POCKET NOTEBOOK

POCKET OBSTETRICS AND GYNECOLOGY

K. Joseph Hurt

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Pocket OBSTETRICS AND GYNECOLOGY

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PREFACE

Pocket Medicine has become as important to the new intern or medical student as her first stethoscope and reflex hammer. All of the books in the series are convenient references with concise and up-to-date information on the most frequent problems encountered by the eager student and busy house officer. This first edition of *Pocket OB-Gyn* now provides a tool of the same high caliber and utility to students of women's health and the unique clinical sciences of obstetrics and gynecology.

We produced this handbook using a now well-tested model of collaborative authorship. Residents prepared evidence-based chapters on the most important topics in ob-gyn, with oversight from fellows and faculty experts. Each chapter contains the brief background, differential diagnoses, clinical algorithms, and literature citations that will allow you to shine during rounds by quickly formulating basic management plans and reviewing key points of pathophysiology. I remember many nights as a student intern, using *Pocket Medicine* to guide my initial management, or at least help formulate thoughtful questions for my chief and attendings. We hope this book will serve just such a purpose in obstetrics and gynecology.

Special appendices on pelvic anatomy, common ob-gyn procedures, ACLS algorithms, and drugs in ob and breastfeeding, may be especially useful quick references. The format is consistent with the other books in the series, so we have grouped problems by organ system. Because ob-gyn involves so much interdisciplinary learning and training, you may find that some closely related topics are spread among different chapters (eg, preeclampsia and eclampsia are found in the cardiovascular and neurology chapters). Don't worry, we have prepared a carefully cross-referenced index to help you find the information you need. We have also carefully selected appropriate references that use the *Pocket Medicine* format and are immediately retrievable in a PubMed search should you wish to read more on a topic.

Of course this book is *not* a comprehensive text, and cannot take the place of years of reading, supervised training, and clinical experience. Furthermore, the information will require continuous revision and the reader's own evaluation and vigilance, as rapid advances in medical knowledge improve our understanding of pathophysiology and raise the standard of clinical care. To that end, we encourage you to submit suggestions, ideas, and feedback, or to let us know if you would like to participate as a future author. I promise to review all comments and incorporate them as we prepare the next edition. Please email me directly at ***LWW.PocketOBGYN.Editor@gmail.com*** and let us know how we can improve this text.

We hope that you find in these pages the core knowledge and practice guidelines that will facilitate excellent patient care and make your life as a student and house officer more efficient and rewarding. From L&D triage to the operating room to the oncology floor, we think you will find *Pocket OB-Gyn* an indispensable aid.

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FOREWORD

Pocket Obstetrics & Gynecology is the most recent addition to the "pocket series" that has helped years of trainees cope with today's complex medical practice. Most medical texts are put together by a few senior experts, with content chosen by those authors alone. In contrast, *Pocket OB/GYN* is user-driven because it contains information the **trainee** has found that he/she needs to know. Residents, fellows, and faculty members have collaborated in condensing the diverse aspects of *OB/GYN* into the fewest possible words, presenting the most important nuggets in a format that facilitates easy extraction.

The subjects vary from generalized common patient complaints to an array of conditions that are commonly, or sometimes very uncommonly, associated with women's health and pregnancy. Therapies, complete with dosages of medications, are included, as well as easily accessible references. An example of the thoroughness of this endeavor is the inclusion even of the credentials of affiliated providers.

Before writing this foreword, I thought I would quickly skim through the text, but I soon found that every chapter contained clinical gems that I had forgotten long ago while pursuing a channeled career in perinatal medicine. Skimming became difficult but the deadline pushed me along, so I took a different approach. I tried to stump the text with some pet, but somewhat esoteric, items that I thought would not be covered. In each instance *Pocket OB/GYN* had the answer. So now I have decided to use this book as my "Google Translator" to decipher the foreign language that my colleagues in other subspecialties are using during their Grand Rounds presentations.

Pocket Obstetrics & Gynecology is a product of remarkable collaboration that does more than suit the needs of those training in obstetrics and gynecology. It is a resource for anyone seeking a thorough, unembellished review of the entire contemporary practice of our specialty. Whether it fits in my pocket or not, I plan to keep it within easy reach.

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WELL-WOMAN (ANNUAL) EXAM

Well-woman Visit (*Obstet Gynecol* 2012;120:421)

- **Purpose:** Promote healthy lifestyle, minimize health risks. Screen, evaluate, counsel, & immunize. Identify reproductive concerns. Address age-specific risks. Offer contraception & preconception planning. Optimize primary care health. Age-related exam components at www.acog.org/About_ACOG/ACOG_Departments/Annual_Womens_Health_Care/Assessments_and_Recommendations.
- **Screening:** Diet/nutrition/exercise, safety/seat belts, diabetes, obesity, metabolic syn, osteoporosis, thyroid dz, breast cancer, cervical dysplasia, colon cancer, & skin cancer.
- **Timing:** 1st Ob/Gyn visit at 13–15 yo
- Hx for well-woman visit:
  - Chief complaint/HPI w/ review of systems/PMH/PSH
  - **Ob hx:** Including dates, gestational age, infant wt, deliv mode, complications
  - **Gyn hx:** LMP: certain?
    - **Menstrual hx:** Age at menarche? Regular cycles? Cycle length (days)? Days of flow? Degree of flow (light, mod, heavy)? Dysmenorrhea? Assoc sx?
    - **STIs:** Gonorrhea, chlamydia, herpes, syphilis, HIV, other? Rx?
    - Abn pap smears ever? Date of last pap smear?
    - # lifetime sexual partners? Current sexual partners (men, women, or both)?
    - Past & current forms of birth control?
    - Any h/o physical, sexual, or emotional abuse?
    - **Incontinence:** Urinary or fecal?
    - **Sexual fxn:** Desire? Pain? Other concerns?
  - Current meds w/ dose, route, schedule, indication
  - Allergies, including nondrug & environmental allergens, w/ rxn & severity
  - **Soc hx:** Including tobacco, EtOH, & illicit drug use
  - **FHx:** Specifically address Gyn cancers including cervical, endometrial, ovarian, breast. Also colon cancer, bleeding/clotting disorders, fetal anomalies/birth defects.
- Physical exam for well-woman visit:
  - VS, ht, wt, BMI, general appearance, general physical exam, breast, thyroid, cardiovascular, pulmonary, abdominal, rectal, & pelvic (speculum/bimanual).
  - **Pelvic exam:** Annual pelvic exam for ≥21 yo (no supporting data). Not req for OCPs. External only <21 yo unless indicated; exam under anesthesia for very young.

Leading causes of death among females of all races in the United States (2010)

Age 15–24	Age 25–34	Age 35–44	Age 45–54	Age 55–64	Age 65+
Unintentional injury	Unintentional injury	Cancer	Cancer	Cancer	Heart dz
Suicide	Cancer	Unintentional injury	Heart dz	Heart dz	Cancer
Homicide	Suicide	Heart dz	Unintentional injury	Chronic respiratory dz	Stroke
Cancer	Heart dz	Suicide	Chronic liver dz	Stroke	Chronic respiratory dz
Heart dz	Homicide	Stroke	Stroke	Diabetes mellitus	Alzheimer dz
Pregnancy complication	Pregnancy complications				

From CDC Leading Causes of Death in Females. At http://www.cdc.gov/women/lcod. Accessed March 20, 2014.

Cancer Screening Guidelines

- **Cervical dysplasia:** See below
- **Breast cancer:** See below (*Obstet Gynecol* 2011;118:372)

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Breast cancer screening modalities		
Screening	**Performance**	**Guidelines**
Mammogram	Sens 74–95% Spec 89–99%	ACOG: >40 yo annual screening, or 10 y younger than 1st-degree affected relative. Stop at age 75. USPSTF: <50 yo screening every 2 y based on individual pts; 50–74 yo every 2 y ACS: >40 yo annual screening NCI: >40 yo, screen every 1–2 y
Ultrasound	Sens 80–85% Spec 60–70%	Adjunct to mammography, esp in young women w/ dense breast tissue. Used for bx guidance. Not 1st line.
Clinical breast exam (5+ min/ breast in studies)	Sens 40–70% Spec 86–99% PPV 3–4%	ACOG: 20–39 yo every 1–3 y; >40 yo annually USPSTF: Insuff data to recommend ACS: 20–39 yo every 1–3 y; >40 yo annually
Self breast exam (monthly exam, day 7–10 of cycle)	Sens 20–30% Difficult to assess	Breast awareness education, all ages. ACOG: Consider for high-risk pts USPSTF: Not recommended ACS: Optional for >20 yo Up to 70% of breast cancer found on self-exam
Breast MRI	Sens 71–100% Spec 37–97% (in younger ♀ w/ denser breast tissue)	For >20% lifetime risk, or known BRCA1 or BRCA2, 1st-degree relative w/ BRCA & no personal testing, h/o chest radiation btw 10 & 30 yo, genetic syndromes (eg, Li-Fraumeni, Cowden). Not recommended for personal h/o breast cancer or dysplasia, & not for avg risk women.

- **Colorectal cancer:** Begin age 50 yo. Consider 45 yo if AA. Younger if FHx. Prefer colonoscopy q10y; other acceptable methods:
  Fecal occult bld or fecal immunochemistry testing q1y w3 collected samples
  Flexible sigmoidoscopy q5y
  Combination of fecal occult bld & flexible sigmoidoscopy
  Double contrast barium enema q5y
- **Skin cancer:** Counsel regarding ultraviolet exposure. Consider annual skin exam & referral for high risk. Use asymmetry/border/color/diameter/enlargement criteria.
- There are no recommended guidelines for routine screening for ovarian, endometrial, or lung cancer. H&P guide investigation.

BENIGN BREAST DISEASE

Workup of a Breast Mass

- Palpable breast mass → mammogram/US → needle bx after imaging or 2 w prior (to avoid artifact) w/ FNA or core needle bx → excision if concerning or rpt exam in 6 w
  Likely benign mass: Mobile, soft, smooth, <2 cm
  Concerning mass: Hard, fixed, single, irreg margins, >2 cm, adenopathy, bloody nipple discharge, overlying skin changes, nonsymmetric breast appearance
- Triple test = clinical exam + imaging + breast bx → >99% NPV for concordant negative triple test. If all negative, monit q6mo by clinical exam alone. If any of these assessments sugg malig → excision.

Mammography, BIRADS (Breast Imaging Reporting and Data System) scoring			
Score	**Description**	**Risk of cancer**	**F/u**
0	Incomplete	NA	Need to rpt mammogram or breast US
1	Negative	Minimal	Continue routine screening
2	Benign finding	Minimal	Continue routine screening
3	Probably benign findings	2%	F/u mammogram in 6 mo to reassess

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Score	Description	Risk of cancer	F/u
4	Suspicious abnormality	25–30%	May need bx
5	Highly suggestive of malig	95%	Core or excisional bx of mass
6	Biopsy-confirmed breast cancer known	100% (known)	Excision, chemo, or radiation

Abnormal Radiology Findings

- Poorly defined soft tissue density, irreg borders – sometimes in a "star" appearance
- Clustered microcalcifications in 1 area
- Calcification w/i a soft tissue mass/density
- Asym w/i the breast, or skewing of breast tissue
- New abnormality not previously seen
- ***Worrisome findings:*** Soft tissue mass, clustered microcalcifications
- Most common breast mass in <25 yo, gradual growth, "lumpy" on exam, low risk for cancer → if increasing in size, consider bx

Benign breast disease	
Mastalgia	**Definition:** Breast pain, can be cyclic or noncyclic. *Cyclic:* Usually most painful before menses, relieved w/ menses, unilateral or bilateral. May be due to edema & inflammation & can form cysts that are relieved w/ aspiration. *Noncyclic:* May be due to hormonal fluctuations, muscle soreness, & mostly w/o an identifiable cause. **Tx:** Most resolve spontaneously, can be helped w/ NSAIDs, supportive bras, OCPs, recommend decreasing caffeine & chocolate intake, magnesium therapy is controversial.
Mastitis	**Definition:** Acute cellulitis that can progress to an abscess, typically seen in breast-feeding women; presents often in a wedge distribution of ducts w/ warmth, erythema, tenderness, fevers, & malaise made by clinical dx. **Tx:** Dicloxacillin 500 mg QID ×10 d, or cephalexin 500 mg QID ×10 d, warm compresses, pt must continue breast-feeding to help provide an outlet for drainage. Infants are safe to breast-feed as bacteria originated from infant's mouth flora. *(Nipple discharge: 95% of time from benign causes)*
Breast cysts	**Definition:** Fluid-filled cyst is usually simple from terminal duct, common in 35–50 yo, causes localized breast pain, usually resolves. **W/u:** Expectant mgmt for 6 w or aspiration or breast US → if sanguineous aspirate recurs, or concerning on radiology, refer for breast bx/excision.
Fat necrosis	**Definition:** Hard or indurated areas usually after trauma (seat belt, bx, radiation, infxn). Common in subareolar region. **W/u:** Can asses w/ mammography or breast US.
Fibroadenoma	**Definition:** Most common breast mass in <25 yo, gradual growth, "lumpy" & mobile on exam, low risk for cancer. **W/u:** If increasing in size, consider bx.

Nipple Discharge

- Very common complaint, usually benign
- **Nml discharge:** Common on stimulation, bilateral, serous
- **Galactorrhea:** Milky discharge unrelated to Preg, bilateral. Causes: Unknown, endocrine abnormalities a/w amenorrhea or hypothalamic dysfxn from endocrine abnormalities or pituitary mass, many psychiatric meds (Dopamine inhibitors).
  - **W/u:** HPI asking about visual changes, HAs, menses, thyroid sx, current meds; PE looking at visual field defects (tunnel vision).
  - **Labs:** Prolactin, TSH, free T4, CT head looking for a pituitary adenoma if elevated prolactin.
- **Nonbenign discharge:** Unilateral, bloody (can guaiac test if not visible), serous, or colored discharge can be a/w breast mass or overlying skin changes. Caused by carcinoma, intraductal papilloma, duct ectasia, fibrocystic changes.
  - **W/u:** Send discharge for cytology, mammogram if >35 yo or breast US if <35 yo. Cytology is of little value & has a low sens.

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BREAST CANCER

Epidemiology

- Breast cancer is the most common cancer among women. 2nd most common cause of cancer death in women (after lung cancer). From 1998–2007 the incid & mortality rates have decreased. Developed nations have a higher incid than developing.
- AA women have a lower incid rate, higher mortality rate, & higher stage at dx.

Risk Factors

- **Age >40 yo:** 95% of breast cancers occur in women >40 yo
- **FHx of breast cancer:** 1st-degree relatives, premenopausal breast cancer, BRCA1 & BRCA2 mutations (tumor suppressor genes, autosomal dominant, account for 5–10% dx, but confer >80% lifetime breast cancer risk).
  BRCA 1/2: 50–85% risk breast cancer, 15–40% risk ovarian cancer → risk reducing mastectomy decreases risk by 90%. BRCA testing recommended for 1st-degree relative w/ breast cancer, relative w/ breast cancer <50 yo, 3+ 1st- or 2nd-degree relatives w/ breast cancer, breast/ovarian cancer in 1st- or 2nd-degree relative, 2+ 1st- or 2nd-degree relatives w/ ovarian cancer, male breast cancer (*Obstet Gynecol* 2008;111:231).
- **Increased hormonal exposure:** Early menarche (<12 yo), late menopause (>55 yo), older age w/ 1st Preg, fewer pregnancies (all these → increased lifetime estrogen exposure)
- **Personal h/o breast cancer:** 0.5–1% risk of developing breast cancer in contralateral breast, majority of recurrences are w/i the 1st 5 y
- **Radiation exposure:** 35% lifetime risk
- **Diet & exercise:** Physical activity & wt control are protective

Premalignant Lesions

- **Atypical hyperplasia:** Ductal or lobular, proliferative lesion similar to carcinoma in situ; includes intraductal papilloma, ductal epithelial hyperplasia, sclerosing adenosis → excision
- **DCIS:** Most common noninvasive breast cancer (1 of 5 new cases), usually dx by mammogram alone, can have breast conserving rx ± tramoxifen ± XRT
- **LCIS:** More common in premenopausal women, 1% risk/y of invasive cancer, sometimes found incidentally → tamoxifen vs. resection

Invasive Cancer

- **Infiltrating ductal:** 60–70% breast cancer; includes mucinous, tubular, & medullary carcinomas, classified by cell type, architecture of mass, & pattern of spread
- **Infiltrating lobular:** 10–15% breast cancer, arising in lobules, multifocal, higher incid of bilaterally
- **Inflamm:** 6% of breast cancer, p/w skin changes, rapid onset in a few weeks, causes diffuse induration & swelling. Dx w/ punch bx of skin & mammogram, tx w/ chemo
- **Phyllodes tumor:** Similar to fibroadenoma, epithelial lined spaces surrounded by monoclonal & neoplastic stromal cells. Classified as benign, intermediate, or malignant based on atypia, mitosis, abundance of stromal cells, median age of dx 40 yo, can metastasize to distant organs w/ lung as primary site; tx w/ wide local incision.
- **Paget dz:** Presents as focal skin changes, assoc mass identified in 60% of cases. Underlying DCIS in 2/3 of cases & invasive cancer in 1/3

Breast Cancer Staging/Prognosis

- Tumor size & nodal metastasis strongly correlated w/ prog
- High expression of estrogen or progesterone a/w better prog
- Overexpression of HER2 (human epidermal growth factor receptor) a/w worse prog
- ER/PR status a/w improved survival rates b/c of targeted therapy of SERMs & aromatase inhibitors (reduce circulating estrogens)

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TNM staging for breast cancer		
T (tumor)	**N (lymph node)**	**M (metastasis)**
Tx: Tumor cannot be assessed	Nx: LN cannot be assessed	M0: No metastasis
T0: No evid of primary tumor	N0: No LN metastasis	M1: Distant clinical, radiologic, or histologic lesions >0.2 mm. *All M1 dx stage 4 prior to neoadjuvant chemo
TIS: Carcinoma in situ	N1: Mets to movable ipsilateral level I, II axillary LNs	
T1 (a, b, c): Tumor <20 mm in greatest dimension	N2: Mets in ipsilateral level I, II axillary LNs clinically fixed or matted; or ipsilateral internal mammary nodes in the *absence* of axillary LN mets	
T2: Tumor >20 mm, <50 mm	N3: Mets in ipsilateral infraclavicular (level III axillary) LN w/ or w/o level I, II axillary LN involvement; or clinically detected ipsilateral internal mammary LN w/ clinically evident level I, II axillary LN mets; or mets in ipsilateral supraclavicular LN w/ or w/o axillary or internal mammary LN	
T3: Tumor >50 mm		
T4 (a, b, c, d): Tumor of any size, direct extension to the chest wall and/or skin (ulceration/nodules)		

From Edge et al. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2011.

Treatment

- Depends on localization of cancer may be chemo, radiation, Surg, any combination of medical & Surg. #1 lawsuit topic for gynecologist (apart from OB): Failure to diagnose or adequately/quickly refer breast cancer (*Med Law* 2005;24:1).
  Surg: Std of care is breast conserving Surg = lumpectomy or partial mastectomy w/ 0.5–1 cm margins often w/ preop wire localization
  General Ob/Gyns refer to breast specialist or general surgeon for eval & excision

CERVICAL CANCER SCREENING

Epidemiology & Definitions (*Obstet Gynecol* 2012;120:1222)

- 2nd most common cancer in women worldwide. Mean age at dx: 40–59 y; bimodal distribution peaks 35–39 y & 60–64 y. Cervical cancer ↓ 50% from 1975 to 6.6/100000 women in 2008 due to pap smear screen.

Pathophysiology

- Caused by HPV infxn. An effective immune system clears HPV infxn; cervical cancer thought to be from long-term HPV infxn. >90% young healthy women clear cervical HPV w/i 1–3 y.
- **HPV:** E (early) & L (late) E6, E7 proteins expressed in malignant cells. E6 → degradation of tumor suppressor p53 → ↑ cell proliferation. E7 binds tumor suppressor pRb (retinoblastoma gene product) → release E2F transcription factors → ↑ replication & cell division. Unchecked cell cycle → ↑ malig.
  High-risk HPV strains: 16, 18, 31, 33, 35, 45, 58 are carcinogenic
  Low-risk HPV strains: 39, 51, 52, 56, 59, 68, 73, 82 (6, 11 cause genital warts)
- **High-risk pts:** Increased sexual contacts, new sexual partner, HIV+ or immunosuppression. These pts do not effectively clear the virus.

Pap Smear Guidelines (*J Low Genit Tract Dis* 2012;16:175)

- Pap smear adequate if transformation zone (junction of squamous & columnar cells w/ embryonic component) is present for cytologic eval. Sens 51%; spec 98%. HPV typing from pap smear cells can also be performed.
  Start screening ≥21 yo regardless of sexual Hx. Do NOT screen ≤21 yo, except HIV+ pts. Recent ↓ in testing frequency retains benefits but minimizes harms & unnecessary procedures. Regardless of pap screening, annual Gyn exam recommended for all. If abn pap, consult current ASSCP guidelines (www.asccp.org).

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Pap smear screening schedules			
	USPSTF	**ASCCP**	**ACOG**
When to start screening	21 yo	21 yo	21 yo
How frequently should you test?			
Age 21–29 yo (pap smear alone if nml)	Every 3 y	Every 3 y	Every 3 y
Age 30 & older			
Pap smear alone if nml	Every 3 y	Every 3 y	Every 3 y
Pap smear w/ HPV cotesting	Every 5 y	Recommended, but no more frequently than every 5 y	Every 5 y as recommended strategy
Age to stop	65 yo if adequate screening	65 yo w/ adequate screening & no h/o CIN 2+ in last 20 y	65 yo if adequate screening & no h/o CIN 2, CIN 3, or adenoCa in situ or cervical cancer in last 20 y
After hysterectomy including cervical removal w/ no h/o CIN 2–3, adenoCa in situ, or prior cervical cancer in last 20 y	No pap screening needed, but annual exam for vaginal & vulvar dz should continue		
HPV vaccinated	No change in screening		
HIV+ women, immunocomp, or in utero DES exposure	Pap twice in 1st year after dx & then annually thereafter; referral to colposcopy w/ ASCUS or high-level dysplasia (*Obstet Gynecol* 2010;116:1492)		

- Pap results reported as:
  ASCUS: Atypical cells of undetermined significance
  LSIL: Low-grade squamous intraepithelial lesion ~ corresponds to CIN 1
  HSIL: High-grade squamous intraepithelial lesion ~ corresponds to CIN 2–3
  AGC: Atypical glandular cells (means columnar cells, has association with CIN 2–3)
- **Management:**
  ASCUS → reflex high-risk HPV testing; if HPV positive refer to colposcopy; if HPV negative rpt according to age appropriate guidelines (www.asccp.org) – OR → rpt pap in 6 mo → if rpt = ASCUS or more refer to colposcopy, if negative return to annual screening
  Pts w/ negative cytology & positive HPV cotesting should either be referred directly to colposcopy or perform high-risk HPV typing. If high-risk type then referral to colposcopy should be made. If no high-risk type (16 or 18) then rpt w/ coscreening in 1 y.
  LSIL/HSIL/AGC: Refer to colposcopy

Special cases: Screening in pregnancy and age <21 y	
Cervical cancer screening in pregnancy (ASCCP)	
ASCUS regardless of HPV	Refer to colposcopy at 6 w postpartum
LSIL	Refer to colposcopy during Preg or at 6 w postpartum, no ECC during Preg
HSIL/AIS/AGS	Refer to colposcopy during Preg, no ECC during Preg
Adols should not be screened before 21 yo, but if they have been:	
Past ASCUS, LSIL, CIN 1	Rpt annually for 2 y & then further screening delayed until 21 yo; refer to colposcopy if persists
Past HSIL, AGC, ASC cannot exclude HSIL, CIN 2–3	Refer to colposcopy w/ ECC
Adols w/ HIV	Pap twice in 1st y after dx & then annually thereafter; referral to colposcopy for ASCUS or higher (*Obstet Gynecol* 2010;116:1492)

Colposcopy

- **Definition:** Direct visualization of the cervix, vagina, & vulva w/ a mobile lighted binocular microscope to identify, map, & bx cervical lesions. Deemed adequate if

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transformation zone is visualized on all sides since this is the region in which abn changes occur. Visualization is aided by:
Acetic acid: Dehydrates cells → lighter appearance in dysplastic cells w/ ↑ n/c ratio/↑ chromatin = "acetowhite changes."
Lugol iodine: Stains nml cervicovaginal epithelial cells dark due to high glycogen content, while dysplastic cells are lighter; used in place of or in addition to acetic acid.
- Abn colposcopic findings include:
Punctation: Small bld vessels visible as small dots
Mosaicism: An interspersing of white & nml epithelial cells
Acetowhite changes: A range of white-hued epithelium w/ diffuse or sharp borders
Atypical vessels: Larger vessels w/i lesions may indicate a more advanced lesion
- Any abn lesions are biopsied to evaluate for preinvasive cancer; colposcopy does not always mean bx; only abn lesions & endocervical canal are sampled.
- **Endocervical curettage:** Curetting the endocervical canal to obtain glandular cells or nonvisualized lesions.
- **Bx results:** Reported as:
CIN 1/mild dysplasia: Confined to lower 1/3 of squamous epithelium
CIN 2/mod dysplasia: Abn cells extending into the middle third of epithelial layer
CIN 3/sev dysplasia: Abn cells extending into the upper third of epithelium
CIS: Full thickness abn cells w/ no invasion of basement membrane

Cervical Dysplasia Management *(Obstet Gynecol 2013;121:829)*
- CIN 1 → can follow conservatively w/ surveillance; consider conization if persists >2 y
- CIN 2 → consider conization or follow w/ rpt pap/colposcopy, esp if young
- CIN 3 → conization/LEEP
- CIS → conization
- Invasive cancer → refer to Gyn oncology (see Chap. 21)
- See ASCCP for most up to date recommendations (www.asccp.org)

LIPIDS & CHOLESTEROL

Definitions and Treatment

Definitions for cholesterol		
LDL – primary target	<100 100–129 130–159 160–189 ≥190	Optimal Near optimal Borderline high High Very high
Total cholesterol	<200 200–239 ≥240	Desirable Borderline high High
HDL	<40 ≥60	Low High

- Cardiovascular dz is the leading cause of death (all ages) in women (24%)
- Start screening total cholesterol, HDL at 20 yo, then once every 5 y
- ACOG: Start every 5 y from age 45; at well-woman visits or initial OB or w/ PCP

When to treat cholesterol (www.nhlbi.nih.gov/guidelines/cholesterol/risk_tbl.htm)			
Risk category	**LDL goal (mg/dL)**	**LDL level to initiate lifestyle changes**	**LDL level to consider drug therapy**
CHD or CHD risk equivalents (10-y risk >20%)	<100 (optional <70)	≥100	≥130 (100–129 optional)
2+ risk factors (10-y risk <20%)	<130	≥130	10-y risk 10–20% and ≥130 *or* 10-y risk <10% and ≥160
0– risk factor	<160	≥160	≥190 (160–189 optional)

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- **CHD risk equivalents:** Clinical coronary, symptomatic carotid dz, peripheral artery dz, abdominal aortic aneurysm, DM.
- **CHD risk factors:** Cigarette smoking, HTN (BP ≥140/90 or on an anti-HTN med), HDL ≤40, FHx of premature CHD (M <55 yo, F <65 yo in 1st-degree relative), age (F ≥55 yo).
- 10-y risk calculated using Framingham point risk scores w/ points for age, total cholesterol, smoking, HDL, & SBP.
- For latest guidelines see: *J Am Coll Cardiol* 2013 (PMID 2422016).

Lipid/cholesterol treatment guidelines

Therapy	LDL	HDL	TG = triglycerides	Side effects
Diet & exercise	Trial for 6 mo–1 y; includes decreased saturated fat (<7% total calories) total daily cholesterol intake <200 mg (NCEP diet), decreased salt intake, exercise 30 min most days of the week			
Statin (1st line): HMG-CoA reductase inhibitor: Simvastatin, atorvastatin	20–60% ↓	15% ↑	30% ↓	*Check LFTs prior to starting GI distress, myalgias, myopathy (10%), rhabdomyolysis rare
Resins: Bile acid sequestrants: Cholestyramine, colestipol	15–30% ↓	5% ↑	Possibly increased	*Can raise TGL, do not use in TGL >250 Bloating, hard stool, constipation
Ezetimibe (cholesterol absorp inhibitor)	20% ↓	5% ↑	—	Dose: 10 mg/d; monit LFTs as w/ statins
Nicotinic acid (niacin)	10–15% ↓	15–30% ↑	40% ↓	Flushing (take w/ meals, tx w/ ASA); monit uric acid gluc, LFTs, DM pts only use w/ A1C <7%
Fibrates: Fenofibrate	5–15% ↓	10–20% ↑	30–50% ↓	GI discomfort, rash, pruritus

- Hormone effects on lipids:
  Estrogen: ↓ LDL, ↑ HDL, & ↑ TG
  Progestin: Antagonized estrogen changes → ↑ LDL, ↓ HDL, & ↓ TG
- ACOG recommends: LDL >160 or multi CAD risk factors, counsel toward nonhormonal contraception. 2× ↑ MI risk in ♀ w/o CAD on hormonal therapy
- Postmenopausal women on HRT (estrogen &/or progestin) → 29% ↑ in CHD events; no indication for HRT to prevent CHD. Women on HRT had a 41% ↑ in stroke events (*JAMA* 2002;288:321). Newer data since the WHI trial sugg younger postmenopausal women (<50 yo) on HRT do not have ↑ CHD. See Chap. 5.

OBESITY

Definitions

Definitions for obesity

CDC wt category	BMI for adults (>21 yo)
Underweight	<18.5
Nml wt	18.5–24.9
Overweight	25–29.9
Obese	≥30
Additional categories used by researchers	
Class 1 obesity	30–34.9
Class 2 obesity	35–39.9
Class 3 obesity	≥40

- BMI = [Wt in lb/(ht in inches)^2] × 709 = [Wt in kg/(ht in inches)^2]

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Epidemiology (CDC NHANES, 2009–2010)
- 35.7% of all US adults are obese, a dramatic ↑ in the past 20 y; affects 1 in 5 pregnant women.
- 17% of all US children & adols are obese → leading to increased rate of heart dz, diabetes, & metabolic syn.

Obesity and Gynecology
- **Infertility:** Oligo-ovulation & anovulation, ↓ gonadotropin resp, primary rx is wt loss.
- **Contraception:** ↓ effectiveness of patch, combined OCPs, & implants. No difference in efficacy for Depo-Provera, few studies on other contraceptives. Metabolic changes → altered half-life or storage in adipose tissue.
- **Anesthesia/surgical risk:** ↑ difficulty w/ spinal/epidural anesthesia, ↑ intubation risk w/ higher Mallampati score, consider preoperative anesthesia consult, ↑ wound breakdown w/ laparotomy. ↑ DVT risk, consider prophylaxis, ambulation, SCDs, compression stockings.
- **Endometrial cancer risk:** Unopposed estrogen (androstenedione → estrogen by adipose tissue aromatase) → endometrial hyperplasia.

Obesity and Obstetrics (*Obstet Gynecol* 2013;121:213)
- **Fetal anomalies:** ↑ anomalies such as cleft lip/palate, neural tube, cardiac defects, ↑ macrosomia, ↑ miscarriage, 2–4× ↑ stillbirth.
- **Antepartum complications:** Obese ♀ ↑ services & testing w/ Preg 2/2 difficulty measuring fundal ht, 57% of time wt gain is higher than recommended (11–20 lb for obese). ↑ large for gestational age infants. ↑ gestational diabetes, gestational HTN, preeclampsia, & fetal macrosomia.
- **Labor & deliv:** Difficult to follow fetal HR w/ tocodynamometer → ↑ interventions such as fetal scalp electrode placement. Protracted labor curve & ↑ labor dystocia → ↑ cesarean deliv. ↓ VBAC success rate. ↑ shoulder dystocia.

Treatment
- **Nonsurgical:** Nutrition & exercise programs, goal setting w/ provider, close f/u appointments, some limited pharmacotherapy; goal BMI <25.
- **Surgical:** Bariatric Surg for BMI >40 or >35 w/ other comorbidities w/ gastric banding, sleeve gastrectomy, or gastric bypass. Attention to contraception should be paid to women who get bariatric Surg as their fertility may ↑.

OSTEOPOROSIS

Definition (*Obstet Gynecol* 2012;120:718)
- Low bone mass, microarchitectural deterioration, increased bone fragility. Defined by WHO based on DEXA T-scores:
  - **T-score:** Std deviation from mean BMD of a healthy young (30 yo) adult
    - **Nml:** T-score ≥–1
    - **Osteopenia:** T-score <–1 but >–2.5
    - **Osteoporosis:** T-score <–2.5
  - **Z-score:** Std deviation from mean BMD of age-matched pop, informative in cases of sev osteoporosis

Epidemiology (*AJOG* 2006;194:S3)
- 8–17% US postmenopausal women have osteoporosis
- Incid increases w/ age → 48–70% affected by age 80
- By age 70, Caucasian women in US have a 40% risk of hip, spine, or forearm fracture

Etiology

Osteoporosis risk factors	
Etiologies	**Risk factors**
Age-dependent bone loss	Age
Low bone mass	Thin, small frame Caucasian, Asian Prev personal fracture FHx of fracture
Estrogen deficiency (hypogonadal states)	Postmenopausal Amenorrhea Anorexia nervosa

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Etiologies	Risk factors
Endocrine disorders	Hyperparathyroidism Hyperthyroidism DM
GI disorders	Celiac dz & malabsorption Pancreatic dz Gastric bypass or GI Surg
Nutrition	Calcium, Vit D, protein deficiency
Meds	Depo-Provera Glucocorticosteroids Gonadotropin-releasing hormone agonists Heparin & anticonvulsants Tamoxifen, cancer chemotherapeutics
Lifestyle	Cigarette smoking, excessive EtOH use Sedentary

Clinical Manifestations

- Clinically silent until fracture. Hip fracture, esp trochanteric vs. intracapsular, is the most serious complication. Vertebral fracture often p/w back pain, kyphosis, & loss of ht. Forearm fracture also possible.

Screening

- **FRAX risk assessment tool** (www.shef.ac.uk/FRAX/) calculates 10-y fracture risk.
- **DEXA** (gold std) at 65 yo, earlier if postmenopausal w/ fracture, or risk factors (h/o fragility fracture, body wt <127 lb, medical causes of accelerated bone loss, smoker, alcoholism, rheumatoid arthritis, FHx of hip fracture in parent). FRAX 10-y risk >9.3% (65 yo risk) → early screening. Rpt screening not earlier than 2 y unless new risk factor.

DEXA screening guidelines	
Organization	**Criteria**
National Osteoporosis Foundation	All women over age 65 Personal h/o bone fracture after 50 <65 & postmenopausal w/ risk factors
USPSTF	All women over age 65 All women whose FRAX fracture risk is >9.3% due to risk factors
ACOG	All women over age 65
	<65 w/ more than 1 risk factor or FRAX 9.3% risk of fracture

- **Other screening modalities** (US, CT, x-ray, photon absorptiometry) are available but are less cost-effective, accurate, & available.
- **Biochemical markers** of bone turnover include:
  Bone resorption markers: Hydroxyproline, pyridinium cross-links
  Bone formation markers: Alk phos, osteocalcin, procollagen I propeptides
  Fasting urinary calcium/Cr ratio indicates balance btw resorption & formation

Treatment and Medications

- **Prevention and nonpharmacologic:** Regular weight-bearing exercise + 800 IU Vit D daily + 1200 mg calcium daily + avoid cigarette smoking & excessive EtOH intake. Fall precautions for older or unsteady pts. ACOG calcium/Vit D recommendations:
  Age 9–18: Calcium 1300 U QD, Vit D 600 U QD
  Age 19–50: Calcium 1000 U QD, Vit D 600 U QD
  Age 51–70: Calcium 1200 U QD, Vit D 600 U QD
  Age ≥70: Calcium 1200 U QD, Vit D 800 U QD
- **Pharmacologic:** Initiate rx for >50 yo & vertebral/hip fracture or T-score ≤–2.5 at the femoral neck or spine or T-score –1 to –2.5 at the femoral neck or spine & 10-y fracture risk ≥3% or 10-y osteoporosis fracture risk ≥20% or low trauma fracture (esp vertebral/hip).
  Bisphosphonates: 1st line, oral or IV administration (alendronate, risedronate, ibandronate, etidronate). Side effects – esophagitis, myalgias
  SERM: Oral (raloxifene). Side effects – vasomotor sx, DVT, leg cramps
  Calcitonin: Subcutaneous or nasal administration. Side effects – nausea, rhinitis
  Parathyroid hormone: Subcutaneous administration. Side effects – HyperCa, nausea, leg cramps
  Estrogen: Oral, transdermal administration. WHI demonstrated ↓ osteoporosis for both estrogen alone & estrogen–progestin therapy. Side effects – ↑VTE, cardiovascular dz, breast cancer

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- **Monitoring resp to therapy:** F/u DEXA 2 y after beginning of therapy, decreased frequency thereafter if adequate resp. N-telopeptide urine measurement is useful in monitoring drug compliance or in pts w/ malabsorption, only useful if on antiresorptive meds.

SKIN CANCER SCREENING

Basal Cell Carcinoma (*J Natl Compr Canc Netw* 2010;8:836; *BMJ* 2003;327:794)

- **Definition:** Arises from epidermal basalis, locally invasive
- **Epidemiology:** Most common skin cancer. Likely 1–3 million BCC/y in US. 30% lifetime risk if Caucasian.
- **Risks:** Age, race, **UV** *light exposure esp intermittent & intense*, chronic arsenic exposure, ionizing radiation, immunosuppression, & PUVA therapy for psoriasis
- **Pathophysiology:** Sun exposure/inflammation. Genetics – PTCH1, chromo 9, tumor suppressor gene, two-hit hypothesis.
- **Clinical manifestations:** 70% on face, 15% on trunk
  - **Nodular:** 60% of cases, flesh-colored papule, pearly or translucent, telangiectatic vessel, may have ulceration
  - **Superficial:** 30% of cases, mostly on trunk, scaly plaque, rimmed w/ translucent micropapules
  - **Morpheaform:** Smooth, flesh-colored plaques, atrophic, ill-defined borders, aggressive
  - **Basal cell nevus syn:** Autosomal dominant inheritance, PTCH1 mutation, p/w multi BCCs at a young age, macrocephaly, bifid ribs, bone cysts, palmar pitting, & medulloblastoma.
- **Tx:** Less aggressive BCC (<6 mm diameter on face/hands/feet, <10 mm on head/neck, <20 mm all other areas; nodular or superficial histopathology, no perineural invasion; primary lesion, defined borders, immunocompetent, no prior radiation) → electrodessication & curettage, surgical excision. More aggressive BCC → Mohs Surg, surgical excision, XRT.
- **Prog:** Excellent, metastasis rate 0.55%, but 40% of pts → 2nd BCC ≤5 y

Squamous Cell Carcinoma (*NEJM* 2001;344:975)

- **Definition:** Arises from epidermal keratinocytes, locally invasive
- **Epidemiology:** 2nd most common skin cancer, 4–9% lifetime risk for US women
- **Risks:** Same as BCC, see above
- **Pathophysiology:** UV light, esp >30000 cumulative hours, similar to BCC. p53 mutation & other tumor suppressor genes. Prevention: Protection from sun exposure, retinoids.
  - **Actinic keratoses:** Precursor lesion, scaly erythematous macules, 1% progress to SCC, 60% of SCC arise from actinic keratoses
- **Clinical manifestations:** 55% on head/neck, 35% on arms/legs
  - **SCC in situ** (Bowen dz): Well-defined borders, scaly plaque, erythematous
  - **Invasive SCC:** Hyperkeratotic papules or nodules, firm, may have ulcerations
  - **Verrucous carcinoma:** Well-defined, cauliflower-like growths
  - **Xeroderma pigmentosum:** Multigenic, autosomal recessive, sev sun sens, degeneration of skin & eyes
  - **Epidermolysis bullosa:** Blister formation w/ no prev trauma, increased risk of aggressive SCC
- **Tx:** Staging based on TNM criteria after full-body exam → surgical excision, cryotherapy, radiation, Mohs Surg, topical 5-fluorouracil per staging
- **Prog:** 5-y cure rate >90%, 1% mortality rate, tumor staging correlates w/ recurrence & metastasis

Melanoma (*NEJM* 2006;355:51)

- **Definition:** Arises from epidermal melanocytes, most fatal form of skin cancer
- **Epidemiology:** 7th most common form of cancer in women
- **Risks:** Age, race, UV light exposure esp acute & intermittent, atypical nevi, high nevus count, FHx. MRAT: www.cancer.gov/melanomarisktool/
- **Prevention:** Insuff evid to recommend universal screening by USPSTF, but remain alert. High-risk pts → yearly screening from a dermatologist
- **Clinical manifestations:**
  - **Superficial spreading melanoma:** 70% of all melanomas, variably pigmented macules, irreg borders
  - **Nodular melanoma:** 15–30% of all melanomas, darkly pigmented, pedunculated nodules

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Lentigo maligna melanoma: Begins as brown macule that grows to be darker, asym, & have raised areas

Acral lentiginous melanoma: <5% of all melanomas, most common form of melanoma in darker-skinned people, most commonly on palms of hands & soles of feet

ABCDE: Asymmetry, border irregularities, color variegation, diameter >5 mm, evolving lesion (*Dermatology* 1998;197:11). Sens 97% if single criterion met, 43% if all 5 criteria met. Spec 36% if single criterion met, 100% if all 5 criteria nml.

Glasgow criteria: Referral if 1 major criterion, presence of minor criteria reinforces need for referral

Major: Change in size or new lesion, change in shape, change in color

Minor: Diameter >6 mm, inflammation, crusting or bleeding, sensory change

Ugly duckling sign: Used to observe a pt w/ multi nevi, refer if a pigmented lesion appears different than the surrounding lesions

- **Tx:** Staging based on tumor thickness, mitotic rate, & ulceration → wide local excision, LN excision, & adjuvant immunotherapy
- **Prog:** Based on tumor thickness (*J Clin Oncol* 2009;27:6199)

Melanoma prognosis by tumor thickness

Tumor stage	Invasion thickness	10-y survival rate
T1	<1 mm	92%
T2	1.01–2 mm	80%
T3	2.01–4 mm	63%
T4	>4 mm	50%

From *J Clin Oncol* 2009;27:6199.

DOMESTIC VIOLENCE

Definitions

- Intentional controlling or violent behavior by someone in a relationship w/ the victim. Includes physical, sexual, verbal, & emotional abuse as well as economic depriv.
- **IPV:** Victim is often intimately involved w/ her abuser.
- **Common couple violence:** Not connected to general control behavior, arises in a single argument where one/both partners are injured.
- **Intimate terrorism:** General pattern of abuser control, emotional & psychological abuse, not mutual, more likely to escalate over time, more likely to involve serious injury.
- **Violent resistance:** Self-defense, violence by victim against abuser.
- **Phases of abuse:** Tension-building: Poor communication, fear, victim tries to pacify the abuser. Acting-out: Outburst of violent, abusive behavior. Honeymoon: End of violence → affection & apology.

Epidemiology

- Affects over 1 million ♀ each year. 54% of ♀ report an abusive relationship in the past.
- Higher prevalence if under age 35, single, divorced/separated, abuse EtOH or drugs, smoke, pregnant, lower socioeconomic class, h/o childhood abuse.
- **Elder abuse:** 10% of women over 65 report physical, sexual, or verbal abuse or neglect. Risks: Advanced age, AA, disability in self-care, dementia, depression, h/o hip fracture, h/o stroke, social isolation, low socioeconomic status, institutional staffing shortages.
- **Preg:** Domestic violence affects 7–20% of pregnancies, 3-fold higher risk if Preg is unintended, Preg can result from reproductive coercion (forced Preg by contraception sabotage). Victims more likely to deliver preterm & by cesarean section. 3-fold ↑ risk of attempted/completed homicide. Highest risk of IPV in 3rd trimester & postpartum.
- No typical abuser or victim, IPV affects all ages, races, & socioeconomic classes.

Clinical Manifestations

- Inconsistent explan of injuries or delay in seeking rx. Somatic complaints (HAs, abdominal/pelvic pain, fatigue). Depression, anxiety, eating disorders.
- Presenting late to prenatal care. Frequent ED visits. Noncompliance w/ rx. Skin tears, bruises, bone fractures, malnutrition, dehyd, & pressure ulcers common in victims of elder abuse.
- Most injuries on breasts, abd, & genitals, esp in Preg. Defensive wounds on hands, arms. Bruises of different ages.

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Diagnostic Workup/Studies
- Screen routinely in all pregnant pts, for well-woman/preventive visits. No strong evid that routine screening decreases harm (USPSTF).
- **SAFE questions** (*JAMA* 1993;269:2367)
  - "Do you feel safe in your relationship?"
  - "Have you ever been in a relationship where you have been threatened, hurt, or afraid?"
  - "Are your family/friends aware that you have been hurt? Could you tell them and would they be able to give you support?"
  - "Do you have a safe place to go and resources you need in an emergency?"
- **Abuse assessment screen:** Identifies physical or sexual abuse in Preg (*JAMA* 1992;267:3176)
  - "Within the last year, have you been hit, slapped, kicked, or otherwise physically hurt by someone?"
  - "Since you've been pregnant, have you been hit, slapped, kicked, or otherwise physically hurt by someone?"
  - "Within the last year, has anyone forced you to have sexual activities?"
- **BASE** & the **CTS** can be used to screen for elder abuse (*JAGS* 2004;52:297)

Treatment and Medications
- **RADAR:** Routinely screen, Ask direct questions, Document your findings, Assess safety, Review options. Provide supportive counseling & validation of a pt's fear.
- **Assess risk for escalation:** Presence of weapons in the home, increasing violence frequency/severity, partner's knowledge that victim is planning to leave, threats of homicide.
- Refer to social workers, safe houses, ER. 1–800–799-SAFE provides information regarding local resources in every state.
- Specific, detailed, accurate, & nonjudgmental documentation is essential in case the victim seeks legal redress. Mandatory reporting of child abuse in all states. Many states require elder abuse reporting. Some states require IPV reporting for adult women as well.

SUBSTANCE ABUSE

Definitions
- **Use:** Sporadic consump, no adverse effects
- **Abuse:** Maladaptive pattern or inappropriate use of a substance, adverse effects from use
- **Dependence:** Individual persists in substance use despite problems
  - **Physical:** Characterized by withdrawal sx if abrupt cessation of substance or antag administered
  - **Psychological:** Need for substance either for positive effects of use or to avoid negative effects of abstinence
- **Addiction:** Behaviors that include impaired control, compulsive use, use despite harm, & craving

Epidemiology
- Affects 10% of the general pop. 48% of 12th graders have reported using an illicit substance at some point. 140 million people worldwide are EtOH dependent.
- 30% of suicides relate to EtOH abuse. Accounts for up to 40% of hospital admissions.

Clinical Manifestations
- Repetitive use → drug tolerance → withdrawal sx when drug is stopped, including depression, anxiety, malnutrition, wt loss, suicidality, agitation, & sleep disturbances.
- **EtOH:** P/w tolerance, blackouts or memory lapses, sleep disturbances, tremors. Intoxication = slurred speech, incoordination, unsteady gait, nystagmus, memory impairment, stupor, or coma.
- **Delirium tremens:** Withdrawal syn of sev EtOH abuse, hallucinations, disorientation, tachycardia, HTN, fever, agitation, diaphoresis.
- **Cocaine:** Acute intoxication = increased energy/alertness/sociability, euphoria, decreased fatigue/need for sleep/appetite, pupillary dilation. Chronic use = cognitive impairment, risk–reward decision making, suicidality. Withdrawal = depression, anxiety, fatigue, difficulty concentrating, anhedonia, increased appetite, increased sleep.
- **Opioids:** Acute intoxication = sedation, euphoria, respiratory depression, pupillary constriction, constipation, slurred speech. Withdrawal = anxiety, irritability, drug cravings, tachypnea, rhinitis, muscle aches, nausea/vomiting, diarrhea, sweating, tremors.
- On **physical exam** note papillary size (dilation/constriction), behavior, tachycardia, speech patterns, skin inspection for injection marks, hepatomegaly, signs of HIV/AIDS, nasal mucosal atrophy/nasal septum perforation, signs of STI.

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Diagnostic Workup/Studies

- **Screening tools:**
  - **CAGE-AID:** Adapted for EtOH & drug abuse (*Wis Med J* 1995;94:135):
    - "Have you ever tried to cut down on your alcohol or drug use?"
    - "Do you get annoyed when people comment on your alcohol or drug use?"
    - "Do you feel guilty about things that you have done while drinking or using drugs?"
    - "Do you need an eye-opener to get started in the morning?"
  - **T-ACE:** Specifically for EtOH abuse in Preg:
    - "How many drinks does it take you to feel high?" (T = tolerance)
    - "Do you feel annoyed by people complaining about your drinking?"
    - "Have you ever felt the need to cut down on your drinking?"
    - "Have you ever had a drink first thing in the morning?" (E = eye-opener)
  - **Single-item screening test:** 100% sens, 73% spec
    - "How many times in the past year have you used an illegal drug or used a prescription med for nonmedical reasons?"
- **Labs:** Urine or serum toxicology screening

Treatment and Medications

- **Stages of change** (*Am Psychol* 1992;47:1102):
  - **Precontemplation:** Lack of awareness of problem, no intention to change behavior.
  - **Contemplation:** Aware of problem, weighing pros & cons to solve problem, no commitment to change action but considering changing behavior in next 6 mo.
  - **Preparation:** Intend to take action in the next month, some reductions in problem behavior.
  - **Action:** Modification of behavior/experiences/environment to overcome problem.
  - **Maintenance:** Extends from 6 mo onward, working to prevent relapse & consolidate gains achieved in the action phase.
- **FRAMES:** Physician motivational interviewing to help trigger pt change. Giving feedback based upon a thorough assessment. Helping the pt take responsibility for changing. Giving clear advice on what behavior must change. Offering a menu of options for making the change. Expressing empathy for the ambivalence & difficulty in making changes. Evoking self-efficacy to foster commitment & confidence.
- **Nonpharmacologic:** Cognitive behavior therapy, family therapy, exposure therapy.
- **Pharmacologic:**
  - **Methadone:** Synthetic opioid, long half-life, used to treat opioid dependence.
  - **Buprenorphine:** Semisynthetic opioid, used to treat opioid dependence.
  - **Naltrexone:** Opioid receptor antag, used to treat opioid & EtOH dependence.
  - **Disulfiram:** Causes acute sens to EtOH leading to adverse affects if EtOH used (ie, nausea & vomiting), used to treat EtOH dependence.
  - **Bupropion:** Antidepressant & smoking cessation aid.
  - **Varenicline:** Aid in smoking cessation, more effective w/ physician support.
- **Prog:** Remission in 35–60% of pts varies based on duration, social support, comorbid conditions, level of functioning at initiation of rx, premorbid functioning.

DEPRESSION AND PSYCHIATRIC DISEASE SCREENING

Definitions

- **Major depression criteria:** Depressed mood or anhedonia + 5 or more of the following sx present most of the day for nearly every day of 2 consecutive weeks: Depressed mood, anhedonia, insomnia/hypersomnia, change in appetite/wt, psychomotor retardation/agitation, low energy, poor conc, thoughts of worthlessness or guilt, recurrent thoughts of death or suicide. Remember, SIGE CAPS: Sleep, Interest, Guilt, Energy, Concentration, Appetite, Psychomotor, Suicide.
- **Bipolar d/o:** Includes both manic episodes (distinct periods of abnormally & persistently elevated, expansive, or irritable mood, lasting at least 1 w) & depressive episodes.
- **Dysthymia:** Depressed mood for at least 2 y w/ less numerous sx than major depression. May have symptom-free periods of <2 mo during this time.
- **Adjustment d/o:** Depressed mood or functional impairment in resp to an identifiable stressor w/i 3 mo of onset of the stressor & resolved w/i 6 mo.

Epidemiology

- 17% lifetime prevalence for major depression, 3% for dysthymia in US. 40% recurrence rate in 2 y. 25–50% of people w/ bipolar dz attempt suicide.
- Women almost twice as likely as men to be affected.

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- **Risks:** Internalizing factors (genetics, neuroticism, low self-esteem, early-onset anxiety d/o, past h/o major depression), externalizing factors (genetics, substance misuse, conduct d/o), adversity (trauma, stressful life events, parental loss, low parental warmth, divorce, marital problems, low social support, low education).

Diagnostic Workup/Studies *(Psychiatry Res 2011;187:130)*

- **Screening** (2-item tool): "During the last month, have you felt down, depressed, or hopeless?" & "During the last month, have you felt little interest or pleasure in doing things?" PHQ-9: Assesses 9 sx of DMS-IV-TR definition of depression.
- **EPDS:** Validated for postpartum depression

Treatment and Medications

- Screen for bipolar dz & manic sx prior to initiating therapy for depression.
- **Psychotherapy:** Similar efficacy to pharmacotherapy. Includes cognitive therapy, behavioral therapy, & interpersonal therapy.
- **Pharmacotherapy:** 50–60% response w/ med (SSRIs, SNRIs, TCAs, MAOIs). SSRIs are 1st-line therapy. Start low dose & ↑ as necessary to minimize side effects. Evaluate pts every 1–2 w in the 1st 8 w of therapy. If no resp in 8 w switch to another antidepressant.
- **Refer** if sev depression endangering the life of the pt or others. Failed to respond to initial rxs. Psychotic depression. Depression that is part of bipolar or schizoaffective d/o.

CONTRACEPTION AND STERILIZATION

Epidemiology *(Contraception 2011;83:397)*

- ~50% of pregnancies in US are unintended.
- **PRAMS:** 33% of ♀ w/ unintended Preg did not think they could get pregnant at the time of conception; 22% stated their partner did not want to use contraception; 16% cited side effects; 10% cited access.
- Contraceptive efficacy should be compared to 85% unprotected Preg rate in 1 y. Assessed by *perfect* (failure rate if used exactly according to guidelines) & *typical* use (failure rate for the usual compliance).

Contraceptive methods (*, see also below)

Method	Perfect use	Typical use	Primary mech of action
Sterilization			
Female*	<1%	<1%	Mechanical obstruction
Male Outpt procedure (urology)	<1%	<1%	Mechanical blockade
Long-acting reversible contraception (LARC)			
Etonogestrel implant* (Implanon/Nexplanon)	<1%	<1%	Cervical mucus thickening
Levonorgestrel IUD* (Mirena)	<1%	<1%	Cervical mucus thickening, sterile inflamm rxn
Copper T IUD* (ParaGard)	<1%	<1%	Sterile inflamm rxn, interferes w/ sperm fxn
Combined hormonal			
OCPs*	<1%	9%	Estrogen-induced inhibition of the midcycle gonadotropin surge prevents ovulation
Patch*	<1%	9%	Estrogen-induced inhibition of the midcycle gonadotropin surge prevents ovulation
Vaginal ring*	<1%	9%	Estrogen-induced inhibition of the midcycle gonadotropin surge prevents ovulation
Barrier			
Male condom ↓ STI/HIV infxns	2%	18%	Mechanical obstruction for sperm

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Method	Perfect use	Typical use	Primary mech of action
Female condom ↓ STI/HIV less than male condom	5%	21%	Mechanical obstruction for sperm
Diaphragm + spermicide*	6%	12%	Mechanical & chemical obstruction for sperm
Cervical cap*	9–26%	16–32%	Mechanical obstruction for sperm

***Special Considerations**

- WHO or CDC criteria for contraceptive considerations w/ medical problems, see www.cdc.gov/reproductivehealth/unintendedpregnancy/usmec.htm
- **Female sterilization** (*Am J Obstet Gynecol* 1996;174:1161):
  Postpartum salpingectomy: Most effective method of female sterilization; after deliv.
  Interval sterilization: Sterilization at other than postpartum period.
  Unipolar coagulation is the most effective method of laparoscopic female sterilization.
  Hysteroscopic sterilization (Essure) was not available for the CREST study, but is highly effective, outpt. Minimally invasive method w/o limitations by BMI, adhesive dz. Requires confirmation of tubal occlusion w/ hysterosalpingogram at 3 mo.
- **Combined hormonal methods (= estrogen + progestin):**
  Side effects – breakthrough bleeding, breast tenderness, HA, nausea/vomiting.
  OCPs: Both estrogen & progesterone or progesterone-only pills. Can interact w/ other meds (Abx, antiretrovirals, antiepileptics) → potential ↓ efficacy of either or both meds. Useful for menorrhagia, dysmenorrhea, hirsutism, & acne. ↓ risk of endometrial & ovarian cancer. Monophasic vs. multiphasic preparations are available. Monthly vs. continuous dosing is feasible, continuous dosing may be preferable for cyst formation prevention, endometriosis, PMS/PMDD, lifestyle reasons.
  Contraceptive patch: Replaced weekly × 3 w then removed for 1 w (menses). ↑ thromboembolic events compared to combined OCPs.
  Vaginal ring: Placed intravaginally × 3 w then removed for 1 w (menses). Small ↑ in vaginitis, vaginal discharge, & leukorrhea compared to OCPs.
- **Progestin-only methods:**
  Mech of action: Thickened cervical mucus, thinned endometrium, ovulation inhib
  Side effects: Breakthrough bleeding, acne, follicular cysts, wt gain, mood changes
  POP: Preg rate <1% perfect use, 9% typical use. Must be taken every day. Shorter half-life, therefore missed doses more signif.
  DMPA: Preg rate <1% perfect use, 6% typical use. One intramuscular or subcutaneous injection every 90 d (12 w). Side effects: Wt gain 3–6 kg/y, esp in obese adols, ↓ BMD, but reversible after discontinuation (DEXA scan not recommended).
  Etonogestrel implant (Implanon/Nexplanon): Placed in upper arm, in-office, effective for 3 y. Side effects: Breakthrough bleeding common → major reason for early discontinuation, no ↓ BMD like DMPA, risks of insertion include pain, bleeding, infxn, expulsion, & difficult removal.
  Levonorgestrel IUD (Mirena): Inserted in-office, lasts for 5 y. Effective for menorrhagia, dysmenorrhea, endometriosis, endometrial hyperplasia, & possibly Grade 1 Stage I endometrial cancer. Adolescence, nulliparity, prev STI, & prev ectopic Preg are ***not*** contraindications to IUD placement. ↑ ectopic Preg w/ IUD, but overall rate of ectopic ↓ due to decreased Preg.
- **Nonhormonal methods**
  Copper IUD: Inserted in-office. Effective for 10 y. Does not impact menstrual regularity, but may cause slightly heavier menses. Adolescence, nulliparity, prev STI, & prev ectopic Preg are *not* contraindications to IUD placement.
  Diaphragm with spermicide: Requires annual fitting, not common in US. Refit if recent Preg or change in wt. Increases risk of urinary tract infxn. Insert 6 h prior to intercourse, remove 6–24 h after intercourse.
  Cervical cap: Requires annual fitting, not common in US. Insert 20 min to 4 h prior to intercourse, remove 24–36 h after intercourse.
  Withdrawal: Preg rate: 4% perfect use, 22% typical use. Used by up to 56% of women using contraception, usually secondary in conjunction w/ condoms.
  Lactational amenorrhea: Preg rate: 2% perfect use, 5% typical use. Effective for 1st 6 mo postpartum ***only if*** exclusive breast-feeding (only nutrition for infant), breast-feeding every 4 h during the day & at least every 6 h at night, no menses if ≥56 d postpartum.
  Rhythm method: Preg rate: 0.4–5% perfect use, 12–23% typical use. Relies on regular menstrual cycles & the limited viability of ova/sperm w/o fertilization. Can use menstrual calendars, cervical mucus changes, basal body temperature, or ovulation kits to avoid intercourse during midcycle fertile days.

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EMERGENCY CONTRACEPTION (EC)

Definition *(Obstet Gynecol* 2010;115:1100)

- Use of drugs or a device (IUD) as an emergency measure to prevent Preg.
- Intended for occasional or back-up use, not as a primary contraceptive method.
- **Indications:** No contraception used during sexual intercourse w/i the prev 120 h. Contraceptive failure or incorrect use of a contraceptive w/i the prev 120 h including condom breakage, 2 missed combined OCPs, POP taken more than 3 h late, 2 w late for DMPA injection, dislodgement of cervical cap/diaphragm/skin patch/vaginal ring, expulsion of IUD.
- **Access:** Physicians should be aware of national & state laws regarding the availability of & prescribing emergency contraception. Available w/o a prescription to people of age 17 or older.

Mechanism of Action

- May include 1 or more of the following: Inhibition or delay of ovulation. Interference w/ tubal transport or fertilization. Prevention of implantation. Regression of corpus luteum.
- EC does *not* interrupt Preg & is ineffective after Preg has been established.
- **Efficacy:** 75% Preg rate reduction w/ the use of oral EC (if 1000 women had intercourse in the middle 2 w of their cycle, 80 would normally become pregnant but w/ use of oral EC the rate is reduced to 20). Efficacy influenced by: Time from unprotected intercourse to administration. Pt's BMI: 2–4× higher risk of Preg if overweight or obese for oral EC. Timing of unprotected intercourse to day of cycle. Further intercourse after use of EC (4× higher risk vs. those that did not report further intercourse).

Treatment and Medications *(Cochrane* 2008;2:3)

- Physical exam & lab tests not req prior to EC. Exclude Preg esp before IUD.
- **Levonorgestrel** (Plan B): 1.5 mg PO in a single dose. Effective up to 120 h from unprotected intercourse, though most effective w/i 1st 72 h. 98% of pts menstruate w/i 21 d (mean 7–9 d). Administer Preg test if no menses w/i 28 d. Side effects – irreg bleeding, nausea/vomiting (give antiemetics). Redose if vomiting w/i 2 h of administration.
- **Ulipristal** (Ella): 30 mg PO in a single dose. Selective progesterone receptor modulator. Effective up to 120 h from unprotected intercourse. Likely more effective than levonorgestrel from 72–120 h after unprotected intercourse.
- **Copper IUD** (ParaGard): Must be inserted w/i 120 h from unprotected intercourse. More effective in overweight/obese women than levonorgestrel. Provides long-term, effective contraception along w/ EC.

VACCINATIONS

Figure 1.1 Recommended United States Adult Immunization Schedule 2014

	Age group (yrs)		
Vaccine	**19–26 yo**	**27–64 yo**	**≥65 yo**
Influenza	1 dose annually		
Tetanus, diphtheria, pertussis (Td/Tdap)	Substitute 1-time dose of Tdap for Td booster; then boost with Td every 10 yrs		
Varicella	2 doses, if non-immune		
Human papillomavirus (HPV) Female	3 doses		
Zoster		>60 yo 1 dose	
Measles, mumps, rubella (MMR)	Born before 1957 give 1 or 2 doses		
Pneumococcal polysaccharide (PPSV23)	1 or 2 doses		1 dose
Meningococcal	1 or more doses		
Hepatitis A	2 doses		
Hepatitis B	3 doses		
Haemophilus influenzae type b (Hib)	1 or 3 doses		

For all in this category who lack documentation or evidence of previous infection. Zoster vaccine regardless of prior history. | Recommended if medical, occupational, lifestyle or other risks. | No recommendation.

From Advisory Committee on Immunization Practices, Department of Health and Human Services, Centers for Disease Control and Prevention. More information and complete recommendations and notes: www.cdc.gov/vaccines/schedules/hcp/adult.html. Accessed April 12, 2014.

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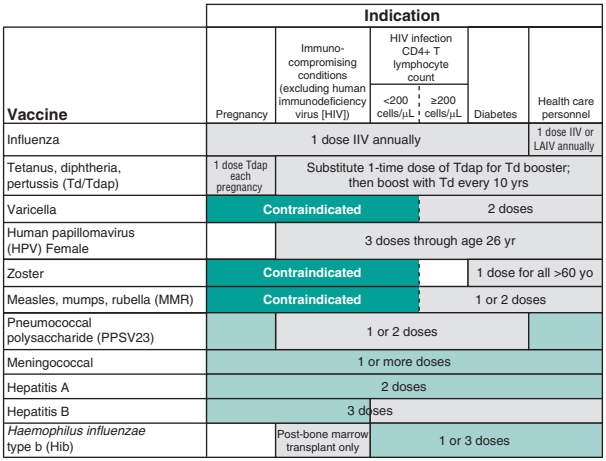
Figure 1.2 Adult vaccines by medical indication 2014



IIV, inactivated influenza vaccine; LAIV, live attenuated influenza vaccine. From Advisory Committee on Immunization Practices. Complete recommendations and notes: www.cdc.gov/vaccines/schedules/hcp/adult.html. Accessed April 12, 2014.

WOMEN'S HEALTH EPIDEMIOLOGY AND RESEARCH

US women's mortality: Top causes for all females, all ages	
1. Heart dz, 23.5%	6. Unintentional injuries, 3.6%
2. Cancer, 22.1%	7. Diabetes, 2.7%
3. Stroke, 6.2%	8. Influenza & pneumonia, 2.1%
4. Chronic lower respiratory dzs, 5.9%	9. Kidney dz, 2.1%
5. Alzheimer dz, 4.7%	10. Septicemia, 1.5%

From CDC "Leading Causes of Death in Females". 2010 data. http://www.cdc.gov/women/lcod/2010/index.htm.

Annual US Gyn cancer deaths		
Cause	**Cases**	**Deaths**
Endometrial	41314	7456
Ovarian	20749	14621
Cervical	12280	4012
Vulvar	4159	865
Vaginal	1149	376

From CDC "Leading Cause of Death in Females". 2008 data, 10/15/12.

Epidemiology terms	
Sens	% w/ dz w/ positive result on a test
Spec	% w/o dz w/ negative result on a test
PPV	% w/ a positive test who *actually have* condition
NPV	% w/ a negative test who do not have the condition; PPV & NPV change w/ prevalence

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Incid	Number of new events in a specific time period per pop at risk at the start of the time interval
Prevalence	Number of people w/ a dz at a *point* in time per pop at risk at that time
OR	Odds of an exposure w/ dz over odds in a control group; common for case-control studies
RR	Proportion of exposed who develop a condition over proportion of unexposed who develop a condition (I_{exp}/I_{unexp}); for cohort studies
AR	Probability of a medical event (as a % of all who could have the event). ARR = difference of ARs btw 2 groups
NNT	1/the ARR in %; number of pts to treat for 1 prevented case (= 1 avoided risk outcome)
CI	If exp repeated 100×, truth is in this range 95× (w/i the 95% CI). If CI crosses 1, the finding is not signif (= no effect)
Intention to treat analysis	Based on how subjects were originally randomized & includes all of them; no dropouts or problem pts subtracted from the groups
Type 1 error (α)	Rejecting the null hypothesis when it is actually true, causes you to believe there was an effect when there was not; usually set at $p < 5\%$
Type 2 error (β)	Accepting the null hypothesis, when it is actually false; causes you to believe there was no effect when there actually was
Power	Ability of your study to detect a true difference ($1 - \beta$); often set at 80%

Calculating sensitivity, specificity, PPV, NPV			
	Dz +	**Dz –**	
Test pos	a (true pos)	B (false pos)	PPV = [a/(a + b)] × 100
Test neg	c (false neg)	D (true neg)	NPV = [d/(c + d)] × 100
	Sens = [a/(a + c)] × 100	Spec = [d/(b + d)] × 100	

Types of studies	
Case series	**What:** Summary of cases & outcomes for an unusual event. **Pro:** Good for rare, interesting, or new conditions or rxs. **Con:** Only descriptive, not controlled, no causality.
Cohort	**What:** Follow exposed & control group for specific outcomes (in real time or after the outcome has already occurred). Looks forward for outcome. Define by exposure → eval outcome. **Pro:** Can be retrospective ("historical cohort") or prospective. **Con:** No causality; prospective is expensive & lengthy.
Case control	**What:** Search for prior exposure in cases (w/ condition) compared w/ controls (w/o condition). Looks backward. **Pro:** Can be run quickly w/ existing databases. Good for rare conditions. **Con:** No causality; matching cases & controls can be difficult.
RCT	**What:** Follow randomized groups of pts w/ rx or placebo to assess outcomes/complications. A "true experiment." **Pro:** Level 1 evid; gold std for clinical research. **Con:** Often difficult to recruit & expensive. May not be feasible or ethical for certain clinical questions (eg, many obstetrical concerns).

Phases of Clinical Trials (Understanding Clinical Trials, NIH, clinicaltrials.gov)

- **Phase 1:** Tests an experimental drug or rx in a small group of people (10–80) to evaluate safety, determine a dosage, & identify side effects.
- **Phase 2:** The experimental study drug or rx is given to a larger group of people (100–300) to see if it is effective & to further evaluate safety.
- **Phase 3:** The experimental study drug or rx is given to large groups (1000–3000) to confirm effectiveness, monit side effects, & collect safety data.
- **Phase 4:** Postmarketing review of risk/benefit & unexpected events.

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Ultrasound (US)

- **Transabdominal US:** 4–5 mHz curvilinear transducer, better if pt's bladder is full
- **TVUS:** 5–10 mHz transducer, better visualization of pelvic organs, pt's bladder should be empty
- **Doppler:** To assess flow, change in frequency of reflected US shows bld flow
- **SIS** (aka SHG): Catheter passed through the cervix → 10–20 cc sterile saline injected → TVUS demonstrates uterine cavity contours. Contraindications: Preg, active pelvic infxn, obst of the cervix or vagina, hematometra. Risk of infxn <1%.
- **Nml measurements:**
  - Uterus is 8 × 5 × 4 cm (smaller in prepubertal or postmenopausal women). Nml AP diameter 3–5 cm & length 6–10 cm.
  - EMS is <15 mm (premenopausal) & <8 mm (postmenopausal). In screening for postmenopausal vaginal bleeding, use nml <5 mm (PPV 9% & NPV 99% for endometrial cancer). EMS measured from echogenic interfaces of the anter & post basalis layers.
  - Ovary vol is 9.8 ± 5.8 cm^3. Ovarian follicles up to 2.5 cm diameter. Avg nml ovary is 3.5 × 2.5 × 1.5 cm → 2 × 1.5 × 1 cm postmenopausal.
  - Fallopian tubes are not normally visible; can see hydrosalpinx.
  - Small amt of fluid in the post cul-de-sac may be nml physiologic.

Radiography (XR)

- Usual indications for fractures, trauma, other nonpregnant conditions. Abd shielding used.
- **HSG:** Inject radiopaque contrast via cervical canal → visualize endocervical canal, endometrial cavity, lumen, & patency of fallopian tubes (via the spill of dye into the pelvis).
- **DEXA:** Assess bone density in the hip & spine.

Computed Tomography (CT)

- In OBGYN, used most frequently to evaluate gyn malignancies or in the ER to evaluate the acute abd, postoperative sx, pelvic abscesses & masses, & rule out nongyn problems like appendicitis & diverticulitis. IV contrast ok in Preg.
- **Noncontrast CT:** Nephrolithiasis, neuropathology (hemorrhagic stroke, head trauma, intracranial hemorrhage, intracranial lesions/masses, skull fracture)
- **Contrast CT:** Vascular pathology (aneurysm, dissection, ischemic stroke), trauma, bowel pathology (diverticulitis, appendicitis), abscesses, pulmonary embolism

Positron Emission Tomography (PET)

- Used mostly for malig. Radiochemical compounds measure specific metabolic processes. Eg, FDG identifies accelerated rates of glycolysis found in neoplastic cells.

Magnetic Resonance Imaging (MRI)

- Used in w/u of uterine fibroids, adenomyosis, Müllerian duct anomalies (eg, to differentiate btw septate & bicornuate uteri), adnexal masses, fetal anomalies.

Imaging During Pregnancy (*Obstet Gynecol* 2004;104:647; *Am J Obstet Gynecol* 2012;206:456)

- No reports of adverse fetal affects w/ US or MRI
- Ionizing radiation from CT or XR → risks depending on exposure & GA
  - Extremely high-dose ionizing radiation → "All or nothing" effect w/ early Preg loss. At <18 w, 500 rad is the estimated threshold for embryonic demise

Fetal radiation exposure during imaging	
Procedure	**Estimated fetal radiation exposure (mrad)**
CXR (2 views)	0.02–0.07
Abdominal film (single view)	100
Hip film (single view)	200
CT scan of head or chest	<1000
CT scan of abd & lumbar spine	3500
CT pelvimetry	250

  - At term, 2000 rad is the threshold & fetal risks same as mat risks.
  - Risk of anomalies, growth restriction, or SAB not increased w/ radiation exposure of <5 rad. True threshold dose is likely >20 rad.
  - Risk of CNS effects (eg, microcephaly, mental retardation) highest at 8–15 w. There is no established risk at <8 w or >25 w.

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The threshold dose of ionizing radiation → mental retardation at <16 w is 35–50 rad. After 16 w, the threshold is 150 rad.
1–2 rad fetal exposure may ↑ leukemia risk by 1.5–2×, but baseline childhood cancer risk is 0.2–0.3%; therefore, overall risk is still low.
No single diagnostic procedure provides radiation dose signif enough for adverse embryonic/fetal effect, esp mid to late Preg.

- **Nuclear medicine:** Radioactive iodine contraindicated in Preg. Tc-99m usually results in fetal exposure of <0.5 rad.
- **Contrast agents:** Iodine-based contrast safe for use in Preg. Gadolinium relative contraindicated in Preg – assess risks/benefits of contrast & obtain consent. Gadolinium crosses placenta → excreted into amniotic fluid. Unk exposure duration & effect on fetus.

ULTRASOUND IN EARLY PREGNANCY

Ultrasound in Pregnancy *(Obstet Gynecol 2009;113:451)*

- **1st trimester US:** TVUS best in early Preg to confirm IUP, evaluate ectopic Preg, determine GA, evaluate twin Preg chorionicity, confirm cardiac activity, evaluate adnexal masses. Also obtain nuchal translucency, nasal bone for prenatal screening.
  GS: Visible by ~4 w GA, eccentrically implanted in the midupper fundus w/ a bright decidual rxn (double-ring sign), visible in 2 planes. *Not* used to determine final GA. Mean sac diameter (the avg of 3 measurements in mm) + 30 = GA (days) ± 3 d.
  Yolk sac: Visible at 5 w GA, should be seen when the mean GS diameter is >13 mm.
  Embryo: Visible at 6 w GA, or when mean GS diameter is ≥20 mm.
  1st trimester CRL is most accurate dating. If ≤9.5 w GA, CRL in mm + 42 = GA (days) ± 3 d.
  FHM: Observed when the embryo is ≥5 mm CRL. FHR = 100 bpm at 5–6 w GA, & → peak 175 bpm at 9 w GA. If FHM is seen, SAB rate is 2–3% in asymptomatic low-risk women. Women <35 yo who p/w VB = 5% SAB rate if the US is nml & shows FHM.
  To quickly estimate EDD from LMP, use Naegele's rule: Add 1 y, subtract 3 mo, & add 7 d (= 280 d from LMP).
- **2nd & 3rd trimester US** – see Chap. 9.
- **US for determination of GA:** US dating takes preference over menstrual dating when the discrep is >7 d in the 1st trimester; >10 d in the 2nd trimester. In the 3rd trimester, accuracy of a US is w/i 3–4 w.

ACUTE PELVIC PAIN

Definitions and Epidemiology *(Natl Health Stat Report 2010;6:1)*

- Lower abdominal or pelvic pain present for <7 d. Most common presenting complaint & primary dx for women of ages 15–64 who are seen in the ER.

Causes of pelvic pain

OBGYN causes of acute pelvic pain	Other causes of acute pelvic pain
Dysmenorrhea	Gastro
Ectopic Preg	Appendicitis
Spont miscarriage	Small bowel obst
Ovarian tumor or cyst	Sev constip
Ovarian torsion	Hernia
PID	Diverticulitis
TOA	Nephrolithiasis
Degenerating leiomyoma	Pyelonephritis
Herpes simplex virus, chancroid	Cystitis
Bartholin duct cyst or abscess	

From Flasar MH, Cross R, Goldberg E. Acute abdominal pain. *Prim Care*. 2006;33(3):659.

Pathophysiology and Clinical Manifestations *(Prim Care 2006;33:659)*

- **Visceral pain:** Stretch, distention, torsion, or contraction of abdominal organs is detected by autonomic, afferent nociceptors → "slow," C-fibers relay the signal to the CNS → pain is usually midline or bilateral, poorly localized, dull, achy, or cramping.

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- **Parietal pain:** Direct irritation of the peritoneal lining is detected by somatic, afferent nociceptors → "fast," A-delta fibers relay the signal → pain is unilateral, localized, sharp.
- **Referred pain:** Visceral nerve afferents carrying stimuli from a diseased organ enter the spinal cord at the same level as somatic afferents from a remote anatomic location. Eg, free fluid in the abd can irritate the diaphragm causing referred pain in the shoulder.

Physical Exam

- Fever, tachy, HoTN → expedite w/u, concern for sepsis/infxn, intra-abdominal bleeding (eg, ruptured ectopic Preg, hemorrhagic ovarian cyst), ovarian torsion, appendicitis.
- **Abdominal exam:** Note prior surgical scars, distention, hyperactive or high-pitched bowel sounds, rebound, guarding, rigidity. Palpate 4 quadrants.
- **Pelvic exam:** Note swelling, erythema, lesions, bleeding, discharge, masses, nodularity, cervical motion tenderness, or pain.

Diagnostic Workup and Studies

- **Labs:** Urine or serum beta hCG (on every reproductive age woman in the ER), CBC, urinalysis & culture, vaginal wet prep, gonorrhea & chlamydia PCR
- **Imaging:** Transabdominal US or TVUS
- **Culdocentesis:** Rarely used. Aspiration of fluid from the post cul de sac. Considered in limited resource settings.
- **Diagnostic laparoscopy:** Consider for the unstable pt w/ abdominal pain.
- Rx & medications depend on dx (see other sections, below).

ECTOPIC PREGNANCY

Definitions & Epidemiology (*Obstet Gynecol* 2008;111:1479; *NEJM* 2009;361:379)

- Preg outside of the endometrial cavity. 2% of 1st trimester pregnancies.
- 6% of all pregnancy-related deaths (leading cause of death in the 1st trimester).
- Ectopic Preg increasing (4.5/1000 pregnancies in 1970 → 19.7/1000 in 1992).
- Rate of rupture w/ ectopic Preg is 20–35%.

Etiology

- Blastocyst implants & invades improperly at nonendometrial site. 97% in fallopian tubes, most frequently in the ampullary region. Other implantation sites include the isthmic portion of the tube, fimbria, uterine cornua, cervix, ovary, prior C/S scar, or abd.
- Heterotopic Preg → 2 or more implantation sites (ie, an IUP & ectopic Preg). Rare, only 1:8000–1:30000 nml pregnancies. Increased to 1.5/1000 after assisted reproductive technologies.
- **Risk factors:** Prior ectopic Preg, prior tubal Surg, tobacco smoking, prior PID, *Chlamydia trachomatis* infxn, 3 or more prior spont miscarriages, age >40 y, prior medical or surgical abortion, infertility >1 y, lifelong sexual partners >5, current IUD use, IVF/ART.

Clinical Manifestations and Physical Exam

- Lower abdominal pain on the affected side. Vaginal bleeding.
- Clinical findings are often unremarkable w/ unruptured ectopic Preg. Only 75% develop marked abdominal tenderness. May p/w shoulder pain, dizziness, syncope. Hx & risk factors are useful to assess risk/suspicion.
- VS & clinical assessment to look for signs of hemodynamic stability.
- **Pelvic exam:** Adnexal mass (20%). Abdominal exam: Tenderness to palpation. Evaluate for surgical abd: Rebound, guarding, rigidity.

Diagnostic Workup and Studies

- **Labs:** CBC (sometimes serial Hgb), bld type (RhoGAM if Rh-negative), CMP for BUN/Cr, & AST/ALT (if considering MTX).
- **Serum (quantitative) hCG:**
  - If hCG above "discriminatory zone" of 1500–2000 mIU/mL, nml IUP seen on TVUS.
  - If hCG >1500–2000 mIU/mL & no IUP on TVUS → likely abn Preg (eg, ectopic Preg, incomplete AB, resolving completed AB)
  - If hCG <1500 mIU/mL & no IUP → rpt hCG in 48 h (at SAME lab).
  - In 85% of women w/ a nml IUP, the hCG will ↑ ≥63% in 48 h.
  - In 99% of women w/ a nml IUP, the hCG will ↑ ≥53% in 48 h.
  - An ↑ in serum hCG of <~60% in 48 h → abn Preg
- **TVUS:** 91% accuracy of TVUS for dx of ectopic Preg. Extrauterine GS or embryo seen in only 15–30% of cases. Most common US finding is a solid mass btw the ovary & uterus.

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Adnexal mass (other than a simple ovarian cyst) is 84% sensitive & 99% specific for ectopic Preg.
Trilaminar endometrial stripe (only) is 38% sensitive & 94% specific for an ectopic Preg.
Pseudosac (intrauterine midline fluid collection) is neither sensitive nor specific for the dx of ectopic Preg. Do not confuse pseudosac for IUP.

- **Serum progesterone:** Often not definitive. Levels from 5–20 ng/mL are equivocal.
  Serum progesterone <5 ng/mL sugg abn Preg (100% specific, 60% sensitive).
  Serum progesterone >20 ng/mL sugg nml IUP (40% specific, 95% sensitive)
- **Endometrial curettage:** For "Preg of unk location," D&C can evaluate POCs (float the villi), & assist in decision for diagnostic laparoscopy vs. dx of abn Preg (eg, missed AB).

Treatment and Medications

- **Expectant mgmt:** 68% → successful resolution (*Lancet* 1998;351:1115)
  If initial hCG is <200 mIU/mL, 88% resolve w/o rx
  Recheck hCG 48 h after initial lab tests to ensure declining serum hCG
- **Medical mgmt:** MTX inhibits dihydrofolate reductase → decreased tetrahydrofolate → ↓ purine nucleotide synthesis → ↓ DNA/RNA in S-phase of cell cycle→ prevent proliferation (in active tissues like trophoblast, bone marrow, buccal/intestinal mucosa). 2 protocols (see below). Multidose regimen more effective for advanced GA & +ve fetal cardiac activity.
  Side effects: Usually self-limited. Most common are nausea, vomiting, stomatitis, conjunctivitis, worsening abdominal pain 2–3 d after MTX dose due to expansion of the affected gestational tissue, transient liver dysfxn, & uncommonly myelosuppression, alopecia, pulmonary damage, anaphylaxis.
  Pt instructions: Stop taking prenatal vitamins & folate supplements, avoid sun exposure, refrain from EtOH consump, intercourse, & vigorous physical activity.
  Strong contraindications to MTX: Tubal rupture or hemodynamic instability, breast-feeding, alcoholism, alcoholic liver dz, or chronic liver dz, immunodeficiency, pre-existing bld dyscrasias (bone marrow hypoplasia, leukopenia, thrombocytopenia, signif anemia), active pulmonary dz, peptic ulcer dz, hepatic, renal, or hematologic dysfxn, Cr >1.3 mg/dL, AST or ALT >50 IU/L.
  Relative contraindications to MTX:
  GS >3.5 cm. Single-dose MTX 93% effective when the GS is <3.5 cm. Decreases to 87–90% efficacy when >3.5 cm. Large GS → ↓ success.
  Embryonic cardiac activity. Single-dose MTX is 87% effective if +ve fetal heart motion.
  Serum hCG level >5000 mIU/mL. Failure w/ single-dose MTX is 14.3% if hCG >5000 mIU/mL (compared to 3.7% failure if hCG <5000 mIU/mL). Consider multidose therapy or surgical mgmt.

Single-dose MTX regimen

89% success rate, MTX dose: 50 mg/m^2
Day 1: Check hCG (& other labs above), administer MTX
Day 4 & day 7: Check beta hCG
↓ in hCG of 15% from day 4–day 7 → continue to monit weekly serum hCG levels until undetectable (Note: hCG may ↑ from day 1–day 4)
If hCG does not fall appropriately from day 4–day 7 → consider rpt US, then rpt MTX dose or perform laparoscopy

Multidose MTX regimen

93% success rate
MTX dose: 1 mg/kg + Leucovorin (folinic acid) dose: 0.1 mg/kg
Day 1: Check hCG, administer MTX
Day 2: Administer Leucovorin
Day 3: Check hCG. If hCG has NOT decreased by 15% from day 1, then administer MTX
Day 4: Administer Leucovorin
Day 5: Check hCG. If hCG has NOT decreased by 15% from day 3, then administer MTX
Day 6: Administer Leucovorin
Day 7: Check hCG. If hCG has NOT decreased by 15% from day 5, then administer MTX
Day 8: Administer Leucovorin
If 4 doses of MTX are given w/o a 15% decline in hCG over 48 h → proceed w/ laparoscopy
If there is a 15% decline in hCG over 48 h → follow weekly serum hCG levels until undetectable

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- **Surgical mgmt:** Laparoscopy preferred if the pt is hemodynamically stable → shorter operative times, less bld loss, less analgesic requirements, shorter hospital stay, no difference in tubal patency rates, similar rates of subseq IUP.
  Salpingostomy: Gold std Surg for ectopic. Open affected tube & evacuate ectopic POCs. Esp useful for pt w/ abn contralateral tube who desires future fertility. Persistent ectopic Preg in 4–15% of cases. Follow weekly serum hCG levels until they are undetectable. Check pathology to confirm POCs.
  Salpingectomy: Removal of entire affected fallopian tube. Appropriate for pts w/ a nml appearing contralateral tube who desire future fertility, or pts who do not desire future fertility. Eliminates risk of persistent ectopic Preg, or recurrent, ipsilateral ectopic Preg. If confident that all trophoblast removed, no need for serial hCGs.

