncontraception benefits, there might be fewer women seeking tubal procedures.

Contraceptive Implants

Contraceptive implants are excellent choices for women with diabetes or prior GDM (47). In the USA, only the single-rod, 3-year etonogestrel (ENG) implant (Nexplanon) is available, but internationally other implant systems are available, including a one-rod, 3-year system (Implanon), and two-rod, 5-year systems with levonorgestrel (Jadelle/Norplant II and Sino II). All share extraordinarily low first-year failure rates (0–0.38%) and virtually no medical contraindications to their use. Obesity does not diminish the efficacy of the method (48). Very little specialized training is needed for placement, although all US providers offering implants must be certified at an FDA-approved, company-sponsored training session. Removal of correctly placed implants is also easy, but removal of deep implants may require additional support or training. Implants are ideal for busy practices, such as primary care clinicians; placement of the implant itself takes 30 s. The mechanism of action of the ENG implant is appealing to the many of the women who are not willing to accept a method that might have a post-fertilization action because the implant suppresses ovulation in 100% of women for 30 months (49). Thickening of cervical mucus prevents sperm entry into the upper genital tract with all implants throughout the approved effective life. Small-scale studies have demonstrated that there were no pregnancies during the fourth year of implant use (50). *Implants have higher failure rates when used with drugs that induce increased metabolism of progestin via the cytochrome P_{450} system.* These drugs include some antiepileptic drugs, rifampicin, and St. John's wort. As a progestin-only method, the implant may slow uterine involution and usually prolongs the duration of lochia. As mentioned, implants have no adverse impact on breast milk composition or breastfeeding patterns and only minor, insignificant impacts on insulin resistance, glucose metabolism, hemostasis, or lipid levels (51). About one-third of women will have satisfactory menstrual bleeding patterns established in the first 3 months; another one-third will do so by 6 months. Only 14% of women requested implant removal for bleeding disturbances during clinical trials in the USA (52).

Intrauterine Devices

There are two major groups of IUDs currently available in the USA: levonorgestrel (LNG)-releasing IUDs and copper IUDs. Elsewhere in the world, there are other copper-bearing IUDs (200–380 mm^2 copper-containing T-shaped devices) and some unmedicated plastic devices (Lippes Loops, Safe-T-coils, etc.). Among the copper IUDs, the Copper T380A is the most effective and can be placed immediately postpartum (53). However, product labeling for the LNG-IUDs advises delayed placement at least 6 weeks postpartum. Recent studies demonstrate that the risk of IUD perforation is around 1/800–1000 placements; the risk is sixfold higher in breastfeeding women (54).

Both the copper T-380A and the LNG-IUSs have first-year failure rates of less than 1%; efficacy is not affected by the woman's BMI. IUD choice depends upon the patient's preferences for bleeding patterns. The LNG-IUS 20 mcg/24 h IUDs offer increasing amenorrhea over time after a transition period of increased spotting and bleeding. The LNG-IUS 8 mcg has lower circulating levels of progestin and has much lower rates of amenorrhea (13% at 3 years). The LNG-IUS 12 mcg has an intermediate dose, 5 years of pregnancy protection, and an amenorrhea rate of 23% at 5 years. The copper IUD generally increases menstrual blood loss by 30–50%, and it is particularly appealing to women with light to normal menses who wish to maintain monthly bleeding and those who cannot or do not want to use any exogenous hormones.

In a randomized trial, the higher dose LNG-IUS had no adverse effect on glucose metabolism in women with type 1 diabetes (55). Similarly, no adverse effects on glucose tolerance were seen over time in a study that compared women with recent GDM given LNG-IUS to women given nonhormonal methods (56). Continuation rates at 12 months for women using the LNG-IUS (86.7%) were the same as for those using the copper IUD (90.3%). Given their safety and efficacy, IUDs are considered to be one of the best methods of contraception for both women with diabetes and those who had GDM (47), but they should be placed only by practitioners who are skilled with conducting pelvic examinations and pelvic procedures.

Progestin-only Injections

Worldwide, the two most common progestin-only injections are depot medroxyprogesterone acetate (DMPA) 150 mg intramuscularly every 11–13 weeks and norethisterone acetate (NETA) 200 mg intramuscularly every 60 days. A lower dose subcutaneous injection (DMPA-SQ 104 mg) is also available for use every 12–14 weeks, but it is infrequently utilized. Only 6% of women using contraception in the USA are on DMPA at this time, but in some sub-Saharan countries, over one-third of women who use contraception rely on progestin-only injections. Of all contraceptive methods, DMPA has the most profound impact on glucose metabolism and insulin resistance due to its high doses. In some women, DMPA may increase body weight or truncal fat deposition (57). In some studies in high-risk populations, such as Hispanic women with a history of GDM, progestin-only methods were associated with subsequent marginally increased risk for development of diabetes, especially among women who breastfed and those who gained weight (58). However, progestin-only injections can be effective as immediate postpartum contraception to bridge the gap before the adoption of more effective methods. Some studies have demonstrated a slight adverse impact on lactation, but the evidence is not consistent. DMPA does not increase the risk of postpartum depression (59). Adverse impacts reported earlier on bone mineralization are now known to be reversible and should not influence injection initiation or longer term use (60). In fact, progestin-only contraception has been shown to prevent bone loss in postpartum breastfeeding women (61).

Combination Hormonal Methods

Oral contraceptives remain the most commonly used reversible method in the USA. Longer term delivery systems have been introduced (transdermal patches and vaginal rings) to increase convenience. Internationally, once-a-month estrogen-containing injections are also available to provide predictable bleeding. In a recent review, it was reported that there was no deterioration in glycemic control or the course of microvascular disease in women with uncomplicated diabetes, although the data are sparse (62). However, because of thromboembolism risks, estrogen-containing methods should be avoided altogether in women with diabetes complicated by cardiovascular disease or severe microvascular disease (nephropathy with proteinuria or proliferative retinopathy).

Estrogen-containing methods may be started as early as 21 days postpartum in women without risk factors for hypercoagulability, such as obesity, cesarean delivery, preeclampsia, excessive blood loss, transfusion, or limited mobility. Women with any of these risk factors, but who are otherwise eligible for combined hormonal contraceptives, should delay their initiation until 42 days after delivery (30). Recent studies have demonstrated that breastfeeding women who started using low-dose combined hormonal methods as early as 3 weeks postpartum had no adverse effects on their lactation (63).

For a woman with multiple medical problems, it is prudent to consult the WHO and US CDC's MEC to rule out any category 4 condition and to consider the totality of her

category 3 conditions in the context of her other contraceptive options (Table 25.1). Earlier observations reported that women with BMI >30 kg/m^2 had higher failure rates with oral contraceptives and vaginal rings than women with lower BMIs did. More recent studies have found that those higher failure rates may be explained by the fact that obese women were more likely not to use their method as consistently; the association with obesity is probably explained by social-economic factors, such as poverty, rather than biologic reasons (64).

Barrier and Behavioral Methods

Historically, these methods were often recommended as first-line options for women with medical problems because they presented no apparent risks and some offered important noncontraceptive benefits (e.g., condoms reduce the risk of sexually transmitted infections [STIs]). However, in view of their comparatively high failure rates in typical use (see Table 25.2), today these methods are offered for contraception only to women who cannot or will not use other more effective methods. However, barriers (particularly condoms) can be added to virtually every other method for HIV and STI protection.

Most of these methods have the benefit of being available over the counter. In Europe, the single-size diaphragm used with spermicide is available without a prescription. The female contraceptive cap (Femcap®) is easily sized on the basis of a woman's obstetrical history (never pregnant, no vaginal deliveries, or vaginal deliveries) and is used with a small amount of spermicidal gel in the bowl of the cap. Female condoms are available in a variety of materials and shapes around the world. Typically, the failure rates are higher with female condoms than with male condoms, but they provide an important benefit when the partner cannot or will not use a male condom. Spermicidal foam and sponges are instantly effective, but spermicidal film and suppositories require 10–15 min to melt and coat the cervix.

Coitus interruptus is always available should a couple not have other protection, and in typical use it is only slightly less effective than the female barrier methods. Fertility awareness methods help women calculate their at-risk days so that they can use abstinence or some other method during that time. The older "rhythm method" has been replaced by computer apps and products (cycle beads and fertility calendars) that more easily calculate at-risk days, and by low-tech approaches such as the 2-day method. In the last method, all a woman has to do is to touch her introitus each day to see if she is dry (no secretions). If she is dry for two consecutive days, the risk of pregnancy is low and intercourse is permitted.

Emergency Contraception (EC)

The most effective form of EC is placement of a copper IUD within 5 days of unprotected intercourse. This reduces the risk of pregnancy to about 1 in 800–1000 placements. Hormonal EC is available either over the counter or by prescription with 1.5 mg LNG for use up to 3 days following the exposure. The LNG-EC tablet is most effective if taken within the first 12 h (0.5% chance of pregnancy); the pregnancy risk rises rapidly thereafter, rising up to 4% at the 72nd hour. It is markedly less effective in women with higher BMIs. The Ulipristal acetate (UPA) 30 mg EC tablet is more effective at every point in time than the LNG-EC and retains more effectiveness in overweight and obese women (65). UPA can be used anytime within 5 days of exposure with no decrease in effectiveness over time. Initiation of hormonal contraception following use of UPA should be delayed until 5 days after the last episode of unprotected intercourse to permit all the sperm to die.

Case Follow-Up

Returning to our patient in this chapter's Case History, given her failure with other contraceptive methods, and the complications

she has faced during the present pregnancy, it would be best to discuss contraception with her prior to labor. She should be strongly urged to breastfeed exclusively. Her intention to use abstinence should be acknowledged, but she should be advised that frequently abstinence plans are often not fulfilled. In light of her previous experience, it is important to inform her that the failure rate of the oral contraceptive pill is 21 times higher than that of the implant or IUD (66).

An implant would also be an excellent choice for her and could be provided anytime during her hospitalization. If she has an elective cesarean for her large fetus, an IUD could easily be placed intraoperatively, with a slightly increased but generally low risk of expulsion. If a vaginal delivery is anticipated, plans can be made for post-placental placement. In countries with insurance-based systems, if her insurance does not cover inpatient contraception, she could be seen in a hospital outpatient clinic for an implant (not IUD) placement after discharge and before she leaves the hospital grounds. If none of these options is available, she should be provided with a bridge method. Short-term use of progestin-only pills is a very safe bridge method until she is seen postpartum. DMPA injections are much more convenient for busy new mothers, but in women with GDM if a 6-week glucose tolerance test is being performed, the results may be affected, especially for women near the threshold of overt diabetes. Combined hormonal methods would not be an option for at least 6 weeks following delivery in this patient, because her BMI is over 30 kg/m^2. Barrier methods are a poor third choice, and should always be accompanied by an offer of EC. Because she has not completed her family, permanent contraceptive methods would not be appropriate. For her long-term health, weight loss through diet and regular exercise will be needed. She should also prepare more completely for her next pregnancy, and that pregnancy should not occur sooner than 18 months.

Future Directions

Many new contraceptive methods are under development, including new longer acting implants, copper IUDs with less bleeding, contraceptive patches with lower estrogen exposure, new easier-to-use male and female condoms, new spermicides, and perhaps implantable chips to provide long-term hormonal contraception. However, even if the most effective and safe methods of contraception become available, women will still need to be motivated to use them. Many women today are not aware of the health risks of pregnancy and the need to optimize their health before conceiving. We need to change the prevailing belief from "Pregnancy just happens" to "We're really ready." The latter may prove much more challenging than the development of new contraceptive methods themselves.

Multiple-Choice Questions

1 Which is the most effective contraceptive option with the fewest medical contraindications for a woman with diabetes?
- **A** Copper IUD
- **B** Levonorgestrel IUS
- **C** Implant
- **D** DMPA injections

Answer: The correct answer is C.

2 Progestins may be concerning for use in women with diabetes because they can:
- **A** increase risk of venous thromboembolism.
- **B** increase risk of endometrial carcinoma.
- **C** increase risk of anemia.
- **D** increase insulin resistance.

Answer: The correct answer is D.

3 IUDs primarily work by which of the following mechanisms?
- A Blocking implantation
- B Preventing fertilization
- C Destroying the fertilized ovum
- D Ovulation suppression

Answer: The correct answer is B.

4 For women who desire to breastfeed their newborns, initiation of progestin-only methods prior to discharge home following delivery:
- A is unnecessary because with lactational amenorrhea, the pregnancy rate is about 2% for the first 6 months.
- B is to be discouraged because it will decrease her chances of establishing lactation.
- C is to be discouraged because the woman will have less incentive to breastfeed.
- D should be offered because many women stop breastfeeding or do not return for postpartum care.

Answer: The correct answer is D.

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Breastfeeding and Diabetes

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PRACTICE POINTS

- The prevalence of breastfeeding in women with type 1 and 2 diabetes prior to pregnancy and with gestational diabetes mellitus (GDM) needs to be ascertained.
- Pregnant women with diabetes should be made aware of the special challenges they and their neonate/infant may experience when initiating and establishing breastfeeding.
- Healthcare professionals should be aware of the effects diabetes can have on lactogenesis, so appropriate advice and reassurance can be given to the woman and her family by appropriately trained healthcare professionals.
- Antenatal harvesting of colostrum for the treatment of neonatal hypoglycemia, if the neonate is unable to breastfeed, should be taught to women who intend to breastfeed.
- Skin-to-skin contact within one hour of birth should be encouraged.
- Separation of the mother and her neonate should be avoided whenever possible.
- Explanation of the short-term benefits to the mother with diabetes and her infant should be given.
- The long-term benefits to the mother with diabetes and her offspring should be emphasized throughout pregnancy and post birth.

Pitfalls

- *Antenatal period*: Failing to give women and their families evidenced-based unbiased information related to the benefits of breastfeeding. For those women who have decided to breastfeed, not instructing them on how to express and store colostrum.
- *Care at birth*: Separating the mother and infant and not giving skin-to-skin contact as early as possible for a minimum of one hour.
- *Post birth*: Not initiating breastfeeding within one hour of birth. If treatment for neonatal hypoglycemia is required, supplementing with formula milk instead of breast milk or, if available, antenatal harvested colostrum.

A Practical Manual of Diabetes in Pregnancy, Second Edition. Edited by David R. McCance, Michael Maresh and David A. Sacks.

Case History

Sally and her partner attended the antenatal clinic following a positive pregnancy test that confirmed that she was 8 weeks pregnant. Sally was 21 years old and had a 5-year history of type 1 diabetes.

A full medical and reproductive history was taken and biochemical exanimation performed. A brief discussion was undertaken regarding how Sally intended to feed her baby. Sally informed the midwife she intended to breastfeed if possible.

Sally subsequently attended at 20 weeks for her fetal anomaly scan, which was normal. At this time, she was given both written and verbal information regarding the benefits of breastfeeding for both her and her baby. The possibility of antenatal expression of colostrum was discussed, and Sally and her partner agreed to return for a detailed explanation and instructions on the practice at 36 weeks gestation.

The pregnancy progressed uneventfully. At 36 weeks, Sally and her partner attended an appointment with the midwife where education and equipment were given to commence antenatal harvesting and storage of colostrum.

At 39 weeks gestation, Sally's pregnancy was induced as per local pregnancy guidelines and resulted in a spontaneous vaginal birth of a 4300 g baby boy.

At birth, the baby received skin-to-skin contact for one hour. A blood glucose was performed while the baby was receiving skin-to-skin contact. The baby was breastfed within one hour of birth and suckled well.

Subsequently, Sally and her baby were transferred to the postnatal ward where she continued to breastfeed on demand. She monitored her capillary glucose levels regularly, and Sally had a carbohydrate snack before or during feeding, especially at night.

The baby's blood glucose was monitored as per guidelines for the detection of neonatal hypoglycemia and was within normal limits.

By discharge on day 3, Sally had established breastfeeding with the support of her family and the ongoing support from healthcare professionals who continued to visit her in the community.

Six months post birth, Sally had exclusively breastfed her baby.

Breastfeeding and Diabetes

Breastfeeding is a major public health issue as it affects the health of both the mother and her infant in the short and long term. Mothers are encouraged to exclusively breastfeed their infants for the first 6 months and continue breastfeeding until their child reaches 2 years of age (1,2). Extensive research documents the diverse and compelling maternal, infant, societal, economic, and environmental advantages of breastfeeding or of giving infants human breast milk (3). For the mother, benefits include decreased vaginal bleeding post birth, quicker return to pre-birth weight, increased bone density, prevention of osteoporosis, and decreased risk of breast and ovarian cancer (4). For the infant, there is a reduced incidence of infectious diseases, sudden infant death syndrome, lymphoma, and leukemia, and enhanced performance on tests of cognitive development (3).

For women living with diabetes and their offspring, additional benefits have been identified. These include: better maternal glycemic control post birth (5), a reduction in the amount of insulin required (6), improvement in the cholesterol profile (7), and a shorter time to return to pre-birth weight, which is especially important for women with type 2 diabetes mellitus (T2DM), as there is a higher incidence of obesity in this cohort (4). It has also been suggested that exposure to cows' milk in infancy may initiate an immune

response that precedes the development of type 1 diabetes mellitus (T1DM) (8–10), and infant nutrition has long been recognized as a risk factor for the development of T2DM in later life (11,12).

The Impact of Diabetes on Lactogenesis

Lactogenesis occurs throughout pregnancy and post birth. This process includes preparation of breasts for the production of breast milk, the manufacture and secretion of breast milk (lactogenesis I), and, post birth following the delivery of the placenta and subsequent withdrawal of progesterone, the initiation and maintenance of the milk supply (lactogenesis II) (13). Research has shown that the preparation of the mammary gland to become competent to produce and secrete milk (lactogenesis I) is not influenced by diabetes (14). However, lactogenesis II can be delayed in women with preexisting diabetes (15–21), and this has also been seen in mothers whose pregnancies were complicated by gestational diabetes mellitus (GDM) (22). Hartmann and Cregan (2001) evaluated the evidence related to the four markers of lactogenesis II (milk citrate, lactose, sodium, and total protein) in mothers with T1DM, and when compared with nondiabetic mothers found a reduced concentration of lactose and total proteins consistent with delayed lactogenesis II (14). It is thought that fluctuating maternal glucose and lactose levels experienced by mothers following birth also cause a reduction in milk volume (17,23), with animal studies showing maternal hyperglycemia can reduce milk production (24).

The Effect of Diabetes on the Composition of Breast Milk

Milk production occurs within 24 h of birth, with initial breast milk, colostrum, being high in lactose, immunoglobulins, and protein and lower in fat. From 5 to 14 days post birth, the composition of breast milk changes and matures from colostrum to transitional milk. The composition of transitional milk is similar to that of colostrum but has a higher fat content. Further changes occur between 4 and 6 weeks post birth, with breast milk becoming mature and having the nutrients to meet the demands of the growing infant. Breast milk also changes its composition during a feed with the balance of nutrients reflecting the needs and demands of the infant. For example, at the beginning of a feed, the fat content is low and lactose high, providing a balance of fat calories for growth and lactose for energy. As the feed progresses, this reverses to higher fat and lower lactose.

Once lactation has been established, some studies have shown no difference between the composition of breast milk of women with T1DM and nondiabetic mothers (25), and maternal glucose levels not affecting glucose concentration in breast milk (26). However, other researchers have found lower mean fat and cholesterol and increased glucose in breast milk of mothers with T1DM, and suggest that fluctuating maternal metabolic control affects breast milk composition (19,27). The impact of diabetes on lactogenesis II, along with the altered composition of breast milk production and volume, can lead to the reduced postbirth availability of breast milk for the neonate, which may increase the known risk of neonatal hypoglycemia.

Neonatal Hypoglycemia

Neonatal hypoglycemia can occur in the newborn as a normal physiological adaptation to extrauterine life. It is usually transient and asymptomatic, with neonates utilizing fats to regulate their blood glucose. However, hypoglycemia is a common complication for the neonate of a mother with preexisting and gestational diabetes due to fetal intrauterine hyperglycemia and hyperinsulinism as a result of maternal hyperglycemia. Treatment of neonatal hypoglycemia is given in accordance with local guidelines as there is limited

consensus regarding a specific concentration of glucose that defines neonatal hypoglycemia (28). Hypoglycemia can affect 35% to 64% of infants born to women with diabetes and is the principal reason for admission to special care baby units (SCBUs) and neonatal intensive care units (NICU) and for separation of the mother–infant dyad (29). To minimize hypoglycemia in mothers with and without diabetes, early and frequent breastfeeding should be encouraged.

Breastfeeding Rates, Duration, and Exclusivity Among Women with Diabetes

Reported breastfeeding initiation rates among women with diabetes compared to the nondiabetic population are conflicting. For example, one study reported 90% of mothers with T1DM start breastfeeding; however, the rates declined markedly at 6 months, with 50% of mothers with diabetes compared to 70% of nondiabetic mothers still breastfeeding (30). However, another study found that initiation rates within 2 h after birth between mothers with and without diabetes were 55% versus 87%, respectively, falling sharply during the postbirth period. At 2 months, it was reported that mothers with diabetes were less likely to partly or exclusively breastfeed than mothers without diabetes (OR: 0.42 [95% CI: 0.18–0.96], $p = 0.041$), and by 6 months this was reduced further (OR: 0.50 [95% CI: 0.27–0.90], $p = 0.022$) (29). A mother's intention to breastfeed has been shown to be the strongest predicator for the initiation and maintenance of breastfeeding in women with preexisting diabetes (33).

For mothers with GDM, breastfeeding initiation and continuation of exclusive breastfeeding rates were similar to those without GDM (32), while a study of women with insulin-treated GDM reported lower breastfeeding rates compared with GDM mothers who were not treated with insulin (33). One study reported that while women with GDM made the decision to breastfeed, they anticipated failure and were accepting of this failure (34). Further studies of women with preexisting diabetes and GDM reported that these mothers feed for shorter durations than the general population. This was attributed to women with diabetes having an increase in factors known to be barriers to breastfeeding (i.e., operative delivery and separation of mother and infant) (35–37). GDM is associated with obesity, and it has been shown that a BMI >30 is linked to low breastfeeding initiation and continuation rates. This observation has been attributed to mechanical difficulties of positioning the infant and latching onto the breast (38).

Interventions to Promote and Facilitate Breastfeeding

To promote and enhance the initiation of breastfeeding in the diabetic cohort, specific steps can be undertaken by the implementation of the WHO Baby Friendly Initiative (BFI) (1,2). BFI advocates that during the antenatal period, all pregnant women, including women with diabetes, should be given the opportunity to discuss their intended feeding choices with a healthcare professional. This discussion should include unbiased, evidence-based information given by 34 weeks gestation, and before hospital admission or birth. The information should include benefits of and practices that facilitate breastfeeding (39). However, some studies have shown that the issue of breast/infant feeding is not routinely discussed with women with types 1 and 2 diabetes or GDM as part of their antenatal care and education, as emphasis is given to diabetes-specific issues (34,40).

Supportive hospital practices such as breastfeeding information literature given in the antenatal period have been shown to increase initiation rates in the general population. Locally or nationally produced information leaflets specifically related to breastfeeding for women with diabetes should be available for all women attending antenatal appointments,

as this has shown to lead to increased initiation and continuation of breastfeeding. Women may have anxieties related to breastfeeding and diabetes, and small-group discussions can address these specific issues (41–43). Furthermore, peer support both face-to-face or via telephone gives mothers information, assistance, and emotional care and has been shown to increase continuation and exclusivity of breastfeeding (44).

The BFI further advocates the teaching of hand expression of breast milk postbirth to help address difficulties such as inadequacy of the milk supply in the early postbirth period and to provide breast milk for the neonate admitted to SCBU/NICU (1,2,45). Hand expression of breast milk can also be undertaken in the antenatal period.

Antenatal Expression and Harvesting of Colostrum

Colostrum can be expressed pre-birth with the harvested and stored colostrum used as a supplementary feed for the treatment for neonatal hypoglycemia (46). The expressed colostrum can also be used if separation of the mother and neonate occurs and the neonate requires care in SCBU/NICU and is unable to feed at the breast, and/or if supplementary feeding is required. It has been suggested that from 34 weeks gestation until birth, women with diabetes hand-express colostrum twice a day for several minutes (47) or from 36 weeks gestation for 10 min twice a day until birth (46). The total reported volume of colostrum expressed by women is quoted as ranging from 2.8 to 322 mL in one study (47) and from 0.21 to 14.1 mL in another (46). The expressed colostrum is collected into a baby cup or syringe with date and identification details and stored in a sealed plastic bag in the home freezer (47,48). On admission to the hospital for birth, the frozen expressed colostrum is transported in a cool bag and stored in the hospital freezer. This can be used for the treatment of neonatal hypoglycemia if early breastfeeding is not sufficient, and giving colostrum will reduce the use of supplemental formula feeds or intravenous dextrose. While women with diabetes have expressed a high degree of satisfaction with the process (47,48), a review of the safety and efficacy of this practice concluded that although the procedure was apparently beneficial, a more thorough evaluation via randomized controlled trials is required (48).

Facilitators and Barriers to Establishing and Maintaining Lactation

As breast milk is the optimum nutrition for all infants and particularly for the neonate at risk of hypoglycemia, facilitating early and exclusive breastfeeding policies and practices should be employed. Among other institutions, the Confidential Enquiry into Maternal and Child Health (CEMACH) recommends that mothers with diabetes should breastfeed as soon after birth as is practicable (49,50).

Skin-to-Skin Contact to Promote Early Feeding

The immediate postbirth care a mother and her neonate receive is important to assist breastfeeding. A strategy that contributes to successful early breastfeeding is skin-to-skin contact (SSC) between mother and neonate. SSC has been defined as the placing of the naked baby prone, head covered with a dry cap and a warm blanket across the back, on the mother's bare chest at birth or soon afterward (51). The benefits of SSC include the facilitation of milk production and supply, improving neonatal glucose levels by increasing blood glucose levels for up to 75–90 min postbirth (52) enhancing neonatal thermoregulation, and early breastfeeding (51). The BFI (2) advocates that all mothers should have SSC immediately postbirth for at least one hour or until after the first breastfeed. However, the practice of SSC may be disrupted by factors such as mode of delivery.

Women with diabetes have a higher incidence of operative deliveries, including

cesarean section (CS), with further evidence showing initiation and establishment of breastfeeding are reduced in women who give birth by CS (53). It has also been found in general that CS can affect time before the first breastfeed, reduce the incidence of exclusive breastfeeding, and increase the likelihood of supplementation of feeds with formula milk (54). As the neonate born by CS to a mother with diabetes may be at greater risk of hypoglycemia, healthcare professionals should be more vigilant for this adverse neonatal outcome (55).

A further factor that may disrupt SSC at birth is the separation of the mother–infant dyad. Neonates of mothers with diabetes are more likely to be separated if the infant requires care in a SSBU/NICU for glucose monitoring due to hypoglycemia and respiratory problems. The separation of mother and neonate has been shown to delay and reduce the frequency of feeding and increase the potential for supplementary feeding (53). A study of infants of mothers with GDM showed those who breastfed in the delivery room had a lower incidence of hypoglycemia than those fed with formula (56). A further study found that when breastfeeding begins in the delivery room, there was increased glycemic stability in neonates (33). When the neonate has been admitted to SCBU/NICU, the mother can initiate and maintain an adequate milk supply by manual or mechanical breast milk expression (45).

Breastfeeding and the Effects on Maternal Glycemic Control

It has been shown that breastfeeding can positively influence glycemic control in mothers with diabetes. Fluctuating maternal glucose levels following birth may delay lactogenesis as lactose levels are lower, resulting in reduced milk volume (17,23). During the first week post birth while breastfeeding is established, mothers may experience hypoglycemic episodes. Therefore, women with T1DM should be advised to reduce their insulin dose immediately after birth to their preconception dose or lower, monitor their blood glucose levels frequently, and self-adjust their insulin accordingly (57,58). Mothers with T2DM and GDM who have been insulin-treated during pregnancy should stop insulin immediately post birth as their insulin requirements will be reduced dramatically (57).