OVARIAN CYSTS

Definitions *(Obstet Gynecol 2011;117:1413; Am Fam Physician 2009;80:815)*

- **Functional ovarian cysts:** Follicular cysts form when an unruptured ovarian follicle fills w/ serous fluid → capsule distention/pain. Corpus luteum cysts, normally present in early Preg; can bleed → distention or active hemorrhage.
- **Benign & neoplastic ovarian cysts** (see also Chap. 21): Dermoid, stromal & germ cell tumors, fibroma, epithelial neoplasm, cystadenoma, endometrioma.

Epidemiology and Etiology

- Incid of ovarian cysts = 5–15%. Lifetime risk 5–10% for adnexal mass Surg
- **Diff dx:** Leiomyomata, TOA, hydrosalpinx, ectopic Preg, paratubal cysts, diverticular abscess, appendiceal abscess, nerve sheath tumors, ureteral diverticulum, pelvic kidney, bladder diverticulum, peritoneal inclusion cysts, malig.

Clinical Manifestations

- Most are asymptomatic, but may p/w pain, pressure sensation, dyspareunia
- Intermittent pain may indicate ovarian torsion. Acute, sev pain may represent ovarian torsion or cyst rupture. Increased abdominal girth, bloating, wt loss, & early satiety raise concern for malig. Hormonal disruption w/ estrogen/androgen secretion.

Physical Exam and Diagnostic Workup

- **Pelvic exam:** 45% sens & 90% spec. ↓ detection w/ BMI >30
- **Labs:** hCG, CBC, coags/other labs depending on presentation & Hx
- **Abdominal & pelvic US:** TVUS sens 82–91% & spec 68–81% for distinguishing benign from malignant dz. Classic US appearance of a simple cyst is anechoic, well circumscribed, echolucent w/ post acoustic enhancement.
- See Chap. 21 for w/u for malig, tumor markers, & referral to gyn oncology

Treatment and Medications

- **Observation:** Most simple ovarian cysts spontaneously regress in 6 mo. ↑ adnexal/ovarian torsion at 6–10 cm mass. 0–1% risk of malig if cyst is unilocular, thin walled, sonolucent, <10 cm in diameter, & has smooth, regular borders.
  Premenopausal women w/ cyst <3 cm do not require f/u
  Premenopausal women w/ cyst 4–10 cm who desire expectant mgmt → rpt US for resolution in 12 w (4–12 w depending on concern)
  Postmenopausal women w/ cysts 4–10 cm & CA-125 <35 U/mL who desire expectant mgmt → serial USs every 4–6 w
- **Surg:** Provides definitive pathologic dx. Indicated for hemodynamic instability, cyst >6–10 cm, concern for malig, concern for torsion, or persistent sx
  Laparoscopy: ↓ operative morbidity, postoperative pain, analgesics, recovery time, & costs
  Laparotomy: Usually for malig (w/ appropriate staging), hemodynamic instability, or failed laparoscopy
  Cystectomy vs. oophorectomy: Consider the pt's age, reproductive desires, menopausal status, & preoperative dx. (If a corpus luteum cyst is removed during Preg at <12 WGA → progesterone supplementation.)

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ADNEXAL TORSION

Definition and Epidemiology (*Am J Obstet Gynecol* 1985;152:456)

- Twisting of adnexal components (most commonly ovary ± fallopian tube) on their ligamentous supports → venous, arterial, & lymphatic obst
- 5th most common gyn emergency; 2.7% of female surgical emergencies
- Females of all ages (fetal/neonat to elderly); however, 70% are of ages 20–39
- Increased risk w/ Preg (20–25% of all cases) & ovarian hyperstimulation

Etiology (*Clin Exp Obstet Gynecol* 2004;31:34; *Am J Obstet Gynecol* 1991;164:577)

- 94% a/w adnexal mass (48% cysts, 46% neoplasms). ↑ w/ masses 6–10 cm
- Congenitally long ovarian ligaments
- ↑ w/ strenuous exercise, intercourse or sudden ↑ in abdominal pressure
- Right ovarian torsion more common than left (protection from sigmoid colon)

Pathophysiology

- Compromise of vascular pedicles impedes arterial inflow & lymphatic & venous outflow → Venous drainage interrupted before arterial due to less compressibility of arterial walls → Marked ovarian enlargement can develop w/ continued perfusion & blocked outflow

Clinical Manifestations and Physical Exam (*Ann Emerg Med* 2001;38:1506)

- **Acute pelvic pain** (83%): Sudden/sharp pain (59%) radiating to back/flank/groin (51%) w/ peritoneal signs (3%)
- **Nausea &/or vomiting** (70%): Colicky or sporadic sx from intermittent torsion
- **Neonates:** Usually in 1st 3 mo of life w/ feeding intolerance, vomiting, abdominal distension, & fussiness/irritability – usually ovarian cysts have already been identified w/ prenatal US (*Arch Pediatr Adolesc Med* 1998;152:1245).
- Resolution of sx seen after ~24 h due to ischemic death of involved structures. Functionality can be preserved w/ immediate intervention.
- **Bimanual exam:** Adnexal mass (72%), tenderness in RLQ or LLQ
- **Fever** (<2%): May be a marker of necrosis, particularly in the setting of increased WBC

Diagnostic Workup/Studies

- Dx confirmed at Surg. ~40% correct preop dx (*J Reprod Med* 2000;45:831)
- **Clinical dx:** (1) Lower abdominal pain, (2) ovarian cyst/mass, & (3) diminished or absent bld flow in the ovarian vessels on color Doppler flow imaging. Rule out ectopic Preg, PID, appendicitis, diverticulitis, nephrolithiasis, & leiomyoma-related sx.
- **Lab studies:** hCG to rule out Preg; labs: CBC, BMP, may see anemia, leukocytosis, or electrolyte abnormalities from vomiting.
- **US:** Cystic or solid mass (70%), free fluid in post cul-de-sac (>50%), enlarged heterogenous appearing ovary (*J Ultrasound Med* 2001;20:1083). Nml ovary on US does *not* rule out torsion.
  - **Doppler:** Controversial; some studies w/ sens & spec of 100% & 97%, others w/ 43% & 92% (*Eur J Obstet Gynecol Reprod Biol* 2002;104:64); color Doppler flow ↑ dx of torsion when absent but not reliable when flow is present.
  - **Whirlpool sign:** Doppler finding in vascular pedicle (*J Ultrasound Med* 2009;28:657)
  - **MRI/CT:** Limited value, can ID ovarian edema; diagnostic criteria not been well defined or validated. CT potentially useful in excluding other diagnoses on diff.

Treatment (*NEJM* 1989;321:546; *Obstet Gynecol Surv* 1999;54:601)

- **Swift operative eval:** Preserve ovarian fxn & prevent infxn from necrosis
- **Laparoscopic detorsion** w/ cystectomy vs. salpingo-oophorectomy: Consider detorsion in premenopausal pts, majority regain prev form & fxn, even if ischemic appearing intraoperatively. No ↑ risk of clot dislodgement/PE in either detorsion or salpingo-oophorectomy. Consider oophoropexy for prevention esp w/ recurrent ovarian torsion.

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PELVIC INFLAMMATORY DISEASE (PID)

Definition and Epidemiology (*Obstet Gynecol* 2010;116:419)

- **PID:** Clinical spectrum of inflamm disorders of the female upper genital tract including endometritis, salpingitis, TOA, & pelvic peritonitis
- >800000 cases/y in US; true magnitude unk due to difficult dx
- **Risk factors:** Age <25, young age at 1st intercourse, nonbarrier contraception, multi sexual partners, oral contraception, cervical ectopy, IUD insertion w/i prev 3 w

Etiology and Microbiology (*NEJM* 1975;293:166; *Ann Intern Med* 1981;95:685)

- ***Neisseria gonorrhoeae:*** 1/3 of cases; 15% w/ endocervical gonorrhea develop PID
- ***C. trachomatis:*** 1/3 of cases; 15% w/ endocervical chlamydia develop PID
- **Other pathogens:** Vaginal flora (eg, anaerobes, *Gardnerella vaginalis, Haemophilus influenzae,* enteric gram-negative rods, & *Streptococcus agalactiae*)

Clinical Manifestations

- Lower abdominal pain (90%). Mucopurulent discharge (75%).
- **Long-term sequelae:** Infertility (18%), ectopic Preg, chronic pelvic pain, dyspareunia

Diagnosis of PID	
CDC diagnostic criteria (Dx is imprecise. Maintain low threshold for rx due to long-term sequelae.)	1. Pelvic or lower abdominal pain
	2. No cause other than PID can be identified
	3. 1 or more minimum criteria are present on physical exam: (a) cervical motion tenderness, (b) uterine tenderness, or (c) adnexal tenderness
Additional criteria (enhance spec)	1. Oral temp. >101°F (>38.3°C)
	2. Abn cervical or vaginal mucopurulent discharge
	3. Presence of abundant # of WBCs on wet mount
	4. Elevated ESR
	5. Elevated CRP
	6. +GC/CT
	7. Lab-proven chlamydia or gonorrhea infxn
Specific criteria (if needed)	Endometrial bx w/ endometritis TV sono or MRI w/ hydrosalpinx or free pelvic fluid Laparoscopic confirmation of pelvic infxn

From CDC. Sexually Transmitted Diseases Treatment Guidelines, 2010. http://www.cdc.gov/std/treatment/2010/pid.htm.

Treatment

- **Indications for hospitalization:** Preg, outpt therapy failure after 72 h, noncompliance, sev illness (eg, N/V, high fever), or TOA
- **IUD:** Do not need to remove IUD, close clinical f/u if remains in place
- Screen for additional STIs. F/u in clinic in 3 d
- EPT is indicated to prevent reinfection: See state-specific legislation: http://www.cdc.gov/std/ept/legal/default.htm

CDC 2010 treatment guidelines		
Inpt	Cefotetan 2 g IV q12h OR Cefoxitin 2 g IV q6h + Doxycycline 100 mg PO or IV q12h × 14 d	D/c parenteral rx 24 h after clinical improv & afebrile
	Clindamycin 900 mg IV q8h + Gentamicin IV or IM (2 mg/kg) ×1, then 1.5 mg/kg q8h	
Outpt	Ceftriaxone 250 mg IM* ×1 OR Cefoxitin 2 g IM ×1 & Probenecid 1 g PO ×1 + Doxycycline 100 mg PO q12h × 14 d & ± Metronidazole 500 mg PO q12h × 14 d	

*Note: Oral cephalosporins no longer recommended to treat gonorrhea due to growing resistance (as high as 6%) in some states. CDC. *MMWR.* 2012;61(31):590.
From CDC. Sexually Transmitted Diseases Treatment Guidelines, 2010. http://www.cdc.gov/std/treatment/2010/pid.htm.

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ACUTE UTERINE BLEEDING

Definition and Epidemiology (*Fertil Steril* 2011;95:2204; *Obstet Gynecol* 2002;99:1100)

- Heavy vaginal bleeding suff to require immediate intervention. May or may not occur in the setting of Chronic Abnormal Uterine Bleeding. See Chap. 5, Abnormal Uterine Bleeding.
- Affects 10–30% of women. 12% of gyn visits in ER. See SABs below, also.

Physical Exam

- **Rapidly determine acuity:** General appearance & stability. Orthostatic VS.
- **Speculum exam:** Rule out nonuterine causes (eg, rectal bleeding, genitourinary, vaginal lacerations, cervical lesions), assess extent of bleeding (eg, active/ongoing hemorrhage)
- **Bimanual exam:** Evaluate for structural abnormalities, such as a prolapsing fibroid

Diagnostic Workup/Studies

- Always rule out Preg – qualitative hCG. Labs: CBC, coags including fibrinogen, type & screen. Imaging: Consider TVUS.

Treatment and Medications

- If unstable: 2 large bore IVs, crystalloid fluid resusc
- Consider xfusion of 2 U packed RBCs if Hgb <7.5
- If anemic, start PO ferrous sulfate at discharge from hospital
- Initiate goal-directed therapy

Medical management of acute uterine bleeding

Category	Agent	Dose	Comments
Estrogen	Premarin (Consider rx for antiemetic)	25 mg IV q4–6h up to 24 h	Avoid in smokers >35 yo, uncontrolled HTN, CAD, Hx VTE, stroke, liver dz
COCs	EE/norethindrone (Consider rx for antiemetic)	35 μg/1 mg TID × 1 w, then QD × 3 w	Avoid in smokers >35 yo, uncontrolled HTN, CAD, h/o VTE, stroke, liver dz
Progestin	Aygestin (norethindrone acetate)	5 mg TID × 1 w, then BID × 3 w	Use w/ caution in pts w/ Hx VTE, stroke or MI, liver dz
	Provera (Medroxyprogesterone)	20 mg TID × 1 w, then BID × 3 w	
Nonhormonal	Tranexamic acid	1.6 g PO TID × 5 d OR 10 mg/kg IV q8h up to 5 d	Avoid in pts w/ active thromboembolic dz or intrinsic risk of thrombosis

From *Obstet Gynecol* 2006;108:924; *J Obstet Gynecol* 1997;37:228; *Am J Obstet Gynecol* 1982;59:285.

Surgical management of acute uterine bleeding

Intracavitary tamponade	Foley balloon (30–50 cc); Bakri balloon
D&C; hysteroscopy	Reserve for emergent cases; may help w/ acute episode, subseq menses unchanged
UAE	Reserve for emergent cases; particularly w/ leiomyoma or suspected AVM
Hysterectomy	Reserve for emergent cases; definitive

From Clinical Guideline for Heavy Menstrual Bleeding, National Institute for Health and Clinical Excellence, 2007.

SPONTANEOUS ABORTION (SAB)

Definition and Epidemiology (*Fertil Steril* 2003;79:577; *Obstet Gynecol* 2005;105:333)

- SAB (miscarriage) occurs before 20 w0d & <500 g
- Early Preg failure complicates 12–15% of known pregnancies & 17–22% of all pregnancies; 80% occur in the 1st 12 w of gest; fertilization → 30% implantation

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failure → 30% early loss (= 60% loss before recognized clinical Preg) → 12–15% clinical Preg SAB → 25% live birth.
- Vaginal bleeding in ~25% known 1st trimester pregnancies → ~50% of those are SABs
- Once fetal cardiac activity is noted, 90–96% have ongoing Preg
- **Risk factors:** ↑ mat age, prev SAB, heavy smoking, EtOH, cocaine, NSAIDs, fevers, caffeine >200 mg daily may be a/w SAB, chronic mat dz (DM, autoimmune, APLA syn), short interpregnancy interval, uterine anomalies.

Types of spontaneous abortions (<20 w 0d)

Name	Sx	Bleeding?	Internal cervical os?	Tissue passed?	Notes
Missed	No sx; no fetal pole or cardiac activity. No cramping.	± (may be scant)	Closed	None	Includes "anembryonic" & "blighted ovum"
Threatened	Any bleeding gives dx, ± pain	Yes	Closed	No	Increases loss & ptb rate
Inevitable	Imminent miscarriage, usually w/ painful cramps	Yes	Open	No	
Incomplete	Bleeding & passage of some POCs	Yes	Open	Partial	Treat medically or surgically
Complete	After passage of POCs, ± cramping	Yes or resolving	Closed	All POCs passed	Usually no intervention
Septic AB	Usually cramping/ uterine tenderness, ± fever/chills/ malaise/ discharge	±	±	No or partial; infected POCs are retained	May be VERY ill
Recurrent	2–3 consecutive early losses	Any of the above			Refer for RPL w/u

Etiologies
- Chromosomal abnormalities (50%); congen anomalies; trauma (early GA uterus generally protected from blunt trauma); host factors (eg, uterine abnormalities [septum]), mat infxn, mat endocrinopathies or corpus luteum dysfxn, mat inherited or Acq thrombophilia; unexplained.
- **Diff:** Cervical bleeding (polyp, malig, trauma), ectopic Preg, infxn, molar Preg, SAB (see above), subchorionic hemorrhage, vaginal trauma.

Clinical Manifestations and Physical Exam
- Amenorrhea, vaginal bleeding, &/or pelvic pain/cramping
- Cessation of nml sx of Preg (eg, nausea, breast tenderness)
- Speculum/digital exam to assess cervical dilation, POCs
- Evaluate extent of bleeding (eg, hemorrhage) & mat stability

Diagnostic Workup *(Obstet Gynecol 1992;80:670; Ultrasound Obstet Gynecol 1994;3:63)*
- **Passed tissue:** "Float villi" in saline to evaluate frond-like chorionic villi; send to pathology
- **Transvaginal US:** Distinguishes IUP vs. extrauterine Preg, viable vs. nonviable, presence of gestational trophoblastic dz, retained POCs, ectopic
  Missed AB: No fetal cardiac activity + CRL >5 mm OR absence of embryonic cardiac activity w/ menstrual age >6.5 w
  Findings suggestive of early Preg failure: Absence of yolk sac w/ MSD >13 mm; absence of embryonic pole w/ MSD >20 mm; enlarged yolk sac (>6 mm), irreg or low lying sac; slow FHT (<100 bpm at 5–7 w); small GS (difference btw MSD & CRL <5 mm); subchorionic hematoma >25% vol of the GS.
- **Quantitative beta hCG:** Low yield once IUP confirmed. If no IUP, serial hCGs q48h to rule out ectopic → ↓ hCG = nonviable IUP or spontaneously resolving ectopic.

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Management of First Trimester Abortions

Management of first trimester abortions	
Spont	If evid of complete passage & no excessive bleeding, no further mgmt needed. If highly desired, no infxn/bleeding, & esp if unsure dating, may manage expectantly.
Missed, Incomplete, or Inevitable	Expectant mgmt if <13 w w/ stable VS & no e/o infxn. ~40% will need D&C eventually; ~80% success w/ expect mgmt for incomplete. **Medical:** Misoprostol (PGE1 analog) in 1st trimester; contraindications, allergy, ectopic or pelvic infxn, hemodynamic instability. **Missed AB:** 800 μg vaginally q24h up to 3 doses OR 400 μg per vagina q4h ×4 OR 600 μg sublingually q3h ×2 if needed (71% success by 3 d, 84% success by 8 d; 12% need D&C). **Incomplete AB:** 600 μg PO OR 400 μg sublingually ×1 (82% success by 5 d, 95% success by 7 d; 3% need for D&C). **Surgical:** Suction D&C or manual vacuum aspiration. Risks include uterine perforation, intrauterine adhesions, cervical trauma, & infxn. Recommended: Doxycycline 100 mg PO preop & 200 mg PO postop. (97% success rate)
Threatened	**Expectant mgmt:** Bleeding precautions, pelvic rest. No effect of progest for threatened AB, but may ↓ recurrent AB. (*Cochrane Database Syst Rev* 2013;10:CD003511).
If Rh(D)-negative & unsensitized, give RhoGAM 50–300 μg IM (prevent alloimmunization). Offer chromosomes/pathology. Grief counseling. Pain meds (NSAID, ± narcotics). Bleeding warnings. Antiemetic for nausea. F/u US in some circumstances (clinical presentation).	
From *Int J Gynaecol Obstet* 2007;99:182; *NEJM* 2005;353:761; *Am J Obstet Gynecol* 2005;193:1338.	

TRAUMA IN PREGNANCY

Epidemiology (*Int J Gynaecol Obstet* 1999;64:87; *Obstet Gynecol* 2009;114:147)

- Leading cause of nonobstetric mat death during Preg. Complicates 3–8% of pregnancies; 2/3 from motor vehicle collisions.
- Up to 20% of pregnant women are victims of DV. Preg alone is an independent risk factor for DV (*Am J Obstet Gynecol* 1991;164:1491).
- Outcomes directly related to GA & severity/mech of injury
- 40–50% fetal loss rate w/ life-threatening mat trauma (eg, mat shock, head injury leading to coma, emergency laparotomy for mat indications) (*Obstet Gynecol Clin North Am* 1991;18:371).
- 1–5% fetal loss w/ nonlife-threatening injuries, but b/c more common, >50% of fetal losses occur w/ minor trauma
- **Blunt trauma:** Placental abruption (40% sev cases, 3% nonsevere cases), direct fetal injury (<1%), uterine rupture (<1%), mat shock, mat death
- **Penetrating trauma:** Gunshot wounds or stab wounds; fetal prog generally worse than mat prog
- **Pelvic fractures:** Fetal mortality rate 35%; may result in signif retroperitoneal bleeding. Not an absolute contraindication for vaginal delivery.

Clinical Manifestations & Physical Exam (*Obstet Gynecol* 2009;114:147)

- **Placental abruption:** Vaginal bleeding, uterine tenderness, abdominal pain, back pain, fetal distress, high-frequency uterine contractions, uterine hypertonus, decreased fetal movement, or even fetal death.
- **Primary survey:** Note that pregnant women can lose a signif amt of bld before tachy & HoTN occur due to their increased intravascular vol.
- **Abd:** Ecchymoses (new & old), seat belt injury, penetrating abdominal injuries, palpate for contractions or tenderness
- **Speculum:** Bleeding, rupture of membranes, vaginal lacerations, pelvic bone fragments

Diagnostic Workup/Studies (*Obstet Gynecol* 2009;114:147)

- **US:** Fetal cardiac activity, fetal GA & presentation, free peritoneal fluid or mat hemorrhage. Consider FAST to assess for free fluid in perihepatic, perisplenic, pelvic, & pericardial areas.
- **Radiologic eval:** Should not be deferred if req for mat assessment

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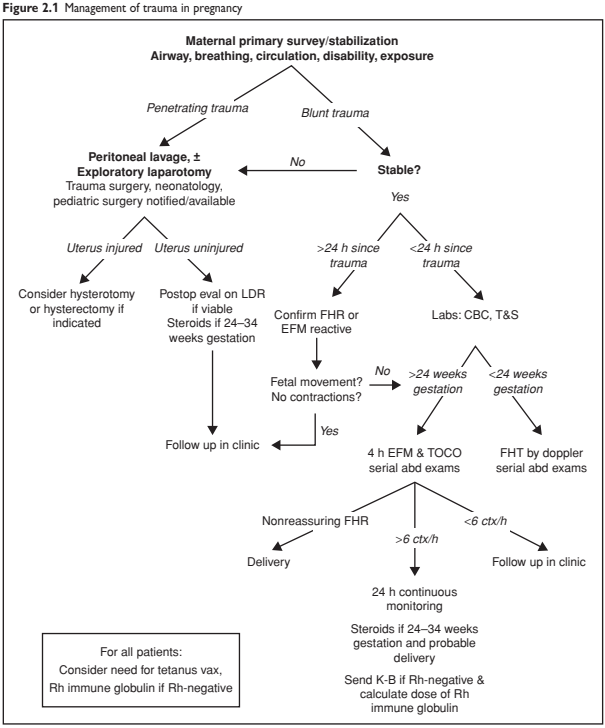
Initial Management *(ACOG 1998)*

- **Mat:** Supplemental O_2; 2 large bore IVs; early IV fluid resusc in ratio 3:1 based on bld loss; left lateral uterine displacement after 20 w (if spinal injury suspected, manual displacement or a wedge under a backboard ok); labs – CBC, type & screen, coags, & hold tube. Kleihauer–Betke & RhoGAM for Rh-negative moms.
- Once mother stabilized, proceed w/ **fetal assessment:**
  GA <24 w0d: Document FHR by Doppler or real time US; tocometer if high concern for abruption by Hx or physical exam
  GA >24 w0d: 4–6 h continuous fetal monitoring (includes FHR & tocodynamometry). If >6 contractions in an hour or sev injury → prolonged monitoring for 24 h. Nonreactive NST → further eval (BPP or prolonged fetal monitoring).
- In setting of mat **cardiopulmonary arrest,** delivery by C/S if >4 min has elapsed. Improves mat resusc by decreasing uterine compression of venous return.

Figure 2.1 Management of trauma in pregnancy



From ACOG PB#252; *Am J Obstet Gynecol* 1990;162:1502; *Am J Obstet Gynecol* 2004;190:1661; *Am J Obstet Gynecol* 2004;190:1461; UNC SOM OB Algorithms 2004; ATLS Course Manual 2008.

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Preoperative Evaluation

- Preop eval is needed for all pts before all procedures, w/ complete **medical/surgical Hx & periop risk assessment.**

American Society of Anesthesiologists' (ASA) physical status classification system	
ASA-I	Normal, healthy
ASA-II	Mild systemic dz
ASA-III	Systemic dz that is not incapacitating
ASA-IV	Incapacitating systemic dz that is constant threat to life
ASA-V	Moribund pt not expected to survive

From ASA. http://www.asahq.org/Home/For-Members/Clinical-Information/ASA-Physical-Status-Classification-System.

- **Review of current meds & allergies:** Discuss holding NSAIDs, antiplatelet agents, anticoagulant supplements (eg, fish oil); consider bridging long-acting anticoagulants to shorter acting meds (eg, warfarin to heparin)
- Review relevant prior **operative reports.**
- Most healthy women w/ no identifiable RFs require no further **testing or consultation.**
- Consider ECG in women >50 y. Depending on invasiveness & urgency of procedure, periop eval by PCP ± anesthesia or other specialist is recommended. Additional testing based on identified risk.
- **Informed consent,** w/ balanced discussion of:
  - Risks, benefits, alternatives (including nontreatment & poss additional procedures), & complications.
  - Healthcare team & their roles including trainee & supportive teams
  - Permission to take photos or videos for documentation or teaching
  - Possibility of bld or bld product use
- Identify existing advance directive & healthcare proxy/power of attorney. Consider creating an advance directive if one does not already exist.
- Discuss expected postop course (hospital stay, recovery, change in fxn, etc.)
- Identify special needs for OR (eg, interpreter services)

Perioperative Optimization

- New or uncontrolled medical conditions → consultation/optimization w/ appropriate specialist + primary care input.
- **Pulm dz:**
  - RFs = older age, current smoking, obesity, obstructive sleep apnea, low serum albumin (<3 g/dL) & BUN >30 mg/dL, higher ASA scores are a/w higher risk for postop pulm complications (*Ann Surg* 2000;232:242; *Ann Intern Med* 2006;144(8):581).
  - Well-controlled asthma not a/w pulm postop complications
  - Advise smoking cessation >8 w before elective Surg (if <8 w, no dec in pulm complications)
  - Preop PFTs/CXR if unexplained dyspnea or respiratory sx; consider if COPD of unclear severity.
  - **Postoperatively:** Deep breathing exercise, incentive spirometry, early ambulation, upright position, & adequate pain control after Surg are effective in preventing postop pulm complications.
- **Cardiovascular dz:**
  - Most abdominal/pelvic Surg is considered as an intermediate risk regarding cardiac morbidity
  - Selected procedures may be of low risk (eg, D&C) or high risk (major debulking Surg)
  - Nonemergent Surg should be delayed or cancelled if pt has (1) unstable coronary syns, (2) decompensated heart failure, (3) signif arrhythmia, or (4) sev valvular dz.

Revised cardiac risk index (RCRI)
Presence of any of the following puts pt at higher risk for major periop cardiac morbidity: 1. Ischemic heart dz (h/o MI, angina, use of sublingual nitroglycerin, positive stress test, Q wave on ECG) 2. Heart failure 3. Cerebrovascular dz 4. Insulin-requiring diabetes 5. Renal insufficiency w/ Cr >2 mg/dL
From *Circulation* 1999;100(10):1043.

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Testing by RCRI factors		
Low risk	No RCRI factors	No testing Consider ECG for >50 yo
Intermediate risk (1–2 RCRI factors)	Good functional status, no h/o angina or PVD	No testing
	Poor/indeterminate functional status, h/o angina or PVD	Consider noninvasive stress test: If negative: No further intervention indicated If positive: Discuss cardiac catheterization & revascularization w/ cardiology Evid does not support periop beta blockade in pts w/ RCRI scores ≤2. Dec risk of MI, but inc risk of nonfatal stroke. (*Lancet* 2008;372:1962)
High risk (3+ RCRI factors)	Primary sx are related to failure, arrhythmia, or valve	Medical optimization
	Pts w/ >2 cardiac RFs who ALSO have extensive stress-induced ischemia on noninvasive testing	Revascularization (*Eur Heart J* 2009;30:2769)
Beta blockers & statins should be initiated only if indication for long-term use. Start rx weeks prior to surgery. Target HR 60–80 bpm. From 2009 ACCF/AHA; *J Am Coll Cardiol* 2009;54:2102. doi:10.1016/j.jacc.2009.07.004.		

- **Hematology:**
  - **Anemia:** Investigate if unexplained; correct anemia w/ iron suppl if there is time before Surg or transfuse if Hgb <7 g/dL, symptomatic, or for high anticipated bld loss. Consider menstrual suppression if menorrhagia is a contributing factor. Consider erythropoiesis-stimulating agents if xfusion is refused.
  - **Thrombocytopenia:** Goal is Plts >50000
  - **Pt on anticoagulation:**
    - Determine risk of stopping anticoagulation perioperatively. Stop warfarin 5 d prior to procedure, goal INR <1.5. Consider heparin bridge if at high risk of thrombosis.
    - Avoid elective Surg w/i 1 mo of acute venous or arterial thrombosis
    - Consider IVC filter if recent thrombosis & high risk of bleeding w/ anticoag
- **Endocrine:**
  - **DM:**
    - Periop gluc problems: (1) surgical stress, (2) preop NPO, (3) decreased PO postop, (4) type of anesthesia (general > neuraxial). Critical considerations: (1) type 1, type 2, or gestational diabetes; (2) timing, length, & invasiveness of procedure; (3) current med regimen.
    - Poor periop gluc control a/w (1) increased risk of infxn, (2) poor wound healing, (3) neuro/cardiac sequelae of hypoglycemia. Postop goals: Maintain euglycemia (<150–180 mg/dL) & prevent ketoacidosis & nonketotic hyperosmolar state.
    - Metformin contraindicated w/ renal insufficiency or poor tissue perfusion; thiazolidinediones may exacerb edema or precipitate CHF.

Perioperative DM management		
PREOP	Type 2 DM, diet controlled	Fingerstick gluc pre- & postop
	Type 2 DM, PO med controlled	Hold meds morning of Surg
	Insulin-controlled DM (type 1 or type 2)	Continue basal/long-acting insulin. Reduce preop intermediate acting PM dose 50% (eg, NPH). D5 in IVF. IV insulin only for very long, complex cases.

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POSTOP	Noninsulin-requiring DM	SS inferior to basal/bolus regimen, use only if needed & NPO (*Diabetes Care* 2011;34:256) Resume home meds if no contraindication, as soon as taking PO well.
	Insulin-requiring DM	Continue basal insulin to prevent ketogenesis. NPO: Home basal insulin + regular SS q6 h, D5 in IVF. W/ PO diet: Home basal/bolus regimen OR 0.5 U/kg divided btw basal & preprandial short acting (AC) insulin at meals.

- **Thyroid dz:**
  - **Hyperthyroid:** If new dx or uncontrolled, postpone Surg, consult endocrinology, continue chronic meds.
  - **Hypothyroid:** Consider endocrinology consult if new dx. Otherwise, continue meds. No need for IV/IM thyroid replacement if NPO for <7 d.
  - **For hypo- & hyperparathyroidism:** Follow for calcium imbalance
- **Adrenal insufficiency:**
  - Higher risk for periop adrenal crisis (HoTN, HoNa)
  - Minimal suppression of the HPA axis in pts w/ <5 mg prednisone (or equiv) daily; <10 mg prednisone every other day; or ANY dose of glucocorticoid for <3 w. These pts do not require supplemental steroids (*N Engl J Med* 2003;348:727).
  - Replacement based on type of Surg (*JAMA* 2002;287:236):
    - **Minor Surg** (outpt Surg or minimally invasive): → consider 25 mg hydrocortisone on day of procedure → pt returns to regular dose.
    - **Obstetric cases & all gynecologic Surg:** → 50 mg hydrocortisone just before procedure → followed by 25 mg IV every 8 h for 24 h → back to maint dose
    - **For sev surgical stress** (consider in extensive debulking surgeries): 100–150 mg hydrocortisone on day of procedure → rapid taper to usual dose over 1–2 d
    - **Critically ill pts** (septic shock): → 50–100 mg hydrocortisone IV q6–8 h or 0.18 mg/kg/h as a continuous infusion & 50 µg/d fludrocortisone until shock is resolved → taper slowly (monit sodium).
- **Elderly pts:**
  - **Polypharmacy:** Carefully review meds & potential interactions
  - Avoid bowel prep due to higher risk of dehyd/electrolyte derangement
  - Higher risk for the following postoperatively (*Am J Obstet Gynecol* 2003;189:1584)
    - Delirium & mental status changes; ensure sleep hygiene, orientation to environment & careful dosing of psychoactive meds. W/u medical causes of delirium.
    - Pulm edema w/ heart failure due to fluid overload; monit fluid balance
    - MI & stroke
    - Slow return of bowel fxn
    - Longer hospital stay
- **Obese pts:**
  - Higher risk for the following postoperatively (*Am J Obstet Gynecol* 2010;202:306):
    - SSI; plan incision & dose Abx appropriately
    - Pulm complications; encourage early ambulation & pulm toilet
    - Thromboembolic complication; consider weight-based anticoagulant dosing per pharmacy guidelines

Preoperative Measures

- **Preg test:** For ALL women of reproductive age
- **Bld type & Ab screen:** Consider cross-match for high-risk surgeries
- **Antibiotic ppx for prevention of SSI:** See below
- **Antibiotic ppx for prevention of SBE:**
  - Not routinely recommended for GU procedures. Used in women w/ highest potential risk (prosthetic valve, prev infective endocarditis, pt w/ unrepaired cyanotic heart dz, repaired heart dz w/i 6 mo of procedure, or repaired dz w/ residual defects near prosthetic material, cardiac xplant w/ signif valvular dysfxn) (*Circulation* 2008;118(8):887).
- **Venous thromboembolism ppx:** See below
- **Bowel prep:** Mechanical bowel preparation (eg, magnesium citrate, polyethylene glycol) not recommended for most gynecologic or colorectal Surg (*Am J Obstet Gynecol* 2011;205:309).
- **Fasting:** Preop NPO reduces aspiration risk. Milk or fried/fatty food: 8 h; light meal not including milk: 6 h; clear fluids: 2 h (*Anesthesiology* 2011;114:495).

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- **Skin prep:** SSI, see below
- **Positioning & incision selection:** Neurologically neutral positioning & padding of all jnts. Avoid prolonged lithotomy (>4 h) or steep Trendelenburg. Select incision for appropriate exposure & to avoid excessive retraction.

Common nerve injury in gynecologic surgery

	Mech/RFs	Measures to avoid injury
1. Femoral nerve (L2–4):	Femoral nerve pierces the psoas muscle to pass under the inguinal ligament. Common neuropathy after gynecologic Surg, esp abd hysterectomy. (~11%). RFs include: Use of self-retaining retractors Wide Pfannenstiel or Maylard incision BMI <20 kg/m^2 Operation >4 h Poorly developed rectus muscle Narrow pelvis Hip hyperflexion or external rotation in lithotomy	Avoid compression of the psoas muscle by the self-retaining retractors Avoid extending Pfannenstiel incision beyond the lateral border of rectus abdominis Avoid hyperflexion & external rotation of the hip
2. Ilioinguinal (T12–L1) & iliohypogastric (T12–L1) nerves	Ilioinguinal nerve & iliohypogastric nerve course ~3 cm inferomedially to ASIS. Risk of entrapment at the lateral edge of Pfannenstiel incision. Prone to neuroma formation after injury.	If need to extend incision lateral to rectus muscle body, curve the fascial incision cephalad Avoid lateral placement of sutures when closing the fascia (no more than 1.5 cm lateral to the edge)
3. Genitofemoral (L1–2) & lateral-femoral (L2–3) nerves	These nerves lie on the belly of the psoas muscle lateral to the external iliac artery – Excessive lateral retraction – Transection during pelvic LN.	Avoid lateral excessive lateral traction on the psoas muscle Isolate the nerves during pelvic LN
4. Obturator nerve (L2–4)	Obturator nerve lies post to the psoas muscle & passes through the obturator canal Direct injury during pelvic LN Passing of the TOT sling	Careful dissection in the obturator fossa Careful passing of the trocar during TOT sling
5. Pudendal nerve (S2–4)	Exits pelvis through the greater sciatic foramen & enters again through the lesser foramen around the ischial spine (lateral 1/3 of the sacrospinous ligament) Injury during sacrospinous fixation Entrapment w/ vaginal mesh kits	Avoid the lateral 1/3 of sacrospinous ligament during fixation
6. Peroneal nerve (L4–5, S1–2)	Wraps around the lateral fibular head Excessive compression on the lateral aspect of the knee	Good padding of the lateral aspect of the knee during Surg Early ambulation after Surg
7. Brachial plexus (C5–8, T1)	Wraps around the lateral aspect of the neck & upper shoulder Hyperabduction of the shoulder Compression w/ shoulder braces	Avoid use of shoulder braces (preferred antislip devices include egg-crate foam or vacuum-beanbag mattresses) Avoid abduction of the shoulder >90°

From *Obstet Gynecol* 2004;103:374.

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POSTOPERATIVE FEVER

Definitions

- Nml temperature ranges from 36.5–37.5°C
- Fever defined as temperature >38.0°C or >100.4°F

Workup

- **Hx:** Review records for preop infxn, intraop complications, xfusion, med list, allergies, urinary catheter, vascular access sites. Ask about diarrhea, productive cough, skin rash, new onset pain, sputum, preop illness.
- **Physical exam:** Temperature (& trends), pulse, bld pres, & respiratory rate. Examine skin (rash), lungs (decreased breath sounds, rales, rhonchi), heart (new murmurs), abd (tenderness or peritoneal signs), operative site (including vaginal cuff, poss), catheter/drain/IV sites, & lower extremities (DVT).
- **Lab:** Based on Hx, exam, & diff. May include urinalysis & culture, CBC w/ diff, bld culture ×2 before Abx (1 set from indwelling central line if present), sputum culture (generally low yield), wound culture (low yield), CXR, lower limb US for DVT, & PE protocol CT scan. W/u for other medical conditions as appropriate.

Common causes of postoperative fever by onset/timing	
Immediate (1st 24 h)	– Primarily noninfectious: Med effect, xfusion rxn, preop infxn, malig hyperthermia (rarely)
Acute (1–7 d)	– Infectious: Nosocomial infxn (most commonly PNA; in critical pts may be VAP, aspiration PNA) & UTI, *Clostridium difficile;* community-acquired infxns; SSI & vascular catheter–related infxns, endometritis. – Noninfectious: Surgical site inflammation—common after uterine Surg (eg, myomectomy); med rxn; thromboembolism (DVT, PE); CVA; pancreatitis; EtOH withdrawal; acute gout; fat embolism; hyperthyroidism
Subacute (1–4 w)	– Primarily infectious: SSI; central venous catheter–related; UTI; sinusitis (esp if NG tube in place); PNA; *C. difficile;* surgical site abscess. – Noninfectious: Med rxns; thromboembolism (DVT, PE). Consider septic pelvic thrombophlebitis
Delayed (>1 mo)	– Primarily infectious: Community-acquired or nosocomial infxns; SBE; *C. difficile;* FB infxn; osteomyelitis; unrelated infxns

- **Mgmt:** Based on etiology, if Abx indicated, target to suspected sources; tailor to culture results when available

SURGICAL SITE INFECTIONS (SSI)

Definition, Microbiology, and Epidemiology

- SSI introduced at time of Surg by endogenous flora
- **Common organisms:** *Staphylococcus aureus,* enterococcus, *Escherichia coli,* coagulase-negative staphylococci. Gyn SSI more likely caused by gram-negative bacilli, enterococci, group B streptococcus, anaerobes
- Infxn rate by category of procedure: Clean 2.6%, clean-contaminated 3.6%, contaminated/dirty 10.5% (*Arch Surg* 1999;134:1041)
- **RFs:** Obesity, existing infxn, diabetes, smoking, corticosteroids, immunosuppression, poor nutrition, long duration of Surg, active bact vaginosis or cervicitis

Prophylaxis (*Infect Control Hosp Epidemiol* 2008 29:S51)

- **Skin prep:** Chlorhexidine-alcohol superior to povidone-iodine (*NEJM* 2010;362:18)
- Sterile technique, avoid razor hair removal (trim/clip instead), avoid hyperglycemia
- **Antimicrobial ppx:** (*Am J Obstet Gynecol* 2008;199:301.e1, *Obstet Gynecol* 2009;113:1180.) Administer <30 min before Surg (*Ann Surg* 2009;250:10), or at time of anesthesia Additional dose may be req for obese pts, Surg >4 h or EBL >1500 mL

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Antibiotic prophylaxis for ob-gyn surgery	
Procedure	**Antibiotic options (single dose)**
Hysterectomy & urogynecologic procedures	Cefazolin* 1 g IV (2 g IV if BMI >35, wt >100 kg or >220 lb) Clindamycin 600 mg IV + gentamicin 1.5 mg/kg IV or ciprofloxacin 400 mg IV or aztreonam 1 g IV Metronidazole 500 mg IV + gentamicin 1.5 mg/kg IV or ciprofloxacin 400 mg IV
Surgical abortion	Doxycycline 100 mg PO/IV 1 h before, 200 mg PO after Metronidazole 500 mg PO BID ×5 d
HSG with PID or hydrosalpinx	Doxycycline 100 mg PO BID ×5 d
Cesarean deliv	A 1st generation cephalosporin (eg, cefazolin 1 g IV) Clindamycin 600 mg IV + gentamicin 1.5 mg/kg IV
No ppx for laparoscopy, laparotomy, hysteroscopy, IUD placement, endometrial bx, or urodynamics.	

*Acceptable alternatives: Cefotetan, cefoxitin, cefuroxime, or ampicillin–sulbactam.
From *Obstet Gynecol* 2009;113:1180; and *Obstet Gynecol* 2011;117:1472.

Clinical Manifestations (*Infect Control Hosp Epidemiol* 1992; 13:606; *Infect Dis Obstet Gynecol* 2003;11:65)

- **Incision cellulitis:** Warmth, swelling, erythema, pain w/o fluid collection
- **Superficial incisional SSI** (skin, subcutaneous tissue): Positive cx, purulent drainage
- **Deep incisional SSI** (fascia, muscle): Spont dehiscence, abscess
- **Vaginal cuff cellulitis:** Edema, induration, & erythema of the vaginal cuff
- **Organ space:** Pelvic abscess, vaginal cuff abscess
- **Nec fasciitis:** Erythema, swelling/edema, pain disproportionate to exam (followed by analgesia), crepitus, gray-colored discharge

Workup

- CBC (leukocytosis ± bandemia), gram stain + cx of incision or abscess fluid, bld culture
- **US:** Inexpensive, sens 56–93%, spec 86–98% for pelvic abscess (*J Emerg Med* 2011;40:170)
- **CT:** Abscess characterized by multilocular (89%), thick enhancing wall (95%) (*J Reprod Med* 2005;50(3):203)

Treatment

- **Incisional cellulitis:** Antimicrobial rx w/ gram-positive coverage, consider MRSA coverage
- **For more complicated SSI:** Parenteral antibiotic therapy ± abscess drainage
- **Nec fasciitis:** *Emergent* wide local debridement + beta-lactam/beta-lactamase inhib + clindamycin (antitoxin effect) + MRSA coverage

PERIOPERATIVE DVT/PE

Definition and Epidemiology

- **VTE:** DVT & PE are common periop complications. See Chapter 16 for full details on diagnosis and management.
- **Rates of postsurgical VTE w/o rx:** 29% for benign Gyn & 38% for Gyn oncology (*Br Med J* 1978;1:272; *Aust N Z J Obstet Gynecol* 1983;23:216)

Perioperative prevention of DVT and PE		
Risk	**Pt & Surg**	**Suggested ppx**
Low	Minor (<30 min) in pts <40 w/ no additional RF	• Early mobilization
Mod	Surg <30 mins w/ RF, Surg >30 min in pts of age 40–60 w/o RF; major Surg in pts <40 w/o RF	• UFH 5000 q12 h *or* • LMWH: Dalteparin 2500 QD or enoxaparin 40 QD • *or* IPCDs or stockings

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Risk	Pt & Surg	Suggested ppx
High	Surg <30 min in pts of age >60 or w/ RF; major Surg in pts >40 w/ RF	• UFH 5000 q8 h *or* • LMWH: Dalteparin 5000 QD or enoxaparin 40 QD • &/*or* IPCD or stockings
Highest	Major Surg in pts >60 yo w/ cancer or prior VTE or hypercoagulable state	• UFH 5000 q8 h *or* • LMWH: Dalteparin 5000 QD or enoxaparin 40 QD • & IPCDs or stockings • & consider LMWH for 4 w

From Use: *Obstet Gynecol* 2007;110:429; *Chest* 2008;133:381S; *Obstet Gynecol* 2012;119:155.

SEPSIS

Definitions (*Crit Care Med* 2003;31(4):1250)
- **SIRS:** 2+ of the following: (1) temp >38 OR <36°C, (2) HR >90 bpm, (3) RR >24/min or arterial CO_2 <32 mm Hg or mechanical vent, (4) WBC >12 K/mm^3 or <4 K/mm^3 or >10% immature forms
- **Sepsis:** SIRS + documented infxn
- **Sev sepsis:** Sepsis + sign(s) of organ hypoperfusion/dysfxn including oliguria, metabolic acidosis, abrupt AMS, thrombocytopenia or DIC, cardiac dysfxn, acute lung injury
- **Septic shock:** Sev sepsis w/ HoTN despite adequate fluid resusc or need for vasopressors to maintain BP.

Epidemiology (*NEJM* 2003 348:16)
- **Incid:** 240 cases per 100000, 9% annual ↑ from 1979–2000
- Rate of sev postop sepsis 0.9%, mortality 34% (*Anesthesiology* 2010;112:917)
- **Sepsis:** Amplified, uncontrolled, self-sustaining intravascular inflamm response
  Bact wall components (endotoxin, LPS) & products (exotoxins) activate host defense
  Initial excessive resp of inflamm mediators (TNFα & IL-1). Activation of coagulation cascade & enhanced formation of microvascular thrombi. Impaired tissue oxygenation & tissue damage. Late shift to anti-inflammatory immunosuppressive state → inability to clear infxn.

Clinical Manifestations
- HoTN, initial ↑ cardiac output, but eventual systolic & diastolic failure
- **AMS** (encephalopathy): Agitation, confusion, obtundation
- **Acute renal failure due to hypoperfusion/hypoxia:** Oliguria, electrolyte abnormalities
- Pulm edema → V/Q mismatch → hypoxemia → ARDS

Workup
- Obtain appropriate cx (eg, bld, urine, wound, catheter tip)
- CXR to assess acute lung injury & ARDS (diffuse bilateral infiltrates)
- Imaging studies (eg, CT) to confirm infxn site & sample poss source

Management (*Crit Care Med* 2008;36:296; see also www.survivingsepsis.org)
- Identify infectious source
- **Early respiratory stabilization:** Pulse oximetry, mechanical ventilation as needed
- **Adequate access:** CVC if sev sepsis or shock
- **Aggressive fluid resusc:** Crystalloid or colloid, necessary to prevent organ dysfxn
  Goals: CVP ≥8 mm Hg (12 mm Hg if ventilated), MAP ≥65% mm Hg, UOP ≥5 mL/kg/h
- **IV Abx:** Begin as soon as poss after cx are collected. Broad spectrum: Directed at most likely pathogens of presumed source.
- **Vasopressors:** If BP not responsive to IV fluid administration, use to maintain MAP >65 mm Hg (norepinephrine generally 1st line. Alternatives include phenylephrine, epinephrine, vasopressin, dopamine)
- **Corticosteroids:** Consider hydrocortisone IV (for adrenal insufficiency) if BPs unresponsive to fluid resusc.
- **Sepsis bundles:**
  Initial resusc bundle: All w/i 6 h of identification of sev sepsis
  Measure serum lactate
  Obtain bld cx prior to Abx (2 sets of bld cxs, other indicated site)
  Broad-spectrum Abx w/i 1 h

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If HoTN &/or lactate >4 mmol/L → fluids + vasopressors to goal MAP >65 mm Hg
If persistent HoTN despite fluid resusc (septic shock) → maintain CVP ≥8 mm Hg & $ScvO_2$ ≥70% or SvO_2 ≥65%

Subseq mgmt bundle: W/i 24 h includes ventilator mgmt of ARDS, bld products, steroids, vasopressors, sedation, maintaining euglycemia, renal replacement therapy, & mgmt of multiorgan dysfxn

PERIOPERATIVE OLIGURIA

Definitions

- Generally, urine output of <30 mL/h for 2–3 h or <500 mL/d
- According to RIFLE criteria for AKI (*Crit Care* 2007:11R31)
  - **Risk:** UOP <0.5 mL/kg/h for 6–12 h; or Cr ↑ 1.5×
  - **Injury:** UOP <0.5 mL/kg/h for >12 h; or Cr ↑ 2×
  - **Failure:** UOP <0.3 mL/kg/h for >24 h or anuria for 12 h; or Cr ↑ 3×, or Cr >4 w/ acute rise >0.5 mg/dL
  - **Loss:** Persistent AKI w/ loss of kidney fxn >4 w
  - **End stage:** >3 mo of loss of kidney fxn

Common causes of perioperative oliguria

Prerenal	– *True vol depletion* – gastrointestinal dz (vomiting, diarrhea), renal losses (diuretics, osmotic diuresis, DI), skin or respiratory losses (insensible losses, sweat, burns), & 3rd space sequestration (edema, crush injury, skeletal fracture, preeclampsia) – *HoTN (septic or cardiac shock); heart failure, cirrhosis, & nephrotic syn; selective renal ischemia*
Renal	– *Tubular* – acute tubular necrosis from prolonged intraop HoTN, nephrotoxic agents (NSAIDs, ACE inhibs, or angiotensin II blockers) – *Glomerular* – vasculitides – *Interstitial* – acute interstitial nephritis from nephrotoxic agents
Postrenal	– *Ureteral injury/blockade* – *Reflex spasm of the voluntary sphincter* b/c of pain or anxiety; use of meds such as antichol & narcotics; detrusor atony as a result of Surg manipulation or anesthesia – *Mechanical* obst from an expanding hematoma or fluid collection or an occluded Foley catheter

Workup

- History & physical exam
- Check the Foley catheter & irrigate as a 1st step.
- Check meds & hold/replace NSAIDs & other nephrotoxic meds. Consider renally dosing other meds as needed.
- Review operative report & anesthesia record: Intraop I/Os & BP
- **Labs**

  Urinalysis w/ review of sediment for muddy brown, granular casts (ATN) & eos (interstitial nephritis)

  CBC, Cr, serum electrolytes & urinary electrolytes/Cr

  Serum BUN/Cr: Ratio >20 generally sugg prerenal dz

  FE_{Na}: <1% in prerenal dz & >2% in intrinsic renal dz. Consider FE_{urea} if recent use of diuretics.
- **Renal US:** Postrenal obst, chronic renal dz

Management

- **Prerenal:** Fluid challenge of 500–1000 cc of crystalloid. Cr resolves in 1–3 d.
- **Renal:** Identification & rx of underlying cause
- **Postrenal:**

  Acute retention: Transurethral or suprapubic catheter

  Ureteric/bladder injuries: Consider percutaneous nephrostomy tube, trial of stenting (antegrade or retrograde) followed by delayed repair. Drain if urinoma.

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POSTOPERATIVE ILEUS

Definition
- Obstipation w/ intolerance to oral intake due to postop intestinal dysmotility.
- Physiologic ileus can last 1–3 d postop depending on procedure. Longer duration may be abnl.

Etiology
- Inhibition of nml motility by postop inflammation, inhibition of spinal reflexes, opioids, vasoactive intestinal polypeptide, substance P, nitric oxide

Clinical Manifestations
- Inability to tolerate PO diet, abdominal pain, distention, tympany on exam, decreased bowel sounds, delayed/decreased flatus

Diagnosis
- Generally clinical, though should rule out small bowel obst (see below).
- Intestinal dilatation w/o evid of transition point on CT, XR imaging of abd.

Treatment
- Bowel rest, NG tube if necessary. Vol resusc, repletion of electrolytes PRN.
- Reduce/eliminate aggravating med (eg, opioids)
- Serial abdominal exams until abdominal decomp/flatus.

Prevention
- Epidural + local anesthesia instead of systemic or epidural opioids (*Cochrane Database Syst Rev* 2000;(4):CD001893)
- Alvimopan (selective opioid receptor antag) postop. FDA has limited access to med as may inc risk MI in some pts.
- Gum chewing immediately postop (*World J Surg* 2009;33(12):2557)
- Scheduled postop laxative use after hysterectomy (*Am J Obstet Gynecol* 2007;196(4):311.e1)
- Minimal manipulation of bowel intraop
- Routine NG tube placement is NOT indicated (*Cochrane Database Syst Rev* 2007 18;(3):CD004929)

BOWEL OBSTRUCTION

Definition
- Failure of intestinal contents to progress normally through the small bowel.

Etiology
- Adhesive dz, malig, hernia most likely. Up to 42% of women w/ ovarian cancer (*Ann Oncol* 1993;4(1):15)
- Stricture (eg, postradiation or from Crohn's dz), intussusception, volvulus, gallstone ileus less likely

Clinical Manifestations
- Nausea, vomiting (± feculent), crampy abdominal pain, inability to tolerate PO
- Extent of abdominal distention may depend on site of obst
- Generally unable to pass flatus as sx progress
- May be clinically hypovolemic
- Peritoneal signs may indicate ischemic bowel or perforation

Diagnosis
- Radiographic evid (XR, CT) of "transition point" w/ prox dilatation & distal decomp of bowel.
- CT more sensitive for signs of bowel ischemia/strangulation, perforation, closed loop (prox + distal) obst, hernia, additional intra-abdominal pathology.
- Consider lactate for biochemical evid of ischemia a/w SBO.

Treatment
- Conservative measures include bowel rest, NG tube to low suction for decomp, vol resusc & electrolyte repletion PRN. TPN if indicated.
- Consider therapeutic use of Gastrografin (water-soluble contrast) (*World J Surg* 2008;32(10):2293)
- Consider medical rx w/ octreotide for pts w/ advanced ovarian cancer (*Cochrane Database Syst Rev* 2010;(7):CD007792)

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- Exploratory laparotomy if concern for strangulation/ischemia, perforation, early SBO after laparoscopic Surg w/ concern for port site hernia, failure of conservative mgmt.
- NG tube may be removed if (1) passage of flatus or stool, (2) residual vol of gastric contents <100 cc after 4 h clamped.

Large-bowel Obstruction

- In gynecologic Surg, most often related to malig
- Unlikely to respond to conservative mgmt
- Rx options include colostomy creation or endoscopic stent, depending on location & clinical situation.

COMPLICATIONS OF LAPAROSCOPY

Incidence (*Clin Obstet Gynecol* 2002;45(2):469)

- Occur in 0.2–10.3% of all laparoscopic cases
- Over 50% during entry into the abdominal cavity

Complications of Laparoscopy (*J Minimally Invasive Gynecol* 2006;13:352)

- **Extraperitoneal insufflation:** Misplacement of Veress needle → peritoneal tenting
  Signs: Immediate insufflation pres >15 mm Hg, abdominal wall fullness/crepitus, hypercarbia, respiratory compromise
  Prevention: Monit of insufflation pres, reposition Veress needle as appropriate.
  Mgmt: Alert anesthesiologist, should resolve w/ expectant mgmt.
- **Nerve injury:** See table with summary above.
- **Vascular injury:** During entry (Veress needle or port placement) or intraop
  Common vessels injured: Inferior/superior epigastric artery, aorta, vena cava, iliac vessels
  Signs: Port site bleeding, intra-abdominal bleeding on entry, tachy, HoTN
  Prevention: Correct needle placement & direct visualization of trocar sites
  Open (Hasson) entry may minimize vascular injury risk (*Aust N Z J Obstet Gynecol* 2002;42:246)
  Manage: Small vessels → tamponade or ligation, large vessels → laparotomy, abdominal packing & fluids if vascular surgeon not immediately available (*J Min Invas Gynecol* 2010;17:692)
- **GI injury:** Incid 13/1000, occurs during entry or intraop (*Br J Surg* 2004;91:1253)
  Signs: If not recognized intraop, worsening abdominal pain, tachy, fever
  Intraperitoneal air not reliable sign, occurs in 38.5% laparoscopy (*J Reprod Med* 1976;16(3):119)
  RFs: Prior Surg, intra-abdominal pathology (endometriosis, PID, adhesions)
  Prevention: NG or OG tube decomp of stomach. In high-risk pts consider nonumbilical entry point (Palmer's point –3 cm below costal margin in left midclavicular line).
  Mgmt: Surgical repair (oversewing or resxn), Abx
- **Postop bleeding:**
  Signs: Tachy, > expected Hgb/Hct drop, HoTN, oliguria, AMS, increased abdominal pain, bleeding from incision or vagina
  Abd compartment syn: Bleeding/ascites → ↑ intra-abdominal pres → ↓ lung compliance, ↓ venous return, ↓ kidney fxn → hypoxemia, oliguria, renal failure
  Manage: Fluid resusc, monit UOP, NPO, trend CBC, poss surgical exploration
- **Urinary tract injury:** Incid in TLH up to 4% (*JSLS* 2007;11:422; *AJOG* 2003;188(5):1273)
  Only 30% recognized during operation
  Signs: Abdominal/flank pain, peritonitis, hematuria, oliguria/anuria, fever, leakage of urine from incision or vagina, elevated Cr. Consider CT ± urogram, sampling free fluid in abd if suspect urinoma; send fluid for BUN/Cr. If close to serum, then transudate (ascites); if higher, suspect urine leak.
  Prevention: Decomp of bladder w/ foley, direct visualization during trocar placement, dissection & visualization of ureters (peristalsis), routine stenting not recommended
  Mgmt: Closure for large cystotomy, postop bladder decomp, ureter repair
- **Trocar site hernia:** Incid 0.5% (*Br J Surg* 2012;99:315)
  Signs: Bulging, small-bowel obst
  RFs: Pyramidal trocars, size ≥12-mm trocars (3% vs. <1%) (*AJOG* 1993;168:1493)
  Prevention: Close port defects >10 mm (*Arch Surg* 2004;139:1246)
  Mgmt: Surgical vs. expectant depending on severity
- **Shoulder pain:** Common, referred pain from diaphragmatic irritation (CO_2, bld, fluid)

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COMPLICATIONS OF HYSTEROSCOPY

Complications and management (*Obstet Gynecol* 2011;117:1486; *Best Pract Res Clin Obstet Gynaecol* 2009;23:619)

- **Fluid overload (5–6%):** Excessive intrauterine Absorp of distending media
  - **Main types of distending fluid:**
    - **Nonelectrolyte** (glycine, mannitol, sorbitol): For use w/ monopolar instruments
    - **Electrolyte** (saline, LR): For diagnostic hysteroscopy & w/ bipolar or mechanical instruments
  - **Pathophysiology:** Vol overload: CHF, pulm edema; metabolic imbalance: HypoNa, ↓ serum osm, ↑ ammonemia, hyperglycemia, acidosis; ↓serum Na by ~10 mmol/L/1000 mL glycine deficit (*Lancet* 1994:344:1187); neurologic sequelae: Cerebral edema, nausea, visual changes, sz, coma. Prevent overload: Select distending media that minimizes risk of overload (isotonic, electrolyte-containing solutions), monit fluid deficit frequently, use automated fluid monitoring system.
  - **Manage:** D/c infusion for (*J Am Assoc Gynecol Laparosc* 2000;7:167)
    Nonelectrolyte solution >1000–1500 mL
    Electrolyte solution >2500 mL
    OR serum Na <130 mmol/L
    If severely hyponatremic → hypertonic saline. Loop diuretics are not indicated unless there is clinical evid for vol overload; may exacerb electrolyte abnormalities. Low threshold for xfer to ICU for intensive monitoring.
- **Hemorrhage (2–3%):** From resection, cervical lacerations, tenaculum site, perforation
  - **Manage:** Electrocautery, inject vasopressin, suturing tenaculum site, balloon tamponade (*AJOG* 1983;147:869), laparoscopic suturing, hysterectomy, UAE
- **Uterine perforation (1–1.5%)** → retroperitoneal hematoma, bowel/bladder injury, or signs of acute bld loss
  - **Prevention:** Careful sounding, adequate cervical dilation, operate resectoscope toward user (not toward uterine wall)
  - **Mgmt:**
    Hemodynamically stable → monit for bleeding, pain, infxn
    Large perforation, unstable or perforation w/ electrocautery → surgical exploration w/ repair
- **Infxn:** Rare complication of hysteroscopy (<1%)
- **Air/CO_2 embolization** (gas rarely used as distention medium) → circulatory collapse (sudden ↓ O_2 sat, ↓ BP, dysrhythmia). Place pt in left lateral decubitus w/ head tilted down, cardiopulmonary support.

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GYNECOLOGIC ANESTHESIA

- Many office procedures & selected transvaginal operations may be performed under local anesthesia, w/ or w/o sedation/analgesia
  - **Examples:** Loop electrosurgical excision procedures, 1st trimester dilation & curettage, hysteroscopy, endometrial ablation
  - **Technique:** Paracervical block or intracervical block
- Local anesthetic toxicity
  - Tox usually occurs following inadvertent intravascular injection
  - CNS effects typically precede CV effects
    - **CNS:** Prodrome of excitation, ringing in ears, perioral numbness, confusion; followed by convulsions; followed by coma
    - **CV:** Initial HTN, tachy; followed by HoTN, arrhythmias, cardiac arrest
    - **Exception:** Bupivacaine-cardiotoxicity predominates; prolonged Na+ channel blockage
  - Epi may be added to ↓ overall uptake & allow increased local effect.
  - Contraindications to use of epi exist. Cardiac: HTN, CHF, arrhythmias, MI. Other relative contraindications: Tricyclic antidepressant use, MAOI use, beta blockade, cocaine use, hyperthyroidism, asthma, diabetes

Common local anesthetics

Mech: Block voltage-gated Na channels, prevent nerve depolarization/action potential

High lipid solubility = favors entry into cells = more potent, longer duration

Anesthetic	Type	Lipid solubility	Concentration	Max dose w/o epi	Max dose w/ epi
Lidocaine	Amide	++	1% 10 mg/mL	4 mg/kg	7 mg/kg
Bupivacaine	Amide	++++	0.25% 2.5 mg/mL	2.5 mg/kg	3 mg/kg
2-chloroprocaine	Ester	+	2% 20 mg/mL	11 mg/kg	14 mg/kg
Ropivacaine	Amide	+++			
Mepivacaine	Amide	++			

From Hawkins JL, Bucklin BA. Obstetrical anesthesia. In: Gabbe SG, ed. *Normal and Problem Pregnancies*. 6th ed. Philadelphia, PA: Saunders, Elsevier; 2012:362.

- Laparoscopic & prolonged gynecologic surgeries usually performed under GA
  - Laparoscopic procedures require complete relaxation of abdominal wall (ie, paralysis)
  - Std anesthesia techniques & precautions apply
  - Many laparoscopic procedures require prolonged Trendelenburg positioning for access to pelvis; in some pts, this may cause hemodynamic compromise, difficulty ventilating
- Transvaginal procedures & many abdominal procedures may be performed under neuraxial anesthesia/sedation, particularly if pt not candidate for GA due to medical comorbidities (though precludes use of paralytics)
  - **Examples:** Dilation & curettage/evacuation, operative hysteroscopy, vaginal hysterectomy or abdominal hysterectomy in pts not candidates for GA
- Both minilaparotomies & some laparoscopic procedures (most commonly sterilization) may be performed under sedation w/ local anesthesia only

PARENTERAL ANALGESIA IN OBSTETRICS

- All nonneuraxial methods provide only partial relief of labor pain.
  - May help laboring women cope w/ pain
  - Useful in cases of absolute contraindication to or pt refusal of neuraxial anesthesia
- Opioids act as opioid receptor agonists: Mu, kappa, delta
  - G-protein–coupled receptors → ↓ intracellular Ca → inhibition of release of pain neurotransmitters. Distributed through brain, terminal axons of spinal cord afferents
- Xfer across the placenta is rapid & signif; fetal effects may limit use
  - Drug xfer affected by prot binding capacity, size, ionization
  - In general, all local anesthetics & opioids transfuse freely across the placenta
  - Fetal acidosis results in ion trapping → fetal drug accum

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- Side effects of systemic opioids
  Maternal: Sedation, respiratory depression, N/V
  Fetal: Decreased fetal HR variability during labor; pseudosinusoidal HR pattern, respiratory depression at birth. Use short-acting opioid w/ no active metabolites, if poss. Monit fetus continuously during administration of systemic opioids. Avoid administration shortly before deliv.
- **Sedatives:** Do not provide analgesia; typical use is for sleep/relaxation in latent labor

Parenteral opioids			
Opioid	**Onset**	**Neonat half-life**	**Disadvantages**
Fentanyl Remifentanil – also fast acting	1 min IV	5.3 h	Short duration; may not control labor pain well
Morphine	5 min IV 40 min IM		Longer duration can result in prolonged sedation
Nalbuphine	2–3 min IV 15 min IM	4.1 h	Partial agonist/antag: Antag properties limit side effects but may also limit relief
Meperidine Historic 1st choice in labor, *no longer widely used*	5 min IV 30–45 min IM	13–22 h, 63 h for active metabolite	Both drug & active metabolite normeperidine cross placenta: Prolonged fetal sedation; risk of lethal serotonin syn in pts taking MAOIs limits use

From *Obstet Gynecol* 2002:100:177.

Methods of administration of parenteral opioids		
Method	**Advantages**	**Disadvantages**
Intermittent administration Administered by nurse Short to medium acting opioids	No pump req, no staff needed to set up apparatus RN oversight of fetal status for administrations	Less autonomy, more delays, more total opioid used
Patient-controlled analgesia Programmed to deliver on-demand boluses Short acting (eg, Fentanyl)	Pt autonomy, less delay in administration; results in less total opioid used	Requires pump apparatus, anesthesia staff for setup Risk of self-administration during period of fetal distress

NEURAXIAL ANESTHESIA IN OBSTETRICS

- Most effective method for labor pain
- Also std for C/S, postpartum tubal ligations, urgent postpartum procedures whenever poss

Mechanisms of pain in labor			
Pain	**Mech**	**Pathways**	**Neuraxial anesthesia**
Visceral 1st stage 2nd stage 3rd stage	a. Contractions → ischemia → release of pain mediators b. Stretch/distention	Sensory nerves follow symp nerve pathways, enter spinal cord at T10–L1	Block T10–L1 afferents
Somatic 2nd stage 3rd stage	Fetal head distends vagina/perineum Pain from lacerations	Pudendal nerves enter spinal cord at S2–4	Extend block to S4 Or: Pudendal block, local infiltration

- Indications for spinal/epidural anesthesia in labor
  Maternal request
  Anticipation of operative vaginal deliv or shoulder dystocia; breech extraction; high risk of C/S; Risk of hemorrhage; difficult intubation
  Maternal condition where signif pain or stress would create medical risk (eg, sev respiratory or cardiac dz)

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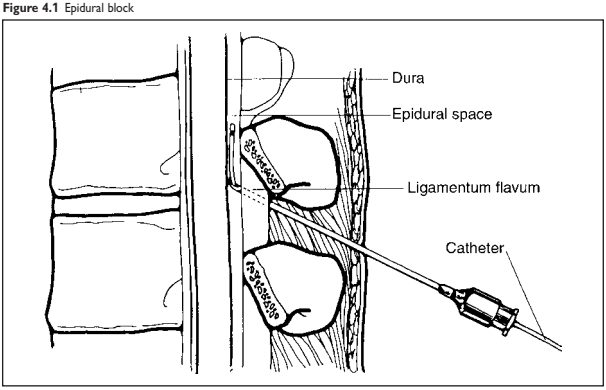
Maternal condition which could worsen & potentially limit use of neuraxial anesthesia later in labor course (eg, worsening thrombocytopenia or coagulopathy)

- Contraindications to spinal/epidural anesthesia in labor
  - **Absolute:** Maternal refusal, uncooperative pt; soft tissue infxn of site; uncorrected hypovolemia; uncorrected therapeutic anticoagulation; Lovenox w/i 24 h; certain spinal conditions (eg, ependymoma); sev thrombocytopenia (<50 K)
  - **Relative:** Certain spinal conditions (eg, discectomy, rod fusion); mod thrombocytopenia (<75 K); LP shunt, some neurologic dzs (ie, multiple sclerosis); fixed cardiac output conditions (ie, AS)
- Types of neuraxial blocks: Spinal, epidural, & CSE
  - **Spinal:**
    Anesthetic/opioid delivered directly into spinal fluid w/ needle through dural puncture
    Benefits: Rapid onset (2 min); 1/20 epidural dose used so less risk tox
    Disadvantages: Limited duration (1–1.5 h)
  - **Epidural:**
    Anesthetic/opioid delivered into epidural space via continuous infusion through catheter
    Benefits: Ability to continuously infuse & adjust dosage as needed; pt controlled
    Disadvantages: Slower onset (20 min), larger doses used (20× spinal doses)
  - **CSE:**
    Meds delivered directly into spinal fluid, then catheter placed in epidural space
    Benefit: Combination of rapid onset & ability to continuously infuse
    Disadvantages: More technically challenging than epidural or spinal alone; increased risk of PDPH compared to spinal alone

Figure 4.1 Epidural block



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Complications of neuraxial anesthesia

Complication	Incid	Mech	Treatment
HoTN	28–31% Prehydration = slightly less	Local anesthetic causes vasodilation via parasympathetics	Prehydration decreases incid to some degree Epi/phenylephrine
Fever >100.4°F (incid above that in women w/ parenteral opioids)	15–33% nullips 1–5% multiples	Not well understood; noninfectious, inflamm resp, altered thermoregulation	Conservative measures Acetaminophen does not reliably treat epidural fever
Fetal HR decelerations (transient)	8%	HoTN, decreased uterine perfusion	Maternal positioning, hydration, oxygen, epi

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Complication	Incid	Mech	Treatment
PDPH ("spinal HA")	1.5–3% spinal 1–2% epidural overall; 80% w/ epidural "wet tap"	Leakage of CSF through dural puncture	Supine position, analgesics, caffeine Bld patch if lasts 24+ hours
Pruritus (w/ opioid in spinals/ epidurals)	1.3–26% epidural 41–85% spinal	Periph morphine agonist effects	Nalbuphine
Inadq blockade	9–15% epidural		
Rare complications: Epidural hematoma, abscess, total spinal blockade, local anesthetic tox			

From *Obstet Gynecol* 2002:100:177.

Neuraxial anesthetics

Combination of local anesthetic & opioid typical. The local anesthetic provides the best anesthetic effect, but also causes motor blockade & potential tox (0.02% after epidural) (*Int J Obstet Anesth* 2004;14:37; *Am J Obstet Gynecol* 2001;185:128) The opioid has a synergistic effect w/ the local anesthetic, allowing for lower dose (20–30% less local anesthetic) & has no intrinsic motor blockade.

Local anesthetic	Advantages	Disadvantages
Bupivacaine Most common choice	Good motor/sensory differentiation Long duration Overall good safety, no tachyphylaxis (acute ↓ in resp to drug after its administration)	Cardiotoxicity, prolonged Na^+ channel block Slower onset: 20 min
Lidocaine	Rapid onset: Used for test dose, rapid bolus for perineal repairs, instrumental deliv	Poor sensory–motor differentiation More tachyphylaxis
Chloroprocaine	Very rapid onset: Used for test dose, rapid bolus for perineal repairs, instrumental deliv	Poor sensory–motor differentiation Very short duration
Opioid	**Advantages**	**Disadvantages**
Fentanyl Most common choice Sufentanil: Similar SE profile, more potent	Less side effects than morphine More rapid onset	Pruritus (occurs w/ all opioids)
Morphine		Pruritus, N/V Slower onset
Hydromorphone	Superior analgesia to fentanyl in some studies; similar crossing of bld–brain barrier as fentanyl but longer half-life	Similar SE profile to morphine limits use

Effect of neuraxial anesthesia on labor course and outcome

1st stage of labor	Statistically but not clinically signif lengthening; may be slower to reach 4–5 cm
2nd stage of labor	Avg 15–30 min longer due to decreased sensation/urge to push
Labor augmentation	Increased rates of labor augmentation (*Lancet* 2001;359:19)
Operative vaginal deliveries	Slightly increased rates of operative vaginal deliveries (*BMJ* 2004;328:1410)
C/S rate	Not a/w ↑ in Cesarean rate (*Cochrane Database Syst Rev* 2005;CD 000331)

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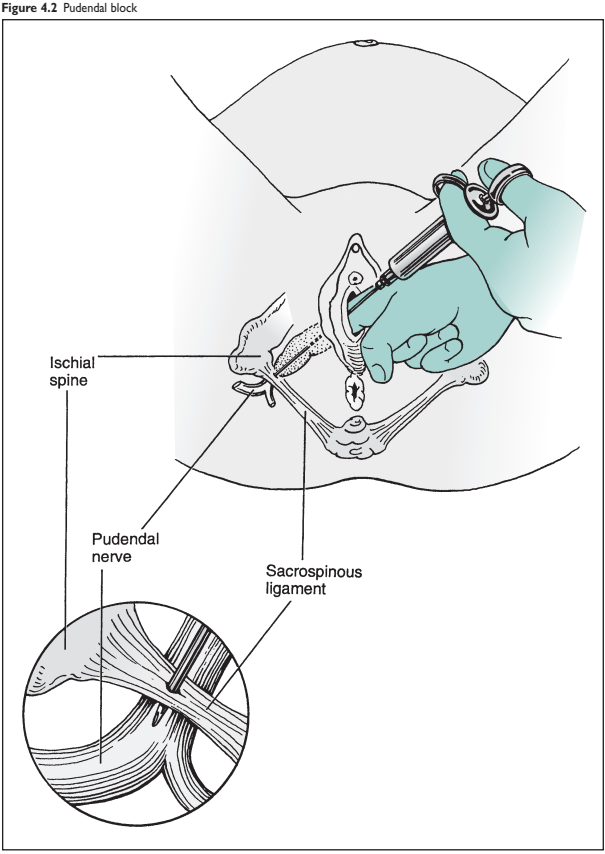
LOCAL ANESTHETICS IN OBSTETRICS

- Indications for local anesthetics
  - Skin infiltration for episiotomies/assisted deliveries (nonemergent settings), laceration repair
  - **Nerve blocks:** Pudendal, paracervical (close proximity to large vessels → higher potential for tox)
  - Spinal & epidural anesthesia
- In an emergent setting where access to general anesthesia will be delayed, local anesthetics may be administered in large amts to perform C/S, followed by general anesthesia when available

Figure 4.2 Pudendal block



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NONPHARMACOLOGIC ANALGESIA IN OBSTETRICS

- **Advantages:** Empowering, few side effects, may improve overall satisfaction w/ labor experience
- **Disadvantages:** Incomplete relief, pts may perceive eventual pharm rx as failure
- **Evid:** Many nonpharmacologic methods have not been well studied

Nonpharmacologic analgesia methods	
Method	**Effect**
Labor support	Decreased analgesic, shorter labor; more likely to have spont vaginal deliv; greater satisfaction. Should be continuous, one-to-one nursing (*Cochrane Database Syst Rev* 2011;2:C003766)
Breathing	Lack of evid for pain control, but may be calming
Touch, massage	Massage & casual touch ↓ anxiety, perception of pain (*J Nurse Midwifery* 1986;31:270)
Music	Improves satisfaction, decreases distress, may ↓ need for analgesia (*Pain Manag Nurs* 2003;4:54)
Hydrotherapy	No change in labor outcome or use of rescue analgesia; does delay request for analgesia by 30 min (*BMJ* 2004;328:314)
Hypnosis	Women using self-hypnosis may have significantly decreased use of epidural anesthesia, better satisfaction. Very limited evid; not all women can successfully use hypnosis (*BR J Anaesth* 2004;93:505)
Acupuncture	Does not provide adequate analgesia. No std; few trials
TENS	Not effective pain relief during labor when compared to placebo
Sterile water injections	Rationale of counter-irritation: Irritate nerves in dermatome of pain. May be useful for back pain a/w labor; however, no change in labor outcomes or use rescue analgesia. Disadvantage of acute somatic pain during injection (*Cochrane Database Syst Review* 2012)

GENERAL ANESTHESIA IN OBSTETRICS

- Rarely indicated for vaginal deliv except for emergent, unanticipated procedures (eg, breech extraction, internal version, shoulder dystocia)
- In US, 10% of C/S are performed under general anesthesia (*Anesthesiology* 2005;103:645)
  - Emergent ("crash") C/Ss are the most common setting for general anesthesia
  - Other situations include nonemergent C/S in a pt w/ absolute contraindications to neuraxial anesthesia
    - **Advantages:** Rapid, complete anesthesia; ability to administer 100% oxygen
    - **Disadvantages:** Risk of difficult intubation; risk of aspiration; small risk of infant respiratory depression; anesthetics cause uterine atony, leading to more bld loss
- **Other uses:**
  - **Uterine inversion:** Obstetric emergency where body of uterus inverts following deliv
    - Nitric oxide or halogenated anesthetics relax uterus & facilitate replacement. Nitroglycerine may be given IV/sublingually if delay in general anesthesia is anticipated.
    - Can be considered in cases of retained placenta due to bandl's ring or head entrapment for breech extraction; must balance w/ risk of uterine atony

POSTOPERATIVE PAIN MANAGEMENT

- Post C/S pain include visceral (uterus) & somatic pain (abdominal wall).
- Multimodal rx regimens
  - **Goals:** (1) Adequate pain control, (2) ↓ opioids to ↓ assoc side effects such as N/V, ileus, sedation, & effects on infant via secretion of active compounds into breast milk

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- Oral pain meds – preferred mgmt once pt is tolerating PO
  - Opioids – carry above side effects
  - NSAIDs – important adjuvant therapy to reduce opioid exposure
    - Esp effective on visceral pain from uterine involution
    - Also available as 12 h IV formulation (ketorolac) for up to 4 doses postop
  - **Breast-feeding:** Opioids & NSAIDs considered generally compatible w/ breast-feeding
    - **Exception:** Meperidine – prolonged infant sedation by active metabolite normeperidine

Postoperative pain management after cesarean section

Method	Advantages	Disadvantages
Epidural/spinal: Single dose long-acting opioid Morphine, morphine XR Fentanyl Sufentanil Hydromorphone	Better pain relief than PCA, less systemic side effects Long acting Can remove catheter after dose	Pruritus N/V Respiratory depression potential – need extended monitoring
PCEA	Same pain relief as above Decreased side effects Pt control → less total drug used	Pruritus N/V Catheter must remain in place
Epidural/spinal: Addition of local anesthetic	↓ dose of opioid side effects	More motor blockade
Patient-controlled IV analgesia: PCA	Superior to IM opioid	Sedation – less w/ demand-only dosing
Wound infiltration Single injection or catheter left in wound	Decreased systemic effects Decreased total dose of analgesic used	No effect unless catheter left in wound for continued infiltration
Transversus abdominis plane block T6–L1 nerve root block w/ local anesthetic	Improves pain control in women who do not receive intrathecal morphine; less side effects (*Can J Anesth* 2012;59:766)	Requires postop procedure

- **Postpartum bilateral tubal ligation:**
  - Avoid long-acting intrathecal/epidural opioid/local anesthetic if goal is discharge soon after procedure. Infiltration of skin, fallopian tubes w/ local anesthetic shown to ↓ total analgesic use, ↑ time to analgesic use postoperatively. Sufentanil, bupivacaine, lidocaine all effective.

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VULVOVAGINITIS

Definition (*Obstet Gynecol* 2006;107:1195)

- Vulvovaginal sx such as itching, burning, irritation, & abn discharge d/t various causes. BV = Most common (MCC), vulvovaginal candidiasis, & *Trichomonas vaginalis*.
- **Nml vaginal flora:** ↑ estrogen → ↑ vaginal epithelial glycogen → ↑ gluc source → ↑ lactobacilli → ↑ lactic acid → ↓ vaginal pH @ 3.8–4.5 (*NEJM* 2006;355:1244)

Pathophysiology & Risk Factors

Pathophysiology & risk factors			
Type of vaginitis	**Pathogenesis**	**Risk factors**	**Sequelae**
BV	2° shift in vaginal flora from lactobacilli to mixed flora.	>1 partner, change in partners (last 30 d), lesbian, douching.	↑ risk of STIs, ↑ complications after Surg, preterm labor.
Candidiasis	Mostly 2° *Candida albicans*. Rarely by nonalbicans species (*Candida glabrata*)	Preg, luteal phase of menses, nulliparity, spermicides, ↓ age, broad-spectrum Abx.	Adverse Preg outcomes (PPROM, PTD, ↓ birth wt).
Trichomonas	Common vaginal parasite. Most common STI in US	New partner, sex ≥2×/ week, 3+ partners/ month, presence of other STI.	

From *NEJM* 2006;355:1244; *MMWR* 2010;59:NO.RR-12.

Clinical Manifestations (*NEJM* 2006;355:1244)

- **BV:** Copious, thin, whitish-gray, fishy-smelling discharge. Less likely pruritus.
- **Candidiasis:** Thick, white, curdy discharge. No odor. + Pruritus, dysuria, vaginal erythema.
- **Trichomonas:** Copious yellow to greenish, frothy discharge. Often foul odor. ± pruritus, postcoital bleeding, dysuria. ± vaginal or cervical erythema ("strawberry cervix").

Diagnostic Studies (*NEJM* 2006;355:1244)

- **BV:** Nugent score = gold std, gram stain w/ scored bacteria & clue cells.

Amsel clinical criteria for BV requires presence of 3 of 4 clinical findings	
1. Vaginal pH >4.5	Touch swab to midportion of vaginal sidewall, then to pH paper. Cervical mucus, semen, or bld can alter pH
2. Thin watery discharge	Visualize/assess on speculum exam.
3. >20% clue cells on wet mount	Clue cells = epithelial cells w/ borders obscured by bacteria
4. "Amine" odor test	Add 10% KOH on slide → + w/ distinctive amine odor

From *Am J Med* 1983;74:14; *Obstet Gynecol* 2006;107:1195.

- **Candidiasis:** Presence of hyphae visible on KOH or wet mount. Yeast cx useful if pt c/o sx but negative wet mount, or if recurrent infxns.
- **Trichomonas:** Presence of mobile trichomonads on wet mount; ↑ PMNCs often present.

Treatment

Treatment of vulvovaginitis		
BV	Metronidazole 500 mg PO BID ×7 d* OR Metronidazole 250 mg PO TID ×7 d* OR Metronidazole gel 0.75% 1 applicator PV QD ×5 d OR Clindamycin 300 mg PO BID ×7 d* OR Clindamycin cream 2%, 1 applicator PV QHS ×7 d	
Candida	Rx PO	Fluconazole 150 mg PO ×1
	OTC PV	Butoconazole 2% cream 5 g PV ×3 d Clotrimazole 1% cream 5 g PV ×7–14 d* or 2% cream 5 g PV ×7 d* Miconazole 2% cream 5 g PV ×7 d*, or 4% cream 5 g PV ×3 d, or 100 mg vaginal suppository. 1 tab PV ×7 d, or 200 mg vaginal suppository. 1 tab PV ×3 d, or 1200 mg vaginal supp. 1 tab PV ×1 Tioconazole 6.5% ointment 5 g PV ×1 application

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	Rx PV	Butoconazole 2% cream (single dose bioadhesive), 5 g PV ×1 Nystatin 10000-U vaginal tab, 1 tab QD ×14 d Terconazole 0.8% cream 5 g PV ×3 d or Terconazole 80 mg vaginal suppository. 1 tab PV ×3 d
	Recurrent (4+/y)	7–14 d of topical therapy Fluconazole 150 mg, or 200 mg PO every 3rd day ×3 doses → weekly 6 w
	Sev infxn	7–14 d of topical azole 150 mg of fluconazole q72h ×2 doses
Trichomonas	Metronidazole 2 g PO ×1* or Metronidazole 500 mg PO BID ×7 d (alternative regiment) Tinidazole 2 g PO ×1 Treat sex partners. Abstain from sex until both partners cured. Avoid EtOH during rx. EPT not routinely recommended for trichomoniasis, b/c ↑ STI comorbidity needs eval & ↑ rx intolerance. Option if partner rx not certain. CDC monits EPT in all states (*Curr Opin Obstet Gynecol* 2012;24:299)	

*Safe/preferred in Preg.

From Workowski KA, Berman S. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010;59(RR12):1.

BARTHOLIN GLAND CYST AND ABSCESS

Definition (*J Obstet Gynaecol* 2007;27:241)

- Bartholin gland secretes mucous vaginal lubrication. Located at ~4- & 8-o'clock on labia minora bilaterally. Not palpable unless pathology. Usually women b/w 20–30 yo.

Etiology & Pathophysiology

- Blockage of gland outflow → accum of mucous → Bartholin duct cyst.
- Superficial infxn of a Bartholin cyst → Bartholin duct abscess. Polymicrobial. Most common bacteria are anaerobic & facultative aerobes.
- Bartholin cyst & abscess uncommon >40 yo. Consider biopsies of cyst wall to r/o cancer.

Clinical Manifestations and Physical Exam

- Small cysts are asx. Larger → vaginal pres or dyspareunia. Typically unilateral, round, & tense.
- Abscess = sev pain → difficulty walking, sitting, engaging in sex. May be tender w/ erythema/induration, purulent drainage.
- **DDx:** Epidermal inclusion cysts, mucous cyst of vestibule, cyst of canal of Nuck, Skene's duct cyst (*J Obstet Gynaecol* 2007;27:241)

Treatment (See also Appendix of Common Procedures)

- Small, asx cyst requires no rx. OTC analgesics, warm compresses, & sitz baths may provide sx relief.
- Abscess may drain spontaneously. Immediate pain relief will occur w/ drainage.
- Surgical mgmt reserved for recurrences, abscesses, or large symptomatic cyst.
  (1) **I&D:** Relief but incision can reseal → reaccumulation of fluid. Word catheter (or pediatric Foley) allows continued drainage & tract epithelialization. High recurrence rates after I&D. Leave catheter 4–6 w. May fall out before then.
  (2) **Marsupialization:** Create new drainage site. Incise roof of cyst → sew edges of cyst wall to adj skin edge. Requires anesthesia, ↑ time, & placement of sutures. Low recurrence after marsupialization.
  (3) **Bartholin gland excision:** Reserved for cyst that recurs repeatedly. ↑ risk of bleeding. Not performed if active infxn.

  Antibiotic therapy often prescribed after surgical rx. Cx rarely change mgmt (*Am Fam Physician* 2003;68:135). Use broad spectrum abx, failure of clinical improv, consider MRSA.

UTERINE FIBROIDS

Definition

- Benign smooth muscle tumors, originating from myometrial tissue (leiomyoma).
- Uterine fibroids can be classified based on their anatomical location.

Epidemiology (*Obstet Gynecol Clin N Am* 2011;38:703)

- By 50 yo, fibroids are found in ~70% of whites & >80% of blacks. Indication for 30–40% of hysterectomies. Risks: >40 yo, black, FHx, nulliparity, obesity.

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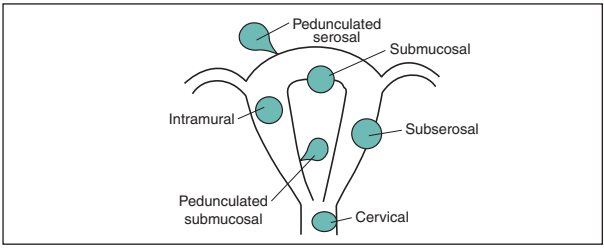
Figure 5.1 Fibroid location & nomenclature



Pathology

- **Gross:** Pearly, round, well circumscribed. Size & location vary. Relatively avascular but surrounded by rich vasculature system → signif bleeding.
- **Histology:** Smooth muscle cells aggregated in bundles.
- **Degenerating leiomyoma types:** Hyaline (65%), myxomatous (15%), calcific (10%, mainly older women), cystic (4%, hylanized areas → liquefaction), fatty (rare), carneous (red) necrosis (esp *pregnant* pts, acute d/t outgrowing bld supply → acute musc infarction → sev pain & local peritoneal irritation).
- Leiomyomas do not transform into leiomyosarcoma. Likely represents a de novo neoplasm & is NOT a result of malig transformation of a benign tumor.

Pathophysiology

- Fibroids are estrogen- (& progesterone-) sensitive tumors. Fibroids create ↑ estrogen environment → ↑ growth & size maint. ↑ estrogen conditions (obesity, early menarche) → ↑ fibroid risk.

Clinical Manifestations

- Mostly asx. Sx depend on size, location, & number. In general, the larger the fibroid, the larger the chance of sx.
- Vaginal bleeding = most common symptom; usually presents as menorrhagia.
- **Other sx:** Pelvic pain & pres, urinary frequency, incontinence, constip, infertility
- Evid sugg that myomas are the primary cause of infertility in a small # of women. Myomas that distort the uterine cavity & larger intramural myomas may have adverse effects on fertility (*Fertil Steril* 2008;90:S125).

Physical Exam & Diagnostic Studies

- **Findings:** Uterine enlargement, irreg uterine contour.
- Must r/o other causes of abn bleeding. Postmenopausal bleeding w/ fibroids should be evaluated the same way as women w/o fibroids.
- Imaging:
  - **US:** Defines pelvic anatomy & effective in locating fibroids.
  - **SIS:** Allows eval of uterine cavity, particularly if infertility or menorrhagia is a concern. Good for submucosal type.
  - **MRI:** Very accurate. Very expensive. Not practical depending on the clinical setting.
  - **Hysteroscopy:** Gold std for submucosal fibroid.

Treatment & Medications

- **Observation:** Asx fibroids do not require intervention, no matter their size.
- **Medical mgmt** (*Obstet Gynecol Clin N Am* 2011;38:703): Should be tailored to alleviating sx. Cost & s/e of rx may limit long-term use.
  - **NSAIDs:** No data to support use as sole agent for therapy. Good for dysmenorrhea based on role of PGs as pain mediators.
  - **OC:** 1st line. Combined OCs may control bleeding & pain, but progestin-only OCs w/ mixed results.
  - **Levonorgestrel IUD:** Beneficial for menorrhagia. ↑ rate expulsion & vaginal spotting.
  - **GnRH agonist (Leuprolide 3.75–11.25 mg/m IM):** Reversible amenorrhea in most, & 35–65% ↓ in size w/i 3 mo. Most useful in women w/ large fibroids. Induces menopause sx + ↓ bone density. Consider add-back therapy for prolonged use (>6 mo) or symptomatic pts. Use preop → ↓ uterine size before Surg.
  - **Aromatase inhibs:** Block ovarian & periph estrogen production → ↓ estradiol level after 1 d of rx. ↓ s/e compared to GnRH w/ rapid results. Little data.

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Antiprogestins (Mifepristone 5 or 10 mg/d × 6 mo): 26–74% ↓ in uterine vol & ↓ recurrent growth after cessation. S/e: Endometrial hyperplasia (dose-dependent) & transient ↑ in transaminase (monit LFTs).

- **Nonsurgical mgmt:**
  UAE: IR injects PVA spheres into bilateral uterine artery → ↓ bld flow → ischemia & necrosis → ↓ size & sx. *Postembolization syn* may require hospitalization postop for pain control. Successful pregnancies occur after UAE, but long-term data limited.
  US ablation under magnetic resonant guidance:
- **Surgical Mgmt:**
  Hysteroscopic myomectomy: 1st line for symptomatic submucosal fibroids.
  Myomectomy: Option for those desiring fertility or decline hysterectomy. Goal to remove visible & accessible fibroids, & reconstruct uterus. Via laparotomy or laparoscopy. Fibroids may recur. When myomectomy invades endometrial cavity (complete wall resxn) consider CS deliv @ 37–38 w gest (*Obstet Gynecol* 2011;118:323).
  Hysterectomy: Definitive surgical rx. Satisfaction rate >90%.

ADENOMYOSIS

Definition & Pathogenesis

- Presence of endometrial glands & stroma w/i the uterine musculature
- Amt & degree of invasion vary. Diffuse or circumscribed focal glandular deposits.

Epidemiology

- Unclear etiology, but several theories. Possibly invagination of endometrium into myometrium, or misplaced stem cells or Müllerian remnants.
- 70–80% of cases seen in 4th & 5th decades. Only 5–25% of adenomyosis seen <39 yo.
- Estrogen & progesterone likely play role in dev & maint. Often develops during reproductive years & regresses after menopause. Risk factors: Parity, ↑ age

Clinical Manifestations & Physical Exam Findings

- Menorrhagia & dysmenorrhea. Many asx. Severity correlates w/ ↑ ectopic foci & extent of invasion. Less common complaints: Dyspareunia, CPP, infertility.
- Ectopic endometrial tissue → proliferates → enlarged globular uterus on exam

Diagnostic Workup (*J Minim Invasive Gynecol* 2011;18:428)

- Dx by histology. Uniform dx based on histology not yet developed.
- ↑ Ca-125 levels may be seen, but not proven to be helpful in mgmt or dx.
- TVUS preferred imaging technique = ill-defined myometrial heterogeneity, may be myometrial cysts (round anechoic areas). MRI may be complementary = large asym uterus, thickened junctional zone (innermost myometrial layer), no fibroids.

Treatment & Medications

- No medical therapy exists at this time to treat sx while allowing pts to conceive.
- Conservative, medical mgmt for symptomatic adenomyosis similar to 1° menorrhagia or dysmenorrhea. Goal = temporarily induce regression of adenomyosis.
- NSAIDs often given. May consider: Continuous oral contraceptives, progestins, Mirena IUD, danazol, & GnRH agonist.
- **Surgical Mgmt** (*J Minim Invasive Gynecol* 2011;18:428):
  Hysterectomy = Std rx option for those done w/ childbearing.
  Endometrial ablation = Treats menorrhagia sx. Less successful if ↑ penetration of adenomyosis into uterus is present.
  UAE: Controversial. Less successful if fibroids also present.
  Focal excision: Must be able to identify area, margins, & extent of dz. Low efficacy (50%). Addition of GnRH agonist ↓ relapse rates by 20% in 2 y. May have fertility & deliv implications depending on size & location of excision.

ENDOMETRIOSIS

Definition and Epidemiology (*Obstet Gynecol* 2011;118:69)

- Defined as presence of endometrial glands & stroma outside of nml location in uterus.
- Hormonally dependent → mostly reproductive aged women (6–10 prevalence %).

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- Prevalence of 38% in infertile women & 71–87% w/ CPP.
- **Risk factors:** Early menarche (<11 yo), menstrual cycles <27 d, heavy & prolonged menses.
- **Protective factors:** ↑ parity, ↑ lactation periods, regular exercise (>4 h/w).

Etiology

- Most commonly accepted theory = retrograde menstruation → attachment of endometrial tissue on peritoneum. Other theories: Bld or lymph transport, stem cells from bone marrow, coelomic metaplasia.

Clinical Manifestations *(Obstet Gynecol 2011;118:69)*

- Often asymptomatic. Common: Dysmenorrhea, CPP, menorrhagia, dyspareunia.
- Pelvic pain described as pain before onset of menses (2° dysmenorrhea), deep dyspareunia (worse during menses), sacral backache during menses.

Diagnostic Workup/Studies *(N Engl J Med 2010;362:2389)*

- **Physical exam findings:** Uterosacral ligament nodularity, adnexal mass
- Laparoscopy w/ or w/o bx for histology (gold std). Path: Endometrial glands/stroma w/ varying amts of inflammation/fibrosis. Bld or hemosiderin-laden macrophages. Bx not req, but definitive.
- **Visual appearance:** Classical lesions = black powder burn. Nonclassical = red or white.
- No correlation b/w severity of visual dz & degree of pain or prog w/ rx.
- No serum markers or imaging studies useful in dx. Imaging studies (MRI, USG) only useful if + pelvic/adnexal mass (chocolate cyst).
- **US:** Ovarian endometriomas appear as cyst w/ low-level, homogenous internal echoes from old bld. TVUS = imaging of choice to detect deeply infiltrating endometriosis of rectum or rectovaginal septum. MRI rarely req.

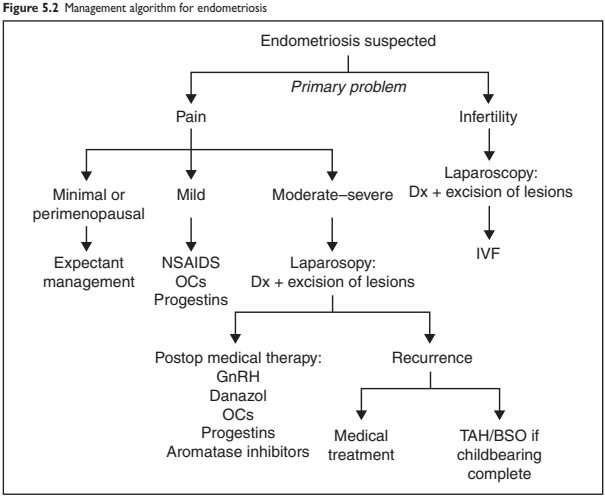
Classification

- Numerous schemes proposed. ASRM classification most common. Value = uniform recording of OR findings & comparing therapeutic interventions.
- **ASRM criteria:** Stage I (minimal) → Stage IV (sev). Based on extent & location of endometriosis lesions seen during operative procedure.

Treatment & Medications

- Best treated medically w/ surgical backup. Surgical mgmt reserved for large endometriomas, palpable dz, or infertility *(Fertil Steril 2008;90:S260)*.

Figure 5.2 Management algorithm for endometriosis



Modified from Hoffman BL, Schorge JO, Schaffer JI, et al., eds. *Williams Gynecology*. 2nd ed. New York, NY: McGraw-Hill; 2012.

- **Medical therapy** *(Fertil Steril 2008;90:S260)*: Medical suppressive therapies are ineffective for infertility *(Int J Gynaecol Obstet 2001;72:263)*
  NSAIDs: COX inhibs → ↓ PG synthesis → ↓ pain & inflammation

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OCs: Can be used in cyclic or continuous fashion. Amenorrhea often result of continual therapy, which is often beneficial for pt w/ pain sx.

Progestins: Antagonize estrogenic effects on endometrium → decidualization → eventual endometrial atrophy.
Medroxyprogesterone acetate 20–100 mg PO QD or 150 mg IM q3mo (depot)
NETA 5 mg QD, ↑ 2.5 mg QD until amenorrhea or → 20 mg/d max reached
Mirena IUD. Unk MOA. Is efficacious, but not approved by FDA for this use.

GnRH agonists: ↓ signaling of HPA-axis → ↓ estrogen → amenorrhea & endometrial atrophy. Nasal spray (nafarelin acetate) or depot formulation (leuprolide acetate) q1–3mo. S/e = menopause sx + ↓ bone density. **Add-back therapy** w/ progesterone or combo (estrogen/progesterone) used to ↓ s/e. Theory = amt necessary to prevent menopause sx < amt to stimulate endometriosis. Can be started immediately w/ GnRH agonist administration. Does not diminish efficacy of pain relief. Norethindrone acetate (only hormone FDA approved for add-back therapy) 5 mg PO QD w/ or w/o CEE (premarin) 0.625 mg QD × 12 mo.

Danazol (600–800 mg QD): Inhibit LH surge → chronic anovulatory state. Substantial androgenic & hypoestrogenic s/e that limit clinical utility.

Aromatase inhibs: Still investigational. Not definitive therapy.

- **Surgical therapy** (*Fertil Steril* 2008;90:S260): Relief of pain after surgical rx = 50–95%. Laparoscopic rx of visible endometriosis improves pain. All visible lesions should be treated.

  Conservative Surg (diagnostic laparoscopy, lysis of adhesions, ablation/fulguration of visible implants, normalization of anatomy) = 1° approach for symptomatic or large endometriomas b/c medical therapy will not lead to complete resolution. Cyst excision in endometriomas has improved outcomes over simple cyst drainage.

  LUNA: Disrupts efferent nerve fibers in the uterosacral ligaments → ↓ uterine pain for intractable dysmenorrhea. No benefit > conservative Surg alone.

  Presacral neurectomy: Interrupts symp innervation to uterus @ level of superior hypogastric plexus. Benefit in midline pain only. Technically challenging w/ signif risk of bleeding. S/e: Constip, urinary dysfxn.

  Hysterectomy (TAH/BSO): For those w/ debilitating sx, have completed childbearing, & failed other therapies. Long-term adherence w/ HRT req to prevent ↑ risk of mortality a/w BSO prior to menopause (*Obstet Gynecol* 2010;116:733). Use estrogen/progesterone therapy d/t risk of unopposed estrogen more likely to cause growth of endometrial implants.

- Surg, followed by medical therapy offers longer sx relief than w/ Surg alone. OC, progestins, GnRH analogs, & danazol have been shown to ↓ pain & ↑ time until recurrence (*Fertil Steril* 2008;90:S260; *Hum Reprod* 2011;26:3).

RECURRENT ABNORMAL UTERINE BLEEDING (AUB)

Definition and Etiology

AUB: Menstrual flow outside of nml vol, duration, regularity, or frequency. Excessive bld loss is based on pts' perception.

PALM-COEIN classification	
Structural causes of AUB	
P	Polyp
A	Adenomyosis
L	Leiomyoma (submucosal, other)
M	Malig, hyperplasia
Nonstructural causes of AUB	
C	Coagulopathy
O	Ovulatory dysfxn
E	Endometrial
I	Iatrogenic
N	Not yet classified

Pair AUB with terms to describe bleeding pattern &/or qualifying letter from above to indicate etiology (eg, AUB-P, AUB-A, AUB-L).
From *Int J Gynaecol Obstet* 2011;113(1):3.

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Pathophysiology
- See PALM-COEIN table.
- Anovulation → no cyclic progesterone production → ↑ estrogen → ↑ endometrial proliferation → amenorrhea → eventually, endometrium overgrown & structurally fragile → random & dyssynchronous endometrial sloughing → irreg vaginal bleeding → AUB/menorrhagia. An anovulatory pt is *always in follicular phase of ovarian cycle & in proliferative phase of endometrial cycle.* No luteal or secretory phase b/c no cycles. Unopposed estrogen ↑ risk of endometrial hyperplasia.

Differential Diagnosis
- Always consider Preg or related complications (SAB, ectopic).
- **Teens:** MCC d/t persistent anovulation d/t immaturity or dysregulation of HPA (= nml physiology), coagulopathy, contraception, infxn, tumor.
- **Reproductive age** (19–39 y): Structural abnormalities (PALM), anovulatory cycles, contraception, endometrial hyperplasia. Cancer less common but may occur.
- **Perimenopause:** Endometrial hyperplasia, cancer, anovulatory bleeding d/t declining ovarian fxn (= nml physiology).

Diagnostic Workup (*BMJ* 2007;334:1110; *Obstet Gynecol Clin N Am* 2008;35:219)
- Detailed history & physical exam, including bimanual exam to evaluate uterus & speculum exam to evaluate cervix & vagina. Complete menstrual Hx is essent & can provide dx w/ suff confidence that rx can begin empirically.
- Regular, heavy menses usually anatomical lesion or bleeding d/o.
- **Lab tests:** Preg test, CBC, TSH. Consider pap smear & chlamydia testing. R/o bleeding disorders, particularly in teens. Serum progesterone in luteal phase >3 ng/mL sugg recent ovulation, but timing of test difficult w/ irreg menses.
- An EMB is not always req, except for >45 yo. Consider before rx if long-term unopposed estrogen exposure present, regardless of age.
- Imaging reserved to evaluate finding on physical, when sx persist despite rx, or suspicious for intrauterine pathology (AUB-P or AUB-L).

Treatment & Medications (*Obstet Gynecol Clin N Am* 2008;35:219; *Menopause* 2011;18:453)
- Treat underlying etiology. If no ↑ risk of endometrial hyperplasia, cancer, or underlying structural abnormalities, start empiric medical rx. Expect improv in 3 mo. Failure to improve → need to r/o other etiologies before changing mgmt. See also Chap. 2 for acute bleeding.
- **Rx goals:** (1) reverse abnormalities of endometrium d/t chronic anovulation, (2) induce or restore cyclic predictable menses of nml vol & duration.
- Surgical mgmt:
  - **Acute surgical mgmt:** Rare. If hemodynamic unstable, bleeding refrac to 2 doses of IV premarin, or bld loss that cannot be replaced w/ xfusion, OR mgmt (D&C) req. Should continue medical therapy after D&C. Informed consent should include hypogastric artery ligation & hysterectomy should D&C fail. Uterine artery embolization may be considered as an alternative, if available.
  - **Endometrial ablation:** High success rate. 25–50% are amenorrheic, & 80–90% have ↓ bleeding. Effective alternative to hysterectomy. ↑ success if pretreated w/ progest or GnRH. R/o cancer prior to Surg. Up to 1/3 will eventually elect for hysterectomy.
  - **Hysterectomy:** High satisfaction, but more morbidity & poor choice in pts w/ medical conditions w/ high risk for Surg.

POSTMENOPAUSAL BLEEDING

Definition, Epidemiology, & Etiology (*Obstet Gynecol* 2010;116:168)
- **PMB:** Vaginal bleeding occurring after ≥12 mo of amenorrhea
- PMB "is endometrial cancer until proven otherwise." Malig w/ PMB = 1–14%. Predictive value depends on age & risks: Obesity, HTN, diabetes, low parity.
- Caused by cancer (10%), atrophy (60–80%), endometrial hyperplasia (2–12%), HRT (15–25%). Tamoxifen increases endometrial cancer risk. TVUS less useful d/t subepithelial stromal hypertrophy. Therefore any bleeding w/ tamoxifen → w/u.

Diagnostic Workup (*Obstet Gynecol* 2010;116:168)
- **Comprehensive H&P:** Pelvic exam to evaluate rectal, vulvar, vaginal, or cervical origin.
- **Goal of endometrial eval:** (1) exclude malig, (2) rx based on proper etiology (anatomic vs. nonatomic pathology)

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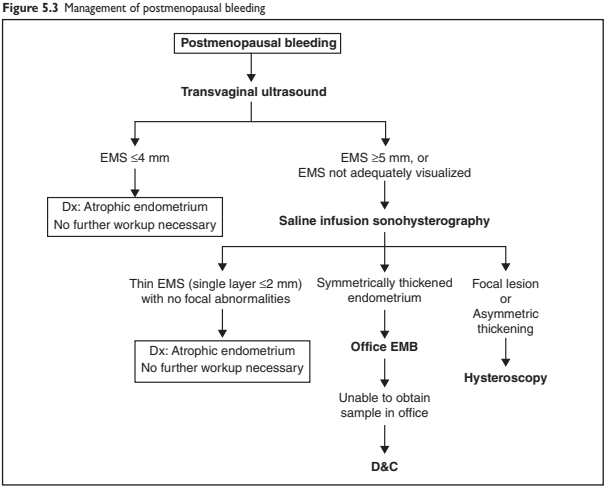
- **Endometrial eval:**
  Transvaginal US allows initial screening in some protocols. An EMS on TVUS <5 mm, has a risk of malig of 1:917. PPV 9% & NPV 99%. Sens 90%, spec 48% for endometrial cancer. About 50% of pts w/ initial TVUS → further eval (*Obstet Gynecol* 2009;113:462). Limitations: EMS not always visible, particularly w/ prior Surg, fibroids, obesity, adenomyosis. Incidental thick EMS in an asx pt does NOT require intervention. Often d/t polyps (82%) → no intervention b/c negligible risk that an asx polyp (ie, no bleeding) will harbor cancer (1:1000).
  EMB: Accurate for excluding cancer, but only samples small focus of endometrium. Sens 99%, spec 98%. False negative ~10%. High rate of insuff or failed sampling (0–54%) → further eval (*Maturitas* 2011;68:155).
  Sonohysterography: Imaging w/ saline infusion (SIS) overcomes some TVUS limitations.
  3D US & Doppler adds no additional information at this time.
  D&C: Useful when unable to obtain EMB (cervical stenosis, pt intolerance, etc.). Invasive: 1–2% complication rate. May miss 10% of endometrial lesions, & of these up to 80% are polyps.

Figure 5.3 Management of postmenopausal bleeding



Modified from Hoffman BL, Schorge JO, Schaffer JI, et al., eds. *Williams Gynecology*. 2nd ed. New York, NY: McGraw-Hill; 2012.

DYSMENORRHEA

Definition & Epidemiology

- Dysmenorrhea = painful menstruation. One of the most common gyn complaints.
- Primary dysmenorrhea (PD) = Menstrual pain in the absence of underlying pathologic pelvic dz. Usually seen near time of menarche. Affects 43–91% of adols (depending on study criteria) (*Contraception* 2010;81:185). PD ↓'s w/ ↑ age. Highest in 20–24 yo's & ↓'s thereafter (*Obstet Gynecol* 2006;108:428).
- Secondary dysmenorrhea (SD) = Menstrual pain d/t pelvic condition or pathology. Risks: BMI <20, nulliparity, depression, premenstrual syn, sterilization, PID, h/o sexual assault, & heavy smoking.

Pathophysiology & Etiology

- PD d/t ↑ PGF2α in secretory endometrium → ↑ uterine contractility → painful menstrual cramps (*Contraception* 2010;81:185)
- SD most commonly d/t endometriosis, followed by adenomyosis, & IUD. Other causes:
  Gyn etiology: Cervical stenosis (hematometria), PID, adhesive dz, fibroids, pelvic congestion, & congen malformations.
  Nongynecologic etiology: Psychosomatic, IBS, inflamm bowel dz, UTI/dz, kidney stones, IC.

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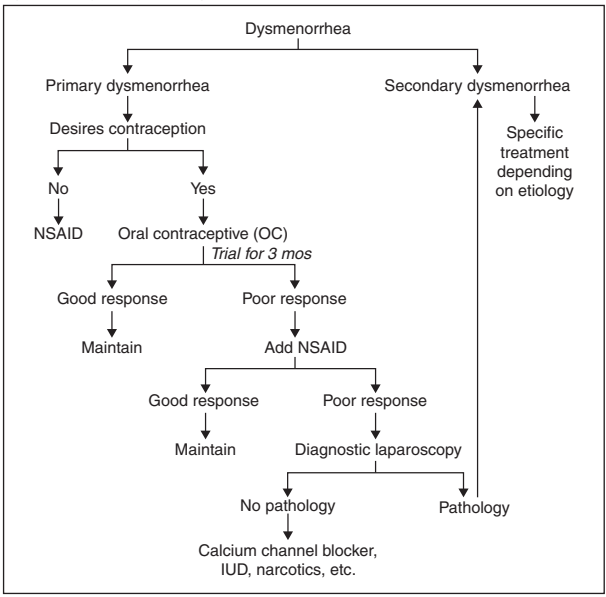
Clinical Manifestations & Diagnosis

- **PD:** Presents w/ or shortly after menarche. Midline, cramping pain, beginning w/ onset of menses. Pain worst 1st 24–36 h, c/w the highest levels of PG release. Resolves over 12–72 h (*Contraception* 2010;81:185). Dx based on hx & nml pelvic exam. May be a/w HA, N/V, backache, & diarrhea. May occur as late as 1 y after menarche, but unlikely & should ↑ suspicion for SD.
- **SD:** Dx based on inconsistent hx & abn pelvic exam (eg, pelvic mass, abn vaginal discharge, pelvic tenderness not limited to time of menses). Consider SD if no resp to NSAIDs & OCPs, or if sx follow years of painless menses.

Treatment & Medications

- **PD:**
  - **NSAIDs:** *1st-line therapy.* Works in ~90% of pts. Start on day *prior* to menses, or *at onset.* If 1 NSAID is ineffective, switch to different class. Specific COX-2 inhibs (celecoxib) also shown to be effective.
  - **OCP:** Suppress ovulation & ↓ endometrial thickening → ↓ PG → ↓ pain. Low-dose OCs (20 mg ethinyl estradiol) can ↓ sx. Continuous OC (vs. monthly) will ↓ pain longer, but s/e extended regimen = breakthrough bleeding.
  - **Depot medroxyprogesterone** (150 mg IM q3mo): Not specifically studied in this pop. Presumed to ↓ endometrium thickness → ↓ PG → ↓ pain.
  - **Levonorgestrel-releasing IUD:** Profound local effect → suppression of endometrial growth → improv in sx.
  - **Nifedipine** (20–40 mg QD): Known effect on uterine contractility, but 1st-line therapy so effective that it is rarely req. S/e = flushing, tachy, & HAs.
  - **Narcotics:** Should be used as last-line therapy
  - **Endometrial ablation:** ↓ endometrium → ↓ sx. Not for those desiring fertility.
  - **Nerve ablation:** Observational studies support LUNA & presacral neurectomy to interrupt cervical pain fibers. Cochrane review sugg presacral neurectomy > LUNA > placebo/no rx. But insuff evid to recommend either (*Obstet Gynecol* 2006;108:428).

Figure 5.4 Management algorithm for dysmenorrhea



Modified from Hoffman BL, Schorge JO, Schaffer JI, et al., eds. *Williams Gynecology*. 2nd ed. New York, NY: McGraw-Hill; 2012.

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- **SD:**
  NSAIDs & hormonal contraceptives are less likely be effective if SD present. Mgmt of SD is rx of the underlying d/o.

PREMENSTRUAL DYSPHORIC DISORDER (PMDD) AND PREMENSTRUAL SYNDROME (PMS)

Definition and Epidemiology (*Am J Psych* 2012;169(5):465)

- PMS in about 30% regularly cycling ♀. PMDD affects 3–8% of ♀ w/ PMS.
- Classification of premenstrual disorders is based on gradation of premenstrual symptomatology: Mild (premenstrual sx) → mod PMS → sev PMDD
- **Proposed DSM-V diagnostic criteria for PMDD:** 5 or more of the following during the week prior to menses, declining w/i a few days after the onset of menses. At least 1 of the 5 sx must be a core symptom, representing 1 of the 1st 4 on the list.
  Marked *affective lability, irritability, or markedly depressed mood or marked anxiety;* decreased interest in usual activities, difficulty in conc, lethargy, marked changes in appetite (overeating or food cravings), hypersomnia or insomnia, feeling overwhelmed, physical sx (breast tenderness, bloating, muscle or joint pain, or HA). Functional impairment in work, school, daily activities, & relationships.
  Dx of exclusion (not exacerbation of another mood d/o like MDD, panic d/o, dysthymic d/o, personality d/o). Not attributed to a substance, medication or general medical condition.
  Dx requires prospective documentation of sx for ≥2–3 menstrual cycles.
- **Dx of PMS:** Timing of sx occurs before menses & declines w/ the onset of menses. 1 or more of the following present, but no functional impairment:
  Mild psychologic discomfort, bloating, wt gain, breast tenderness, periph swelling, aches/pains, ↓ conc, sleep disturbances, changes in appetite.

Etiology

- No specific mech identified. Variety of mood changes/destabilization involving serotonin, triggered by physiologic hormonal changes in susceptible individual.

Initial Workup

- Hx, physical, CMP, CBC, serum TSH. Menstrual hx w/ an eval of regularity of menstrual cycles; ovulation is req for dx.
- A 2–3-mo prospective menstrual calendar: Document sx & relationship to menses; sx ↑ at the time of ovulation & decline w/ onset of menses; a symptom-free week occurs during the follicular phase.
- **DDx:** Mood & personality disorders, domestic abuse, thyroid disorders, perimenopause, anemia, endometriosis, chronic fatigue syn, IBS, fibromyalgia

Treatment and Medications

- Goal to ↑ unaffected days & ↓ symptom severity → ↑ psychosocial functioning
  No effective medical rx for PMS in empirical studies. High placebo resps (30–80%). Recommend: Support, lifestyle changes, diet, relaxation, exercise in mild–mod PMS. Limited/no efficacy: Vit B6 100 mg/d (max dose), Vit E 400 IU/d, calcium 600 mg BID (↓ 48% vs. 30% in placebo in PMS sx) & magnesium 200–360 mg/d.
- SSRIs are 1st-line rx for PMDD (meta-analysis of RCT demonstrated 60% resp rate) (*Obstet Gynecol* 2008;111(5):1181): Fluoxetine 20 mg/d, paroxetine 20–30 mg/d, citalopram 20–30 mg/d & sertraline 50–150 mg/d. Clomipramine & venlafaxine may be also be effective. Luteal phase only → smaller rx effect than daily dosing (*Obstet Gynecol* 2008;111(5):1175).
- **Other rxs for PMDD:**
  Alprazolam 0.25 mg TID or QID prn. Use limited by dependence risk.
  Medical oophorectomy w/ GnRH agonists: Leuprolide (add back therapy if rx is continued >3–6 mo) & danazol (limited use d/t s/e).
  Surgical oophorectomy last form of permanent therapy when all other rxs have failed & trial of medical oophorectomy successful.
  Less effective: Oral contraceptives w/ drospirenone & a 4-d pill-free interval, diuretic w/ spironolactone

CHRONIC PELVIC PAIN

Definitions and Etiology (Chapter 27. Chronic Pelvic Pain. *Hopkins Manual of Gyn-OB*, 4th ed. 2011)

- Noncyclic pain, at least 6 mo duration in the abdominal wall at or below the umbilicus or in the anatomic pelvis; causes functional disability or request for medical care.

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- Pain is subjective & may or may not be a/w pelvic pathology or physical findings. Requires WIDE diff, possibly team eval/approach.
- Causes may be gastrointestinal (38%), urologic (31%), gyn (20%), musculoskeletal, neurologic, psychological (*Br J Obstet Gyn* 1999;106:1156)

Clinical Manifestations
- **Gastrointestinal:** Diarrhea, constip, flatulence, relationship of bowel mvmts w/ pain, hematochezia
- **Urologic:** Urgency, frequency, urinary incontinence, dysuria, nocturia, hematuria
- **Gyn:** Vaginal bleeding/discharge, dysmenorrhea, dyspareunia, infertility
- **Neuropathic/musculoskeletal:** Trauma, postural changes

Initial Workup
- **Most common diagnoses:** IBS (50–80%), IC (35–85%), endometriosis (33%), adhesions (24%), psychological or sexual abuse (40–50% prevalence).
- A detailed history & physical exam. Obtain pain hx, medical, surgical & gyn factors, pathology, operative reports, & prior pain evals
- **Abdominal exam:** Pain map, + Carnett's sign (bilateral leg raise, or sit up; worsening pain consider musculoskeletal etiology as true visceral pain improves w/ tension of abdominal muscles.) Exam elements directed toward suspected cause.
- **Lab:** CBC, UA & cx, GC/CT, Preg test, wet prep, ESR

Diagnostic Workup/Studies
- If physical exam findings consistent w/ mass, TVUS to evaluate pelvic mass, hydrosalpinx. If abn→ consider MRI or CT.
- Diagnostic laparoscopy for endometrial implants w/ biopsies & histology (visual dx is correct only 10–90%)
- Validated questionnaire w/ the O'Leary-Sant Interstitial Cystitis Symptom Index: If score of ≥5 on screening (94% sens & 93% NPV) → cystoscopy + for glomerulations, ulcer (8%), ↓ bladder capacity → IC (*Obstet Gynecol* 2002;100:337); validity of potassium intravesical sens test is uncertain (85% positive in CPP pts evaluated in general ob/gyn office).
- Colonoscopy as sx or exam indicate.

Treatment and Medications
- Multidisciplinary approach
- Empiric medical rx for the most likely cause. Endometriosis: NSAIDs, OCPs, medroxyprogesterone acetate 30–100 mg QD, danazol for 2–9 mo or Lupron 3.75 mg QMO. If no improv in 2–3 mo → invasive diagnostic testing. Chronic infectious etiology (~18–35% of acute PID develop CPP, sterile pyuria in urethral syn), doxycycline 100 mg BID × 14 d. Manual therapy of myofascial pelvic trigger points – 65–70% improv (*J Urol* 2001;166:2226).
- Endometrial implants, windows, & endometriomas → excised & fulgurated; pain relief at 1 y in 45–85%; recurrence usually at 40–50 mo. Hysterectomy; no RCT (75% pain relief at 1-y f/u) (*Obstet Gynecol* 1995;86:941).

VESTIBULODYNIA

Definitions, Epidemiology, and Etiology (*J Reprod Med* 2004:49:772)
- Sev, localized pain of the vulva provoked by focal touch or pres, lasting >3 mo & not explained by another condition.
- 11–16% prevalence
- Unk cause. Current hypothesis: Insult to mucous membrane of the vulvar vestibule → chronic inflammation → central nervous system sensitization → allodynia. Risks include vulvovaginal candidiasis, OCP use, presence of IC.

Clinical Manifestations
- **Cardinal sign:** Sev pain upon vaginal penetration, touch or focal vulvar pres for 3–6 mo w/o relevant visible findings or clinically characterized neurologic d/o. Most common site of provoked pain → post fourchette.
- Provoked by coitus, vulvar contact w/ tampon, speculum, tight clothing, washing, or wiping vestibule; sitting, biking, or horseback riding.

Physical Exam and Diagnostic Workup
- **Pelvic exam:** Gross inspection, mapping by palpation w/ cotton tipped applicator to localize pain, single digit exam, speculum exam; tenderness in vulvar vestibule w/ or w/o areas of erythema; no pathognomonic features, no bx needed.

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- A clinical dx of exclusion w/ history & physical exam
- **Labs:** Vaginal pH & microscopy, yeast culture
- **R/o other causes:** Infectious, inflamm, neoplastic, neurologic, musculoskeletal, psychosexual; depression, domestic abuse or relationship discord; DDx include fungal vulvitis, lichen planus, lichen sclerosus, lichen simplex chronicus, atopic or contact dermatitis, vulvar intraepithelial neoplasia

Subsequent Workup

- Treat vulvar dermatosis w/ steroids, if no improv in sx → poss LPV. Serial yeast cx if culture negative yet pt experiences recurrent vulvovaginal pruitus or burning.

Treatment and Medications

- Extensive pt education (www.nva.org) & vulvar care (unscented products, 5–10 min sitz baths)
- **1st-line therapy:** Pelvic floor muscle rehabilitation w/ either topical gabapentin 6% or topical 5% lidocaine gel; 5 mL of topical lidocaine to the vestibule 20–30 min prior to vaginal intercourse
- Tricyclic antidepressants w/ nortriptyline or desipramine gradual max daily dose of 100–150 mg PO; alternative regimen w/ gabapentin (64% showed ↓ 80% of sx) (*J Reprod Med* 2007;52(2):103)
- Botulinum toxin type A injections
- Surgical intervention as a last rx (~30–50%: Improv) Woodruff's original perineoplasty, post, modified, or simplified vestibulectomy & vestibuloplasty.

FEMALE SEXUAL DYSFUNCTION

Definitions (DSM-IV-TR)

- 4 major categories of disorders characterized by recurrence or persistence of sx: Sexual desires, arousal, orgasmic, sexual pain. Each must be accompanied by distress or interpersonal difficulty.
- HSDD deficiency or lack of sexual thoughts, desire or receptivity. Sexual aversion d/o is an aversive resp to genital contact w/ a sexual partner.
- Sexual arousal d/o is inability to achieve sexual excitement subjectively or objectively.
- **Sexual orgasmic d/o:** Difficulty achieving orgasm w/ suff sexual arousal
- **Sexual pain d/o:** Dyspareunia or vaginismus & noncoital pain

Epidemiology

- **43% prevalence:** Low sexual desire (22–39%); arousal problems (14–26%); orgasm (21%), sexual pain (7%) (*JAMA* 1999;281:537; *Obstet Gyn* 2008;112, 976)

Etiology

- Organic or psychological or a mix of both; more than 1 dysfxn may coexist. Risks: ↓ age, ↓ educational attainment, ↓ social status, urinary tract sx, sexual trauma
- Medical (depression, anxiety, urinary incontinence, ESRD, anemia, thyroid, DM, substance or EtOH abuse, cancers), meds (SSRIs – most commonly, beta-blockers, antipsychotics), current relationship, sociocultural factors, estrogen deficiency, abn gyn etiology

Pathophysiology

- ♀ sexual resp cycle has 4 phases: Desire, plateau, orgasm, resolution as described by Masters & Johnson in 1966. Nonlinear model integrates emotional intimacy, sexual stimuli & relationship satisfaction; a sexual encounter may begin w/o desire initially present (Clin Update Women's Health Care 2003;11(2):1).

Diagnostic Workup/Studies

- The Brief Sexual Symptom checklist, a screening questionnaire (*J Sex Med* 2010;337)
- Lab eval as clinically indicated: TSH, PRL, etc. H&P for most eval.

Treatment and Medications

- **Nonpharmacologic therapy (1st line):** Identify rx goals, treat reversible causes; psychoanalysis, sex therapy w/ requisite exercises (dilators, vibrators) & Eros Therapy (FDA approved), pelvic floor physical therapy, desensitization, Kegel, & relaxation exercises
- **Pharmacologic therapy:** For HSSD, non-FDA approved rx w/ 300-μg testosterone patch 2× weekly + ET for ≤6 mo; ET, a testosterone cream (0.5 g QD) topical (combined estrogen & testosterone therapy ↑ multi sexuality measures) (*Menopause* 2006;13:770).

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- HRT for vasomotor & atrophy, low-dose vaginal postmenopausal ET for atrophy only; vaginal lubricants or moisturizers as an estrogen alternative; for dosing see Chap. on Menopause & therapy for urogenital atrophy.

MENOPAUSE

Definitions and Epidemiology *(Fertil Steril* 2012;97(4):843)

- Final menstrual period (FMP) defined by 12 mo of amenorrhea from a loss of ovarian activity. Perimenopausal transition: Wide fluctuation in hormonal profiles; ↑ irreg cycle length; quantitative FSH of >25 IU/mL on a random bld sample.
- FMP at <40 y = premature menopause (~1%)
- Growing number of menopausal women. 37.9 million over 55 yo (2010) → 45.9 M (2020).
- Median age 51.4 y (*Am J Epidemiol* 2001;153:865). Gaussian distribution of 40–58 y.
- Leading cause of mortality is cardiovascular dz related (45%) > stroke > cancer.

Figure 5.5 Stages of reproductive aging

Menarche						FMP (0)			
Stage	–5	–4	–3b	–3a	–2	–1	+1a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION		POSTMENOPAUSE			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	Variable				Variable	1–3 yr	2 yr (1+1)		3–6 yr	Remaining lifespan
PRINCIPAL CRITERIA										
Menstrual cycle	Variable to regular	Regular	Regular	Subtle changes in flow/ Length	Variable length persistent ≥7-day difference in length of consecutive cycles	Interval of amenorrhea of >–60 days				
SUPPORTIVE CRITERIA										
Endocrine FSH AMH inhibin B			Low Low	Variable* Low Low	↑Variable* Low Low	↑>25 IU/L** Low Low	↑ Variable* Low Low	Stabilizes Very Low Very Low		
Antral follicle count			Low	Low	Low	Low	Very Low	Very Low		
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor symptoms *Likely*	Vasomotor symptoms *Most likely*			*Increasing* symptoms of urogenital atrophy

*Blood draw on cycle days 2–5↑ – elevated
**Approximate expected level based on assays using current international pituitary standard

(From Harlow SD, Gass M, Hall JE, et al. Executive summary of the stages of reproductive aging workshop + 10: Addressing the unfinished agenda of staging reproductive aging. Fertil Steril. 2012;97(4):843–851)

Etiology

- Reproductive axis is a negative neuroendocrine feedback loop. Reduced quality & quantity of aging follicles → ↓ inhibin & ↓ ovarian estrogen → ↑ FSH → accelerated loss of ovarian follicles → depleted ovarian follicle supply→ ovarian senescence
- α- & β-estrogen receptors are located throughout the body; ↓ estrogen → sx.

Clinical Manifestations

- **Vasomotor instability:** Hot flushes & night sweats (~75%); most common during late menopausal transition (Stage –1) through early postmenopausal period (Stage +1). Self-limited w/ resolution in 1st 5 postmenopausal years; 25% symptomatic >5 y; high variability among individuals & cx.
- **Urogenital atrophy:** Pruritus, recurrent UTI, vaginal neuropathy in the distribution of pudendal nerve, sexual dysfxn, dyspareunia (up to 75%); most common during late postmenopause (Stage +2)
- **Alterations in menstrual patterns:** Chronic anovulation → heavy dysfunctional bleeding during late reproductive stage (Stage –3a) & menopausal transition (Stages –2, –1)
- Infertility secondary to oocyte depletion
- **Increased cardiovascular dz risk:** ↑ total cholesterol, ↑ markedly LDL-C.
- **Accelerated bone loss:** Spine bone density ↓ by 15–30% in 1st 5–7 postmenopausal years. Thereafter, it is 1–2% per year as compared to premenopausal bone loss rate of 13% per year. The effect is predominantly on trabecular bone (*Hormone Therapy* 2010;115(4):844).
- **Decreased collagen support:** ↓ skin collagen by 30% in 1st 5 years after menopause. There is an ~2% ↓ per year for the 1st 10 y after established menopause.

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- Increased endometrial & breast cancer risk d/t unopposed endogenous estrogen production

Physical Exam

- Habitus, race, serial ht. Pelvic exam: Vagina may appear thin, pale, dry, inflamed, lack rugae, petechial hemorrhages, cervical atrophy, narrowed or shortened vagina is a possibility; urethral caruncle may be present.

Diagnostic Workup/Studies

- Clinical dx from longitudinal assessment of absence of menses over 12 mo.
- Risk assessment for CVD (lifestyle, FHx, lipid profile) & osteoporosis. DEXA scan of the hip & vertebrae w/ resultant T-score (1–2% accuracy & precision). BMD may be used to diagnose osteoporosis, predict fracture risk & identify who would benefit from therapy. See Chap. 1 Osteoporosis.

Treatment and Medications

- **Perimenopausal transition:** Prolonged maximal physical energy, social & mental activities.
- VMSx classified mild (transient heat), mod (heat + sweating + permits continuation of activity), sev (heat + sweating + discontinuation of activity). Mod–sev VMSx = 7 hot flashes/d or 50–60 per week. HRT most effective for VMSx therapy (see section below).
- Mild urogenital atrophic sx, vaginal moisturizing agents on a regular basis before bedtime several times weekly & lubricants during intercourse, regular sexual activity.
- **Urogenital atrophy:** Systemic ET is the most effective for mod–sev sx; local vaginal Est Rx (rings, creams, tablets) w/ minimal systemic absorp & increased safety up to 1 y. Long-term effects lacking (*Obstet Gynecol* 2010;115(4):843).

Treatment for menopausal atrophic vaginal/genitourinary symptoms	
Vaginal estrogen preparations	**Regimen**
Vaginal ring with estrogen sustained-release 07.5 μg/d	Replace ring q90d
Vaginal tablet 10–25 μg	Insert 1 tablet daily × 2 w, then twice weekly
Vaginal cream 0.5 mg conj estrogen/g of cream	0.5 g of cream twice weekly

- **Sexual dysfxn:** Local estrogen for lubrication by increasing bld flow & sensation of vaginal tissues. Oral systemic ET is approved for rx of dyspareunia.
- **Urinary sx:** Vaginal ET Est Rx (in RCT ↓ risk of recurrent UTI) (*Am J Obstet Gynecol* 1999;180:1072)
- See Chap. 1 for osteoporosis mgmt.
- Primary & secondary prevention of CHD, stroke, VTE, osteoporosis. Recommend modifiable lifestyle change for primary & secondary prevention: Smoking cessation; control of HTN, dyslipidemia, & DM. Calcium suppl (1200–1500 mg daily), Vit D suppl (800 IU daily).

HORMONE THERAPY

Definitions

- HT comprises estrogen & progesterone therapy.
- ET comprises solely estrogen therapy.
- "Timing hypothesis" – timing of initiation of HT in relation to chronologic age/length of menopause affect risk of primary endpoints (*Am J Epidemiol* 2007;166;511); secondary analysis of WHI/observational studies → initiation of HT before 60 y of age or w/i 10 y of menopause may confer maximal cardioprotection for 6 or more years, improved QOL measures over 5–30 y (*Climateric* 2012;15(3):217).

Indications

- Principal indication for HT is rx of VS. VS classified as mild, mod, or sev. FDA: Mod–sev VS is 8 hot flashes per day or 60 per week
- Use HT when benefits outweigh risks. Benefit:risk ratio changes w/ age & w/ onset of menopausally related sx (eg, VS, sleep disturbance, vaginal atrophy, dyspareunia, or diminished libido, affecting QOL).
- "Timing hypothesis" implies benefits of short-term HT use for VS outweigh CV risk when initiation of HT occurs in close proximity to onset of menopause in appropriately selected pts (*Hormone Therapy* 2010;115(4):847).

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Contraindications

- **HT:** H/o breast cancer, endometrial cancer, CHD, prev VTE or CVA, active liver dz, or high risk for these complications.

Physical Exam

- Estrogen deficiency → thin, pale vaginal mucosa, loss of elasticity & rugal folds, diminished secretions, shortened or narrowed vagina, moisture content ↓, the pH ↑ (usually >5), & mucosal inflammation & petechiae.

Assessment of the Risk–Benefit Ratio

- Women enrolled in WHI, a RCT w/ primary CV event had a mean age of 63–64 y & >10 postmenopausal years.
- In a secondary analysis of WHI data ET arm, statistically signif reduction in CV endpoints (MI, coronary artery revascularization, & coronary death) in those aged 50–59.

Women's Health Initiative (WHI): Main outcome of HT

Event	Relative risk (95% CI)	Increased absolute risk per 10 K/ person/y	Increased absolute benefit per 10 K persons/y
CV event(MI)	1.29	7	
Stroke	1.41	8	
TE	2.13	18	
Breast cancer	1.26	8	
Colorectal cancer	0.63		6
Hip fracture	0.66		5
Global index	1.15		

From Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The Women's Health Initiative randomized controlled trial. *JAMA.* 2004;291(14):1701–1712.

Treatment and Medications

- **HT:** Systemic ET is most effective rx for mod–sev VS; only therapy approved by the FDA for this indication (↓ 75% symptom).
- HT should be guided by use of smallest doses & shortest duration for symptomatic relief.

Hormone therapy regimens

Low-dose combined regimens: 0.45 mg CEE/1.5 mg MDPA or 0.3 mg CEE/1.5 mg MDPA	In RCTs, low-dose combined regimens is as effective as high-dose combined std regimens
High-dose combined std regimen: 0.625 mg CEE/2.5 mg MDPA	
Other formulations: Transdermal estradiol (E2) patches w/ std doses: 0.1 mg/d or 0.05 mg/d or lower doses: 0.025 mg/d, 0.014 mg/d Oral estradiol (E2): 0.5 mg/d or 1 mg/d Oral OCP for hot flushes in nonsmoking, healthy, perimenopausal women	
Progesterone therapy: Medroxyprogesterone acetate 20 mg q orally or IM q3mo	Use when estrogen may be contraindicated & in all ♀ w/ a uterus on ET

From Shifren JL, Schiff I. Role of hormone therapy in the management of menopause. *Obstet Gynecol.* 2010;115(4):839–855.

- Nonhormonal therapy as alternative in noncandidates for HT & mild VS: Lifestyle changes (reduction in body temperature, healthy wt maint, smoking cessation, relaxation techniques, acupuncture)
- Meds acting on central neurotransmitter pathways, decreasing central noradrenergic tone: Clonidine 0.1 mg weekly transdermal patch, (mainstay of nonhormonal therapy, but not FDA approved) paroxetine 10–20 mg/d or controlled release 12.5–25 mg/d, venlafaxine extended release 37.5–75 mg/d, gabapentin 300 mg/d to 300 mg TID.
- **Duration of rx:** Short-term therapy goal (≤2–3 y) is symptomatic relief; annual reassessment of HT need.
- **Discontinuation of rx:** Abrupt withdrawal of exogenous estrogen → return of hot flashes & other sx. Based on WHI, ~55% recurrence w/ abrupt cessation. Estrogen

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taper is not more effective than abrupt cessation. Limited trial data; if recurrent hot flashes w/ no resolution→ nonhormonal medication. If ineffective, restart estrogen at the lowest dose poss (risk:benefit ratio) w/ plan to attempt discontinuation in the prox future.

- **QOL:** Whether HT improves HQOL is unk; data not available of effect of HT on global QOL (the sense of well-being w/ or w/o sx or physical impairments).

PREGNANCY TERMINATION

Early Medical Termination

- Utilizes an established medical regimen to induce an abortion up to 63 d of EGA; A failed medical abortion is defined as the presence of a gestational cardiac activity on transvaginal USG 2 w following medical abortion.
- 6% of all abortions in US are medical; <1% of medical terminations <49 d fail, <1% require surgical intervention by D&C for hemorrhage

Protocols for medical management of pregnancy termination

Common regimens	EGA	Success	% of continuing Preg
Mifepristone 600 mg, misoprostol 400 μg PO 36–48 h later (FDA-approved regimen)	49 d	92%	<1% fail, initiated <49 d; 49% aborted w/i 4 h, 75% w/i 24 h
Mifepristone 200 mg PO, misoprostol, 800 μg vaginally, simultaneously (alternative evidence-based regimen; preferred regimen)	63 d	95–99%	<1% fail if initiated <49 d, continuing Preg 2% if <63 d
Methotrexate, 50 mg/m^2 IM or 50 mg vaginally & misoprostol 800 μg vaginally 3–7 d later	49 d	92–99%	May require up to 4 w for complete abortion to occur, <1% fail if initiated <49 d
Misoprostol, 800 μg vaginally repeated up to 3 dose q3–24h	63 d	88%	<1% if initiated <49 d, <72 d, rate of continuing Preg increases 4–10%

From *Obstet Gynecol* 2014;123:676.

Contraindications to medical abortion

Avoid medical termination in the following pts	
Contraindications to mifepristone	Confirmed or suspected ectopic Preg, undiagnosed adnexal mass, IUD in situ, current long-term systemic Cort rx, chronic adrenal failure, sev anemia, known coagulopathy or anticoagulant rx, mifepristone intolerance or allergy
Relative contraindications to mifepristone	Sev liver, renal, respiratory dz, uncontrolled HTN, CVD (angina, valvular dz, arrhythmia, or cardiac failure) or sev anemia
Contraindications to misoprostol	Uncontrolled sz d/o or those who have an allergy or intolerance to misoprostol
Other factors	Pt is able to assume responsibility for care, are anxious for completion of abortion, are able to f/u, no language or comprehension barriers to counseling, IUP w/ GA confirmed, hemodynamically stable.

From *Obstet Gynecol* 2014;123:676.

Medical Terminations in the Second Trimester or Termination by Induction

- Upper limit for 2nd trimester surgical termination varies by state.
- Induction abortion is the termination of Preg by stimulation of labor-like contractions that cause eventual expulsion of the fetus & placenta from the uterus.
- US physicians must comply w/ the federal Partial-Birth Abortion ban Act of 2003, which bans abortions wherein the physician deliberately delivers a living fetus vaginally, the point at which any part of the fetal trunk above the navel is outside the woman's body, & after the fetus reaches the specified point in either presentation breech or vertex, the physician performs an overt & separate maneuver from deliv to kill the fetus.

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- 10–15% occur in the 2nd trimester; ≥13 EGA (12%); 16–20 EGA (3.8%); >21 EGA (1.4%) (*MMWR Surveill Summ* 2008;57:SS–13)
- Mifepristone & misoprostol (mean 6–11 h for completion). Alternatively, prostaglandin E1 when mifepristone is not available (mean 9–20 h for completion).

Surgical Terminations

- Univ periabortal antibiotic ppx is effective & inexpensive (↓ 42% decreased risk of postabortal infxn): Doxycycline 100 mg PO 1 h preoperatively & a single 200 mg PO dose postprocedure.
- Unsensitized Rh(D) women should receive Rh(D) Ig w/i 72 h postabortion. 50 μg dose at <13 wga & 300 μg dose <13 wga.
- Contraceptive care initiation w/ long-acting reversible contraceptives may ↑ contraceptive use, improve continuation, reduce rpt Preg & rpt abortion.
- Potential complications may be immediate (intraoperatively or in recovery room) or delayed (w/i few hours postprocedure to 2 w): Retained products of conception, hemorrhage, uterine injury: Cervical tears, uterine perforation, syncope, thromboembolic & cardiorespiratory disorders. Delayed complications also include infxn, persistent intrauterine or ectopic Preg.
- **D&C:** Most commonly performed for 7–13 w EGA. By convention D&C = <14 w.
  Manual vacuum aspiration – use at <10 w EGA, 60 mm Hg suction
  Electric vacuum aspiration – for all GAs, 60 mm Hg suction
- **D&E:** By convention, D&E = >14 w EGA.
  Mechanically dilate uterine cervix, permitting evacuation of fetal & placental tissue. Most common technique for 2nd trimester terminations (>96%)

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Definitions

- **Puberty:** Nml physiologic transition from childhood to reproductive & sexual maturity
- **Adrenarche:** Onset of increased adrenal androgen production, leads to pubarche
- **Gonadarche:** Pulsatile GnRH secretion & activation of HPO axis
- **Thelarche:** Onset of breast dev
- **Pubarche:** Onset of pubic & axillary hair dev
- **Menarche:** Onset of menstruation
- **PHV:** Growth spurt characterized by acceleration in growth rate age 9–10, leading to peak height velocity (PHV) around age 11–12

Physiology

- Requires intact HPO axis. Re-emergence of GnRH secretion → ↑ LH ↑ FSH → gonadal maturation & sex-steroid production.
- 20% pubarche precedes thelarche (esp AA). Avg thelarche → menarche, 2 y.

Sequence of puberty

Sequence	Thelarche →	Pubarche →	PHV →	Menarche
Age* AA	9.5	9.5	10.8	12.1
Age H	9.8	10.3	—	12.2
Age C	10.3	10.5	11.5	12.7

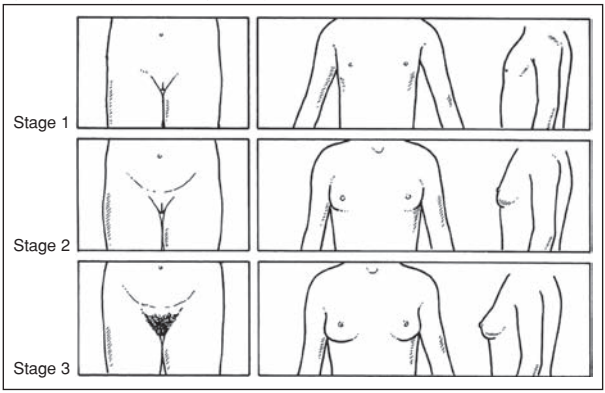
*Mean age in years at indicated stage.
AA, African american; H, Hispanic; C, Caucasian; PHV, Peak hight velocity.
From *J Pediatr* 2006;148:234; *Pediatrics* 2002;110:911; *Stat Med* 1993;12:403.

Tanner stages

Stage	Breast dev	Pubic hair
1	Prepubertal: Papilla elevation only	Prepubertal: No pubic hair
2	Breast bud: Elevation of breast & papilla; enlargement of areola	Sparse, long, slightly pigmented hair on labia majora
3	Further enlargement of breast & areola; no separation of contour	Dark, coarse, curled hair, spreading sparsely over mons
4	Areola & papilla form secondary mound above level of breast	Adult-type hair, abundant, limited to mons
5	Projection of papilla only, recession of areola to contour of breast	Adult-type hair, distribution to the medial thigh

From *Arch Dis Child* 1969;44:291; *J Pediatr* 1985;107:317.

Figure 6.1 Tanner staging, female developmental stages



(*continued*)

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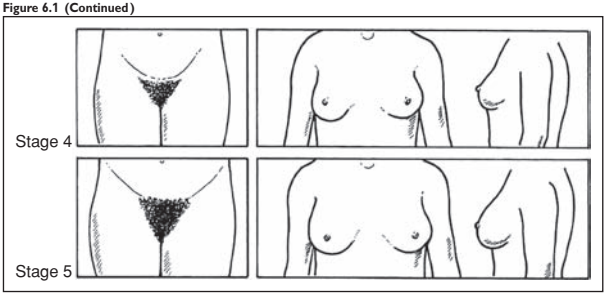
Figure 6.1 (Continued)



Modified From Strasburger VC, Brown RT. *Adolescent Medicine: A Practical Guide*. Boston, MA: Little, Brown & Co.; 1991:4

PRECOCIOUS PUBERTY

Definition (*N Engl J Med* 2008;358:2366)

- Dev of breast or pubic hair >2.5 SD below mean age. Traditional definition <8 yo. Trend of decreasing age of puberty → now <7 yo in C girls, <6 y in AA girls (*Pediatrics* 1997;99:505; *Pediatrics* 1999;104:936).

Initial Workup

- **Hx:** Onset, family members' ages of puberty, h/o neurologic dz or trauma, exposure to sex steroids, headache, sz, abdominal pain
- **PE:** Height, weight, growth chart, Tanner staging, fundoscopic exam (papilledema in ↑ intracranial pres), visual field eval (sellar mass lesion), skin exam.
- **Bone age eval:** Plain film X-ray of left hand & wrist
- **Lab eval:** Basal LH, LH following GnRH stimulation, FSH, estradiol
  LH <0.1 IU/L = premature thelarche or nml
  LH >0.3 IU/L = true precocious puberty
  LH >5 mIU/L = central (gonadotropin-dependent) precocious puberty

Treatment Goals

- Postpone dev until nml pubertal age, maximize adult height, reduce risk of psychosocial problems a/w early sexual maturation

Gonadotropin-*dependent* (Central) Precocious Puberty (GDPP)

- Early maturation of HPO axis → breast & pubic hair dev, w/ usually nml sequence of pubertal events at nml pace, & isosexual (appropriate for gender)
- **Etiology:** Idiopathic – 90%; dx of exclusion. CNS lesions – tumors, irradiation, hydrocephalus, cysts, trauma, inflamm dz, midline developmental defects. Sev hypothyroidism (rare).
- **Dx:** Accelerated linear growth for age (>75% of height at dx), advanced bone age, pubertal levels of FSH, LH, estradiol, & ↑ w/ GnRH stimulation test. MRI in all pts to evaluate for CNS lesion. TFTs if clinical concern for hypothyroidism. Evaluate ↓ growth hormone if h/o cranial irradiation. Abdominopelvic US – repeated exposure to sex steroids from periph sources can induce secondary premature maturation of HPO axis.
- **Rx:** Treat intracranial lesions or hypothyroidism if present. Idiopathic GDPP, treat if:
  sexual maturation progresses to next stage w/i 3–6 mo,
  onset puberty <6 yo,
  growth velocity >6 cm/y,
  Bone age advanced by 1 y or more, or
  predicted adult height below target range or decreasing on serial determinations.
  Long-acting GnRH agonist → prepubertal hormone level, prevents pubertal dev, growth acceleration, & bone advancement (*N Engl J Med* 1981;305:1546). Treat until epiphyses fused or pubertal & chrono ages are appropriately matched.

Gonadotropin-*independent* (Peripheral) Precocious Puberty

- Due to excess exposure of sex steroid hormones from gonads, adrenals, or environment. May be contrasexual or isosexual. Pubertal sequence progression may be altered.
- **Etiology:** Functional ovarian follicular cysts – most common cause, w/ transient breast dev & vaginal bleeding, 1+ unilateral or bilateral ovarian cysts >15 mm, bone age nml. Ovarian tumors (rare) – granulosa cell tumor → isosexual, Leydig cell/gonadoblastoma → contrasexual. Adrenal – androgen-secreting tumors, CAH. McCune–Albright

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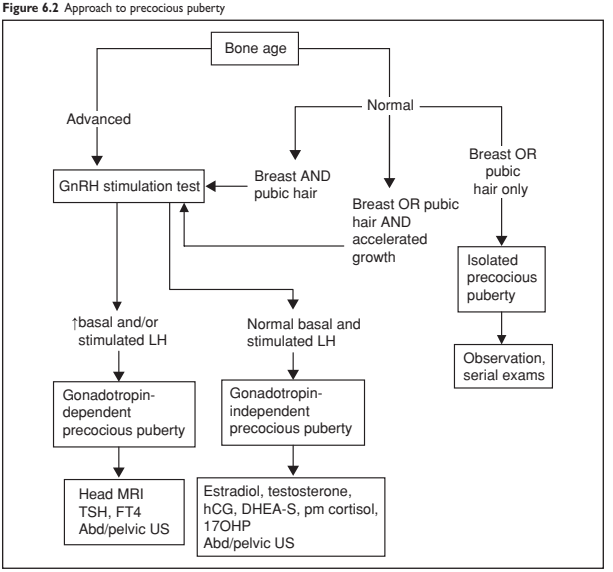
syndrome (rare) – triad of periph precocious puberty, café-au-lait spots, fibrous bone dysplasia → recurrent formation of follicular cysts & cyclic vaginal bleeding.

- **Dx:** Low or nml FSH & LH levels, do not ↑ w/ GnRH stimulation. Labs: Testosterone, estradiol, FSH, afternoon cortisol (screen Cushing syn), DHEA, DHEAS, 17-OHP (screen CAH). Abdominopelvic US for ovarian cyst/tumor.
- **Rxs:** Surgical removal (tumor); tamoxifen for vaginal bleeding, bisphosphonate for bone dysplasia; aromatase inhibs lack long-term effectiveness; exogenous estrogens as cream, ointment, spray (contrasexual); remove exogenous source; for functional cysts → observation, usually self-limited, surgical removal if persistent or torsion; GnRH agonist ineffective for gonadotropin independent.

Isolated Precocious Puberty

- Isolated premature thelarche or adrenarche. Usually benign nml variants. If bone age nml, precocious puberty unlikely.
- Expectant mgmt w/ re-evaluation at 6 mo. ~20% progress to gonadotropin-dependent precocious puberty. Requires regular exams.
- **Isolated premature thelarche:** Unilateral or bilateral, <8 y, absence of other secondary sexual characteristics, nml linear growth, nml bone age. Estradiol level usually prepubertal – girls typically <3 yo, nonobese. Unk cause.
- **Isolated premature adrenarche:** Isolated pubic &/or axillary hair <8 y. Dx: DHEA-S appropriate for pubic hair stage. Girls typically overweight. 17-OHP & testosterone appropriate for age. Bone age & growth rate ↑ but w/i nml limits. Risk factor for PCOS. Further w/u: ACTH stimulation to r/o CAH when bone age advanced, predicted adult height abnormally low, or serum testosterone & DHEA-S elevated – may be only manifestation of mild CAH. Rx: Observation, regular exams to detect other signs of precocious sexual dev.

Figure 6.2 Approach to precocious puberty



(From Fritz MA, Speroff L. *Clinical Gynecologic Endocrinology and Infertility*. Philadelphia, PA: Lippincott Williams & Wilkins; 2011)

DELAYED PUBERTY

Definition (*N Engl J Med* 2012;366:443; *Pediatr Clin North Am* 2011;58:1181)

- Absence of secondary sexual characteristics by age 13 (≥2 SD from mean age), or absence of menses by age 15.

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Etiology (*J Clin Endocrinol Metab* 2002;87:1613)

- 30% const del, 26% hypergonadotropic hypogonadism, 20% permanent hypogonadotropic hypogonadism, 19% transient (functional) hypogonadotropic hypogonadism, 5% other causes.

Clinical Manifestations

- **Hx:** Anorexia, bulimia, excessive exercise, chronic dzs (eg, celiac dz, Crohn dz), radiation, chemo, meds, nutritional status, psychosocial functioning
- **Sx:** Neurologic sx, inability to smell, weight gain or loss, chronic dz
- **FHx:** Relatives w/ delayed puberty, heights of relatives, age of menarche & fertility status of female relatives, relatives w/ genetic abnormalities (CAH, adenocarcinoma in situ (AIS), gonadal dysgenesis), relatives w/ autoimmune dz

Physical Exam

- Height & weight measurements, growth chart, Tanner staging, examine for stigmata of Turner syn, midline facial defects, scoliosis, thyromegaly.
- Arm span greater than height >5 cm sugg delayed epiphyseal closure
- **Neurologic exam:** Optic fundi, cranial nerves, visual fields, sense of smell
- **Pelvic exam:** Clitoral enlargement, hymenal ring patency, degree of vaginal rugation, presence or absence of mucus (indicates degree of estrogen effect)

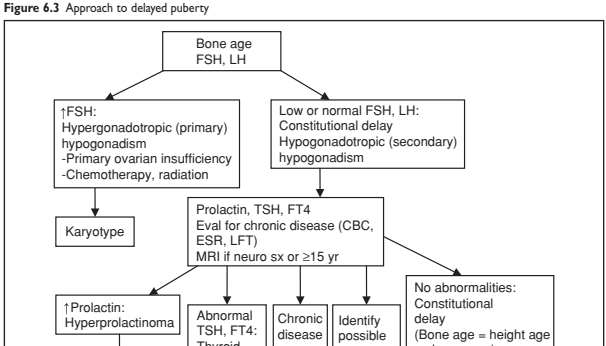
Workup

- Hx, physical exam, bone age, labs (LH, FSH)
  - Elevated FSH/LH = hypergonadotropic hypogonadism
  - Low FSH/LH = hypogonadotropic hypogonadism
- Further w/u if LH, FSH nml:
  - PRL – screen for hyperprolactinemia
  - TSH, FT4 – screen for thyroid dzs
  - MRI – when si/sx CNS lesion present or if indicated by other eval (hyperprolactinemia, Kallmann syn); otherwise may defer until age 15
  - CBC, ESR, LFTs – screen chronic dzs (IBD, liver dz, anorexia)
  - Pelvic US – determine presence/absence uterus if undetermined by physical exam
- Unusually no apparent alternate cause on initial eval – const del likely dx; no test can reliably differentiate const del from hypogonadotropic hypogonadism; therefore, observe, & diagnose isolated hypogonadotropic hypogonadism if endogenous puberty has not begun by age 18; eventual nml progression of puberty confirms const del.

Treatment Goals

- Induce appearance of secondary sexual characteristics or acceleration of growth to mitigate pubertal delay & short stature, & promote nml bone mass
- Predict adult height w/ Bayley-Pinneau tables, although overestimate adult height in const del.

Figure 6.3 Approach to delayed puberty



(From Fritz MA, Speroff L. *Clinical Gynecologic Endocrinology and Infertility*. Philadelphia, PA: Lippincott Williams & Wilkins; 2011)

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Hypergonadotropic (Primary) Hypogonadism

- **Dx:** Elevated LH & FSH due to lack of negative feedback from gonads. Additional w/u: Karyotype, autoimmune dz eval.
- **Etiology:** Primary ovarian insufficiency (idiopathic, resistant ovary syn, autoimmune oophoritis, 17a-hydroxylase deficiency, galactosemia, aromatase deficiency), Gonadal dysgenesis (45,X; 46,XX; 46,XY), radiation, chemo. Special cases:
  Turner syn: 45,X (*Semin Reprod Med* 2011;29:342) – phenotype: Female, short stature, ptosis, low-set ears, micrognathia, short "webbed" neck, broad shield-like chest, hypoplastic areolae, short 4th &/or 5th metacarpals, renal abnormalities (eg, horseshoe kidney), cardiovascular abnormalities (eg, coarct of the aorta). Risk of aortic dissection & rupture (1.5%). "Streak" gonads consist of fibrous tissue w/o germ cells. External female genitalia, uterus, fallopian tubes develop normally until puberty when estrogen-induced maturation fails to occur. Menstruation & Preg may occur in mosaic karyotype (45,X/46,XX). Rx: Growth hormone prior to estrogen initiation.
  Swyer syn: 46,XY complete gonadal dysgenesis. Phenotype: Female, w/ vagina, cervix, uterus, fallopian tubes, & external genitalia. Rx: Requires early gonadectomy due to risk of gonadal tumors.
  Primary ovarian insufficiency: See Chap. 8.

Permanent Hypogonadotropic (Secondary) Hypogonadism

- **Dx:** Low to nml LH & FSH due to hypothalamic or pituitary disorders.
- **Etiology:** GnRH deficiency, CAH, CNS tumors, combined pituitary hormone deficiency, chemo, radiation
  Kallmann syn: Anosmia or hyposmia; 1/50000 females
- **Further w/u:** MRI
- **Rx:** Initial low-dose estrogen titrated to mimic nml puberty to initiate sexual maturation
  After 6–9 mo, cyclic progesterone to induce endometrial shedding
  Transition to combination OCP when breast dev optimized for hormonal replacement
  If fertility desired, pulsatile GnRH or injectable gonadotropin

Transient (Functional) Hypogonadotropic Hypogonadism

- **Dx:** Low LH & FSH due to delayed maturation of HPO axis due to underlying condition
- **Etiology:** Systemic illness (IBD, celiac dz, anorexia nervosa or bulimia, hypothyroidism, hyperprolactinemia, DM, Cushing dz), CNS disorders (tumors [eg, craniopharyngioma, prolactinoma], infxn, trauma), adrenal (Cushing syn, Addison dz), psychosocial (excessive exercise, stress, depression), drugs (marijuana).
- **Rx:** Treat underlying cause (treat dz or modify behavior)
- **Const Del:**
  Dx: Low LH & FSH, HA = bone age < chrono age. Adrenarche & gonadarche often later than avg; isolated hypogonadotropic hypogonadism has adrenarche at nml age.
  Rx: Expectant observation. If puberty has started (clinically or biochemically) & stature not a major concern, reassurance w/ adult height prediction.
  Hormone rx is controversial (goal of preventing developmental psychosocial stress). Use low-dose estrogen until puberty progresses, then stop. Progesterone not needed as similar long period of unopposed estrogen in early puberty. Growth hormone, anabolic steroids, aromatase inhibs not recommended.

AMENORRHEA

Definitions (*Pediatrics* 2006;118:2245; *Obstet Gynecol Clin North Am* 2003;30:287)

- **Primary amenorrhea:** Absence of menstruation by age 13–14 in absence of growth or sexual dev, or age 15–16 in presence of nml growth & sexual dev
- **Secondary amenorrhea:** Absence of menses for ≥3 consecutive menstrual cycles in women w/ previously nml menses

Epidemiology

- Primary amenorrhea 1–2% prevalence in US. Amenorrhea not caused by Preg ≤5% prevalence during menstrual lives. Most common causes of primary amenorrhea: Ovarian failure (48.5%), Müllerian agenesis (16.2%), gonadotropin deficiency (8.3%), constitutional delay (6%) (*Am J Obstet Gynecol* 1981;140:372).

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History

- **Hx:** Stress, change in weight, diet, exercise, sugg functional hypothalamic etiology
  - New meds – evaluate for hyperprolactinemia due to meds
  - New illnesses – sugg chronic illness etiology
  - Acne, hirsutism, deepening of voice – sugg hyperandrogenism: PCOS or adrenal etiology
  - Headache, visual field defects, fatigue, polyuria, polydipsia – sugg CNS lesion
  - Hot flashes, vaginal dryness, poor sleep, decreased libido – sugg primary ovarian insufficiency
  - Galactorrhea – sugg hyperprolactinemia
  - H/o postpartum hemorrhage, D&C, endometritis – sugg Asherman or Sheehan syn

Physical Exam

- Height, weight (BMI <18.5 at risk for functional hypothalamic amenorrhea; BMI >30 in ~50% pt w/ PCOS.
- Tanner staging if primary amenorrhea. Assess estrogen status: Adequate if breasts present, moist & rugated vaginal mucosa, abundant cervical mucus.
- Assess for presence of uterus, cervix, or signs of obstructed tract.
- Assess for signs of excessive testosterone: Hirsutism, acne, acanthosis nigricans
- Evaluate for galactorrhea
- Parotid gland swelling &/or erosion of dental enamel sugg bulimia nervosa
- Evaluate for stigmata of Turner syn.

Initial Workup

- History & physical exam. Lab: Urine hCG, TSH, FSH, PRL (↑ by stress, sleep, intercourse, meals, nipple stimulation). If signs of hyperandrogenism: Testosterone, ± 17-OHP (CAH), DHEA-S (adrenal etiology).
- **Progesterone challenge test:** Determine if adequate estrogen present, competent endometrium, patent outflow. Medroxyprogesterone acetate 10 mg PO daily for 7–10 d.
- Withdrawal bleed expected w/i 2–7 d of stopping progesterone:
  - **+ bleed:** Nml estrogen production & ovarian fxn
  - **– bleed:** Hypoestrogenic or anatomic outflow tract obst

Etiologies of amenorrhea	
Anatomic defects: Lack of uterus or obstructed outflow 20% of 1° amenorrhea 5% of 2° amenorrhea	Imperf hymen Transverse vaginal septum Müllerian anomalies AIS Cervical stenosis Asherman syn
Ovarian dysfxn: Ovarian follicles depleted or resistant to stimulation by FSH & LH 50% of 1° amenorrhea 40% of 2° amenorrhea	Primary ovarian insufficiency (premature ovarian failure) Idiopathic Resistant ovary Chemo, radiation Gonadal dysgenesis Turner syn (45,X) X chromo long-arm deletion (46,XXq5) 46,XX; 46,XY (Swyer syn) Gonadal agenesis Autoimmune oophoritis/ovarian failure
Pituitary: Abn FSH/LH production 5% of 1° amenorrhea 19% of 2° amenorrhea	Prolactinoma Other pituitary tumors: Corticotroph adenoma Other tumors: Meningioma, germinoma, glioma Empty sella syn Infarction (Sheehan syn) Radiation Infiltrative lesions: Hemochromatosis, hystiocytosis

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Hypothalamic: Disruption of pulsatile release of GnRH 20% of 1° amenorrhea 35% of 2° amenorrhea	GnRH deficiency: Congen, Kallmann syn Functional hypothalamic amenorrhea: Weight loss, excessive exercise, obesity, stress Drugs: Marijuana, tranquilizers Psychogenic: Anxiety, pseudocyesis, anorexia Neoplastic: Craniopharyngioma, hamartoma, germinoma, teratoma, metastases Brain injury, irradiation Infxn: TB, syphilis, sarcoidosis, meningitis Infiltrative dzs: Histiocytosis, hemochromatosis Chronic medical illness
Other endocrinopathies	Hypothyroidism, hyperthyroidism Cushing syn Late-onset adrenal hyperplasia DM Exogenous androgen use
Multifactorial	PCOS

From Practice Committee of American Society for Reproductive Medicine. Current evaluation of amenorrhea. *Fertil Steril.* 2008;90(5 suppl):S219.

Congenital Anatomic Lesions

- Menses cannot occur w/o an intact uterus, endometrium, cervix, vaginal conduit. Clinical manifestations: Cyclic pelvic &/or lower abdominal pain from accum & subseq dilation of vaginal vault &/or uterus by menstrual bld.
- **Imperf hymen:** Bulging membrane just inside the vagina, often purple-red discoloration.
- **Transverse vaginal septum:** Occurs at any level btw hymenal ring & cervix; absence of bulging hymen as septum much thicker.
- **Vaginal agenesis:** See Chap. 8.
- **Rx:** Surgical correction

Asherman Syndrome *(Semin Reprod Med* 2011;29:83)

- Acq scarring of the endometrial lining, usually secondary to postpartum hemorrhage or endometrial infxn followed by dilation & aggressive curettage. Prevents nml buildup & shedding of endometrial cells → very light or absent menses.
- HSG shows uterine filling defects. No withdrawal bleed following estrogen & progesterone. Hysteroscopic eval demonstrates uterine synechiae.
- **Rx:** Surgical lysis of adhesions by hysteroscopy. Estrogen postoperatively to help promote endometrial regeneration.

Primary Ovarian Insufficiency (Premature Ovarian Failure)

See Chap. 8.

Hyperprolactinemia *(Curr Opin Obstet Gynecol* 2004;16:331; *J Reprod Med* 1999;44:1075)

- **Etiology:** Hypothyroidism, PRL-secreting pituitary adenomas (20% secondary amenorrhea), pituitary or hypothalamic tumors, meds (amphetamines, benzodiazepines, metoclopramide, methyldopa, opiates, phenothiazines, reserpine, tricyclic antidepressants, SSRIs). Occurs due to dopamine receptor antagonism.
- **Clinical manifestations:** ± galactorrhea.
- **Dx:** Elevated serum PRL; r/o hyperthyroidism. Further w/u: MRI to evaluate for pituitary tumor if persistent ↑ PRL or >100 ng/mL
- **Rx:** Dopamine agonist (bromocriptine or cabergoline) or transsphenoidal resxn of CNS lesion.

Sheehan Syndrome

- Acute infarction & ischemic necrosis of pituitary gland from postpartum hemorrhage & hypovolemic HoTN. More common in low resource settings.
- **Clinical manifestations:** Failed postpartum lactation, fatigue, weight loss, loss of sexual hair

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- **Dx:** Hx, growth hormone, LH, FSH, PRL, ACTH, TSH deficiencies.

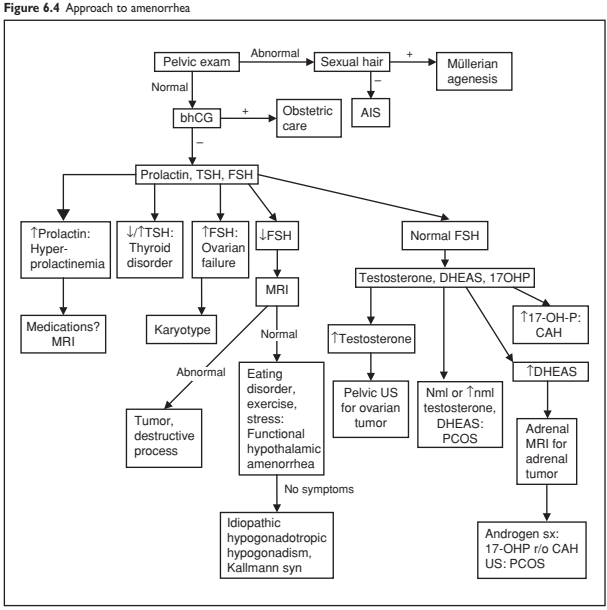
Functional Hypothalamic Amenorrhea *(N Engl J Med 2010;363:365)*

- Abn GnRH pulses → decreased gonadotropin pulsations → low/nml serum LH concentrations → absent LH surge → absence of follicular dev, anovulation, low estradiol.
- **Etiology:** Stress, weight change, decreased nutrition, excessive exercise, anorexia nervosa or bulimia, chronic dz (DM, ESRD, malig, AIDS, IBD), isolated gonadotropin deficiency (congen, Kallmann syn), Sheehan syn.
- **W/u:** MRI for CNS/hypothalamic/pituitary dz.
- **Rx:** Behavior modification if indicated, treat chronic dz, hormonal therapy to prevent bone loss, ovulation induction w/ clomiphene citrate, gonadotropin injection, pulsatile GnRH.

Polycystic Ovarian Syndrome (PCOS)

See Chap. 8.

Figure 6.4 Approach to amenorrhea



(From Fritz MA, Speroff L. *Clinical Gynecologic Endocrinology and Infertility*. Philadelphia, PA: Lippincott Williams & Wilkins; 2011)

ANDROGEN INSENSITIVITY SYNDROME

Definition and Epidemiology *(J Pediatrc Surg 2005;40:133; J Clin Endocrinol Metab 2001;86:4151)*

- Male pseudohermaphroditism from muts in AR & decreased end organ sens. 1.1% incid of CAIS in a premenarcheal child w/ inguinal hernias.
- 1 in 20000–99000 genetic males

Etiology

- 70% of AR muts are X-linked recessive leading to decreased resp to androgens; 30% de novo sporadic muts. Multi syns.

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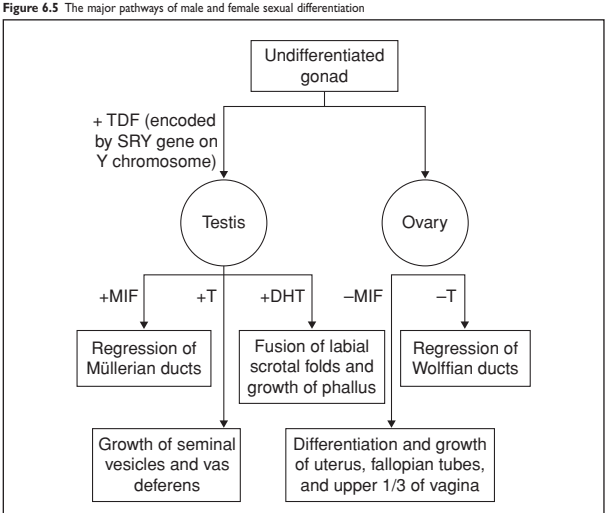
Androgen abnormality/insensitivity syndromes					
	Complete	**Incomplete**	**Reifenstein**	**Infertile**	**5α-reductase**
Inheritance pattern	X-linked recessive	X-linked recessive	X-linked recessive	X-linked recessive	Autosomal recessive
Spermatogenesis	—	—	—	↓	↓
Müllerian structures	—	—	—	—	—
Wolffian structures	—	♂	♂	♂	♂
External genitalia	♀	♀ – clitoromegaly Partial labioscrotal fusion	♂ – hypospadias	♂	♀
Breasts	♀	♀	Gynecomastia	Gynecomastia	♂

From Griffin JE. Androgen resistance—the clinical and molecular spectrum. *N Eng J Med* 1992;326:611–618; Kim HH, Laufer MR. Developmental abnormalities of the female reproductive tract. *Curr Opin Obstet Gynecol* 1994;6:518–525.