Mothers may also experience hypoglycemia during breastfeeding as it has been suggested that 50 g of glucose is required for successful lactogenesis in mothers with T1DM and GDM (58). Therefore, 40–50 g extra carbohydrates are required to maintain an adequate milk supply. It is advisable for mothers with diabetes to have a meal or snack either before or during a feed, particularly at night. It has been reported that insulin requirements remain significantly lower over the first and second months post birth (59) in women with diabetes who are breastfeeding. A study that examined the basal insulin requirements of breastfeeding mothers with T1DM reported that due to the increased glucose use during lactation, there is a decreased need for basal insulin (58). Other studies found better maternal glycemic control in women with diabetes who breastfed (5), while still others noted hyperglycemia in breastfeeding mothers with T1DM (18). It has been suggested that the use of continuous subcutaneous insulin infusion (CSII) could be useful for women with T1DM who are breastfeeding, as CSII reduces the frequency of hypoglycemic episodes and improves glycemic control. The latter may improve lactogenesis and facilitate breastfeeding (59).

Breastfeeding and Medication

A small study that explored the levels of insulin in breast milk in mothers with T1DM and T2DM demonstrated that endogenous and exogenous insulin are actively transported from maternal blood into breast milk. It is suggested that insulin in breast milk may have a functional or developmental role for the infant (60).

Oral hypoglycemic agents such as metformin and glibenclamide (glyburide) have been deemed safe for women who are breastfeeding. Women with preexisting T2DM can resume or continue taking these post birth (57). Drugs used for the treatment of diabetes complications, such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), statins, calcium-channel blockers, and obesity drugs, should be avoided as their safety for the newborn and transmission into breast milk have not been established (57).

Benefits of Exclusive Breastfeeding For 6 or More Months

The majority of mothers with diabetes do not exclusively breastfeed their infants. This may be due to the increased use of supplementary feeding with formula milk for the treatment of neonatal hypoglycemia if the neonate is unable to breastfeed or if expressed breast milk is not available. Research concludes that there is a higher risk of the infant developing T1DM, especially if formula is introduced earlier than the recommended 6 months of life. This risk is even greater in infants deemed to be at high risk of T1DM and to have predisposing factors such as an immediate family member with T1DM (9). Although the mechanism is not fully understood, it has also been suggested that exclusive breastfeeding is protective against the infant developing T2DM in later life (61).

Long-Term Benefits of Breastfeeding for Mother and her Offspring

There is evidence in the general population that exclusively breastfeeding reduces the risk of developing T2DM in both the mother and her offspring. There is also evidence that breastfeeding is associated with a reduced incidence of T2DM in women who have had pregnancies complicated by GDM. Further evidence suggests that the longer the duration of breastfeeding, the lower the incidence of metabolic syndrome in women with previous GDM (61,62).

There has been much discussion related to the protective effect breastfeeding may have on childhood obesity. The results of a recent meta-analysis using adjusted ORs and 95% CIs from each study, thus accounting for residual confounding factors, suggest that breastfeeding is a significant protective factor against childhood obesity, especially if breastfeeding is continued for more than 7 months (63). Some studies have reported that the breastfed child who is overweight may not progress to obesity in adolescence and adulthood. The reasons for and mechanism of how breastfeeding reduces the prevalence of obesity are complex and include many confounding variables (62).

Conclusion

Women living with diabetes may choose to breastfeed as often as women without diabetes. Healthcare professionals should provide care that is supportive of the promotion, initiation, and continuance of exclusive breastfeeding that is appropriate to the women and her family. Antenatal preparation, supportive in-hospital care, SSC, early and frequent breastfeeding, and keeping the mother and infant dyad together are among the steps that can be taken to enhance successful and exclusive breastfeeding for women with diabetes.

Summary Box

Breastfeeding and/or breast milk is the optimum nutrition for all infants.

There are many benefits of breastfeeding for both the mother with diabetes and her infant.

For mothers with diabetes, there are additional challenges for the initiation, establishment, and continuation of exclusive breastfeeding.

Healthcare professionals should be aware of these challenges; support the mother, her infant, and the family to overcome them; and assist and facilitate the mother and infant to breastfeed successfully.

Multiple Choice Questions

1 Women with pregnancies complicated by diabetes should receive antenatal education regarding the benefits of breastfeeding:
- A by 18 weeks gestation.
- B by 34 weeks gestation.
- C by 28 weeks gelation.
- D up to the time of birth.

The correct answer is B.

2 Following birth, the neonate should have skin-to-skin contact with the mother:
- A for a minimum of 45 minutes.
- B only following pediatric assessment and following blood glucose monitoring.
- C for a minimum of 30 minutes.
- D for a minimum of 1 hour.

The correct answer is D.

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Section V

Implications for the Future

27

Implications for the Mother with Diabetes

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PRACTICE POINTS

- The micro- and macrovascular complications of types 1 and 2 diabetes may persist or recur following pregnancy.
- The majority of evidence suggests that pregnancy in and of itself does not cause or contribute to the progression of diabetic vascular disease.
- The improvement in metabolic control delays the appearance of early stages of nephropathy and may also decrease the risk of development and progression of cancer in women who have diabetes.
- Psychological and social well-being during and after pregnancy should be integral for good pregnancy outcome, for both mother and baby.

Case History

A 28-year-old woman gravida 1 para 0 has had type 1 diabetes since the age of 7. Her records revealed poor compliance with diet and insulin therapy prior to conception. Nonproliferative diabetic retinopathy was diagnosed at age 22, and she underwent two photocoagulation treatments during pregnancy due to deteriorating retinopathy. At age 26, she had stenting of her right coronary artery following an acute myocardial infarction. Additional problems presenting prior to pregnancy included hypertension requiring pharmacological treatment and nephropathy manifested by 376 mg/24 h of proteinuria and an initial serum creatinine of 1.2 mg/dl (106 μmol/l). Because of uncertainty whether her progressive increase in quantitated proteinuria and hypertension during the third trimester were due to incipient preeclampsia, exacerbation of her underlying chronic hypertension, or both, she had a cesarean delivery at 32 weeks. At her postpartum visit, 3 months after delivery, her blood pressure had returned to its pre-pregnancy levels and her weight was 3 kg above her pre-pregnancy weight. A levonorgestrel-containing IUD was inserted at that visit.

- How might the pregnancy affect the future course of this woman's type 1 diabetes and/or attendant complications?
- How might pregnancy affect the life of a woman who entered pregnancy with type 2 diabetes?
- What therapeutic modalities, if any, may be applied to women with type 1 or type 2 diabetes to prevent progression of their diabetes and attendant complications?

A Practical Manual of Diabetes in Pregnancy, Second Edition. Edited by David R. McCance, Michael Maresh and David A. Sacks.

Background

The prevalence of both type 1 and type 2 diabetes during pregnancy has increased in recent years (1). As discussed in Chapters 22 and 23, the care of the woman whose diabetes antedated her pregnancy offers unique challenges and concerns. This chapter will focus on the potential problems that may occur following pregnancy in women who have types 1 and 2 diabetes preceding pregnancy. Considerations of both immediate and long-term challenges to these women as well as interventions that may moderate or alleviate undesired consequences will be discussed.

Immediate Postpartum Period

For purposes of this discussion, the *immediate postpartum period* will be defined as birth to 1 year after delivery.

Type 1 Diabetes

In women who have type 1 diabetes mellitus (T1DM), postpartum glycemic control may vary, depending upon the quality of pre-pregnancy glycemic control, maternal weight, and breastfeeding. Pregnancy is characterized by insulin resistance, a major source of which is hormones of placental origin. Immediately following delivery of the placenta, a dramatic decline in insulin resistance occurs, which most often leads to a period of decline in insulin demand of variable duration. Factors that have been associated with a shorter time (less than 4 h) to resumption of exogenous insulin after delivery include a longer interval from discontinuation of insulin during the intrapartum period, increased body mass index (BMI) at term, and lower serum creatinine at term, but not hemoglobin A1c (HbA1c) at term (2). In one report of women with a normal pre-pregnancy BMI (mean 24.6 kg/m^2) and whose median HbA1c was 6.4% (46 mmol/mol), a 34% decline in total daily insulin demand comparing postpartum to preconception periods was noted. Dosage was not influenced by breastfeeding or route of administration of insulin (continuous vs. intermittent) (3). That postpartum maternal glycemia may be modified by pre-pregnancy intervention is suggested by the finding of lower pre-pregnancy and 1-year postpartum HbA1c values in women who enrolled in a program of preconceptional planning compared with those who did not (4).

In addition to the maternal and neonatal benefits presented in Chapter 26, breastfeeding has been found to have a positive effect on improvement of maternal glycemic regulation for women who have T1DM during the first 6 months postpartum. In a study of postpartum T1DM women, those who exclusively or predominantly breastfed (defined as at least six feedings per day) had lower hyperglycemic indices and less variability in continuously monitored blood glucose than those who bottle fed. Consistent with the increased need of glucose for milk synthesis, breastfeeding women had higher dietary carbohydrate intake than bottle-feeding women. While there were no significant differences in overall hypoglycemic indices between groups, blood glucose less than 72 mg/dl (4.0 mmol/l) was noted in a minority of breastfeeding women 2–3 h after initiation of suckling. However, there was a positive association between hypoglycemia and time since the last meal as well as a negative association with time since the last rapid-insulin dose (5).

Excessive postpartum weight and weight retention are associated with inflammation and insulin resistance. In women with T1DM, both poor glycemic control (6) and excessive weight retention postpartum may exacerbate their risk of diabetes-attributable vascular disease. Whether poor glycemic control is associated with maternal weight and postpartum weight retention was explored in 136 women who had T1DM and who were followed from pre-pregnancy to 12 months postpartum. For the entire cohort, the mean HbA1c increased from 6.6% at

6 weeks postpartum to 7.5% at 10 months postpartum. Overall, there was a decreasing trend of postpartum weight retention (defined as the difference between postpartum weight and pre-pregnancy weight). However, women who retained greater than 5 kg at 30 weeks postpartum had a mean 0.34% greater HbA1c than those who retained less than 5 kg. A similar difference in HbA1c at 1 year following delivery (0.31%) was noted between women whose pre-pregnancy BMI was ≥25 kg/m^2 compared with those whose BMI was <25 kg/m^2 prior to conception (7). From these data, it seems that reduction in weight retention might serve to improve glycemic control. However, there are no long-term data following the evolution of both outcomes.

Type 2 Diabetes

Although many of the problems found in the postpartum period are similar for women who have either T1DM or type 2 diabetes mellitus (T2DM), certain challenges are unique to the recently pregnant woman who has T2DM. Given the pathophysiology of T2DM (increased insulin resistance and inability of the beta cells to produce a sufficient amount of insulin to overcome it), and given that insulin resistance is greatly magnified during pregnancy, it is possible that some women who entered pregnancy with T2DM may revert to normoglycemia postpartum. While the literature examining this possibility is sparse, one study found that among women diagnosed as having overt diabetes based on a glucose tolerance test during pregnancy, 37% reverted to normal glucose tolerance at 6–8 weeks after delivery (8). The degree of glucose intolerance meeting the definition of overt diabetes and first discovered during pregnancy may or may not have existed prior to pregnancy. While no investigations of interventions to decrease glucose intolerance during the postpartum period have been conducted specifically in women with pre-gestational T2DM, it may be reasonable to extrapolate from intervention studies for women with gestational diabetes (GDM). Two major interventions have been investigated to prevent T2DM, namely breastfeeding and lifestyle modifications.

As with T1DM, women who have T2DM stand to derive benefit from breastfeeding. Although there is no evidence that breastfeeding assists in the postpartum reversion to normoglycemia in women who have T2DM, breastfeeding of variable duration has been shown to improve glucose tolerance as well as improve the lipid profile during the postpartum period in women who had GDM (9,10). The addition of weight loss may further augment the glucose-lowering effect of breastfeeding. In at least one study, postpartum breastfeeding women who had GDM and who underwent weight loss greater than 2 kg had a greater decrease in fasting and 2 h glucose as well as lower plasma insulin than their peers who did not lose that amount of weight (11).

A concern specific to breastfeeding postpartum women who have T2DM is the resumption of oral hypoglycemic agents. Drawing definitive conclusions about the use of these drugs while breastfeeding is hampered by the sparse amount of data available. One report found non-detectable amounts of glyburide (glibenclamide) in breast milk and nursing infants' blood (12). Two studies of breastfeeding women found maternal metformin milk–plasma ratios of 0.35 (13) and 0.63 (14), respectively. Corresponding infant doses received from breast milk were 0.28% and 0.65% of mothers' weight-adjusted doses. In the latter study, the blood glucose concentrations measured in three infants 4 h after breastfeeding were normal. No breastfeeding data are available for other classes of oral hypoglycemics, such as DPP4-inhibitors such as sitagliptin, thiazolidinediones such as pioglitazone, alpha-glucosidase inhibitors such as acarbose, and GLP1 agonists such as exenetide and liraglutide. The use of drugs for other indications for breastfeeding women who have diabetes is discussed in Chapter 26.

Long-Term Effects of Pregnancy on Women with Diabetes

The end-organ effects of diabetes occur primarily as a result of disease-associated changes in large and small blood vessels. Because micro- and macro-vascular changes occur in both T1DM and T2DM, albeit at different rates in different organs, the relationship between an antecedent pregnancy and development of outcomes subsequent to pregnancy will be discussed together for both types of diabetes.

The impact of pregnancy on the development and progression of vascular complications after pregnancy has been the subject of intensive research for more than 20 years. The heterogeneity of study groups, including diverse metabolic control, differing assessment of the severity of vascular lesions, and new monitoring and treatment of vascular complications, may contribute to the discrepancies found in the literature. With these caveats in mind, we will review some of the major complications that arise in diabetic women following pregnancy.

Pregnancy and Diabetic Retinopathy

The topic of diabetic retinopathy in pregnancy is discussed in Chapter 21. Certain points pertaining to long-term consequences of retinopathy antedating or discovered during pregnancy bear emphasis. The prevalence of diabetic retinopathy is positively associated with duration of disease, hyperglycemia (15), dyslipidemia (16), hypertension (17), and nephropathy (18). In that these complications frequently occur concurrently in the same individual, separating the relative contribution of each to the development and persistence of retinopathy is extremely difficult. Further difficulty is encountered in determining the independent influence of pregnancy per se on development and/or worsening of diabetic retinopathy because of differences in maternal age, the duration of diabetes, control of maternal glycemia prior to and during pregnancy, and the development of complications specific to pregnancy. The prevalence and worsening of diabetic retinopathy during and following pregnancy in women with pre-gestational diabetes have been recorded. However, whether pregnancy alone is responsible for these adverse changes is unclear. One report found that 10% of women with T1DM were found to have moderate to severe retinopathy on their initial ophthalmologic examination in the first trimester. Of the latter, progression was noted in nearly 50%. Those who did progress had a longer duration of diabetes than those who did not. Women whose retinopathy progressed also had higher initial HbA1c and a greater fall in HbA1c from initial examination to 24 weeks, but these differences did not achieve statistical significance (19). The Diabetes Control and Complications Trial (DCCT) studied reproductive-age women who initially were not pregnant. The difference in baseline HbA1c between the 500 who did not become pregnant and the 180 who did during the duration of the study was not significant. Fifty-three percent of the women who became pregnant and 47% of the women who remained nonpregnant had some degree of retinopathy at the start of the study (p = NS). In both the intensively controlled and conventionally controlled groups, pregnant women had significantly greater deterioration in retinopathy compared with nonpregnant women. A positive correlation was noted between the decrease in HbA1c during pregnancy and progression of retinopathy during pregnancy. However, no significant differences were found in residual retinopathy between women who had and those who had not become pregnant during the trial involving an average 6.5-year follow-up (20). In another study, women who had been pregnant had a greater prevalence of proliferative retinopathy. However, the women who had been pregnant were older and had developed diabetes at a younger age (21). Similar observations were made in the EURODIAB (European Diabetes Complications) multicenter study, where a

long diabetic history and poor metabolic control, but not pregnancy, were factors associated with the progression of the retinopathy after pregnancy (22). Finally, whether the frequency of progression of retinopathy is greater in type 1 or type 2 diabetes was examined in a study of 185 pregnant women. Significantly greater progression in diabetic retinopathy among those who had type 1 (31%) than among those who had type 2 diabetes (12%) was reported ($p = 0.001$). As in other reports, progression of retinopathy was associated with a greater initial HbA1c and greater fall in this variable from first to third trimesters (23).

Postpartum, the severity of diabetic retinopathy may regress or complete remission may occur, especially if there was no retinopathy before the pregnancy (24). Proliferative retinopathy may not regress and should be followed by specialists experienced in the treatment of diabetic retinopathy for at least 1 year.

Pregnancy and Diabetic Nephropathy

Diabetic nephropathy, another manifestation of vascular disease characteristic of long-term diabetes, is estimated to occur in 20–30% of patients with T1DM and T2DM, and is the leading cause of end-stage renal disease in developed countries (25). Two markers of chronic kidney disease are in use. The first, the urine albumin-to-creatinine ratio (UACR), is considered abnormal if ≥30 mg/gCr. However, besides kidney disease, the UACR may be elevated in the presence of marked hyperglycemia, marked hypertension, fever, infection, congestive heart failure, and menstruation (26). The second marker, estimated glomerular filtration rate (eGFR), is calculated from a formula derived by the Chronic Kidney Disease Epidemiology Collaboration. This formula is based on serum creatinine, age, race, and gender, and is available at http://www.niddk.nih.gov/health-information/health-communication-programs/nkdep/lab-evaluation/gfr-calculators/adults-conventional-unit-ckd-epi. Whereas the UACR is a marker of severity of chronic kidney disease, the eGFR, a marker of kidney function, may also serve to classify its severity, estimate disease progression, and manage complications (27). It must be noted, however, that the validity of eGFR in pregnancy is not known. The suggestion has been made that, absent data specific for pregnancy, either creatinine clearance or serum creatinine be used as measures of kidney function during pregnancy (28).

Elevations in UACR from 30 to 299 mg/gCr are markers of both diabetic kidney disease and cardiovascular disease (CVD) in T1DM and T2DM (29,30). This measure may spontaneously decrease, however, and should not be used exclusively to define the presence of diabetic nephropathy (31). Increased risk for end-stage renal disease is indicated by a persistent UACR >300 mg/gCr (32). Diabetic retinopathy in a patient whose UACR is >300 mg/gCr strongly suggests the presence of diabetic kidney disease. However, if the UACR is less than 300 mg/gCr, and the eGFR is reduced but diabetic retinopathy absent, a nondiabetic cause of chronic kidney disease should be sought (33).

Whether pregnancy per se increases the likelihood of development or progression of diabetic kidney disease has been examined. In one study, the prevalence of kidney disease (microalbuminuria) early in pregnancy was found to be 2.5% in 445 women with T1DM and 2.3% in 220 women with T2DM (p = NS). Although those with T1DM were administered antihypertensives more frequently than those with T2DM, pregnancy duration and birthweights were not significantly different between groups. Serum creatinine remained stable throughout pregnancy, and no end-stage renal disease occurred (34). In another study, kidney function in women with T1DM and T2DM with nephropathy was compared with that of diabetic women without nephropathy from pre-pregnancy to 1 year after delivery. Within each group, there were no significant changes in urine albumin excretion or creatinine clearance from the pre-pregnancy to 1 year postpartum measurements, suggesting the absence of an association between pregnancy

and development and progression of diabetic nephropathy (35).

An earlier study followed women with T1DM from pre-pregnancy to 3 or more years following delivery. Approximately 10% of women who began pregnancy with no nephropathy developed it within 18 years of delivery. Those women who ultimately developed nephropathy had higher mean HbA1c and more pregnancies complicated by hypertensive disorders than those who did not. However, analysis of women who began pregnancy with nephropathy found no differences in either HbA1c or hypertensive disorders between those who did and those who did not progress to end-stage renal disease. Parity in both studies was unrelated to development or progression of kidney disease. Because the development and progression of diabetic nephropathy were less than those reported over time in nonpregnant populations, the authors concluded that pregnancy itself did not have an independent effect on these complications (36).

Preeclampsia is seen more frequently in pregnancies complicated by diabetes (37). In addition to an increased risk of chronic hypertension and chronic renal disease, the development of preeclampsia is associated with higher risk of cardiac complications and the metabolic syndrome subsequent to pregnancy (38–40).

For the woman who has diabetes, both development and progression of chronic kidney disease may be prevented or delayed by selected interventions. Restricting total protein intake to 0.8 g/kg/day may slow glomerular filtration rate (GFR) decline and progression of albuminuria (33). In both T1DM and T2DM, normalization of glycemia has been shown to delay onset and progression of albuminuria and reduced eGFR (32,41). Finally, control of hypertension with ACE inhibitors or ARBs has been associated with reductions of adverse kidney events in women who have diabetes, an eGFR <60 ml/min/1.73 m^2, and a UACR >300 mg/gCr (42).

Macrovascular Complications and Pregnancy

Diabetic gastropathy, neuropathy, and CVD are common macrovascular complications associated with diabetes. Their frequency increases with the duration of diabetes and the age of the patient.

Neuropathy is a poorly understood and underdiagnosed complication of diabetes, despite its frequent occurrence and negative role in the quality and length of life of patients (43). The symptoms associated with autonomic neuropathy are especially problematic during pregnancy, as damaged fibers of the autonomic nervous system can cause problems in the cardiovascular system, genitourinary system, and gastrointestinal tract. Gastroparesis manifested by nausea, vomiting, and loss of appetite is a symptom of autonomic neuropathy. The difficulty of determining whether this symptom is due to pregnancy alone, diabetic gastroparesis, or both, especially in women who have T1DM, is discussed in Chapter 13. Diabetic gastroparesis should be suspected in every pregnant woman suffering from pre-gestational diabetes with prolonged, severe vomiting, and metabolic control disorders, especially in cases when routinely recommended treatments for hyperemesis are ineffective.

GDM was found to be an independent risk factor for CVD occurring within 9 years of pregnancy, but only in overweight women. In the same report, the development of overt diabetes subsequent to pregnancy was a major independent risk factor for CVD, and it minimally attenuated the adjusted odds ratio for CVD after GDM (44). Hyperglycemia promotes hypercoagulability, platelet dysfunction, and endothelial dysfunction. Hyperglycemia also induces oxidative stress, which may lead to decreased nitric oxide production and consequent decreased vasodilatation (45). The factors predisposing to CVD (i.e., inflammation, low HDL [high-density lipoprotein] cholesterol, and insulin resistance) may be a link between GDM and future CVD (46).

Diabetes and Cancer

Compared with those who do not have diabetes, an increased risk for several types of cancers has been found for women who have T1DM (47) and T2DM (48). Normal cells that contain oncogenic genetic material have to be stimulated to undergo malignant transformation and growth. In diabetes, proposed mechanisms promoting this transformation include hyperinsulinism, insulin resistance, hyperglycemia, changes in adipokines, and inflammation (49,50).

Pregnancy, gestational diabetes, and T2DM have in common insulin resistance and hyperinsulinemia. In T1DM, although an insulin deficiency dominates as the primary mechanism of the disease, an insulin excess often occurs due to the long-term administration of exogenous insulin. As a consequence, this may also lead to transient hyperinsulinemia and subsequent increased insulin resistance. During pregnancy, increased production of steroid hormones, placental lactogen, and a number of adipocytokines may contribute to insulin resistance and subsequent hyperinsulinemia. This may be particularly severe in patients who develop GDM. Thus, hyperinsulinemia in T1DM and T2DM is augmented during pregnancy. One consequence of increased insulin is a decrease in insulin-like growth factor binding proteins (IGFBP1 and IGFBP2). Insulin and insulin-like growth factor-1 (IGF1), respectively, activate insulin and IGF1 transmembrane cellular receptors. Both receptors are expressed at increased levels in malignant cells. Activation of these receptors results in activation of intracellular insulin response substrate-1 (IRS1). This leads to downstream activation of pathways initiated by mitogen-activated protein kinase (MAPK), phosphoinositol-3 kinase–Akt (PI3K/Akt), and Janus kinase–signal transducer and activator (JAK/STAT). Activation of these pathways results in protein synthesis, cellular proliferation, protection from apoptosis, and propagation of cancer cells (49–51). In addition, chronic inflammation and elevated levels of interleukins such as interleukin-6 or tumor necrosis factor-α (TNFα) promote enhanced tumor development, survival, and invasion. Changes in concentrations of adipokines characteristic of T2DM also influence tumor growth and survival. Increased leptin is associated with proliferation, migration, and invasion of cancer cells. Adiponectin is decreased in T2DM. When present in normal concentrations, this adipokine may decrease tumorigenesis by decreasing available insulin and glucose as well as activating AMPK (AMP-activated protein kinase), which in turn increases PP2A, a tumor suppressor that is decreased or absent in breast cancer (49). Decreased adiponectin results in decreased activation of AMPK.

It is clear that there is an increased frequency of certain types of cancer (breast, stomach, pancreas, colon, rectum, endometrium, and bladder) in patients who have both T1DM (47) and T2DM (48) diabetes. Whether this concurrence is due to shared risk factors (e.g., age and obesity) is unclear. Given that the risks of both diabetes and cancer in women who have diabetes are decreased by healthful diet, physical activity, and weight management, these three actions are to be encouraged (51).

Psychosocial Issues of Diabetic Women Transitioning to Motherhood

Women with T1DM experience a variety of psychosocial issues in their transition to motherhood: increased levels of anxiety, diabetes-related distress, guilt, a sense of disconnectedness from health professionals, and a focus on medicalization of pregnancy rather than the positive transition to motherhood (52). In addition, they may experience frequent hypoglycemic episodes during breastfeeding, requiring the support of relatives. This dependency may lead to feelings of self-pity and inadequacy compared with other mothers (53). Consequences of not being able to handle episodes of hypoglycemia contribute to behavior changes that may be detrimental to their health, such as allowing their blood glucose levels to rise to abnormally high levels (54). Fear of hypoglycemia among

diabetic mothers creates insecurity and the feeling that breastfeeding could be risky. Given the benefits of breastfeeding, these women should get special support during their stay at the maternity ward and after discharge from hospital, during the first months after childbirth. Women should and do feel the need to take responsibility for their blood glucose levels after the birth, a goal to which their partners may contribute (54,55).

Summary

Prevention of long-term adverse outcomes of T1DM and T2DM begins in the immediate postpartum period. There is little evidence that pregnancy alone causes or exacerbates any of the complications of diabetes. Breastfeeding contributes to maternal weight reduction and retention, and betterment of glycemic and lipid regulation. Breastfeeding and weight reduction have an apparent synergistic effect on glucose regulation. Following pregnancy, a normal intake of dietary protein and the use of ACE inhibitors may slow the progression of diabetic nephropathy. Finally, weight normalization and control of glycemia along with healthy lifestyle modifications and regular physical exercise are of general benefit for women with diabetes and may reduce their propensity for development of cardiovascular disease and malignancy.

Multiple-Choice Questions

1 A 32-year-old woman with type 1 diabetes mellitus has had progressive renal failure for the past 2 years. She is not yet on dialysis. Examination shows no abnormalities. Her hemoglobin concentration is 9 g/dL, hematocrit is 28%, blood pressure in regular control is 150/100 mmHg, proteinuria over 0.7 g/d, and HbA1C is 5.7%. She is going to plan pregnancy. What consequences may she expect during pregnancy? (*Choose all that apply*.)

- **A** Preeclampsia
- **B** Progression of nephropathy
- **C** Fetal congenital malformations
- **D** Fetal macrosomia
- **E** No complications
- **F** Premature delivery

Answer: A, B, and F.

2 A 25-year-old woman with 10 years lasting type 1 diabetes comes to your office seeking pregnancy advice. Although she is not currently pregnant and has never been pregnant, she and her spouse are planning to have their first child. She has previously managed her diabetes with diet, exercise, and taking basal insulin twice a day and occasionally with short-acting insulin before meals. Approximately 4 months ago, she started to monitor her glycemia more regularly, and she noticed that her fasting blood glucose levels were consistently elevated above 150 mg/dl. Her hemoglobin A1c level at that time was 9%. She has no specific complaints today, and her physical examination is unremarkable. She would like to know how she should modify her diabetic medications to deliver a healthy baby and have no progression of diabetic complications. Which of the following is the most appropriate way of treatment to help achieve these goals?

- **A** She may continue this treatment, because with that HbA1C level she has the prospect of delivering a healthy baby and will have no progression of diabetic complications.
- **B** Add metformin twice a day to insulin, to achieve better glycemic control.
- **C** Start intensive insulin therapy, try to achieve target glycemic control, and if HbA1C falls below 8%, she

may try to get pregnant to avoid complications.