Pathophysiology

- Nml male dev only occur if adequate androgen production acting on target tissues (sex differentiation). Muts in AR leads to a defective resp to androgens at all stages of dev. Production of testosterone occurs at ~8–16 w via placental hCG; after 16 w, fetal LH controls circulating androgens.
- Testosterone (produced by Leydig cells in testes) is responsible for Wolffian dev & formation of the epididymis, vas deferens, & seminal vesicles. DHT is responsible for formation of male external genitalia & fusion of labioscrotal folds. Androgens control descent of testes into scrotum → in AIS, testes remain in pelvis.
- Androgens → secondary male sex characteristics at puberty (axillary & pubic hair) & spermatogenesis. MIS is produced normally by Sertoli cells in testes causing regression of Müllerian ducts → no uterus, oviducts, & upper vagina.

Figure 6.5 The major pathways of male and female sexual differentiation



TDF, testis-determining factor; MIF, Müllerian inhibitory factor; T, testosterone (From Ostrer H. Genetics of Sexual Differentiation. Glob. libr. women's med., (ISSN: 1756–2228) 2008. doi:10.3843/GLOWM.10347)

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Clinical Manifestations

- Karyotype 46XY
- Male pseudohermaphroditism: Variety of phenotypes ranging from male infertility to nml female external genitalia. May present w/ ambiguous genitalia or infantile male genitalia. + MIS → short vagina, absent uterus & cervix.
- Primary amenorrhea/infertility
- **CAIS:** No activity at the AR → nml female phenotype. Nml breast dev w/ pale areola (estrogens produced by testes & circulating androgens fail to antagonize estrogens). Sparse or absent pubic & axillary hair (vellus hair only, if present). Nml or slightly advanced height, however decreased bone density. 50% w/ inguinal hernias: Gonads (testes) intra-abdominal or in the inguinal rings. Serum testosterone in the range of pubertal male. No issues regarding gender identity or sexual preference given they are not exposed to male androgen levels → brain dev along w/ physical dev is female.
- **PAIS:** Varying degrees of female virilization or male feminization due to differing degrees of AR activity. Labial fusion, bifid scrotum, hypospadias, micropenis, &/or clitromegaly. Blind vas deferens. Testes in labioscrotal folds. Nml breasts & pubic & axillary hair. Higher rates of bisexuality, homosexuality, & gender identity d/o.
- **Mild AIS:** Phenotypic & genotypic males. Male infertility (oligospermia w/ nml T & LH). Gynecomastia in young men. Minor hypospadias.

Physical Exam

- Female infant or toddler w/ an inguinal hernia → attempt to pass a sterile Q-tip into vagina (consider exam under anesthesia in toddlers). Consider karyotype.
- Adol → full physical exam (note breast dev, pubic & axillary hair, & external genitalia including hymenal anatomy), rectal exam to r/o lower vaginal obst.

Diagnostic Workup/Studies

- **CAIS:** ↑T & ↑ LH. Diff:
  - MRKH syn or Müllerian agenesis; distinguish by karyotype; XX genetic females; nml testosterone; presence of pubic & axillary hair (absent in CAIS)
  - Swyer syn = XY complete gonadal dysgenesis. No breast dev & short stature; XY genetic males.
- **PAIS:** Nml T & ↑ LH (*Clin Endocrinol Metab* 2006;20:577), MRI (gold std) or pelvic US to document internal anatomy, localize testes, r/o testicular tumors, karyotype, genetic counseling for parents.
  - Differential diagnoses (DDx)
  - Partial gonadal dysgenesis
  - 17β-hydroxysteroid dehydrogenase deficiency
  - 5α-reductase deficiency
  - Mixed gonadal dysgenesis w/ mosaic Turner syn (45XO/46XY)
  - Defect in LH receptor

Treatment

- Prophylactic gonadectomy in CAIS b/c of ↑ rate of malig degeneration & formation of dysgerminomas/gonadoblastomas after pubertal dev, then estrogen replacement
- Incid of 0.5% malig in CAIS, 5.5% in overall AIS pop; as high as 50% in PAIS if gonads in nonscrotal position (intra-abdominal location inc risk for malig). If dx prior to puberty, serial US monitoring for pelvic masses (*Acta Endocrinol* 1990;123416; *Int J Gynecol Pathol* 1991;10:126; *J Clin Endocrinol Metab* 2005;90:5295)
  - Rate of malig in pts w/ AIS prior to puberty is 0.8% (CAIS) & 5.5% (overall) (*Endocrine Rev* 2006;27:468; *J Pathol* 2006;208:518)
- Hormone replacement
  - CAIS → estrogen replacement during late adolescence/early adulthood to aid final Tanner 5 breast dev, help build bone, Vit D, regular weight-bearing exercise; DEXA or bisphosphonates prn
  - PAIS → large doses of androgens to promote phallic growth
- ± vaginal dilators for increased vaginal length; d/c once regular vaginal intercourse
- ± genital reconstructive Surg when pt voices desire to proceed
- Multidisciplinary support including a mental health provider, social worker, geneticist

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CONGENITAL ADRENAL HYPERPLASIA (CAH)

Definition and Epidemiology

- Autosomal recessive disorders of cortisol &/or aldosterone biosynthesis, result in **cortisol deficiency, ± aldosterone deficiency, & androgen excess.** There are two forms:
- **Classic CAH** (sev form, 1/15–16000 live births)
  (a) salt wasting (67%)
  (b) nonsalt losing (simple virilizing; 33%)
- **NCAH** (mild or late onset); asymptomatic or postnatal

Pathology & Pathophysiology

- Caused by a mut in cortisol producing enzymes.
- ↑ corticotrophin → adrenal hyperplasia
- ↑ cortisol precursors which are diverted to the biosynthesis of sex hormones → androgen excess → ambiguous genitalia in newborn girls, rapid postnatal growth in both sexes
- Aldosterone deficiency → salt wasting → FTT, hyponatremic hypovolemia, shock
- HyperK
  Classic CAH – abn cortisol, sex hormone, ± aldosterone production
  NCAH – nml cortisol & aldosterone, but mild to mod ↑ sex hormones
- **Muts:**
  CYP21 (CYP21A2; 95% of cases; codes for adrenal 21-hydroxylase) → *CYP21* mut → **21-hydroxylase deficiency** → inadeq cortisol synthesis → inadeq negative feedback to hypothalamus & pituitary → increased ACTH secretion → adrenal gland hyperplasia. Adrenal steroids are converted to adrenal androgens.
  CYP11B1 mut → **11β-hydroxylase deficiency** → ↑ 11-deoxycortisol & 11-deoxycorticosterone → salt retention → hypervolemia, HTN.
  HSD3B2 mut → 3β-hydroxysteroid dehydrogenase deficiency → sev adrenal insufficiency, ↑ ACTH → ↑ pregnenolone, 17-hydroxypregnenolone, & DHEA → mild virilization, ± salt wasting.

Clinical Manifestations

- Salt-losing adrenal crisis in neonat period for 3/4ths newborns w/ classic CAH.
- **46 XX female pseudohermaphroditism:** Nml uterus, fallopian tubes & ovaries but varying levels of ambiguous genitalia depending on degree & type of enzyme deficiency
- **Ambiguous genitalia:** Classic CAH – newborn ambiguous genitalia (clitoral hypertrophy, labioscrotal fusion – partial or complete, common urogenital sinus). Boys have no overt sx except hyperpigmentation & penile enlargement. NCAH – presents in adolescence; rapid growth, premature pubic or axillary hair, hirsutism.
- **Hyperandrogenism:** Hirsutism, acne, oligomenorrhea/amenorrhea, polycystic ovaries, precocious puberty.
- **Infertility:** 80% women w/ simple virilizing & 60% women w/ salt-wasting CAH are fertile. (*Endocrinol Metab Clin North Am* 2001;30:207)
- Metabolic syn/insulin resistance/obesity
- **Short stature:** Untreated, long-term sex hormone exposure leads to advanced skeletal age & premature epiphyseal fusion. Mean adult height = 10 cm below nml pop.
- Issues of gender & sexuality (*Endocrinol Metab Clin North Am* 2001;30:155)
- Iatrogenic Cushing syn

Workup

- **Serum electrolytes, aldosterone, & plasma renin:** HyperK, ↓ aldosterone, hyperreninemia (use age-specific reference for renin).
- **Random 17-OHP:** >242 nmol/L (nml 3 nmol/L) at 3 d in full-term infants. False positives in premature infants. Use weight & gestational age–based reference ranges.
- **Corticotrophin-stimulation test:** 250 μg cosyntropin followed by measurement of 17-OHP 60 min later. 17-OHP level >10 ng/mL (30.3 nmol/L)
- **Early morning (before 0800 h) 17-OHP:** >2.5 nmol/L in children & >6 nmol/L in women during follicular phase r/o NCAH
- Genetic analysis, neonat screening or gene-specific prenatal dx

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Treatment

- **Glucocorticoids** (short acting in children to avoid growth suppression). Stress dosing during febrile illness, Surg, trauma, etc. (Double or triple daily dose.)
  Hydrocortisone 12–18 mg/m^2 divided into 2 or 3 doses. Longer-acting glucocorticoids can be used in adults.
  Prednisone 5–7.5 mg QD in 2 doses or *dexamethasone* 0.25–0.50 mg QHS. Good in Preg (does not cross the placenta). Goal early morning 17-OHP 12–36 nmol/L.
- Mineralocorticoides
- **Fludrocortisone** 100–200 μg QD; adjust to maintain plasma rennin in midnormal range
- NaCl suppl (salt-losing CAH) 1st 6–12 mo of life
- Infertility → ovulation induction
- Hirsutism → antiandrogens (w/ OCPs as antiandrogens are teratogens)
- **Prenatal rx:** Mat dexamethasone suppresses fetal HPA axis & ↓ genital ambiguity
  Start prior to 8 w of gest when masculinization of external genitalia begins
  CVS or amniocentesis for gender, if male or unaffected female → d/c steroids
  85% of prenatally treated female infants are born w/ nml or slightly virilized genitalia
- **Neonat rx:** Hydrocortisone dose ≤25 mg/m^2 QD. Monit weight, length, adrenal steroid conc, plasma renin, & electrolytes.
- **Surgical mgmt of ambiguous genitalia** (controversial): Age 2–6 mo in virilized girls; technically easier than at later ages (std of care) vs. later ages when psychosexual identity is established.

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PHYSIOLOGY AND MECHANISMS OF MICTURITION

Innervation of Bladder and Urethra (*Nature Rev Neurosci* 2008;9:453)

Control of micturition					
Target	**Effect**	**Nerve**	**Type**	**Transmitter**	**Receptor**
Bladder (detrusor)	Contraction/ voiding	Pelvic plexus efferents (S2–4)	Parasymp	ACh	M3 muscarinic
	Relaxation/ filling	Hypogastric (T11–L2)	Symp	NE	β3-adrenergic
Urethral sphincter	Contraction/ filling	Hypogastric	Symp	NE	α1-adrenergic
External urethral sphincter	Contraction/ voluntary retention	Pudendal (S2–4)	Somatic	ACh	Nicotinic cholinergic

- **CNS involvement (pontine micturition center)** – afferent signal through spinothalamic tracts & dorsal columns → intensity of signal reaches threshold of consciousness triggering void when socially acceptable → efferent signal through reticulospinal & corticospinal tracts

PHYSIOLOGY AND MECHANISMS OF DEFECATION

Anatomy

- EAS – striated muscle innervated by **hemorrhoidal branch** of pudendal nerve, voluntary squeeze
- IAS – continuation of smooth circular muscle of rectum under autonomic control, constant contraction contributes **70–80%** of resting anal tone
- Levator ani complex – defines prox border of anal canal – PR muscle – striated musc sling originating from pubic bone supporting the rectum, innervated via direct branches from **S3, S4,** & pudendal nerve, constant tone at rest creates the **anorectal angle (~90°)**

Mechanism of Normal Defecation

- Rectum acts as reservoir → receptors in PR sense distention → IAS reflexively relaxes to sample contents & then contracts RAIR → voluntary relaxation of pelvic floor (PR) & EAS straightens anorectal angle by >15° & allows passage of contents

PELVIC ORGAN PROLAPSE (POP)

Definitions

- Loss of support of the anter, apical, or post compartments of the vagina that result in protrusion of pelvic organs into or out of the vaginal canal (bladder, rectum, small bowel, sigmoid, colon, or uterus/cervix).
- **Anter:** Cystocele: Prolapse of bladder into the vagina
- **Apical:** Uterine prolapse: Prolapse of uterus & cervix into the vagina or vaginal vault prolapse: Prolapse of the vaginal vault or cuff after hysterectomy
- **Post:** Rectocele: Prolapse of rectum into the vagina

Epidemiology (*Obstet Gynecol* 1997;89:501)

- Risk of POP requiring Surg by the age of 80 is ~11%
- POP is the 3rd most common indication for hysterectomy following leiomyomata & endometriosis

Pathophysiology (*Cochrane Database Syst Rev* 2010;4:3)

- Risk factors – Preg, childbirth, congen or Acq connective tissue abnormalities, denervation or weakness of the pelvic floor, aging, hysterectomy, menopause & factors a/w chronically raised intra-abdominal pres, & race (Black & Asian w/ lowest risk, Hispanic w/ highest risk)

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- 3 levels of support of the vagina (*Am J Obstet Gynecol* 1992;166:1717)
  - **Level I:** Apical & uterine support comprised of cardinal & uterosacral ligament attachment to the cervix & upper vagina → defects in this support complex may lead to apical prolapse
  - **Level II:** Lateral support of the vagina including paravaginal attachments (pubocervical fascia & arcus tendineus fasciae pelvis) contiguous w/ the cardinal/uterosacral complex at the ischial spine → defects in this support may lead to lateral, paravaginal, & anter wall prolapse
  - **Level III:** Support of distal 3rd of the vagina comprised of perineal body, superficial & deep perineal muscles, & fibromuscular connective tissue → defects in this support may lead to anter & post vaginal wall prolapse, gaping introitus, & perineal descent

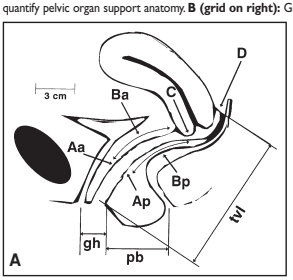
Clinical Manifestations

- **Assoc sx** (Note: Many women may be asymptomatic):
  Bulge, pelvic heaviness, backache, urinary incontinence, frequency or urgency, difficulty in initiating & maintaining urinary flow, incomplete emptying, sexual dysfxn, incontinence of stool or flatus, constip, or need for splinting
- **Physical exam:**
  Perform a full physical exam to determine pathology outside of the pelvis
  Vaginal exam:
  Routine external & bimanual exam while in lithotomy position
  Elicit bulbocavernosus reflex & anal wink reflex to determine if sacral pathways are nml
  Ask the pt to Valsalva while gently spreading the labia to determine overall prolapse
  Inspect each compartment of the vagina separately w/ the pt performing max Valsalva. Use 1 blade of the speculum to assist in visualizing the anter or post compartment individually. During assessment determine the location & degree of prolapse relative to the hymenal ring.
  Perform a rectovaginal exam to assess post wall defects, enterocele, & determine anal sphincter strength
  A PVR by catheterized specimen will help determine adequate emptying. Will also provide opportunity for urinalysis.

Pelvic Organ Prolapse Quantification (POP-Q)

- Provides an objective site-specific system for determining location & staging of POP w/ the hymen as the fixed point of reference
- Negative numbers indicate support above the hymen where a positive value indicates prolapse beyond the hymen

Figure 7.1 A (diagram on left): POP-Q. There are site points labeled Aa, Ba, C, D, Bp, and Ap that correspond to points above or below the hymenal remnants and are stated in centimeters above (negative) or below (positive) that point. The genital hiatus (gh), perineal body (pb), and total vaginal length (tvl) are also listed as lengths in centimeters. They are used to quantify pelvic organ support anatomy. **B (grid on right):** Grid for recording quantitative description of pelvic organ support



anterior wall **Aa**	anterior wall **Ba**	cervix or cuff **C**
genital hiatus **gh**	perineal body **pb**	total vaginal length **tvl**
posterior wall **Ap**	posterior wall **Bp**	posterior fornix **D**

B

(From Bump RC, Mattiasson A, Bø K, et al. The standardization of terminology of female pelvic organ prolapse and pelvic floor dysfunction. *Am J Obstet Gynecol* 1996;175:10)

Stages of Prolapse

- **Stage 0:** No prolapse is demonstrated
- **Stage I:** Most dependent portion of prolapse is >1 cm above the hymen
- **Stage II:** Most dependent portion of prolapse is ≤1 cm prox or distal to the hymen

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- **Stage III:** Most dependent portion of prolapse is >1 cm below the hymen but extends no further than 2 cm ≤TVL – 2 cm
- **Stage IV:** >TVL – 2 cm

Diagnostic Workup/Studies

- Physical exam is generally suff to determine type & stage of prolapse
- Urodynamic studies may be useful to determine occult urinary incontinence

Treatment: Nonsurgical Management

- Assurance & observation
- Pelvic floor muscle exercises (Kegel exercises)
  Minimal risk & low cost, but no high-quality evid supporting prevention or rx of prolapse
- Pessary
  Indications – poor operative candidate, desire to avoid Surg, used as diagnostic tool to determine if urinary incontinence resolves w/ restoration of anatomy
  Continuation rate 50–80% after 1 y of use (*Int Urogynecol J* 2011;22:637)

Treatment: Surgical Management

- **Apical support** (uterine or vault prolapse):
  Sacrocolpopexy: Mesh (typically polypropylene) suspension of the vagina or uterus to the anter longitudinal ligament of sacrum via abdominal, laparoscopic, or robotic-assisted approach
  Risks: Mesh erosion 2–11% (*Obstet Gynecol* 2004;104:805), GI complications including SBO, other abdominal surgical complications, de novo stress incontinence, thus need to consider concomitant anti-incontinence procedure (*NEJM* 2006;354:1557)
  Sacrocolpoperineopexy: Same technique as above, w/ addition of post arm of mesh extending to the perineal body
  Uterosacral ligament suspension: Suspension of the vaginal cuff after hysterectomy to the bilateral uterosacral ligaments at the level of the ischial spines
  Risks: Ureteral obst up to 11% (cystoscopy recommended)
  Sacrospinous ligament fixation: Suspension of the vaginal apex to the sacrospinous ligament either unilaterally or bilaterally, typically using an extraperitoneal approach
  Risks: Anter prolapse rate 6–28%, pudendal & inferior gluteal vessels & nerves lie behind the sacrospinous ligament & may be injured during procedure causing hemorrhage or postop gluteal pain
  Iliococcygeal suspension: Attaches the vaginal apex to the fascia of the iliococcygeus muscles bilaterally
  Risks: No randomized trials that support the use of this procedure & may shorten vagina
- **Anter compartment defect:**
  Anter colporrhaphy: Midline plication of endopelvic fibromuscularis of the anter vagina w/ removal of excess vaginal mucosa, ± graft reinforcement
  Benefits: Easy to perform
  Risks: Only 50% anatomic cure
  Paravaginal repair: Same as above w/ addition of lateral dissection to the arcus tendineus or obturator fascia w/ reinforcement sutures placed in these structures. Can be performed by laparoscopic, vaginal, or abdominal approaches.
- **Post compartment defect:**
  Post colporrhaphy: Midline plication of the rectovaginal fibromuscularis in the post vagina w/ removal of excess vaginal mucosa
  Benefits: Cure rate is 76–96%
  Risks: Excessive removal of vaginal mucosa can result in vaginal narrowing & dyspareunia, 25% rate of postsurgical dyspareunia alone
  Site-specific repair: Identification of isolated defects in the rectovaginal fibromuscularis & subseq repair
- **Obliterative procedures in nonsexually active individuals:**
  Complete colpocleisis – removal of vaginal epithelium w/ suturing of the anter & post vaginal walls together, thus obliterating the vaginal lumen & effectively closing the vagina.
  LeFort colpocleisis – partial excision of the anter & post vagina w/ closure of the vaginal lumen distal to the cervix (uterus in situ), lateral tracts left patent to allow for egress of cervical & vaginal mucus or discharge
- **Mesh augmentation & mesh kit procedures:**
  Biologic: Autologous (self), allograft (donor), or xenograft (porcine/bovine)

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Synthetic: Types I–IV based on pore size, type I monofilament most used due to large pore size & decreased rates of infxn

Mesh kits: Various types of kits: There is an FDA warning about the increased risk of complications including mesh erosion, GI involvement, pain, & need for reoperation. ACOG recommends vaginal mesh be reserved for high-risk pts including those w/ recurrent prolapse &/or medical comorbidities precluding a lengthier Surg (*Obstet Gynecol* 2011;118:1459–1464).

URINARY INCONTINENCE

Definition

- **Involuntary leakage of urine:**
  - **Stress urinary incontinence (SUI):** Complaints of involuntary leakage of urine w/ cough, sneezing, or exertional maneuvers that ↑ abdominal pres
  - **Urge urinary incontinence (UUI):** Complaints of involuntary leakage of urine w/ sensation of urgency, often referred to as OAB
  - **Mixed urinary incontinence (MUI):** Combination of both SUI & UUI
  - **Continuous urinary incontinence:** Complaint of continuous leakage
  - **Overflow incontinence:** Complaint of involuntary loss of urine preceded by an inability to empty the bladder (a/w overdistention & urinary retention due to obst or neurologic causes)

Epidemiology

- Prevalence of 25–55% in Western countries
- May be as high as 50% in nursing home pts & 40% in postmenopausal women
- Many women will not address this issue w/ their physicians due to embarrassment. May lead to signif impairment in QOL

Etiology

- Age, childbearing, obesity, medical diagnoses (diabetes, stroke, spinal cord injury)
- Hysterectomy & menopause w/ inconsistent results

Pathophysiology (*N Engl J Med* 1985;313:800; *Obstet Gynecol* 2005;105:1533)

- Impairment in the physiologic voiding mech
- Functional incontinence – incontinence occurring b/c of factors unrelated to the physiologic voiding mech
  Remember mnemonic **DIAPPERS** (**D**elirium, **I**nfxn, **A**trophic urethritis & vaginitis, **P**harmacologic [diuretics, sedatives, anticholinergics, CCB, α blockers], **P**sychologic [depression], **E**ndocrine [calcium, gluc], **R**estricted mobility, **S**tool impaction)
- Genitourinary etiologies include filling & storage disorders (SUI, UUI, MUI), fistulae (vesicovaginal, ureterovaginal, or urethrovaginal), congen (ectopic ureter, epispadias)

Clinical Manifestations

- **Hx:** Provides the most insight to cause, type, & rx. Include the following: Voiding frequency, noctural voiding frequency, number of episodes of incontinence & vol a/w episodes, number of pads used, bowel incontinence, bulge sx, diet (including caffeine & EtOH intake), medical & surgical hx, obstetrical & gynecologic hx, neurologic conditions (diabetes, multi sclerosis, disk dz, & stroke), pulm conditions, smoking, & meds
- Consider having the pt keep a voiding diary over 3–7 d
- **Physical exam:** Complete full physical exam including gynecologic, rectal, & genital/lower neurologic exam. Include POP-Q (see POP section)
- **Urethral mobility:** May be assessed w/ the *Q-tip test* & helps aid in the dx of stress incontinence
  A Q-tip is placed in the urethra to the level of the vesical neck & assessment of the change of axis is performed while asking the pt to Valsalva.
  An angle of >30° is indicative of urethral hypermobility
- Cough stress test
- PVR to determine if urinary retention an issue <50 mL adequate bladder emptying, >200 mL considered inadeq.

Initial Workup

- **Lab test:** Clean midstream or catheterized urine sample for **urinalysis** & **culture prn.** Bld testing including BUN, Cr, gluc, & calcium

Subsequent Workup

- **Urodynamic testing:** A test that evaluates stress incontinence, detrusor instability, 1st sensation, desire to void, bladder compliance, & bladder capacity

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Recommended in the following circumstances: (1) dx unclear, (2) Surg being considered, (3) marked POP present which may have underlying de novo incontinence, or (4) a neurologic condition exists.

Measurements:

Uroflowmetry: Assesses ability to empty bladder, meter assesses flow rate

Filling cystometry: Measures detrusor fxn including sensation, compliance, capacity, & evid of uninhibited detrusor contractions Pres catheters are placed in the bladder & vagina or rectum while the bladder is retrofilled. Detrusor activity is determined by Pves (pres in bladder) – Pabd (pres in abd, measured by vaginal/rectal catheter). Individual measurements are recorded throughout the tracing including *LPP, 1st desire & maximal bladder capacity* → ISD – Valsalva LPP <60 cm H_2O

Urethral pres profile: Evaluate for ISD, dual sensor catheter is used to determine *MUCP* & *functional urethral length* → **ISD** – MUCP is 20 cm H_2O or less

- **Cystourethroscopy:** May be req for eval of microscopic hematuria, irritative voiding sx w/o evid of infxn & persistent hematuria in women >50 yo, or suspicion of suburethral mass

Treatment

- **Behavioral approaches:**

Lifestyle modification: Weight loss, caffeine, EtOH, or fluid intake reduction, decreased weight bearing, smoking cessation, & constip relief, "bladder diet"

Bladder training: May aid in UUI & MUI

Kegel exercises: Strengthen the voluntary periurethral & perivaginal muscles, may be augmented w/ biofeedback training or electrostimulation via a pelvic floor physical therapist

- **Medical management:**

Estrogen may ↑ urethral bld flow, α-adrenergic receptor sens, & build collagen but is not proven to help in incontinence & some trials suggest incontinence may be worsened

Antichol medication is often used for UUI or MUI

- **Nonsurgical rx:**

Incontinence pessary: Help w/ SUI during exercise-need fitting

Urethral plugs: Help w/ SUI during exercise-need fitting

- **Surgical rx:**

See sections under stress & detrusor instability

OVERACTIVE BLADDER AND URGE INCONTINENCE

Treatment

- **Medical management** generally involves antichol or antimuscarinic meds

Antichol may be best for MUI

Side effects of anticholinergics include dry mouth, constip, blurry vision (contraindicated in pts w/ narrow-angle glaucoma)

Medications for mixed or urge incontinence

Name	Drug type	Dosage
Oxybutynin (Ditropan)	Antimuscarinic	2.5–5 mg PO TID
Oxybutynin ER (Ditropan XL)	Antimuscarinic	5–10 mg PO daily
Oxybutynin patch (Gelnique)	Antimuscarinic	1 patch 5 mg twice weekly
Tolterodine (Detrol/Detrol LA)	M_3 – selective antimuscarinic	1–2 mg PO BID (short acting) 2–4 mg PO daily (long acting)
Trospium chloride (Sanctura)	Antimuscarinic quaternary amine	20 mg PO BID
Darifenacin (Enablex)	M_3 – selective antimuscarinic	7.5–15 mg PO daily
Solifenacin (Vesicare)	M_3 – selective antimuscarinic	5–10 mg PO daily
Fesoterodine (Toviaz)	M_3 – selective antimuscarinic	4–8 mg PO daily
Imipramine (Tofranil)	Antichol, α-adrenergic	10–25 mg PO daily – QID
Mirabegron (Myrbetriq)	β3-adrenergic	25 mg once daily

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- **Surgical management:**
  Used for refrac urge incontinence
  Botulinum toxin type A (Botox) injection:
  Act to inhibit periph cholinergic nerve endings by inhibiting ACh release from the presynaptic terminal. Intradetrusor injections typically done by cystoscopy prevent the detrusor muscle from being stimulated thus preventing bladder contractions
  May cause postinjection urinary retention requiring self-catheterization
  May have up to a 73% continence rate (*Eur Urol* 2004;45:510)
  Sacral nerve stimulation:
  Performed in two phases: (1) Percutaneous nerve eval to determine resp w/ placement of implantation electrode adj to the 3rd sacral nerve root. Trial of 3 w is typical to determine resp. (2) If >50% resp a permanent electrode is placed attached to a generator.
  Up to 80% resp, but 30% removal or revision rate due to pain or complications at the implant or generator site (*J Urol* 1999;162:352)

STRESS INCONTINENCE

Treatment

- **Medical management** not generally useful
  Pessary or urethral plugs can be attempted
- **Surgical management:**
  Retropubic colposuspension (Burch & MMK):
  Previously considered the gold std for SUI
  Involves suspension of the pubocervical fibromuscularis to pubic symphysis periosteum (MMK) or Cooper's ligament (Burch)
  Retropubic sling:
  Has largely replaced colposuspension & thought to be as effective
  Objective cure rates 63–5% for the TVT procedure compared to Burch colposuspension 51–87% (*AJOG* 2004;190:324)
  Polypropylene mesh (most common material) is placed under the midurethra w/ minimal tension through the retropubic space
  Operative risks include bladder, ureteral, urethral, bowel or bld vessel injury thus mandating cystoscopy postplacement
  Transobturator sling:
  Directed bilaterally through the obturator foramen & underneath the midurethra
  Compared to TVT w/ 80.8% cure rate TOT had a 77.7% objective cure rate. Voiding dysfxn was improved in the TOT group. Nerve & musc pain in the leg is more common in the TOT compared to TVT (*NEJM* 2010;362:2066)
  Designed to reduce complications of retropubic trochar placement
  Operative risks of bladder, ureteral, & bld vessel injuries are less than the retropubic sling approach; however, pts may experience more groin pain
  Minislings (single-incision slings):
  Newer slings which include 1 transvaginal incision & either placed into an H position or a U (retropubic position)
  Facial bladder neck slings:
  Utilizing fascia from the rectus muscle or elsewhere to perform a retropubic bladder neck sling → preserved for complicated cases

OVERFLOW INCONTINENCE

Definition and Etiology

- Involuntary loss of urine due to inability to adequately empty the bladder
  AKA chronic retention of urine, neurogenic bladder
  Neuromuscular disorders – interfere w/ nml bladder reflexes
  Multi sclerosis, diabetic neuropathy, CNS trauma, CNS tumors, etc.
  Obstructive disorders – urethral obst leads to retention & overdistension
  POP, anti-incontinence procedures, malig, fecal impaction
  Meds – anticholinergics, antimuscarinics

Clinical Manifestations

- Inability to void or fully empty bladder voluntarily

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- Loss of small amounts of urine w/o sensation of emptying
- Medication hx important to exclude causes of urinary retention

Physical Exam and Workup/Studies
- Nonpainful bladder that is palpable after voiding
- Signif PVR (typically >300 mL)
- Urodynamics

Treatment
- Therapy directed at treating the underlying cause
- CIC or indwelling catheter to ↓ overdistention
- Sacral nerve stimulation – see OAB section, above
- α blockers are not FDA approved for use in women, but have been useful in BPH in males

BYPASS INCONTINENCE AND UROGENITAL FISTULAE

Definition and Etiology
- Leakage of urine from extraurethral sources
  - AKA extraurethral incontinence
  - Urogenital fistulae –VVF, ureterovaginal fistula: Most common cause in developed countries is gynecologic Surg (0.1% of all hysterectomies), other causes include radiation, trauma, malig, complications of parturition. Most common cause in developing countries is obstetric trauma (pres necrosis)
  - Ectopic ureter
  - Urethral diverticulum

Clinical Manifestations
- Continuous leakage of urine common in urogenital fistula
- Pts w/ urethral diverticula may complain of pre- or postvoid "dribbling"
- May present with recurrent UTIs, vaginal candidiasis, perineal irritation

Diagnostic Workup/Studies *(Female Pelvic Med Reconstr Surg* 2012;18:71)
- Urinalysis, urine culture
- Voiding cystourethrogram – 1st-line imaging
- Cystourethroscopy – helpful to determine location in bladder
- Intravenous pyelogram may be performed if there is a suspicion for ureteral fistula
- CT/MRI may be used to further characterize size & location

Treatment
- Surgical rx to correct the anatomic abnormality
- May consider conservative management of small VVF w/ prolonged bladder drainage
- Genitourinary fistulas can be repaired vaginally, laparoscopically, or abdominally depending on size, location, & surgeon skill set
  - Vaginal repair preferred for uncomp VVF
    - Latzko procedure – partial colpocleisis w/o excision of fistulous tract
    - Layered closure – surrounding tissues mobilized, fistulous tract excised, multi layers closed w/ absorbable interrupted sutures
    - Martius flap – transposition of labial fat pad, useful for large VVF w/o adequate vaginal tissue
  - Abdominal or laparoscopic repair may be needed for prox, complex VVF & ureterovaginal fistulae

INTERSTITIAL CYSTITIS

Definition
- Syn characterized by chronic pelvic pain, urinary urgency & frequency, dyspareunia, nocturia

Epidemiology
- Prevalence 10–67/100000 women in US (*Obstet Gynecol* 2002;100:337)
- Up to ~40% women w/ chronic pelvic pain

Pathophysiology
- Poorly understood, potential theories include mast cell activation, upregulation of sensory nerves, altered bladder wall permeability

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Diagnostic Workup/Studies
- Rule out UTI & other causes of chronic pelvic pain
- Bladder diary may show frequent small voids
- Cystourethroscopy w/ hydrodistention ± bx
- Bladder filled to near capacity, emptied, & then inspected for petechial hemorrhages, Hunner ulcers (diagnostic), glomerulations (not diagnostic)
- Potassium sens test – instillation of nml saline into bladder followed by KCl solution, positive if pain present w/ KCl instillation (low spec)

Treatment
- Avoidance of spicy foods, coffee, tea, carbonated beverages, tomatoes
- Hydrodistention can improve sx by 20–30%
- DMSO bladder instillation – anti-inflammatory, bladder anesthetic, decreases mast cell activation, relaxes muscle
- Pentosan polysulfate sodium – heparin analog, 100 mg PO TID, only FDA approved oral drug for IC
- Tricyclic antidepressants – inhibit pain fiber activation, amitriptyline 10–75 mg nightly has shown improv in 2/3 of women

ANAL INCONTINENCE

Definition and Epidemiology
- Involuntary passage of flatus or stool
- Fecal incontinence – inability to prevent passage of stool until socially acceptable
- Prevalence 2–17% general pop, up to 50% of nursing home residents (*NEJM* 2007;356:1648)
- **Risk factors:** Female sex, pelvic radiation, obstetric trauma, neurologic d/o, prev anorectal Surg, chronic diarrhea (IBD, IBS, celiac sprue), fecal impaction, urinary incontinence, nursing home placement, smoking, obesity

Etiology
- Chronic constip is very common in women & can lead to overflow incontinence & pelvic floor dysfxn if untreated
- Etiology is commonly multifactorial
- Most common cause in otherwise healthy women is damage to anal sphincter at time of vaginal deliv
- Pseudoincontinence – fecal soiling only (rectovaginal fistula, external hemorrhoids, incomplete rectal emptying)

Clinical Manifestations
- Direct questioning or written questionnaires are important
- Detailed hx including onset, frequency, severity, consistency of stool, presence of bld, pus, or mucus, pad use, effect on QOL, bloating, fecal urgency, straining, insensible loss of stool, fecal soiling
- Thorough medication hx important (laxatives, meds causing constip [anticholinergics, iron, narcotics, etc.] can lead to overflow incontinence)

Physical Exam
- Inspection of perineum & anus – external hemorrhoids, dermatitis, nml perineal skin creases, rectal prolapse, scars from prev lacerations or episiotomies, patulous anus (indicative of denervation), fissures
- Dovetail sign – loss of anter perineal creases (disruption of EAS)
- Inspection w/ squeeze to evaluate symmetry of folds & mvmt of perineum
- Inspection w/ bearing down to evaluate excessive perineal descent (>3 cm)
- Perineal sensation – dull & pinprick sensation should be tested in S2–4 dermatomes
- Bulbocavernosus reflex – cotton swab touched over bulbocavernosus muscles should elicit contraction of EAS
- Digital rectal exam – evaluates resting tone, contraction of EAS & PR, areas of tenderness, fecal impaction, masses

Diagnostic Workup/Studies
- Daily stool diary, validated questionnaires
- Rule out systemic & metabolic causes (infectious, autoimmune, malig, endocrine)
- **Colonoscopy:** Indicated for *any pt >50 yo* or w/ concerning sx (weight loss, melena/hematochezia, chronic diarrhea), family h/o colon cancer, HNPCC or Lynch syn, evaluate for IBD, celiac sprue
- **Endoanal US:** Useful when there is clinical suspicion for anal sphincter injury, evaluates structure *only (best 1st-line test for poor anal squeeze)*

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- **Anal manometry:** Useful study in pts w/ nml anal tone who reports *abn* sensation to defecate, evaluates rectal sensation, compliance, & RAIR, evaluates fxn *only*
- **Other studies:** Electromyography (mapping EAS defects), pudendal nerve conduction studies, defecography (evaluates perineal descent, anorectal angle, rectocele, etc.), dynamic pelvic MRI, colonic transit studies

Treatment (*NEJM* 2007;356:1648)

- Management directed at primary cause
- Behavioral modifications
  Pelvic floor exercises (Kegel)
  Biofeedback: Improves perception of rectal sensation & sphincter contraction
- Medical management

Common medications for treatment of constipation

Type	Name	Mech	Maximal dose	Side effects
Bulk laxative	Psyllium (Metamucil)	Increases colonic residue, stimulates peristalsis	Titrate up to 20 g	Bloating, flatus
Osmotic laxative	Magnesium hydroxide (MOM)	Draws water into intestines	15–30 mL up to BID	Hypermagnesemia
	Magnesium citrate		150–300 mL prn	
	Sodium phosphate (Fleet)		10–25 mL w/ 12 oz water prn	Hyperphos
Poorly absorbed sugars	Lactulose	Poorly absorbed, draw water into intestines	15–30 mL 1–2 times a day	Bloating, flatus
	Sorbitol			
	Polyethylene glycol (Miralax, GoLytely – electrolytes)		17–36 g 1–2 times a day	Less bloating & discomfort
Stimulant laxative	Senna	Stimulates intestinal motility or secretion	187 mg daily	Melanosis coli
	Bisacodyl (Dulcolax)		5–10 mg QHS	Cramping
	Docusate sodium (Colace)	Ionic detergents allow incorporation of water into stool	100 mg BID	Diarrhea
Enema/ suppository	Tap-water enema	Distends rectum to initiate evacuation, lubrication	500 mL daily	Electrolyte abnormalities can occur if retained
	Soapsuds enema		1500 mL daily	
	Mineral oil enema		100 mL daily	
	Bisacodyl suppository	Topical stimulation of colonic muscle	10 mg daily	Cramping
Prokinetic	Tegaserod (Zelnorm)	5-HT_4 agonist	6 mg BID	Diarrhea

From *NEJM* 2003;349:1360–1368.

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- Modification of stool consistency & deliv
  Increased fiber intake increases solid stool bulk & may facilitate emptying (may worsen diarrhea in some pts) (*Gastroenterology* 1980;79:1272)

Common medications for treatment of diarrhea

Name	Mech	Dosage	Side effects
Loperamide (Imodium)	Inhibits peristalsis	2 mg PO TID Max 8 mg/d	Constip, nausea
Diphenoxylate–atropine (Lomotil)	Inhibits circular smooth muscle	5 mg PO QID	CNS effects, nausea
Hyoscyamine sulfate	Anticholi	0.325 mg BID	Constip, dry mouth

From Lentz GM. Anal incontinence: Diagnosis and management. In: Lentz GM, ed. *Comprehensive Gynecology*. 6th ed. Philadelphia, PA: Mosby; 2012:503–518.

- **Surgical management:**
  Generally surgical rx is the last resort & usually not effective
  Overlapping anal sphincteroplasty – 85% short-term improv, 50% at 5 y
  Note: Studies have not shown a difference in outcomes btw end-to-end vs. overlapping sphincteroplasty for perineal laceration repair after vaginal delive
  Rectal prolapse repair – transrectal, transabdominal, or laparoscopic rectopexy
  Sacral nerve stimulation – see OAB section, above, 37–74% continence rate at 24 mo (*NEJM* 1993;329:1905)

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INFERTILITY EVALUATION

Definitions and Epidemiology (*Fertil Steril* 2008;90:S60)

- **Infertility:** No Preg after 1 y of regular unprotected intercourse. Consider eval & rx for woman >35 yo after 6 mo. Affects 7–8% of US women (*Fertil Steril* 2006;86:516). ↑ w/ age; ♀ >40 yo → greatest infertility.
- **Fecundity:** Probability that a single menstrual cycle results in live birth

Causes of infertility

Dx	% affected
Ovulation disorders	17
Tubal dz	23
Endometriosis	7
Male factor	24
Unexplained	26
Other	3

From Smith S, Pfeifer SM, Collins JA. Diagnosis and management of female infertility. *JAMA.* 2003;290(13):1767–1770.

History (*Fertil Steril* 2004;82:S169)

- Gravidity, parity, Preg outcomes/assoc complications
- Age at menarche, cycle length & characteristics, dysmenorrheal moliminal sx
- Methods of contraception used in the past; frequency & timing of intercourse
- Duration of infertility & results of any prev eval & rx
- H/o thyroid dz, pelvic or abdominal pain, galactorrhea, hirsutism, dyspareunia
- Full medical & surgical Hx, including STIs & PID, prior abd/pelvic Surg
- Prev abn pap smears & any subseq rx
- Current meds including supplements & allergies
- Social history (SHx). Occupation, tobacco, EtOH, drug use
- Family history (FHx) of birth defects, mental retardation, or infertility
- Partner's reproductive Hx (conceptions/children in other pairings, testicular trauma, chronic medical conditions, & meds). Remember male factor on diff dx.

Physical Examination

- Weight & BMI. Thyroid enlargement, nodule, or tenderness. Breast exam. Signs of androgen excess or acanthosis nigricans. Pelvic or abdominal tenderness, masses. Vaginal or cervical abnormality, secretions, or discharge. Uterine size, shape, position, & mobility. Adnexal mass or tenderness. Cul-de-sac mass, tenderness, nodularity.

Diagnostic Evaluation

- **Ovulatory fxn:** Oligomenorrhea (>35 d btw menses) or amenorrhea (>3 mo btw menses) → no further w/u. Luteal phase (cycle day 21 or 7 d after ovulation) serum prog >6 ng/mL confirms ovulation. Urinary LH (commercial ovulation predictor kits) generally reliable & correlate w/ serum LH. Serum FSH/LH ratio & estradiol (cycle day 3) or AMH (any time in cycle) indicate ovarian reserve. If ovulatory dysfxn → TSH, prolactin, & FSH for etiology.
- **Anatomy assessment:** *HSG* evaluates tubal patency & uterine cavity, endometrial polyps, submucosal fibroids. Schedule 2–5 d after last menses. Rx doxycycline 100 mg PO BID for 5 d if h/o PID or dilated tubes (*Obstet Gynecol* 2009;113(5):1180). Beware HSG contrast can → tubal spasm (false + tubal blockage). *TVUS* shows uterine cavity contours & small intrauterine lesions. *Sonohysterography* (saline infusion sonogram) more accurate than HSG, as accurate as hysteroscopy for cavity assessment. 2D & 3D TVUS more sensitive than HSG for fibroids & polyps. *Hysteroscopy* for definitive dx + rx of cavity pathology. *Laparoscopy* definitive for tubal & pelvic pathology. *Chromopertubation* (the injection of indigo carmine dye through cervical canula w/ direct intra-abdominal observation of tubal spill for eval of tubal occlusion) & rx of mild dz (fimbrial agglutination, adhesion, endometriosis).
- See also **male factor** w/u & other diagnoses, below

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PREMATURE OVARIAN INSUFFICIENCY (POI)

Definition & Epidemiology (*Obstet Gynecol* 2009;113:1355; *Lancet* 2010;376:911)
- Decline in nml ovarian fxn in a woman <40 yo. A form of hypergonadotropic hypogonadism. 0.3% of reproductive age ♀; 5–10% ♀ w/ secondary amenorrhea.

Etiology
- Accelerated follicular atresia due to genetic syn (Turner XO → oocyte apoptosis; fragile X premutation → oocyte toxic prot). Autoimmune ovarian failure secondary to systemic autoimmune dz (check for type 1 DM, thyroiditis, hypoadrenalism). Ovarian toxins (chemo w/ alkylating agents, XRT, smoking, infxn such as mumps or CMV).
- Abn follicular stimulation due to defects in steroidogenic enzymes or defects in ovarian gonadotropin receptors (eg, FSH receptor mut)
- Result is ↓ ovarian estrogen production → ↓ negative feedback on pituitary → ↑ FSH, LH

Clinical Manifestations
- Primary or secondary infertility. Irreg menses vs. primary or secondary amenorrhea
- W/ fragile X – mental retardation, ataxia, premature ovarian failure
- W/ Turner syn – short stature, shield chest, web neck, low hairline, low set ears, aortic coarct, streak ovaries
- ↓ estrogen w/ primary infertility → impaired secondary sexual dev, dyspareunia (secondary to vaginal dryness), decreased bone density
- ↓ estrogen & secondary infertility → hot flashes, night sweats, emotional lability, dyspareunia, decreased bone density

Initial Workup
- ↓ estrogen → ↑ FSH, ↑ LH. POI if:
  FSH >10 mIU/mL (except during the midcycle preovulatory LH surge)
  FSH > LH w/ E2 <50 pg/mL (× 2 if ↑ FSH) = absent/nonfunctioning follicles
- Clomiphene citrate challenge test – check FSH on cycle day 3 & 10 after 100-mg clomiphene PO daily on cycle day 5–9; ↑ FSH after clomid sugg low ovarian reserve
- AMH–secretion by small preantral & early antral follicle granulosa cells reflects size of primordial follicle pool, declines w/ age, undetectable at menopause. Early marker of ovarian reserve, & AMH level is not cycle dependent. AMH >1 ng/mL – adequate ovarian reserve.
- AFC by transvaginal US – high variability, useful if equivocal labs

Follow-up Studies
- Genetics. Karyotype (identify individuals w/ any form of gonadal dysgenesis characterized by an absent or abn X chromo & those w/ any portion of a Y chromo), genetic testing for FMR1 gene permutations
- Adrenal autoantibodies by immunofluorescence assay
- Anti-islet cell Ab (given association w/ type 1 DM)
- Serum TSH, thyroid-stimulating Ig, thyroid peroxidase antibodies
- Bone mineral density to detect osteopenia

Treatment and Medications
- HT to ↓ sx of estrogen deficiency & prevent bone loss
- Daily calcium (1200–1500 mg) + Vit D (600–800 IU) for bone health
- Exogenous androgen – unclear role in mgmt; no high-quality evid
- Clinician sensitivity, additional psychological support
- IVF using donor oocytes – controversial in women w/ Turner syn

POLYCYSTIC OVARIAN SYNDROME (PCOS)

Definition (*Nat Rev Endocrinol* 2011;74:219)
- A d/o of ovarian fxn characterized by anovulation, elevated androgen levels, & polycystic ovaries. A/w obesity & insulin resistance (metabolic syn). Different diagnostic criteria used:
  1990 NIH – NICHD – hyperandrogenism or hyperandrogenemia, oligoanovulation, & exclusion of other endocrine disorders
  2003 Rotterdam criteria – 2 of following 3: Clinical or biochemical hyperandrogenism, oligo- or anovulation, polycystic ovaries. Other endocrine disorders must be excluded.
  2006 androgen excess – PCOS society – clinical or biochemical hyperandrogenism w/ oligo-/anovulation &/or polycystic ovaries

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Epidemiology & Pathophysiology
- 6–10% of women, depending on diagnostic criteria. Uncertain etiology, but hyperandrogenism may cause ovulatory dysfxn & abn gonadotropin secretion.
- Androgen excess → follicular arrest & ↑ LH. Hyperinsulinemia may also → follicular arrest & phenotypic features.
- Presentation may include excess body or facial hair, frequent shaving/plucking, irreg menstruation, infertility, alopecia, acne, obesity, metabolic syn.

Physical Exam
- Assess weight & BMI, hair pattern/growth, thyroid, galactorrhea (prolactin-secreting tumor), acanthosis nigricans
- Deep voice, male pattern facial/body hair, clitoromegaly may suggest androgen-secreting tumor or congen adrenal hyperplasia

Diagnostic Workup
- Document oligo- or anovulation by Hx, serum progesterone, or urinary LH testing
- Labs: Consider testing for serum androgens esp if no clinical hyperandrogenism – or – if frank virilization. TSH, FSH, & prolactin if pt anovulatory. 75 g, 2-h oral gluc tol test for women w/ hyperandrogenism w/ anovulation + acanthosis nigricans +
  Obesity (BMI > 30 kg/m^2, or >25 in Asian pop) + FHx of T2DM or GDM (*Fertil Steril* 2012;97(1):28)
- TVUS ovaries: ≥12 follicles in each ovary measuring 2–9 mm in diameter, &/or ovarian volume >10 mL indicates polycystic ovaries
- Endometrial bx if long Hx of oligomenorrhea due to ↑ endometrial cancer

Treatment (*Fertil Steril* 2008;89:505)
- Exercise & weight loss improve ovulation rate – 1st-line rx
- In women not attempting Preg, low-dose combination OCP may ↓ hyperandrogenism & risk of endometrial cancer
- Clomiphene citrate 1st-line ovulation induction in women desiring Preg (see below)
- Limit to 6 ovulatory cycles before considering 2nd-line rx
- Ovulation induction w/ exogenous gonadotropins is 2nd-line therapy. IVF is 3rd-line therapy.

TUBAL FACTOR INFERTILITY

Definition & Epidemiology (*Curr Opin Infect Dis.* 2004;17(1):49;2005)
- Infertility caused by obliteration of the fallopian tube, usually by prior pelvic infxn. 20–30% of infertility may be tubal factor. Very common.

Etiology
- Obliteration of the fallopian tube or damage to fimbriae by infectious or inflamm process. Most cases caused by prev Hx of PID.
- Less common causes are inflammation related to endometriosis, inflamm bowel dz, & surgical adhesions

Clinical Manifestations
- Usually asymptomatic but may have dysmenorrhea & dyspareunia if endometriosis
- Hx of PID, ectopic Preg, or prior pelvic Surg

Diagnostic Workup/Studies
- HSG – diagnostic, but also may ↑ fertility
- Consider laparoscopy w/ chromopertubation if endometriosis suspected
- Chlamydia Ab testing may be helpful to screen pts at high risk for tubal factor infertility, but role of testing has not been clearly defined yet (*Fertil Steril* 1994;62:305)

Treatment and Medications (*Fertil Steril* 2012;97:539)
- Prox tubal obst → tubal cannulation
- Mild hydrosalpinges → laparoscopic fimbrioplasty or neosalpingostomy
- Irreparable hydrosalpinges → IVF. Salpingectomy or prox tubal occlusion improves IVF Preg rates.
- Decision to pursue Surg vs. IVF based on age of woman, number of children desired, extent of tubal dz

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RECURRENT PREGNANCY LOSS (RPL)

Definition (*N Engl J Med* 2010;363:1740)
- 3 or more consecutive Preg losses before 20 w gest; some recommend w/u after 2 consecutive losses, esp if age >35 yo or pt requests

Epidemiology & Etiology
- 1% of all couples attempting Preg. Increases in women <18 yo & >35 yo.
- Most very early (<10 w) miscarriages due to aneuploidy
- Autoimmune dz, anatomic abnormalities, & thrombophilias may lead to vascular insufficiency for developing conceptus, leading to miscarriage

Evaluation
- Determine actual gestational age at time of miscarriage rather than time of onset of sx if poss
- Ask about Hx of thrombosis or prev fetal death; Hx of prev Preg w/ breech presentation, dysmenorrhea, or menorrhagia (may suggest uterine anomaly or fibroids); chronic medical conditions such as thyroid dz, diabetes, or autoimmune dz such as lupus; smoking, obesity, EtOH use, caffeine use

Diagnostic Workup (*Int J Gynaecol Obstet* 2002;78:179)
- Parental karyotype for balanced translocations. Aneuploid karyotype of prior loss fetuses makes other causes less likely.
- Antiphospholipid Ab syn w/u: Lupus anticoagulant (RVVT and hexagonal phospholipid, or aPTT with mixing studies), β2 glycoprotein Ab (IgM/IgG), anticardiolipin Ab (IgM/IgG). Need 2 positive tests 12 w apart to make dx.
- Consider thrombophilia w/u only if pt has a Hx of thromboembolism. Test for Factor V Leiden, prothrombin G20210A mut, prot C, prot S, antithrombin III deficiency.
- Evaluate uterine cavity using HSG, hysteroscopy, sonohysterography, or transvaginal US
- No dx is made in 50% of cases of recurrent Preg loss (*Fertil Steril* 2012)

Treatment (*N Engl J Med* 2010;363:1740)
- If positive antiphospholipid antibodies, heparin 5000 U subcut twice daily & low-dose ASA can ↓ miscarriage rates. Low-molecular-weight-heparin dose not established.
- If genetic abnormality such as balanced translocation present, up to 70% live birth w/o intervention, but may consider preimplantation genetic screening
- If uterine septum → hysteroscopic resxn. Repair of bicornuate or unicornuate uterus not necessary as obstetric outcome often good & repair has higher risk.
- No rx for women w/ thrombophilias thus far has been found beneficial

MÜLLERIAN ANOMALIES

Definitions and Epidemiology (*Hum Reprod Update* 2011;17:761)
- An anomaly of the uterus, tubes, or upper vagina due to failure of dev, fusion, or resorption of Müllerian structures
  5–6% of women (arcuate uterus 3.9%, septate uterus 2.3%, bicornuate 0.4%, unicornuate 0.3%, didelphys 0.3%). ↑ to 8% w/ infertility. ↑ to 13% w/ recurrent miscarriage. ↑ to 25% w/ mixed infertility & recurrent miscarriage. Many also have a GU abnormality.

Etiology (Fritz MA, Speroff L. *Clinical Gynecologic Endocrinology & Infertility.* Philadelphia, PA: Lippincott Williams & Wilkins; 2011.)
- **Sporadic:** Multifactorial & polygenic. 46 XX (92%); sex chromo mosaicism (8%).
- **Risk factors:** Hypoxia during Preg, MTX, DES, thalidomide, radiation, viral infxn
- Vertical fusion failure (canalization) → urogenital sinus & Müllerian tubercle separate
- Lateral fusion failure (duplication) → failure to merge bilateral Müllerian ducts
- Dev of the uterus, fallopian tubes, & upper vagina:
  2 Müllerian (paramesonephric) ducts form from celomic epithelium beside the wolffian (mesonephric) ducts. In the *absence* of the SRY gene on the Y chromo & subseq MIS or AMH, Müllerian ducts proliferate & grow caudally & medially extending from the vaginal plate of the urogenital sinus to beside the developing ovary. In *absence* of testosterone, wolffian ducts involute. Canalization of the ducts occurs w/ a cranial lumen opening into peritoneal cavity. The paired ducts fuse in the midline forming the body of the uterus & the unfused lateral arms form the fallopian tubes. Resorption of medial aspects.

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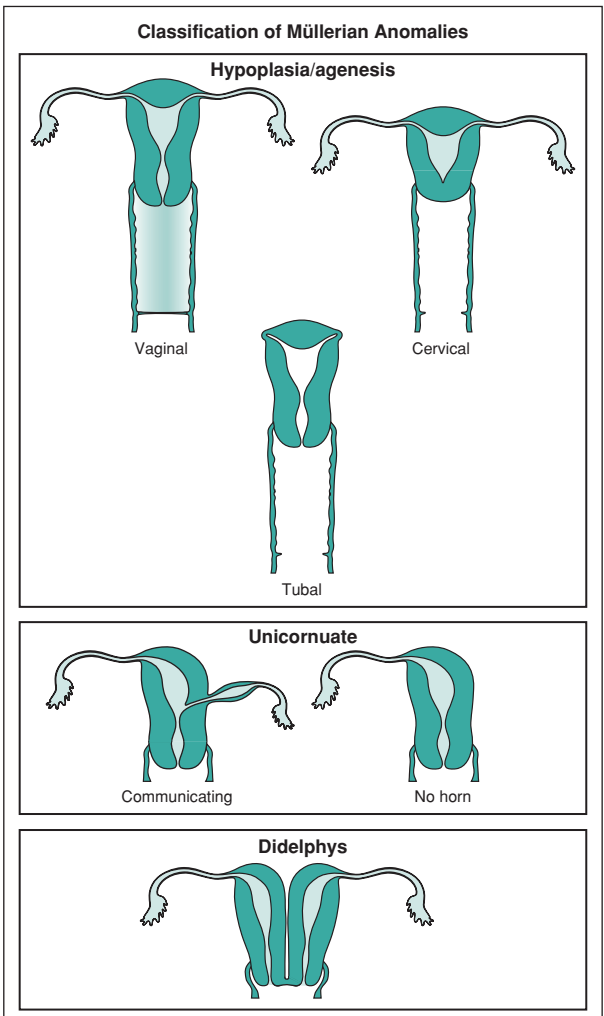
- Dev of urogenital sinus forms *lower* vagina, bladder, urethra
  Urogenital sinus develops from the ventral portion of the cloaca (terminal hindgut; confluence of the urethra, rectum, & vagina). The caudal aspect of the paramesonephric ducts fuses w/ the urogenital sinus to form the vaginal & cervix.

Figure 8.1 Types of congenital uterine anomalies



(*continued*)

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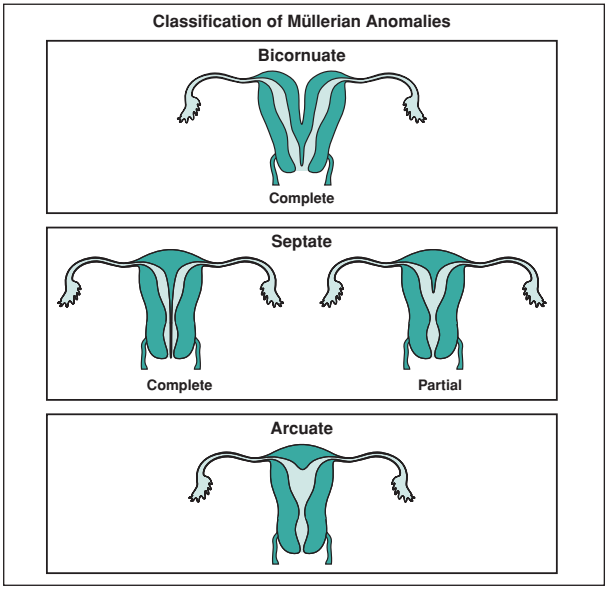
Figure 8.1 (Continued)



(From Fritz MA, Speroff L. *Clinical Gynecologic Endocrinology & Infertility*. Philadelphia, PA: Lippincott Williams & Wilkins; 2011)

Clinical Manifestations (*Curr Opin Obstet Gynecol* 2010;22:381; *Fertil Steril* 2008;89:219)

- Most often asymptomatic w/ nml secondary sex characteristics
- Sx *can* include primary amenorrhea or changes in menstrual cycle (uterine or vaginal malformations); dysmenorrhea or cyclic acute ± chronic pelvic pain;
  Abn vaginal bleeding; foul-smelling vaginal discharge (worse at the time of menses); difficulty inserting a tampon; pelvic mass (from hematometra/hematocolpos); dyspareunia; infertility; recurrent Preg loss (esp septate uterus)
- Preg complications (higher rates of SAB, preterm birth, fetal malpresentation, labor dystocia, PPROM, placental abruption of previa, IUGR, & increased c-section) (*Am J Obstet Gynecol* 2011;205:558)

Risk of pregnancy outcome by uterine anomaly			
	Preg loss (%)	**Premature delivery (%)**	**Fetal survival (%)**
Bicornuate uterus	40		62
Septate uterus	>60		6–28
Uterine didelphys	35	19	60
Unicornuate uterus	44	25	43

From Ribeiro SC. Müllerian duct anomalies: Review of current management. *Sao Paulo Med J.* 2009;127:92.

Specific anomalies (*Obstet Gynecol* 2013;121:1134)

- **Vaginal agenesis/MRKH syn**
  Müllerian agenesis of upper vagina, ± uterus/tubes → blind pouch vagina. Affects 1 in 4000–10000 women. Nml ovarian & sexual dev. ↑ urinary tract, skeletal, & anter abdominal wall anomalies.
- **Vaginal atresia**
  15% are segmental. Nml uterus, cervix, upper vagina. Primary amenorrhea. Hematocolpos → cyclic pelvic pain. Ddx: Imperf hymen, transverse septum. Segmental has ≥1 cm btw the upper & lower vaginal tract.

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- **Transverse vaginal septum**
  Defect in resorption, affects 1/2100–1/72000 women. Presents like vaginal agenesis. Preoperative dilation can thin the septum to improve mobilization of the vagina at repair
- **Uterovaginal abnormalities (longitudinal vaginal septa)**
  Defect in resorption → Preg loss, preterm deliv, dyspareunia, dysmenorrhea. 20% w/ renal anomalies. Up to 50% w/ endometriosis.
- **Uterine didelphys**
  Defect in lateral fusion w/ double uterus & cervix ± double vaginas → postmenarchal dysmenorrhea, abd pain, palpable abdominal mass. Linked w/ ipsilateral renal agenesis (OHVIRA/Herlyn–Werner–Wunderlich syn)
- **Unicornuate uterus**
  Only 1 Müllerian duct formed, w/ absent/incomplete contralateral side. 5% of all uterine anomalies; 1/4020–1/5400 ♀. 74% have rudimentary horn, generally not communicating w/ hemiuterus. 40% w/ renal anomalies. 15% w/ endometriosis. Rarely extrapelvic or absent ovaries. Ectopic Preg can occur in uterine rudimentary horn; for rupture → prompt surgical mgmt ± MTX. Recommend removal of rudimentary horns prior to Preg. Obstetric & infertility complications: Late 1st & early 2nd trimester SAB (25%), decreased fecundity, preterm deliv (20%), 3rd trimester fetal demise (10%), placenta accreta, postpartum atony.
- **Cervical atresia**
  4 categories: (1) Agenesis, (2) fragmentation, (3) fibrous cord, (4) obst. 50% also w/ vaginal agenesis. 33% w/ uterine anomalies. ↑ endometriosis, hematosalpinx, & pelvic adhesive dz. Rx unclear given very rare condition.

Diagnostic Workup/Studies *(Fertil Steril* 2008;89:219)

- **Goal:** Identify dilated/obstructed uterus &/or mass, pelvic anatomy, distance of an obstructed vagina from the perineum, thickness of a vaginal septum or atretic segment, & presence/absence of urinary tract anomalies
- Physical exam including pelvic ± rectal exam (adol/young adults). Exam under anesthesia ± vaginoscopy (pediatric pop).
- MRI is most sensitive imaging test for uterine anomalies & is preferred
- Pelvic US & HSG also imaging tools
- Vaginoscopy (gold std for vaginal or cervical anomalies)
- Laparoscopy (gold std for uterine anomalies)
- ± intraoperative HSG. ± karyotype.

Treatment and Medications *(Fertil Steril* 2008;89:1)

- **Uterine/vaginal obst** → immediately relieve obst (Surg)
  If unable to proceed to OR immediately, place Foley catheter to avoid urinary retention. Consider percutaneous drainage, laparoscopic drainage, continuous OCPs to suppress endometrial growth until surgical repair.
- **Vaginal anomaly → surgical or mechanical repair.** If not emergent, medical/surgical intervention when emotionally mature/reproductive age. Vaginal dilators are used post-op to prevent stenosis. Overall pts have a satisfactory sex life similar to the nml pop. Discuss Preg options, IVF, surrogacy. Pts need multidisciplinary support including mental health providers & social work.
  Progressive perineal dilation: *1st-line therapy* as surgical neovagina ↑ stenosis & multi reoperations. More successful if greater depth of vaginal dimple, increased frequency of dilation, & sexual intercourse.
  Surgical mgmt:
  Vecchietti procedure (abdominal or laparoscopic technique w/ gradual traction on the vaginal dimple) → creation of a neovagina in 6 mo for 90% of pts. Must use vaginal mold continuously for the 1st 3 mo post-op.
  McIndoe neovagina (dissection btw the urethra & rectum) → place split-thickness skin graft
  Davydov neovagina (abdominal or laparoscopic-assisted technique w/ dissection of rectovesical space, mobilization of the peritoneum, creation of vaginal fornices, & attachment of the peritoneum to the introitus)
  Williams vulvovaginoplasty (uses a vulvar flap to make a vaginal tube). Dilation is needed for a long period. Abn angle of neovagina.
  Rotational flaps (use pudendal thigh, gracilis myocutaneous, labia minora, & other fasciocutaneous reconstruction). Also can create vagina from bowel.
- **Septum** → hysteroscopic resxn of uterine or longitudinal vaginal septum. Low or midtransverse vaginal septum approached vaginally; high septum & segmental vaginal atresia combine vaginal & abdominal approach. Pull through vaginoplasty if small length of atretic segment. Skin flaps or bowel if segment btw upper & lower vagina is larger.

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- **Bicornuate uterus** – Strassman metroplasty unifies the 2 cavities. Rarely performed given difficulty & risk of future uterine rupture in labor.
- Rudimentary horn, obstructed hemivaginas, etc. → laparoscopic resxn
- **Cervical atresia** → hysterotomy & uterovaginal anastamosis vs. hysterectomy
- **Didelphys, bicornuate** rarely require repair. **Uterine septum** outcomes improved w/ resxn if 1st trimester loss or desires IVF.

MALE FACTOR INFERTILITY

Definition and Epidemiology (*Fertil Steril* 2006;86:S202)

- Inability of a male to achieve a Preg w/ a fertile female
- 20% due to purely male factors. Additional 30–40% combined male & female factors.
- **Risk factors:** Occupational or environmental exposure to chemicals, radiation, or heat; Hx of varicocele, mumps, hernia repair, pituitary tumor, anabolic steroid use, testicular injury, impotence

Etiology

- **Hypogonadotropic (secondary) hypogonadism** – hypothalamic/pituitary dz. Congen eg, Kallmann syn (abn neuronal migration resulting in anosmia & hypothalamic hypogonadism). Tumors – macroadenoma, craniopharyngioma. Infiltrative dz – sarcoidosis, TB, hemochromatosis. Vascular – infarction, aneurysm. Drugs. Obesity.
- **Hypergonadotropic (primary) hypogonadism** – testicular failure. Congen eg, Klinefelter syn (XXY), cryptorchidism (failure of descent of testes during fetal dev). Varicocele – dilation of the pampiniform plexus of spermatic veins in scrotum (left more common than right). Acq – cancer, infxn (viral orchitis, mumps), drugs (alkylating chemotherapeutic agents, antiandrogen agents), torsion, radiation, smoking, hyperthermia, antisperm antibodies.
- **Other: Posttesticular defects** – Dz of epididymis or vas deferens (infxn, vasectomy, CF). **Retrograde ejaculation. Idiopathic** (40–50%).

Clinical Manifestations and Workup

- **Assess Hx:** Prior pregnancies fathered, coital frequency & timing, childhood illness (mumps orchitis), developmental/pubertal Hx, systemic medical illnesses, prior surgeries (hernia repair), environmental exposures (heat), meds, Hx of STIs, trauma to genitals, sexual dysfxn
- **Physical exam:** Assess secondary sexual characteristics: Body habitus, hair distribution, gynecomastia. Examine penis including location of urethral meatus. Palpate testes & estimate testicular volume w/ Prader orchidometer. Assess presence/consistency of vas deferens & epididymidis, presence of varicocele. Digital rectal exam to assess masses.
- **Semen analysis:** Collect after 2–3 d of abstinence; 2 samples 1 mo apart; see Table 8.3 for assessment & nml values, & also eval leukocyte count, microscopic debris/agglutination, immature germ cells

Semen analysis reference values	
On at least 2 occasions:	
Ejaculate volume	>1.5–5 mL
pH	>7.2
Sperm conc	>20 million/mL
Total sperm count	>40 million/ejaculate
Motility	>50%
Forward progression	>2 (scale of 0–4)
Nml morphology (depends on source)	>50% nml[a] >30% nml[b] >14% nml[c]
And:	
Sperm agglutination	<2 (scale of 0–3)
Viscosity	<3 (scale of 0–4)

Fertil Steril 2006;86:S202.
[a]WHO, 1987.
[b]WHO, 1992.
[c]Kruger (Tygerberg) Strict Criteria WHO, 1999.

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- **After initial w/u:** Uro consult if indicated. Additional semen studies (sperm autoantibodies, biochemistry, culture, sperm-cervical mucus interaction, sperm fxn tests [sperm analysis, acrosome rxn, zona-free hamster oocyte penetration test, human zona pellucida binding test, sperm chromatin & DNA assays]). Endocrine eval: Testosterone, LH, FSH, prolactin. Postejaculatory urinalysis in pt w/ low volume semen to rule out retrograde ejaculation. Transrectal & scrotal US to identify obst & nonpalpable varicocele. Genetic testing – CFTR gene (a/w congen absence of vas deferens), karyotype to detect chromosomal abnormalities (a/w impaired testicular fxn), PCR to detect Y chromo microdeletions (a/w isolated spermatogenic impairment).

Treatment and Medications

- Treat underlying etiology if known. Improve coital practice – intercourse q2d during most fertile interval (3 d prior to & including day of ovulation).
- Sperm aspiration for obstructive azoospermia – TESE or MESA followed by IVF w/ ICSI (see below)
- Use ARTs as described below, ICSI useful for male factor infertility (see below). May need to consider donor sperm.

OVULATION INDUCTION AND ASSISTED REPRODUCTION

Definition

- Use of medication to stimulate nml ovulation in pts w/ oligo/anovulation

Clomiphene Citrate (Clomid) (*Fertil Steril* 2004;82:90)

- **Indications:** Initial rx of oligo- or anovulation, also for unexplained fertility & age-related decline in fertility. Contraindication: Preg.
- **Mech of action:** Estrogen agonist/antag – antag properties predominate, competitively binds estrogen receptors in hypothalamus → ↑ GnRH by hypothalamus → ↑ FSH, LH by pituitary → follicular growth & ovulation
- Administer 50–150 mg PO daily for 5 d, starting cycle day 2–5 of menstrual cycle. Combined w/ timed intercourse or intrauterine insemination. Monit for ovulation using BBT, urine LH, elevated progesterone in midluteal phase, or US demonstrating preovulatory follicle prior to ovulation & subseq follicular collapse.
- Success rate for ovulation 80% – absence of ovulation or no Preg w/ known ovulation over 6 mo indicates failure of rx; many pts go to IVF if clomiphene citrate unsuccessful. Addition of metformin may improve live birth rate (*Fertil Steril* 2010;94:2659).

Gonadotropin Injection (*Fertil Steril* 2008;90:S13)

- Many protocols based on nml physiology of menstrual cycle
- **Mech of action:** FSH stimulates granulosa cell proliferation & follicle dev. LH stimulates theca cell production of androgen (converted to estrogen by granulosa cells). hCG stimulates follicular maturation of oocyte from prophase I through metaphase II & ovulation; may be used as alternative to LH for stimulation of ovulation.
- **Typical administration:** Gonadotropins (hMG or FSH) administered SQ or IM shortly after menstruation (~day 3 of cycle) → hCG, LH, or GnRH agonist once follicle growth reaches target size (18–20 mm). Timed intercourse, intrauterine insemination or oocyte retrieval typically 34–36 h following hCG administration. Progesterone or hCG for corpus luteum support following conception.
- **Monitoring:** Transvaginal US to assess follicular dev (diameter > 18 mm) & endometrial thickness prior to stimulation of ovulation w/ hCG. Estradiol level correlates w/ follicular maturation (E2 > 200 pg/mL per follicle). Progesterone level prior to hCG administration to determine premature LH surge.
- Complications of gonadotropins include multi gest (↑ w/ lower mat age & higher number of embryos transferred), & OHSS.

Intrauterine Insemination (IUI) (*Cochrane Database Syst Rev* 2012;4:CD003357)

- **Advantages:** Most cost-effective intervention prior to proceeding w/ IVF. Disadvantages: Requires patency of at least 1 fallopian tube.
- **Indications:** Sexual dysfxn (coitus can be avoided), cervical factor infertility, male factor infertility, unexplained fertility, endometriosis. Contraindications: Preg, bilateral fallopian tube occlusion, active pelvic infxn.
- **Procedure:** Wash ejaculated semen specimen to remove prostaglandins. Concentrate sperm in culture media. Inject sperm suspension directly into upper uterine cavity using a small catheter threaded through the cervix – timed to occur just prior to ovulation (check urine LH).
- Cumulative Preg rate of 5–20%, may attempt 3–6 cycles before proceeding w/ IVF

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In Vitro Fertilization (IVF) (*Cochrane Database Syst Rev* 2012;18:CD003357)

- **Advantages:** Highest chance of success. Disadvantages: Expensive, higher risks of multi gest & OHSS given use of gonadotropins.
- **Indications:** Tubal factor infertility, failure of less invasive therapies, male factor infertility, diminished ovarian reserve, ovarian failure (egg donor use), uterine factor infertility (surrogacy). Contraindications: Mat dz in which Preg contraindicated (eg, malig), active pelvic infxn.
- **Procedure:** Controlled ovarian hyperstimulation as above → follicle aspiration – usually transvaginally under US guidance, may also be done laparoscopically. Oocytes mixed w/ prepared sperm in vitro, fertilization occurs w/i next 18 h. Embryo(s) transferred into uterine cavity on cycle day 3–5. Preg test (serum hCG) 10–12 d following xfer.
- Live birth rate of 45% – decreases w/ advancing mat age

Intracytoplasmic Sperm Injection (ICSI) (*Fertil Steril* 2008;90:S187)

- **Advantages:** Assists fertilization process by direct injection of sperm into oocyte. Disadvantages: Technically demanding, high cost.
- **Indications:** Male factor infertility, select rare types of female infertility (morphologic anomalies of oocytes or zona pellucida inhibiting nml fertilization process). Contraindications: Same as for IVF.
- **Procedure:** Controlled ovarian hyperstimulation & follicular aspiration as outlined above
- Direct injection of single spermatozoon into cytoplasm of human oocyte
- Live birth rate of 30%

FERTILITY PRESERVATION

Epidemiology (*Semin Reprod Med* 2011;29(2):147)

- The probability of a cancer dx in a premenopausal female is 11%
- Survival for many types of childhood malignancies is >80%
- Rx for many of these cancers can lead to infertility, so consideration of future reproductive desires important *before* Surg, chemo, or XRT

Pathophysiology

- Primary oocytes are arrested in prophase of the 1st meiotic division at birth
- Continuous apoptosis depletes the pool of primary follicles
- Alkylating chemo agents affect resting follicles & carry a high risk of ovarian failure
- Antimetabolites affect only metabolically active oocytes & granulosa cells, leading to a lower risk of ovarian failure
- Radiation also affects developing oocytes; dose of 24 Gy → ovarian failure
- Intensive multiagent chemo & total body irradiation needed for bone marrow stemcell xplant results in >90% risk of permanent ovarian failure

Approaches

- **Nonsurgical:** Sperm cryopreservation or embryo cryopreservation are established methods for fertility preservation (*Fertil Steril* 2005;83:1622). Experimental techniques: If embryo cryopreservation is not poss due to lack of partner or desire to avoid creation of surplus embryos, some centers are capable of oocyte cryopreservation after a COH cycle. Some centers perform cryopreservation & in vitro maturation of oocytes from nonstimulated ovaries if a COH cycle is not poss.
- **Surgical:** Ovarian transposition Surg can be used to move an ovary out of the pelvis or abd if a pt is to undergo radiation. Ovarian tissue cryopreservation is a still experimental procedure where ovarian tissue is harvested, frozen, then thawed & retransplanted or individual follicles are isolated & grown in vitro. Cortical strips can be either transplanted back into pelvis or to abd or forearm. Fxn has been reported up to 7 y from transplantation (*Fertil Steril* 2010;93(3):762).
- Fertility preserving surgeries for gynecologic malignancies:
  - **Cervical cancer** → trachelectomy in pts w/ tumor <2 cm in size & w/o lymph node metastasis; cerclage must be placed at time of Surg. Higher risk of 2nd trimester loss & preterm deliv.
  - **Endometrial cancer** → progest therapy if well-differentiated tumor w/o lymph node involvement. Initial resp rate >60% in selected pts. Definitive therapy w/ hysterectomy should be performed as recurrence risk >50%.
  - **Ovarian cancer** → unilateral salpingo-oophorectomy & lymph node dissection in malig germ cell tumor or early stage epithelial ovarian cancer

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PREIMPLANTATION GENETIC TESTING

Definition (*Fertil Steril* 2008;90:S136)
- New technology for pts undergoing ART w/ goal of assessment for gene mut & aneuploidy prior to implantation to establish unaffected Preg
- **PGD:** Genetic testing of embryo when 1 or both of genetic parents are known to carry a specific gene mut or balanced chromosomal rearrangement
- **PGS:** Screening of embryo for aneuploidy in chromosomally nml couples

Indications
- Avoid Preg termination w/ fetus at risk for heritable debilitating dz, or medically indicated sex selection
- Reduce recurrent Preg loss in pts w/ known balanced chromosomal translocations

Procedure
- Small opening created in zona pellucida, cell or polar body extracted using small suction pipette, genetic analysis performed by PCR to assess gene defects, FISH for chromosomal anomalies
- 1st & 2nd polar bodies may be removed from oocytes after retrieval if genetic mother carrying detectable mut
- Blastomeres may be aspirated from embryo 3 d following fertilization

Counseling
- Embryo bx & culture may lower viability of Preg (*NEJM* 2007;357:9). Unanticipated birth of affected offspring – unprotected sex resulting in Preg, xfer of wrong embryo, misdiagnosis. Disposition of embryos found to have genetic anomalies & not used for xfer. False-positive results may result in discard of potentially nml embryos. Confirmatory prenatal testing after PGD recommended – CVS or amniocentesis.

OVARIAN HYPERSTIMULATION SYNDROME (OHSS)

Definition and Epidemiology (*Fertil Steril* 2008;90:S188)
- Life-threatening complication of ovulation induction characterized by ovarian enlargement due to multi ovarian cysts & acute fluid shift out of intravascular space. Occurs in 0.2–6% ovulation induction cycles.
- **Risk factors:** Prior Hx of OHSS, age <35 y, low body weight, PCOS, higher doses of exogenous gonadotropins, high absolute or rapidly rising serum E2 levels. Preg increases likelihood, duration, & severity of OHSS.

Pathophysiology
- Main trigger: hCG – physiologic or exogenous
- Ovarian enlargement due to stimulation by gonadotropins → ↑ ovarian hormones & vasoactive substances (cytokines, angiotensin, VEGF) → ↑ capillary permeability & acute 3rd space sequestration
- Massive extracellular exudative fluid accum & sev intravascular volume depletion & hemoconcentration → multi organ system failure

Clinical Manifestations
- **Signs/sx:** Bloating, abdominal discomfort & distention, emesis, diarrhea, rapid weight gain, tense ascites, hemodynamic instability, respiratory difficulty (tachypnea), oliguria, HoTN, other signs of intravascular hypovolemia
- **Lab findings:** Hemoconcentration (↑ Hct, leukocytosis, thrombocytosis), electrolyte imbalance (HoNa, hyperK, metabolic acidosis), ↑ Cr, ↑ liver enzymes
- **Life-threatening complications:** Acute renal failure, ARDS, heart failure, hemorrhage from ovarian rupture, thromboembolism

Treatment
- **Self-limited:** Rx mostly for symptomatic relief & stabilization
- **Outpt mgmt for mild cases:** Analgesia for pain, oral hydration, monitoring for progression. Serial labs, serial US, daily weights. No intercourse, no strenuous activity to reduce risk of cyst rupture or ovarian torsion.
- **Hospitalization & ICU care – supportive:** Fluid mgmt – strict I&O, IV fluids (D5 NS MIVF 25% albumin prn) to maintain urine output & BP. Thoracentesis, culdocentesis, & paracentesis under US guidance as needed. Ppx against thromboembolism – venous support stockings, pneumatic compression devices,

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prophylactic heparin or lovenox. ICU admission for mgmt of thromboembolic complications, pulm compromise, or renal failure. Cardiac: Invasive monitoring of CVP, PCWP. Pulm: Oxygen suppl, assisted ventilation, thoracentesis. Renal: Low-dose dopamine for renal compromise → renal vessel dilation → ↑ renal bld flow. May require short-term dialysis.

Prevention (*Fertil Steril* 2010;94:389)

- Carefully monit after gonadotropins, esp for rapidly rising E2 levels, E2 >2500 pg/mL, or US evid of emergence of large number of intermediate-sized follicles (10–14 mm). Use minimum dose & duration of gonadotropin therapy necessary to achieve therapeutic goal. Delay administration of hCG until estradiol levels plateau or ↓. Use GnRH agonist (eg, leuprolide) instead of hCG (can only be used in antag cycles). Use cabergoline (dopamine agonist) to reduce ovarian resp to FSH.

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ROUTINE PRENATAL VISITS

Common Obstetric Terms

- **Gravidity:** Number of times a woman has been pregnant (including current Preg)
- **Parity:** Preg outcomes, using TPAL system. 4 numbers indicating prior ***Term*** deliveries/***Preterm*** deliveries/***Abortions***/***Living*** children (eg, G3P1021). Deliv refers to a single event, not the number of births (ie, multiples count as 1 deliv event). Eg, G3P0112 = currently in 3rd preg, after 1 abortion & 1 preterm deliv of twins (both alive)
  - **T** = Term: ≥37 w0d
  - **P** = Preterm: 20 w0d–36 w6d
  - **A** = Abortus: Spont or induced losses <20 w0d
  - **L** = Living: Living children at the time of the encounter
- **EDD:** Initially determined from 1st day of LMP. Accurate dating is crucial for Preg mgmt. EDD is 280 d (±13 d; or 40 w) from LMP. Dating can be confirmed by US if menses are irreg, LMP uncertain, if conception occurred while on contraception, or if there is a size-dates discrep. US most accurate prior to 12 w & should be compared to LMP. Later sono dating less accurate (±2 w in 2nd trimester, ±3 w in 3rd trimester). US = LMP EDD if w/i:
  4 d btw 6–9 w6d gest
  7 d btw 10–13 w6d gest
  10 d btw 14–20 w0d gest
- **Viability:** ~24 w0d. Previable: <~24 w0d
- **Early term:** 37 w0d–38 w6d. **Full term:** 39 w0d–40 w6d. **Late term:** 41 w0d–41 w6d
- **Post term:** ≥42 w0d, ↑ stillbirth risk (*JAMA* 2013;309:2445)
- **Primigravida:** 1st Preg
- **Nulliparous** (nullip): No prior birth events (regardless of outcome)
- **Primiparous:** Gave birth once (ie, >20 w, or once for "T + P" in TPAL system)
- **Multiparous:** Gave birth more than once (parity does not include ABs)
- **Grand multipara:** Woman who has delivered 5 or more times
- **NT:** Thickness of nuchal fluid on 1st trimester sono, ↑ in Down syn
- **Triple screen:** uE3 + hCG + AFP to evaluate for Trisomy 21, Trisomy 18, NTDs
- **Quad screen:** Triple screen + inhibin A
- **IUGR** = <10%ile for gestational age
- **GLT** (screening): 50 g oral gluc → 1 h serum gluc
- **GTT:** 100 g oral gluc after fasting → 1, 2, 3 h post gluc
- **FH:** FH-measurement from pubic bone to top of fundus correlates w/ GA after 20 w (20 w = umbilicus, add 1 cm/w after that). FH misses 30% IUGR.

Summary of prenatal care by gestational age	
GA	**General mgmt & special screening by approximate weeks GA**
1st trimester (Weeks 0–14)	Complete H&P w/ careful review of Ob-Gyn Hx, FHx, meds, nutrition, social history (SHx). Determine EDD, Viability (US). Social services (if high risk), social & DV screen. Prenatal 1st visit labs (CBC, T&S, HBsAg, RPR, Rubella, HIV, ±Hgb electrophoresis, ±HCV, ±CF, HbA1c if suspect DM [or do early GLT], GC/CT, Pap, UA/C&S, PPD [or QuantiFERON]) Offer aneuploidy screening: NT @ 10–13 w, mat serum screening (1st trimester 10–13 w6d; 2nd trimester 15–22 w6d; or mat cell free fetal DNA). See Genetic Screening. Visits every 4 w to check fetal heart tones.
2nd trimester (Weeks 14–28)	15–22 w6d: AFP, Quad screen, or 2nd part of integrated/sequential screen. 18–22 w: Sono for fetal anatomy, placentation, AFI, adnexae, CL. 25–28 w: 3rd trimester labs (GLT → ±GTT, CBC, recheck RPR, T&S, HIV if ↑ risk). Rhogam for Rh negative. Visits every 4 w for FH, fetal heart tones. Plan contraception & feeding.
3rd trimester (Weeks 28–42)	35–36 w: Perineal swab for GBS; clinic sono for presenting part; deliv planning & counseling; GC/CT rpt if high risk. If CHTN, GHTN, DM, GDMA2, other high-risk factors: ±fetal testing 1–2×/w (BPP or NST starting 32–36 w, depending on problem). 25–33 w: Visits q4w to check for FH & fetal heart tones; 33–37 w: q2w; 37 w – deliv: Visits qw; induce after 41 w, or continue to 42 w0d w/ twice weekly NST/AFI for fetal assessment.

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Considerations in Routine Prenatal Care

- **OB review of systems:** Every encounter ask about VB, LOF, CTX, & FM, & other systems by complaint.
  1st FM: 16–18 w if multiparous, 18–20 w if nulliparous
- **Physical:** BP, weight (current & interval change), FHR, & FH at each visit. Complete PE & pelvic exam at 1st prenatal visit.
  FHR: Detected by Doppler at 10–12 w & by fetoscope at 18–20 w (w/ nml BMI)
- **Cervical exam:** Assess dilation, effacement, station near term.
- **Psychosocial screening:** Tobacco use, EtOH use, DV, nutrition, psychosocial situations, job-related risks & high-risk behaviors.
  Tobacco: Encourage tobacco cessation each visit; ~50% of ♀ quit smoking during or before their Preg. ~50% resume smoking w/i 1-y postpartum. A/w IUGR, low birth weight, placental abruption, placenta previa, PPROM, ectopic Preg, & perinatal mortality. Children of smokers ↑ asthma, colic, obesity, & SIDS. Counsel using 5 A's strategy (Ask, Advise, Assess, Assist, Arrange). Nicotine replacement not well assessed, but likely safer than smoking. Bupropion & varenicline less used in Preg.
  EtOH: *No safe threshold* a/w mental retardation, neurologic deficits, fetal EtOH syn (esp w/ chronic EtOH use; growth restriction, facial anomalies, & CNS deficits).
  DV: Red flags include unwanted Preg, late presentation for PNC, substance abuse, poor weight gain, & multi somatic complaints.
- **GDM screening:** 2-step approach w/ GLT then GTT. See Chap. 17. Perform btw 24 & 28 w. Opt out for extremely low risk considered (age <25, BMI <25, no FHx of DM, no personal h/o gluc intolerance, no h/o adverse obstetrical outcomes a/w DM, & not of an ethnic group w/ ↑ risk DM).
- **Vaccines:** See Chap. 1. Influenza vaccine recommended for all pregnant women. TDaP recommended for all in 3rd trimester (↑ transplacental IgG immunity for neonate) or postpartum if >10 y since last dose. (*MMWR* 2011;60:1424). Postpartum vax for rubella or varicella if nonimmune.
- **GBS screening** at 35–37 w or if deliv anticipated (every Preg) (*Obstet Gynecol* 2011;117:1019). See Chap. 10. Swab lower vagina, introitus, & rectum. Cx valid for 5 w. For pts w/ sev PCN allergy (anaphylaxis, angioedema, respiratory distress, urticarial) → request clindamycin & erythromycin sens testing.

Physiologic Changes of Pregnancy (*Best Pract Res Clin Obstet Gynaecol* 2008;(5):801)

- **Cardiovascular:** ↓ SVR → ↑ HR. BP ↓ early (~10% by 7–8 w) → nadir at 24 w → gradual ↑ to term. Cardiac output ↑ in 1st trimester → peaks in 2nd trimester at 30–50% above nonpregnant values. See Chap. 12.
- **Respiratory:** O_2 consump ↑ 30–50 mL/min (2/3 due to mat requirement, 1/3 for fetal). Tidal vol ↑ to 500–700 mL (prepregnancy of 200 mL). Respiratory rate unchanged. Minute ventilation ↑ from 7.5–10.5 L/min. Functional residual capacity ↓ by 500 mL. Vital capacity unchanged. See Chap. 13.
- **Renal:** Renal bld flow ↑ 35–60%. Kidneys ~1 cm larger w/ ↑ in bld vol; renal pelves, calyces, & ureters ↑ in size in resp to progesterone. GFR ↑ 40–50%, peaks at 180 mL/min by the end of 1st trimester. See Chap. 14.
- **Gastrointestinal:** Progesterone → ↓ esoph sphincter tone → GERD. Delayed gastric emptying & ↑ intestinal transition time. Increased constip. See Chap. 15.
- **Hematologic:** Plasma vol ↑s rapidly. 10% ↑ by 7 w → plateau at 32 w ~50% above nonpregnant → dilutional anemia of Preg. Red cell mass ↑ 18–25% secondary to ↑ erythropoietin. Nml Preg Hgb 11–12 g/dL. WBC ↑ in 1st trimester → plateau at 30 w. Nml Preg WBC 5000–12000/mm^3. Platelet count ↓ due to dilution &/or increased consump. Mild thrombocytopenia (100000–150000/mm^3) seen in ~8% of pregnancies. Preg is a procoagulable state, predisposing to thromboembolisms w/ 4–6 fold ↑ DVT. Factors VII, VIII, IX, X, & XII; fibrinogen; von Willebrand factor; antithrombin III; & prot C ↑. Factor XI & prot S ↓. Prothrombin & Factor V are unchanged. See Chap. 16.
- **Endocrine:** ↑ hepatic production of thyroid-binding globulin → ↑ total T4. Free T4 essentially unchanged (except for transient ↑ from hCG's thyrotropin-like activity in 1st trimester). TSH falls in 1st trimester, then normalizes. No real change in mat thyroid status. Pancr islet cells undergo hyperplasia → ↑ insulin secretion. Placental factors ↓ mat insulin sens. Pituitary ↑ 135%, but no optic nerve compression. Prolactin levels peak at term. See Chap. 17.

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NUTRITION IN PREGNANCY

Weight Management

- **Caloric intake:** Encourage balanced diet.
  1st trimester: No additional caloric intake from baseline
  2nd trimester: ↑ 340 kcal/d from baseline
  3rd trimester: ↑ 452 kcal/d from baseline

Recommended weight gain during pregnancy by BMI		
Category	**BMI**	**Weight gain**
Underweight	<18.5 kg/m^2	12.7–18 kg (28–40 lb)
Nml weight	18.5–24.9 kg/m^2	11.3–15.8 kg (25–35 lb)
Overweight	25–29.9 kg/m^2	6.8–11.3 kg (15–25 lb)
Obese	≥30 kg/m^2	0.45–9.1 kg (11–20 lb)

- **Obesity in Preg:** ↑ complications w/ ↑ BMI. Encourage preconception weight loss. Preg is high-risk period for excessive weight gain → long-term obesity. Nutrition consultation: Encourage adherence to 0.45–9.1 kg (11–20 lb) weight gain. Pregnant women w/ BMI >30: ↑ rates of GHTN, preeclampsia, gestational diabetes, macrosomia, & cesarean deliv. Consider HbA1C or early GLT for pre-existing diabetes.
- **Exercise in Preg:** ACOG recommends ≥30 min of mod daily exercise. Avoid activities w/ high risk for abdominal trauma (eg, horseback riding, skiing/snowboarding), or Scuba diving. Terminate exercise w/ bleeding, preterm labor, ↓ FM, LOF, chest pain, dizziness, dyspnea prior to exertion. Absolute contraindications to exercise: Heart or lung dzs, incompetent cervix, multi gest, VB, placenta previa, pregnancy-induced HTN, rupture of membranes (*Int J Gynaecol Obstet* 2002;77:79).

Food Warnings

- **Methylmercury:** High levels can cause CNS damage & mild dysfxn in fetus. Avoid: Shark, swordfish, king mackerel, or tilefish. Limit albacore tuna to 6 oz/w. Encourage 12 oz (~2 servings) of low mercury fish weekly.
- **Caffeine:** Mod consump safe (<200 mg/d). One 8 oz coffee = ~95 mg caffeine. Mod (<200 mg/d) consump not a/w miscarriage (*Am J Obstet Gynecol* 2008;198:279). No clear evid for caffeine ↑ risk of IUGR (*JAMA* 1993;269:593).
- **Vit A:** Limit to 750 μg/d (*Lancet* 2010;375:1640). Deficiency common in developing countries. Supplements improve night blindness & anemia w/o teratogenicity. >3000 μg/d (10000 IU) → ↑ fetal malformations.
- **Food-borne illness:** Encourage good hand hygiene & thorough cooking
  Listeriosis: Processed meats, soft cheeses, meat spreads, & pate.
  Brucellosis: Unpasteurized milk & cheese made from raw milk.
  Toxoplasmosis: Undercooked meats & contaminated vegetables > cat feces.
- **Pica:** Consuming nonfood substances (*J Am Diet Assoc* 1991;91:34). More common in Preg. Avoid pica & screen for iron-deficiency anemia (unclear mech). Can → lead tox or infectious dz (esp developing settings).

Nutrients in Pregnancy

Macro- and micronutrients in pregnancy			
	Nonpregnant	**Pregnant**	**Comments**
Prot	0.8 g/kg/d	1.1 g/kg/d	Vegetarian women may be advised to supplement specific amino acids not found in vegetable prot sources
Carbs	130 g/d	175 g/d	
Iron	15 mg/d	30 mg/d	If anemic, need btw 30 & 120 mg daily
Calcium	1000 mg/d	1000 mg/d	Body mobilizes calcium stores in Preg so ↑ intake generally not needed.
Folic acid	0.4 mg/d preconception	0.4–4 mg/d	See Folic acid below

- **Folic acid:** ↓s NTDs. NT forms during week 4 of gest → start folate prior to Preg. Low-risk women, use 0.4 mg/d (common dose in prenatal vitamins). Women w/ h/o NTD in prior Preg → 4 mg/d (72% ↓ in recurrence risk). If on antiepileptic drugs, also ↑ folate dose.

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- **Vit D:** Deficiency common in Preg (newborn levels dependent on mat levels), esp vegetarians, limited sun exposure, & dark-skinned ethnicity. Deficiency = 25-OH-D < 20. No routine screening for Vit D in Preg. Suppl w/ 1000–2000 IU/d *(Obstet Gynecol* 2011;118:197).

CLINICAL PELVIMETRY

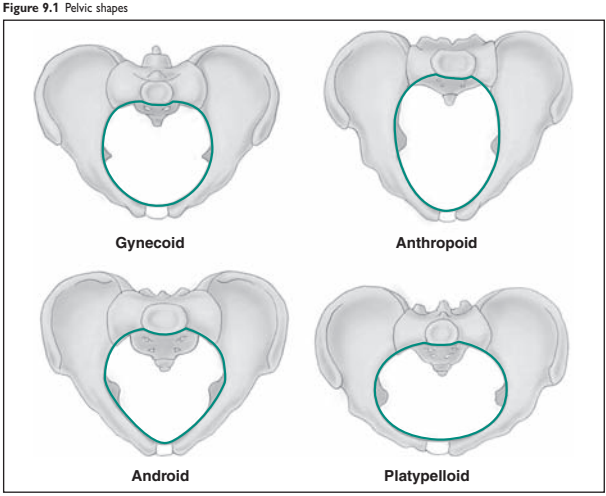
Pelvic Anatomy

- **Pelvis:** Sacrum, coccyx, & *innomin bones*. Innomin = *ilium, ischium,* & *pubis* → join sacrum at *sacroiliac jnts* & each other at *symphysis pubis*.
- **Linea terminalis** (aka innomin line): Divides false & true pelves
  - **False pelvis:** Above linea terminalis, bounded by lumbar vertebra, iliac fossa, & anter abdominal wall
  - **True pelvis:** Clinically important for parturition; it includes:
    - **Post:** Anter surface of the sacrum
    - **Lateral:** Inner surface of ischial bones
    - **Anter:** Pubic bones & ascending rami of ischial bones

Planes and Diameters of the Pelvis

- **Obstetric Conjugate** (OC; aka AP diameter): Obstetrically relevant diameter. Shortest distance btw the promontory of the sacrum & the symphysis pubis. Measured indirectly by subtracting 1.5–2 cm from the *diagonal conjugate*.
- **Diagonal conjugate:** Distance btw lower margin of symphysis to sacral promontory. Measured clinically w/ examining hand & used to calculate OC.
- **Transverse diameter:** Distance btw linea terminalis on either side. At right angle to obstetrical conjugate. Largest diameter of pelvis.
- **Interspinous diameter:** In midpelvis. Smallest pelvic diameter, but usually >10 cm.

Figure 9.1 Pelvic shapes



(From Klossner NJ, Hatfield NT. *Introductory Maternity & Pediatric Nursing*. 2nd ed. Philadelphia, PA: Wolters Kluwer Health; 2010)

Normal AP and transverse diameters of pelvis by shape				
	Gynecoid	**Anthropoid**	**Android**	**Platypelloid**
AP diameter	12 cm	>12 cm	12 cm	12 cm
Transverse diameter	11 cm	<12 cm	11 cm	10 cm
Description	"Ideal"	Upright oval	Heart shaped	Sideways oval

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Pelvic Shapes

- **Caldwell & Moloy classification:** Describes 4 ideal types, recognizing there are variations in pelvic shape. Characterized primarily by the transverse & interspinous diameter.
- **Gynecoid:** Deemed "ideal" w/ wide pelvic inlet & outlet & straight sidewalls
- **Anthropoid:** Narrow transverse diameter but wide AP diameter
- **Platypelloid:** Wide inlet & outlet w/ narrow AP diameter & sacral inclination
- **Android:** Straight sidewalls w/ narrow subpubic arch & narrow incline of sacrum

Pelvimetry in OB Practice

- **Clinical:** Clinical exam of pelvis to predict CPD
  Clinical pelvimetry = poor predictor of CPD
- **Radiologic pelvimetry:** X-ray or MRI to predict CPD. Radiographic pelvimetry studies → no impact on mat or neonat morbidity or mortality (*Cochrane Database Syst Rev* 2000:CD000161).
- Pelvimetry largely replaced by trial of labor. No evid to recommend Cesarean deliv for concerns for CPD based on clinical or radiographic pelvimetry.

COMMON PRENATAL COMPLAINTS

Nausea and Vomiting (*Obstet Gynecol* 2004;103:803)

- **NVP:** 70–85% of pregnancies. ↑ hCG & estrogen → NVP. Typically presents <9 w ± abdominal pain. If abd pain & fever → broader diff. 50% resolves by 14 w; 90% by 22 w (*Am J Obstet Gyn* 2000;182:931).
  Therapy: Small, frequent meals w/ bland low-fat foods (BRAT diet). Use of ginger can be effective. Encourage hydration.
  1st-line meds: Vit B6 (10–15 mg TID-QID) & antihistamines (doxylamine)
  2nd-line meds: Promethazine, metoclopramide, then ondansetron
- **Hyperemesis Gravidarum (HEG):** NVP significant enough to cause dehyd, metabolic alkalosis, ketonuria, weight loss (>5%), hypokalemia. <1% of pregnancies. Risks: Multi gest, FHx, or personal Hx in prior Preg.
- **W/u:** Labs may show elevated transaminases (<300), Amy, & lipase; hypochloremic metabolic alkalosis; suppressed TSH & ↑ thyroxine; ketones on UA
- **Therapy:** IV hydration (w/ dextrose ± thiamine), enteral nutrition (eg, tube feeding), hospitalization for monitoring & suppl as above

Carpal Tunnel Syndrome (CTS) (*Muscle Nerve* 2006; 34:559)

- **Incid** btw 2 & 35%; most often in 3rd trimester. Risks: H/o CTS in prior Preg, age >30, nulliparous, edema. Caused by compression of median nerve related to edema in Preg. Sx include numbness, pain, paresthesias of thumb, index, & middle fingers, often worse at night. Exacerbated by flexion or extension of wrist, improved by mvmt of hands.
- **Exam:** ± median nerve sensory deficit. Phalen test: Pain reproduced w/ prolonged (>60 s) flexion of wrists. Tinel test: Pain reproducible w/ percussion at wrist over median nerve.
- **Rx:** Low salt diet, physical therapy, wrist bracing, Tylenol → consider Cort injections for refrac cases. Surgical intervention generally not indicated, sx improve w/i 1 y of deliv (4–50% persist at 1 y).

Round Ligament Pain

- **Anatomy:** Origin at uterine fundus → inguinal canal, terminates in labia majora.
- **Presentation:** Lower abdominal pain (more common in right lower quadrant). Exacerbated by mvmt, often reported as "shooting pain into vagina." Case reports of association w/ endometriosis, lipomas, & varicosities. Dx depends on ruling out other etiologies (eg, torsion, appendicitis, preterm labor).
- **Rx:** Typically self-limited. Advise acetaminophen, rest, & reassurance. Belly-band can be helpful.

Lower Extremity Edema

- **Physiologic changes** in Preg predispose to edema dev. SVR ↓, venous return impeded by gravid uterus. Water retention mediated by ↓ plasma osmolality due to osmolar reset of vasopressin & thirst thresholds (*Br J Obstet Gynaecol* 1985;92:1131).
- **Rx:** Elevation of feet & support stockings. Counsel women to report nonsymmetric edema or nondependent edema as these can be signs of pathology such as DVT or preeclampsia.

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Low Back Pain (*Obstet Gynecol* 2004;104:65)

- Up to 70% report LBP during Preg. Risks: LBP outside of Preg, in a prev Preg, or w/ menstruation.
- **Presentation:** Attributed to changes in posture & joint laxity. Pain exacerbated by mvmt, relieved by rest. ± assoc neurologic sx.
- **Exam:** Eval motor/sensory fxn & reflexes to detect radiculopathy. Paraspinal or joint tenderness to palpation & ↓ range of motion. Imaging not indicated in the absence of progressive neuro signs or trauma.
- **Rx:** Avoid excessive weight gain, lifting heavy objects, prolonged standing, bending from waist. Recommend shoes w/ arch support & sleeping on side w/ pillow btw knees. Use of good body mechanics when lifting & getting out of vehicles is critical. Exercise, acupuncture, support belts may be helpful adjuncts (*Cochrane Database Syst Rev* 2007;18(2)).

Lower Extremity Varicosities

- **Pathophysiology:** Femoral venous pres ↑ in Preg up to 24 mm Hg secondary to uterine compression on IVC. Pressures closer to 8 mm Hg (pregravid state) in lateral recumbent position (*Surg Gynecol Obstet* 1950;90:481).
- **Presentation:** Sx vary from cosmetic complaints to a range of discomfort. Throbbing pain that may worsen w/ advancing Preg, weight gain, & standing.
- **Rx:** Periodic elevation of feet & support stockings. Surgical correction during Preg generally avoided unless sev sx.

Vulvar Varicosities

- **Pathophysiology:** 4% lifetime prevalence, most often occurring during Preg b/c of ↑ venous pressures & ↑ pelvic bld flow. "Vulvar veins lack valves"
- **Presentation:** Often asymptomatic & noted only on exam. Pelvic discomfort & swelling worsened with standing or intercourse.
- **Mgmt:** Reassurance – most vulvar varicosities regress postpartum. Vulvar support belt for sev sx or local excision for thrombosis. Vaginal deliv not contraindicated despite theoretical risk of hemorrhage w/ laceration.

Hemorrhoids

- **Pathophysiology:** Arise w/i plexus of inferior & superior hemorrhoidal veins. ↑ venous pressures in Preg → engorgement both internally & externally → venous stasis → thrombosis & pain/swelling.
- **Presentation:** Painless bleeding w/ defecation or anal pruritus. Sev pain or complaints of a palpable lump can occur w/ thrombosis. External hemorrhoids visualized as dilated veins; thrombosis felt on palpation during rectal exam.
- **Rx:** Supportive w/ local anesthesia, hydration, & stool softeners. Topical anesthetics or steroid creams along w/ warm soaks can provide local relief. Thrombosis can be treated w/ excision under local anesthesia.

FETAL ULTRASOUND: ANATOMY AND ECHOCARDIOGRAPHY

Basic Second Trimester Ultrasound (*Obstet Gynecol* 2009;113:451)

- **Fetal viability:** Fetal cardiac activity (including HR & any abn rhythms)
- **Fetal number:** In multi gestations, document chorionicity (number of placentas), amnionicity (number of membranes), fetal gender, comparison of fetal size, amniotic fluid.
- **AFV:** Described subjectively or by semiquantitative methods
  - **AFI:** Sum of depth (cm) of fluid pockets not containing cord or fetal extremities in each of 4 quadrants of the uterus. Quadrants divided by intersection of umbilicus & linea nigra.
  - **SDP:** Vertical depth (cm) of deepest pocket of fluid not containing cord or fetal extremities. Also called MVP, other.
- **Placental location:** Describing location (anter/post) & relation to internal os. Endovaginal US should be performed if internal cervical os not clearly visualized. Placental abnormalities (eg, previa) should be followed up w/ 3rd trimester US.
- **Umbilical cord:** The number of umbilical arteries should be noted.
- **CL:** Not currently a rec for low-risk pop. Recommendations for CL screening are evolving. Screening CL at anatomy US after 16 w GA is reasonable. Endovaginal US w/ empty bladder more accurate.
- **GA:** Most accurate in 1st trimester; 2nd trimester determination includes:
  - **BPD:** Measured at level of thalamus & cavum septum pellucidum.

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HC: More reliable than BPD if head shape flattened or rounded.
AC: Measured at junction of umbilical vein, portal sinus, & stomach. Can compare to BPD to determine symmetric macrosomia or IUGR.
FL: Long axis of femur not including the distal & prox epiphyses.
- **EFW:** Combination of BPD, HC, AC, & FL to determine EFW. EFW compared to known values to establish %ile & establish macrosomia/IUGR.

Fetal Anatomy Ultrasound (*J Ultrasound Med* 2010;29:157)
- Routinely performed at 18–20 w GA. Thorough assessment of fetal structures.
  Head, face, neck: Cerebellum, choroid plexus, cisterna magna, lateral cerebral ventricles, midline falx, cavum septum pellucidum, upper lip
  Chest: Cardiac exam including 4-chamber view & outflow tracts
  Abd: Stomach, kidneys, bladder, umbilical cord insertion, umbilical cord vessels
  Spine: Including cervical, thoracic, & sacral spine
  Extremities: Arms & legs including feet & hands
- **Routine screening:**
  RADIUS trial: 15151 women randomized to screening US vs. US only if other indications; detection rate of 34% vs. 11%, respectively, for fetal anomalies; no change in other outcomes (*Am J Obstet Gynecol* 1994;171:392).
  Eurofetus trial: Large 3-y study revealing 61% sens of US to detect fetal anomalies. Neurologic/urologic anomalies more commonly detected than cardiac (88/89% vs. 20%) (*Am J Obstet Gynecol* 1999;181:446).
  Detection depends on prevalence of anomalies. Detection of anomalies higher in academic compared to community centers. Image quality has improved tremendously since these trials. More anomalies can be identified, though the clinical implications are unclear.
- **Aneuploidy screening:** US alone not adequate for trisomy 21 (T21) or other aneuploidy. Presence or absence of fetal anomalies a/w T21, such as cardiac anomalies & duodenal atresia, confers ↑ or ↓ risk, respectively. ↑ NT on 1st trimester US identifies ↑ risk of aneuploidy. **Soft markers:** Echogenic bowel, EIF, short femur or humerus, & dilated renal pelvis. Absence of "soft markers" for Down syn on US ↓ a priori risk of T21 or mat serum screening risk by 50%.

Fetal Echocardiography (*J Ultrasound Med* 2011;30:127)
- **CHD:** Leading cause of mortality & morbidity. Prenatal dx offers planning for infant & intervention at birth.
- **Indications:** Used as adjunct to routine US screening, btw 18 & 22 w
- **Mat indications:** Autoimmune antibodies, familial inherited cardiac d/o, 1st- or 2nd-degree relative w/ CHD or syndromes w/ CHD, IVF, metabolic dz, cardiac teratogen exposure, rubella exposure 1st trimester
- **Fetal indications:** Abn cardiac screening exam, abn HR or rhythm, fetal chromosomal anomaly, extracardiac anomaly, hydrops, ↑ NT, monochorionic twins, unexplained sev polyhydramnios

CONGENITAL ANOMALIES

Definitions and Terminology
- **Terminology:** Description related to etiology
  Malformation: Due to an intrinsic process in embryonic dev (prior to 8 w).
  Deformation: Due to intrauterine process unrelated to fetus (eg, tumor, multi gest).
  Disruption: Due to interference w/ nml dev (eg, amniotic band syn).
  Dysplasia: Due to abn growth of cells into tissues.
- **Patterns of anomalies:** Multi anomalies can be described by overarching descriptors.
  Syndrome: Assoc anomalies due to single pathologic etiology (eg, Turner syn)
  Sequence: Group of anomalies related to a common upstream pathologic cause (eg, Potter's sequence in which renal agenesis → oligohydramnios → bone fractures).
  Developmental field defect: Due to disruption of dev in a particular region of the embryo that leads to disruption in related areas (eg, bladder exstrophy)
  Association: Group of anomalies unrelated pathologically occurring more commonly than one would expect by chance (eg, VACTERL association).

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Teratogens

- **Definition:** An agent that causes an anomaly in the developing fetus.
  Mat illness: Due to toxic metabolites or antibodies from mother crossing placenta.
  Pregestational diabetes: 6–7% risk (2× nml pop) of congen anomalies including NTDs, congenital heart disease (CHD) & caudal agenesis (rare but 15–20% causes a/w DM).
  Systemic lupus erythematosus: A/w fetal congen complete heart block.
  Infxn: Commonly TORCH infxns, varicella, or parvovirus B19. Nonspecific US findings: Microcephaly, calcifications, IUGR, HSM, hydrops, cardiac malformations.
  Meds: Thalidomide & its association w/ limb reduction is classic example.
  Environmental: Lead, ionizing radiation, fever, hyperthermia, & mercury consump.

Embryologic development by organ system

System	Embryology	Timing
Neural tube	Neural plate → neural folds → fuse to form neural tube	Weeks 3–4
Cardiovascular	Primitive heart tube → looping & division → formation of primitive structures (BC, outflow tracts, sinus venosus, PA, & PV) → septum primum/ secundum separate RA & LA → endocardial cushions divide atria & ventric → BC becomes RV & PV becomes LV separated by musc ventricular septum → outflow tract septates & divides & remodeling forms semilunar valves	Weeks 4–8: Week 4 primitive heart tube is formed & begins looping → weeks 4–5 atria divided by septum primum → week 6 ventricles divided → weeks 7 & 8 outflow tract divided
Pulm	Bronchial tree & assoc pulm arteries undergo branching & division	Weeks 3–16 Surfactant production starts at 20 w
Gastrointestinal	Physiologic herniation of abdominal contents into extraembryonic coelom to allow space for growth of abdominal organs	Weeks 9–11. Physiologic herniation resolved by 12 w
Genitourinary	Pronephros → mesonephros → ureteric bud → invades metanephric blastema to make metanephros → kidney → migrates caudally. Metanephros fuses w/ cloaca to make bladder	Develops weeks 4–6. Producing urine by week 11 Bladder fusion begins at week 5

Neural Tube Defects (*Int J Gynaecol Obstet* 2003;83:123)

- **Epidemiology:** 1.4–2 per 1000 pregnancies; 2nd most common anomaly worldwide.
- **Etiology:** NTDs not a/w syndromes can be genetic or environmental.
  Genetic: Risk of NTDs higher in pts who have a child w/ prior NTD; only 5% of NTDs have familial association.
  Environmental: Assoc factors include diet (low folic acid consump), teratogen exposure (anticonvulsants, Vit A), mat diabetes w/ poor 1st trimester gluc control, high mat core temperature in the 1st trimester.
- **Pathophysiology:** Failure of closure
  Cranial defects: Egs, anencephaly, encephalocele, exencephaly, iniencephaly. All cranial defects except small encephaloceles (failure of skull formation w/ extrusion of brain into membranous sac) are lethal. Termination of Preg valid option.
  Spinal defects: Often a/w ventriculomegaly (often require shunt placement)
  Spina bifida: Failure of fusion of caudal portion of neural tube
  Meningocele: Failure of fusion, meninges exposed
  Meningomyelocele: Failure of fusion, meninges & neural tissue exposed
- **Clinical manifestations:** Higher lesions generally indicate worse prog
  Bladder/bowel: Dysfxn common, even w/ lower spinal lesions. Bladder dysfxn → UTIs, stones, & significant morbidity. Sexual dysfxn common.

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Neuro: Sensory & motor handicap correlated w/ level of lesion; ventriculomegaly a/w ↓ intelligence quotient.

- **Dx:** ↑ amniotic fluid & mat serum AFP
  Screening: 89–100% of pregnancies w/ NTD have ↑ MSAFP
  Other causes of ↑ MSFAP: (1) incorrect GA, (2) multi gestations, (3) abdominal wall defects, (4) abnormalities of placentation such as accreta (↑ MSAFP risk factor for placental abruption), (5) IUFD, (6) Finnish nephrosis, (7) sev skin anomalies such as lethal ichthyosis.
  US able to identify many causes – done after MSAFP collection at a GA that will allow for detailed analysis of fetal anatomy.
  US: 97% sens & 100% spec for NTD in experienced centers.
  Dx: 2% of women w/ positive MSAFP have fetus w/ NTD. Confirmatory test can be an amniocentesis for AFP.
  If ↑ amniotic AFP → confirmatory testing (AF acetylcholinesterase – 2.2/1000 false positive rate)
- **Prevention:** Avoidance of teratogens & suppl w/ folic acid (see *Nutrition*)
  This behavior should start prior to Preg & continue throughout Preg.
- **Rx:** Deliv at hospital w/ NICU support; consideration of fetal Surg
  Breech presentation common in fetus w/ NTD necessitating Cesarean deliv; vaginal deliv should be considered if fetus in cephalic presentation.

Other Neurologic Anomalies

- **Ventriculomegaly:** ↑ vol of cerebral ventricles on US.
  Isolated: Often found to be a/w NTD or other malformations after birth.
  Associations: Can be related to infxn (toxoplasmosis, CMV, lymphocytic choriomeningitis virus), genetic syndromes, or aneuploidy.
  W/u: Amniocentesis should be offered for aneuploidy/infxn w/u. F/u 3rd trimester scan should look for progression or other identifiable causes.
- **Hydrocephalus:** Pathologic ventriculomegaly from ↑ pres
- **CPCs:** Cystic sonolucent lesions w/i choroid plexus
  Not a true anomaly, but identified as marker of aneuploidy (esp Trisomy 18). Isolated CPCs usually benign & typically resolve by 3rd trimester.

Cardiovascular Anomalies

- **Nonimmune hydrops fetalis NIHF:** Cardiac anomalies cause up to 40% of NIHF.
  Manifestations: Pts can present w/ size > dates & ↓ FM. US: Ascites (visualized as rim of fluid around abdominal organs), pleural effusions, pericardial effusions, skin edema (late finding), polyhydramnios, & placentomegaly.
  Associations: Structural heart dx, tachyarrhythmias (treated by giving rate-controlling agents to mother or directly to fetus), or bradyarrhythmias.
- **Hypoplastic left heart syndrome HLHS:**
  Anatomy: Underdeveloped LV w/ hypoplasia, stenosis, or atresia of aortic valve, MV, &/or aorta. Survival dependent on PDA & ASD to allow for flow from RV to aorta.
  Dx: Identified on US w/ findings of small or nonfunctioning LV, small aortic root, small aortic arch, ↑ or absent Doppler velocities through the aortic valve, abn MV, & restricted or reversed flow through the foramen ovale (usually right to left flow in utero).
  Associations: Trisomy 18, trisomy 13, Turner syn, or sporadic
  Mgmt: Identification can allow for birth planning (administration of prostaglandins to ensure persistent PDA) & poss fetal intervention. Dilation of AS can reverse HLHS physiology. In utero atrial septostomy can allow for ASD creation.
- **AVSDs:** Atrial & ventricular septal defects w/ singular, multileaflet atrioventricular valve. Diagnosed on US, confirmed w/ echo. AVSDs a/w aneuploidy.
- **Conotruncal anomalies:** Tetralogy of Fallot, persistent truncus arteriosus. Should prompt testing for DiGeorge syn (microdeletion of chromo 22q11, detectable by FISH).

Thoracic Anomalies

- **CCAM:**
  Sporadic lesion due to abnormalities in branching of pulm tree → cystic or solid lung lesions. Classified based on size cystic or solid components. Different types confer varying risks of regression, progression, or malig transformation.
  Type 1: Large (>2 cm) multiloculated cysts
  Type 2: Smaller uniform cysts
  Type 3: Not grossly cystic → "adenomatoid" type

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Can lead to hydrops if large enough to cause mediastinal shift. Rx usually resxn at birth w/ peds at deliv.

- **Congenital diaphragmatic hernia CDH:** Defect in diaphragm → herniation
  Diagnosed as solid (on right due to liver) or cystic (on left due to bowel) mass on US.
  Occurs as isolated finding, as part of a sequence, or w/ aneuploidy (10–20%).
  Left-sided lesions more common. Right-sided lesions confer worse prog (liver herniation). ↑ fetal lung vol improves prog. Can lead to NIHF & dextroposition.
  Further w/u includes fetal echo, fetal karyotype, & poss MRI.

Gastrointestinal Anomalies

- **Omphalocele:** Defect in abdominal wall holding herniated abdominal wall contents.
  Dx: Diagnosed on US after week 12 GA (before week 12 herniation of contents physiologic). Hernia covered by amnion & peritoneum; herniation at site of cord insertion. Classified by whether or not defect contains liver (liver-containing defect never nml regardless of GA). Causes elevated MSAFP.
  Associations: 50% association w/ cardiac lesion (fetal echo recommended); Beckwith–Wiedemann syn, OEIS syn, & amniotic band syn. Association w/ aneuploidy in nonliver containing lesions (chromo analysis recommended).
- **Gastroschisis:** Evisceration of abdominal contents through abdominal wall defect.
  Dx: Seen as full thickness abdominal wall defect, generally to right of cord insertion (nml cord insertion is seen on US). Bowel may become thickened & matted w/ increasing GA. No overlying peritoneum.
  Associations: No ↑ risk of chromosomal aneuploidy but a/w other GI problems. ↑ risk of recurrence w/i families.
- **Echogenic bowel:** ↑ echogenicity (brightness) of bowel noted on US.
  Etiology: A/w bleeding events, aneuploidy, CF, growth restriction, infxn, & idiopathic. Idiopathic = most common etiology.
  Aneuploidy: 3–25% association w/ aneuploidy, primarily trisomy 21. Offer amniocentesis for chromosomes, CF, & CMV testing.

Genitourinary Anomalies

- **Renal agenesis:** Ureteric bud fails to develop & induce differentiation of kidney.
  Etiology: Can be bilateral or unilateral. Bilateral usually due to embryonic issue; unilateral difficult to distinguish agenesis from dysplasia & hypoplasia.
  Dx: Bilateral renal agenesis diagnosed w/ nonvisualization of kidneys & bladder w/ oligohydramnios. Unilateral diagnosed by absent or abn kidney location (amniotic fluid nml). Full fetal bladder is good indicator of renal fxn.
  Prog: Bilateral renal agenesis incompatible w/ life due to pulm hypoplasia. High rate of IUFD due to cord accidents from oligohydramnios.
  Associations: 50% association w/ other anomalies; high rate of single umbilical artery
- **VACTERL:** Vertebral anomalies, Anal atresia, Cardiac defects, TE fistula, Renal defects, Limb defects
- **Müllerian anomalies:** Defects in female reproductive tract including separate or absent reproductive systems. See Chap. 8.
- **OEIS complex:** Omphalocele, Exstrophy of the bladder, Imperf anus, Spinal defects
  Etiology: Due to abnormalities of cloaca – blind pouch from which rectum & urogenital sinus develop. Typically sporadic & not a/w aneuploidy.
- **Bladder exstrophy:** Diagnosed w/ absent bladder filling, low-set umbilicus, lower abdominal mass increasing in size throughout Preg. Independent of OEIS complex, can be other assoc abdominal wall, musculoskeletal, & genital deficits.

Musculoskeletal and Anomalies

- **Skeletal dysplasias:** Qualitatively or quantitatively abn bones on prenatal US.
  Dx: FL or HL <5%ile based on GA.
  Etiology: Constitutionally short fetus (isolated abn FL), IUGR (a/w small AC), or skeletal dysplasia. Can be marker of aneuploidy.
  W/u: Interval growth in 3–4 w can show normalization of FL or nml interval growth. Comparison to other parameters (AC, BPD, HC) can reveal IUGR. If continued short FL compare to qualitative description of other bones.
- **Talipes equinovarus (clubfoot):** Excessive plantar flexion w/ foot facing medially.
  Etiology: Primarily idiopathic or isolated (familial recurrence); can be due to aneuploidy (trisomy 18), deformation (extrinsic).

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GENETIC SCREENING

Maternal Serum Aneuploidy Screening *(Obstet Gynecol 2007;109:217)*

- Aneuploidy screening should be offered to all pts. Counseling includes what is being screened for, potential results, advantages/disadvantages (including cost), & how the results might impact their decisions about the Preg.
- Reported as "risk" of aneuploidy (w/ regard to trisomy 21 & trisomies 13/18) compared to age-matched reference, not as positive or negative (except for cell-free fetal DNA, see below). Overall: 5% positive screen rate (predetermined).
- **Screening parameters:** Combination of values used in various screening approaches
  NT: Defined anatomic area behind fetal neck measured sonographically as width (mm) btw ~11–14 w. ↑ in aneuploidy & other conditions. Lower false positive rate if combined w/ serum markers. Useful in multiples when serum markers not accurate (ie, each fetus evaluated).
  NB: Used w/ NT for trisomy 21 eval
  Serum markers: Preg hormones used in combination to calculate risk (AFP, β-hCG, PAPP-A, inhibin A, UE3)
- **1st trimester screening:** NT, PAPP-A, & β-hCG in mat serum at 11–14 w. Comparable detection rates to 2nd trimester screen but higher screen positive rate in women >35 yo compared to 2nd trimester screen. Advantages: Time for CVS as diagnostic test & earlier termination options. Disadvantages: More costly approach. In case of sequential strategy, pts must wait for results until 2nd trimester.
- **2nd trimester screening:** AFP, hCG, unconjugated estriol (UE3), and inhibin A in screen at 15–18 w & some labs up to 24+ weeks. Detection 69% for triple screen, 81% for quadruple screen (using inhibin A). Advantages: Does not rely on NT (operator dependent test). Serum markers may suggest other problems (eg, ↑ AFP for NTD). Disadvantages: Only screening → amniocentesis for dx. Given later GA, if anomaly found, options may be more limited.

Second trimester maternal serum analytes				
	AFP	**UE_3**	**hCG**	**Inhibin A**
T21	↓	↓	↑	↑
T18	↓	↓	↓	↓
NTD	↑	N/A	N/A	N/A

- **Combined approaches:** Uses both 1st & 2nd trimester screening protocols. When 1st & 2nd trimester protocols used independently, false positive rate ↑.
  Integrated screening: Integrates 1st & 2nd trimesters → results given in 2nd trimester
  94–96% detection rate w/ full integrated (NT, PAPP-A, quad screen)
  Sequential screening: 1st & 2nd trimester screens performed w/ results reported after 1st & then altered after 2nd trimester. Benefits: Allows CVS for those at highest risk & ↓ anxiety of waiting. 95% detection rate by 2nd trimester.

Cell-free Fetal DNA

- **Definition:** Free fetal DNA in mat circulation likely from syncytiotrophoblast cells, extracted from mat serum, & proportion of target genetic material measured by sequencing. Imbalance of genetic material sugg extra or missing chromo.
- Commercial testing for screening for trisomy 21 & trisomy 18 available. Single bld test w/ >99% sens & spec for T21 & T18. Rapidly evolving technology.
- **Applications:** Aneuploidy, sex determination (presence of Y chromo), Rh typing. Performed after 10 w.

Screening for Hemoglobinopathies *(Obstet Gynecol 2007;109:229)*

- Offered to individuals of African, Southeast Asian, & Mediterranean ancestry. If a woman is aware of her status, screening does not need to be repeated. Many US-born women were screened at birth. See Chap. 16.
- **Sickle cell:** Screen w/ CBC & HbEP in African descent. HbEP allows for detection of HbS & other variants. If positive, partner should undergo carrier screening. Dx: If both partners positive for HbS, refer for genetic counseling to discuss CVS or amniocentesis for diagnostic genetic testing of fetus.
- **Thal:** Screen w/ CBC & MCV in Southeast Asian & Mediterranean descent
  Beta-thalassemia: In pts w/ anemia, MCV < 80, & nml iron status (nml ferritin) HbEP should be performed for screening for thal. HbEP shows elevated HbA & HbF for beta-thalassemia. If positive, partner requires screening.

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Alpha-thalassemia: HbEP unable to detect alpha-thalassemia, if of Southeast Asian ancestry w/ microcytic anemia, nml iron studies, & nml HbEP offer DNA testing for abn alpha-globin gene. If positive, partner requires screening.
Dx: If both parents are carriers & have described genetic mutations → offer CVS or amniocentesis for fetal genetic testing

Other Inherited Diseases (*Obstet Gynecol* 2010;116:1008)

- **CF:** Autosomal recessive condition due to >1700 of mutations in CFTR gene. Routine testing for common mutations offered to all pts (regardless of ethnicity) after appropriate education regarding the implications of testing & results. Detection rate of test related to prevalence in pop. Pts w/ personal Hx or FHx of CF or related conditions should undergo genetic counseling to determine if expanded mut screens are warranted. If pt positive, partner should be screened & consider amniocentesis/CVS.
- **Fragile X:** Most common *inherited* form of MR. Due to ↑ triplet repeats on FMR1 gene. Offer carrier testing in FHx of fragile X-related disorders, unexplained MR, autism, or premature ovarian failure. Variable penetrance based on number of triplet repeats. Only test for FMR1 triplet rpt is diagnostic test using CVS or amniocentesis for known carriers.
- **Tay–Sachs:** Ashkenazi Jewish, French Canadian, or Cajun descent
- **Familial dysautonomia or Canavan dz:** Ashkenazi Jewish descent
- Offer other screening tests (musc dystrophy, Huntington's) based on FHx

AMNIOCENTESIS AND CHORIONIC VILLUS SAMPLING (CVS)

Invasive Prenatal Diagnostic Testing

- Definitive diagnoses for specific conditions. Discuss the difference btw screening & diagnostic tests, risks & benefits, alternate screening tests, & interpretation of results.

Amniocentesis (*Obstet Gynecol* 2007;110:1459)

- **Definition:** Removal of AF using transabdominal approach. Procedure performed using spinal needle typically w/ US guidance. For both diagnostic & therapeutic indications. Genetic amniocentesis typically btw 15 & 20 w.
- **Diagnostic amniocentesis:** Usually for prenatal genetic testing, but several applications.
  Genetics: Allows for culture of fetal cells & dx of aneuploidy via karyotype FISH or CGH
  Infxn: AF can be used for cell count, gluc, & culture for suspected chorio or can be used to perform diagnostic tests for infxn such as CMV
  Hemoglobin: Fetal hemoglobin can be obtained for eval of fetal anemia, fetal bld type, or eval of hemoglobinopathies
  Other indications: Can be used to test fetal lung maturity or for NTDs.
- **Therapeutic amniocentesis:** Amnioreduction (removal of AF) can be therapeutic for pts w/ twin-to-twin xfusion syn & preterm CTX from polyhydramnios.
- **Risks:** Higher w/ early amniocentesis (11–13 w; not recommended). 1 in 300–500 Preg loss, lower at experienced centers. 1–2% vaginal spotting or LOF; <1:1000 for chorio. AF cells can fail to culture leading to nondiagnosis after amniocentesis. Small risk of transmission of HCV or HBV but data limited. Small risk of transmission of HIV if pt on antiretroviral therapy/undetectable viral load. Rh-negative women should get anti-D RhIg prior to procedure to prevent sensitization

Chorionic Villus Sampling (CVS)

- **Definition:** Removal of chorionic villi via TA or TC catheter w/ needle under sono guidance. Typically used for dx using karyotype analysis, FISH, or genetic testing for specific alleles. Performed btw 9 & 16 w gest.
- **Risks:** Complication rate of TA-CVS lower than rates of TC-CVS. Fetal loss (0.7–1.3%) higher than amniocentesis but background rate of fetal loss at earlier GA is higher. Rates of loss at similar GAs are the same btw amniocentesis & CVS. Up to 30% vaginal spotting w/ TC-CVS, less after TA-CVS. Limb reduction or oromandibular defects after 9 w, risk = 6 in 10000 (similar to risk in general pop). Rh-negative women should get anti-D RhIg prior to procedure to prevent sensitization. Nondiagnostic procedure due to operator failure or cell culture failure; higher than for amniocentesis. Higher rate of chromosomal mosaicism (presence of more than one cell line) in CVS compared to amniocentesis (1% vs. 0.25%); if mosaicism, amniocentesis may be indicated. Infxn or leakage of amniotic fluid <0.5%.
- **Counseling:** Offer to pts interested in 1st trimester diagnostic testing. Advantage of CVS is early GA at dx = more options.

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ANTENATAL FETAL TESTING

Goal of Testing

- **Goal:** Measure changes in fetal physiology or behavior w/ suff sens for fetal hypoxemia or acidemia to allow intervention to prevent stillbirth
- Primary outcome of interest is a reassuring result to rule out fetal demise w/i 1 w of testing

Indications for antenatal testing

Mat conditions	Fetal conditions
• Antiphospholipid Ab syn • Hyperthyroidism (poorly controlled) • Hemoglobinopathies • Cyanotic heart dz • Systemic lupus erythematosus • Chronic renal dz • Type 1 DM • Hypertensive disorders	• Gestational HTN or preeclampsia • Decreased fetal mvmt • Oligo- or polyhydramnios • Intrauterine growth restriction • Postterm Preg • Isoimmunization • Prev fetal demise • Multi gest w/ signif growth discrep

From *Int J Gynaecol Obstet.* 2000;68(2):175–185.

Testing Modalities *(Obstet Gynecol 2009;113:687)*

- **Fetal mvmt count** ("kick count") *(Cochrane Database Syst Rev 2007:CD004909)*
  Variable protocols, usually 2 h, 3–7× per week
  10 mvmts → reassuring; insuff evid to recommend this method of surveillance
- **Nonstress test**
  Continuous fetal heart monitoring × 20–40 min
  At least 2 15 bpm × 15 s accelerations (or 10 × 10 at <32 w) → reassuring
  Occasional, brief variable decelerations do not affect negative predictive value
  Performance for prediction of stillbirth w/i 1 w: Sens 99.7%, spec 45%
- **Biophysical profile** (From US exam of fetus up to 30 min)
  Elements (2 points each if nml/reassuring):
  Continuous fetal breathing, 1 episode >30 s
  3+ fetal limb or body mvmt
  1+ episodes of flexion/extension of a limb or hand
  2 × 2 cm or greater pocket of amniotic fluid (or amniotic fluid index >5 cm)
  Reactive nonstress test
  <6/10 = abn (consider deliv); 6/10 = equivocal (rpt in 6–24 h); >6/10 = reassuring.
  Prediction of stillbirth w/i 1 w: Sens 99.92%, spec 50%.
- **Contraction stress test** (oxytocin or nipple stimulation to produce 3 contractions in 10 min of >40 s, w/ continuous FHR monitoring)
  Negative = No late or signif variable decelerations
  Positive = Late decelerations w/ >50% of contractions
  Equivocal = Anything btw "negative" & "positive"
  Unsatisfactory = Uninterpretable fetal heart tracing or insuff contraction frequency
  Prediction of stillbirth w/i 1 w: Sens 99.96%, PPV 70%
- **Umbilical artery Doppler velocimetry** (US measurement, *only* indicated in fetuses w/ growth restriction)
  Low resistance system should allow forward flow throughout cardiac cycle
  Absent or reverse end-diastolic flow is a/w increased perinatal mortality (5× greater w/ reversed flow) *(Lancet 1994;344:1664)*
- **Middle cerebral artery Doppler velocimetry**
  US measurement of peak systolic velocity, indicated if concern for fetal anemia
  Velocity >1.5 MoM has sens for mod/sev anemia 100%, spec 88% *(N Engl J Med 2000;342:9)*. Optimal screening interval likely 1–2 w

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FETAL LUNG MATURITY TESTING BY AMNIOCENTESIS

General Considerations
- Consider testing for planned deliv btw 32 & 39 w
- Before 32 w low likelihood of maturity
- Test performance worsens at earlier GAs
- All tests more accurately predict absence of respiratory distress (w/ mature result) than predict respiratory distress (w/ immature result) (*Obstet Gynecol* 2001;97:305)

Specific Assays
- **Lamellar body count** (direct assessment) or optical density at 650 nm (indirect assessment)
  >50000/μL or optical density (OD) >0.15 sugg maturity. May vary by institution.
- **L/S ratio** (L/S about equal till ~35 w, then lecithin increases)
  Threshold value for "mature" varies by institution. Generally mature at >2 (2–3.5)
- **PG measurement** (appears ~35 w & rapidly increases)
  Quantitative or qualitative measurement. Not affected by mec or bld.
- **Foam stability index**. Measures functional surfactant. >47 signifies maturity.
- Surfactant/albumin ratio, TDx-FLM II (phased out by manufacturer in 2011)

NEWBORN RESPIRATORY DISTRESS

Epidemiology (*Am Fam Physician* 2007;76:987)
- 7% of infants. Most common causes: Transient tachypnea of the newborn, respiratory distress syn, mec aspiration syn.
- Less common causes: Delayed transition, infxn, persistent pHTN, PTX, nonpulmonary causes (anemia, CHD)

Signs and Symptoms
- Tachypnea (>60 breaths/min), nasal flaring, poor feeding, grunting, sub- or intracostal retractions, insp stridor, apnea, cyanosis

Transient Tachypnea of the Newborn
- >40% of cases of respiratory distress
- Inadeq fluid clearance from lung → decreased pulm compliance → tachypnea
- Onset w/i 2 h of birth; usually resolves in <72 h
- CXR: Diffuse parenchymal infiltrates

Respiratory Distress Syndrome (Hyaline Membrane Disease)
- Affects 24000 infants in US annually
  Most common before 28 w gest
  1/3 of infants 28–34 w gest
  <5% of infants after 34 w gest
- Surfactant deficiency causing atelectasis & V/Q mismatching → hypoxemia
- Incid ↑ for newborns of diabetic moms
- CXR: Homogenous, opaque infiltrates, & air bronchograms

Meconium Aspiration Syndrome
- Mec-stained amniotic fluid = 15% of deliveries → 10–15% of those get mec aspiration syn; mec = irritative, obstructive, medium for bact culture
- Usually term or postterm infants; signif respiratory distress immediately after deliv
- CXR: Patchy atelectasis or consolidation

General Management
- Diagnostic CXR; CBC, bld gas, bld cx
- Supplemental oxygen therapy, w/ assisted ventilation if necessary
- Supportive care w/ fluid/electrolyte mgmt & neutral thermal environment
  Oral feeding often withheld w/ respiratory rate >80 breaths/min
- Empiric ampicillin & gentamicin if risk factors for sepsis or refrac/persistent sx
- Surfactant administration may be req

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GROUP B STREPTOCOCCAL DISEASE

Definition and Epidemiology *(MMWR 59(RR10):1)*

- Intrapartum vertical transmission of GBS is the leading cause of infectious morbidity/mortality in neonates; incid is ~0.35/1000 births
- Caused by GBS infxn of fetal mucosal surfaces by GBS in amniotic fluid or birth canal
- 10–30% of pregnant women are colonized w/ GBS in GI tract or vagina
- Risk factors for invasive perinatal dz include:
  - <37 w at deliv
  - Ruptured amniotic membranes for >12 h
  - Intra-amniotic infxn
  - Young mat age
  - Black race
  - Low levels of anti-GBS Ab

Clinical Manifestations

- Sepsis, PNA, & meningitis in the 1st w of life
- Fatal in 2–3% full-term infants & 20–30% of preterm newborns <33 w GA

Screening and Diagnosis

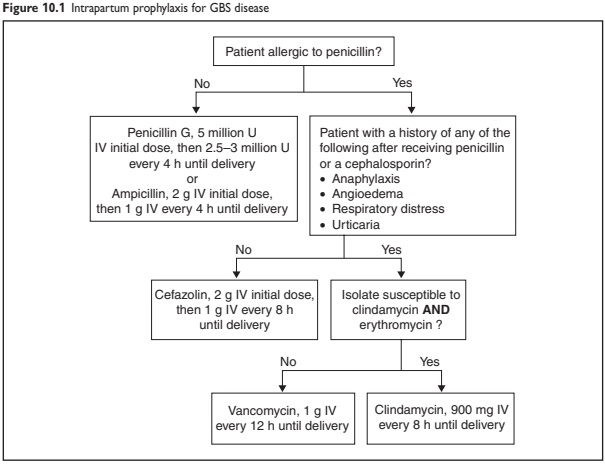
- Pregnant women should routinely be screened by rectovaginal swab at 35–37 w. Culture results are valid for up to 5 w, then should be repeated at >5 w.
- NAAT for GBS is currently only indicated in women w/ (1) culture data unk, (2) at term, & (3) w/o prolonged rupture of membranes or fever

Treatment

- Intrapartum Abx indicated for:
  - Positive rectovaginal culture during this Preg
  - GBS bacteriuria at any time during this Preg (exempt from routine screening)
  - H/o perinatal GBS dz in a prior Preg (exempt from routine screening)
  - Culture data unavailable & <37 w OR term w/ rupture of membranes >18 h or temperature >100.4°F
- Intrapartum ppx NOT indicated at the time of cesarean deliv at any GA for women delivered *prior to labor w/ intact membranes*

Antibiotics for GBS prophylaxis at delivery	
Recommended	PCN G 5 million U IV loading dose → 2.5 million U IV q4h until deliv
Alternative	Ampicillin 2 g IV loading dose → 1 g IV q4h until deliv
If PCN-allergic follow protocol to use cefazolin, clindamycin, or vancomycin	

Figure 10.1 Intrapartum prophylaxis for GBS disease



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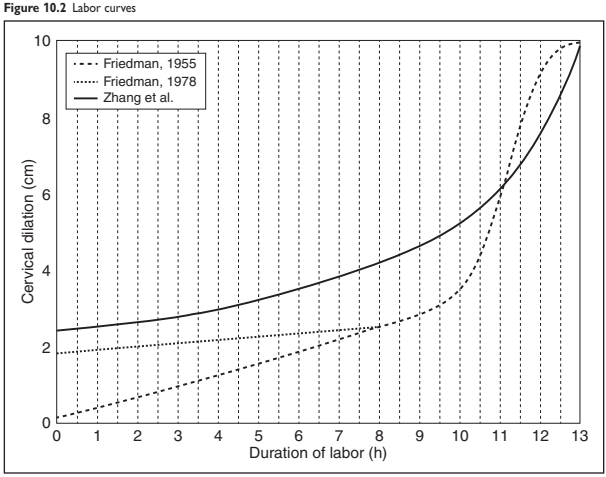
SPONTANEOUS LABOR AND DELIVERY

Definitions

- **Labor:** Regular uterine contractions & cervical change
- **1st stage of labor:** Onset of labor → full cervical dilation
  - **Latent phase:** Early labor until acceleration of rate of cervical change
  - **Active phase:** Period of accelerated cervical change until full dilation
  - **Historically, minimum rate of cervical change:** Nulliparas ~1.2 cm/h, multiparas, ~1.5 cm/h (*NY Acad Med* 1972;48:842)
  - **Labor curve:** Friedman (1955) described ideal labor progress at term; Zhang (2002) showed women enter active phase at 3–5 cm, w/ variable labor course & no deceleration phase
- **2nd stage of labor:** Full cervical dilation → deliv of the infant
  Consider 2nd stage arrest in nulliparas after 2 h (no epidural) or 3 h (w/ epidural), or in multiparas after 1 h (no epidural) or 2 h (w/ epidural)
- **3rd stage of labor:** Deliv of the infant → deliv of the placenta
- **4th stage of labor:** 1–2 h immediately following deliv of the placenta
- **Cervical assessment:** Cervical dilation is measured in cm. Cervical effacement is documented as percentage of full length (4 cm) cervix lost (0% is full length & 100% is paper thin), or as cm of length. Fetal station is descent of the *bony* fetal presenting part in centimeters above or below the mat ischial spine (–5–+5 cm scale).
- **Fetal position:** Orientation of the presenting part relative to the mat pelvis
  Cephalic presentation w/ occiput documented on mat left/right, rotated post/anter/transverse (eg, ROA). The sacrum may be used for fetuses in breech presentation, the acromion for transverse lie, the mentum for face presentations

Figure 10.2 Labor curves



(Reprinted with permission from Zhang J, Troendle JF, Yancey MK. Reassessing the labor curve in nulliparous women. *Am J Obstet Gynecol.* 2002;187:824)

Median [and 95%ile] hours in labor (4–10 cm)		
	Nulliparas	**Multiparas**
Spontaneous labor	3.8 [11.8]	2.4 [8.8]
Induced labor	5.5 [16.8]	4.4 [16.2]
Active phase (6–10 cm) was similar amongst all groups, w/ median ~1 h		

From Harper LM, Caughey AB, Odibo AO, et al. Normal progress of induced labor. *Obstet Gynecol.* 2012;119(6):1113–1118. doi:10.1097/AOG.0b013e318253d7aa.

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Cardinal Movements of Labor

- **Engagement:** Passage of widest diameter of presenting part below pelvic brim
- **Descent:** Passage of presenting part downward into pelvis
- **Flexion:** Allows optimal descent by presenting smallest cranial diameter
- **Internal rotation:** Mvmt of the fetal head from transverse to anteroposterior
- **Extension:** Mvmt of the fetal head under the pubic symphysis & out the introitus
- **External rotation ("restitution"):** Mvmt of the head to align w/ torso
- **Expulsion:** Deliv of the fetal body

Management of Labor

- Physical exam on presentation: Mat VS; cervical dilation, effacement, fetal station, rupture of membranes (± mec), presence of vaginal bleeding, & estimated fetal weight (by Leopold's)
  Fetal heart assessment (intermittent in low-risk, or continuous in high-risk pts) & uterine tocometry to assess fetal status & contractions
- Consider CBC, bld type & screen, urinalysis
- IV access, avoid solid foods (*Obstet Gynecol* 2009;114:714)
- Walking & upright positioning in early labor may ↓ the 1st stage by 1 h (*Cochrane Database Syst Rev* 2009,2:CD003934)
- Assess desire for pain control, w/ or w/o regional anesthesia
- GBS ppx if indicated

Management of Delivery

- Pushing may begin w/ full cervical dilation or be delayed until presenting part descends ("laboring down"); pushing generally accompanies contractions. Delayed pushing ↑ length of the 2nd stage by ~1 h, but ↓ the need for instrumented deliveries (but not cesarean deliveries) (*J Obstet Gynecol Neonatal Nurs* 2008;37:4). Pushing should not be delayed if there is an indication to expedite deliv (eg, infxn).
- No indication for routine episiotomy. If necessary, midline a/w ↓ bld loss & ↑ anal sphincter injury compared to mediolateral.
- Warm compresses to the perineum may ↓ incid of 3rd/4th-degree lacerations (*Cochrane Database Syst Rev* 2011;12:CD006672)
- In women w/o epidural anesthesia, pushing while upright was a/w ↑ risk of EBL >500 cc & ↓ abn FHTs w/o signif impact on length of 2nd stage (*Cochrane Database Syst Rev* 2012;5:CD002006)
- Deliv of the fetal head:
  Care should be taken to control speed of deliv & to protect the anter vaginal wall, urethra, & clitoris
  The perineum should be eased over the fetal head
  The head should be allowed to restitute
  Gentle downward traction of the head to deliver the anter shoulder (difficulty w/ this maneuver should prompt consideration of shoulder dystocia)
  The body should be delivered w/ gentle upward traction, supporting the perineum as poss
- The cord should be clamped & cut → delayed cord clamping ↓ risk of fetal/neonat anemia, but ↑ need for phototherapy (*Cochrane Database Syst Rev* 2008:CD004074; *BMJ* 2011;343:d7157). Delaying cord clamping by 45 s in premature infants <37 w may ↓ risk of IVH & neonat xfusion (*Cochrane Database Syst Rev* 2004;4:CD003248)
- Active mgmt of 3rd stage w/ suprapubic pres & controlled cord traction may ↓ mat hemorrhage (*Cochrane Database Syst Rev* 2011;11:CD007412)
- Consider deliv onto mat abd to promote immediate breastfeeding & bonding (*Cochrane Database Syst Rev* 2012;5:CD003519)
- Give oxytocin in the 3rd stage to ↓ postpartum hemorrhage (*Cochrane Database Syst Rev* 2001;(4):CD001808)
- Inspect the placenta to identify anomalies & to ensure intact disc
- Fetal cord bld gas analysis & postpartum hemorrhage (see sections below)

INDUCTION OF LABOR (IOL)

Definition and Epidemiology

- Stimulation of uterine contractions w/ intent to cause vaginal deliv prior to spontaneous onset of labor
- 23.2% of births in 2009 were after IOL (National Vital Statistics Report, 2011)
- "CR" is the softening, thinning, & dilating to facilitate successful IOL

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Indications

- Risks (to mother or fetus) of continuing Preg outweigh the risks a/w effecting deliv, & no contraindication to vaginal birth
- Labor should not be electively induced prior to 39 w gest due to significantly elevated neonat morbidity

Simplified Bishop Score for determining successful IOL				
Points scored	0	1	2	3
Dilation (cm)	0	1–2	3–4	≥5
Station	–3	–2	–1 or 0	+1 or +2
Effacement (%)	0–30	40–50	60–70	≥80

Total score: Successful IOL (sens/spec)
>4: 59.2/67.9
>5: 40.6/82.6
>6: 18.8/94.2
Note: Cervical consistency (firm, soft) & position (anter, post) are included in the "full" Bishop Score, but do not add predictive power beyond the simplified score above

From Laughon SK, Zhang J, Troendle J, et al. Using a simplified Bishop score to predict vaginal delivery. *Obstet Gynecol.* 2011;117(4):805–811. doi:10.1097/AOG.0b013e3182114ad2.

- Overall, multiparas are less likely than primiparas to fail induction or require cesarean deliv at a given Bishop Score

Methods of Cervical Ripening & Induction of Labor

- **Oxytocin** – most commonly used induction agent
  - Various dosing regimens; titrate to contractions q2–3min
    - Low-dose regimen (start 0.5–2 mU/min w/ 1–2 mU/min ↑ q15–40min)
    - High-dose regimen (start 6 mU/min w/ 3–6 mU/min ↑ q15–40min)
    - Note: High-dose regimen decreases time to deliv, but increases rate of tachysystole w/ FHR changes (*Cochrane Database Syst Rev* 2012;3:CD001233)
- **Misoprostol (PGE_1)** – for CR or IOL
  - Oral misoprostol superior to vaginal misoprostol for CR/IOL (fewer 5-min Apgars <7)
    - Dosage 25 mcg PO q2h or 50 mcg PO q4h (*Cochrane Database Syst Rev* 2006;(2):CD001338)
  - Vaginal misoprostol may be used for CR/IOL at dose of 25 mcg PV q3–6h
  - Contraindicated if h/o uterine Surg (including prior cesarean) given elevated risk of uterine rupture
- **Dinoprostone (PGE_2)** – for CR or IOL
  - Each insert contains 10 mg of dinoprostone → releases mean dose of 0.3 mg/h
  - Dosed q12h
  - Upon removal of insert, quickly eliminated from mat circulation
- **Amniotomy alone** (*Cochrane Database Syst Rev* 2000;(4):CD002862)
  - Insuff evid regarding efficacy
  - ↑ need for oxytocin augmentation vs. vaginal prostaglandin
- **Balloon catheter** (*Cochrane Database Syst Rev* 2012;3:CD001233) – for CR or IOL
  - Placement of balloon catheter w/ 30–60 cc of saline through internal os into extra-amniotic space
  - ↓ efficacy for multiparous women & ↓ risk of tachysystole compared w/ prostaglandin
- **Membrane stripping** (*Cochrane Database Syst Rev* 2005;(1):CD000451)
  - Manual detachment of inferior pole of fetal membranes during vaginal exam
- **Sexual intercourse:** Insuff evid. Likely ineffective (*Obstet Gynecol* 2007;110(4):820–826; *Cochrane Database Syst Rev* 2001;(2):CD003093).
- **Breast stimulation:** Decreased postpartum hemorrhage compared to no intervention. No difference in rates of cesarean when compared to no intervention or oxytocin. Not effective in women w/ unfavorable cervix (*Cochrane Database Syst Rev* 2005;(3):CD003392).

Complications of Induction

- Tachysystole (greater than 5 contractions in 10 min). Rx: Stop/↓ uterine stimulation, consider tocolysis
- Uterine tetany (contraction lasting greater than 2 min). Rx: Stop/↓ uterine stimulation, consider tocolysis
- Cord prolapse (w/ amniotomy). Rx: Cesarean deliv.
- HoNa (w/ extended infusion of oxytocin). Rx: Stop oxytocin infusion, consider free water restriction, recheck, & resume.
- Cesarean deliv ↑ compared to spontaneous labor, but elective IOL at 41+ w, compared w/ expectant mgmt may ↓ c-section (*Cochrane Database Syst Rev* 2012;6:CD004945)

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INTRAPARTUM FETAL MONITORING

Background

- Justification for intrapartum FHR monitoring based on expert opinion & medicolegal precedent
- Continuous FHR monitoring a/w (1) reduction in neonat seizures, w/o significant differences in cerebral palsy, infant mortality or other std measures of neonat well-being; & (2) ↑ in cesarean deliv & instrumental vaginal births when compared to intermittent auscultation or no monitoring (*Cochrane Database Syst Rev* 2006;3:CD006066)

Methods of Monitoring

- FHR: External via Doppler US -or- internal via fetal scalp electrode
- Contractions:
  External pres transducer (qualitative)
  Intrauterine pres catheter (quantitative). Measurement in MVU: Add up peak minus baseline uterine pres for each contraction over 10 min; >200 MVU considered adequate for labor (*Obstet Gynecol* 1986;68:305).

Definitions (*Obstet Gynecol* 2008;112:661)

- **Baseline:** Avg FHR, exclusive of accelerations, decelerations, & marked variability, taken over a 10-min interval, rounded to nearest 5 bpm
  Tachy: Baseline > 160 bpm
  Brady: Baseline < 110 bpm
- **Variability:** Beat-to-beat fluctuations in the baseline FHR, exclusive of accelerations & decelerations. Measured from peak to trough of rapid fluctuations.
  Absent: Amplitude undetectable
  Minimal: Amplitude btw 1 & 5 bpm
  Mod: Amplitude btw 6 & 25 bpm
  Marked: Amplitude > 25 bpm
- **Accelerations:** Increased FHR ≥15 bpm for ≥15 s (before 32 w, use ≥10 bpm & ≥10 s). Time from baseline to peak HR is <30 s. Prolonged acceleration lasts 2–10 min.
- **Decelerations:** ↓ in FHR
  Early deceleration: Nadir w/ peak of contraction. Baseline to nadir takes >30 s.
  Late deceleration: Nadir after peak of contraction. Baseline to nadir >30 s.
  Variable deceleration: ↓ ≥15 bpm from baseline lasting at least 15 s. Baseline to nadir <30 s.
  Prolonged deceleration lasts 2–10 min

Fetal heart tracings in labor

Category	Definition	Interpretation
I	Baseline FHR btw 110 & 160 • w/ mod variability • w/o late or variable decelerations • w/ or w/o accelerations • w/ or w/o early decelerations	Nml & requires no additional action. Accelerations (particularly >2 in 30 min) are highly predictive of favorable fetal acid–base status (*Am J Obstet Gynecol* 1982;142:297; *Am J Obstet Gynecol* 1979;134:36).
II	Any tracing not Category I or Category III	Indeterminate significance & requires close follow-up. Trial of supportive measures reasonable (see Category III).
III	Absent variability w/ • late decelerations during >50% of contractions over 20 min, or • variable decelerations w/ >50% of contractions over 20 min or brady OR • sinusoidal pattern (sine wave-like pattern in FHR baseline w/ a frequency of 3–5/min, persisting for 20 min)	Abn & requires immediate eval. Initial intrauterine resusc: • Change mat position • Administer mat oxygen • D/c labor stimulation • Consider tocolytics • Correct mat HoTN or compromised placental perfusion If supportive measures fail to correct the Category III pattern, deliv may be indicated.

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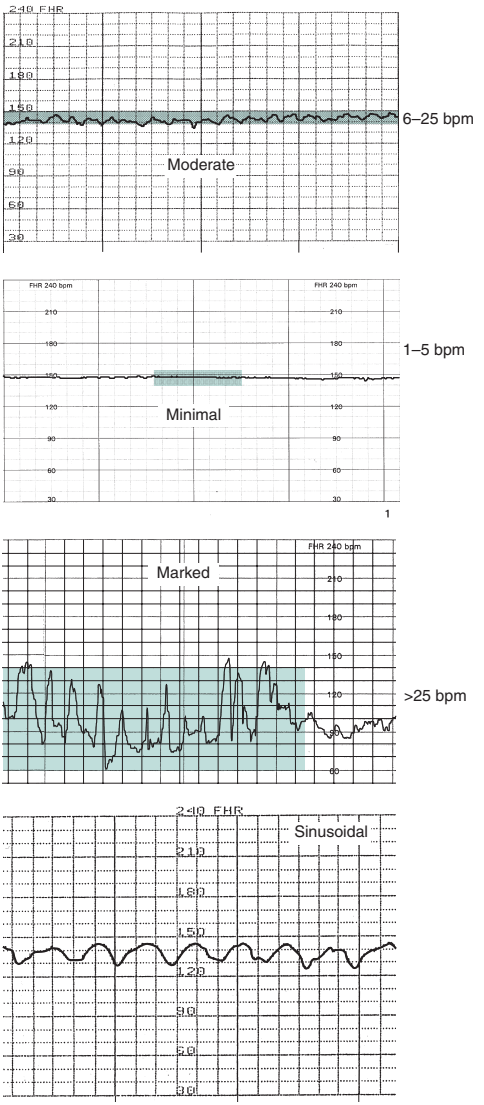
Sample Fetal Heart Tracings

Figure 10.3 Fetal heart rate variability



(Revised and reprinted with permission from Menihan CA, Kopel E. *Electronic Fetal Monitoring: Concepts and Applications*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2007)

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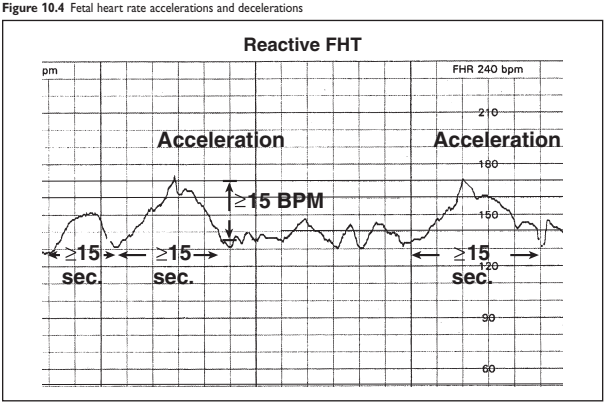
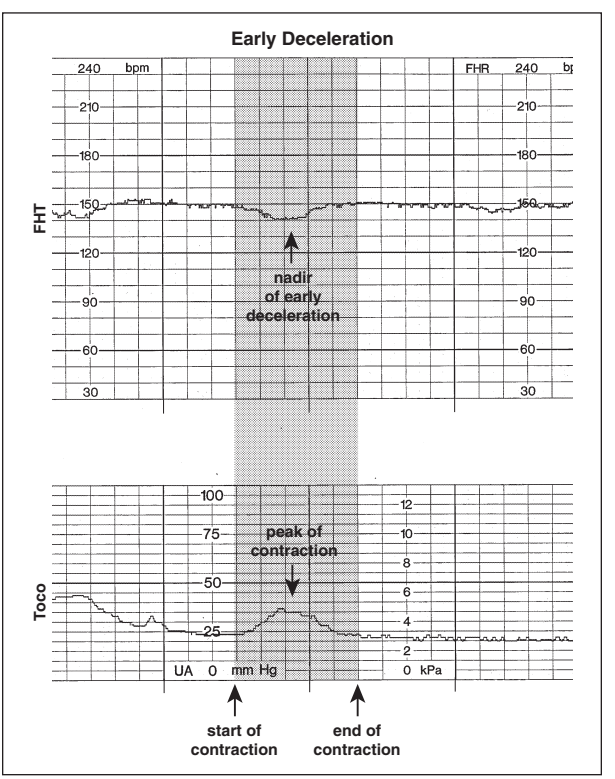
Figure 10.4 Fetal heart rate accelerations and decelerations





(*continued*)

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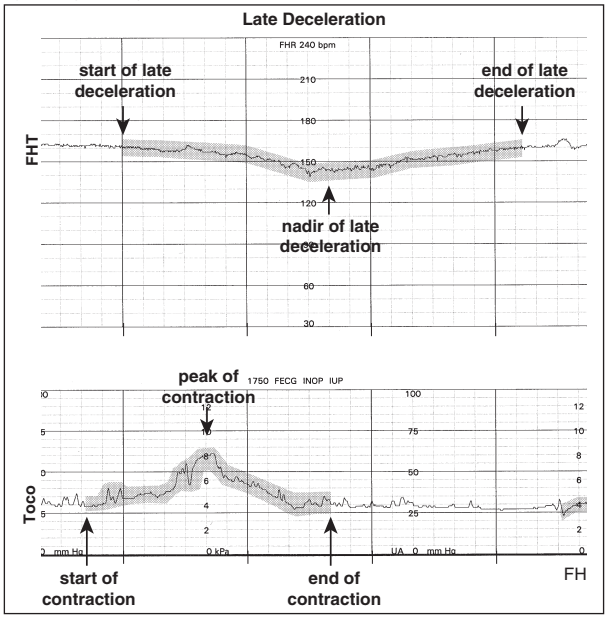
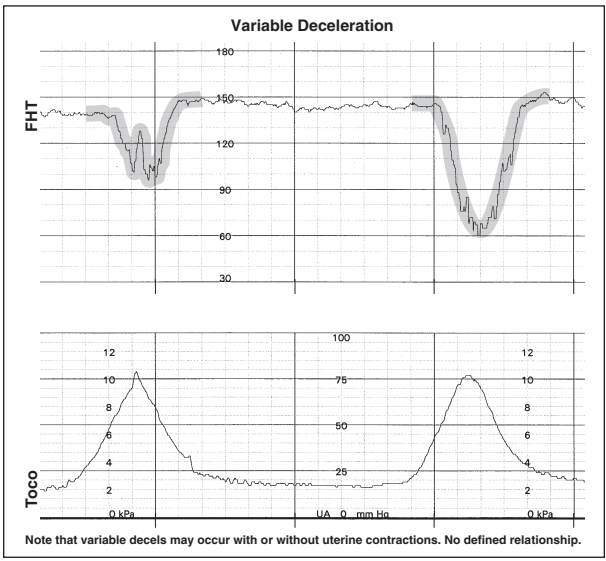
Figure 10.4 (Continued)





Note that variable decels may occur with or without uterine contractions. No defined relationship.

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OPERATIVE VAGINAL DELIVERY

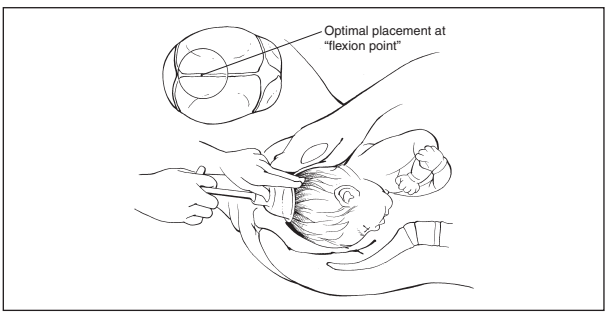
Definition and Epidemiology (ACOG Practice Bulletin #17, Operative Vaginal Delivery, Reaffirmed 2012))
- Deliv using forceps or vacuum. In 2009, 5.5% of vaginal births were operative (National Vital Statistics Report, 2011)

Indications
- Prolonged 2nd stage of labor (see 2nd stage labor arrest, above)
- Suspicion of immediate or potential fetal compromise
- Potential mat intolerance of Valsalva (eg, cardiac dz)

Requirements (All Must Be Met)
- Position of fetal head is known, including asynclitism. Head should be occiput anter or occiput post for forceps, unless operator is skilled w/ rotation.
- Cervix is fully dilated. Station is +2 cm or greater.
- Pelvis is adequate. Bladder is empty.
- Anesthesia is adequate

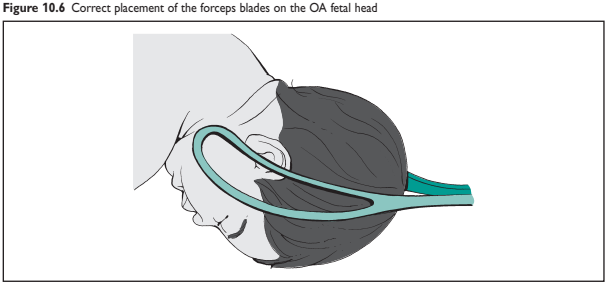
Contraindications (None Should Be Present)
- <34 w GA for vacuum (elevated risk of IVH)
- Fetal bone demineralization d/o (eg, osteogenesis imperfecta)
- Presence of bleeding d/o (eg, hemophilia, von Willebrand dz) OR mat anticoagulation w/ agent that crosses the placenta (eg, warfarin)
- Unk position of fetal head or head unengaged in pelvis
- Macrosomia is NOT a contraindication; caution for shoulder dystocia is advised, however

Figure 10.5 Placement of vacuum cup on fetal head



(Reprinted with permission from Scott JR, Gibbs RS, Karlan BY, et al. *Danforth's Obstetrics and Gynecology*. 9th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003)

Figure 10.6 Correct placement of the forceps blades on the OA fetal head



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Complications of Operative Delivery

- Neonat
  - Vacuum: Scalp laceration, cephalohematoma (11–16%), subgaleal hematoma (2.6–4.5%), intracranial hemorrhage (0.2%), retinal hemorrhage (up to 75% → disappear w/i weeks) (*BMJ* 2004;329:24; *Ophthalmology* 2001;108:36)
  - Forceps: Superficial laceration, cephalohematoma (6%), intracranial hemorrhage (0.2%), retinal hemorrhage (0.1–17%) (*BMJ* 2004;329:24)
- Mat (*BMJ* 2004;329:24)
  - Vacuum: Perineal laceration: 3rd degree (9.6%), 4th degree (6.2%)
  - Forceps: Perineal laceration: 3rd degree (12.5%), 4th degree (9.8%)
- Episiotomy may ↑ all mat lacerations, but may be necessary for deliv. Risk of persistent pelvic floor dysfxn difficult to quantitate. Mat laceration more likely w/ operative deliv, but should be weighed against risks of cesarean. Complications are highest w/ multi instruments (ie, vacuum plus forceps). If 1 fails → typically proceed w/ cesarean deliv.

VAGINAL BIRTH AFTER CESAREAN

Definitions (*Obstet Gynecol* 2010;116:450)

- TOLAC: Trial of labor after prior cesarean delivery
- VBAC: Vaginal birth after prior cesarean delivery
- ERCD: Elective repeat cesarean delivery

Selection of Candidates

- 1 or 2 cesarean deliveries via low transverse OR low vertical hysterotomy. Unk scar is NOT contraindication to TOLAC unless high suspicion for classical hysterotomy.
- No contraindication to vaginal deliv (eg, placenta previa)
- Overall success rate of TOLAC is 60–80%
- ↑ rate of successful TOLAC: Prior vaginal birth, spontaneous labor
- ↓ rate of successful TOLAC: Recurring indication for prior c/s (labor dystocia), increased mat age, nonwhite ethnicity, GA > 40 w, mat obesity, preeclampsia, short inter-Preg interval, increased birth weight
- Online NICHD VBAC success rate calculator https://mfmu.bsc.gwu.edu/PublicBSC/MFMU/VGBirthCalc/vagbirth.html

Maternal risks associated with TOLAC

	Elective rpt c-section (%)	TOLAC w/ 1 prior c-section (%)	TOLAC w/ 2+ prior c-sections (%)
Endometritis	1.5–2.1	2.9	3.1
Operative injury	0.42–0.6	0.4	0.4
Bld xfusion	1–1.4	0.7–1.7	3.2
Hysterectomy	0–0.4	0.2–0.5	0.6
Uterine rupture	0.4–0.5	0.7–0.9	0.9–1.8
Mat death	0.002–0.004	0.002	—

Neonatal risks associated with TOLAC

	Elective rpt c-section (%)	TOLAC (%)
Stillbirth 37–38 w	0.08	0.38
Stillbirth >39 w	0.01	0.16
Hypoxic/ischemic encephalopathy	0–0.13	0.08
Respiratory morbidity	1–5	0.1–1.8
Hyperbilirubinemia	5.8	2.2
Neonatal death (<1 mo) no signif change; perinatal death (<1 w) 0.01% w/ ERCD; 0.13% w/ TOLAC		

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Delivery Considerations

- Misoprostol should NOT be used for IOL given elevated risk of uterine rupture
  Risk of uterine rupture: 24.5/1000 (*NEJM* 2001;345:3)
- Continuous fetal monitoring should be employed
- Maintain high suspicion for signs/sx of uterine rupture, including: New onset uterine pain, loss of fetal station, new abnormalities of the fetal heart tracing, vaginal bleeding, & mat hemodynamic instability
- Staff (OB & anesthesia) must be immediately available for emergent c-section

FETAL CORD BLOOD GAS ANALYSIS

- Provides an assessment of neonat metabolic status
- May be useful to determine whether an asphyxic event (acidemia + metabolic acidosis + hypoxia) accompanied neonat depression
- If nml, rules out asphyxia at time of deliv as a cause of neonat complications
- Collect 1–2 mL of bld from both umbilical vein & artery in heparinized syringes. Can collect from clamped cord for up to 60 min w/ valid result. If samples are not immediately sent to laboratory, store on ice for up to 60 min.

Indications (*Obstet Gynecol* 2006;108:1319)

- May be obtained w/: Cesarean deliv for suspected fetal compromise, low 5-min Apgar score, abn FHR tracing, mat thyroid dz, intrapartum fever, multifetal gest, other indications

Interpretation

- Obst of bld flow through umbilical cord leads to retention of fetal CO_2 (ie, respiratory acidosis) → prolonged respiratory acidosis leads to mixed respiratory/metabolic acidosis & then metabolic acidosis alone

Normal values	
Term	**Preterm**
pH: 7.15–7.38	pH: 7.14–7.40
pCO_2: 49.2–50.3	pCO_2: 49.2–51.6
HCO_3^-: 22–23.1	HCO_3^-: 22.4–23.9
BE: −2.7–−3.6	BE: −2.5–−3.3

From Riley RJ, Johnson JW. Collecting and analyzing cord blood gases. *Clin Obstet Gynecol*. 1993;36(1):13–23.