D Start intensive insulin therapy, try to achieve target glycemic control, and if HbA1C falls below 6.5%, she may try to get pregnant and avoid complications.

E Because she didn't treat her diabetes effectively, even if she improves her glycemic control now, she has no chance for a healthy baby and the risk for progression of complications is very high.

Answer: D.

3 A 28-year-old patient with type 1 diabetes, who has been treated with insulin pump (HbA1C = 6.3%) and with ACE inhibitors because of mild hypertension, got pregnant. In first trimester, her proteinuria was 0.3 g/24 h; her mean blood pressure during first and second trimesters of pregnancy was kept below 130/85 mmHg; but in third trimester, it rose to 160/100 mmHg and proteinuria increased to 0.9 g/24 h. She was delivered in the 35th week of pregnancy because of fetal distress.

Which of the following answers is correct?

A All these changes in kidney function will remain after delivery, because every pregnancy worsens permanently renal function.

B The patient has the chance to resume the pre-pregnancy status in her vascular disease, because the majority of evidence suggests that pregnancy in and of itself does not cause or contribute to the progression of diabetic vascular disease.

C Kidney function after pregnancy always progresses to severe nephropathy, but hypertension will probably get back to normal value.

D Preeclampsia that was present in that pregnancy always contributes to kidney insufficiency after puerperium.

E The patient has no chance to resume the pre-pregnancy status in her vascular disease, because the majority of evidence suggests that pregnancy causes or contributes to the progression of diabetic vascular disease.

Answer: B.

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28

Diabetes in Pregnancy: Implications for the Offspring

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PRACTICE POINTS

- Maternal hyperglycemia during pregnancy may cause adverse short-term outcomes for the offspring, including macrosomia, congenital malformations, neonatal hypoglycemia, and respiratory distress syndrome.
- Exposure to maternal diabetes during pregnancy has been associated with increased risk of adverse long-term outcomes for the offspring, including obesity, diabetes, and cardiovascular disease.
- Mild maternal hyperglycemia among women without diagnosed pre-gestational or gestational diabetes is associated with offspring size and adiposity at birth; long-term offspring consequences of mild hyperglycemia have not been conclusively demonstrated.
- While short-term adverse outcomes may be minimized through maternal glycemic control, it is unknown whether long-term outcomes may also be prevented.

In this chapter, we discuss the implications of exposure to a diabetic intrauterine environment for the offspring. There are numerous neonatal consequences of intrauterine hyperglycemia, many of which are preventable with good maternal glycemic control. Of concern is the accumulating evidence that exposure to maternal diabetes *in utero* has long-term consequences for the offspring and may increase the risk of chronic diseases, including obesity, metabolic syndrome, and diabetes, into childhood and adulthood (Figure 28.1).

Risks in the Neonatal Period

Macrosomia

Infants of mothers with both pre-gestational and gestational diabetes are more likely than infants of normoglycemic mothers to be born large for gestational age (LGA), defined as birthweight above the 90th percentile for gestational age; or macrosomic, often defined as birthweight above 4000 g (1). Macrosomia is associated with obstetric complications, including shoulder dystocia and the corresponding risk of brachial plexus injury, and increased likelihood of emergency cesarean delivery (2). Results from the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study indicate a linear association between maternal glycemia and odds of LGA birthweight, with an odds ratio of 1.38 for each standard deviation increase in maternal fasting plasma glucose (3).

Congenital Malformations

Offspring of women with diabetes diagnosed prior to pregnancy have more than twice the

A Practical Manual of Diabetes in Pregnancy, Second Edition. Edited by David R. McCance, Michael Maresh and David A. Sacks.

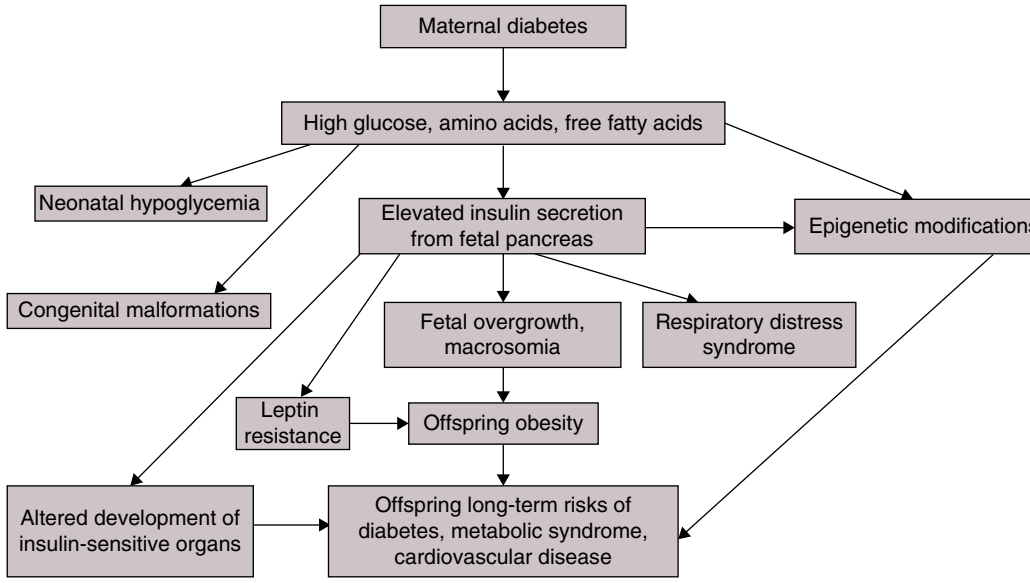

Figure 28.1 Diagram of potential pathways by which maternal diabetes leads to adverse short-term and long-term outcomes for offspring.

risk of congenital malformations compared to the general population, and are at particularly high risk for neural tube defects and congenital heart disease (4,5). Major predictors of congenital anomaly in the offspring of women with pre-gestational diabetes are peri-conceptional glycemic control (as indicated by glycated hemoglobin) and preexisting nephropathy (6,7). The fact that much of organogenesis is complete by the end of the first trimester adds weight to the importance of family planning and pre-conception management of diabetes (see Chapter 11).

Neonatal Hypoglycemia

One possible short-term consequence of fetal overnutrition and hyperinsulinemia *in utero* is neonatal hypoglycemia, which in severe cases may threaten neurologic function or even survival (8). The results of the HAPO study confirmed a weak but positive association of neonatal hypoglycemia with the maternal glucose tolerance test at 24–28 weeks of pregnancy, and with umbilical cord concentration of C-peptide (9). LGA infants and very preterm infants are at greater risk of hypoglycemia in the first few hours after birth (8,9).

Respiratory Distress Syndrome

Offspring of mothers with diabetes during pregnancy are at significantly elevated risk of respiratory distress syndrome (10). Fetal hyperinsulinism resulting from maternal hyperglycemia has been linked to delayed lung maturation (11). While infants of mothers with pre-gestational or gestational diabetes are more likely to be born preterm (12), and preterm birth is itself a risk factor for respiratory distress syndrome, maternal gestational diabetes mellitus (GDM) was observed to be an additional independent risk factor for severe respiratory complications in late preterm births (34–36 weeks' gestation) (13).

Risks in Childhood and Adulthood

Type 2 Diabetes

Offspring exposed to maternal diabetes *in utero* are at higher risk of certain chronic diseases, including obesity, diabetes, and the metabolic syndrome. Foundational studies in

a population with very high incidence of T2DM, the Pima Indians of Arizona, demonstrated that offspring of women with T2DM during pregnancy had an elevated risk of early-onset T2DM compared to offspring of mothers without diabetes (14,15). In an ethnically diverse population from Chicago with lower background risk of T2DM, the prevalence of impaired glucose tolerance among offspring exposed to maternal pre-gestational or gestational diabetes *in utero* was 20% by age 16, ten times the prevalence in the general population of that age (16). The prevalence of T2DM or pre-diabetes among the adult offspring of Danish women with GDM was 21%, compared to 12% among offspring of women screened for GDM but found to be negative (17).

These associations are not limited to offspring of mothers with T2DM and GDM; elevated rates of T2DM and impaired glucose tolerance have also been reported among adult offspring of mothers with type 1 diabetes (T1DM) during pregnancy. In the Chicago study described in this section, the majority of mothers with pre-gestational diabetes had insulin-dependent diabetes (16). In an Austrian cohort study of children aged 5–15 who were exposed to maternal T1DM *in utero*, children without autoimmune antibodies had higher fasting and post-load glucose, insulin, and C-peptide compared to an unexposed control group (18). Among Danish adult offspring of mothers considered to be at low risk for T2DM, the prevalence of T2DM or prediabetes was 11% among those exposed to maternal T1DM *in utero*, compared to 4% among the unexposed (17).

While studies have documented positive associations between intrauterine exposure to T2DM and subsequent risk of diabetes in the offspring, some suggest that these results may be confounded by the high degree of genetic heritability of T2DM (19,20). Heritability estimates range from 0.26 to 0.69, indicating that up to 69% of the liability for T2DM may be explained by genetic factors (21,22). Additionally, family members share behavioral characteristics that may lead to correlated risks of diabetes; for example, having a spouse with diabetes is associated with a 26% increase in diabetes risk in the other spouse (23). Innovative study designs have been used to circumvent confounding by shared familial and genetic backgrounds. A study of sibling pairs in the Pima Indian population found that the sibling born before the mother's diagnosis of T2DM had a lower prevalence of diabetes and a lower mean Body Mass Index (BMI) compared to their sibling born after the diagnosis (24), suggesting that the elevated risk of diabetes in the younger sibling was likely attributable to exposure to the diabetic intrauterine environment, rather than to genetic predisposition or postnatal family environment. Other studies have observed an excess frequency of maternal versus paternal transmission of diabetes (25–28), although this finding has not been consistent across all studies (29).

Obesity

Exposure to maternal diabetes during pregnancy is also associated with elevated adiposity and risk of obesity among offspring. Among Danish offspring of mothers with T1DM, the prevalence of overweight ($BMI > 25\,kg/m^2$) was 41%, compared to 24% among unexposed controls (30). In a Colorado population, exposure to maternal GDM was associated with higher BMI and waist circumference among children aged 6–13 (31). In the Pima Indian population, offspring of mothers with T2DM during pregnancy were at greater risk of obesity and higher body weight for age than the offspring of nondiabetic or prediabetic mothers (24,32).

Particularly with regard to GDM and T2M, the increased incidence of obesity in offspring of mothers with diabetes must be disentangled from the familial aggregation of obesity. Both maternal and paternal BMI are positively associated with obesity and high waist circumference in the offspring (33,34), suggesting an influence of shared genetic factors and a shared postnatal environment.

Adjustment for parental obesity, and for postnatal environmental factors to the extent possible, may be important to avoid confounding bias in studies of the long-term risk of obesity associated with intrauterine exposure to diabetes (19,35).

Some studies of the association between mild maternal hyperglycemia and offspring obesity have adjusted for parental obesity, with inconsistent results. Examinations of the offspring of women in the Belfast HAPO study found no associations between maternal hyperglycemia and offspring adiposity or obesity at 2 (36) and at 5–7 years (37), after adjustment for maternal BMI. Similarly, a study of nondiabetic Caucasian women in Exeter, UK, reported no positive associations between maternal fasting plasma glucose at 28 weeks of gestation and offspring weight at any time point after birth, after adjustment for both maternal and paternal BMI (38).

By contrast, an analysis within the Pregnancy, Infection and Nutrition study in North Carolina reported significant associations between maternal post-load plasma glucose and offspring BMI at age 3, which remained significant after adjustment for maternal BMI (39). Additionally, a study of Mexican-American women without pre-gestational or gestational diabetes found a positive association between maternal post-load glucose concentration and offspring BMI *z*-score between 2 and 7 years old, independent of maternal pre-pregnancy obesity (40). In subsequent stratified analyses, findings were only significant among the offspring of women without pre-pregnancy obesity, suggesting an interaction between maternal BMI and plasma glucose in their associations with offspring obesity.

It should be noted here that adjustment for maternal pre-pregnancy BMI may partially obscure the full effect of fetal overnutrition, as maternal obesity may also contribute to elevated intrauterine glucose and a fuel-rich environment (41,42). Additionally, screening for GDM is often not universal and is more likely to be offered to women who are overweight or obese, which may result in underdiagnosis of GDM among normal-weight women and consequently underestimation of the true association between maternal GDM and offspring obesity/diabetes, after adjustment for maternal BMI (41).

Data from intervention studies have been used to examine whether reductions in maternal glucose concentrations during pregnancy may prevent the offspring from experiencing increased risks of obesity and insulin resistance later in life. One large observational study found that offspring of mothers with untreated (milder) GDM had a nearly doubled risk of obesity at 5–7 years old, compared to offspring of mothers with treated (more severe) GDM; however, this study did not adjust for maternal BMI (43). In contrast, two randomized controlled trials (one in Australia and one in Ottawa, Canada) reported no difference in offspring BMI at age 4–5 years old or impaired glucose tolerance at 9 years old between offspring of treated versus untreated (or minimally treated, in the Ottawa study) mothers with GDM (44,45). In one study (44), authors considered that the effects may not be detectable until later in childhood, consistent with some observational studies in which higher offspring body weight associated with maternal diabetes was not evident until school age (46). The second study had an insufficient sample size to draw conclusions regarding differences in offspring obesity (45). Finally, the recent Maternal-Fetal Medicine Units multicenter trial found no differences in the frequency of overweight or obesity (BMI above the 85th or 95th percentile, respectively) at ages 5–6 or 7–10 among offspring of women treated versus untreated for mild GDM (47). Whether or not the long-term risks of obesity and T2DM in the offspring of mothers with GDM or T2DM may be reduced through maternal glycemic control therefore remains inconclusive.

Cardiovascular Disease

Offspring exposed to maternal diabetes *in utero* may have elevated risks of cardiovascular disease later in life. LGA offspring of

mothers with GDM according to Carpenter–Coustan criteria had a higher prevalence of components of the metabolic syndrome at ages 6–11 years than did children who were unexposed to GDM or were exposed to GDM but born with a birthweight appropriate for gestational age (48). Other cardiovascular disease risk factors that have been elevated in children exposed to pre-gestational diabetes or GDM *in utero* include markers of endothelial dysfunction, higher LDL cholesterol, and higher systolic blood pressure (49,50). These risk factors have been found in offspring of women with T1DM as well (51). One Danish study reported an elevated risk of metabolic syndrome in adult offspring of women with GDM as well as a lower, but still elevated, risk among offspring of women with T1DM (30). A separate Danish registry-based study, however, reported that offspring who had fathers with T2DM were also at elevated risk of cardiovascular and cerebrovascular diseases (52), lending support to the contribution of genetic and postnatal environmental factors.