- Approach to interpretation of fetal bld gas:
  If pH is lower than nml limits, ACIDEMIA exists
  If pCO_2 is higher than nml limits, RESPIRATORY ACIDOSIS exists
  If BE is more negative than nml limits, METABOLIC ACIDOSIS exists
- **Potentially clinically significant acidemia requires pH <7 & metabolic acidosis w/ BE <–12** (*Obstet Gynecol* 2003;102:628). 10% of neonates w/ BE −12–−16, & 40% w/ BE <−16 will have mod or sev complications (CNS, respiratory, renal, CV).
- Respiratory acidosis alone at the time of birth is not considered suff to cause CP
- Criteria to define acute intrapartum hypoxic event suff to cause CP:
  Arterial cord pH <7 w/ BE −12 or worse
  Early onset of mod or sev encephalopathy
  CP of spastic, quadriplegic, or dyskinetic type
  Exclusion of other identifiable etiologies

ROUTINE POSTPARTUM CARE

In Hospital Care

- **Monitoring:** Frequent VS (q15mins × 2 h; q shift [8–12 h] thereafter); assess uterine size & tone, perineal integrity, abdominal incisions; note quantity of vaginal bleeding; high vigilance for intra-abdominal or pelvic hemorrhage & urinary retention
- **Pain:** NSAIDs & cold compresses to the perineum, w/ opioids reserved for breakthrough or postsurgical pain (*Cochrane Database Syst Rev* 2011;(5):CD004908)
- **Constip:** Stool softeners & laxatives as needed & w/ opioids; longer stool softener rx for 3rd/4th-degree laceration repairs

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- **Urinary retention:** Mobilize early to facilitate voiding; use intermittent or indwelling catheter if unsuccessful
- **Malodorous lochia/discharge:** Inspect perineum for wound breakdown or retained sponge
- **HA:** Most likely are tension, but consider preeclampsia & postdural puncture HA (*Am J Obstet Gynecol* 2007;196:318). See Chap 18.
- **Fever:** W/u source, considering UTI, wound infxn, mastitis/breast abscess; breast engorgement; endometritis; septic pelvic thrombophlebitis; clostridium-difficile infxn; drug or anesthesia rxn
- Discharge w/i 24–48 h after Uncomp vaginal deliv & 48–96 h after routine cesarean deliv

Clinic Follow-up Care

- Postpartum visit recommended for all women at 4–6 w postpartum & 7–14 d postcesarean or complicated vaginal deliv (eg, sev laceration)
- **Hx should assess:** Mat–infant bonding, including feeding; breast complaints; mat mood/coping & social supports; urinary & fecal continence; resumption of intercourse & contraceptive plan; consider thyroid dysfxn (hyper- & hypo-) (*Thyroid* 2006;16:573)
- **Exam should include:** VS (including weight & BP); breasts, abd, & pelvis

Postpartum Contraception

- Mean resumption of ovulation in nonlactating women occurs 45–94 d (25 d at earliest) postpartum (*Obstet Gynecol* 2011;117(3):657)
- **Exclusive** breastfeeding is 98% effective as contraception in the 1st 6 mo postpartum if amenorrheic (*Contraception* 1989;39:477)
- Sterilization (by tubal ligation) may be performed immediately (w/i ~24 h) postpartum or as an interval procedure (after 6 w)
- Barrier methods may be used on resumption of intercourse
- Progest-only methods safe to initiate postpartum in any woman w/o a contraindication, & do not influence breast milk production (*Contraception* 2010;82:17)
- IUD (copper or levonorgestrel) may be placed either immediately postpartum (w/i 10 min of deliv of placenta) or 6–8 w postpartum
- Estrogen-containing contraceptives may be initiated 21 d postpartum in women w/o additional risk factors for VTE, & otherwise may be considered at 6 w postpartum. CDC & ACOG recommend 4–6-w delay before starting estrogen-containing contraceptives in breastfeeding women depending on VTE risk profile (*MMWR Morb Mortal Wkly Rep* 2011;60:878; *Obstet Gynecol* 2006;107:1453). Estrogen may suppress breast milk production.

BREASTFEEDING

Physiology and Initiation

- Copious milk secretion begins w/ progesterone withdrawal 2–7 d postpartum. Longer in primiparas & after cesarean deliv (*Pediatrics* 2003;112:607). Maint of lactation depends on adequate frequency of breastfeeding &/or pumping (*Obstet Gynecol* 2007;109:479). During the 1st 2 w, feeding initiated on infant demand (8–12× daily).
- Initiation of successful breastfeeding (unless medical issues take precedence; *Pediatrics* 2012;129:e827):
  Maintain direct skin-to-skin contact btw mother & infant until 1st feeding is completed.
  Avoid commercial formulas & sugar water.
  Avoid use of pacifier.
  Room-in newborns w/ mother.
  Discharge w/ contact information for breastfeeding support.

Benefits (AHRQ Pub No. 07-E007)

- Full-term infant: ↓ incid of otitis media; atopic dermatitis, & asthma; GI & lower respiratory tract infections; diabetes (weak association); childhood leukemia; SIDS
- Preterm infant: ↓ incid of nec enterocolitis, sev retinopathy of prematurity
  Improved neurodevelopmental outcomes (*Pediatrics* 2012;129:e827)
- Mat: ↓ incid of breast & ovarian cancer; & dev of type II diabetes

Relative Contraindications (*ACOG Clin Rev* 2007;12:1S; *Obstet Gynecol* 2007;109:479; *Pediatrics* 2012;129:e827)

- Contraindicated:
  Mat use of illicit drugs or uncontrolled EtOH use
  Mat infxn w/ brucella, HIV, HTLV-I, or HTLV-II
  Mat active, untreated varicella, TB, or herpes simplex w/ breast lesions
  Infant galactosemia

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- Breastfeeding does NOT ↑ the risk of vertical transmission of hepatitis C (*Clin Infect Dis* 1999;29:1327)
- Infants born to hepatitis B positive mothers should receive HepBIg & be vaccinated at birth; breastfeeding is safe thereafter (*Obstet Gynecol* 2002;99:1049)

Lactational Mastitis

- **Dx:** Fever >38.3°C + swollen, red, indurated breast in breastfeeding mother
- Labs not necessary, milk culture only in sev or refrac case
  US only if abscess suspected
- Typical pathogens are group A streptococci & MSSA
- **1st-line antibiotic:** Dicloxacillin (500 mg QID) × 10–14 d
  PCN-allergic or MRSA: Clindamycin (300 mg QID) or TMP/SMX (1–2 BID)
- Continue breastfeeding, w/ NSAID & warm compresses as needed
- **Diff includes:** Obstructed milk duct, galactocele, inflamm breast cancer

Breastfeeding and Maternal Medications

- **LactMed:** Comprehensive database on pharmaceuticals & lactation http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT

AFFILIATED OBSTETRICAL PROVIDERS

	Midwives		
	Education/Training	**Accreditation**	**Other**
CNM	APRN: Registered nurse, plus Master's/ Doctoral degree	American College of Nurse-Midwives	Licensed in 50 states
CM	Master's degree in midwifery	American College of Nurse-Midwives	Licensed in NY, NJ, RI; authorized in DE, MO
CPM	No formal requirements (can be DEM or CNM/CM) Written exams & eval of skills Must have some out-of-hospital practice	North American Registry of Midwives	Regulated variously in 26 states
DEM	No formal education requirements unless req by state law Informal/formal workshops or apprenticeships	None	Legal status varies Practice outside hospital setting

From American College of Nurse-Midwives; www.midwife.org

Doulas

- **Definition:** Women who provide continuous, nonmedical intrapartum/postpartum support to laboring women
- Scope of practice includes emotional support, attention to physical comfort, nonmedical advice, & advocacy
- Credentialing/certification varies by organization

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Definition and see Chap. 12 (Hypertension in Pregnancy, ACOG Task Force, 2013).

- **Chronic HTN:** SBP ≥140 or DBP ≥90 prior to Preg, prior to 20 w gest, or persisting longer than 12 w postpartum
- **Gestational HTN:** SBP ≥140 or DBP ≥90 after 20 w w/o proteinuria
- **Preeclampsia:** New onset HTN (as below) w or w/o proteinuria >20 w
  - **Nonsevere:** SBP ≥140 or DBP ≥90; proteinuria ≥300 mg/24 h (or 1+ urine dip or protein: creatinine ratio ≥0.3)
  - **Sev:** SBP ≥160 or DBP ≥110; proteinuria ≥5 g/24 h (or 3+ urine dip); oliguria <500 mL/24 h; sx such as HA, visual changes, difficulty breathing, or RUQ pain; elevated liver fxn tests, low Plts. Preeclampsia can → eclampsia. Newest guidelines do *not* use proteinuria to rule out preeclampsia. New onset HTN with sxs = diagnosis [thrombocytopenia (<100,000/uL) or serum Cr >1.1 mg/dL or elevated LFTs (2× upper limit normal) or pulmonary edema or cerebral/visual symptoms].
- **Chronic HTN w/ superimposed preeclampsia:** Worsening HTN w/ new onset proteinuria
- All BP should be taken on 2 occasions 4 h apart (after pt has been seated quietly for several minutes, cuff level w/ heart). Also see HELLP (Chap. 15) & Eclampsia (Chap. 18).

See detailed discussion and management of these disorders in Chap. 12.

Epidemiology and Etiology

- Preeclampsia found in ~7% of pregnancies. True cause unk.
- **Risk factors:** Age <18 or >40; nulliparity; h/o preeclampsia, FHx of preeclampsia
- **Poss causes:** Endothelial damage, altered metabolism, inflammation, oxidative stress

Clinical Manifestations

- **Preeclampsia:** HA, visual changes (scotomata, photophobia), edema, abdominal pain (specifically epigastric or RUQ). Often asymptomatic.

Physical Exam

- **Perform full neurologic exam:** Evaluate for HA, visual changes, clonus
- Palpate abd to assess abdominal tenderness (specifically RUQ)
- Visualize/palpate extremities to evaluate for periph edema

Diagnostic Workup/Studies

- CBC, CMP (evaluate liver & renal fxn), assessment of proteinuria (by spot prot to Cr ratio, urinalysis, or 24 h urine collection)
- CT can show cerebral edema in the post hemispheres, a form of PRES (Post reversible encephalopathy syn)

Treatment and Medications

- **Acute HTN** (*Chest* 2007; 131:1949; *Obstet Gynecol* 2011;118:1465):
  - **Labetalol:** 20 mg IV, rpt at 10-min intervals, double dose w/ max dose of 80 mg at one given time; total max dose of 300 mg (eg, 20 mg → 40 mg → 80 mg → 80 mg → 80 mg)
  - **Hydralazine:** 5 mg IV over 1–2 min, rpt at 20 min intervals, max dose at one time of 20 mg; not 1st line as can see mat HoTN
  - **Nifedipine:** 10–20 mg PO q30min
  - **Nitroprusside:** 0.20-4 mcg/kg/min iv drip, titrate to effect. Only in critical illness resistant to max dose of other agents. Risk of cyanide toxicity with prolonged use.
  - **Nicardipine:** 2.5 mg/h IV titrating, do not exceed 15 mg/h
  - **DO NOT USE:** ACEI, or ARB
  - **Goal:** ↓ risk of mat stroke but maintain pres for placental perfusion
- **Oral, outpt treatments**
  - **Labetalol:** 100–800 mg PO BID–TID (max dose 2400 mg/24 h)
  - **Methyldopa:** 250 mg PO BID (max dose 3 g/24 h)
  - **Nifedipine XR:** 30–90 mg PO daily (max dose 120 mg/24 h)
- **Preeclampsia with severe features, or chronic HTN w/ superimposed preeclampsia**
  - **Magnesium sulfate** ($MgSO_4$): Bolus 4–6 g IV w/ maintenance of 1–2 g/h for sz prevention, titrate and consider no bolus if pt has renal failure
  - Goal magnesium level = 4–6 mg/dL
  - Monit closely for pulm edema as $MgSO_4$ is a smooth muscle relaxer
- Timing for deliv based on limited scientific evid & should always be dependent upon the individualized clinical picture (*Obstet Gynecol* 2011;118:327)

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Chronic HTN: On no meds (38–39 w), controlled on meds (37–39 w), not well controlled on meds (36–37 w)
Gestational HTN: 37–38 w
Preeclampsia: Nonsevere (37 w), sev (at time of dx if ≥34 w, otherwise dependent upon clinical picture)

HYDROPS FETALIS

Definition and Epidemiology

- Accum of fluid in 2 of the following 5 extravascular compartments: Heart (pericardial effusion), lungs (pleural effusion), abd (ascites), subcutaneous tissue best seen around fetal skull (edema), amnion (polyhydramnios)
- **Immune Hydrops:** Rh isoimmunization
  RhD– Mom w/ RhD+ fetus has 16% chance of undergoing isoimmunization
  ↓ to 2% w/ postpartum anti-D immune globulin administration
  ↓ to 0.1% w/ additional administration in the 3rd trimester (*Transfus Med Rev* 1988:2:129)
  6/1000 live births undergo Rh isoimmunization
  2nd Preg more affected than 1st (1st usually mildly affected, if affected at all, as 1st Ig produced is IgM – DOES NOT cross placenta)
- **Nonimmune Hydrops:** All other causes
  Genetic (aneuploidy, Turner syn, trisomies), CV (structural, arrhythmias, vascular abnormalities), hematologic (α-thal), respiratory (pulm hypoplasia), infectious (CMV, syphilis, Parvovirus, Rubella)
  1/1500–1/3800 births affected

Etiology

- **Immune:** Unclear, possibly from fetal anemia/hypoxia leading to heart failure
  Mom RhD–, fetus RhD+ → Mom makes antibodies → cross placenta → antibodies bind to fetal bld → hemolysis of fetal bld → release of bilirubin & fetal anemia → fetal cardiac failure & damaged myocardium → fluid accum → hydrops fetalis
- **Nonimmune:** Dependent upon the underlying d/o

Clinical Manifestation

- US findings can include enlarged liver/spleen/placenta/heart, ascites
- **Fetal HR tracings:** Sinusoidal pattern indicative of fetal anemia
- **Mirror syn:** Mother gets edema that mimics the hydropic fetus

Physical Exam

- Mother may appear edematous if experiencing mirror syn
- Infant can range from hyperbilirubinemic to pale, limp, edematous

Diagnostic Workup/Studies

- **Immune:** All women have Rh(D) typing & Ab screening at 1st prenatal visit → if antibodies present *indirect Coombs* test detects Ab titer
  Titer <1:32
  Rpt titer every 4 w
  After 24 w gest, rpt titer every 2 w
  If remains <32 deliver at term vs. if ≥32 proceed w/ w/u below
  Titer ≥1:32
  Test father's Ag & genotype
  Homozygous: *MCA Dopplers* q1–2w starting at 18–24 w gest
  Heterozygous: Perform amniocentesis for fetal DNA
  RhD+: Proceed w/ MCA Dopplers
  RhD–: Deliver fetus at term, no further testing
- **Nonimmune:**
  Detailed personal (inquire about infectious contacts) & FHx
  Perform detailed US & consider fetal ECHO
  Obtain MCA Dopplers to assess fetal anemia
  Offer amniocentesis (karyotype, TORCH panel)
  Obtain mat bld (anemia w/u, type & screen, serologies for CMV, parvovirus B19, toxoplasmosis, syphilis)

Subsequent Workup

- MCA Dopplers
  Peak MCA velocity >1.5 MoM → check fetal HCT via PUBS → transfuse fetus if HCT <30%
  Peak MCA velocity ≤1.5 MoM → continue MCA Dopplers q1–2w
  Nomogram to monit MCA Doppler results is valid until 35 w gest

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Treatment and Medications
- **Immune:** PUBS, intrauterine fetal bld xfusion when needed, Phenobarb 30 mg PO TID to mother prior to deliv if received multi PUBs and need for delivery
- **Nonimmune:** Prog dependent upon etiology; worse prog when diagnosed earlier in gest & w/ pleural effusions or polyhydramnios
  CV issues: ~40% of nonimmune hydrops
  Fetal arrhythmias (eg, SVT) can be treated w/ mat rate controlling meds
  Mortality rate 50–98% (approaches 100% if <30 w gest w/ pleural effusions)
  Often may require supportive care or offering termination of Preg
  Continue to monit MCA Dopplers as above if dx is anemia

INTRAUTERINE GROWTH RESTRICTION

Definition and Epidemiology (*Obstet Gynecol* 2013;121:1122)
- Defined as sonographic EFW <10th percentile
- By definition is present in 10% of all gestations. Often, not signif until EFW <5%

Etiology
- **Mat factors:**
  Behavioral: Smoking, substance use, decreased nutritional intake
  Medical: Extremes of reproductive age, HTN, renal dz, lung dz, lupus, cyanotic heart dz, collagen vascular dz, viral or protozoal illness
- **Fetal factors:**
  Congen d/o (eg, aneuploidy), constitutional

Clinical Manifestation
- Small for gestational age infant (<10%)
- Neonat morbidity: Dependent on cause; infants born constitutionally small generally have no sequelae & those w/ congen anomalies have poorer outcomes
- Perinatal morbidity & mortality is increased, particularly below 3%ile EFW

Physical Exam
- Lagging fundal height compared to gestational age. Nml fundal height measurements from 20–36 w are defined as 1 cm per week of gest ±2 cm.

Diagnostic Workup/Studies
- Goal: Identify true placental insufficiency causing IUGR vs. constitutional or other
- Clinical dx:
  Screening is accomplished via fundal height measurements
  Lagging fundal height (≥3 cm) → US eval for growth
- US:
  Eval after identifying lagging fundal height includes EFW using fetal biometry
  Fetal biometry: Head circumference, biparietal diameter, abdominal circumference, & femur length
  EFW <10% = IUGR
  AFI should be performed for prog
  Oligohydramnios (AFI <5 cm) correlates w/ an increased risk of fetal death
- Umbilical artery Doppler:
  Measurement of velocity of flow through umbilical artery during systole & diastole
  Peak systolic velocity is elevated in IUGR → indicates ↑ placental resistance
  W/ progression of IUGR, diastolic flow ↓ as placental resistance ↑ → AEDF or REDF
  AEDF: Risks of continuing Preg begin to outweigh the risks of prematurity
  REDF: Move toward deliv

Management (*Am J Obstet Gynecol* 2011;204:34.e1)
- Initial US is performed after lagging fundal height is found (65–85% sens and 96% spec). Growth US repeated in 3–4 w
- At least weekly antenatal testing is indicated & may include:
  NST, BPP, modified BPP + umbilical artery Doppler
  Negative predictive values are >99% for each of the above tests – ie, a negative test is highly reassuring that IUFD will not occur w/i 1 w
- **Deliv:** (*Obstet Gynecol* 2011;118:323)
  38–39 w6d gest w/ nml testing and isolated IUGR; Deliv plan tailored to individual risks and ongoing eval
  34–37 w6d gest w/ abnormal umbilical artery Dopplers or other risk factors (eg, oligo, maternal comorbities)
  Earlier delivery (≤34 w) considered for the most severe cases (eg, REDF), after steroids for FLM and with MgSO4 for fetal neuroprotection (for ≤32 w GA)

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MULTIPLE GESTATION

Definition and Epidemiology *(Obstet Gynecol 2014;123:1118)*

- Pregnancies in which more than one fetus implants in the uterus
- Multi gestations account for 3% of all births
- 65% rise in twins & 500% rise in triplets or higher since 2002, likely secondary to ART

Etiology

- Described in terms of zygosity – number of eggs initially fertilized
  - **Monozygotic** = one egg fertilized by one sperm; splitting of initial zygote
  - **Dizygotic** = usu two eggs fertilized by two sperm; two separate fertilization events
- Chorionicity vs. amnionicity
  - Determined by timing of embryonic splitting
    - 0–4 d after fertilization → dichorionic diamnionic twins
    - 4–8 d after fertilization → monochorionic diamnionic twins
    - 8–12 d after fertilization → monochorionic monoamnionic twins
    - >12 d post fertilization → conjoined twins
  - **Chorionicity:** Number of placentas shared by embryos (di = 2, mono = 1)
  - **Amnionicity:** Number of amnionic sacs around embryos (mono = both embryos in 1 sac)

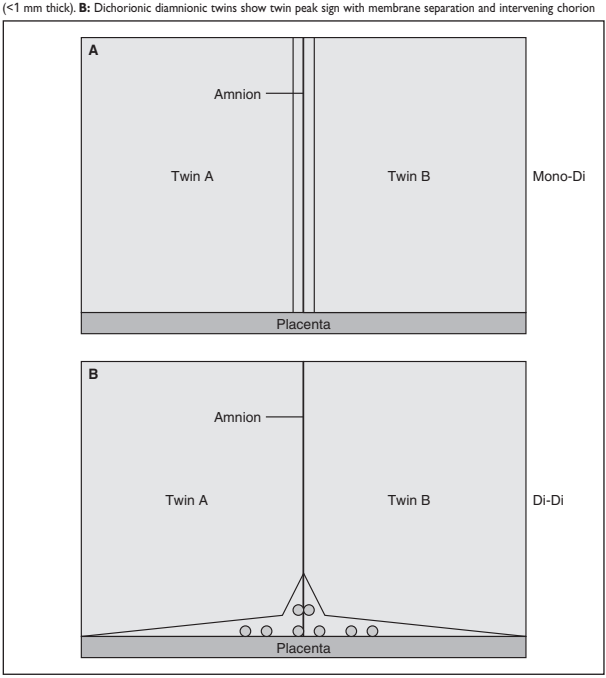
Physical Exam

- Measurement of size > dates

Diagnostic Workup/Studies

- Best test is US in early Preg → determines number of embryos
  - Cannot always tell chorionicity
  - 1st trimester twin peak sign = dichorionic gest

Figure 11.1 A: Monochorionic diamnionic twins have fused amnionic membranes with no intervening placental tissue (<1 mm thick). **B:** Dichorionic diamnionic twins show twin peak sign with membrane separation and intervening chorion



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Complications
- Almost all complications of Preg are more likely w/ multi gestations
- **Discordance:** One twin larger than the other; clinically signif when greater than 20%. Calculate discordance % as: [(larger EFW – smaller EFW) / larger EFW] × 100.
- **Monochorionic monoamnionic twins:** Cord entanglement & subseq cord accident; delivered early at 32–34 w
- **Monochorionic diamnionic twins:** Twin to twin transfusion syndrome (TTTS)
  Due to bld vessel anastomoses w/i single placenta w/ pressure diff
  Occurs in ~15% of monochorionic diamniotic twin gestations
  Donor twin: Bld shunted away
  Recipient twin: Bld shunted toward
  Stages of TTTS (*J Perinatol* 1999;19:550):
  1. Polyhydramnios/oligohydramnios, donor bladder present
  2. Poly/oli, donor bladder absent
  3. Poly/oli, abn Dopplers
  4. Poly/oli, hydrops of recipient
  5. IUFD of one or both fetuses

  Rx:
  Laser photocoagulation of vessel anastomoses (Stage II or worse)
  Serial amnioreduction
  Selective reduction (termination) of one fetus

CERVICAL INSUFFICIENCY/SHORT CERVIX

Definition and Epidemiology (*Obstet Gynecol* 2012;120:964)
- Inability of cervix to maintain a Preg until term
- Weakened cervical tissue leading to loss of Preg, often 2nd trimester

Etiology
- **Congen:** Collagen dz, Müllerian fusion anomalies, h/o DES exposure in utero
- **Acq:** Cervical trauma, D&C, cervical manipulation (LEEP, cold knife cone)
- Abnormality in cervical remodeling (4 steps: Softening, ripening, dilation, repair)

Clinical Manifestation
- Asymptomatic/painless cervical dilation/effacement
- Often h/o painless dilation & deliv in the 2nd trimester w/ prior pregnancies

Physical Exam
- Speculum exam can show a dilated cervix
- Digital exam reveals soft, effaced, & possibly dilated cervix

Diagnostic Workup/Studies
- When performing fetal anatomy US at 18–22 w, can perform CL via transabdominal US. CL <25 mm on transabdominal → transvaginal US

Treatment and Medications
- **For short cervix:** Vaginal progesterone 200 mg micronized or 90 mg gel daily
- **For short cervix or cervical insufficiency:** Cervical Cerclage (*Obstet Gynecol* 2014;123:372)
  Surgical stitch placed circumferentially around the cervix
  McDonald: "Purse-string" placed at cervicovaginal junction
  Shirodkar: Requires dissection of the vesicovaginal & rectovaginal fascia to the level of the internal os
- **When to treat:**
  Singleton Preg w/:
  No prior spont preterm births → offer vaginal progesterone suppl if CL ≤20 mm at ≤24 w
  Prior spont preterm birth (start progesterone injections weekly from 16–36 w) → consider cerclage if CL ≤25 mm at ≤24 w
  Dilated cervix <24 w → consider rescue cerclage on individual basis
  Multiples show no improv w/ progesterone & worse outcomes w/ cerclage

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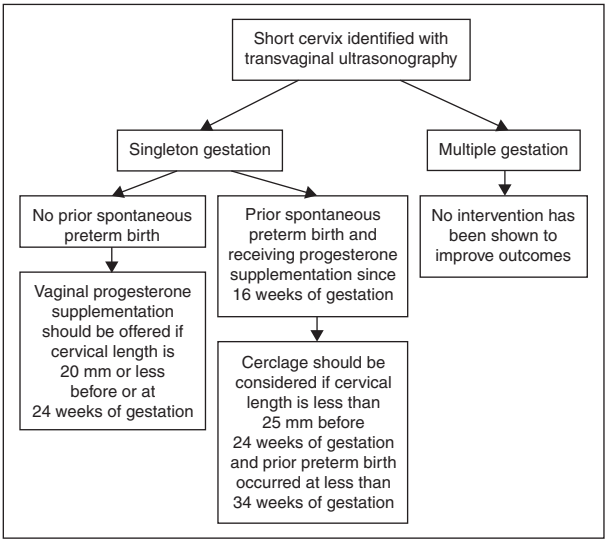
Figure 11.2 Management of short cervix



(From Committee opinion no. 522: Incidentally detected short cervical length. *Obstet Gynecol.* 2012;119(4):879–882.)

PRETERM PREMATURE RUPTURE OF MEMBRANES

Definition and Epidemiology (*Obstet Gynecol* 2013;122:918)

- **PROM:** Rupture of membranes before the onset of active labor ("premature" to labor)
- **PPROM:** Premature rupture of membranes <37 w (preterm GA *and* prior to labor)
- Occurs prior to 1/3 of preterm births

Etiology

- No consensus on the cause of PPROM – thought to be on spectrum of preterm labor
- Risk factors include intra-amniotic infxn, uterine over distension, smoking, connective tissue disorders, 2nd & 3rd trimester bleeding, nutritional deficiency, prior preterm deliv, symptomatic contractions, amniocentesis (leakage after amniocentesis more likely to stop & not lead to deliv)

Clinical Manifestation

- Leakage of amniotic fluid prior to labor
- If accompanied by mat fever or tachy, uterine fundal tenderness, fetal tachy, purulent or malodorous fluid there should be concern for intra-amniotic infxn

Physical Exam

- Sterile speculum exam (*Obstet Gynecol.* 1992;80:630; *Am J Obstet Gynecol.* 2000;183:1003)
- Avoid digital exam, esp if preterm. Single digital exam decreases latency to deliv.

Diagnostic Workup/Studies

- **Clinical dx:**
  - Leakage of fluid per vagina that is consistent w/ amniotic fluid (see below)
  - Signs of infxn should prompt deliv, regardless of prematurity, to ↓ risk of mat & neonat sepsis
  - Sterile speculum exam: Pooling of fluid in the vaginal vault sugg ROM
  - US: Oligohydramnios is often present, though not diagnostic
  - NST: Fetal tachy is often present w/ intra-amniotic infxn
  - Oligohydramnios → variable decelerations
- **Lab tests:**
  - **Ferning:** Place fluid from vaginal vault on a dry slide; salts in the amniotic fluid produce a delicate ferning pattern under microscope.

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pH: Amniotic fluid has a basic pH → turns pH paper blue (nitrazine test)
Also nitrazine positive: Bld, bact vaginosis, semen.

- Diagnostic procedures
  Indigo carmine amniotic infusion "tampon test"
  Indigo carmine injected into the amniotic sac via amniocentesis
  Tampon inserted vaginally to detect blue color indicating leakage of amniotic fluid
  If amniocentesis performed to assess chorioamnionitis, get cell count, gram stain, gluc, & cx (aerobic/anaerobic/myco- and ureaplasma)

Management

- **Previable** (<24 w): May be managed outpt, w/o Abx, until viability
  Major complications: Limb contractures, pulm hypoplasia
  Should be offered termination via D&E or induction
- **Early preterm** (24–34 w):
  Antenatal corticosteroids (up to 32–34 w depending on institutional protocol)
  Admit to inpt observation in nearly all cases
  No indication for tocolytics
  Collect GBS culture
  Latency Antibiotics
  ↑ duration of Preg ("latency period") on avg 1 w
  ↓ neonat morbidity (respiratory distress, NEC)
  Does not ↓ incid of chorio
  Induction at 34 w gest or w/ signs of preterm labor, chorio, abruption, fetal distress

Latency antibiotics regimen*
Ampicillin 2 g IV q6h × 48 h → Amoxicillin 250 mg PO q8h × 5 d AND Erythromycin 250 mg IV q6h × 48 hr → Erythromycin 330 mg PO q8h (or 250 mg q6h) × 5 d
*, other regimens can be employed (eg, azithromycin instead of erytho). For severe PCN allergy, use erythro alone. Augmentin should NOT be used in place of amp (inc risk of NEC).
From Mercer BM, Miodovnik M, Thurnau GR, et al. Antibiotic therapy for reduction of infant morbidity after preterm premature rupture of the membranes. A randomized controlled trial. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. *JAMA.* 1997;278(12):989–995.

- **≥34 w** (*PLoS Med* 2012;9:e1001208):
  Unless contraindications exist to vaginal deliv, induction may be attempted
  After 34 w, no difference in neonat sepsis btw induction & conservative mgmt, but trend toward ↓ neonat morbidity w/ induction
  More likely to see variable decelerations during labor → ↑ CD for fetal intolerance
  GBS status should be assessed during latency & appropriate therapy in labor

PRETERM LABOR

Definition and Epidemiology

- Labor (ctx + cervical dilation) occurring before 37 w gest
- Preterm labor occurs in ~40–50% of all pregnancies
- Preterm deliv occurs in roughly 12% of pregnancies → ~35% of all health care spending for infants in US

Etiology

- Poorly understood, but risk factors include multi gest/uterine over distension, bact infxn, placental abruption, cervical insufficiency, prior preterm labor

Clinical Manifestation

- Physical exam findings of labor including persistent uterine contractions (>4/20 min or 8/h) leading to changes in cervical effacement & dilation.
- Occ includes rupture of membranes

Physical Exam

- Painful uterine contractions leading to cervical change, and eval for PPROM, abruption, etc

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Diagnostic Workup/Studies (*Obstet Gynecol* 2012;120:964)

- **Pelvic exam:**
  Sterile speculum and digital exam to evaluate cervical dilation
  Collect fFN swab
  GBS swab if deliv is not imminent & has not been collected previously
  Sterile vaginal exam to directly assess cervix (must be after fFN collected!)
- **Labs:**
  fFN: Basement membrane peptide present in amniotic membranes. Can be tested via cervical swab – not reliable w/ vaginal bleeding, recent (<24 h) intercourse or vaginal exam. If negative, 95% do *not* deliver in 14 d (*Br J Obstet Gyneacol* 1996;103:648)
- **US:**
  Transvaginal US measurement of cervical length <25 mm is a/w preterm deliv

Treatment and Medications (*Obstet Gynecol* 2012;119:1308)

Tocolytic medications				
Category	**Example**	**Contraindication**	**Mat effects**	**Fetal effects**
Beta-mimetics	Terbutaline	Arrhythmias	Pulm edema, MI, HTN	Tachy, hyperglycemia
Magnesium sulfate	Magnesium sulfate	Myasthenia gravis	Flushing, muscle weakness, pulm edema, MI	Hypotonia, respiratory depression
CCBs	Nifedipine	Cardiac dz, renal dz (relative)	Flushing, HoTN, nausea	None
Prostaglandin synthetase inhib	Indomethacin	Renal or hepatic dysfxn; peptic ulcer dz, coagulopathy	Nausea, heartburn	Closure of ductus arteriosus, oligohydramnios

- **Prior to 34 w gest:**
  Administer corticosteroids for fetal lung maturation
  Tocolytics only to allow for Cort administration or mat xfer – no pharmacotherapy proven to stop preterm labor
- **Prior to 32 w gest:**
  Magnesium sulfate administration for fetal neuroprotection (*N Engl J Med* 2008;359:895)
- **Prevention of recurrent preterm birth:**
  17-OH progesterone caproate (250 mg IM weekly) starting at 16 w until 36 w (30% reduction in recurrent preterm deliv) (*N Engl J Med* 2003;348:2379)
  Serial cervical length measurements starting at 16–24 w/ poss cerclage placement if cervical length <25 mm. See short cervix, above. (*Am J Obstet Gynecol* 2009;201:375)

POSTPARTUM HEMORRHAGE (PPH)

Definition and Epidemiology (*Obstet Gynecol* 2006;108:1039)

- Bld loss >500 cc w/ a vaginal deliv or >1000 cc w/ a CD (total EBL)
- Common, w/ incid 2–3% of all births in the United States (*Am J Obstet Gynecol* 2010;202:353). Clinically, excessive bld loss causing symptomatic anemia (palps, SOB, lightheadedness) &/or signs of hypovolemia (tachy, HoTN, hypoxemia)
- Major cause of mat mortality (*Cochrane Database Syst Rev* 2007;1:CD003249). Risk of death 1:1000 births in developing countries & 1:100,000 births in developed countries.
- **Primary (Early) PPH:** W/i 24 h of deliv, caused by **uterine atony,** genital tract lacerations, bladder or urethral lacerations, retained products of conception, invasive placentation (eg, accreta), uterine rupture or inversion, coagulopathy
- **Secondary (Late) PPH:** From 24 h–12 w after deliv, caused by infxn, retained products of conception, placental site subinvolution, coagulopathy

Etiology

Uterine atony (most common cause) from: Distended uterus (multi gest, polyhydramnios); impaired uterine contractility (tocolytic meds or anesthetics, prolonged use of meds for labor induction) (*Am J Obstet Gynecol* 2011;204:56); intraamniotic infxn (chorio); distended bladder (prevents lower uterine segment contraction)

- Trauma: Genital tract laceration (vaginal or cervical); surgical injury
- Retained placental tissue (normally or abnormally implanted)

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- Coagulopathy: Consumptive coagulopathy from ongoing hemorrhage; HELLP syn; sev preeclampsia; amniotic fluid embolism (w/ DIC); sepsis; fetal demise
- Bleeding may not be apparent if intra- or retroperitoneal bleed, or if genital tract hematoma

Physical Exam

- Bimanual exam to assess for atony or retained placental tissue. Consider bedside US to evaluate for retained placental tissue.
- Thorough inspection of the genital tract for laceration or hematoma
- Tachy & HoTN seen when bld loss approaches 1500–2000 cc

Diagnostic Workup/Studies

- Identify origin of bleeding:
  - Visualize cervix & vagina to evaluate for lacerations
  - Bimanual uterine massage to assess for uterine atony
  - Bedside US to view poss retained products
  - Manual evacuation of uterine cavity for poss extraction of retained products
  - Place Foley catheter (distended bladder may contribute to poor uterine tone)
- **Labs:** Bld type & cross, CBC, PT/INR, PTT, fibrinogen. 5 mL of bld in red top tube at bedside → clot in 8–10 min if fibrinogen >150 mg/dL.
- Immediately begin treating for the suspected origin of hemorrhage (eg, for uterine atony administer uterotonics, perform bimanual uterine massage)

Medical Therapies for PPH

- Oxytocin (Pitocin) Routine use during the 3rd stage of labor significantly reduces the incid of PPH (*Cochrane Database Syst Rev* 2001;(4):CD001808). Can bolus for PPH, though some risk for HoTN. Onset of action: ~1 min (IV), 3–5 min (IM).
- Misoprostol May cause fever, chills/shivering, GI distress. Onset of action: 100 min (PR) (vs. 8 min PO, 11 min SL, 20 min PV)
- Methylergonovine Onset of action: 2–5 min (IM).
- Carboprost tromethamine (Hemabate) May cause bronchospasm in asthmatics. May rpt q15–90 min as needed, w/ max cumulative dose 2 mg. Onset of action: 15–30 min (IM).

Medical intervention for postpartum hemorrhage

Agent	Dose	Route	Dosing frequency	Side effects	Contraindications
Oxytocin (Pitocin)*	20–40 U in 1 L crystalloid or 10U IM	IV+ IM/IU	Continuous	N/V, emesis, water intoxication	None
Misoprostol (Cytotec)	600–1000 ug	PR+ PO	Single dose	N/V, diarrhea, fever, chills	None
Methylergonovine (Methergine)	0.2 mg	IM+ IU	Every 2–4 h	HTN, HoTN, N/V	HTN, preeclampsia
Prostaglandin $F_{2\alpha}$ (Hemabate)	0.25 mg	IM+ IU	Every 15–90 min (8 dose max)	N/V, diarrhea, flushing, chills	Active cardiac, pulm, renal, or hepatic dz
Prostaglandin E_2 (Dinoprostone)	20 mg	PR	Every 2 h	N/V, diarrhea, fever, chills, HA	HoTN

*1st line; + preferred route.

Procedural Therapies for PPH

- Uterine massage for atony (external, bimanual)
- Manual extraction of placenta
- D&C/ Suction curettage of the uterus for retained placenta
- Uterine tamponade: Balloon catheter placement (Foley or Bakri balloon, or lap packing) for tamponade, esp lower uterine segment atony
- Uterine compression sutures (eg, B-Lynch) or mattress sutures
- Uterine artery embolization (interv radiol)
- Exploratory laparotomy
  - Compression sutures: B-Lynch, Hayman, Pereira (physically ↑ uterine tone)
  - Vessel ligation: Uterine arteries (O'Leary sutures), hypogastric arteries (↓ perfusion)
- Hysterectomy (definitive therapy)

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Figure 11.3 Management of uterine atony with bimanual massage

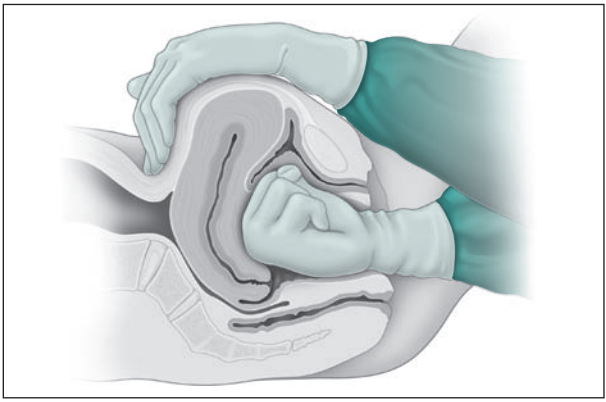

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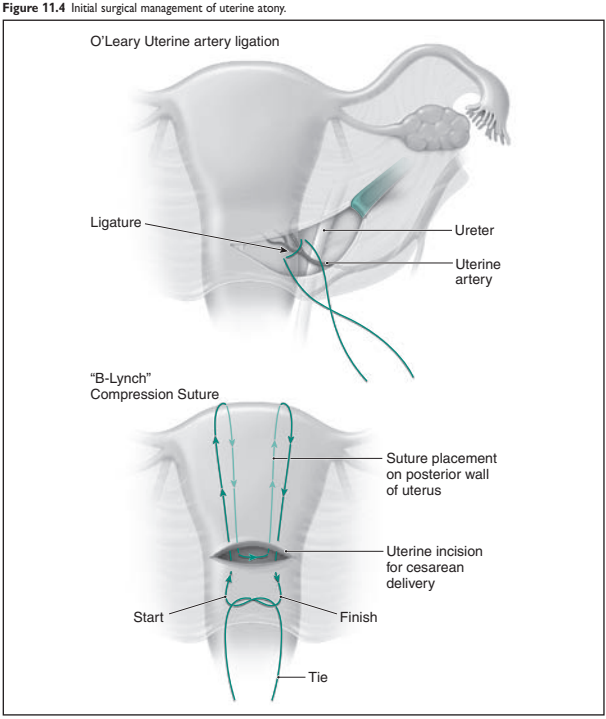
Figure 11.4 Initial surgical management of uterine atony.



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Example postpartum hemorrhage protocol		
Assessments	**Meds/Procedures**	**Blood bank**
Routine measures		
Assess for risk for PPH Quantify EBL routinely	Oxytocin IM or IV Fundal massage	Type & screen or crossmatch
Bld loss: >500 mL vaginal or >1000 mL cesarean or VS changes (by >15% or HR >110, BP <85/45, O_2 sat <95%)		
Notify nursing & anesthesia Continuous VS & calculation of EBL Bimanual & visual exam of genital tract, placenta, & (if intra-op) uterus, strict I/Os	Notify anesthesia team. Ensure adequate IV access. ↑ oxytocin rate. Fluid resusc. Continue bimanual uterine massage Methergine 0.2 mg IM if not hypertensive. May rpt if good resp, otherwise use another uterotonic. Empty bladder, place Foley	Crossmatch 2 units of pRBCs if not already done. Request FFP when requesting 3rd unit pRBC.
Continued bleeding w/ total bld loss under 1500 mL		
Mobilize 2nd obstetrician, rapid resp team (per hospital) Continue q5- 10min VS, EBL Reexamine uterus, genital tract for bleeding source Send labs, including coagulation panel Consider uterine inversion, amniotic fluid embolism	Hemabate 0.25 mg IM &/or Misoprostol 800–1000 mcg PR 2nd IV access Vaginal birth Move to OR - Repair lacerations Consider D&C for retained placenta Place intrauterine balloon for tamponade Consult interventional radiology for selective embolization Cesarean birth Inspect broad ligament, post uterus, retained placenta B-Lynch suture Place intrauterine balloon for tamponade	Notify bld bank of OB hemorrhage 2 units RBCs to bedside, transfuse for clinical signs & *anticipated loss* (not lab values) Use bld warmer for xfusion Consider thawing 2 units FFP, use if transfusing >2 units RBCs at 1:1 Determine availability of additional RBCs & other bld products
Bld loss over 1500 mL, or >2 units pRBCs given or VS unstable or suspicion of DIC		
Prepare for postpartum hysterectomy. Call 2nd anesthesia provider, OR staff Rpt labs including coags/ABG Consider central line Social worker/family support – Keep family updated	Activate massive hemorrhage protocol B-Lynch suture Uterine artery ligation Hysterectomy Fluid warmer Upper body warming device Sequential compression devices	Transfuse aggressively Near 1:1 pRBC:FFP 1 platelet pack per 6 units pRBCs & as needed If coagulopathy unresponsive after 10 units pRBCs & coagulation factor replacement, consider rFactorVIIa

From The California Maternal Quality Care Collaborative, Obstetric Hemorrhage Care Summary 2010.

PLACENTAL ABRUPTION

Definition and Epidemiology (*Am J Epidemiol* 2001;153:332)

- Decidual hemorrhage causing premature separation of the placenta
- **Incid:** 1/120 pregnancies. ↑ w/ PPROM (2–5%)

Pathophysiology

- Decidual hemorrhage → decidual cells release tissue factor → thrombin (uterotonic) is formed, up-regulates apoptosis, induces expression of inflamm cytokines → tissue necrosis (*Am J Obstet Gynecol* 2004;191:1996)

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Etiology
- Mechanical force (trauma) or abn uteroplacental vessels (constriction from vascular dz such as smoking or hypertensive dz)
- **Acute:** High pres arterial bleeding
- **Chronic:** Low pres venous hemorrhage, often due to inflamm necrosis
- **Factors a/w abruption:** Smoking, cocaine use, mat vascular dz, prolonged ruptured membranes, abruption in prior Preg, uterine leiomyoma, multiparity, advanced mat age, HTN

Clinical Manifestation and Physical Exam
- **Acute:** Vaginal bleeding, abdominal/back pain, contractions (high frequency, low amplitude), abdominal/uterine tenderness, bright red bld in vaginal vault
- **Chronic:** Intermittent vaginal bleeding, often in small amounts, dark/old bld in vagina
- Couvelaire uterus: Purple tinged uterus due to bld in myometrium seen at cesarean
- Placenta: Gross retroplacental clots & histologic decidual necrosis or placental infarction

Diagnostic Workup/Studies
- Clinical dx by Hx, exam, sono, & suspicion
- Continuous electronic fetal monitoring & uterine tocometry: Frequent uterine contractions (tetany) & nonreassuring fetal heart tracing
- **US:** 25–50% sens
  - **Retroplacental clot:** Elevated region of placenta less echogenic than placental tissue → if seen, likelihood of abruption HIGH
  - **Subchorionic clot:** Elevated highly echogenic region of membrane
  - Thickened placenta that moves w/ mat mvmt
- **Labs:** CBC, T&C, coags, Kleihauer–Betke (trauma, Rh-mother)
  - ↑ early mat serum AFP: 10× risk of abruption if AFP not a/w a fetal anomaly (*Prenat Diagn* 2007;27:240)
  - ↓ fibrinogen (<200 mg/dL) = most sensitive lab predictor for sev abruption
  - DIC commonly seen w/ abruption

Treatment and Medications
- Large bore IV placement & fluid/bld resusc as necessary
- **Term or near term:** Deliv. If nonreassuring fetal heart tones → emergent CS
- **Preterm:** Generally delay deliv if fetal well-being is reassuring
  - Many chronic abruptions will not require deliv
  - Antenatal steroids if deliv anticipated prior to 34 w gest
  - Tocolysis not used in women w/ acute abruption
  - Antenatal testing & serial growth ultrasounds w/ expectant mgmt
  - Be prepared w/ uterotonics in the postpartum period

PLACENTA PREVIA

Definition and Epidemiology
- Placenta overlying or proximate to internal cervical os (definitions have varied)
  - **Complete:** Placenta completely covers os (>20–30%)
  - **Partial:** Placental edge partially covers os
  - **Marginal:** Placental edge w/i 2 cm of the internal os but does NOT cover os
  - **Low-lying placenta:** Placental edge extends into lower uterine segment
- **Incid:** 0.4% of pregnancies over 20 w (*J Matern Fetal Neonatal Med* 2003;13:175)
- ↑ w/ increasing parity, cigarette smoking, h/o placenta previa, prior uterine Surg, & prior CD
  - 1–4% in the Preg following a CD
  - Up to 10% if ≥4 CDs

Etiology
- **Trophoblastic implantation:** Scarred endometrium may ↑ this process
- Increased need for placental oxygen or nutrient deliv (smokers, multi gest, higher altitude residence)
- ↑ risk of previa at earlier gestational age as the unidirectional growth of trophoblastic tissue toward fundus (trophotropism) is limited. Lower uterine segment ↑ w/ gestational age → Over 90% of placenta previa identified in the 2nd trimester resolve at term

Clinical Manifestation and Physical Exam
- **Painless vaginal bleeding** in the 2nd & 3rd trimesters
- DO NOT perform digital cervical exam on a pt suspected to have a previa
- A sterile speculum exam is used to visually assess cervical dilation

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Diagnostic Workup/Studies
- Identification of placenta during routine US, usually performed from 18–22 w
- If concern for previa → rpt US to assess extent of previa or verify resolution
- Prior CSs + previa = look carefully for evid of placenta accreta (below)

Treatment and Medications
- Pelvic rest (no intercourse or digital exams for duration of Preg)
- **Outpt mgmt:** Small bleeds resolved for >7 d, live close to the hospital, & are highly compliant
- **Inpt mgmt:** Actively bleeding placenta previa, ≥2 episodes of vaginal bleeding
  If pt can be stabilized & deliv is not needed immediately for fetal distress:
  Large-bore IV access
  Baseline labs (H/H, platelet count, type & screen, coags)
  Antenatal steroids should be administered <34 w gest
- CD at 36–37 w gest (*Obstet Gynecol* 2011;118:326)

VASA PREVIA

Definition and Epidemiology (*Ultrasound Obstet Gynecol* 2001:109)
- Umbilical vessels cross internal cervical os in front of fetal presenting part
- Prevalence: **1:2500** deliveries (*OBG Survey* 2004:245)
- Type 1: From a velamentous cord insertion (vessels not surrounded by Wharton's jelly)
- Type 2: From vessels btw lobes of a bilobed or succenturiate lobed placenta

Clinical Manifestation
- Vaginal bleeding w/ rupture of membranes → fetal vessel laceration
- Sinusoidal fetal HR (indicating fetal anemia)

Diagnostic Workup/Studies
- Transvaginal US w/ color Dopplers to diagnose before labor
- Once identified, continue to monit w/ US throughout Preg
  15% resolve (*Obstet Gynecol* 2000;95:572)
  Begin NSTs twice weekly from 28–30 w to evaluate for cord compression
- **Apt test:** Qualitative test on vaginal bleeding + fetal bld = indicative of vasa previa
  Negative = mat bld, no ruptured vasa previa. Rarely used test in clinical practice.

Treatment and Medications
- Highly consider administration of antenatal corticosteroids prior to 34 w gest
  CD pior to rupture of membranes. Suggested gestational age: 34–36 w.
- Pelvic rest (no intercourse or digital exams for duration of Preg)

PLACENTA ACCRETA

Definition and Epidemiology
- Abn placental implantation: Placental villi attach to the myometrium or grow through it instead of being contained by decidual cells
- Risk of accreta ↑ w/ placenta previa & increasing number of CDs (*Obstet Gynecol* 2006;107:1226)

CS and risk for placenta accreta

# of prior CDs	Risk w/ no placenta previa	Risk w/ placenta previa
0	Minimal	1–5%
1	0.3%	11–25%
2	0.6%	35–47%
3	2.4%	40%
≥4	Not given	50–67%

Pathology
- **Accreta:** Chorionic villi attached to myometrium
- **Increta:** Chorionic villi invade the myometrium just up to the serosa
- **Percreta:** Chorionic villi protrude through the uterine serosa

Risk Factors
- Advanced mat age, smoking, advanced parity, submucosal fibroids, Asherman's syn
- Most strongly correlated w/ placenta previa + prior uterine incision (eg, CD, myomectomy)

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Clinical Manifestation
- Given US advancements, often diagnosed prior to clinical presentation
- Placenta does not detach after deliv → PPH.

Diagnostic Workup/Studies
- Women w/ placenta previa or low lying anter placenta & prior uterine Surg → sono for accreta at 20–24 w
- Ultrasonographic findings suggestive of placenta accreta:
  Loss of hypoechoic boundary btw placenta & bladder or thin myometrium <1 mm
  Placental lacunae w/ turbulent flow
  Irreg bladder wall w/ extensive vascularity
  Loss of retroplacental clear space
- Consider color Doppler sono, 3D sono, & MRI. Cystoscopy if bladder invasion suspected

Subsequent Workup
- If accreta identified, pt should be seen by a team of physicians (Anesthesia, General Surg, Interventional Radiology, Uro) to prepare for cesarean hysterectomy
- Monit closely for vaginal bleeding & abdominal pain throughout Preg

Treatment and Medications
- CD at 34–36 w, be prepared for hysterectomy (*Obstet Gynecol* 2011;118:323)
- Steroids for fetal lung maturity if deliv prior to 34 w gest
- PPH w/ extreme bld loss likely. Maintain IV access & T&C for bld products. Consider internal iliac artery balloon catheters, postsurgical embolization. See Chap. 16 for massive xfusion protocol & bld products.

UTERINE INVERSION

Definition and Epidemiology
- **Complete:** Internal lining of fundus extrudes through cervical os
- **Incomplete:** Portion of fundus extrudes to the cervix but not through the os
- 1 in 2500 deliveries (*J Reprod Med* 1989;34:173)

Etiology
- Excessive umbilical cord traction during 3rd stage of labor on a fundally implanted placenta
- Impaired uterine contraction after deliv of placenta
- Uterine malformations. Abn placentation (eg, placenta accreta)

Physical Exam
- Visualization of endometrial lining through the cervical os (meaty, red tissue)
- Inability to palpate fundus of uterus

Treatment and Medications
- Reinvert the uterus w/ constant/gentle pres, in a cephalad direction, on the fundally inv portion of the uterus. Reinversion becomes more difficult w/ delay. Bleeding ↑↑↑
- General anesthesia & tocolytic agents may be needed to assist w/ replacing the uterus; monit closely for HoTN & increased bleeding, such as:
  Magnesium sulfate 2 g IV
  Terbutaline 0.25 mg IV or IM
  Nitroglycerine 50 mcg IV
  Halogenated anesthesia (isoflurane, sevoflurane)
- Obstetrical emergency if reinversion is not successful → laparotomy → elevate fundus by round ligaments & restore cephalad with a hand below in the vagina.

AMNIOTIC FLUID EMBOLISM

Definition and Epidemiology
- Presence of amniotic fluid in mat circulation, occurring usually at deliv
- Incid of 7.7/100000 births. Unpredictable & unpreventable

Pathology
- Poorly understood. Amniotic fluid enters mat circulation → precipitation of DIC & shock in mother (cardiogenic vs. distributive)
- Thought to be due to tumultuous labor or uterine manipulation, but unk

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Clinical Manifestation and Physical Exam
- Sudden profound HoTN from cardiogenic shock, hypoxemia, DIC
- Acute in onset & sev, life threatening → ICU admission. Often rapidly fatal
- Acute destabilization of vital signs – usually becoming unresponsive rapidly

Diagnostic Workup/Studies
- ***Clinical* dx:** HoTN, hypoxemia, cardiorespiratory failure
- **Ddx:** Placental abruption, uterine rupture, peripartum cardiomyopathy, sepsis, PE, anaphylaxis, MI

Treatment and Medications
- If deliv has not yet occurred, emergent (often bedside) deliv of the fetus is warranted
- Supportive rx of hemodynamic instability is the mainstay of rx. Call for help.

MALPRESENTATION

Definition and Epidemiology
- Fetal presentation refers to the presenting part of the fetus (lowest or nearest cervix). Poss presentations include:
  Cephalic presentation divided into vertex, sinciput, brow, & face
  Breech presentation divided into frank, complete, & footling
    Incid of breech presentation declines w/ increasing gestational age, starting at ~33% at 21–24 w → 11% at 32 w → 3–4% at ≥37 w
  Other presentation: back (up or down), shoulder, etc

Breech presentations		
Frank breech	**Footling breech**	**Complete breech**
Fetal hips flexed, fetal knees extended; "butt 1st"	Fetal foot or knee is below the breech; "foot 1st"	Fetal hips flexed, fetal knees flexed

Etiology and Diagnosis
- Uterine anomalies (bicornuate, septum), fibroids, placentation defects (previa), multiparity, poly/oligohydramnios, contracted mat pelvis, fetal or neuro defect, short umbilical cord
- Presenting part is felt w/ vaginal exam, identified on Leopold maneuvers. Verify w/ sono.

Treatment
- Breech & mentum post face presentations → usually CD. *Planned* vaginal breech deliv a/w ↑ perinatal mortality, neonat mortality, & serious neonat morbidity than planned CD (5% vs. 1.6%) (*Lancet* 2000;356:1375)
- **External cephalic version** may be attempted (at >36 w, usu 36–38 weeks) to convert a breech presentation to a cephalic. Contraindicated in pregnancies where CD is indicated (eg, placenta previa), gestational age <36 w (high rate of reversion). (ACOG Practice Bulletin #17, Reaffirmed 2012)

FETAL MECONIUM

Definition and Epidemiology
- Fetal mec stool usu passed in the 1st days of life. If prior to deliv → meconium-stained amniotic fluid, which if breathed by fetus can → mec aspiration syn
- Meconium-stained amniotic fluid in ~9% of live births w/ 0.1% mec aspiration syn
- Most common in pregnancies reaching 41–42 w gest (post term)
- More likely during labor c/b fetal hypoxia → possibly indicating fetal stress resp

Pathology
- Aspiration of mec by the fetus → dz in neonat lungs. Hypoxemia in neonate secondary to pulm injury
- Injury from mechanical obst of the airway, inflamm damage caused by irritation in the lungs, or by inactivation of surfactant w/i alveoli

Clinical Manifestations
- Dark brown to green amniotic fluid when membranes rupture or after (describe as thin, mod, thick)
- Note color & presence or absence of particulate matter

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Diagnostic Workup/Studies
- Mec aspiration can occur during deliv – mec aspiration syn is diagnosed w/ neonat hypoxemia in the presence of aspiration

Treatment and Medications
- Amnioinfusion does not prevent mec aspiration syn
- Peds should be at deliv when mec is noted on rupture of membranes
- To prevent aspiration, nonvigorous neonates should *not* be initially stimulated at the perineum. Allow peds to evaluate & perform tracheal suction w/ laryngoscope.

CHORIOAMNIONITIS

Definition and Epidemiology
- Infxn of the amniotic membrane & chorion of the placenta
- Complicates 1–4% of all births in US
- Risk factors – ↑ duration of membrane rupture, GBS bacteriuria, prolonged labor, multi vaginal exams, internal monitoring

Etiology
- Infxn is present in the chorionic membranes, umbilical cord, or placenta
- May be transmitted via ascending infxn from lower genital tract, transplacentally from mat bld stream, or iatrogenically (eg, via amniocentesis)
- **Typical organisms:** *Ureaplasma, Mycoplasma hominis* (more common in ascending infections), *GBS, Escherichia coli, Gardnerella vaginalis, Listeria monocytogenes* (more common w/ transplacental spread from mat infxn)

Physical Exam
- Mat: Fever (>38°C or 100.4°F), fundal tenderness, purulent or foul smelling discharge, tachy >100 bpm. Fetal: tachy >160 bpm
- Mat fever + tachy is highly suggestive. *Clinical dx.*
- Rule out other causes fever/tachy (eg, epidural fever, administration of ephedrine)

Diagnostic Workup/Studies
- **Clinical dx:** Mat fever is the most important marker of the condition
- **Lab eval:** Rarely performed, though amniotic fluid culture is the gold std for dx; other suggestive amniotic fluid markers include gluc ≤15 mg/dL, IL-6 >7.9 ng/mL, positive MMP, WBC > 30/mm^3, leukocyte esterase positive on dipstick. IL-6, MMP, & leukocyte esterase ↑ sens/spec.

Treatment and Medications
- Acetaminophen for fever control → ↓ incid of neonat encephalopathy
- IV Abx:
  - **Vaginal deliv:** Ampicillin 2 g IV q6h + Gentamicin 1.5 mg/kg IV q8h until deliv; one additional dose after deliv of each antibiotic → ↓ endomyometritis
  - **CD:** Same as vaginal deliv + Clindamycin 900 mg IV once OR Metronidazole 500 mg IV once; consider continuing Abx until pt is afebrile for 24–48h (generally w/ Gentamicin/Clindamycin or Ampicillin/Gentamicin/Clindamycin).

ENDOMYOMETRITIS

Definition and Epidemiology
- Infxn of the endometrial, parametrial, or myometrial tissue usually >24 h after deliv (low grade mat fever common during this period). Clinical suspicion guides dx.
- Incid varies w/ mode of deliv:
  - **Vaginal deliv:** 0.2–0.9%; higher if chorio was present
  - **CD:** 5–30%; decreased w/ perioperative prophylactic Abx

Etiology
- Similar to chorio (ascending infxn from lower genital tract). Also introduced infxn from surgical trauma. Usually polymicrobial.
- Infxn from genital tract can invade the surgical wound

Physical Exam
- Physical exam is similar to chorio w/ mat fever & fundal tenderness
- Malodorous lochia may be present

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Diagnostic Workup/Studies

- ↑ WBC (although commonly elevated in labor & postoperatively anyway)
- Largely clinical dx & depends on context/suspicion. Imaging generally unnecessary unless suspecting pelvic abscess or larger/progressing infxn.
- Cx for chlamydia & gonorrhea could be considered if not already obtained
- Routine endometrial culturing is not helpful secondary to genital tract contamination

Treatment and Medications

- Treat w/ broad spectrum Abx. >90% respond to Gentamicin (5 mg/kg IV q24h) + Clindamycin (900 mg IV q8h). IV Abx until asymptomatic/afebrile for 24–48 h; no data exist to support continued oral antibiotic rx. Clinical response guides antibiotic coverage/spectrum (eg, broaden if no response in ~24 h or clinically worsening) and duration of treatment.
- Acetaminophen/Ibuprofen for mat fever. Breastfeeding okay.

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CARDIOVASCULAR DISEASE IN PREGNANCY

Epidemiology

- CVD = leading cause of death in women in US. More women than men die from CVD annually (*Circulation* 2011;123:e18)
- ↑ incid of CVD in Preg due to ↑ age at 1st Preg & ↑ prevalence of risk factors (DM, HTN, obesity) (*Eur Heart J* 2011;32:3147)
- Hypertensive disorders occur in 6–8% of pregnancies. Other CVD complicates 0.2–4% of pregnancies (in western countries).

Maternal Cardiac Risk Estimation

- **Prepregnancy counseling:** Risk of Preg depends on specific heart dz & current clinical status. Risk assessment should be performed prior to Preg, including medication review.
- **Mat risk assessment:** WHO risk classification integrates all known mat CV risk factors

WHO maternal cardiac risk classification

WHO class	Definition & mgmt	Example
1	Low risk, limited cardiology follow-up in Preg	MV prolapse, isolated ectopic atrial or ventricular beats
2	Low or mod risk, cardiology follow-up every trimester	Most arrhythmias, repaired tetralogy of Fallot, unrepaired ASD/VSD
3	High risk, frequent cardiology follow-up	Mechanical valve, cyanotic heart dz
4	Very high risk, Preg "contraindicated." Recommend termination of Preg, otherwise frequent cardiology follow-up.	Pulm arterial HTN, sev ventricular dysfxn (NYHA III–IV), sev MS or AS, prev peripartum cardiomyopathy w/ residual impairment

From Thorne S, MacGregor A, Nelson-Piercy C. Risks of contraception and pregnancy in heart disease. *Heart.* 2006;92(10):1520–1525.

Cardiac disease in pregnancy score (CARPREG)

1 point earned for each of the following:
NYHA functional class >II or cyanosis
Left heart obst w/ MV area <2 cm^2, AVA <1.5 cm^2, or L ventricular outflow tract gradient >30 mmHg
LVEF <40%
H/o prior cardiac event or arrhythmia
Risk of cardiac complication (eg, pulm edema, tachy/bradyarrhythmia req rx, MI, stroke, cardiac death): 0 points = 5%; 1 point = 27%; >1 point = 75%

From Siu SC, Sermer M, Colman JM, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. *Circulation.* 2001;104(5):515–521.

CARDIOVASCULAR CHANGES IN PREGNANCY

Blood Volume

- Plasma vol ↑ 45% from 6–32 w gest to 4700–5200 mL
- RBC mass ↑ by 20–30% (from ↑ production of RBCs)
- Plasma vol ↑ more than RBC vol, causing physiologic hemodilution → anemia
  ↑ erythrocyte 2,3-diphosphoglycerate conc, ↓ affinity of mat Hgb for O_2 → facilitates dissociation of oxygen from Hgb → preferential xfer of O_2 to fetus

Hemodynamic Profile

- CO ↑ 30–50% during Preg (50% of that during 1st 8 w)
  Turning from supine to left lateral recumbent position → release of vena caval compression by gravid uterus can ↑ CO by 25–30%
- Uterine bld flow ↑ 10-fold to 500–800 mL/min (17% of total CO at term)
- Renal bld flow ↑ by 50%. No change in perfusion to brain or liver.

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- ↑ HR at 5 w → max ↑ 15–20 beats/min by 32 w to term (*Am J Physiol* 1989;256:H1060)
- ↓ BP from 7 w to nadir 5–10 mmHg systolic & 10–15 mmHg diastolic by 24–32 w, then ↑ toward nonpregnant values at term (*Am J Med* 1980;68:97)

Heart Sounds (*Am Heart J* 1966;71:741)

- Benign systolic flow murmur develops in more than 95% of pregnant women: ↑ CO → turbulent flow over pulmonic or aortic valve
  Audible 1st btw 12 & 20 w w/ regression usually by 1 w postpartum

Intrapartum Hemodynamic Changes

- **1st stage labor:** 12–31% ↑ CO. 2nd stage: 49% ↑ CO. ≈2-fold ↑ from nonpregnant.
- Contractions cause 300–500 mL xfer of bld from uterus to general circulation
  SBP & DBP ↑ by 35 & 25 mmHg respectively

Maternal hemodynamic profiles in the 3rd trimester

	Nonpregnant	Pregnant	Change
CO (L/min)	4.3 ± 0.9	6.2 ± 1	+43%
HR (beats/min)	71 ± 10	83 ± 10	+17%
SVR (dyne-sec cm^{-5})	1530 ± 520	1210 ± 266	–21%
PVR (dyne-sec cm^{-5})	119 ± 47	78 ± 22	–34%
CVP (mmHg)	3.7 ± 2.6	3.6 ± 2.5	—
COP (mmHg)	20.8 ± 1	18 ± 1.5	–14%
PCWP (mmHg)	6.3 ± 2.1	7.5 ± 1.8	—
COP–PCWP (mmHg)*	14.5 ± 2.5	10.5 ± 2.7	–28%

**Important factor in dev of pulm edema throughout Preg.*
From Clark SL, Cotton DB, Lee W, et al. Central hemodynamic assessment of normal term pregnancy. *Am J Obstet Gynecol.* 1989;161:1439.

Postpartum Hemodynamic Changes

- **60–80% ↑ CO w/i 10–15 min of vaginal deliv:** Release of venocaval obst, autotransfusion of uteroplacental bld, rapid mobilization of extravascular fluid → *watch for pulm edema.* CO returns to prelabor value by 1-h postpartum.
- Important to monit women w/ CVD closely until at least 24 h after deliv
- CV measurements (SV, SVR, CO) take up to 24 w to return to prepregnancy values

ECG Changes in Pregnancy

- Majority of pregnant pts have a nml ECG (*Eur Heart J* 2011;32:3147)
- Change in heart position (rotated to left) → 15–20° L axis deviation; mimics LV hypertrophy
- **Common ECG changes:** Transient ST segment & T wave changes; Q wave & inv T wave in lead III; attenuated Q wave in lead AVF; inv T wave in leads V_1, V_2, & occ V_3
- Premature beats & sustained tachyarrhythmia ↑ in Preg. Ventricular & atrial ectopy in up to 50–60% of pregnant women. Symptomatic exacerbation of paroxysmal SVT in Preg in 20–44% of cases. 15% of pregnant women w/ CHD develop arrhythmia. Most palps are benign, but warrant a Holter monit. Limited data on antiarrhythmic meds: Weigh mat risk against potential fetal teratogenicity.

CHRONIC HYPERTENSION (CHTN)

Definitions

- **CHTN in Preg:** Use of antihypertensive medication prior to Preg, OR onset of HTN before Preg, prior to 20 w gest, or that persists beyond 12 w postpartum

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Epidemiology and Etiology

- **Nonpregnant:** 10–15% Caucasian adults, 25% AA adults
- **Pregnant:** Occurs in up to 5% of pregnant women. Hypertensive disorders overall represent the most common medical complications of Preg (incid 6–8%)
- Essent (95%)
- **Secondary:**
  Renal (4%): Renal artery stenosis, parenchymal
  Endocrine (0.5%): Pheo, primary hyperaldo, Cushing's
  Coarct of the aorta (0.2%)
  Other: Collagen vascular dz, sleep apnea

Hypertension definitions		
Category	**Systolic (mmHg)**	**Diastolic (mmHg)**
Nonpregnant (JNC VII Classification)		
Nml	<120	<80
Pre-HTN	120–139	80–99
Stage 1 HTN	140–159	90–99
Stage 2 HTN	≥160	≥100
Pregnant		
Mild HTN	≥140, <160	≥90, <110
Sev HTN	≥160	≥110

From Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 report. *JAMA.* 2003;289(19):2560–2572.

Risk stratification of CHTN in pregnancy	
Low risk	**High risk**
Uncomp essent HTN No prior perinatal loss SBP < 180 mmHg & DBP < 110 mmHg	Secondary HTN End-organ damage (LV dysfxn, retinopathy, microvascular dz, stroke) Prior perinatal loss SBP ≥ 180 mmHg or DBP ≥ 110 mmHg

From Sibai BM. Chronic hypertension in pregnancy. *Obstet Gynecol.* 2002;100(2):369–377.

Gestational complications of CHTN		
	Mild HTN (%)	**Sev HTN (>160/110) (%)**
PEC	10–25	50
Placental abruption	0.7–1.5	5–10
Preterm deliv	12–34	62–70
SGA infant	8–16	31–40

From Obstet Gynecol 2002;100:369.

Workup

- **H&P:** Including fundoscopic, cardiac, abdominal, vascular, & neurologic exams
- **Studies:** Electrolytes, BUN/Cr, gluc, Hgb/Hct, UA, lipids, ECG
- **W/u for secondary causes:** Age <20 or >50, sudden onset, sev, refrac
- **Additional w/u for Preg:** Baseline HELLP labs including Hgb, Plt, Cr, AST/ALT, uric acid, 24-h urine prot

Complications

- **Nonpregnant:** Mostly long term, including TIA/CVA, CAD, CHF, CKI
  ↑ of 20 mmHg SBP or 10 mmHg DBP doubles CV complications (*Lancet* 2002;360:1903)
- **Pregnant**: Additional mat risks: Pulm edema, hypertensive encephalopathy, retinopathy, cerebral hemorrhage, acute renal failure

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Additional fetal risks: Perinatal mortality ↑ 3–4×
Rx goal: <140/90 mmHg (<130/80 mmHg w/ DM or renal dz) (*NEJM* 2003;348:610)

Medication for treatment of CHTN	
Drug	**Notes**
Methyldopa	No known teratogenicity; rarely used in nonpregnant women
β-blockers	Used w/ angina, post-MI, CHF Labetalol: Drug of choice in Preg. No known teratogenicity. Avoid atenolol in Preg: ↑ risk for IUGR Avoid atenolol & metoprolol postpartum: Concentrate in breast milk
Nifedipine	Used w/ DM & vascular dz in Preg No known teratogenicity
Thiazide diuretic	1st line for essent HTN Reduces plasma vol expansion in Preg D/c if evid of reduced uteroplacental perfusion
ACEI/ARB	Used in atherosclerosis, DM, CKI, CHF, post-MI Avoid in Preg: ACEI fetopathy
A successful prepregnancy BP regimen generally can be continued w/ the exception of ACEI/ARB	

Additional Management in Pregnancy (*Obstet Gynecol* 2002;100:369)

- Lifestyle modifications preconception (each ↓ SBP by 5 mmHg)
  Weight loss, diet (low saturated & total fat, low sodium), exercise, ↓ EtOH
- **Low risk:** No antihypertensive drugs. US at 16–20 w, rpt at 28–30 w then monthly for growth assessment till term. Deliver at 38–39 w.
- **High risk:** Antihypertensive meds to keep BP <140/90 mmHg. US at 16–20 w, rpt at 28 w, then every 3–4 w until deliv. Serial fetal testing (NST, AFI) beginning at 28–32 w. Deliver at 39 w if BP controlled & no fetal growth restriction, otherwise deliver at 37–38 w.

HYPERTENSIVE CRISIS

Definition

- **Hypertensive emergency:** Elevated BP w/ target organ damage
- **Hypertensive urgency:** SBP > 210 or DBP > 120 w/ minimal or no target organ damage

Treatment

- **Hypertensive emergency:** ↓ MAP by 25% in minutes to 2 h using IV agents
- **Hypertensive urgency:** ↓ BP in hours using oral agents

IV & oral agents for treatment of hypertensive crisis			
IV agents		**Oral agents**[a]	
Agent	**Dose**	**Agent**	**Dose**
Nitroglycerin	17–1000 μg/min	Labetalol	Initial 100 mg BID; max 800 mg TID
Labetalol[b]	10–80 mg q10min or 2–4 mg/min	Clonidine	0.2 mg load → 0.1 mg qh. Max dose 0.7 mg.
Hydralazine[b]	10–20 mg q4–6h	Hydralazine	Initial 10 mg QID; max 300 mg daily
Phentolamine	5–15 mg bolus prn		

[a]Nifedipine is not used for acute HTN due to reported serious CV morbidity.
[b]Recommended for use in acute sev HTN in Preg.

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PREGNANCY-RELATED HYPERTENSION

Definitions (And see chapter 11; For up to date details, Hypertension in Pregnancy, ACOG Task Force, 2013)

Gestational hypertensive disorders			
Dz	**BP**	**Proteinuria***	**Notes**
gHTN	SBP ≥ 140 or DBP ≥ 90 Sev: SBP ≥ 160 or DBP ≥ 110 On 2 occasions at least 4 h apart & no more than 7 d apart	<300 mg prot in 24-h urine	1st diagnosed beyond 20 w gest
Mild (nonsevere) PEC	SBP ≥ 140 or DBP ≥ 90 On 2 occasions at least 4 h apart & no more than 7 d apart	≥300 mg prot in 24-h urine OR At least 1+ on 2 random urine samples collected at least 6 h apart & no more than 7 d apart	1st diagnosed beyond 20 w gest gHTN plus proteinuria *Newest guideline does NOT use proteinuria to r/o PEC
sPEC	SBP ≥ 160 or DBP ≥ 110 On 2 occasions at least 4 h apart while the pt is on bed rest. BP should be measured seated upright.	Not used. Evaluate for Severe Features such as: thrombocytopenia (<100,000/uL) *or* serum Cr >1.1 mg/dL *or* elevated LFTs (2× upper limit normal) *or* pulmonary edema *or* cerebral/visual symptoms	Criteria for nonsevere PEC plus: Sev-range BP *or* proteinuria *or* 1 of the following: Oliguria: <500 mL in 24 h Cerebral or visual disturbances Pulm edema or cyanosis Epigastric or RUQ pain Impaired liver fxn: AST > 2× nml Thrombocytopenia: Plt < 100000/mm^3 New guidlines do not use fetal growth as dx criterion

Epidemiology (*Obstet Gynecol* 2003;102:181)

- **Risk factors for Preg-related HTN:** Nulliparity, multifetal gest, obesity, AMA, prior PEC, CHTN, renal dz, DM, vascular & CTD, antiphospholipid Ab syn, AA race
- **gHTN:** 6–17% in nulliparous & 2–4% multiparous women
- **PEC:** 4–8% of all pregnancies; up to 18% in women w/ a h/o PEC
- **Eclampsia:** 1 in 2000–3448 pregnancies

Other disorders associated with HTN in pregnancy	
Dz	**Definition**
Superimposed PEC	CHTN + PEC: New onset proteinuria (≥300 mg 24-h urine) in a woman w/ CHTN but no proteinuria prior to 20 w gest OR sudden ↑ in proteinuria, BP, or evid of multiorgan system involvement in a woman w/ known HTN & proteinuria prior to 20 w gest
Eclampsia	Seizures not attributed to another cause in a woman w/ PEC
HELLP	**H**emolysis, **E**levated **L**iver enzymes, **L**ow **P**latelets (sev PEC variant)
AFLP	**A**cute **F**atty **L**iver of **P**regnancy. Very elevated LFTs, low gluc.

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Etiology/Pathophysiology

- Poorly understood. Potential causes: Abn trophoblast invasion of uterine bld vessels, immunologic intolerance btw fetoplacental & mat tissues, maladaptation to the CV/inflamm changes of Preg, dietary deficiencies, genetic abnormalities (*Obstet Gynecol* 2003;102:181)

Prevention

- ↑ **risk:** H/o PEC, other hypertensive d/o, DM, abn uterine artery dopplers, nulliparity, multi gest → therefore, reduce risk factors early
- Low-dose ASA in mod- to high-risk pts (*Obstet Gynecol* 2010;116:402)
  Prior PEC: Start ASA by 16 w: RR 0.47 (95% CI 0.34–0.65); NNT 9
  Prior sPEC: Start ASA by 16 w: RR 0.09 (95% CI 0.02–0.37); NNT 7
  Starting after 16 w → no benefit. Stop ASA ~1 w prior to deliv.

Clinical Manifestations of PEC

- **Cerebral:** HA, dizziness, tinnitus
- **Visual:** Diplopia, scotomata, blurred-vision, amaurosis
- **GI:** Nausea, vomiting, epigastric/RUQ pain, hematemesis
- **Renal:** Oliguria, anuria, hematuria

Initial Workup

- Collect baseline bld work at 1st prenatal visit or at time of dz presentation
  Hgb, Plt, Cr, AST/ALT, uric acid, 24-h urine prot. Rpt if ↑ clinical concern.
- Fetal eval: NST/AFI, growth US

Management/Treatment

Management & treatment of PEC

	Mat surveillance	Fetal surveillance	Deliv
gHTN	No hospitalization or bedrest Monit for sev gHTN or PEC	Daily kick counts Serial NST/AFI or BPP (1–2×/w) Serial fetal growth US (q4w)	37–38 w gest Sev gHTN managed as sPEC
Nonsevere PEC	Hospitalization per provider No bedrest Monit for sPEC Evaluate for organ dysfxn Weekly labs	Daily kick counts Serial NST/AFI or BPP (1–2×/w) Serial fetal growth US (q3–4w)	37–38 w gest
Sev PEC (expectant mgmt) OR Superimposed PEC w sev features	Evaluate organ dysfxn Serial labs (q6h → daily if stable) $MgSO_4$ sz ppx Antihypertensive meds for BPs	Daily fetal assessment Serial NST/AFI (2×/w) Serial fetal growth US (q3w) Betamethasone for fetal lung maturity <34 w gest	Expectant mgmt if <32 w gest & nml labs/growth/assessment Deliv by 34 w
Eclampsia	Stabilize mother Rx: IM: "Give 2 high fives" – 5 mg $MgSO_4$ IM to each buttock IV: $MgSO_4$ 4–6 g loading dose → 2 g/h	Fetal brady frequently occurs during eclamptic sz → managed by mat resusc Continuous monitoring	Deliv "in timely fashion" Method dependent on gestational age, presentation, cervical dilation, & mat stability Cesarean NOT always indicated
HELLP/AFLP	Stabilize mother $MgSO_4$ for sz ppx Supportive therapy postpartum	Continuous monitoring	

NOT ELIGIBLE for expectant mgmt: Imminent eclampsia (persistent sev sx), suspected placental abruption, nonreassuring fetal testing, HELLP or AFLP, abn mat labs or end-organ damage.
From Sibai BM. Diagnosis and management of gestational hypertension and preeclampsia. *Obstet Gynecol.* 2003;102(1):181–192.

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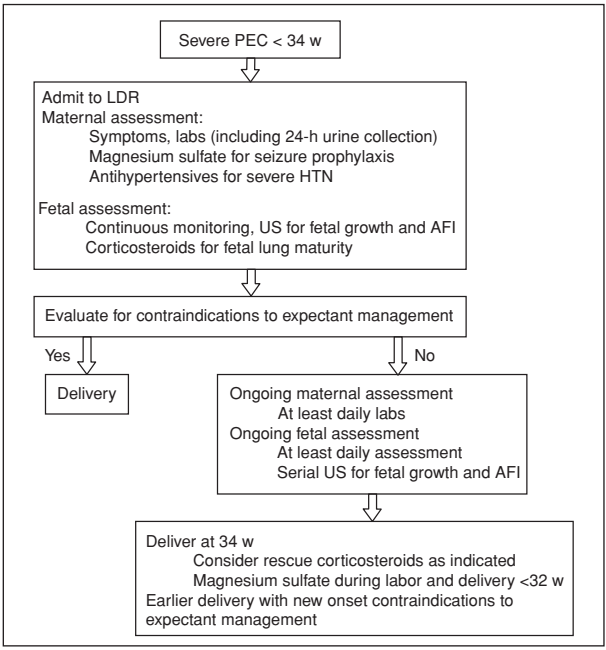
Figure 12.1 Algorithm for management of sPEC <34 weeks



(From Sibai BM. Evaluation and management of severe preeclampsia before 34 weeks' gestation. *Am J Obstet Gynecol.* 2011;205(3):191–198)

Intrapartum Management

- sPEC/Eclampsia is *not* an indication for cesarean deliv; IOL by obstetric indications
- Mat precautions: Frequent BP monitoring, sz precautions
- Fetal precautions: Continuous fetal monitoring
- $MgSO_4$ to prevent sz *(Clin Obstet Gynecol* 2005;48:478)
  - $MgSO_4$ superior to other antiepileptics (diazepam, phenytoin, or lytic cocktail) in PEC. Lower rate of recurrent seizures (RR = 0.41 [95% CI, 0.32–0.51]). Lower rate of mat death (RR = 0.62 [95% CI, 0.39–0.99]). Use intrapartum & 12–24 h postpartum. NNT for sPEC: 71; NNT for nonsevere PEC: 400.
  - **Magnesium tox:** Monit closely throughout rx. Lower dose (eg, 1 g/h) if mat renal impairment. Therapeutic level: 4–6 mEq/L. Loss of patellar reflexes: 8–10 mEq/L. Respiratory depression: 12 mEq/L. Mental status changes: >12 mEq/L. Cardiac arrest: >24 mEq/L.
  - **Rx of magnesium tox:** D/c magnesium, obtain serum level, give calcium gluconate: 1 g IV over 5 min, supportive therapy & close monitoring

Dosing magnesium sulfate		
IM	Loading dose	5 g IM each buttock
	Maint dose	5 mg IM q4h
IV	Loading dose	4–6 g IV over 10–20 min
	Maint dose	1–2 g/h IV

Postpartum Management

- Continue to monit BPs closely. BP decreases w/i 48 h, but may ↑ 3–6 d postpartum. Monitor 72 h postpartum in hospital, then check at home daily, and 1 w postpartum BP check in clinic.

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- If magnesium initiated intrapartum, continue until 12–24 h postpartum or until adequate diuresis has been documented (fluid balance net negative). Consider furosemide diuresis daily × 5 d (*Obstet Gynecol* 2005;105(1):29).
- Follow labs daily until clinically stable & trending toward nml
- **Postpartum HTN** (*Am J Obstet Gynecol* 2012;206(6):470): Persistence of gHTN, PEC, CHTN vs. de novo dev. Treat w/ magnesium sulfate × 24 h or until clinical improv w/ PEC. Prevalence: 0.3–27.5%.
  Ddx for postpartum HTN includes PEC spectrum, pre-existing or undiagnosed HTN, hyperthyroidism, primary hyperaldo, pheo, renal artery stenosis, cerebral vasoconstriction syn, cerebral venous thrombosis/stroke, thrombotic thrombocytopenic purpura/hemolytic uremic syn

Management of Maternal Complications/Sequelae

- **Convulsions:** See Eclampsia in Chap. 18
- **Pulm edema:** Diurese w/ furosemide (10–40 mg IV) → monit urine output, intubation if necessary
- **Acute renal or liver failure, liver hemorrhage, DIC, stroke:** Supportive therapy → consider xfer to ICU

Complications/Sequelae

Progression to preeclampsia with mild gHTN

Weeks' gest	% who developed PEC
34–35	37.3
32–33	49.3
30–31	50
<30	52.1

From Barton JR, O'brien JM, Bergauer NK, et al. Mild gestational hypertension remote from term: Progression and outcome. *Am J Obstet Gynecol.* 2001;184(5):979–983.

Pregnancy outcomes in women with PEC

Outcome	Nonsevere[a]	Sev[b] (%)
Preterm deliv	14–25.8%	33–66.7
SGA infant	4.8–10.2%	11.4–18.5
Placental abruption	0–3.2%	1.4–6.7
Perinatal death	0–1%	1.4–8.9
Mat mortality	Rare	0.2
Mat morbidity[c]	Rare	5

[a]Rates similar to normotensive & gHTN pregnancies.
[b]Rates similar to sev gHTN.
[c]Convulsions, pulm edema, acute renal or liver failure, liver hemorrhage, DIC, stroke.
From Sibai BM. Diagnosis and management of gestational hypertension and preeclampsia. *Obstet Gynecol.* 2003;102(1):181–192.

CORONARY ARTERY DISEASE/ACUTE CORONARY SYNDROME

Definition and Epidemiology (*Circulation* 2012;125:188; *Clin Cardiol* 2012;35(3):141)

- CAD → MI, angina pectoris (AP), or both
- **ACS:** Atherosclerosis → plaque rupture → thrombosis → acute myocardial ischemia. Other causes of ischemia: Coronary artery spasm, embolism, aortic dissection, vasculitis, myocarditis.
- **Risk factors:** Age, smoking, HTN, hyperlipidemia, DM, FHx
- **Prevalence:** CAD: ♂ 8.3%, ♀ 6.1%. MI ♂ 4.3%, ♀ 2.2%. AP: ♂ 3.8%, ♀ 4%
- 1 of 6 deaths in US in 2008 due to CAD; ↑ mortality in women <55 yo

Presentation and Physical Exam

- Angina + dyspnea, diaphoresis, N/V, palps, lightheadedness
- Women often present w/ nonclassic sx (eg, GI distress)
- Signs of ischemia or heart failure: S3, S4, new murmur, ↑ JVP, crackles

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Diagnostic Studies
- **ECG:** ST segment deviation or T wave inversion
- **Cardiac enzymes:** Troponin = most sensitive & specific. Detectable 4–6 h after injury, peaks 24 h after injury, ↑ up to 10 d. CK-MB = less sensitive/specific.

Treatment
- NSTEMI: Meds – Anti-ischemic (nitrates, β-blockers, CCBs) & antithrombotic (ASA, clopidogrel, heparin, LMWH, GPIIb/IIIa inhibitors); angiography generally only w/ recurrent ischemia
- STEMI: Primary PCI by 90 min; antifibrinolytics if no PCI; meds same as NSTEMI

Pregnancy Considerations *(Eur Heart J 2011;32:3147)*
- Risk of MI 3–4× higher compared to nonpregnant women. ACS: 3–6/100000 deliveries → mortality 5–10%. All stages of gest, but more common in 3rd trimester. Most commonly involves anter wall.
- Preg can be considered if CAD & no residual ischemia or LV dysfxn
- **Rx:** PCI for STEMI. AVOID ACEI & ARB. Clopidogrel or GPIIb/IIIa no data.
- **Intrapartum mgmt:** SVD generally preferred. AVOID methergine for postpartum hemorrhage: May induce coronary artery vasospasm.

PULMONARY HYPERTENSION

Definition and Epidemiology
- Mean PA pres > 25 mmHg at rest or >30 mmHg w/ exertion
- **Idiopathic pHTN:** 1–2 per million. Mean age of onset: 36 (men older than women). Female:male 1.7–3.5:1.

Etiology *(JACC 2003;43:5S)*
- **Pulmonary arterial HTN:** Idiopathic, familial, or related to risk factors or assoc conditions (collagen vascular dz, portal HTN, HIV, congen systemic-to-pulm shunts → Eisenmenger syn). A/w left heart dz, lung dz, hypoxemia, chronic thrombotic/embolic dz, sarcoidosis, histiocytosis X, lymphangiomatosis, pulm vessel compression, drugs (cocaine, appetite suppressants).

Diagnosis
- Dyspnea, syncope or chest pain on exertion, sx of right-sided heart failure
- Prominent P2, right-sided S4, RV heave, PA flow murmur, PR, TR
- **Signs of RV failure:** JVD, periph edema, ascites, hepatomegaly
- **Definitive dx w/ cardiac cath:** ↑ RA, RV, & PA pres, ↑ PVR, ↓ CO, nml PCWP
- **W/u:** CXR, ECG, PFTs, ABG, echocardiogram

Treatment
- Oxygen, diuretics, dig, anticoagulation
- **Vasodilators:** CCB, prostacyclin, prostacyclin analogues, endothelin-1 receptor antag
- Lung xplant if refrac
- **Preconception counseling:** Women w/ pHTN should be discouraged from Preg; if Preg occurs, termination should be offered
- Antepartum mgmt often requires hospitalization
- **L&D:** RV filling is important; modest elevations in CVP → increasing RV dysfxn & rapid deterioration

Prognosis
- **Nonpregnant:** 2.5-y median survival if untreated; if respond to nifedipine: 95% 5-y survival; nifedipine nonresponder (requiring prostacyclin): 54% 5-y survival; lung xplant: 45–55% 5-y survival
- **Pregnant pop:** 17–33% mortality w/ sev pHTN & Eisenmenger syn *(Eur Heart J 2009;30:256)*; mod pHTN (PAP <40 mmHg) up to 30% develop cardiac failure or die w/i 3 mo postpartum *(Eur Heart J 2009;30:256)*; death occurs in last trimester & in 1st months after deliv from hypertensive crisis, pulm thrombosis, refrac right heart failure. 75% mortality occurs postpartum.

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VALVULAR HEART DISEASE

Etiology

Pregnancy concerns with valvular heart disease		
Valvular abnormality	**Pathophysiology**	**Preg considerations**
MS rheumatic heart dz, congen, myxoma, thrombus, valvulitis, or infiltration	Valve stenosis impedes bld flow from LA to LV in diastole	↑ CO cannot be achieved → pulm congestion Relative tachy shortens diastole & ↓ LV filling
MR Leaflet abnormalities, ruptured chordae tendineae, papillary muscle dysfxn, annulus dilatation	↑ Regurg → LV dilatation & impaired contractility	↓ SVR promotes forward flow ↑ CO exacerbates LV vol overload ↑ SVR in PEC may impair forward flow Catecholamine release during L&D impairs forward flow
MV prolapse Myxomatous involvement of MV, a/w connective tissue dzs	Displacement of MV leaflet Classic = leaflet redundancy	Generally well tolerated
AS CHD (congen stenosis), rheumatic heart dz	Pres overload → concentric LVH	Sensitive to loss of preload a/w HoTN
Aortic insufficiency Valve dz, root dz	LV compensates for loss of forward flow w/ ↑ in LVEDV	SVR reduction → improv in cardiac performance

Clinical Manifestations and Diagnostic Studies

- Dyspnea, pulm edema, Afib
- ECG, CXR, echocardiogram, cardiac cath

Physical exam	
Valvular abnormality	**Physical exam findings**
MS	Low-pitched, diastolic rumble at apex. Loud S1. Opening snap (high-pitched early diastolic sound)
MR	High-pitched, holosystolic murmur at apex, radiating to axilla Obscured S1
MV prolapse	Midsystolic click ± mid to late systolic murmur
AS	Harsh, systolic, cres-decres murmur at RUSB radiating to carotids & down left sternal border Delayed carotid upstroke
Aortic insufficiency	High-pitched, diastolic decrescendo murmur at LUSB PMI diffuse & laterally displaced

Classification of mitral stenosis		
Stage	**Mean gradients (mmHg)**	**MV area (cm^2)**
Nml	0	4–6
Mild	<5	1.5–2
Mod	5–10	1–1.5
Sev	>10	<1

Classification of aortic stenosis		
Stage	**Mean gradients (mmHg)**	**AVA (cm^2)**
Nml	0	3–4
Mild	<25	1.5–2
Mod	25–50	1–1.5
Sev	>50	<1

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Pregnancy Considerations/Prognosis (*Eur Heart J* 2011;32:3147)

- **MS:** Decompensation depends on severity, heart failure ↑ w/ mod or sev MS. Mortality: 0–3%. W/ mod or sev MS, counsel against Preg. Offer termination in early Preg. Avoid signif tachy.
- **AS:** Morbidity related to severity, heart failure in 10% & arrhythmias in 3–25% of women w/ sev AS, mortality low. Get preconception exercise testing. Peak gradient < 60 mmHg → typically Uncomp prenatal courses.
- **Mitral regurg or aortic regurg:** Prepregnancy eval for sx, echo, LV dimension & fxn; exercise testing for mod to sev; preconception Surg for sev regurg, sx, or LV dysfxn due to ↑ heart failure risk

Treatment/management		
Valvular abnormality	**Medical rx (generally same in pregnant & nonpregnant)**	**Surgical rx**
MS	Na restriction, diuretics, β-blockers, anticoagulation (if Afib)	Percutaneous valvuloplasty
MR	Only if nonoperative; ↓ afterload: ACEI, hydralazine/nitrates; ↓ preload: Diuretics, nitrates; ↑ inotropy: Dig; consider anticoagulation	Repair → replacement
MV prolapse	ASA or anticoagulation w/ prior neurologic event; β-blockers if symptomatic	No Surg needed
AS	Only if not operative; gentle diuresis; control of HTN; avoid vasodilators & negative inotropes	Valve replacement; valvuloplasty in young adults w/o calcifications
Aortic insufficiency	Only if not operative; ↓ afterload w/ LV dysfxn or dilatation	Valve replacement

Labor and Delivery Considerations

- Pain → tachy that can exacerb valvular pathology
- Contractions → ↑ venous return therefore pulm congestion
- Abrupt elevation of PAPs in the immediate postpartum period from autotransfusion
- Cesarean deliv for obstetric indications only

Specific labor and delivery considerations	
Valvular abnormality	**Specific L&D considerations**
MS	± PAC monitoring for sev dz; early epidural; β blockade; ↓ pushing in 2nd stage → passive descent → consider operative deliv; aggressive postpartum diuresis
MR	± PAC to ensure appropriate LV filling; aggressive postpartum diuresis
MV prolapse	None
AS	± PAC monitoring for sev dz; ↓ pushing in 2nd stage → passive descent → consider operative deliv; aggressive postpartum diuresis: Use predelivery hemodynamic parameters as end point
Aortic insufficiency	PAC not usually necessary

Endocarditis Prophylaxis (*Circulation* 2007;116:1736)

- **Cardiac conditions *a/w infxn* that warrant abx ppx:** Prosthetic cardiac valve; prev infective endocarditis; CHD; unrepaired cyanotic CHD; completely repaired CHD w/ prosthetic material during 1st 6 mo after procedure; repaired CHD w/ residual defect at adj to the site of a prosthetic patch or device

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Types of prosthetic valves (*Obstet Gynecol* 1994;83:353)

- **Mechanical:** Durable but require anticoagulation; ↑ miscarriage & thromboembolic events
- **Bioprosthetic:** Less durable, but do not require anticoagulation; Preg seems to adversely impact life of a porcine valve

Medical management of prosthetic valves

	Mechanical valve	Bioprosthetic valve
Nonpregnant	Warfarin + ASA	Warfarin + ASA × 3 mo → ASA (w/o risk factors*)
Pregnant	Heparin/LMWH during Preg; can consider warfarin after organogenesis given improved outcomes w/ mechanical valves; heparin at 36 w → d/c 4–6 h prior to deliv; LMWH or warfarin postpartum	No anticoagulation after initial postsurgical ppx

Endocarditis ppx & anticoagulation generally indicated for all prosthetic valves.
*Risk factors = AFib, ↓ EF, prior embolic event, hypercoagulable state
From ACC/AHA guidelines for the management of patients with valvular heart disease. A report of the American College of Cardiology/American Heart Association. Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). *J Am Coll Cardiol.* 1998;32(5):1486–1588.

PERIPARTUM CARDIOMYOPATHY

Definition and Epidemiology

- Heart failure w/i the last month of Preg to 5 mo postpartum
- Diagnostic criteria based on risk for idiopathic DCM (*Obstet Gynecol* 1999;94:311): Absence of prior heart dz; no alternative cause; echocardiographic evid of LV dysfxn (EF <45% or fractional shortening <30%, LVED dimension > 2.7m^2)
- Incid 1 in 3000–4000 live-births (*JAMA* 2000;283:1183); ↑ risk w/ multiparity & age

Pathophysiology

- Cause unk; dev of pulm edema 2/2 LV dilation & dysfxn

Clinical Manifestations and Diagnostic Studies

- **S/sx of pulm edema:** Dyspnea, cough, orthopnea, tachy, hemoptysis, elevated JVP, S3 present
- **CXR:** Cardiomegaly, pulm edema, pleural effusions
- **ECG:** Look for Afib, bundle branch block
- **Echocardiogram:** LV dilation, ↓ EF, regional or global LV HK, poss RV HK, poss mural thrombi

Treatment

- β-blockers improve cardiac fxn & survival in stable, euvolemic pts
- OK to use implantable defibrillators in Preg (*Circulation* 1997;96:2808)

Labor and Delivery Management

- **Pain control w/ epidural:** ↓ cardiac work & ↓ tachy
- Cesarean for obstetric indications only

Prognosis

- **Peripartum:** Mortality 6–10%; cardiac xplantation 4–7% (*Circulation* 2005;111(16):2050; *N Engl J Med* 2000;342(15):1077); w/i 6 mo, ½ of pts demonstrate resolution of LV dilation → good prog, the other ½ → 85% 5-y mortality
- **Subseq Preg:** Recurrence up to 50% (*Circulation* 1995;92 (Suppl 1):1; *N Engl J Med* 2001;344(21):1567; *Ann Intern Med* 2006;145(1):30)
  >8% mortality if LV dysfxn has not resolved → discourage Preg; <2% mortality if LV dysfxn has resolved

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Management of peripartum cardiomyopathy	
Goal	**Drug**
↓ preload	Diuretic
↓ afterload	Hydralazine (antepartum), ACEI (postpartum)
Relieve pulm congestion	Diuretic
↑ contractility	Dig
Rate control w/ AF	Dig
Anticoagulation	Heparin/LMWH (antepartum), warfarin (postpartum)

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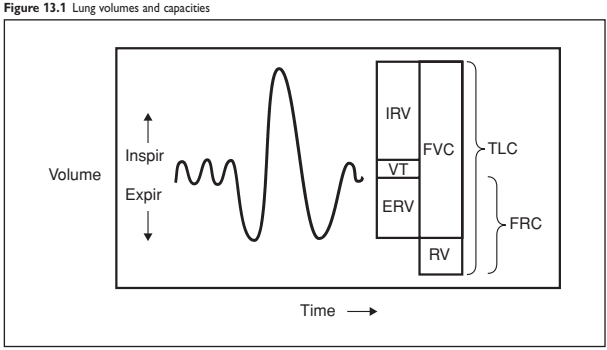
Definitions

- Total lung capacity (TLC) = sum of Forced Vital Capacity (FVC) + Residual Volume (RV); total volume of air in the lungs at full inhalation.
- FVC = sum of Inspiratory Reserve Volume (IRV), Tidal Volume (VT), and Expiratory Reserve Volume (ERV); total volume of air exhaled after max insp with max exp effort.
- Functional residual capacity (FRC) = sum of ERV + RV; volume after tidal exhalation.
- Forced expiratory volume in one second (FEV1) = volume of air exhaled in 1st second of maximal expiratory effort. FEV1/FVC: % of total expiration in 1st second.

Figure 13.1 Lung volumes and capacities



(From Hyatt RE, Scanlon PD, Nakamura M. *Interpretation of Pulmonary Function Tests: A Practical Guide*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008)

Spirometry *(Am Fam Physician* 2004;69(5):1107)

- Indicated for dx of pulm dz, follow-up of known dz, preoperative eval of pts w/ known pulm dz or prior to thoracic procedures
- Pt inhales maximally, then exhales w/ maximal effort as long as poss (at least 6 s). Contraindicated if Valsalva would be poorly tolerated. Time & vol vs. flow graphed. Rpt 3× for reliability/pt effort.
- FVC, FEV1, FEV1/FVC compare to % predicted values based on height/weight, age, sex, race
- **Interpretation of spirometry:** Ensure reliability & good pt effort (ie, valid study). If FVC, FEV1 nml & FEV1/FVC >70% → nml spirometry. If FVC nml or ↓, FEV1 ↓ & absolute FEV1/FVC <70% → obstructive physiology. If parameters correct after bronchodilator → reversible airway dz. If FVC ↓, FEV1 ↓ or nml & absolute FEV1/FVC >70% → restrictive physiology. Refer to pulm lab for lung volumes & DL_{CO}.
- **Obstructive diff dx:** Asthma, chronic obstructive pulm dz (chronic bronchitis, emphysema)
- **Restrictive diff dx:** Intrinsic lung dz (acute pneumonitis, interstitial lung dz) Extrinsic dz (mechanical abnormality of chest wall/pleura preventing expansion) Neuromuscular d/o of respiratory muscles

Peak Flow Measurements

- Peak flow meter measures current PEFR; compare to personal best. Assesses relative obst & sx control. Does NOT establish dx – for surveillance only. Use in conjunction w/ asthma action plan.
- See http://www.perinatology.com/calculators/peakc.htm for expected peak flow calculator

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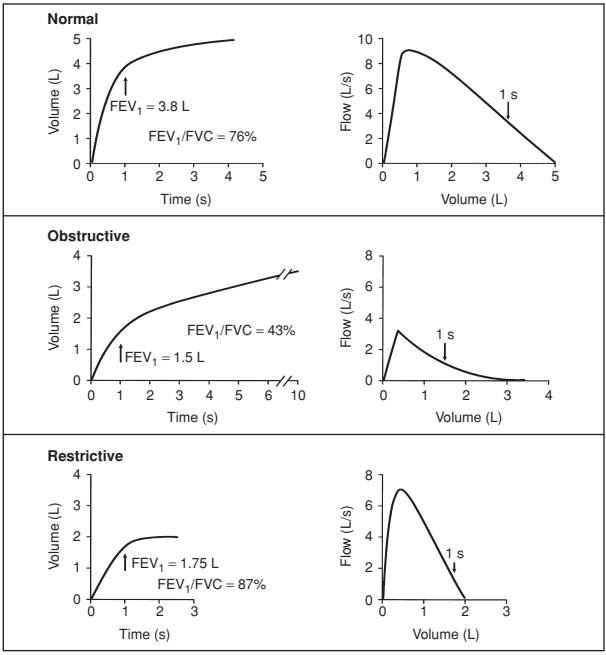
Figure 13.2 Basic pulmonary function testing



(From Hyatt RE, Scanlon PD, Nakamura M. *Interpretation of Pulmonary Function Tests: A Practical Guide*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008)

RESPIRATORY CHANGES IN PREGNANCY

General *(Clin Chest Med* 2011;32:1)

- **Upper airway:** Mucosal hyperemia, edema, glandular hypersecretion. May contribute to disordered breathing in sleep from obst. ↑ Mallampati score, ↑ neck circumference. "Rhinitis of Preg" present during last 6 w of Preg, disappears postpartum in absence of allergy or other pulm pathology.
- **Chest wall:** Compliance decreased. Widened subcostal angle, increased anteroposterior dimension mediated hormonally by relaxin. Changes peak at 37 w. Diaphragmatic excursion increased. Max inspiration/expiration pressures same as prior to Preg.

Lung Function

- Minute ventilation ↑ 20–50% by term (most ↑ during 1st trimester). ↑ progesterone & ↑ CO_2 production (V_{CO2}) ↑ central stimuli for hyperventilation. Physiologic dyspnea of Preg may be awareness of ↑ stimulus to breathe. VT ↑.
- Oxygen consump (V_{O2}) is increased; respiratory exchange rate (V_{CO2}/V_{O2}) unchanged vs. minimally increased
- FRC ↓ by diaphragm elevation, ↓ chest wall recoil, ↓ abd pull. (Note: Obesity → ↓ FRC & ↑ RV [air trapping]. In Preg, ↓ FRC w/ ↓ RV.) Airway resistance unchanged.
- (IC; IRV + VT) increases 5–10%. TLC is unchanged or ↓ minimally at term.
- FEV1, FEV1/FVC, flow/vol curve not significantly changed. Abn spirometry sugg pathology.
- DL_{CO} no change. Increased cardiac outpt offset by decreased Hgb.

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Intrapartum/Postpartum Changes

- Hyperventilation ↑ w/ pain/anxiety. Analgesia mitigates this. Minute ventilation varies widely.
- Hypocarbia can cause placental vasoconstriction → hypoperfusion
- Postpartum, all above changes resolve, except for widened subcostal angle.

ARTERIAL BLOOD GAS (ABG) ANALYSIS

Procedure

- Sterilely prep area overlying radial, femoral, brachial, dorsalis pedis, or axillary artery
- Consider local anesthesia over puncture site. Assess for collateral circulation.
- Obtain 2–3 mL bld in heparinized syringe. Remove air bubbles, place on ice for transport.
- Consider indwelling arterial catheter for serial ABGs.

Considerations in Pregnancy (*Clin Chest Med* 2011;32(1))

- ↓ pCO_2 from hyperventilation. ↓ serum bicarb compens for chronic respiratory alkalosis. ↑ pH (7.42–7.46).
- Chronic alkalosis stimulates ↑ 2,3-DPG w/ shift of Hgb dissociation curve; aids in placental O_2 exchange. ↑ pO_2 facilitates placental O_2 exchange. PO_2 significantly lower supine vs. sitting. High metabolic rate can cause rapid desaturation if apneic.

Definitions

- **Acidemia:** Arterial pH lower than nml (<7.35)
- **Alkalemia:** Arterial pH higher than nml (>7.45)
- **Metabolic acidosis:** Process that decreases serum HCO_3 → ↓ pH (bicarb consump)
- **Respiratory acidosis:** Process that increases serum pCO_2 → ↓ pH (hypoventilation)
- **Metabolic alkalosis:** Process that increases serum HCO_3 → ↑ pH (bicarb excess)
- **Respiratory alkalosis:** Process that decreases serum pCO_2 → ↑ pH (hyperventilation)

Normal Values

- Nonpregnant: pH, 7.35–7.45; pCO_2, 32–45 mmHg; pO_2, 72–104 mmHg; HCO_3, 22–30 mEq/L

Mean ABG values in pregnancy

N = 20	12 w	24 w	32 w	38 w	Postpartum
pH	7.46	7.44	7.44	7.43	7.41
pCO_2	29.4 (0.4)	29.5 (0.7)	30.3 (0.5)	30.4 (0.6)	35.3 (0.7)
pO_2	106.4 (1.1)	103.1 (1.6)	102.4 (1.2)	101.8 (1)	94.7 (1.5)

From Templeton A, Kelman GR. Maternal blood-gases, (PAO_2–PaO_2), physiological shunt and VD/VT in normal pregnancy. *Br J Anaesth*. 1976;48(10):1001–1004.

Diagnosis (*Harrison's Principles of Internal Medicine*, 18th ed)

- Obtain ABG & electrolytes simultaneously. Use HCO_3 from electrolytes.
- Determine whether simple or mixed d/o by assessing whether expected compensatory resp is present. "Compens" cannot change alkalemia to acidemia or vice versa. If apparent insuff or overexuberant compens, mixed d/o likely exists.
- If acidosis present, calculate AG: $(Na - [Cl + HCO_3])$ w/ adjustment for albumin (nml AG ≈ 2.5 × albumin)

Predicted changes for acid–base disorders

D/o	Compens
Metabolic acidosis	$PaCO_2 = (1.5 \times HCO_3) + 8 \pm 2$
Metabolic alkalosis	$PaCO_2$ will ↑ 6 mmHg per 10 mmol/L ↑ in $[HCO_3]$
Respiratory acidosis	
Acute	$[HCO_3]$ will ↓ 0.2 mmol/L per mmHg ↓ in $PaCO_2$
Chronic (>3–5 d)	$[HCO_3]$ will ↓ 0.4 mmol/L per mmHg ↓ in $PaCO_2$
Respiratory alkalosis	
Acute	$[HCO_3]$ will ↑ 0.1 mmol/L per mmHg ↑ in $PaCO_2$
Chronic (>3–5 d)	$[HCO_3]$ will ↑ 0.4 mmol/L per mmHg ↑ in $PaCO_2$

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- Consider $\Delta AG/\Delta HCO_3$ ratio to determine if simple high AG metabolic acidosis (ratio btw 1 & 2). If ratio >2, likely additional metabolic alkalosis. If <1, likely additional nongap metabolic acidosis.
- Ddx guides clinical assessment & final dx:
  For high AG metabolic acidosis: Renal failure, lactic acidosis, toxins, ketoacidosis. W/o high AG: Renal tubular acidosis, GI loss.
  For metabolic alkalosis: Exogenous alkali, extracellular fluid contraction w/ hypoK, extracellular fluid expansion w/ hypoK/Mineralocort excess
  For respiratory acidosis: Hypoventilation (obst, CNS depression, neuromuscular d/o, impaired gas exchange)
  For respiratory alkalosis: Hyperventilation (secondary to hypoxia, Preg, pain, sepsis, drugs)

PNEUMONIA

Definitions (*Am J Respir Crit Care Med* 2005;171:388; *Clin Infect Dis* 2007;44 Suppl 2:S27)
- **CAP:** PNA Acq as outpt; no risk factors for HCAP
- **HAP:** PNA developing >48 h after admission, not incubating at time of admission
- **VAP:** PNA developing >48–72 h after intubation
- **HCAP:** PNA in pt w/ any 1 of the following:
  Hospitalized >2 d in last 90 d
  Resides in long-term care facility
  Received IV Abx, chemo, wound care w/i last 30 d
  Attended hospital or hemodialysis clinic in last 30 d
- **Risk factors for MDR infxn:** Any of the HCAP factors above
  High prevalence of MDR pathogens in community or inpt unit; chronic heart, lung, liver, renal dz; functional or surgical asplenia; malig; immunocompromise or immunosuppression; recent use of Abx (PO or IV) w/i last 90 d

Diagnosis
- **Signs & sx:** Cough, dyspnea, pleuritic chest pain, sputum production (fewer reported by elderly); tachypnea, fever, decreased oxygen sat, abn lung exam. Imaging: New lung infiltrate on XR or CT
- **Microbiology:** Consider induced sputum, influenza assays, urine strep or legionella assays; bld cx if febrile (& prior to Abx); bronchoscopy/washings. Limited sens for cx; consider diff (include pt factors for uncommon causes) & often treat empirically.
- Multi decision tools to assess severity of dz on presentation; PSI may be most rigorous (*N Engl J Med* 1997;336(4):243). Calculator available at http://pda.ahrq.gov/clinic/psi/psicalc.asp.

Common etiologies of pneumonia	
Bacteria	Mycoplasma, *Chlamydia pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Legionella, Klebsiella, Staphylococcus aureus, Pseudomonas, Escherichia coli, Enterobacter, Serratia, Acinetobacter,* mycobacteria
Viruses	Influenza, parainfluenza, RSV, CMV, HSV, SARS
Fungi	PJP, *Aspergillus, Cryptococcus, Candida,* mucormycosis
Other	Chemical pneumonitis (acid/bile/other irritant), parasites (strongyloides, toxoplasmosis)

Treatment: Antibiotic Selection
- For outpt rx of CAP *w/o* risk factors for MDR
  Macrolide (erythro-/clarithro-/Azithro)
- For outpt rx of CAP *w/* risk factors for MDR or for inpt CAP
  Respiratory quinolone (moxi-/gemi-/Levo) **OR** β-lactam plus macrolide
- For HAP, early onset, *w/o* risk factors for MDR
  Ceftriaxone OR levo-/moxi-/ciprofloxacin OR ampicillin/sulbactam OR ertapenem
- For HCAP/VAP/HAP, late onset *w/* risk factors for MDR
  Antipseudomonal cephalosporin (cefepime/ceftazidime) or carbapenem (imipenem/meropenem) or piperacillin/tazobactam &
  Antipseudomonal fluoroquinolone (cipro-/Levo) or aminoglycoside (amikacin/gentamicin/tobramycin) &
  Linezolid or Vanco for MRSA coverage
  If *Legionella* is suspected, add macrolide or use quinolone instead of aminoglycoside

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- For aspiration w/ concern for bact infxn
  Clindamycin (preferred), ampicillin/sulbactam or imipenem; may use metronidazole if added on to an MDR regimen above. Consider d/c Abx if no infiltrate 48–72 h after aspiration event.

Treatment: Duration
- In outpts, 5 d **w/** or w/o MDR risk factors; may dose Azithro × 3 d b/c of long half-life
- In inpts, reassess clinical status after 2–3 d of rx
  If improved & neg cx, consider d/c Abx or continue for 7–8 d w/o pseudomonal/MRSA coverage. If cx +, tailor Abx & consider rx for 7–8 d (15 d if *Pseudomonas*, 21 d if *S. aureus*).
  If no improv, consider broadening/adjusting Abx, search for alt infxn, dx, or pathogens
- Suspected PNA in Preg is rarely treated outpt given increased morbidity & mortality. Low threshold for inpt rx.

Prevention
- Avoid intubation & reintubation. Ensure ventilator circuit is well maintained.
- If risk for aspiration, keep head of bed >30 deg
- Enteral feeding preferred to parenteral feeding to ↓ risk of bact translocation from gut
- Minimize time w/ NGT in place to ↓ risk of nosocomial sinusitis
- Formal eval & diet changes for pts w/ difficulty speaking/swallowing
- Postoperatively, consider incentive spirometry, optimize pain control, avoid routine NGT.
- Pneumococcal vax if >65 yo or w/ high-risk medical illness. Splenectomy vax if indicated. Flu vax for all pts.

PULMONARY EDEMA

Definition/Diagnosis
- Inappropriate accum of fluid in pulm interstitium & alveoli
- **Sx:** Dyspnea, orthopnea. Signs: Tachypnea, desaturation, rales, rhonchi, wheezes, respiratory failure, S3 gallop. Imaging: Peribronchial thickening, prominent vascular markings, Kerley B lines, alveolar infiltrates.

Etiology
- Fluid accum/retention OR redistribution into tissues from vasoconstriction/dilation
- **Cardiogenic:** Left ventricular dysfxn → elevated hydrostatic pres in pulm veins, extravasation of fluid into lung tissue
- **Noncardiogenic:** Direct lung injury (chest trauma, aspiration, PNA, oxygen tox, smoke inhalation, reperfusion post PE); hematogenous lung injury (sepsis, pancreatitis, xfusion, IV drug use); elevated hydrostatic pressures (re-expansion, high altitude, neurogenic)

Treatment
- Target cause (eg, cardiogenic vs. noncardiogenic). Consider echocardiogram to diagnose new/worsening cardiac fxn. Initial measures: Supplemental oxygen, positive pres ventilation. ↓ preload w/ loop diuretics (furosemide), consider nitrates, morphine, ACEI (not in Preg), pt should be upright in bed if poss. Consider transition to intensive care.

Considerations in Pregnancy (*Anaesthesia* 2012;67:646)
- Increased incid 0.08–0.5%. Rapid appearance of flash pulm edema.
- Risk factors in Preg: Preeclampsia, preterm labor, sepsis, AFE, PE, β-adrenergic tocolytics, magnesium sulfate, corticosteroids, positive fluid balance, multifetal gest

INFLUENZA IN PREGNANCY

Vaccination and Prevention
- Pregnant women are at ↑ risk for sev infxn & death than the general pop (*Obstet Gynecol* 2010;116:1006)
- ACOG & the CDC's Advisory Committee on Immunization Practices recommend that all pregnant women be vaccinated against influenza, regardless of trimester (*MMWR* 2010;59(rr08)) mat/fetal safety of influenza vaccination in Preg is well established (*Am J Obstet Gynecol* 2012;207(3 Suppl)). Antepartum vaccination → decreased stillbirth, neonat death & premature deliv, w/ no ↑ in congen anomalies (*Obstet Gynecol* 2012;120:532).

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- Mat vaccination provides passive immunity to the neonate through 6 mo of age (*N Engl J Med* 2008;359(15):1555). Pregnant women should receive the trivalent inactivated (killed) injection vaccine only, & *not* the LAIV; FluMist.
- Pregnant/postpartum women do not need to avoid contact w/ those who have received LAIV. Postpartum/breastfeeding women can receive LAIV.
- Data do not support adverse effects attributable to preservative thimerosal (*MMWR* 2010;59(rr08)). Preservative eliminated or reduced in most preparations. Proven protection against serious dz outweighs theoretical concerns regarding preservative.

Prophylaxis and Treatment (*MMWR* 2011;60(1):1)

- Clinical dx is preferred (abrupt onset fever, cough, myalgia) to lab dx for rapid rx
- Oseltamivir & zanamivir are both Preg Category C. Zanamivir may be preferable in Preg b/c of limited systemic Absorp, but avoid in pts w/ comorbid respiratory dz. Most effective if ≤48 h of sx (*Obstet Gynecol* 2010;115(4):717).
- **For ppx** after exposure during Preg or up to 2 w postpartum:
  Zanamivir 10 mg (2 puffs inhaled) daily
  Oseltamivir 75 mg PO daily
  Duration: 10 d (household exposure), 14 d (hospital exposure), 7 d (other)
- **For rx** w/ onset of sx
  Zanamivir 10 mg (2 puffs inhaled) daily × 5 d
  Oseltamivir 75 mg PO twice daily × 5 d
  Can consider longer rx for severely ill pts

Additional Considerations

- Women w/ influenza hospitalized on labor & deliv wards should have respiratory precautions per hospital std for influenza
- Discuss the need for neonat antivirals or mat–neonat separation w/ pediatricians
- Postpartum, women w/ influenza should express breast milk, rather than breastfeed. Milk may still go to the infant, as oseltamivir is poorly excreted (*Int J Infect Dis* 2008;12:451).

ASTHMA AND PREGNANCY

(*Obstet Gynecol* 2008;111:457; NIH pub no. 08-4051)

Definitions/Pathophysiology

- Chronic airway inflammation w/ hyperresponsiveness to various stimuli & partially reversible airway obst
- Sev cases a/w increased prematurity, cesarean deliv, preeclampsia, growth restriction, & mat morbidity/mortality
- Mat–fetal pathology caused by mat hypoxia. Decreased FEV1 → ↑ low birth weight/prematurity.

Diagnosis

- Wheeze, cough, SOB, chest tightness; fluctuating; often worse at night; worse w/ known triggers (allergens, exercise, infections). Consider GERD, postnasal drip w/ cough, bronchitis in diff
- Airway obst on spirometry, reversible w/ bronchodilator therapy
- Document h/o hospitalization, ICU stay, intubation, & steroid rx. Preg may improve, worsen or have no effect on asthma severity (rule of ⅓'s). Past pregnancies may better predict course of subseq pregnancies.

Asthma severity classification

Severity	Symptom freq	Nighttime awakening	Interference w/ activity	FEV1 or peak flow (% of best)
Mild intermittent	<2 d/w	<2×/mo	None	>80
Mild persistent	2–6 d/w	>2×/mo	Minor	>80
Mod persistent	Daily	>1×/w	Some	60–80
Sev persistent	All day	>4×/w	Extreme	<60

From Dombrowski MP, Schatz M, ACOG Committee on Practice Bulletins-Obstetrics. ACOG practice bulletin: Clinical management guidelines for obstetrician-gynecologists number 90, February 2008: Asthma in pregnancy. *Obstet Gynecol.* 2008;111(2 Pt 1):457–464. doi:10.1097/AOG.0b013e3181665ff4.

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Treatment

Asthma management, outpatient therapies	
Severity	**Mgmt**
Mild intermittent	Short-acting β-agonist (albuterol) as needed
Mild persistent	ADD: Low-dose inhaled Cort. Alternative: Cromolyn, leukotriene receptor antag (montelukast), or theophylline.
Mod persistent	ADD: Long-acting β-agonist (salmeterol), OR change to medium-dose inhaled Cort ± salmeterol. Alternative: Low-dose or medium-dose inhaled Cort + leukotriene receptor antag or theophylline.
Sev persistent	CHANGE to high-dose inhaled Cort + salmeterol ± oral Cort (prednisone). Alternative: High-dose inhaled Cort w/ theophylline ± oral Cort.

From Dombrowski MP, Schatz M, ACOG Committee on Practice Bulletins-Obstetrics. ACOG practice bulletin: Clinical management guidelines for obstetrician-gynecologists number 90, February 2008: Asthma in pregnancy. *Obstet Gynecol.* 2008;111 (2 Pt 1):457–464. doi:10.1097/AOG.0b013e3181665ff4.

- **Rx for acute asthma exacerbation**
  - Supplemental O_2 to maintain sat >95% (important for fetal oxygenation)
  - Albuterol nebulizer q20min × 3, then q4h
  - Consider inhaled ipratropium on presentation (0.5 mg neb/8 puffs MDI)
  - Systemic corticosteroids; prednisone 40–80 mg PO × 5–10 d (until PEFR >70%)
- **Triage for acute presentation of asthma in Preg**
  - FEV1 or PEFR >70% after rx, no distress, reassuring fetal status → discharge
  - FEV1 or PEFR 50–70% after rx → individualize disposition
  - FEV1 or PEFR <50% after rx → hospitalize
  - If poor resp/sev sx, drowsiness, confusion, pCO_2 >40 mmHg consider ICU admission ± intubation
  - Arrange follow-up w/i 5 d postdischarge

Surveillance During Pregnancy

- Assess asthma status w/ PEFR at each prenatal visit; adjust maint regimen
- Prepare Asthma Action Plan & instruct on use. Eg, www.nhlbi.nih.gov/health/public/lung/asthma/asthma_actplan.pdf.
- Focus on avoidance of allergens/irritants (eg, tobacco smoke, GERD, mold, dust mites, dander, cockroaches)
- Albuterol & budesonide are preferred short-acting β-agonist/inhaled steroid in Preg. Consider weekly fetal testing (NST, AFI, or BPP) from 32–34 w if mod–sev asthma or poor control.

Intrapartum Considerations

- Maintain hydration, continue asthma meds, including systemic steroids
- Consider cesarean deliv if unstable asthma & mature fetus
- Avoid carboprost tromethamine (Hemabate)
- ASA, indocin, other NSAIDs can cause asthmatic bronchospasm
- No contraindication to breastfeeding postpartum for asthma meds above

ANAPHYLAXIS

Definition and Diagnosis

(*J Allergy Clin Immunol* 2006;117(2):391)

- Sev, potentially fatal, systemic allergic (IgE mediated) rxn, occurring suddenly after exposure to an allergen. Dx requires **1** of the following:
  - Acute onset w/ involvement of the skin, mucosae, or both & compromise of respiratory, CV, or other end-organ fxn;
  - Acute onset of compromise of fxn of at least 2 organ systems (skin, GI, respiratory, CV) after exposure to likely allergen;
  - HoTN after exposure to known allergen.
- Skin sx present in ≥80% of cases. Consider total tryptase level (drawn when pt symptomatic) to confirm dx.

Treatment

- Removal of potential allergen(s). Mobilize resources (EMS, ICU, or Code team)

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- Prompt dosing of 0.3–0.5 mg (at 1:1000 dilution) epi intramuscularly. May rpt q5–15min.
- Position supine, apply oxygen, monit vital signs, obtain IV access w/ crystalloid support as needed. Consider albuterol, H2/H1 blockers, methylprednisolone (1–2 mg/kg q6h). Consider glucagon if refrac sx in pt on β-blocker.
- Consider observation for biphasic rxn (recurrence of sx w/i 72 h in 1–20% of cases)
- Ensure appropriate follow-up w/ allergist; discharge w/ >1 epi autoinjector if appropriate

Considerations in Obstetric and Gynecologic Populations

- Sx & rx in Preg are generally the same as for nonpregnant women. Consider AFE (bronchospasm more likely w/ anaphylaxis, coagulopathy more likely w/ AFE), or preeclampsia-related airway/subcutaneous edema depending on clinical setting. Breastfeeding reported as a rare cause of anaphylaxis (*Obstet Gynecol* 2009;114(2 Pt 2):415).
- Monit fetal cardiac activity continuously, w/ deliv for persistent category III tracings despite aggressive mat intervention. Consider hospital exposures when anaphylaxis is diagnosed inpt (latex, perioperative Abx, oxytocin, laminaria, chemotherapeutic agents).

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- **Renal changes:** Kidney increases in size, 30% ↑ vol. Dilatation of renal collecting system (right > left) due to hormonal changes (progesterone, relaxin, endothelin) & mechanical obst more in the right side (uterus is usually dextro-rotated).
- **GFR:** Increased GFR (50%) w/ an even greater ↑ in plasma renal flow due to increased cardiac output & decreased renal vascular resistance. Renal plasma flow peaks in 1st trimester, decreases at the end of 3rd trimester. GFR increases 25% by 2 w after conception, 50% ↑ by 2nd trimester. Increased GFR → ↓ serum Cr (*J Am Soc Nephrol* 2009;20:14). In Preg, nml Cr range = 0.4–0.8 mg/dL.
- **Testing:** Due to altered Cr clearance in Preg, use 24-h urine Cr to estimate GFR
- **Other:** ↑ proteinuria (up to 300 mg/d), ↓ serum bicarbonate due to respiratory alkalosis, ↑ glycosuria (decreased renal threshold <150 mg/dL), ↓ serum Na (HoNa)

ACUTE RENAL FAILURE (ARF)

Definition and Epidemiology (*JAMA* 2008;299:793)

- ↑ in serum Cr by 0.3 mg/dL (or 50% ↑ from baseline) in 24–48 h OR urine output reduction <0.5 mL/kg/h for >6 h. This definition also applies in Preg.
- Incid 2/1000. Pregnancy-associated ARF ~1/15000 (*Cur Op Crit Care* 2011;17:548; *Crit Care Med* 2005;33:S372). See also Chap. 3 (periop oliguria).

Etiology & Pathophysiology

Etiology & pathophysiology of acute renal failure

Location		Etiology	Pathophysiology
Prerenal (decreased renal perfusion)		Hypovolemia	
		HoTN	
		↓ cardiac output	
		NSAIDs	↓ prostaglandin production → ↓ vasodilation renal afferent art
		ACE-inhibitors/ARB	↓ angiotensin II production → ↓ vasoconstriction renal efferent art "contraindicated in Preg"
Intrarenal (damage to renal parenchyma)	Glomerular	Glomerulonephritis	Nonproliferative vs. proliferative (pathophysiology differs)
		Glomerulo-endotheliosis	↓ glomerular size, increased cytoplasm in glomerular epithelial cells → ↓ capillary diameter → capillary occlusion "pathognomonic for preeclampsia"
	Vascular	Antiphospholipid Ab syn	Microvascular thrombosis → ischemia
		Malig nephrosclerosis	
		TTP/HUS	
		Radiation nephritis	
		Scleroderma	
	Tubules/ Interstitium	Sepsis	Endothelial damage → microvascular thrombosis → free radical production, leukocyte migration/ adhesion → tubule damage

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Location		Etiology	Pathophysiology
		Ischemia	Cytoskeletal tubule breakdown, apoptosis, tubular obst → inflammation, filtrate backleak across damaged tubular epithelium, tubular obst → cortical necrosis
	Nephrotoxins	Aminoglycosides	Filtered across glomerulus → accum in renal cortex → ARF seen after 5–7 d of rx
		Amphotericin B	Binds to tubular membrane cholesterol → pore introduction → polyuria, nonanion gap metabolic acidosis, hypomagnesemia, HypoCa
		Cisplatin/carboplatin	Accumulates in prox tubular cell → necrosis/apoptosis
		Ethylene glycol	Metabolite 2-HEAA → tubular injury
		Iodinated contrast	Renal outer medulla hypoxia from small vessel occlusion, cytotoxic tubular damage, tubule obst
		Rhabdo	Prox tubular tox, intrarenal vasoconstriction, distal nephron obst (myoglobin/hemoglobin + Tamm–Horsfall prot → precipitation)
		Tumor lysis syn	Cytotoxic therapy → uric acid release → uric acid precipitation in tubules
Postrenal (obst)		Bladder obst Bilateral ureteral obst	Preg: Partial obst may lead to urinary distention
		Nephrolithiasis	
Preg (*Crit Care Med* 2005;33:S372)		Preeclampsia/HELLP	ARF in 1.5–2% Glomeruloendotheliosis is pathognomonic
		Acute fatty liver	ATN, fatty infiltration of kidney
		Amniotic fluid embolism	DIC, cardiovascular dysfxn, hemorrhage → ARF
		TTP/HUS	ARF develops in 2/3 (microvascular thrombosis → ischemia

Clinical Findings & Exam

- Uremia, oliguria/anuria, hematuria
- **Prerenal:** Tachy, dry mucous membranes, orthostatic HoTN
- **Intrarenal:** Pulm hemorrhage, palpable purpura → vasculitis + glomerulonephritis, livedo reticularis → atheroembolic dz, limb ischemia → rhabdo
- **Postrenal:** Flank pain which radiates to groin, suprapubic pain

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Diagnostic Workup

Study findings			
Study	**Prerenal**	**Intrarenal**	**Postrenal**
UA: Prot	0 to trace	Mild to mod	0 to trace
UA: Leukocyte esterase	0	±	±
UA: Bld	0	±	±
Microscopy	Hyaline casts	Cellular or granular casts	None
Urine Na (mEq/L)	<20	>40	Varies
FENa = (UNa/PNa)/(UCr/PCr)	<1	>2	
Urine Osmol (mOsm/kg)	>500	<350	

Subsequent Workup

- **Renal bx:** Consider when etiology is unk. 5% complication rate (perirenal hematoma, gross hematuria). Preg: Consider pts <28 w w/ ARF of uncertain etiology when results will change mgmt (*Am J Perinatol* 2008;25:385)

Treatment

- Correct underlying factors, remove renal toxins, adjust dosing of renally cleared meds. Prevent/treat infxn
- **Fluid mgmt:** Goal = adequate hydration to reverse preischemic change
- HyperK → polystyrene sulfonate
- Metabolic acidosis → sodium bicarbonate
- RRT (*JAMA* 2008;299:793)

  For ARF refrac to medical mgmt, as evidenced by metabolic acidosis, hyperK, hypervolemia, etc. Mode: IP, intermittent hemodialysis, continuous RRT.

  Continuous RRT: Slower solute clearance/min, continuous anticoagulation

  Use in Preg:

  Symptomatic uremia (changes in mental status, pericarditis, neuropathy)
  HyperK not corrected by medical mgmt
  Metabolic acidosis
  Vol overload

CHRONIC RENAL FAILURE

Definition and Epidemiology (*MMR* 2007;56:161)

- **CKD** = abn kidney fxn + progressive decline of estimated GFR for >3 mo
- **CRF:** Irreversible nephron number reduction
- **ESRD:** GFR <15 mL/min per 1.73 m^2 OR need for dialysis &/or xplant
- **Prevalence of CKD in US:** 16.8% of adults ≥ age 20 (11.1% stages 1–2, 5.8% stages 3–5), & increased prevalence w/ comorbidities such as DM (40.2%), cardiovascular dz (28.2%), & HTN (24.6%)

Etiology

- **Glomerular dz:** Diabetes, systemic infxn, autoimmune dz
- **Vascular dz:** HTN, ischemia, atherosclerosis, vasculitis, thromboembolic
- **Tubular/interstitial dz:** Urinary tract stones, infxn, obst, nephrotoxic meds

Pathophysiology

- **Initiating mechanisms:** Specific to etiology of CKD
- **Progressive mechanisms:** Increased renal bld flow/pres → renin–angiotension axis stimulation → nephron hyperfiltration & hypertrophy → glomerular distortion, sclerosis, permanent damage to nephrons → reduction in nephron number
- Failure of renal excretion → accum of toxins (including Cr, urea → uremic syn). Failure of other renal functions → anemia, abn metabolism, fluid/electrolyte imbalance, hormone regulation (glucagon, insulin, Vit D, sex hormones, parathyroid hormone). Progressive inflammation (elevated C reactive prot + acute phase reactants).

Clinical Manifestations

- Edema (from nephrotic syn), fatigue (from anemia), decreased appetite → malnut, inability to perform activities of daily living (uremic syn).
- **Preg** (*CJASN* 2011;6:2587): 3 factors correlate w/ ↑ complications: Proteinuria, decreased GFR, HTN

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Maternal complications: Gestational HTN, preeclampsia/eclampsia, nephrotic syn, maternal death (higher incid w/ lupus nephropathy)
Fetal complications: Preterm birth, IUGR, IUFD, neonat death

Physical Exam
- Most pts are asymptomatic until mod or sev renal failure develops
- Findings may include periph edema, pericardial friction rub (in presence of uremic syn), sensory neuropathy (evid of end-organ damage)

Diagnostic Workup/Studies
- GFR (mL/min per 1.73 m^2) = 1.86 × (PCr) – 1.154 × (age) – 0.203
  P_{Cr} = serum Cr; multiply by 1.21 for AAs or 0.742 for women
- GFR peak = 120 mL/min per 1.73 m^2 btw age 20 & 30 (lower for women)
- GFR then declines 1 mL/min per 1.73 m^2 per year

Laboratory trends in CKD	
Test	**Result**
Serum phosphorus	Increased
Serum calcium	Decreased
Serum PTH	Increased
Bone alk phos	Increased
24-h urine total prot	>300 mg
Serum/urine prot electrophoresis	Bence Jones proteins (multi myeloma)

Stages of CKD GFR (mL/min per 1.73 m^2)
- Stage 1: ≥90 + kidney damage (proteinuria, abn renal imaging)
- Stage 2: 60–89
- Stage 3: 30–59
- Stage 4: 15–29
- Stage 5: <15

Imaging
- Renal US (preferred modality in Preg)
  CKD: Small kidneys bilaterally
  Polycystic kidney dz: Cystic, enlarged kidneys
  >1 cm discrep in length: Developmental abnormality, arterial insufficiency which affects one kidney more
- **Voiding cystogram:** To evaluate for reflux nephropathy
- **CT, MRI:** Avoid IV dye if poss in Preg
- **Renal bx:** Should be avoided during Preg
- Serial renal fxn measurements (to differentiate acute vs. subacute vs. CKD)

Treatment and Medications
- **Potassium sparing meds:** ACE inhibitors, ARB, spironolactone, eplerenone, amiloride, triamterene
- Dietary adjustments (decreased salt intake)
- HTN control (*Lancet* 2005;365:331)
  Goal = 130/80 (125/75 in pts w/ diabetes & proteinuria > 1 g/24 h)
  Reduce intraglomerular HTN to slow nephron injury progression
- **Renal replacement therapy:** IP vs. intermittent hemodialysis vs. continuous RRT. Initiate when GFR = 10 mL/min per 1.73 m^2
- **Preg:** 24-h urine total prot in the 1st trimester + HTN control (BB, CCB, hydralazine, clonidine) + Serial USs for fetal growth + antepartum testing: Initiate btw 28 & 32 w. *Avoid ACE inhibitors/ARBs.*

URINARY TRACT INFECTION (UTI)

Definitions
- **Asymptomatic bacteriuria:** 10000–100000 CFU/mL in urine culture (*Obstet Gynecol* 2005;106:1085)
- **UTI:** ≥100000 CFU/mL in urine culture w/ or w/o sx
- **Uncomp:** Healthy female w/ nml urinary tract fxn
- **Complicated:** UTI+ one of the following: Urologic abnormality, urinary calculi, FB (catheter), DM, Preg, spinal cord injury

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- **Recurrent UTI:** 2 Uncomp UTIs in 6 mo or 3 positive cx w/i the preceding 12 mo (*Obstet Gynecol Clin North Am* 2008;35)

Epidemiology

- 50% ♀ will have a UTI in their lifetime; 10% ♀ will have a recurrent UTI by age 70
- Asymptomatic bacteriuria in Preg: 20–30× increased risk of pyelo

Etiology

- *Escherichia coli* = 75–95% (*NEJM* 2012;366:1028), Proteus (can cause renal calculi). Klebsiella, Enterobacter, Pseudomonas, *Staphylococcus saprophyticus* (common in young women)

Pathophysiology

- **Ascending infxn:** Vagina → urethra → bladder
- ***E. coli:*** Virulence factors P fimbria, S fimbria, Type 1 fimbria → ↑ uroepithelial/vaginal cell binding, ↑ resistance to host phagocytosis, ↑ resistance to bactericidal activity

Clinical Manifestations and Exam

- Dysuria, increased urgency, increased urinary frequency, suprapubic pain
- Suprapubic tenderness to palpation
- Pyuria, urethral tenderness (seen w/ urethritis)

Diagnostic Workup/Studies

- **UA:** Leukocyte esterase or nitrites: 75% sensitive, 82% specific (*NEJM* 2003;349:259); WBC ± RBC; bacteria on gram stain
- **Urine culture:** ≥100000 CFU/mL

Treatment

Medications for UTI

Diagnosis	Treatment	Dose	Duration	Comments
Asymptomatic bacteriuria				Treat in Preg. Rescreen each trimester
1st line (PO)	Nitrofurantoin monohydrate	100 mg q12h	7 d	Do not use in pts w/ gluc 6 phosphate dehydrogenase deficiency
Alternative (PO)	Amoxicillin	250 mg q8h	7 d	
	Ampicillin	250 mg q6h	7 d	
	Cephalosporin	250 mg q6h	7 d	
	TMP/SMX	160/800 mg q12h	7 d	Do not use in 3rd trimester (kernicterus)
Uncomp UTI				
1st line (PO)	TMP–SMX	160/800 mg q12h	3 d	Do not use if local resistance >20%
Alternative (PO)	Trimethoprim	100 mg q12h	3 d	
	Ciprofloxacin	250 mg q12h	3 d	Contraindicated in Preg
	Ofloxacin	200 mg q12h	3 d	
	Lomefloxacin	400 mg daily	3 d	
	Levofloxacin	250 mg daily	3 d	
	Nitrofurantoin	100 mg q6h	5–7 d	
	Nitrofurantoin monohydrate	100 mg q12h	5–7 d	
Complicated UTI (outpt, PO therapy)				
	Ciprofloxacin	500 mg q12h	10–14 d	Contraindicated in Preg
	Ofloxacin	200–300 mg q12h	10–14 d	
	Lomefloxacin	400 mg daily	10–14 d	
	Levofloxacin	250 mg q12h	10–14 d	

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Diagnosis	Treatment	Dose	Duration	Comments
Complicated UTI (inpt)				
Initial IV therapy	Ampicillin	500 mg q6h	Treat IV until afebrile, clinically improved	
	Gentamicin	1 mg/kg q8h		
	Ciprofloxacin	400 mg q12h		
	Levofloxacin	250 mg daily		
	Ceftriaxone	1–2 g daily		
	Ticarcillin/ clavulanate	3.1 mg q4–6h		
	Aztreonam	1 g q8–12h		
	Imipenem–cilastatin	250–500 mg q6–8h		
Subseq PO therapy	TMP–SMX	160/800 mg q12h	10–21 d	
	Ciprofloxacin	500 mg q12h	10–21 d	
	Ofloxacin	200–300 mg q12h	10–21 d	
	Lomefloxacin	400 mg daily	10–21 d	
	Levofloxacin	250 mg q12h	10–21 d	
≥3 symptomatic UTIs/y				
Suppression (PO)	TMP/SMX	80/400 mg	Daily or 3 times/w	
	Trimethoprim	100 mg	Daily or 3 times/w	
	Nitrofurantoin	50 mg	Daily or 3 times/w	
Preg: ≥2 UTIs or asymptomatic bacteriuria				
Suppression (PO)	Nitrofurantoin	50–100 mg	qhs	

PYELONEPHRITIS

Definition
- Infxn of renal pelvicalices/parenchyma from ascending bladder infxn or renal bacteriuria. Clinical syn defined by flank pain, fevers, chills.

Epidemiology
- 23/10000 women ages 15–34 (*NEJM* 2012;366:1028)
- 1–2% of pregnancies, >50% present in the 2nd trimester (*Obstet Gynecol* 2005;106:1085)
- Untreated asymptomatic bacteriuria in Preg → 1/4 will develop pyelo

Etiology
- Same as for UTIs (above). Most are *E. coli.*

Pathophysiology
- **Risk factors:** Same as for UTI (see UTI section)
- **ARDS:** IV antibiotic therapy → endotoxin release 24–48 h later → damage to alveolar capillary membranes
- Preg complications
  Increased risk of preterm labor if pyelo is not aggressively treated
  Pulm insufficiency: Increased risk if temperature >103°F, tachy >110 bpm, gestational age ≥20 w

Clinical Manifestations and Exam
- Chills, fever, flank pain, dysuria, urinary frequency/urgency
- Costovertebral angle tenderness

Diagnostic Workup/Studies
- Urinalysis
- Urine culture w/ susceptibilities
- If no resp to initial therapy, consider bld cx

Treatment and Medications
- Inpt admission is recommended for all women w/ pyelo during Preg (*Obstet Gynecol* 2005;106:1085)

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IV hydration to maintain adequate urine output
Acetaminophen: Hyperthermia can be teratogenic in 1st trimester
IV therapy 24–48 h (avoid fluoroquinolones), follow w/ oral therapy 10–14 d
- Suppression therapy for remainder of Preg: Nitrofurantoin 100 mg PO daily
- Rpt urine culture each trimester

Treatment

Medications for pyelonephritis

	Rx	Dose	Duration	Comments
Outpt PO therapy	Ciprofloxacin	500 mg q12h	10–14 d	Can load w/ ciprofloxacin 400 mg IV Avoid ciprofloxacin if resistance >10%
	TMP–SMX	160/800 mg q12h	10–14 d	Use only if above choices cannot be used. Fluroquinolones not used in Preg
	Gatifloxacin	400 mg daily	10–14 d	
	Ofloxacin	400 mg q12h	10–14 d	
	Levofloxacin	750 mg daily	5 d	
	Amoxicillin–clavulanate	875/125 mg q12h	10–14 d	
Inpt IV therapy (if unable to tolerate PO, or if evid of sepsis)	Ciprofloxacin	400 mg q12h	Treat IV until afebrile for 24 h, follow w/ PO therapy	
	Ceftriaxone	1–2 g q12–24h		
	TMP–SMX	2 mg/kg q6h		
	Cefotaxime	1–2 g q8h		
	Levofloxacin	500 mg daily		
	Cefepime	2 g q8h		
	Cefotetan	2 g q12h		
Preg (inpt IV therapy)	Ampicillin	2 g q6h	24–48 h	Use w/ gentamicin
	Gentamicin	3 mg–5 mg/kg/d	24–48 h	Use w/ ampicillin
	Ceftriaxone	1 g q24h	24–48 h	

NEPHROLITHIASIS

Definition and Epidemiology
- **Calcium-based:** Calcium oxalate, calcium phosphate (80%) (*NEJM* 2010;363:954)
- **Noncalcium-based:** Uric acid, cystine, struvite (may form staghorn calculi)
- 10% of the US pop will have one kidney stone in lifetime (*J Urol* 2012;188:130)
- **Preg:** Btw 1/200 to 1/1500 women have symptomatic nephrolithiasis (*Cur Op Uro* 2010;20:174)

Pathophysiology
- Increased excretion rate or increased water conservation → supersaturation of urine w/ insoluble substances → crystal formation → crystal aggregation into stone(s)
- Stones become symptomatic when entering ureter or occluding uteteropelvic junction

Clinical Manifestations
- Flank pain (episodic, may radiate to abd), nausea, vomiting, hematuria, difficulty finding a comfortable position

Diagnostic Workup/Studies
- CT w/o contrast = imaging modality of choice
- Renal US
- **Abdominal radiograph (KUB):** Only + if radio-opaque stones
- **Preg:** Renal US = preferred modality
- **Recurrent symptomatic nephrolithiasis:** Evaluate poss etiologies
  Serum: Calcium, uric acid, electrolytes
  Urine: pH, vol, calcium, citrate, oxylate, 24-h urine collection (2 occasions)

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Treatment and Medications

- **Conservative mgmt:** Hydration, pain control (most stones smaller than 0.5 cm pass spontaneously)
- **Medical mgmt:** Alpha-1 blockers to ↑ motility
- Active intervention req for persistent pain, progressive obst, infxn, solitary kidney obst (*J Urol* 2012;188:130)
  - ***Shock wave lithotripsy:*** May require multi treatments
  - ***Semirigid ureteroscopy:*** Higher stone free rate after one rx, fewer retreatments needed. Improved success w/ distal ureteral stones.
  - ***Percutaneous nephrolithotomy:*** Most invasive. Use for large stone burden, renal stones.
- **Preg:** (*Cur Op Uro* 2010;20:174)
  - **Temporary drainage:** Ureteral stent or percutaneous nephrostomy (risk of infxn, bacteriuria, migration/dislodgement)
  - **Definitive rx:** Ureteroscopy is preferred
  - Avoid shock wave lithotripsy in Preg (increased risk of miscarriage, congen malformations, abruption)

FLUIDS AND ELECTROLYTES

IV fluid composition

IVF	Na	Cl	K	Ca	Mg	Buffers	pH	Osmolality	Osmotic pres
	mEq/L							mOsm/L	mm Hg
Plasma	140	103	4	5	2	Bicarb (25)	7.4	290	20–25
Crystalloid: 75% enters interstitial space									
0.9% NaCl	154	154					5.7	308	
7.5% NaCl								2465	
Lactated ringers	130	109	4	3		Lactate (28)	6.4	273	
5% dextrose (50 g dextrose/L)							4	278	
Colloid: 50–75% remains intravascular									
5% Albumin (50 g/L)									20
Hetastarch (6% in NS)	154	154							30
Hextend	143	125	3	5	0.9	Lactate (28)			

IVF	Comments
0.9% NaCl	Increased risk of hyperchloremic metabolic acidosis
7.5% NaCl (hypertonic saline)	Intracellular → extracellular shift is 5 times amt infused; 2 fold ↑ in plasma vol
Lactated ringers	Calcium binds drugs (aminocaproic acid, amphotericin, ampicillin) Calcium binds bld products' citrated anticoagulant → increased clot formation
5% dextrose (50 g dextrose/L)	Can ↑ risk of hyperglycemia in critically ill pts <10% remains intravascular, 2/3 intracellular
5% Albumin (50 g/L)	250 mL aliquots in isotonic saline 70% remains intravascular → lost in 12 h
25% albumin (250 g/L)	50 mL or 100 mL aliquots Increases plasma vol 3–4 times amt infused Consider in hypovolemia due to fluid shift to interstitial space
Hetastarch (6% in NS)	High molecular weight (450000 daltons) broken down by Amy → 50000 daltons → kidney clearance (takes 2–3 w) Oncotic effect lasts 24 h Inhibits vWF, Factor VII, platelet adhesion → limit use to 1500 mL/24 h
Hextend	Contains 6% Hetastarch

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Hyperkalemia

- **Definition:** Serum potassium (K^+) >5.5 mEq/L
- **Clinical manifestations:**
  - **ECG changes** (seen when K^+ >6 mEq/L): Peaked T waves → 1° heart block → complete heart block → Vfib → asystole
  - Abdominal pain, myalgias, diarrhea, flaccid paralysis
- **Dx:**
  - Rule out pseudohyperkalemia
  - Urine K^+
    - >30 mEq/L → transcellular shift
    - <30 mEq/L → impaired renal excretion
- **Rx & meds:** (*J Int Care Med* 2005;20:272)
  - Continuous telemetry
  - **Sodium polystyrene sulfonate (Kayexalate):** Cation exchange resin binds K^+ → fecal excretion
    - **PO:** 30 g diluted in 50 mL of 20% sorbitol, rpt q2h
    - **Rectal:** 50 g diluted in 200 mL of 20% sorbitol, rpt q2h
    - Do not use in pts w/ bowel obst, ileus, bowel ischemia
  - If ECG changes are present
    - ***Calcium gluconate:*** 10 mL of 10% (1 ampule): IV push over 2 min. Rpt in 5 min.
    - ***Calcium chloride:*** 10 mL of 10% (1 ampule): Use in pts w/ circulatory compromise. 3× more calcium than calcium gluconate → improved cardiac contractility
    - ***Insulin/gluc:*** Give 10 U insulin & 25 g dextrose (1 amp of D_{50}). Hold D_{50} if bld gluc >250 mg/dL
    - ***Albuterol:*** 10–20 mg of 5 mg/mL nebulized solution
    - ***Sodium bicarbonate:*** Use only in pts w/ sev metabolic acidosis
  - Dialysis (hemodialysis faster at removing K^+ than peritoneal dialysis)
  - **Digitalis tox:** Magnesium sulfate 2 g IV bolus. Do NOT use calcium (can potentiate digitalis tox)

Hypokalemia

- **Definition:** Serum potassium (K^+) <3.5 mEq/L
- **Clinical manifestations:**
  - Muscle weakness
  - **Nonspecific ECG changes:** Prolonged QT interval, flattened inv T waves, U wave (Amp >1 mm)
  - Digitalis-induced arrhythmia
- **Rx:**
  - Treat causes of transcellular K^+ shifts
  - **Replace K^+:** KCl soln w/ 10, 20, 30, or 40 mEq K^+. Infuse 20 mEq in 100 mL NS over 1 h
  - Replace serum magnesium

Hypercalcemia

- **Definition:** Total serum calcium >11 mg/dL, ionized calcium >3 mmol/L
- **Clinical manifestations** (seen when ionized calcium >3 mmol/L):
  - **GI:** Constip, N/V, ileus, pancreatitis
  - **Renal:** Polyuria, nephrocalcinosis
  - **Neuro:** Altered mental status, coma
  - **Cardiovascular:** HoTN, hypovolemia, decreased QT interval, AV block
- **Rx & meds:**
  - **Correct hypovolemia:** IV hydration w/ isotonic saline
  - **Furosemide:** 40–80 mg IV q2h to maintain urine output of 100 mL/h
  - **Calcitonin:** To ↓ bone resorption. 4 U/kg q12h SC or IM. Will ↓ serum calcium by 0.5 mmol/L
  - **Hydrocortisone:** 200 mg IV daily (divided 2–3 doses). Use w/ calcitonin.
  - **Bisphosphonates:** Max resp seen in 4–10 d
    - Zoledronate 4 mg IV, infuse over 15 min
    - Pamidronate 90 mg IV, infuse over 2 h

Hypernatremia

- **Definition:** Serum sodium (Na^+) >145 mEq/L
- **Clinical manifestations:**
  - Altered mental status
  - Rhabdo
  - Absence of thirst vs. intense thirst
  - Polyuria
  - Diarrhea

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- **Diagnostic w/u/studies:**
  Document fluid intake & urine output
  Serum osmolality, urine osmolality, urine electrolytes
- **Rx & meds:** (*NEJM* 2000;342:1493)
  Stop any continuing causes of HyperNa
  Correct serum sodium: Give hypotonic fluid PO or parenterally
  Calculate water deficit & daily water loss
    Total body water = total body weight × 0.5 in women
    Free water deficit = [(serum Na − 140)/140] × TBW
    Free water clearance = (V[1 − (UNa + UK)])/PNa
      V = urine vol; UNa = urine [Na^+]; UK = urine [K^+]; PNa = plasma [Na^+]
    Insensible losses: 10 mL/kg/d
  Replace daily water loss, correct water deficit
    Chronic HyperNa: ↓ serum Na^+ by 10 mmol/d
      Avoid correcting too quickly to prevent cerebral edema
    Acute HyperNa: ↓ serum Na^+ by 1 mmol/L/h
    Fluids: Give hypotonic fluids only (0.2% NaCl, 0.45% NaCl)
      The more hypotonic the fluid, the lower the rate of infusion
    Calculate change in serum Na^+ w/ 1 L infusion:
      [(infusion Na + infusion K) − serum Na^+]/(total body water + 1)
    Avoid dextrose solutions (hyperglycemia → osmotic diuresis → worsening HyperNa)
      Avoid 0.9% NaCl

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- Inhibition of GI motility in Preg theorized to be due to progesterone effects
- GERD due to ↓ gastric emptying & ↓ lower esoph sphincter tone
- N/V exacerbated by GI motility
- Constip from increased GI transit time & increased nutrient Absorp
- Enlarging uterine fundus also thought to impact early satiety & GERD
- In nml Preg, most liver parameters are unchanged (size, hepatic bld flow, overall histology, PT, total bilirubin, AST, ALT, GGT), but synthetic fxn increases

Changes in proteins and enzymes in pregnancy		
Total serum prot conc	↓	Due to fall in serum albumin
Coagulation factors (fibrinogen, Factors VII, VIII, IX, X)	↑	Due to ↑ estrogen
Cytochrome P-450	↑	Due to ↑ progesterone
Total alk phos	↑	Due to placental production
Binding globulins	↑	Due to hormonal stim of liver

CHOLELITHIASIS

Epidemiology

- 10–15% prevalence in adults overall; 1–3% of pregnant women
- **Risk factors:** Preg (impaired gallbladder emptying, increased biliary sludge); ↑ estrogen (gender [♀ 2× > ♂], obesity, rapid weight loss, Preg); ethnicity (75% of Native Americans); age (>40 y); drugs (OCPs, estrogen, clofibrate, octreotide, ceftriaxone, TPN); bile acid metabolism disorders; hyperlipidemia syndromes (↑ biliary cholesterol secretion & cholesterol sat of bile)

Pathophysiology

- Bile = pathway for elimination of excess cholesterol either as free cholesterol or as bile salts; cholesterol-saturated bile → crystal formation → bile stasis → aggregation
- Types of stones: Mixed; cholesterol (up to 80% of gallstones, up to 80% radiolucent); black pigments (unconjugated bilirubin + calcium, sterile; radiopaque); brown pigments (calcium soaps, infected ducts; radiolucent)

Clinical Manifestations

- 70–80% asymptomatic; biliary colic = acute episodic RUQ or epigastric abdominal pain radiates to right scapula or shoulder; typically resolves w/i hours; a/w nausea ± emesis; precipitated by fatty food; often nocturnal; sev includes perforation, fistulae, pancreatitis, obstructive jaundice
- **Physical exam:** Afebrile, ± RUQ tenderness or epigastric pain

Workup

- **RUQ US:** Mobile echogenic focus w/ acoustic shadow; sens & spec >95% for gallstones >1.5 mm in diameter
- **Labs:** AST, ALT, Amy, lipase, CBC

Treatment of Symptomatic Cholelithiasis

- **Initial medical mgmt:** IVF, analgesia, NG suction (rare), no Abx for cholelithiasis w/o infxn/cholecystitis
- **Cholecystectomy if symptomatic:** Failed medical mgmt, ascending cholangitis, common bile duct obst, pancreatitis. 36% pregnant women initially managed conservatively → Surg (*Glasgow Surg Endosc* 1998;12: 241). Prophylactic cholecystectomy only if large stones or ↑ risk gallbladder cancer.
- **For poor surgical candidates:** Oral dissolution rx (ursodiol); extracorporeal shock wave lithotripsy for mild, uncomp biliary colic (contraindicated in Preg)

CHOLECYSTITIS

Definition and Epidemiology

- **Inflammation of the gallbladder:** Acute (rapid onset, gallstone obst); chronic (transient obst → low-grade inflammation/fibrosis); acalculous (inflammation w/o obst)
- ♀ >> ♂ due to estrogen (↑ cholesterol secretion) & progesterone (↓ bile acid secretion & ↑ stasis)

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- 1:1600 to 1/10000 pregnancies; 2nd most common cause of Surg during Preg

Pathophysiology
- >90% due to cystic duct stone → inflammation
- Gallbladder stasis/ischemia → acalculous cholecystitis; in sev injury, major nonbiliary Surg, sev trauma, burns, sepsis, infxn (CMV, crypto, HIV), vasculitis (polyarteritis nodosa)

Clinical Manifestations
- Similar to acute cholelithiasis, but steady and sev w/ RUQ/epigastric pain; tenderness, *fever,* nausea, ± emesis
- **Physical exam:** RUQ tenderness, Murphy sign (increased RUQ pain & insp arrest w/ R subcostal palpation), guarding/rebound, 15% palpable gallbladder
- **Acalculous cholecystitis:** Unexplained fever or RUQ pain w/i 2–4 w of major Surg; critically ill pt w/ prolonged NPO; multiorgan failure

Workup
- **Labs:** ↑ WBC ± ↑ bilirubin, mild ↑ AST/ALT, ± mod ↑ Amy (if vomiting)
- **Abdominal XR:** Radiopaque stones in 15%
- **RUQ US:** Gallbladder wall thickening, pericholecystic fluid, sono Murphy sign
- MRI in Preg if RUQ sono nondiagnostic; dilated common bile duct = choledocholithiasis
- **HIDA scan (99m Tc hepatobiliary imaging):** Most sensitive if bilirubin <5 mg (98% sens & 81% spec); demonstrates an obstructed cystic duct

Treatment
- NPO, IVF, NGT if intractable vomiting, analgesia
- IV Abx (2nd or 3rd gen cephalosporin + metronidazole; fluoroquinolone + metronidazole for sev cases)
- Cholecystectomy – laparoscopic, w/i 2–4 d after admission; cholecystostomy or percutaneous drainage if too ill for Surg. Surg in Preg may be more difficult, but may ↓ morbidity; perform in 2nd trimester if poss (*Surg Endosc* 2010;24:108).

APPENDICITIS

Definition and Epidemiology
- Inflammation of appendiceal wall → ischemia or perforation
- Most common nontraumatic surgical emergency during Preg; 1:1600 pregnancies; usually in 2nd trimester
- Peak incid in 2nd & 3rd decades of life; rare at extremes of age
- Incid much lower in developing countries & in lower socioeconomic groups
- Morbidity & mortality often higher in Preg due to delay in dx

Pathophysiology
- Appendiceal luminal obst (50–80%) usually by fecalith (accumulated/hardened fecal matter around vegetable fibers) → inflammation/distention/ulceration/rupture. Other causes: Lymphadenitis (viral infections), inspissated barium, parasites (eg, pinworm, *Ascaris, Taenia*), & tumors (eg, carcinoid or carcinoma).
- Visceral pain poorly localizes to periumbilical or epigastric region; spread of peritoneal inflammation eventually localizes to RLQ

Clinical Manifestations
- Vague periumbilical or RLQ pain, anorexia, nausea, vomiting, low-grade fever
- In Preg appendix displaced by gravid uterus → RUQ pain possible
- Tender McBurney point = ⅓ distance from anterior-superior iliac spine & umbilicus; psoas sign = pain w/ right hip flexion; Rovsing sign = LLQ palpation elicits RLQ pain; referred rebound tenderness often absent early & in Preg
- Temperature >38.3°C (101°F) & rigidity suggest perforation
- ↑ abortion or PTL risk; no impact on fertility unless ruptured appendix w/ subseq adhesive dz

Workup
- **Labs:** Mod leukocytosis (not helpful in Preg), elevated CRP/ESR
- US (1st-line in Preg) = enlarged thick-walled appendix; useful to exclude ovarian cysts, ectopic Preg, or tuboovarian abscess
- Contrast-enhanced or nonenhanced abdominal CT (gold std in nonpregnant pts): Distended, noncontrast-filled appendix, thickened appendiceal wall w/ periappendiceal stranding & often the presence of a fecalith (PPV 95–97%, overall accuracy 90–98%). MRI preferred in Preg.

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Treatment and Medications
- Electrolyte correction & IVF
- **Perioperative Abx:** Broad coverage for gram-positive/negative & anaerobes (2nd gen cephalosporin + metronidazole or clindamycin). Conservative mgmt w/ antibiotic alone may be successful in some nonpregnant pts (*BMJ* 2012;344:e2156).
- Immediate appendectomy (laparoscopic preferred, safe during all trimesters of Preg)

PANCREATITIS

Definition and Etiology (Acute Pancreatitis)
- Inflammation of the pancreas; diagnosed w/ 2 of the following criteria: Characteristic abdominal pain, elevation of Amy/lipase greater than 3× upper limit of nml, CT evid of acute pancreatitis
- Incid ~0.1% in Preg
- **Consider:** Gallstones, EtOH use, meds, hypertriglyceridemia, HyperCa, Pancr neoplasm or trauma. Consider dx if pain, N/V in pts after upper abd procedures, eg, splenectomy.

Clinical Manifestations
- Periumbilical or epigastric pain radiating to the back; nausea, vomiting, fever
- Life-threatening complication of AFLP (*Am J Obstet Gynecol* 2004;190(2):502)

Workup
- Detailed Hx for etiology; lab: Electrolytes, Amy, lipase, triglycerides, WBC
- Abd US. CT if no etiology identified.
- Severity best assessed by APACHE II criteria (www.mdcalc.com/apache-ii-score-for-icu-mortality/)

Treatment
- NPO, IV hydration, electrolyte replacement. NG suction if persistent N/V.
- Cholecystectomy ± ERCP if secondary to gallstones

Chronic Pancreatitis
- Primary cause is alcoholism, less likely hereditary, CF, stones
- Permanent fibrotic damage to pancreas from obst of ducts
- Sx include pain, recurrent acute pancreatitis, steatorrhea, gluc intolerance
- Complications include diabetes, pseudocysts, splenic vein thrombosis
- Rx is supportive/symptomatic

IRRITABLE BOWEL SYNDROME (IBS)

Definitions
- Functional bowel d/o characterized by abdominal pain or discomfort & altered bowel habits in the absence of detectable structural abnormalities

Subtypes of IBS		
Subtype	% hard stool	% loose watery stool
IBS w/ constip	>25	<25
IBS w/ diarrhea	<25	>25
Mixed IBS	>25	>25
Unsubtyped IBS	Insuff to meet criteria for other subtypes	

From Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. *Gastroenterology.* 2006;130(5):1480–1491.

Epidemiology
- 10–20% adults & adolescents affected worldwide w/ female predominance (2–3× >men)
- Most present w/ 1st sx before age 45

Pathophysiology (*Gastroenterol Clin North Am* 2003;32:385)
- Altered gut motility. Visceral hypersensitivity to stimuli. Abn CNS modulation.

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- Proposed mechanisms include visceral hypersensitivity in which pt has increased motor reactivity of colon & small bowel to variety of stimuli w/ lowered sensation threshold
- Intestinal infxn, psychological or emotional stress may be triggers

Clinical Manifestations

- **Rome Criteria** (*Gastroenterology* 2006;130(5):1480): Recurrent abdominal pain or discomfort at least 3 d/mo in the last 3 mo a/w 2 or more of the following:
  - Improv w/ defecation
  - Onset a/w a change in frequency of stool
  - Onset a/w a change in appearance of stool
- **Supportive sx (not diagnostic):** Defecation straining, urgency or tenesmus, passing mucus & bloating, alternating bowel habits (constip alternating w/ diarrhea), dyspepsia, heartburn, nausea, & vomiting
- Location of abdominal pain variable, frequently episodic & crampy & often exacerbated by eating, emotional stress or premenstrual sx; often improved by passage of stool or flatus

Diagnostic Workup/Studies

- Dx based on clinical presentation; diff dependent on location of sx
- Studies to rule out other etiologies dependent on pt sx & presentation
- Workup can include CBC, endoscopy, stool specimens (O&P) for those w/ diarrhea

Differential diagnosis of presenting IBS symptoms

Primary symptom	Diff diagnoses
Epigastric or periumbilical pain	Biliary tract dz, peptic ulcer disorders, intestinal ischemia, carcinoma of stomach & pancreas
Lower abdominal pain	Diverticular dz, inflamm bowel dz, colon cancer
Postprandial pain	Gastroparesis, intestinal obst
Diarrhea	Intestinal infxn, lactase deficiency, laxative abuse, malabsorption, celiac sprue, hyperthyroidism
Constip	Side effect of drugs, endocrinopathies, intermittent porphyria, lead poisoning

Treatment and Medications

- Avoid food precipitants (common triggers include coffee, disaccharides, legumes, cabbage, artificial sweeteners)
- High-fiber diets & bulking agents (may have no benefit)
- Increased physical activity & psychosocial therapy
- Diarrhea → antispasmodics, loperamide as needed
- Constip → psyllium, methylcellulose, calcium polycarbophil, lactulose, polyethylene glycol, lubiprostone, magnesium hydroxide
- Abdominal pain → smooth-muscle relaxant, TCA, SSRI

INFLAMMATORY BOWEL DISEASE

Definitions

- Immune-mediated, noninfectious, chronic intestinal inflammation
- **Ulcerative colitis (UC):** Idiopathic continuous inflammation of colonic mucosa
- **Crohn's disease (CD):** Idiopathic granulomatous transmural inflammation of GI tract, from mouth to anus, w/ skip lesions

Etiology

- Multifactorial; theoretically a chronic state of dysregulated mucosal immune fxn that is further modified by specific environmental factors (eg, smoking)

IBD and Pregnancy

- Preg does not ↑ likelihood of IBD flare
- Calcium suppl to combat osteoporosis risk
- **Quiescent IBD:** Nml fertility rates however fallopian tubes can be scarred by the inflamm process of CD (esp on the right)
- SAB, preterm birth, low birth weight, fetal growth restriction, & developmental defects ↑ w/ increased dz activity in CD
  Effect on Preg correlates w/ dz activity at conception
  Recommend pt to be in remission for 6 mo prior to conception

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- Cesarean recommended only for sev anorectal & perirectal abscesses & fistulas. Reduces likelihood of fistula dev or extension into episiotomy scar.

Features of Crohn's disease and ulcerative colitis

	Crohn's disease	Ulcerative colitis
Epidemiology	Incid 0.03–15.6/100000 persons per year Prevalence 3.6–214/100000 Bimodal peak age of onset: 15–30 y, 60–80 y A/w female gender, smoking, OCPs, & genetic predisposition	1.2–20.3/100000 new diagnoses per year 7.6–246/100000 prevalence Bimodal peak age of onset: 15–30 y, 60–80 y Appendectomy prior to age 20 & tobacco use may be protective factors (Danese. *N Engl J Med* 2011;365:1713)
Pathology	Macroscopic: Transmural inflammation that can affect any portion of GI tract from mouth to anus. "Skip lesions," nonfriable mucosa, long ulcers & fissures w/ "cobblestone" appearance, perirectal fistulas, fissures, abscesses, anal stenosis Microscopic: Loose aggregations of macrophages form noncaseating granulomas in all layers of bowel wall 30–40% small bowel only, 40–50% dz affects small & large bowel, 15–25% colon only	Mucosal inflammation, ulceration, & chronic mucosal damage of colon, begins at rectum & extends proximally in a continuous fashion Macroscopic: Granular, friable mucosa w/ diffuse ulceration, pseudopolyps Microscopic: Inflammation limited to mucosa & superficial submucosa, crypt abscesses 40–50% dz limited to rectum & rectosigmoid, 30–40% dz extend beyond sigmoid but not entire colon, 20% w/ total colitis
Clinical Manifestations	Either fibrostenotic-obstructing pattern or a penetrating-fistulous pattern Chronic h/o recurrent abdominal pain & nongrossly bloody diarrhea, fever, malaise, bowel obst Extraintestinal sx: Erythema nodosum (15%), periph arteritis (15–20%), ankylosing spondylitis (10%), sacroilitis, uveitis, episcleritis, hepatic steatosis, cholelithiasis, nephrolithiasis, low bone mass, thromboembolic events	Chronic relapsing & remitting attacks of bloody mucoid diarrhea; often grossly bloody diarrhea Abdominal cramping, tenesmus, colickly lower abdominal pain relieved by defecation Fever, weight loss Fulminant dz can result in toxic megacolitis or megacolon Extraintestinal manifestations: Erythema nodosum (10%), pyoderma gangrenosum (1–12%), sacroilitis, uveitis, hepatic steatosis, thromboembolic events
Diagnostic Workup/ Studies	Elevated ESR, CRP Hypoalbuminemia, anemia, leukocytosis in sev dz Endoscopy reveals rectal sparing, aphthous ulcerations or strictures Barium enema shows filling defects CT enterography shows radiographic "string sign"; areas of circumferential inflammation & fibrosis resulting in luminal narrowing ASCAs in 60–70% Colorectal cancer risk similar to UC, same recommendations as UC regarding surveillance	Elevated CRP, Plts, ESR Decreased Hgb, leukocytosis Negative stool cx for bacteria, *Clostridium difficile*, O&P Sigmoidoscopy w/ colonic biopsies to confirm dx via histology Barium enema – fine mucosal granularity, "collar-button" ulcers, loss of haustra: "Lead pipe" appearance pANCAs in 60–70% Monit for colon cancer w/ annual or biennial colonoscopy w/ multi biopsies if >8–10 y of pancolitis or 12–15 y left-sided colitis

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Treatment and medications for IBD			
	Drug/Intervention	**Dose**	**Notes**
Mild IBD	Diet & lifestyle		Not primary rx, avoid aggravating foods
	Sulfasalazine	500 mg/d–6 g/d	Antibacterial (sulfapyridine) & anti-inflammatory (5-ASA); safe in Preg w/ folate suppl
	5-ASA Olsalazine Mesalamine	Olsalazine: 1.6 g TID Mesalamine: 1 g QID or delayed-release: 500 mg BID; Mesalamine, enema: One application BID	Safe in Preg & breastfeeding
Mod IBD	Corticosteroids Prednisone Hydrocortisone Methylprednisolone	40 mg/d PO w/ taper 300 mg/d IV 60 mg/d IV	Use if not responsive to 5-ASA; not maint drug; safe in Preg; animal studies show association w/ cleft palate & SAB
	Abx Metronidazole	1–1.5 g/d PO, maint therapy 750 mg/d	No role in UC, use for inflamm, fistulous, & perianal CD
	Immunosuppressives 6-mercaptopurine Azathioprine MTX	1 mg/kg 1.5 mg/kg	Rx & maint of remission, steroid sparing agents; MTX contraindicated in Preg & breastfeeding
Sev IBD	Immunosuppressives Cyclosporine Tacrolimus Anti-TNF Ab	4 mg/kg/d IV; 8 mg/kg/d PO	Use if refrac to IV steroids
	Surg	50% UC patients undergo Surg w/i 1st 10 y, most CD patients require at least 1 Surg in their lifetime; Indications for Surg: Intractable dz, toxic megacolon, colonic perforation, massive hemorrhage, extracolonic dz, colonic obst, intestinal stricture & obst, fistula, abscess, colon cancer ppx	

Note: CD & UC severity can be determined by using dz activity calculator (www.gastrotraining.com/calculators/cdai)

From Rajapakse R, Korelitz BI. Inflammatory bowel disease during pregnancy. *Curr Treat Options Gastroenterol.* 2001;4(3):245–251.

VIRAL HEPATITIS

Clinical Manifestations

- **Sx of acute hepatitis:** Anorexia, nausea & vomiting, fatigue, malaise, arthralgias, myalgias, HA, photophobia, pharyngitis, cough, coryza 1–2 w prior to jaundice
  Low-grade fever more common in HAV & HEV
- Dark urine & clay-colored stools may occur 1–5 d prior to onset of jaundice
- Jaundice w/ enlarged & tender liver w/ RUQ pain
- Splenomegaly & cervical adenopathy 10–20%
- During "recovery phase," constitutional sx resolve but liver enlargement & abn liver enzymes may persist for 2–12 w

Diagnostic Labs/Exams

- Elevated AST & ALT (40–4000 U/L). Elevated bilirubin (jaundice visible when serum bilirubin >2.5 mg/dL [typically 5–20 mg/dL]). Assess PT/PTT, albumin, gluc.