Mechanisms of Long-Term Effects

Fuel-Mediated Teratogenesis

Offspring of diabetic pregnancies may be exposed to an excess of fuels (glucose, amino acids, and free fatty acids) at critical windows of development, which may lead directly to altered metabolic function throughout life. This pathway, called fuel-mediated teratogenesis, is believed to operate primarily via beta-cell hyperplasia in the fetal pancreas (53,54). Excess maternal circulating glucose crosses the placenta and stimulates the fetal pancreas to produce insulin, which in turn promotes growth (55). Fetal hyperinsulinemia may cause alterations in insulin-sensitive organs, including the development of insulin resistance or the downregulation of insulin secretion (56). Other changes occurring *in utero* may include modified adipocyte metabolism or hypothalamic set-points determining appetite and satiety (reviewed in (57)). Prolonged increases in insulin may also cause increased leptin secretion (58), and central resistance to the appetite-reducing effects of leptin has been observed in animal models of diet-induced obesity (59).

Glucose may not be the only fuel received in excess by the fetus; GDM is also associated with lipid abnormalities. Triglycerides may be hydrolyzed to free fatty acids, which can cross the placenta and could lead to increased number and size of fetal adipocytes (60,61). Among women without diagnosed gestational or pre-gestational diabetes, maternal fasting triglycerides in early pregnancy and free fatty acids in late pregnancy were significantly correlated with neonatal percentage of body fat within 24 h of birth, independent of maternal BMI (62). The relative contribution of excess maternal lipid exposure *in utero* to long-term offspring adiposity is unknown (53).

Epigenetics

Intrauterine hyperglycemia may affect offspring cardiometabolic health later in life through epigenetic changes to offspring DNA, leading to persistently altered gene regulation. Suggestive evidence has been produced in support of this hypothesis. Post-load glucose concentrations in women with impaired glucose tolerance during pregnancy have been associated with altered DNA methylation in placental cells at the leptin and adiponectin genes (63,64). Lower methylation levels of the MEST gene, which has been linked to obesity, have been observed in cord blood and placental cells from women with GDM (65). Additionally, epigenome-wide DNA methylation analysis of peripheral blood cells in children ages 8–12 revealed multiple differentially methylated regions (DMRs) in 11 children exposed to GDM *in utero* compared with 11 unexposed children (66). Although none of the associations survived correction for multiple testing, two of the DMRs showed partial mediation of the association between exposure to maternal

GDM and offspring VCAM-1 level, a marker of vascular endothelial dysfunction. To our knowledge, such a mediation analysis has not yet been performed on data from epigenetic markers in fetal or neonatal cells, which would more strongly indicate persistent effects of the intrauterine environment (20,67).

Summary and Future Directions

Maternal metabolic dysregulation during pregnancy has been linked with short- and long-term adverse health outcomes for the offspring. While the neonatal consequences of exposure to maternal diabetes may be minimized through adequate maternal glycemic control, more research is needed to determine whether or not the long-term consequences may also be preventable. Long-term follow-up of intervention studies to treat GDM will be important to address this question. Childhood obesity and T2DM have emerged as public health crises, and prevention is a high priority. A hyperglycemic intrauterine environment may be an important risk factor that enhances the offspring's risk of metabolic disease, complementing shared genetic and behavioral risk factors and intensifying an intergenerational cycle of obesity and diabetes.

Multiple-Choice Questions

1 Which of the following epidemiologic study designs may be used to distinguish between the effect of genetic predisposition shared between mother and offspring, and the direct effect of exposure to the maternal diabetic intrauterine environment, on the offspring's risk of diabetes?

- **A** Family studies to compare the risk of diabetes in offspring that is associated with maternal diabetes versus paternal diabetes
- **B** Sibling studies to compare the risk of diabetes among offspring born prior to the mother's diagnosis of diabetes, with the risk of diabetes among offspring born after the mother's diagnosis of diabetes
- **C** Cross-sectional studies to compare the prevalence of diabetes among offspring of mothers with T2DM to the prevalence of diabetes among offspring of mothers without T2DM
- **D** Both A and B

The correct answer is D. Both study designs described in A and B may help to separate the influence of (1) the genetic contribution from each parent, and (2) the specific intrauterine environmental influences from a mother with diabetes during pregnancy, on the offspring's risk of diabetes.

2 Which of the following is *not* a possible mechanism by which maternal diabetes during pregnancy may lead to adverse offspring health outcomes?

- **A** Epigenetic modification of fetal cells
- **B** Overproduction of insulin by the fetal pancreas
- **C** Transfer of maternal insulin across the placenta to promote fetal growth
- **D** Changes to adipocyte metabolism, including the production of adipokines

The correct answer is C. Maternal insulin does not cross the placental barrier; however, maternal glucose may cross the placenta and stimulate insulin production by the fetal pancreas.

Abbreviations

BMI	body mass index
DMR	differentially methylated region
GDM	gestational diabetes
HAPO	Hyperglycemia and Adverse Pregnancy Outcomes (study)
LGA	large for gestational age
T1DM	type 1 diabetes
T2DM	type 2 diabetes
VCAM-1	vascular cell adhesion molecule 1

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29

From the Bench to the Bedside: Potential Future Therapies for Gestational Diabetes – The Enhancement of β-Cell Mass and Function During Pregnancy

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Introduction

The prevalence of gestational diabetes mellitus (GDM) is increasing, with rates of up to 18% of pregnancies in the USA now being reported; this is related to the increasing numbers of pregnant women who are obese (1), and also changes in the international diagnostic criteria for GDM. GDM not only carries immediate health risks to the mother but also is a precursor of later type 2 diabetes mellitus (T2DM), and it confers risk for childhood obesity and future T2DM in the offspring (2). Whilst genetic predisposition to GDM has been demonstrated, the majority of gene polymorphisms identified are shared also by T2DM, such that the identification of at-risk individuals on a genetic profile alone has not been useful (3). A pharmacological approach to the prevention of GDM during pregnancy is complicated by the trans-placental passage of drug, and only metformin has been demonstrated to prevent pregnant women with polycystic ovarian syndrome from developing GDM, but with variable degrees of effectiveness (4). Attention has therefore focused on lifestyle interventions to help women at risk of developing GDM by using dietary modification, increased exercise, or both. Three recent studies demonstrated mixed results (5–7), with only one demonstrating a reduction in the incidence of GDM (5), although a second demonstrated improvements in maternal glycemia (6). Pregnancy is associated with a physiological increase in insulin resistance and an adaptive increase in pancreatic β-cell mass, due to both hyperplasia and hypertrophy, and insulin secretion. Failure to undergo such functional adaptations can increase the risk of GDM. Looking to the future, enhancing the physiological increase in β-cell mass that occurs naturally in pregnancy could help prevent GDM in at-risk women. However, such strategies require a detailed understanding of the mechanisms underlying adaptive changes to β cells during pregnancy as a first step (Figure 29.1).

Adaptation of β-Cell Mass During Pregnancy

A maternal adaptive expansion of β-cell mass occurs during pregnancy in all mammalian species examined, including human (Figure 29.2). This is followed by a regression of β-cell mass following delivery, largely through a targeted apoptosis of β cells. In the pregnant mouse, an increased rate of β-cell mitogenesis results in a 2–3-fold increase in β-cell mass, peaking at around gestational

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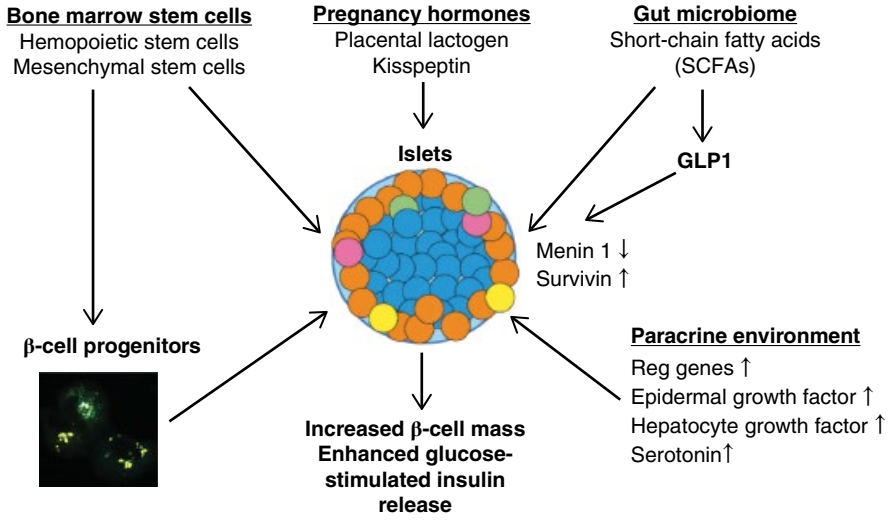

Figure 29.1 Potential therapeutic pathways and mediators for increasing maternal pancreatic β-cell mass during pregnancy to prevent gestational diabetes.

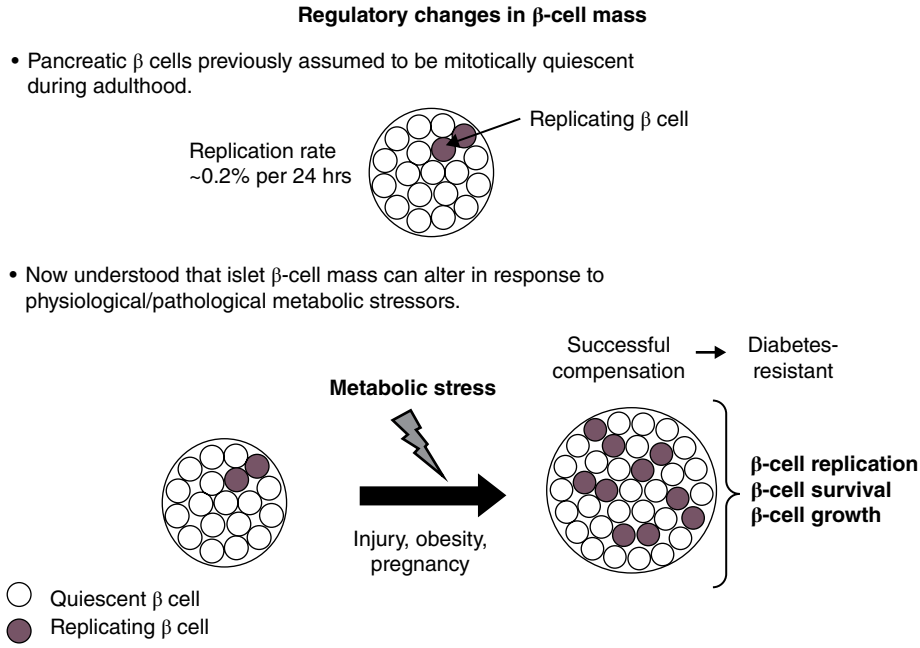

Figure 29.2 Physiological and pathological regulatory changes in β-cell mass. Although β-cells are normally quiescent in adult life, they can respond to the metabolic stress of injury, obesity, or pregnancy through hyperplasia, hypertrophy, and increased survival. *Source*: Rieck & Kaestner 2010 (92). Reproduced with permission of Elsevier.

days 13–15 (term: 19 days) (8). Van Assche *et al.* (9) were the first to report that a doubling of fractional area of β cells occurred during pregnancy in women who had died during third trimester or at parturition, when compared to age-matched, nonpregnant controls. Subsequently, Butler *et al.* (10) measured the fractional area of β cells in

pancreata from women who died during pregnancy and found a 1.4-fold increase during pregnancy, although this data set also included women who died in first trimester. Importantly, an implied failure of β cells to undergo adaptive change after the first trimester of pregnancy has been linked with GDM (11). Future strategies to reverse GDM might include a targeted increase in maternal β-cell mass, especially if this has failed to undergo optimal adaptive expansion. This could be achieved by: (1) manipulation of the hormones normally associated with the β-cell expansion, (2) a targeted manipulation of the paracrine environment of the islets of Langerhans with small molecules, (3) cell-based therapies, or (4) nutritional mediators.

Hormonal Control of β-Cell Mass

An increased β-cell mass during pregnancy and the resulting increased insulin-secreting capacity are necessary to counterbalance the increasing maternal peripheral insulin resistance. The latter is caused, in part, by the increasing presence in the maternal circulation of placentally derived variant growth hormone (GH-V) (12), which suppresses pituitary growth hormone release. A combination of placental lactogen (PL) and GH-V also promotes hepatic gluconeogenesis and lipolysis in support of nutritional transfer to the fetus. However, the risk of maternal hyperglycemia is countered by the ability of PL to expand β-cell mass. The increase in maternal β-cell mass during pregnancy in rodents correlates with the appearance and rise of PL (13). A functional linkage was demonstrated by targeted overexpression of PL in β cells, which resulted in increased proliferation (14).

Although placental lactogen presence could account for the compensation in β-cell mass that occurs during pregnancy, it does not appear to directly enhance glucose-stimulated insulin secretion (GSIS). This may be achieved by a second placentally derived peptide, kisspeptin. Kisspeptins are posttranslationally modified proteins expressed from the *kiss1* gene of which the amidated kisspeptin-54 form, also known as metastin, is the most abundant (15). The receptor for kisspeptin is the G-protein-coupled receptor (GPCR), GPR54, which signals by coupling to the G protein $G\alpha_q$ subunit, leading to an activation of phospholipase C-β (PLC-β) and a subsequent increase in intracellular Ca^{2+} and the activation of protein kinase C (PKC) (16,17). PKC isomers have been shown to regulate the transport of newly synthesized proinsulin from the endoplasmic reticulum, and the conversion of proinsulin to insulin (Figure 29.3).

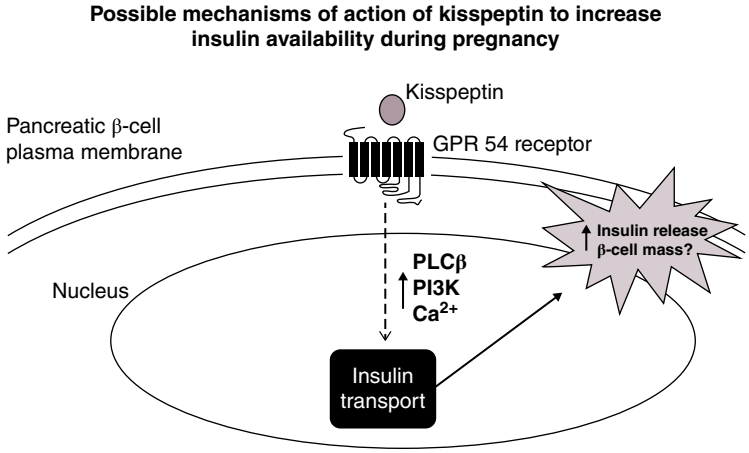

Figure 29.3 Possible mechanisms of action of kisspeptin on β cells to increase insulin release during pregnancy. Kisspeptin binding to the GPR54 receptor results in an increase in intracellular levels of activated phospholipase C (PLC), phospoinositol-3 kinase (PI3K), and increased intracellular calcium levels, triggering insulin release.

Kisspeptin and GPR54 are expressed by the placental trophoblasts, and kisspeptin-10, the shortest sequence capable of activating the GPR54 receptor, is released into the maternal circulation (15,18). The highest placental messenger RNA (mRNA) expression for both KISS1 and GPR54 occurs in first trimester, coincident with the peak of trophoblast invasiveness (18), and expression levels are reduced in pregnancies associated with small-for-gestational age infants, preeclampsia, or type 1 diabetes mellitus (T1DM) (19,20). While circulating levels of kisspeptin are normally low in humans, they increase substantially during pregnancy with a peak concentration of 20 nM or more observed in the third trimester (19,21). Intravenous administration of kisspeptin in rodents resulted in a prompt, fourfold increase in plasma insulin, which persisted for 90 min (22), with similar findings in rhesus monkey (23). In human, circulating levels of kisspeptin are reduced in women with GDM (24), suggesting that a coordinated presence of placentally derived PL and kisspeptin may increase both cell mass and GSIS. The use of kisspeptin to amplify insulin release and prevent GDM has not been examined.

Cellular Mechanisms Accounting for β-Cell Plasticity in Pregnancy

In adult life, pancreatic β cells are normally quiescent with a very low rate of proliferative turnover. However, during pregnancy in rodents, maternal β cells become mitotically active, resulting in at least a doubling of β-cell mass by day 15 of gestation in mice, followed by involution postnatally (8). The reactivation of β-cell mitosis is driven by PL, which overcomes β-cell quiescence and induces proliferation by binding and activation of prolactin receptors. Transgenic deletion of the prolactin receptor results in a failure of β-cell compensatory growth, impaired insulin release, and glucose intolerance (25,26). Conversely, prolactin receptor overexpression results in overgrowth of β cells (26). Downstream, the prolactin receptor activates a number of intracellular second messenger pathways through an association with Jak2 that results in the activation of Stat5 (27), mitogen-activated protein kinases (MAPKs), and PI3K and Akt (28) (Figure 29.4). The activation of Stat5 by either PL or prolactin within β cells of pregnant rodents can induce B-cell lymphoma 6 (Bcl6) gene expression, a transcriptional repressor of the tumor suppressor gene, menin 1. Islets where the prolactin receptor was deleted demonstrated an increased expression of menin 1 during pregnancy (28). Conversely, a downregulation of menin 1 within islets during pregnancy resulted in inhibition of the cell cycle regulatory proteins p18 and p27, and the release of β cells from cell cycle arrest (29). A downregulation of menin 1 is therefore critical to compensatory islet growth since a targeted overexpression of menin 1 within mouse maternal β cells prevented their proliferation and resulted in glucose intolerance (29). However, it is unclear if Stat5 activation is the only pathway responsible for a downregulation of menin 1 in β cells, since glucose alone can suppress menin 1 *in vitro* (30). The actions of glucose were dependent on signaling via the PI3K–Akt pathway, suggesting that this may be an integral upstream step for modulation of menin 1. The ability of prolactin to increase β-cell mass in mice also depends on the expression of survivin (BIRC5) since a targeted deletion of the survivin gene in the β cells of mice prevented any adaptive change during pregnancy (31). Small molecule antagonists of menin 1, or agonists of survivin, could theoretically promote an increased maternal β-cell mass.

An adaptive increase in β-cell mass during pregnancy may not only result from a re-entry of quiescent cells into the cell proliferation cycle, but also derive from the differentiation of pancreatic β-cell progenitors. Multilineage potential progenitor cells capable of becoming β cells have been identified in both mouse and human pancreas, and in particular are present in small endocrine clusters much smaller than islets, and around the pancreatic ducts (32).

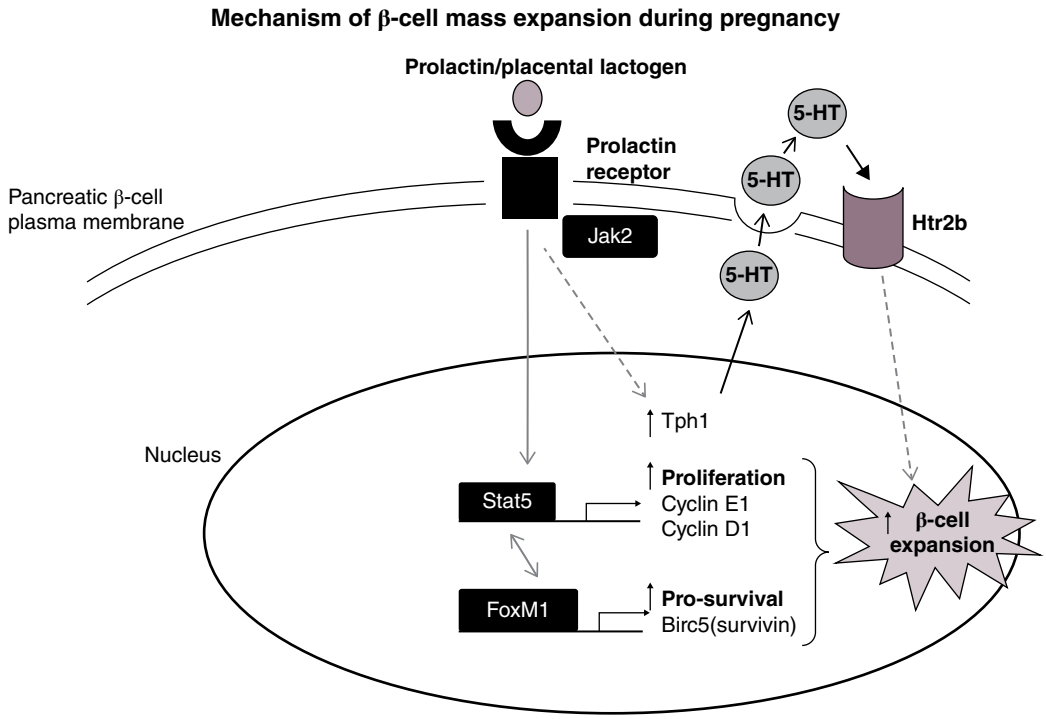

Figure 29.4 Mechanisms by which β-cell mass can increase during pregnancy. Prolactin or placental lactogen binds to the prolactin receptor. Phosphorylation of Jak2 and Stat5 results in an increased expression of cell cycle progression genes, such as cyclin D1 and E1, resulting in β-cell replication. Stat5 can also increase the expression of FoxM1, leading to increased expression of the pro-survival gene, *Birc5*. Activation of the prolactin receptor can also increase the expression of tryptophan hydroxylase-1 (Tph1), causing the generation and release of serotonin (5-HT). Serotonin can activate β-cell proliferation following signaling through the Htr2b receptor.

Smukler *et al.* (33) reported that such cells could express insulin in low amounts, but showed extremely low expression of the glucose transporter, Glut2. Such progenitors are therefore poorly responsive to glucose for insulin release, but could differentiate under metabolic stress to become mature, functional β cells. The activation of such resident progenitors could contribute to an increased β-cell mass during pregnancy. When β-cell progenitors in a mouse model were genetically tagged, a dilution of lineage marked cells was observed during pregnancy, suggesting that some new β cells had been generated from progenitor cells (34).

Whether similar mechanisms account for an adaptive change in β-cell mass during human pregnancy has not been examined critically. Butler *et al.* (10) used human postmortem samples and found no change in β-cell mitotic index or the relative area of β cells per islet between pregnant and non-pregnant subjects, but they observed an increase in the numbers of isolated insulin-expressing cells scattered throughout the acinar tissue and in juxtaposition to the pancreatic ducts. This suggests that neogenesis of β cells from progenitors can occur during human pregnancy, as well as the mitotic activation of existing β cells. Such a mechanism is supported by the reappearance of C-peptide during pregnancy in a cohort of 90 pregnant women with preexisting T1DM with a mean duration of disease of 17 years, where residual β cells would be expected to be few (35).

Changes in transcription factor expression are also required for the activation of

compensatory β-cell growth in pregnancy, and these might also signal via changes in menin 1. For instance, hepatocyte nuclear factor-4α (HNF4α) activates the Ras-Erk1/2 kinase mitogenic pathway (36) and forkhead box protein M1 (FoxM1), which is activated downstream of the PI3K signaling pathway, suppresses menin 1 levels, and activates apoptosis-inhibiting factors such as survivin (37,38).

Changes to the Islet Paracrine Environment During Pregnancy

Changes in the trophic environment of the islets of Langerhans during pregnancy are far more extensive than the added presence of PL, and the wider microenvironment needs to be understood for the selection of candidate molecular targets to increase β-cell mass. Multiple paracrine factors are altered in abundance in the maternal pancreas during pregnancy. A genomic study of islet adaptation to pregnancy in rats identified a 2.5-fold increase in the expression of regenerating protein gene-3a (*Reg3a*) and a threefold increase in epidermal growth factor (EGF) expression (39). *Reg* genes activate cyclin D1 expression and β-cell proliferation through a PI3K-mediated phosphorylation of activating transcription factor-2 (ATF2). Treatment of normal adult mice with mouse or human Reg3 peptides caused an increase in the mean size of small islets due to cell proliferation and the appearance of increased numbers of insulin-expressing cells (40). Similarly, mice expressing a mutant EGF receptor failed to undergo adaptive β-cell growth after feeding of a high-fat diet or during pregnancy, demonstrating that EGF signaling is required for β-cell plasticity in adult animals (41).

Adult mice bearing a targeted deletion of the hepatocyte growth factor (HGF) receptor, c-Met, were unable to regenerate β cells following treatment with the selective toxin, streptozotocin (STZ), or partial pancreatectomy, whereas in wild-type animals, where regeneration occurred, the endogenous levels of c-Met on β cells were elevated (42). HGF action is essential for β-cell expansion in the pregnant mouse since targeted pancreatic deletion of *c-Met* resulted in a failure of adaptive β-cell proliferation and an increased rate of apoptosis (43). Deletion of *c-Met* was associated with a reduction in the levels of prolactin receptor mRNA in islets, a reduced activation of Stat5, a lower expression of FoxM1, and a failure to suppress p27, all of which suggest that HGF is necessary for a PL-initiated mitogenic response by β cells. The pregnant mice lacking *c-Met* expression developed GDM, with hyperglycemia and impaired glucose tolerance. Changes in the presence of growth factors known to stimulate β-cell proliferation and suppress apoptosis occur in the human maternal circulation also, including HGF (44) and insulin-like growth factor-1 (IGF1) (45). However, it is not known if this reflects an increased paracrine presence within the islets. Since peptide hormones do not cross the placenta, peptide agonists of c-Met could potentially be used to increase β-cell mass.

Serotonin produced locally within the islets of Langerhans has also been linked to both an increase in β-cell mass and increased GSIS, and is activated via the prolactin receptor. This is mediated, in part, through the increased expression of the serotonin-synthesizing enzymes, tryptophan hydroxylases 1 and 2, during pregnancy, resulting in an increase in the islet content of serotonin (Figure 29.4) (46). Serotonin regulates GSIS through the activation of the 5-hydroxytryptamine (5-HT) 3a and 3b receptors, whereas the ability of serotonin to increase β-cell mass is mediated by HTr2b in mid-gestation in mouse and HTr1d in late gestation (47). Consequently, animals null for HTr3a demonstrated glucose intolerance during pregnancy despite undergoing an adaptation of β-cell mass (48).

Cell-Based Therapy to Prevent Gestational Diabetes

Regeneration of β cells requires a parallel expansion of the islet microvasculature, at least in rodents, and this can be induced by transplantation of endothelial progenitor cells, which contribute to angiogenesis. Endothelial progenitor cell presence in the human maternal circulation increases throughout the course of pregnancy, and correlates with increasing levels of serum estradiol (49,50). In mouse, the proliferation rate of bone marrow hematopoietic stem cells, a fraction of which develop into endothelial cells, is enhanced by estradiol (51). Correspondingly, women with gestational diabetes or impaired glucose tolerance during pregnancy showed a reduced number of circulating endothelial progenitor cells (52). Whether endothelial progenitor cell presence is a stimulus to adaptive changes to human β-cell mass during pregnancy remains to be demonstrated. However, the transplantation of human mesenchymal stem cells derived from either umbilical cord blood or adipose tissue has been shown to increase C-peptide and reduce autoregulatory T cells in patients with either T1DM or T2DM (53,54), suggesting that the concept of a stem cell–induced β-cell expansion might also be feasible for gestational diabetes.

We and others showed that transplantation of bone marrow stem cell fractions resulted in the reversal of diabetes in experimental animals (55,56). Trans-differentiation of bone marrow cells directly into insulin-expressing cells is possible, but the frequency of this happening is rare and could not account for a rapid normalization of blood glucose and increased insulin release. It is more likely that β-cell regeneration results from the differentiation of bone marrow–derived vascular progenitors into endothelial progenitor cells, present as isolated cells infiltrating the islets and/or pancreatic ducts, or by direct incorporation into the microvasculature during neovascularization (55). Neovascularization is followed by an increase in endogenous β-cell replication, or by neogenesis of new islets from the pancreatic ducts (55,57).

Further refinement of this approach for clinical use requires knowledge about which fraction of bone-marrow stem cells optimally induce endogenous β-cell expansion. Bone marrow contains both pro-angiogenic hematopoietic progenitors (hematopoietic stem cells [HSCs]) of myeloid/monocyte lineage, and true endothelial progenitor cells that are of mesenchymal lineage (mesenchymal stem cells [MSCs]) (58). HSCs may function as paracrine support cells for vasculogenesis, or, as we have demonstrated, could directly differentiate into functional endothelial cells (55). We utilized mice expressing a genetic reporter under the control of the *Vav* gene promoter to label the HSCs. The *Vav* gene is ubiquitously expressed by all hematopoietic lineage cells and remains active on differentiated cell progeny, including T cells, B cells, and macrophages (59). Tagged cells were located within the pancreas at all ages, lining the pancreatic ductal epithelium as well as around and within the islets (60). Small islets originating from the ductal epithelium were surrounded by hematopoietic lineage cells. Following the induction of diabetes with STZ, the abundance of HSC-derived cells within islets and around ducts significantly increased, corresponding with a recovery of β-cell mass. Although such cells did not express insulin, approximately 30% co-stained with the endothelial cell marker, CD31, and this significantly increased after STZ treatment, strongly suggesting that endogenous HSC-derived endothelial progenitor cells were involved in the expansion of β-cell mass.

The MSC component of bone marrow can reverse hyperglycemia in experimental T1DM through an induction of endogenous β-cell regeneration (61), but MSCs may additionally transdifferentiate into insulin-expressing cells within the islets and ducts, the latter possibly representing islet neogenesis

(62,63). Bone marrow–derived MSCs possess chemokine receptors, allowing them to hone quickly to the diabetic pancreas in response to chemokines present in islet cell extracts (64), to improve islet vascularization (65) and maintain islet morphology (66). We showed that MSCs, identified by CD44 localization, were more abundant in pancreas after damage with STZ, but were found dispersed within the exocrine tissue and not within the islets (67).

We have directly compared the ability and mechanisms by which bone marrow–derived MSCs or HSCs can induce β-cell regeneration following grafting directly into the pancreas of diabetic mice, and the importance of the age of the donor animals (67). Hyperglycemia and plasma insulin improved in diabetic mice 21–40 days after grafting with either HSCs or MSCs from young donors, compared to sham-grafted controls. Glucose tolerance was improved following stem cell grafting within 7 days for MSCs, and 14 days for HSCs. HSC treatment caused an increase in the proliferation of β cells remaining within the islets, whereas MSC treatment caused the proliferation and differentiation of β-cell progenitors within the extra-islet small endocrine cell clusters. The ability of both HSCs and MSCs to promote β-cell regeneration decreased with the age of donor, but MSCs could be "reconditioned" by the induction of hypoxia *in vitro* prior to grafting (68). Therefore, both MSCs and HSCs are mobilized following pancreatic β-cell loss, and can induce β-cell regeneration, but by different mechanisms that are likely to be complementary. Such studies should be repeated in pregnant animals made mildly diabetic to examine the ability of HSCs or MSCs to increase the adaptability of β-cell mass to pregnancy.

Microbiota and Short-Chain Fatty Acids (SCFAs)

There are estimated to be over 5000 bacterial species present within the human gut, although 95% of these belong to three phyla, Bactereoides, Firmicutes, and Actinobacteria (69). Differences in the proportional presence of these are associated with obesity, and in humans the amount of weight loss achieved during lifestyle interventions is related to the initial constitution of the microbiome (70). During pregnancy, the proportional presence of Bacteroides and Staphylococcus is increased in overweight compared to normal-weight women, and substantial changes in gut microbiome composition occur during second and third trimesters (71). When a human third-trimester microbiome was transferred to aseptic mice, there was an increased adiposity and the appearance of insulin resistance, suggesting that changes in the human microbiome may contribute to the insulin resistance of pregnancy (72). Patients with GDM showed a further alteration in the diversity of their gut microbiome compared to nonpregnant subjects (72). Could modification of the microbiome through probiotic treatment therefore offer protection against the development of gestational diabetes? Two recent trials have examined this possibility. A study from Finland examined 256 pregnant women at risk of GDM who were randomized in first trimester to a probiotic dietary intervention group or a control group, with or without intensive dietary and lifestyle counseling (73). Maternal glycemia was reduced during pregnancy in the women receiving probiotics, and the rate of GDM was reduced to 13% compared to 36% in controls for women also receiving lifestyle counseling. Women who received probiotics had improved insulin sensitivity indices, higher circulating insulin, and improved glucose tolerance. A second trial focused on a group of 138 obese women at 24–28 weeks gestation who were at high risk of GDM (74). Women receiving probiotic supplements showed no difference in the percent developing GDM, or in glucose tolerance. A third randomized controlled trial to examine the effects of probiotics in the prevention of GDM in overweight and obese women, the SPRING study, is presently in progress (75).

The possible mechanisms of action of probiotics, should this improve glycemic control in women at risk of GDM, are likely to be related to the effects of the gut microbiome on energy availability and metabolism. The gut microbiome facilitates the anaerobic fermentation of otherwise indigestible polysaccharides to yield SCFAs such as butyrate, propionate, and acetate. When the gut microbiome from conventional mice was transferred to aseptic mice, there was an increase in fat mass within 10 days and a decrease in insulin sensitivity (76). SCFAs are rapidly and actively transported across the lower gut epithelium. Butyrate can be used as an energy source by the colonic epithelium; acetate for energy production by muscle, adipogenesis, and the inhibition of lipolytic activity; and propionate enhances hepatic gluconeogenesis (77). Pregnancy is associated with changes in SCFA production and appearance in the maternal circulation, presumably reflecting the altered microbiome of pregnancy (78). Serum acetate levels were positively correlated with maternal weight gain during pregnancy and maternal adiponectin levels, while propionate negatively correlated with maternal leptin levels and offspring birthweight. SCFA production is therefore likely to influence maternal metabolic control. Furthermore, genomic analysis of the microbiome demonstrated changes associated with T2DM, including a reduction in species involved in the production of butyrate (79), although data from gestational diabetes are lacking.

How could alterations in SCFA generation from the microbiome cause changes in maternal metabolic control and relate to the risk of GDM? SCFAs activate intracellular signaling pathways through interaction with the GPCRs free fatty acid receptor-3 (FFAR3), also called Gpr41, and FFAR2, or Gpr43 (80). Both receptors are widely expressed, including the entero-endocrine cells of the gut epithelium, adipocytes, and pancreatic β cells (81). Within adipose tissue, activated FFAR3 has been shown to stimulate the release of leptin production and to increase lipid metabolism, whilst generally reducing modulators of chronic inflammation that contribute to insulin resistance such as tumor necrosis factor-α (TNFα) and interleukin-12 (IL12) (82). Mice lacking the *Ffar2* gene were more obese than wild-type mice, whereas mice overexpressing *Ffar2* only in adipose tissue were excessively lean under normal dietary conditions (83). No differences were found if the mice were maintained in a germ-free environment, showing that FFAR2 regulates adipose insulin signaling by SCFAs that derive from the gut microbiome. FFAR2 activation can therefore suppress fat accumulation. In similar studies, mice lacking the *Ffar3* gene demonstrated increased body fat content and reduced energy expenditure (84).

Recently, FFAR2 and FFAR3 have been identified within enteroendocrine L cells, where stimulation by SCFAs mediates the downstream release of the appetite-reducing hormone, peptide-YY (PYY) (85), and the release of the incretin, glucagon-like peptide-1 (GLP1) (86). GLP1 potentiates GSIS, inhibits β-cell apoptosis, and improves insulin sensitivity (87). However, SCFA can also have a direct effect on GSIS from the pancreas (Figure 29.5). Exposure of MIN6 cells to SCFAs caused an immediate increase in intracellular Ca^{2+}. Also, perfusion of isolated mouse islets with SCFAs resulted in an increased GSIS, mediated by both FFAR2 and FFAR3, while perfusion of islets from *ffar2*−/− mice showed a reduced GSIS when compared to wild-type animals (88). Similarly, treatment of human islets with a SCFA agonist to FFAR2 increased insulin release (89). Changes in SCFA availability associated with an altered microbiome could, therefore, specifically alter glycemic control during pregnancy at the level of GLP1 release, β-cell insulin release, and adipokine secretion at the adipocytes. Interestingly, dietary supplementation with SCFA was shown to protect against the diabetogenic effects of a high-fat diet in mice by causing a PPARγ-dependent switch from lipogenesis to lipid oxidation (90).

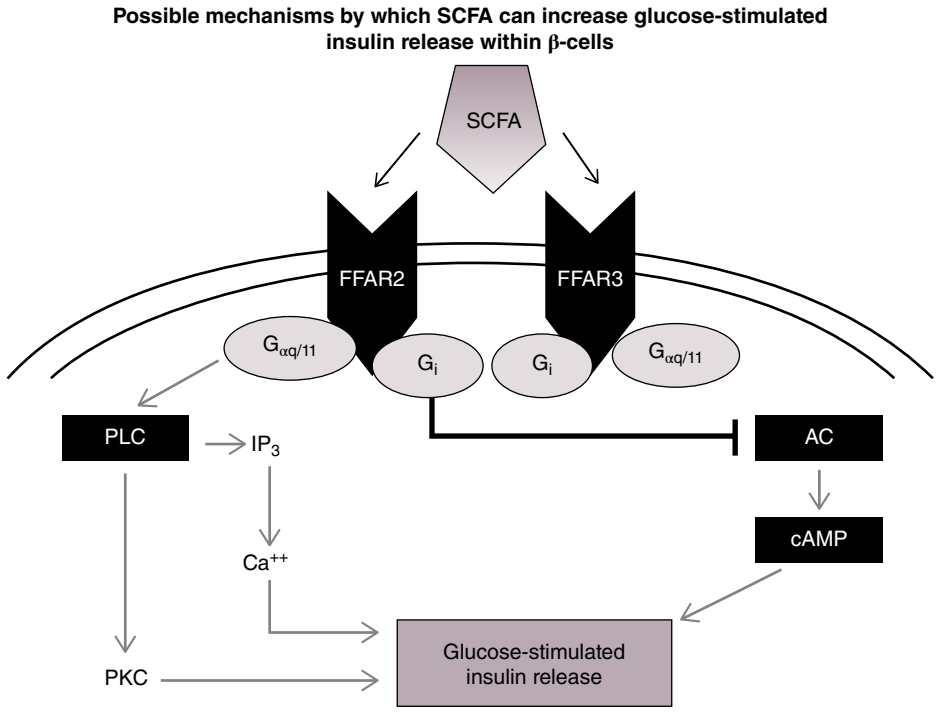

Figure 29.5 Possible mechanisms by which short-chain fatty acids (SCFAs) can increase glucose-stimulated insulin release from β cells. SCFAs bind to the free fatty acid receptors, FFAR2 and FFAR3, causing the activation of the G-protein subunits $G\alpha_{q/11}$ or G_i. $G\alpha_{q/11}$ activation causes the activation of phospholipase C (PLC), further activating protein kinase C (PKC) and generating inositol triphosphate (IP_3). IP_3 causes an increase in intracellular calcium, resulting in insulin release. Conversely, activation of G_i can block the action of adenylate cyclase (AC) to decrease levels of cyclic adenosine monophosphate (cAMP) to reduce insulin release. A net change in the balance of these two pathways in response to SCFAs can result in increased insulin secretion.

Supplementation studies with specific SCFAs for the prevention of GDM in humans have not been reported, but in animal studies, supplementation with butyrate improved glycemia and increased insulin levels and the proliferation rate of β cells in obese, pregnant mice (91).

In conclusion, a failure of physiological adaptation of maternal β-cell mass and/or function during pregnancy can result in GDM, for which there is, as yet, no effective prevention strategy. Future therapeutic strategies could target an increase in functional β-cell mass through manipulation of the nutritional, paracrine, and cellular environment of the maternal endocrine pancreas. Since maternal β-cell mass normally involutes to nonpregnant amounts following parturition, the discontinuation of such theoretical therapies after birth should not result in long-term pathology.

Multiple-Choice Questions

1 What does pancreatic β-cell mass do during normal pregnancy?
- **A** Increase
- **B** Decrease
- **C** Stay the same

Answer: A.

2 The placenta produces both (A) variant growth hormone and (B) placental lactogen directly in the maternal circulation during pregnancy. Which hormone predominantly drives the insulin resistance of pregnancy?

Answer: A, variant growth hormone.

3 Does probiotic supplementation during pregnancy increase the production of (A) long-chain fatty acids or (B) short-chain fatty acids in the gut?

Answer: B, short-chain fatty acids.

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Abbreviations

Akt	protein kinase B (or PKB)
ATF-2	activating transcription factor-2
Bcl6	B-cell lymphoma-6 gene
Birc5	baculoviral IAP repeat containing 5 protein (survivin)
c-Met	hepatocyte growth factor receptor
cyclin D1	a cell cycle progression protein
EGF	epidermal growth factor
Erk1/2	extracellular-signal-regulated kinases-1/2
FFAR	free fatty acid receptor
FoxM1	forkhead box protein M1
GH-V	placental growth hormone
GLP1	glucagon-like polypeptide-1
Glut2	glucose transporter-2
GPCR	G-protein-coupled receptor
GPR54	kisspeptin receptor
GSIS	glucose-stimulated insulin release
HGF	hepatocyte growth factor
HNF4α	hepatocyte nuclear factor-4α
HSC	hematopoietic stem cell
5-HT	5-hydroxytryptamine
HTr	5-hydroxytryptamine (serotonin) receptor
IGF1	insulin-like growth factor-1IL12 interleukin-12
Jak2	Janus kinase 2
kiss1	kisspeptin 1 gene
MAPK	mitogen-activated protein kinase
MSC	mesenchymal stem cell
PI3K	phosphoinositol 3 kinasePL placental lactogen
PLC-β	phospholipase C-β
PYY	peptide YY
Ras	a small GTPase protein
Reg	regenerating protein gene
SCFA	short-chain fatty acid
Stat5	signal transducer and activator of transcription-5
STZ	streptozotocin
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TNFα	tumor necrosis factor-α
Tph1	tryptophan hydroxylase-1
Vav	a guanine nucleotide exchange factor gene

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