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Hepatitis A

- Nonenveloped RNA picornavirus. Replication limited to liver, but virus present in liver, bile, stools, & bld.
- Prevalence increases as a fxn of age & decreasing socioeconomic status
- **Transmission:** Fecal–oral route. 15–45-d incubation period, mean 4 w
- **Dx:** Active infxn = anti-HAV IgM (can persist for several months)
  Prior exposure = anti-HAV IgG, detectable indefinitely → protective
- **Rx:** Supportive, recovery w/i 4–6 w
- No evid that HAV is teratogenic; transmission to fetus has not been reported

Hepatitis B

- Small, circular DNA hepadnavirus
- Prevalence increases w/ lower socioeconomic status, older age groups, & persons w/ risk for exposure to bld
- Acute HBV occur in 1–2/1000 pregnancies; chronic HBV occur in 5–15/1000 pregnancies
- **Transmission:** Bld, sexual, perinatal (esp in infants born to HBsAg carrier mothers or mothers w/ active infxn, transmission correlates w/ presence of HBeAg). 30–180-d incubation period, mean 8–12 w.
- 85–90% complete resolution of infxn after acute phase, 10–15% chronic infxn
- Chronic HBV may develop cirrhosis, fulminant liver failure, & increased risk for hepatocellular carcinoma
- **Dx-Serology**
  HBsAg: 1st detectable marker, before LFTs or sx, acute or chronic infxn
  Anti-HBs: Detectable indefinitely after disappearance of HBsAg or after Vz
  HBcAg: Not typically detectable in serum
  Anti-HBc: Present 1–2 w after HBsAg, may be only serologic marker during "window" period; anti-HBc IgM sugg acute infxn
  HBeAg: Increases w/ infectivity

Diagnosis of hepatitis B by serology

Dx	HBsAg	Anti-HBs	Anti-HBc	HBeAg	Anti-HBe
Acute hepatitis	+	–	IgM	+	–
Window period	–	–	IgM	±	±
Recovery	–	+	IgG	–	±
Immunization	–	+	–	–	–
Chronic hepatitis	+	–	IgG	±	–

- **Prevention:** 3-dose pre-exposure vaccinations (at 0, 1, 6 mo)
  HBIg postexposure ppx (including sexual exposure, needle stick, newborns)
- **Rx:** Acute HBV → supportive. Chronic HBV → IFN-α, lamivudine, adefovir dipivoxil, pegylated IFN, entecavir
- HBV in Preg
  Routine screening at 1st prenatal visit
  Increased risk of PTB, transplacental infxn uncommon, **not** teratogenic
  Most neonat infxn vertically transmitted by peripartum exposure
  High perinatal transmission rate. 30% in HBeAg (–) mothers; >85% in HBeAg (+) mothers (*N Engl J Med* 1975;292(15):771)
  Cesarean deliv & bottlefeeding does not lower risk of transmission

Hepatitis C

- RNA virus; in US 70% genotype 1 (& most common worldwide), 30% genotype 2 or 3
  1–5% prevalence in Preg, highest rates in urban populations
- **Transmission:** Bld exposure; 15–160-d incubation period, mean 7 w
- ~20% chronic HCV lead to chronic active hepatitis or cirrhosis, increased risk of hepatocellular carcinoma
- **Serology**
  HCV antigens not detectable in serum ∴ difficult to diagnose acute HCV
  Anti-HCV (ELISA) positive in 6 w–6 mo, does not imply recovery
  If + Anti-HCV, use HCV RIBA or HCV RNA (via PCR) to confirm dx

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Diagnosing HCV – serologic testing			
Dx	**HCV RNA**	**Anti-HCV (ELISA)**	**Anti-HCV (RIBA)**
No infxn	–	–	–
False positive	–	+	–
Early acute hepatitis	+	–	–
Past infxn	–	+	+
Chronic hepatitis (active/ongoing)	+	+	+

- **Rx:** Pegylated IFN, ribavirin
- HCV in Preg
  - Prenatal screening in high-risk women (concurrent alcoholism, IVDU, coexisting HIV infxn, prior bld xfusion, tattoos)
  - May be a/w low birth weight, need for assisted ventilation, NICU admit (*Am J Obstet Gynecol* 2008;199(1):38.e1)
  - Unclear effect on progression of hepatic fibrosis
  - Vertical transmission 5–10%. 3× higher w/ HIV coinfection (*Lancet* 1995;345(8945):289)
  - Risk for vertical transmission increases w/ viral load. Cesarean deliv does not ↓ risk of transmission. Prolonged rupture of membranes may ↑ transmission.
  - Ribavirin contraindicated in Preg. Breastfeeding not contraindicated.

Hepatitis D

- Defective RNA virus that requires coinfection or superinfection w/ HBV for replication & expression. In nonendemic areas, HDV infxn confined to persons exposed frequently to bld (IVDUs, hemophiliacs). In endemic areas, HDV infxn predominantly by nonpercutaneous means.
- **Transmission:** Bld, sexual. 30–180-d incubation period, mean 8–12 w
- **Dx:** Anti-HDV, HDV RNA
  - No screening indicated as counseling & rx same as HBV
  - May consider screening if w/ symptomatic HBV
- **Rx:** Similar to HBV

Hepatitis E

- RNA virus common to India, Asia, Africa, & Central America
- **Transmission:** Fecal–oral, rarely secondary person-to-person spread
  - 14–60-d incubation period, mean 5–6 w
- **Dx:** IgM anti-HEV
- **Rx:** Supportive
- Fatality rate 1–2% & up to 10–20% in pregnant women
- Can cause fetal/neonat hepatitis

Prevention/Vaccinations

- HAV & HBV Vz safe during Preg. Vaccinate high-risk pts (more than 1 sex partner during prev 6 mo, treated for an STI, recent or current IVDU, having had an HBsAG-positive sex partner). May be vaccinated during Preg.

INTRAHEPATIC CHOLESTASIS OF PREGNANCY (ICP)

Definitions and Epidemiology

- Dz of intrahepatic biliary tree or hepatocellular secretory system resulting in elevated bilirubin & other solutes eliminated in bile (bile salts & cholesterol) that occurs during Preg
- 0.1–0.2% incid in North America
- Chronic hepatitis C a/w 20-fold ↑ in incid of cholestasis

Pathophysiology

- Unk but likely genetically susceptible alterations in steroid & bile acid metabolism
- HLA-B8 & HLA-BW16 & gene mutations in hepatocellular transport systems (MDR3)
- May be related to circulating estrogen levels (incid in twin pregnancies > singletons)
- Bile acids incompletely cleared & accumulate in plasma w/ assoc dyslipidemia
- ↑ mec & intrapartum fetal distress (22–41%), preterm birth (19–60%), & fetal demise (0.75–1.6%); esp if bile acids >40 μmol/L (Glantz. *Hepatology* 2004;467)

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Clinical Manifestations and Physical Exam
- Generalized pruritus in 2nd or 3rd trimester esp on palms & soles of feet
- Jaundice (20–75%)
- No assoc rash, but excoriations from scratching

Diagnostic Workup/Studies
- Pruritus precedes lab abnormalities by several weeks
  - Hyperbilirubinemia (rarely exceeds 4–5 mg/dL)
  - ↑ serum bile acids (chenodeoxycholic acid, deoxycholic acid, cholic acid) > 10 μmol/L
  - ↑ alk phos more than nml Preg
  - Nml to moderately ↑ AST/ALT but seldom >250 U/L
- Liver bx shows mild cholestasis w/ centrilobular dilation w/ bile plugs (rare to bx)
- Rule out preeclampsia, not likely in setting of nml pressures & absence of proteinuria
- RUQ US to rule out cholelithiasis & biliary obst

Treatment and Medications
- Sx & labs nml 2–4 w after deliv but likely to recur in subseq pregnancies or w/ exogenous estrogen use
- Antihistamines & topical emollients for symptomatic relief of pruritus
- Ursodeoxycholic acid (probably superior rx), cholestyramine, naltrexone
- Consider antepartum testing after dx; consider deliv at 37–38 w

HELLP SYNDROME

Definition and Epidemiology (*BMC Pregnancy Childbirth* 2009;9:8)
- Variant of sev preeclampsia characterized by microangiopathic hemolysis, elevated serum transaminases, & low platelet count. Partial HELLP includes those w/ sev preeclampsia & those w/ either "ELLP" (elevated liver transaminase & low Plts) or "EL" (elevated liver enzymes). "Partial HELLP" = "sev preeclampsia," on a spectrum. See also Chapters 11 and 12.
- 0.5–0.9% of all pregnancies. 10–20% of those w/ eclampsia. See Chapter 18.
- Increased risk for eclampsia, preterm birth, & perinatal mortality

Pathophysiology
- Microangiopathic hemolysis leading to elevation of serum lactate dehydrogenase level & fragmented red bld cells on periph smear. Same process as PEC, but more severe.
- Decreased Plts due to increased consump.

Clinical Manifestations
- Signs & sx of preeclampsia (elevated BP, proteinuria, focal edema, HA, vision changes)
- RUQ abdominal or midepigastric pain, nausea, vomiting
- Intensity of sx characterized by exacerbation during the night & recovery during day (*J Matern Fetal Neonatal Med* 2006;19:93)
- Sev complications: Spont rupture of subcapsular liver hematoma, placental abruption, DIC

Physical Exam and Diagnostic Workup/Studies (*Am J Obstet Gynecol* 2011;205:192)
- RUQ or epigastric tenderness
- Differing diagnostic criteria reported, 2 most common:
  - Sibai criteria: Hemolysis on periph smear, LDH > 600 U/L, or total bilirubin >1.2 mg/dL
    + AST > 70 U/L
    + Thrombocytopenia < 100000 cells/mm^3
  - Martin criteria: LDH > 600 U/L
    + AST or ALT > 40 IU/L
    + Platelet count < 150000 cells/mm^3
- Abdominal imaging (RUQ US, CT, MRI) to assess hepatic hemorrhage that may result in subcapsular hematoma ± rupture. Consider if ↑↑ elevation in transaminases.

Treatment and Medications
- Rx similar as that for sev preeclampsia (eg, antihypertensives, magnesium sulfate, deliv after steroids [for FLM] if <34 w or earlier depending on severity of dz)
- Presence of HELLP → immediate deliv due to ↑ mat death (1%) & increased mat morbidities: Bld xfusion (25%), DIC (15%), wound disruption (14%), placental abruption (9%), pulm edema (8%), renal failure (3%), & intracranial hemorrhage (1.5%) (*Obstet Gynecol* 2004;103:983)
- Dexamethasone may improve sev thrombocytopenia, but probably does not improve outcomes (*Cochrane Database Syst Rev* 2010;(9):CD008148)

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- Increased risk for recurrence of HELLP in subseq pregnancies (5–25%); higher incid of preterm deliv, fetal-growth restriction, placental abruption & cesarean deliv in subseq deliveries w/o recurrence of HELLP

ACUTE FATTY LIVER OF PREGNANCY (AFLP)

Definitions and Epidemiology

- Accum of microvesicular fat a/w Mitoc dysfxn & impairment of hepatocyte fxn that can result in acute liver failure
- 1/10000 pregnancies
- A/w Mitoc abnormalities of fatty acid oxidation from autosomal inherited mut (ie, LCHAD deficiency)
- Occurs more often w/ nulliparas, male fetus, preeclampsia, & multifetal gest

Clinical Manifestations

- Presents late in 3rd trimester – often w/ PTL or lack of fetal mvmt
- Nonspecific sx including persistent nausea & vomiting, malaise, fatigue, anorexia, epigastric pain, progressive jaundice, low-grade fever
- 50% w/ sx concerning for preeclampsia including HTN, proteinuria, edema
- If sev: Ascites, coagulopathy & spont bleeding, SOB due to pulm edema, stillbirth, hepatorenal syn, hepatic encephalopathy, renal failure

Diagnostic Workup/Studies

- **Labs:** LFTs – ↑ bilirubin (>10 mg/dL), ↑ AST/ALT (typically less than 1000 U/L), CBC (hemoconcentration, leukocytosis, thrombocytopenia), coags (hypofibrinogenemia, hypoalbuminemia, hypocholesterolemia, prolonged clotting times, prolonged PT), hypoglycemia, or hyperglycemia secondary to pancreatitis
- Mother should undergo testing for LCHAD; can be lifesaving for neonate/inform risk for future pregnancies
- **Imaging** – RUQ US shows increased echogenicity; CT &/or MRI demonstrates lower liver density
- Liver bx, std for confirming dx but rarely used in clinical practice, shows microvesicular steatosis

Differentiating between AFLP and HELLP

Signs & sx	AFLP (%)	HELLP (%)
HTN	50	85
Proteinuria	30–50	90–95
Fever	25–32	Absent
Jaundice	40–90	5–10
Nausea & vomiting	50–80	40
Abdominal pain	35–50	60–80
Hypoglycemia	Present	Absent

From Sibai BM. Imitators of severe preeclampsia. *Obstet Gynecol.* 2007;109(4):956–966.

Treatment and Medications

- **Supportive care:** Gluc infusion, reverse coagulopathy, fluid resusc
- **Deliv recommended** when dx confirmed; spont resolution after deliv, typically takes 1-w postpartum for hepatic dysfxn to resolve. During recovery period, 25% w/ transient diabetes insipidus & 50% w/ acute pancreatitis.
- May recur in subseq pregnancies, even if no LCHAD mut in mother. Historically w/ 70% mat mortality rate, improved w/ early dx to <10%.
- Perinatal mortality 13% due to high rate of preterm deliv

TOTAL PARENTERAL NUTRITION (TPN)

Definition, Indications, and Contraindications

- **TPN:** Intravenous supplementary nutrition including prot, caloric fat & dextrose, electrolytes, vitamins, minerals, & fluids. Generally a *temporary* intervention for severely limited po intake (eg, intractable vomiting/diarrhea, gastrointestinal

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ischemia, high output fistula) or conditions of sev bowel dysfxn (eg, bowel obst, protracted ileus).
- **Contraindications:** Hyperosmolality, sev hyperglycemia, sev electrolyte abnormalities, vol overload, sepsis. Not recommended in advanced cancer (*J Parenter Enteral Nutr* 2009;33(5):472).

Ordering TPN

- Parameters depend on specific dysfxn; consult nutritionist for TPN regimen
- TPN initiated w/ slow continuous feed, can be advanced to 12-h cycle if tolerated

Example of initial TPN orders, by patient weight

TPN component	Nutrition goal	Sample initial order
Prot	0.8 g/kg/d	1–1.5 g amino acids/kg
Carbohydrate	~60–70% nonprot calories	5 g dextrose/kg/d
Fat	25–40% nonprot calories, no less than 2–4% total kcal as fat	~1050 fat kcal/w
Electrolytes & minerals	1–2 mEq Na/kg 1–2 mEq K/kg 10–15 mEq Ca/kg 20–40 mmol PO4/d 8–20 mEq mg/d	~80 mEq Na ~60 mEq K ~9.6 mEq Ca ~28 mmol PO4 ~16 mEq mg
Vitamins & trace elements	MVI, thiamine & folate for chronic EtOH abuse Add zinc to promote wound healing Add folate ± prenatal Vit for Preg Add trace elements if desired	~100 mg thiamine, 1 mg folate ~5 mg zinc ~1 mg folate 10 mcg chromium, 1 mg copper, 0.5 mg manganese, 60 mcg selenium

From Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. *JPEN J Parenter Enteral Nutr.* 2002;26:1SA–138SA.

TPN Monitoring

- **Baseline:** Chemistry panel, LFTs, lipids, albumin, transferrin, prealbumin
- **Daily (while increasing feed rates):** Electrolytes, fluid balance, gluc ≥4×/d
- **Weekly:** Triglycerides, LFTs, albumin, transferring, prealbumin
- Insulin sliding scale initially & transition to insulin in TPN mix when feasible

Complications

- **Access related:** Line infxn, PTX, hemothorax, brachial plexus injury; metabolic effects: Hyperglycemia, electrolyte alterations (ie, hyperK), nutrient excess or deficiency, Wernicke encephalopathy, hepatic dysfxn, refeeding syn (hypophos, hypokalemia, hypomagnesemia)
- Fetal complications of mat TPN uncommon; supplement Vit K for pregnant patients on TPN, & follow serial growth sonos (*Obstet Gynecol* 2003;101(5 Pt 2):1142)

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HEMATOLOGIC CHANGES OF PREGNANCY

Plasma Volume
- ↑ by 40–50% of baseline plasma vol
- Plasma vol ↑ begins at ~6 w gest & continues until 30–34 w

RBC Mass
- 20–30% ↑ in RBC mass during Preg beginning at ~10 w gest
- 1000 mg iron req for Preg (RBCs – 500 mg, fetus – 300 mg, bleeding – 200 mg)
- Most common cause of anemia in Preg is iron deficiency

Leukocytes
- Plasma levels variable throughout Preg, WBC = 5000–12000/μL
- Physiologic leukocytosis in labor & puerperium, WBC = 14000–16000/μL

Coagulation System
- 5-fold increased risk of thromboembolic dz; absolute risk 1/1500 pregnancies
- ↑ risk from venous stasis (uterine mass effect), vessel wall injury, hypercoagulable state (↑ procoagulants; ↓ prot S; decreased fibrinolysis due to ↓ tPa)
- Coagulation factors normalize 2 w postpartum

Blood Loss with Delivery
- Avg EBL: Vaginal deliv = 500 mL; cesarean deliv = 1000 mL
- Cesarean hysterectomy = 1500 mL (nonurgent) & 2500 mL (emergent)
- Majority of bld loss w/i 1st hour after deliv → ~80 mL lochia over next 72 h

ANEMIA

Definition
- **Gravid:** Hb ≤11 g/dL in 1st trimester; ≤10.5 g/dL in 2nd trimester; ≤11 g/dL in 3rd trimester
- **Nongravid woman:** ≤12 g/dL
- IOM recommends decreasing cutoff for anemia by 0.8 g/dL for AAs
- **Risks:** Non-Hispanic Black, malabsorption (eg, celiac sprue), gastric bypass, iron-poor diet, menorrhagia, teenage, minority, low socioeconomic status, short Preg interval

Pathogenesis of anemia	
↓ production	Iron deficiency, B_{12}/folate deficiency, GI dz, chronic dz, bone marrow suppression
↑ destruction	*Extravascular:* Sickle cell dz, thalassemias, G6PD deficiency, spherocytosis, liver/spleen dz, infxn (malaria, babesia), autoimmune hemolysis (SLE) *Intravascular:* HELLP, TTP–HUS, DIC, xfusion rxn, infxn
Bld loss	Trauma, Surg, GI bleed
Dilution	IV fluids, *Preg*

Clinical Manifestations
- Fatigue, IUGR, preterm deliv, perinatal mortality, pica, restless leg syn
- Hb <6 g/dL a/w NRFHT, oligohydramnios, fetal death, CHF (Hb <4 g/dL)
- **Signs:** Pallor (conjunctiva), tachy, orthostatic HoTN, jaundice (hemolysis), splenomegaly (thal, sickle cell, spherocytosis), petechiae (TTP, HUS, DIC)

Diagnostic Evaluation
- **CBC** w/ indices at 1st OB visit & 24–28 w gest; note MCV, RDW, retic count
- *Periph smear, iron, iron sat, ferritin, TIBC, folate, B_{12}, Hb electrophoresis*
- **Additional labs:** LFTs, BUN/Cr, TFTs, hemolysis labs (↑ indirect bili, ↑ LDH, ↓ haptoglobin)
- Bone marrow aspirate/bx
- RI = [retic count × (pt's Hct/nml Hct)]/maturation factor
  Maturation factor dependent on Hct; Hct ≤15% = 2.5, >16% = 2, >26% = 1.5, >36% = 1 (Nml is 1–2% for healthy ♀. >2–3% = adequate retic for anemia. <2% = inadeq.)

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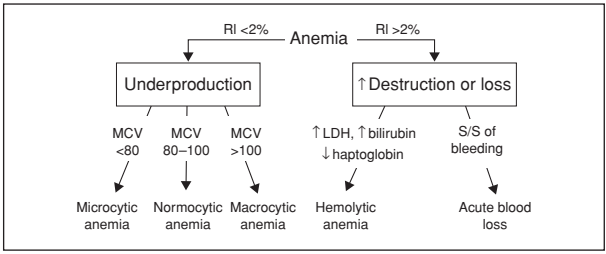
Figure 16.1 Initial approach to anemia



(From Sabatine MS. *Pocket Medicine*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011)

Normal iron indices		
Test	**Nml pregnant**	**Nml nonpregnant**
Serum iron level	40–175 μg/dL	60–150 μg/dL
TIBC	216–400 μg/dL	300–360 μg/dL
Transferrin sat	16–60%	20–50%
Serum ferritin level	>10 μg/dL	40–200 μg/dL

From ACOG Practice Bulletin No. 95: Anemia in Pregnancy. *Obstet Gynecol*. 2008;112(1):201–207.

Microcytic Anemia (MCV <80 fL)

- **Eval:** Serum Fe, TIBC (transferrin), ferritin, transferrin sat
- 30 mg/d of elemental iron req during Preg for prevention of anemia
- **Rx:** Fe rich foods (cream of wheat, red meat, spinach, dried beans; take w/ Vit C rich foods for ↑ Absorp), Fe supplements, IV iron (intolerance to PO), xfusion (for symptomatic anemia or Hb <6), erythropoietin

Diagnosis of iron deficiency anemia		
Pathophysiology	**Lab profile**	**Additional testing**
Fe deficiency anemia	↓ Fe, ↑ TIBC, ↓ ferritin	↓ transferrin sat *Fe/TIBC < 18%*
Thal	Nml Fe, TIBC, & ferritin	Periph smear – basophilic stippling Hb electrophoresis
Anemia of chronic dz	↓ Fe, ↑ TIBC, ↑ ferritin	↓ transferrin sat *Fe/TIBC > 18%*
Sideroblastic anemia	↑ Fe, nml TIBC, ↑ ferritin	Periph smear – basophilic stippling Bone marrow bx – ringed sideroblasts

Iron supplementation			
Form	**Preparation**	**Dose**	**Elemental iron**
PO	Ferrous gluconate	325 mg	37–39 mg
	Ferrous sulfate	325 mg	60–65 mg
	Ferrous fumarate	325 mg	107 mg
IV	Iron dextran (1% risk anaphylaxis)	Dose (mL) = 0.0042 (Desired Hb – Observed Hb) × LBW + (0.26 × LBW). Max 100 mg	50 mg/mL
	Iron sucrose	100 mg daily; max 10 d	20 mg/mL
	Sodium ferric gluconate	125 mg daily; max 8 d	12.5 mg/mL

LBW = (9270 × total body weight [kg])/(8780 + (244 × BMI)).

From Samuels P. Hematologic complications of pregnancy. In: Gabbe SG, et al. *Normal and Problem Pregnancies*. 6th ed. Churchill Livingstone; 2012:967–970.

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Normocytic Anemia (MCV 80–100 fL)

- DDx includes *acute bld loss, early Fe deficiency,* bone marrow suppression (marrow invasion, RBC aplasia, aplastic anemia), chronic renal insufficiency, hypothyroidism, pancytopenia, anemia of chronic dz, sideroblastic anemia

Macrocytic Anemia (MCV > 100 fL)

- **Megaloblastic anemia:** *Hypersegmented neutrophils* on periph smear is pathognomonic
  Folate deficiency: Age, malnut (alcoholism), malabsorption (celiac sprue), meds (trimethoprim, methotrexate), ↑ requirement (Preg, malig, dialysis)
  B_{12} deficiency: *May cause neurologic sx;* causes – pernicious anemia, gastritis, bariatric Surg, malabsorption (Crohn's, ileal resxn, tapeworm), meds (metformin, PPIs)
- **Nonmegaloblastic anemia:** Causes include liver dz, alcoholism, reticulocytosis, hypothyroidism, myelodysplastic syn, medication (AZT, acyclovir, azathioprine)
- **Eval:** Serum B_{12}/folate, periph bld smear, homocysteine, methylmalonic acid
  ↑ homocysteine in B_{12} & folate deficiency, ↓ methylmalonic acid in B_{12} *deficiency only*
  Schilling test, anti-IF antibodies → positive in pernicious anemia
- **Rx:** Folate deficiency – 1–5 mg PO QD → will treat anemia but, not neuro sx; B_{12} deficiency – 1 mg IM QD × q7d then weekly × 4 w then monthly as needed

Hemolytic Anemia

- **Eval:** ↑ retic count (RI >2%), ↑ LDH, ↓ haptoglobin, ↑ indirect bilirubin
- Direct Coombs test, periph smear, Hb electrophoresis, osmotic fragility test

Diagnosis of hemolytic anemia	
Sickle cell anemia	Hb electrophoresis; sickled RBC/Howell–Jolly bodies on smear
Autoimmune	+ warm AIHA:IgG; + direct Coombs
Microangiopathic	Schistocytes on smear, ↓ Plts; *DIC:* ↑ PT; *TTP–HUS:* ↑ Cr
HELLP	↑ LFTs; ↓ Plts; ↑ LDH; pregnancy; preeclampsia
Hereditary spherocytosis	+ osmotic fragility test

HEMOGLOBINOPATHIES

Pathophysiology

- Adult Hb structure = 2 α-chains + 2 β-chains (HbA) or 2 δ-chains (HbA_2)
- Fetal Hb = 2 α-chains + 2 γ-chains (HbF) (12–24 w gest)

Thalassemias (*Lancet* 2012; 379:373)

- Abn or ↓ synthesis of α- or β-chains → microcytic anemia; classified by absent chain
- **α-thal:** 4 α-chains (αα/αα) from 2 genes on chromo 16
  Absence of ≥1 of 4 genes → abn Hb assembly → hemolysis & ↓ production

Types of alpha thalassemia		
Genes	**Description**	**Manifestations**
(α-/αα)	α-thal trait	At risk: Southeast Asian, African, W. Indian, & Mediterranean; asymptomatic, nml labs
(α-/α-) (αα/–)	*Trans* *Cis*	*Cis* ↑ incid w/ Southeast Asian descent & ↑ risk HbH/Hb Bart in children; mild, asymptomatic microcytic anemia
(α-/–)	HbH dz	Mild–mod hemolytic anemia
(–/–)	Hb Bart's dz	Hydrops fetalis, IUFD; a/w preeclampsia

- **β-thal:** Nml state = 2 β-chains from 1 gene on chromo 11
  At risk: Mediterranean, Asian, Middle Eastern, Hispanic, & West Indian
  1 β-chain mut → β-thal minor → mild anemia
  2 β-chain mutations → β-thal major (Cooley's anemia) → sev anemia
  β-thal intermedia = 2 β-chain mutations w/ milder sx
- **Dx:** CBC (MCV < 70), ferritin (exclude Fe deficiency anemia), Hb electrophoresis, periph smear → basophilic stippling
- **Screening in Preg:** Pts in high-risk groups → CBC & Fe indices → ↓ MCV & no iron deficiency → Hb electrophoresis; If Southeast Asian, DNA testing for α-thal

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- Prenatal testing for α- & β-thal if mut/deletions in both parents via CVS, amnio, or PGD
- Preg in β-thal major recommended only if nml cardiac fxn & prolonged hypertransfusion → Hb >10 & w/ iron chelation
- **Rx:** xfusion for anemia + iron chelation; splenectomy; hematopoietic xplant

Sickle Cell Anemia (*Lancet* 2010;376:2018; *Obstet Gynecol* 2007;109(1):229)

- Autosomal recessive β-chain mut (valine replaces glutamic acid at 6th amino acid) resulting in abn Hb structure (HbS replaces HbA)
- HbS (heterozygote) = sickle cell trait (carrier); HbSS (homozygote) = sickle cell anemia
- HgbSS: ↓ oxygen tension → RBC sickles → hemolysis & microvascular occlusion
- 1 in 12 AAs w/ trait, 1 in 500 w/ dz; ↑ risk African, Mediterranean, Arab-Indian
- **Signs/sx:**
  - Anemia hemolysis, splenic sequestration, aplastic (parvovirus B19)
  - Infarction: Painful crises, acute chest syn, CVA, multiorgan failure: Functional asplenia, kidneys (renal papillary necrosis), heart, & brain (CVA)
  - Infxn encapsulated organisms (*Hib, S. pneumoniae, Meningococcus*), osteomyelitis
- Acute chest syn = new pulm infiltrate + a pulm symptom (chest pain, T > 38.5, resp sx, hypoxemia) from infxn/vaso-occlusion of pulm vessels; 3% mortality
- **Dx:** bld smear w/ sickle-shaped RBCs & Howell Jolly bodies; Hb electrophoresis
- **Rx:** hydroxyurea → ↑ HbF → ↓ frequency of painful episodes, acute chest syn & need for bld xfusion; bld xfusion → simple vs. exchange xfusion (indications: Preop, acute/chronic organ failure, acute anemia, acute pain); iron chelation; hematopoietic stem cell xplant (selected pts w/ sev dz)
  - Acute pain crisis → Opioids are mainstay, O2 for oximetry <95%, IV hydration
  - Infxn → vaccination against *Hib, S. pneumoniae, N. meningitidis,* influenza, & HBV
  - Acute chest syn/CVA → simple vs. exchange xfusion (ACS = respiratory symptoms, chest pain, or fever and a new pulmonary infiltrate on XR)
- **Sickle cell variants:** HbC not a/w dz, HbSC same as HbSS but ↓ frequency; HbS + thal a/w varying severity of dz
- **Preg:** HbSS a/w ↑ mat risk acute pain crises, acute chest syn, PROM, preeclampsia, pyelo, bld xfusion, alloimmunization, & infxn; ↑ fetal/neonat risk SAB (30%), IUFD (OR = 2), IUGR, PTD (25%), ↓ birth weight (20–40%). Prenatal diagnosis available
  - Mgmt: Stop hydroxyurea (teratogenic), start 1–4 mg folate daily, avoid cold, physical exertion, dehyd, & stress to avoid painful crises. If xfusion → monit serial Hb & % HbS, goal: Hb ~10 g/dL & ≤40% HbS (*Obstet Gynecol* 2007;109(1):229)
  - Serial growth USs & antenatal testing at 32 w for fetal monitoring
  - HbSS & HbS (trait) w/ ↑ risk of pyelo w/ asymptomatic bacteriuria. Consider daily UTI ppx & monthly urine cx.

THROMBOCYTOPENIA (Plt <150000/μL)

- Plt 50000–100000 – no increased surgical risk; ↑ risk for bleeding w/ major trauma
- Plt 20000–50000 – ↑ risk w/ minor trauma or Surg
- Plt <20000 – risk spont bleeding (<10000 ↑ risk of life-threatening bleeding)

Etiology of thrombocytopenia by mechanism	
↑ destruction	ITP, infxn (HIV, HSV, HCV), SLE, APS, CVVH, meds (Heparin, quinidine, AZT, sulfonamides), DIC, TTP–HUS
↓ production	Viral infxn, chemo, radiation, EtOH, folate/B_{12} deficiency, MDS, leukemia, malig infiltrating bone marrow, myelofibrosis
Abn distribution	Splenic sequestration, dilution, hypothermia
Preg assoc	Gestational thrombocytopenia (66%), pregnancy-associated HTN (21%), HELLP syn, NAIT

Etiology

- *Gestational thrombocytopenia* → 8% of pregnancies; most common cause of ↓ Plt in Preg (66%); Plt typically >70000/μL; resolves 2–12 w postpartum
- ITP → IgG-mediated; persistent Plt <100000/μL; dx of exclusion (nml bld smear, no systemic dz); 15% of neonates have Plt <50000/μL if MoM has ITP (trans placental IgG).
- HIT → see Section below
- *TTP–HUS* → thrombocytopenia + microangiopathic hemolytic anemia ± renal failure ± fever ± Δ mental status; etiology: Meds (quinine, chemo, cyclosporine), *Preg,* Shiga toxin-producing *E. coli,* SLE, *sev ADAMTS 13 deficiency*

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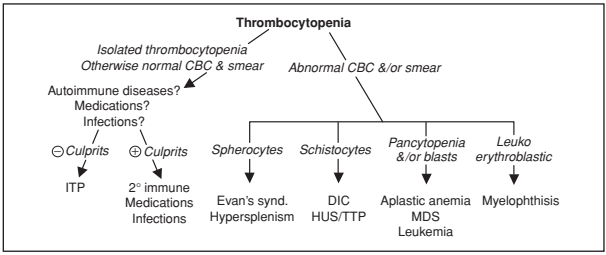
- DIC → etiology: Sepsis, Preg (abruption, HELLP, PPH, IUFD, septic AB, preeclampsia), Surg, hepatic failure, xfusion rxn
  NAIT → mech similar to RhD dz; *1st Preg can be affected;* ~0.1% live births; risk of IVH, petechiae, bleeding; ~100% recurrence for future pregnancies if fetus has same Plt Ag
- *HELLP syn* → see Chap. 15.

Evaluation

- **H&P:** PMHx, meds, infxns, splenomegaly, LAD, petechiae, mucosal bleeding
- **Labs:** CBC ± periph smear; retic count, LDH, haptoglobin, bilirubin, PT/aPTT, fibrinogen, D-dimer, Coombs, ANA, enzyme-immunoassay for HIT, HIV, HCV, Parvovirus, CMV, antiphospholipid antibodies, bone marrow bx

Figure 16.2 Initial approach to thrombocytopenia



(From Sabatine MS. *Pocket Medicine*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011)

Management of thrombocytopenia	
Gestational	Monthly to bimonthly CBC; check for resolution postpartum
ITP	1st line: PO corticosteroids, IVIG, Anti-RhD Ig (*Blood* 2010;115(2):169) 2nd line: Splenectomy, rituximab, immunosuppression, danazol
HIT	Stop heparin; consider alternate agent (lepirudin, argatroban, danaparoid) vs. no rx w/ screening for DVT
TTP–HUS	Plasma exchange ± glucocorticoids; FFP if delay in rx & bleeding
DIC	Rx underlying cause; Plts & FFP/cryoprecipitate (goal fibrinogen >100 mg/dL)
NAIT	MFM consult → determine fetal Plt count/mat Ab, likely C/S deliv
Neuraxial analgesia: No threshold predicts complications (eg, epidural hematoma); generally safe if Plt >100 K; contraindicated for Plt <50 K; may be safe for Plt 50–100 K, requires consensus among OB, anesthesia, & pt From Practice guidelines for obstetric anesthesia: An updated report by the American Society of Anesthesiologists Task Force on Obstetric Anesthesia. *Anesthesiology*. 2007;106(4):843–863.	

Heparin-induced Thrombocytopenia (HIT)

- Type 1 (Nonimmune), occurs w/i 2 d of heparin; clinically inconsequential
- Type 2 (Ab-mediated resp to heparin-PF4 complex), w/i 4–10 d; Plt 30–70 K; risk thrombosis – venous (DVT, PE) & arterial (MI, CVA)
- Pts w/ >1% risk of HIT → CBC every 2–3 d from day 4–14.
- **Dx:** Pts w/ intermediate or high pretest probability require confirmatory testing Ag assays (Anti-heparin/PF4 ELISA) vs. *functional* assays (serotonin release assay (gold std), heparin-induced Plt aggregation)
- **Rx:** Acute HIT – stop heparins & start argatroban or danaparoid; use danaparoid (1st line) or fondaparinux (2nd line) for pregnant pts; avoid warfarin alone, LMWH or prophylactic Plt xfusion (if pt NOT actively bleeding); may use warfarin alone in nonpregnant pts when INR therapeutic (after bridging w/ nonheparin) AND Plt >150 K

Incidence of HIT after ≥4 d of heparin exposure (% HIT)	
Postop pts	Prophylactic heparin (1–5%); therapeutic heparin (1–5%); prophylactic or therapeutic LMWH (0.1–1%)
Medical pts	Cancer pts (1%); prophylactic or therapeutic heparin (0.1–1%); prophylactic or therapeutic LMWH (0.6%); OB pts (<0.1%)
From Linkins LA, Dans AL, Moores LK, et al. Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 suppl):e495S-530S. doi:10.1378/chest.11-2303.	

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Pretest probability of HIT			
4 "T's"	**2 points**	**1 point**	**0 points**
Thrombocytopenia	Plts fall >50% & nadir ≥20 K	Plts fall 30–50% & nadir 10–19 K	Plts fall <30% & nadir <10000
Timing of Plt count fall	Onset 5–10 d after heparin rx *OR* fall ≤1 d if heparin rx w/i last 30 d	Onset 5–10 d (but unclear) *OR* onset after day 10 *OR* fall ≤1 d if heparin rx w/i last 30–100 d	Onset <4 d w/o recent heparin rx
Thrombosis	Thrombosis, skin necrosis, or acute systemic rxn after heparin	Recurrent thrombosis on anticoagulation *OR* suspected thrombosis (awaiting confirmation) *OR* nonnecrotizing skin lesion	None
O**T**her causes	None likely	Poss	Probable (see Etiology)
Probability (based on score) 0–3: Low (<1%) 4–5: Intermediate (~10%) 6–8: High (~33%)			

From Lo GK, Juhl D, Warkentin TE, et al. Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. *J Thromb Haemost.* 2006;4(4):759–765.

VENOUS THROMBOEMBOLIC DISEASE

Definition

- DVT & PE most common presentations
- **DVT:** Most commonly in legs; Calf-vein thrombosis → 80% resolve spontaneously Prox vein thrombosis (popliteal/femoral/iliac veins) → ↑ risk embolism
- **PE:** Thrombus from venous system mobilizes to pulm arterial circulation
- **VTE:** Up to 600000 pts affected annually causing up to 100000 VTE-related deaths
- **DVT & Preg:** 50–66% occurs antepartum, left leg = 80% of thrombi

Pathology

- Virchow's triad:
  1. *Endothelial injury* – Surg, tobacco use, trauma, atherosclerosis, age
  2. *Hypercoagulable state* – thrombophilia, hyperestrogenic state, malig
  3. *Alterations to nml bld flow* – prolonged immobilization, cardiac dz, sickle cell

Clinical Manifestations

- **DVT:** Most asymptomatic, some have unilateral ext pain, swelling, erythema. Exam: >2 cm midleg diameter asymmetry, Homan's sign (pain in calf w/ ankle dorsiflexion)
- **PE:** Dyspnea, pleuritic chest pain, cough, syncope. Exam: Tachy, tachypnea, low pulse oximetry, crackles, fever

Physical Exam

- **DVT:** Lower ext edema (3+ cm > unaffected leg), erythema, calor, tenderness, palpable cord, (+) Homan's sign (calf pain on dorsiflexion in <5% of pts)
- **PE:** Crackles, Homan's sign, cyanosis, pleural rub, loud P_2, *massive:* ↑ JVP, R-sided S_3

Diagnostic Evaluation (DVT)

- **Studies:** Mod/high sens D-dimer <500 ng/mL → NPV = 94% for absence of DVT, (Not reliable in postop state or in Preg or if high pretest probability), CUS (PPV = 94%), contrast venography, MRI

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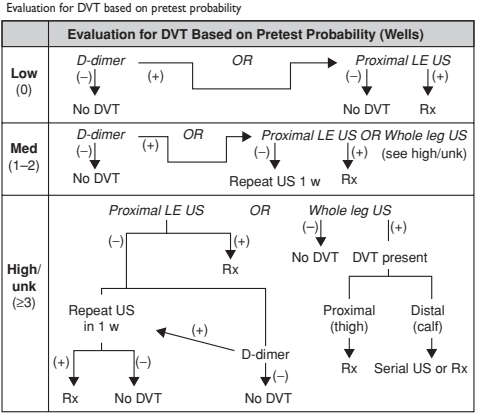
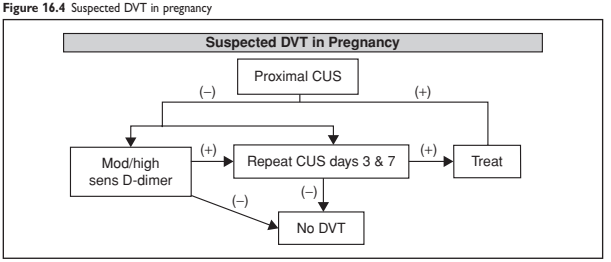
Pretest probability of DVT (Wells DVT score)	
Factors increasing score (1 point for each factor)	
Active cancer Paralysis/paresis/immobilization Bed rest ≥3 d or major Surg w/i 4 w Localized tenderness along veins	Entire leg swollen Calf swelling ≥3 cm c/w asymptomatic side Pitting edema in symptomatic leg only Collateral superficial veins Prev Documented DVT
Factor decreasing score (–2 points)	
Alternate dx at least as likely as DVT (eg, muscle strain, lymphangitis, Baker's cyst)	
Score: ≥3 → high probability DVT; 1–2 → mod probability; ≤0 → low probability	
From Wells PS, Anderson DR, Bormanis J, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. *Lancet.* 1997;350(9094):1795–1798.	

Figure 16.3 Evaluation for DVT based on pretest probability



(From Bates SM, Jaeschke R, Stevens SM, et al. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 suppl):e351S–e418S. doi:10.1378/chest.11-2299)

Figure 16.4 Suspected DVT in pregnancy



(From Bates SM, Jaeschke R, Stevens SM, et al. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 suppl):e351S–e418S. doi:10.1378/chest.11-2299)

Diagnostic Evaluation (PE)

- **D-dimer:** <500 ng/mL may exclude DVT/PE; may be difficult to interpret in Preg
- **ABG:** Hypoxemia, hypocapnia, respiratory acidosis, ↑ A-a gradient; *not routine for PE screen*
- **ECG:** Most common: Sinus tachy, also $S_1Q_3T_3$ or RBBB (*Am J Cardiol* 1991;68(17):1723)
- **CXR:** Atelectasis, effusion, ↑ hemidiaphragm, Hampton hump, Westermark sign; 1st study for PE workup in pregnant pts if *no* leg sx; not routine in nongravid pts for PE eval
- **Echocardiography:** ↑ RV size, ↓ RV fxn, tricuspid regurgitation, RV thrombus signs more likely w/ large PE; use *in critically ill pts w/ high probability* of PE

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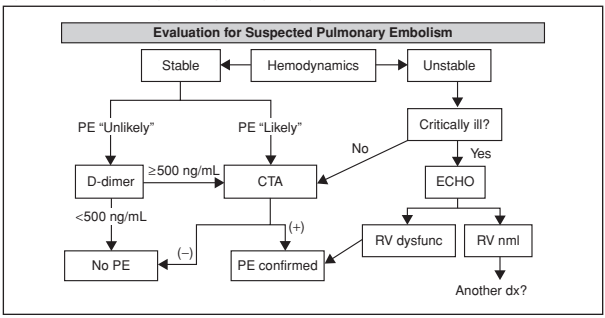
- **Compression US:** Suff to rule in PE; 2% false (+) (*Ann Intern Med* 1997;126(10):775)
- **CTA:** *Most common 1st-line test;* sens 83% & spec 96% w/ MDCT & institutional experience; contraindications include renal dz, contrast allergy, or prior rxn
- **V/Q:** Use for pts w/ contraindications to CTA, centers not experienced w/ CTA, or pregnant women w/ nml CXR & w/o leg sx. Abn CXR obscures findings.
- **MRA/MRV:** Sens 78% & spec 96% if technically adequate; 52% of studies inadeq; sens 100%, 84%, & 40% for lobar, segmental, & subsegmental PE
- **Pulm angiography:** Reserved for pts w/ consideration for endovascular rx of PE

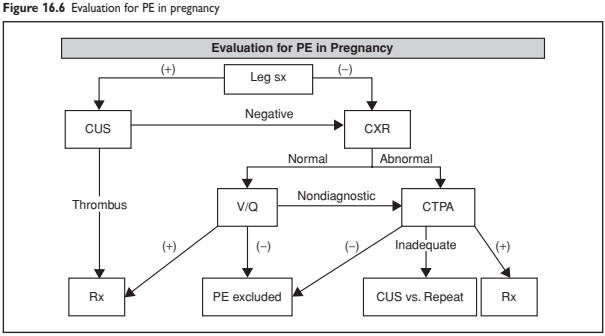
Pretest probability scoring of PE	
Points	**Factors**
3 each	(1) Alternate dx less likely than PE, (2) clinical S/S of DVT
1.5 each	(1) Prior PE/DVT, (2) HR > 100
1 each	(1) Surg w/i 4 w or bed rest ≥3 d, (2) hemoptysis, (3) cancer
Dichotomized Wells Score (use for CTA)	
Score ≤4: PE "unlikely"	Score >4: PE "likely"

Figure 16.5 Evaluation for suspected PE by pretest probability



(From *NEJM* 2010;363:3 and *Chest* 2012;141:e351S)

Figure 16.6 Evaluation for PE in pregnancy



(From Bates SM, Jaeschke R, Stevens SM, et al. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 suppl):e351S–e418S. doi:10.1378/chest.11-2299)

Treatment

- If high clinical suspicion treat immediately, do not wait for diagnostic testing. If hemodynamically unstable, consider thrombolysis.
- **Initial rx:** ≥5 d of UFH, LMWH, fondaparinux + warfarin, or thrombolysis/embolectomy
- **Long-term rx:** ≥3 mo warfarin w/ INR target 2–3

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Acute treatment of VTE	
LMWH	*Preferred* medication class due to ease of use • Enoxaparin 1 mg/kg SQ q12h • Tinzaparin 175 U/kg SQ QD; contraindication if pt >70 yo w/ renal failure • Dalteparin 200 U/kg QD (max 18,000 U); *Avoid if pt >90 kg*
UFH	Target aPTT 1.5–2.5 times reference range; may use if renal dz • IV: Bolus 80 IU/kg or 5000 IU, then 18 IU/kg/h • SQ: 17500 U or 250 U/kg q12h
Factor Xa inhib	• Fondaparinux 5 mg (<50 kg), 7.5 mg (50–100 kg), & 10 mg (>100 kg) QD; use pts w/ current or prior PE; contraindication in renal failure
IVC filter	• Pts w/ contraindication to anticoagulation, failed anticoagulation, or complication w/ rx
Thrombolysis	• tPA reserved for acute PE w/ sev HoTN & no bleeding risk
Embolectomy	• Unstable pts w/ failed or contraindication to thrombolysis
Long-term anticoagulation after VTE	
Warfarin	• Start after heparin, initial max 5 mg daily, titrate to goal INR 2–3

From *Chest* 2008;133;844S.

Duration of anticoagulation	
Clinical scenario	**Duration**
1st DVT or PE due to provoked event	3 mo
1st unprovoked DVT or PE After 3 mo, reassess long-term need; if no contraindication → rx	≥3 mo Long-term rx
Recurrent DVT or PE or high-risk thrombophilia	Long-term rx
DVT or PE secondary to cancer (rx while cancer is "active")	>3–6 mo

From Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. *Lancet.* 2012;379(9828): 1835–1846.

Pregnancy Considerations (*Obstet Gynecol* 2011;118(3):717)

- Preg w/ 4–5-fold risk VTE; 0.5–2/1000 pregnancies, 80% = DVT, 20% = PE; increased risk across all trimesters, but 3rd trimester highest risk
- Thrombophilia present in 20–50% of women w/ VTE during Preg
- **D-dimer:** Levels ↑ during Preg & w/ preeclampsia, not for use as independent screen
- *Warfarin contraindicated in Preg* (except in setting of mechanical heart valve); crosses placenta, greatest risk of teratogenicity @ 6–12 WGA; safe during lactation
- May use UFH or LMWH during Preg & lactation, use UFH after 36 w gest
- Stop anticoagulation @ onset of labor. Delay neuraxial anesthesia for 10–12 h after prophylactic dose LMWH & 24 after therapeutic dose LMWH.
- Resume UFH & LMWH usually 6–12 h after vaginal deliv or 12–24 h after C/S

PERIOPERATIVE VTE PREVENTION

VTE perioperative risk stratification	
Points	**Risk factors (Points given for each factor present)**
1	Age 41–60; minor Surg; BMI >25; swollen legs; varicose veins; Preg/postpartum; h/o recurrent SAB; OCPs/HRT; sepsis <1 mo; lung dz (ie, PNA) <1 mo; abn pulm fxn; acute MI; CHF <1 mo; h/o IBD; bed rest
2	Age 61–74; open Surg >45 min; laparoscopy >45 min; cancer; >72 h bed rest; central venous access
3	Age ≥75; h/o VTE; family h/o VTE; FVL; G20210A; lupus anticoagulant; anticardiolipin Ab; ↑ homocysteine; HIT; thrombophilia
5	Stroke <1 mo; hip/pelvis/leg fx, spinal cord injury

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Thromboprophylaxis		
Points (Risk VTE)	**Average-risk bleed**	**High-risk bleed**
0 (<0.5%)	Early ambulation	
1–2 (~1.5%)	Mechanical ppx, preferably (IPC)	
3–4 (~3%)	LDUH or LMWH or IPC	Mechanical ppx, prefer IPC
≥5 (~6%)	LDUH or LMHW + ES or IPC	IPC alone until bleeding risk gone, then add LDUH or LMWH
Cancer	LDUH or LMWH + ES or IPC + LMWH for 4 w after discharge	IPC alone until bleeding risk gone, then add LDUH or LMWH
Contraindication to heparin	Fondaparinux or low-dose ASA (160 mg) + IPC	IPC until bleeding risk gone → add ASA or fondaparinux
Dosing	LDUH = UFH 5000 U SQ q12h or q8h LMWH = Enoxaparin 40 mg SQ daily; dalteparin 5000 U SQ daily Fondaparinux = 2.5 mg SQ daily	

From *Chest* 2012;141;e227S.

THROMBOPHILIA EVALUATION

- **Coagulopathy:** Alteration in the ability of the bld to coagulate (either ↑ risk to bleed or to clot)
- **Thrombophilia:** Dz state that ↑ risk of thrombosis (Acq or hereditary)

Inherited thrombophilias					
	FVL het	**G20210A het**	**AT-III (<60% activity)**	**Pro C deficiency (<50%)**	**Pro S deficiency (<50%)**
Prevalence (%)	1–15	2–5	0.02	0.2–0.4	0.03–0.13
VTE risk (%) (annual)	0.25–0.45	0.55	0.9–1.6	0.43–0.72	0.5–1.65
VTE risk Preg (%) (no h/o VTE)	<0.3	<0.5	3–7	0.1–0.8	0.1
VTE risk Preg (%) (prior VTE)	10	>10	40	4–17	0–22
Test reliable during Preg?	Yes	Yes	Yes	Yes	No*
Test reliable w/ thrombosis?	Yes	Yes	No	No	No

*May obtain free protein S antigen.
FVL het, Factor V Leiden heterozygosity; G20210A het, Prothrombin G20210A heterozygosity;
From *Obstet Gynecol* 118(3):717; *NEJM* 2001;344:1222.

Indications for Testing

- Personal h/o VTE a/w nonrecurrent risk factor
- 1st-degree relative w/ h/o high-risk thrombophilia, or VTE at <50 yo in absence of other risk factors (*Obstet Gynecol* 2011;118(3):717)
- See antiphospholipid Ab syn for Acq thromboembolic d/o

Diagnostic Evaluation

- **FVL:** Activated prot C resistance assay, if abn → DNA analysis
- **G20210A:** PCR DNA analysis
- **AT-III:** Antithrombin activity assay
- **Prot C & prot S** deficiencies functional assays for prot C & prot S

Clinical Considerations

- No clear association btw inherited thrombophilias & fetal loss, preeclampsia, IUGR, or abruption → screening not routinely recommended in these scenarios
- Avoid estrogen-containing contraceptives in pts w/ inherited thrombophilias
- **Low-risk thrombophilias:** Factor V Leiden heterozygous; prothrombin G20210A heterozygous; prot C or prot S deficiency

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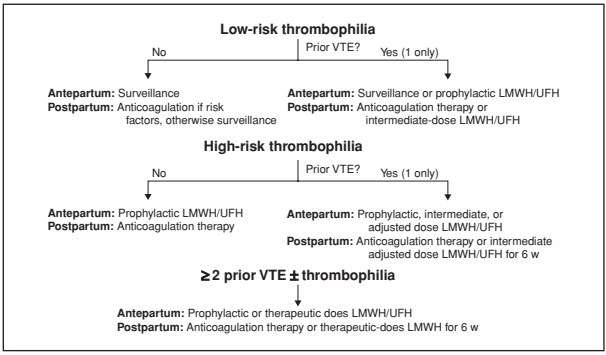
- **High-risk thrombophilias:** Antithrombin deficiency; double heterozygous for prothrombin G20210A mut & factor V Leiden; factor V Leiden homozygous or prothrombin G20210A mut homozygous

Figure 16.7 Thromboprophylaxis for pregnancy complicated by inherited thrombophilia



Anticoagulation regimens	
Prophylactic LMWH	Enoxaparin 40 mg SQ daily, dalteparin 5000 U SQ daily or tinzaparin 4500 U SQ daily. NO MONITORING needed.
Therapeutic LMWH	Enoxaparin 1 mg/kg q12h, dalteparin 200 U/kg daily or 100 U/kg q12h, tinzaparin 175 U/kg daily
Prophylactic UFH	1st trimester: UFH 5000–7500 U SQ q12h 2nd trimester: UFH 7500–10000 U SQ q12h 3rd trimester: UFH 10000 U SQ q12h, unless aPTT is elevated
Therapeutic UFH	UFH ≥10000 U SQ q12h to target aPTT (1.5–2.5 × nml range) 6 h after injection
Anticoagulation therapy	Prophylactic LMWH/UFH for 4–6 w or warfarin 4–6 w w/ target INR 2–3 (need UFH or LMWH therapy until INR is 2 for ≥2 d)

From *Obstet Gynecol* 2011;118(3):717 and *Obstet Gynecol* 2013;122:706

Monitoring Treatment

- Preg causes ↑ renal clearance which may ↑ heparin clearance & require ↑ dose
- UFH → check aPTT 6 h after injection (midinterval), goal 1.5–2.5 × nml range, long-term rx check aPTT every 1–2 w; monit for thrombocytopenia (see section on "HIT")
- LMWH → reliable dose-dependent resp; may monit rx w/ antifactor Xa level
- Monitoring req IF pregnant or CrCl <30 mL/min or obese pts
- Check antifactor Xa levels 4 h after injection of LMWH, target 0.5–1 IU/mL

COAGULOPATHIES

Signs/Symptoms

- Mucocutaneous bleeds (ie, epistaxis, gingival bleeding), menorrhagia, bleeding w/ dental extraction, petechiae, ecchymoses, postop bleeding, PPH, hemoarthrosis

Disseminated Intravascular Coagulation (DIC)

- **Pathogenesis:** Systemic activation of coagulation → thrombosis of small–mid-size vessels → depletion of coagulation factors → hemorrhage, thrombosis, multiorgan failure
- **Etiology:** Sepsis, trauma, shock, cancer, obstetric (abruption, amniotic fluid embolus, IUFD)
- **Dx:** ↑ PT/aPTT, ↓ Plt (<100 K), ↓ fibrinogen, ↑ fibrin-related marker (ie, D-dimer, fibrin degradation products), ↓ haptoglobin, schistocytes on periph smear
- **Rx:** Manage underlying condition; for bleeding or high risk of bleed, give platelet or FFP xfusion (Plt <20 K or Plt <50 K & bleeding; goal fibrinogen >100 mg/dL)

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Von Willebrand's Disease (vWD) (*Am J Obstet Gynecol* 2010;203(3):194)
- Most common bleeding d/o
- **Pathogenesis:** vWF forms bridge btw Plts/Plts & subendothelial surfaces; carrier of FVIII; deficiency → bleeding predisposition
- **Inherited:** Quantitative vs. qualitative deficiency
  Type 1: ~80% of cases; partial quantitative deficiency; autosomal dominant
  Type 2: Qualitative deficiency (4 subtypes); autosomal dominant
  Type 3: Rare, autosomal recessive; sev quantitative deficiency; high risk of bleeding
- **Acq:** ↑ clearance/inhibition of vWF (autoimmune dz), ↑ destruction of vWF (VSD, AS, pulm HTN), or medication (ie, ciprofloxacin, valproate)
- **Dx:** aPTT ↑ or nml; if ↑ aPTT get mixing study to eval for FVIII inhib; ↓ vWF:Ag (vWF assay), ↓ vWF activity (ristocetin cofactor assay), ↓ factor VIII activity
- **Rx:** Trial of desmopressin (IV or intranasal) w/ Types 1 & 2 can ↑ vWF & FVIII → recheck vWF & FVIII levels for resp; risk for HoNa
  vWF replacement: For acute bleeding, risk bleeding, or planned Surg; FVIII concentrates (also contains vWF), cryoprecipitate, recombinant vWF
  Menorrhagia: OCP, levonorgestrel-IUS, endometrial ablation, tranexamic acid
- **Preg:** vWF/FVIII levels ↑ during Preg & fall postpartum, ↑ risk delayed PPH; check FVIII levels q trimester; maintain >50 IU/dL prior to procedures, intrapartum & 2 w postpartum; avoid operative vaginal deliveries; offer genetic counseling antepartum

Hemophilias (*Lancet* 2012;379:1447)
- X-linked recessive deficiency of factors VIII (hemophilia A) or IX (hemophilia B); wide phenotypic variation in heterozygous carriers → variable propensity to bleed in carriers
- **Mild:** (5–25% nml factor activity), mod (1–5%), sev (<1%)
- **Dx:** ↑ aPTT that resolves w/ mixing study, nml PT & vWF, ↓ factor VIII or IX
- Mixing study for ↑ PT or aPTT, mix pt's plasma 1:1 w/ nml plasma & retest PT/aPTT
  PT/aPTT normalizes w/ mixing → factor deficiency; remains elevated → factor inhib
- **Rx:** Recombinant or A-purified factor replacement (factor VIII or IX); desmopressin (↑ FVIII for mild hemophilia A); antifibrinolytics, cryoprecipitate (FVIII only)

Coagulation Factor Inhibitors
- Alloimmune antibodies directed against coagulation factors (FVIII inhib most common)
- **Etiology:** Repeated factor replacement in pts w/ hemophilia, autoimmune dz (ie, SLE), postpartum, malig
- **Dx:** ↑ aPTT (remains prolonged after mixing study; Bethesda coagulation assay titer)
- **Rx:** Acute bleed – FVIII concentrates for low titer; recombinant FVIIa or activated prothrombin complex for high titer; eliminating inhib – prednisone, rituximab, cyclophosphamide, plasma exchange

ANTIPHOSPHOLIPID ANTIBODY SYNDROME (APS)

Criteria for diagnosis of antiphospholipid antibody syndrome

APS present if one ≥1 clinical *AND* ≥1 laboratory criteria are met

Clinical criteria	Laboratory criteria
Vascular thrombosis: ≥1 arterial, venous, or small vessel thrombosis in *ANY* organ ***Preg morbidity:*** ≥1 unexplained deaths of morphologically nml fetus (U/S or exam) at ≥10 w OR ≥1 premature births of morphologically nml neonat at ≤34 w due to (i) sev preeclampsia or eclampsia or (ii) placenta insufficiency OR ≥3 unexplained *consecutive* SABs <10 w	LA: Present in plasma on 2 tests ≥12 w apart* aCL: IgG &/or IgM in serum or plasma (>40 mcg/mL [ie, >99th %ile]) on 2 tests ≥12 w apart *Anti-β2 glycoprotein-I Ab:* IgG &/or IgM in serum or plasma (>99th %ile) on 2 tests ≥12 w apart

*Patient cannot be anticoagulated during testing.

From Miyakis S, Lockshin M D, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost.* 2006;4:295–306.

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Epidemiology
- 40% of SLE pts have APLA. Of these, 40% w/ h/o thrombosis
- Antiphospholipid Abs present in 10–15% of pts w/ RPL

Pathophysiology
- Clinical manifestations likely result from interference w/ phospholipid-dependent steps of the coagulation pathway

Clinical Manifestations
- Arterial/venous thrombosis, thrombocytopenia (40–50%), nephropathy, hemolytic anemia, skin (livedo reticularis/ulcers), stroke/TIA/multi-infarct dementia, cardiac valvular dz
- **Pregnancy-specific:** ↑ risk thrombosis (up to 25% w/o rx), IUGR (15–30%), IUFD, sev preeclampsia/eclampsia, recurrent Preg loss, preterm deliv
- **Catastrophic APS:** Requires (1) involvement of ≥3 organs, (2) dev in <1 w, (3) histopathology of small vessel occlusion, (4) presence of aPa; up to 50% mortality

Screening/Diagnosis
- **Indications:** Prior unexplained or pregnancy-associated arterial/venous thromboembolism, h/o 1 fetal loss, or ≥3 (ACOG) or ≥2 (ASRM) consecutive embryonic losses, unexplained prolonged aPTT (see "Recurrent pregnancy loss workup")
- Detection not poss if pt on UFH, & difficult w/ LMHW or Coumadin
- Preg c/b APS → consider serial US assessment in 3rd trimester

Management of APS

Clinical scenario	Rec
Venous thrombosis	Indefinite anticoagulation w/ INR 2–3 (heparin if pregnant)
Arterial thrombosis	Indefinite anticoagulation w/ INR 3–4
SLE + LA	Hydroxychloroquine ± 81 mg daily ASA
APS + RPL (no prev thrombosis) + Preg	81 mg daily ASA ± UFH (5000–7500 IU SQ q12h) or prophylactic LMWH
APS + Preg + thrombosis	81 mg daily ASA + therapeutic UFH/LMWH
APS + h/o fetal death or prior PTD <34 w	If deliv due to sev preeclampsia or placenta insufficiency 81 mg daily ASA + heparin 7500–10000 U SQ q12h 1st trimester; 10000 U SQ 2nd & 3rd trimesters
Antiphospholipid Ab	Strict control of vascular risk factors (eg, smoking cessation)
Contraceptive counseling	Avoid estrogen-containing contraceptives
Surg	Adequate thromboprophylaxis

From Ruiz-Irastorza G, Crowther M, Branch W, et al. Antiphospholipid syndrome. *Lancet.* 2010;376(9751):1498–1509. ISSN 0140-6736, http://dx.doi.org/10.1016/S0140-6736(10)60709-X.

ALLOIMMUNIZATION

Definition, Etiology, Epidemiology
- Mat antibodies to any fetal bld group factor inherited from father
- RhD Ag most commonly implicated; minor antigens include C, c, E, e, Kell
- Mat exposure to paternal Ag on fetal RBC → Ab formation → IgG crosses placenta & directs immune-mediated destruction of fetal RBCs
- 0.1 mL fetal bld may result in mat Ab formation; 2nd exposure → anamnestic immune resp
- 6.8/1000 live births affected by alloimmunization; 10% prior to routine testing/prevention
- Minor antigens present in ~2% of pregnancies

Clinical Manifestations
- Positive Ab screen on bld typing

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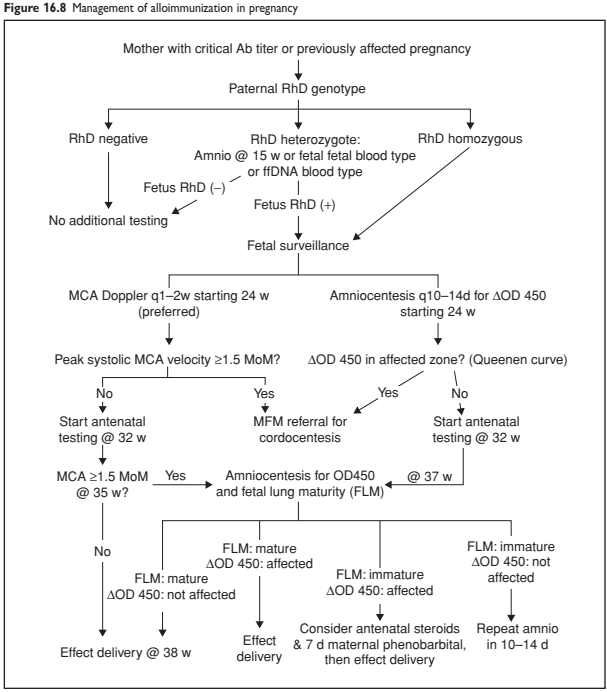
- Fetal anemia → hydrops fetalis (≥2 of the following: Ascites, pleural effusion, pericardial effusion, skin edema, polyhydramnios)
- Fetal complications (death, hemolytic dz of newborn)

Screening/Diagnosis (see also Chap. 11)

- **1st OB visit:** Mat bld type & Ab screen; consider rpt @ 28 w if RhD neg
- If mat RhD neg & paternity known → obtain paternal bld type
- Anti-RhD Ab (+) → indirect Coombs; *Critical titer typically 1:8–1:32* (lab dependent)
- **Prior affected Preg:** ↑ risk fetal anemia; Ab titers do not correlate w/ severity
- **FMH testing:** Rosette – qualitative, K-B – quantitative. If rosette + → K-B used to determine dose of anti-RhD Ig.
- **cfDNA:** Fetal DNA in mat bld used to determine fetal RhD status
- **RhD genotyping:** Determines if RhD Ag gene present on 1 (heterozygote) or both (homozygote) chromosomes
- **MCA Dopplers:** Records PSV of MCA; PSV >1.5 MoMs for GA predictive of mod–sev fetal anemia

Figure 16.8 Management of alloimmunization in pregnancy



(From Moise KJ Jr. Management of rhesus alloimmunization in pregnancy. *Obstet Gynecol.* 2008;112(1):164–176. doi:10.1097/AOG.0b013e31817d453c)

Prophylaxis/Treatment

- Anti-RhD Ig → 300 mcg neutralizes 30 mL whole bld (15 mL fetal RBCs) after FMH
- 50 mcg if <12 w gest; human serum-derived product; effect up to 12 w; max dose 1500 mcg/24 h; give w/i 72 h of indication for *prevention* of alloimmunization
- Weak RhD pos (D^u) → treat as RhD pos, ppx not indicated
- Rx → deliv; intrauterine bld xfusion if remote from term

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Indications for anti-RhD Ig in RhD (–)/antibody (–) patient		
Postdelivery (baby RhD +)	24–28 w gest	2nd/3rd trimester bleeding
Ectopic Preg	Amniocentesis	Chorionic villus sampling
Trauma	Threatened abortion	Cordocentesis
External cephalic version	IUFD	Molar gest

Minor Antigens (Ag) (*Obstet Gynecol* 2006;108(2):457)

- Minor antigens present in ~2% of pregnancies
- Many may case RBC destruction; no prophylactic rx available; mgmt of sensitization is Ab dependent, but typically mirrors RhD
- Lewis & I most common → do not cause erythroblastosis fetalis
- Anti-Kell Ab → may cause sev anemia, follow w/ MCA Dopplers, titers unreliable
- Anti-RhD Ig indicated in RhD neg pts w/ minor antigens but no RhD antibodies

BLOOD PRODUCTS FOR HEMORRHAGE AND CRITICAL CARE

Blood products	
pRBCs (240 mL)	Contains RBCs, WBCs, plasma; ↑ Hct 3% & ↑ Hb 1 g/dL Critically ill pts → Hb goal 7–9 g/dL; consider Hb 10–12 g/dL if coronary ischemia (*NEJM* 1999;340:409; 2001;345:1230)
Plts	Collection: Apheresis – single donor (predom method) Whole bld – multi donors. Contain: Plts, plasma, WBC/RBC. 6 U Plt (whole bld) = 1 U Plt (apheresis) → ↑ Plt count by 25–30 K Ind: Plt <10000/μL; Plt <20000/μL w/ bleeding risk or infxn; Plt <50000/μL w/ active bleed or preop; ABO match not essent Contraindication: HIT, HELLP, TTP–HUS *Refrac xfusion:* Plt ↑ <5000/μL; DIC, sepsis, splenomegaly, alloimmunization. Serial CBCs → if refrac, give ABO matched Plts & screen plasma for HLA Abs. Consider HLA-matched Plts.
FFP (250 mL)	Contains all coagulation factors; ↑ fibrinogen 10 mg/dL Ind: (1) Fibrinogen <100 mg/dL, (2) INR >1.6 preop, (3) bleeding due to factor deficiency → inherited (ie, Factor XI deficiency) or Acq dz (ie, DIC, TTP–HUS, liver dz, warfarin tox)
Cryoprecipitate (10–20 mL)	Contains fibrinogen, Factors VIII & XIII, vWF; ↑ fibrinogen 10 mg/dL Bleeding in factor deficiency (vWD or factor XIII) or fibrinogen <100 mg/dL
Leukoreduced	WBCs removed (>99%) from pRBCs; ↓ risk febrile nonhemolytic rxn, alloimmunization & infxn (esp CMV); "univ leukoreduction" at many centers, Ind: Prior xfusion rxn, frequent xfusions, risk for CMV infxn, bypass Surg
Irradiated	Destroys donor lymphocytes in pRBCs; reduces risk xfusion assoc GVHD; Ind: Immunodeficiency (ie, BMT, fetal/neonat xfusion, SCID, AIDS)
CMV negative	From CMV seronegative negative donors; use for xfusion of CMV seronegativity in Preg or immunodeficiency
Whole bld	Contains all bld components; use limited, use in neonat xfusion for hemolytic dz newborn, cardiac Surg, ECMO
Factor VIII	Human or recombinant; for bleeding a/w hemophilia A Preop → min Surg: 15–25 IU/kg bolus, then 20–25 IU/kg q8–12h Major Surg: 50 IU/kg until factor VIII level 100% then PRN 10–14 d
Autologous donation	↓ risk infxn or xfusion rxn for elective procedures; need Hb >11 g/dL before donation; safe in Preg, but generally reserved for pts w/ rare Abs

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Transfusion complications (# per unit transfused)	
xfusion reactions	
For *ALL* reactions, stop xfusion & send remaining bld product to bld bank	
Febrile nonhemolytic (1:100)	S/S: Fever/rigors 0–6 h after xfusion (↑ 1°C w/i 2 h)
	Cause: Abs to donor WBCs; dx: *r/o infxn & hemolysis*
	Rx: Acetaminophen ± meperidine 25–50 mg IV/IM
Acute hemolytic (<1:250000)	S/S: Fever, ↓ BP, oliguria, flank/chest pain, DIC, may be fatal
	Cause: ABO incomp
	Rx: Maintain UOP w/ IVF & diuretics ± pressors
Delayed hemolytic (1:1000)	S/S: Same as acute (less sev); 5–7 d after xfusion
	Rx: Typically none req; follow Hct, Cr, LFTs, & coags
Allergic (1:100)	S/S: Mild – urticaria; sev – airway compromise, ↓↓ BP
	Rx: Mild: Antihistamines; sev: Epi ± glucocorticoids
TRALI (1 per 5000)	S/S: Dyspnea, fever, hypoxia, pulm edema, HoTN
	Rx: Supportive respiratory care ± ICU admission; intubation
Infections	
CMV: ~1:100 (leukocyte reduced)	HIV (1:1800000)
Hepatitis B (1:220000)	Hepatitis C (1:1600000)
Bacteria (1:500000 per U pRBC; 1:12000/U Plt)	
TRALI	

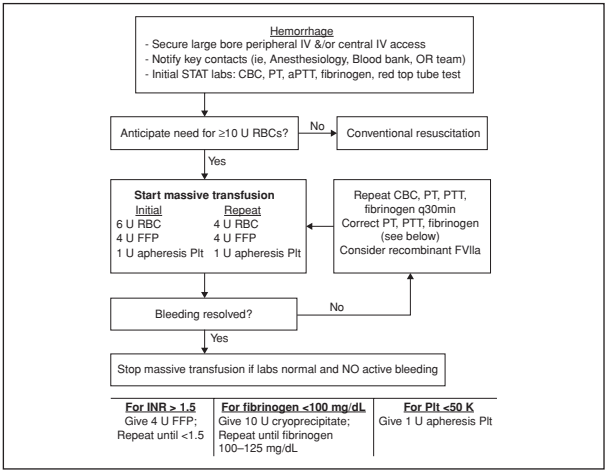
From Busch MP, Kleinman SH, Nemo GJ. Current and emerging infectious risks of blood transfusions. *JAMA*. 2003;289(8):959–962.

Massive Transfusion (*Transfusion* 2007;47(9):1564; *Clin Obstet Gynecol* 2010;53(1):196)

- **Red top tube test:** 5 mL bld in nonheparinized tube; nml = clot in 8–10 min; lack of clot or partial dissolution in 8–10 min is a/w fibrinogen <150 mg/dL
- Recombinant FVIIa → reserve for bleeding refrac to intervention (ie, after 10–12 U RBC, 6–12 U FFP, & 2–3 U Plts); ↑ risk thrombosis; FDA approved rx for hemophilia A & B
- Core temp <30°C → ventricular arrhythmias, use bld warmer if ≥3 U pRBCs or cold RBCs/plasma infused @ >100 mL/min for 30 min to prevent hypothermia
- Periodic eval for ↓ Ca^{++} & ↑ K^{+}; risk citrate tox (↓ cardiac output/↓ SVR, met alkalosis)

See also Chap. 11 for OB PPH.

Figure 16.9 Massive transfusion protocol



(From *Transfusion*. 2007;47(9):1564–1572 and *Clin Obstet Gynecol*. 2010;53(1):196–208)

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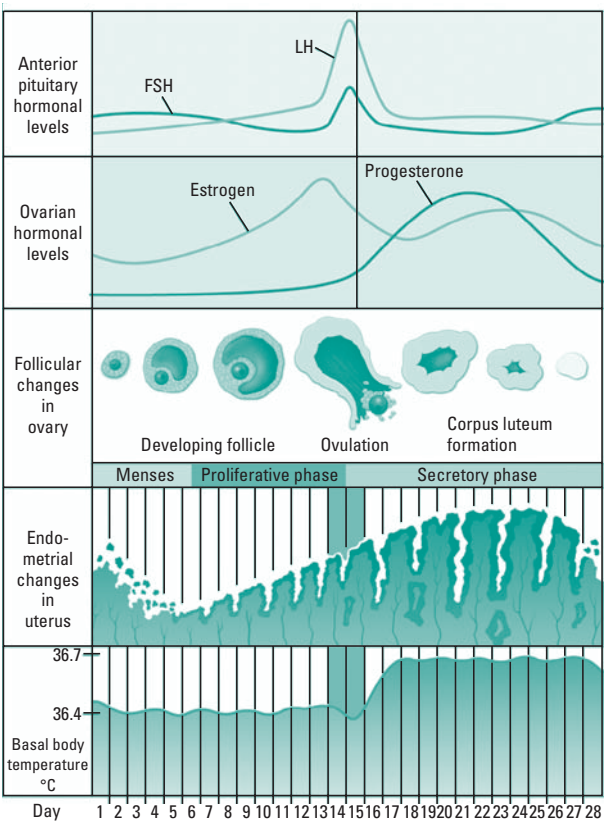
The Menstrual Cycle

- **Mean age of menarche:** 12.4 y. Mean age of menopause: 51 y.
- 1st day of vaginal bleeding = day 1 of cycle; mean duration of bleeding is 4 ± 2 d; avg bld loss of 35 mL. Mean cycle length 21–34 d (*Clin Obstet Gynaecol* 2010;2:157)
- **Follicular phase:** Lasts 10–14 d, variable in duration, determines menstrual cycle length
- **Ovulation:** Estrogen reaches very high levels (around day 14) → LH surge → dominant follicle rupture/oocyte release. Follicle remnant → corpus luteum which secretes progesterone & maintains the endometrial lining (*Am J Hum Biol* 2001;4:465). If fertilization occurs, the trophoblast cells synthesize hCG to maintain the corpus luteum.
- **Luteal phase:** Lasts 12–15 d, constant in duration. In the absence of Preg, the corpus luteum regresses → progesterone levels drop → uterine lining is shed & marks the beginning of the next period.

Figure 17.1 Menstrual cycle and hormones



(From Medical-Surgical Nursing Made Incredibly Easy! 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2007)

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Hormones of Pregnancy

- **hCG** is secreted by placental trophoblast. Detected in the mother's bld 8 d after conception. Maintains corpus luteum progesterone production. Structurally similar to LH, FSH, & TSH (same alpha-subunit). Doubles q48h early Preg. Max 8–10 w, ~100000 mIU/mL → decline at 10–12 w → nadir at 20 w.
- **hPL** is produced by syncytiotrophoblasts. Detected at 2–3 w after fertilization. Levels rise steadily until 34–36 w to a peak 5–10 μg/mL. Effects include **mat lipolysis** → ↑ circulating free fatty acids to provide a source of energy for mother & fetus; **anti-insulin action** → increased mat insulin levels → increased prot synthesis; **angiogenic action** → fetal vasculature formation
- **Progesterone** is mainly produced by the ovary until 6–7 w gest when the placenta begins to produce. Maintains endometrial lining in early Preg & uterine quiescence. Production ~250–600 mg/d (prepregnancy 0.1–40 mg/d).
- **Relaxin** is secreted by the corpus luteum → uterine relaxation, systemic vasodilation, & ↑ cardiac output. Serum concentrations peak at 1 ng/mL at 12–13 w → fall to 0.5 ng/mL for the remainder of the Preg (*Am J Physiol Regul Integr Comp Physiol* 2011:R267).

TYPE I DIABETES MELLITUS

Definition and Epidemiology (*Diabetes Care* 2012;35(suppl 1):S64)

- Gluc intolerance due to insulin insufficiency. Often caused by cell-mediated autoimmune Pancr β-cell destruction. Only about 5% of all diabetes.
- Incid increasing 2–5%. Prevalence 1 in 300 by age 18 (*Endocrinol Metab Clin North Am* 2010;3:481)
- A/w other autoimmune diseases (eg, Graves, Hashimoto, Addison dz) (*Diabet Med* 2011;28(8):896)

Etiology and Pathophysiology

- **Genetic:** 95% have either HLA-DR3 or HLA-DR4. Also positive for anti-GAD, anti-islet cell, & anti-insulin Abs.
- **Environmental:** Congen rubella infxn, enterovirus, coxsackievirus B, CMV, adenovirus, & mumps (*Diabetes Care* 2012(suppl 1):S64)
- Lymphocytic infiltration, β-cell ↓ → insulin deficiency (*Diabetes Metab Res Rev* 2011;8:778)
- Hyperglycemia at ~80–90% β-cell loss

Clinical Manifestations

- Polyuria, polydipsia, polyphagia w/ weight loss, fatigue, weakness, muscle cramps, blurred vision, nausea, abdominal pain, changes in bowel mvmt
- Most present w/ acute sx of diabetes & markedly elevated bld gluc levels

Diagnostic Workup

- Screen high-risk individuals (h/o transient hyperglycemia or relative w/ type I DM)
- Islet auto Abs ↑ risk of developing type I DM. Criteria for DM same for type I or II (below).

Diabetic screening in the nonpregnant patient

	Fasting glucose level (mg/dL)	Glucose level 2 h after 75 g load (mg/dL)	Management
Normal	<110	<140	Annual screening
Carbohydrate intolerant	110–125	140–199	Diet and exercise modification; annual screening
Diabetic	≥126	≥200	Treatment as indicated

The fasting plasma glucose test is preferred. An initial abnormal value must be confirmed on a different day, by repeat fasting glucose level, plasma glucose level after glucose load, or random plasma glucose level if symptoms are present.
From Position statement: Standards in medical care in diabetes. *Diabetes Care* 2009;32(S1):S13–S61.

Treatment and Medications (*JAMA* 2003;289(17):2254)

- Lifelong insulin therapy is started w/ either MDI therapy, or CSII. See insulin types, below.
- Gluc measurements can be done either preprandial only, or pre- & postprandial (shows greater improv in glycemic control) (*Clin Med* 2011;2:154)

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- MDI nonphysiologic regimens – do not mimic nml insulin secretion
  - Once daily long-acting insulin (at bedtime)
  - Twice daily intermediate-acting insulin (breakfast & dinner time)
- MDI physiologic regimens – attempt to mimic nml insulin secretion
  - Twice daily intermediate-acting insulin w/ short-acting insulin (breakfast & dinner time)
  - Once daily long-acting insulin (at bedtime) w/ mealtime rapid-acting insulin
  - Twice daily intermediate-acting insulin (breakfast & bedtime) w/ rapid acting insulin w/ each meal
  - Premixed insulin (70% NPH/30% regular) given twice daily
- CSII – Rapid-acting insulin preparation administered through a catheter that is inserted into the SQ tissue. There is a basal insulin infusion rate (1 U/h) w/ patient-directed boluses given before meals.
- **Nonpregnant goal:** HgA1c <7%, fasting gluc 70–130 mg/dL, postprandial gluc <180 mg/dL

Insulin types and pharmacodynamics

	Onset (min)	Peak (h)	Duration (h)
Rapid-acting			
Lispro (humalog)	15–30	0.5–2.5	3–6.5
Aspart (NovoLog)	10–20	1–3	3–5
Glulisine (Apidra)	10–15	1–1.5	3–5
Short-acting			
Regular (Humulin R, Novolin R)	30–60	1–5	6–10
Intermediate-acting			
Isophane insulin (NPH, Humulin N, Novolin N)	60–120	6–14	16–24
Insulin zinc (Lente, Humulin L, Novolin L)	120–240	4–12	12–18
Long-acting			
Glargine (Lantus)	66	—	Up to 24
Detemir (Levemir)	48–120	—	Up to 24
Insulin zinc extended (Ultralente, Humulin U)	360–600	10–16	18–24
Premixed			
BiAsp 70/30 (BIAsp 30)	10–20	1–4	Up to 24
Lispro 75/25 (Humalog Mix 75/25)	15–30	1–6.5	Up to 24
70% NPH/30% regular (Humulin 70/30)	30–60	2–16	Up to 18–24

From *JAMA*. 2003;289:2254 and *Int J Clin Pract*. 2010;64:305.

DIABETIC KETOACIDOSIS (DKA)

Definition

- An acute life-threatening complication due to insulin deficiency, w/ hyperglycemia, dehyd, & acidosis. Typically due to insulin noncompliance, acute illness/infxn, drugs, or new onset DM.
- Occurs in 5–10% of all pregnancies w/ DM. Can develop more rapidly & at less sev levels of hyperglycemia than in nonpregnant pts.

Pathophysiology *(Clin Med* 2011;2:154)

- Insulin deficiency → ↑ glucagon → ↑ hepatic gluconeogenesis & ↑ glycogenolysis → hyperglycemia → inability to use gluc → ↑ lipolysis → free fatty acids metabolized by liver (ketogenesis) as an alternative energy source → large quantities of ketones → acidosis

Clinical Manifestation *(Hormones* 2011;4:250)

- Nausea, vomiting, abdominal pain, confusion, Kussmaul respirations (deep labored breathing seen in metabolic acidosis).

Diagnostic Workup

- Bld gluc, bld gas (pH), Chemistry (bicarbonate, anion gap), serum ketones

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Diagnostic criteria for DKA			
	Mild	**Mod**	**Sev**
Plasma gluc (mg/dL)	>250	>250	>250
Arterial pH	7.25–7.30	7–7.24	<7
Serum bicarbonate (mEq/L)	15–18	10–15	<10
Serum ketone	Positive	Positive	Positive
Anion gap	>10	>12	>12
Mental status	Alert	Alert/drowsy	Stupor/coma

From Kitabchi AE, Nyenwe EA. Hyperglycemic crises in diabetes mellitus: Diabetic ketoacidosis and hyperglycemic hyperosmolar state. *Endocrinol Metab Clin North Am.* 2006;35(4):725–751, viii.

Treatment

- Treat the underlying cause (eg, infxn). Inpatient admission.
- **Fluids:** 1 L NS 1st hour, then 250–500 mL/h. When gluc <250 mg/dL → change to 5% dextrose in ½ NS, and continue insulin till ketonemia resolved.
- **Insulin:** 0.1–0.4 U/kg IV bolus → 0.1 U/kg/h continuous infusion (or 2–10 U/h). Try for 50–70 mg/dL/h correction of serum gluc, or about 25% in 1st 2 h. When plasma gluc is ~200 mg/dL → ↓ insulin to 0.05 U/kg/h (or about 1–2 U/h) until urine ketones cleared. Adjust till gluc ~150–200 mg/dL. When pt can tolerate food, start her usual SQ insulin injection regimen.
- **Potassium:** K >5 mEq/L, no additional req. (Insulin drives K into cells w/ gluc → ↓ serum K.)
  K 4–5 mEq/L → add 20 mEq/L to each liter of replacement fluid
  K 3–4 mEq/L → add 40 mEq/L to each liter of replacement fluid
  K <3 mEq/L → hold insulin, give 10–20 mEq/h until K >3.3, then 40 mEq/L in IVF
- **Bicarbonate:** pH <6.9 → give 100 mEq & 20 mEq of KCl in 400 mL of H_2O over 2 h
  pH <7 or bicarbonate <5 mEq → give 50 mEq in 200 mL of water over 1 h until ph ↑ to >7
  Do not give bicarbonate for pH >7
- **Phosphate:** If <1 mg/dL → give 20–30 mmol potassium phosphate over 24 h
- **Calcium:** Monit serum Ca level & replete prn
- **Fetal HR monitoring** for >24 w gest. Fetal loss 9–85% depending on severity of DKA.

TYPE II DIABETES MELLITUS

Definition and Epidemiology *(Diabetes Care* 2012;35(suppl 1):S64)

- Insulin resistance ± inadeq insulin production (ie, inadeq production for the sens of the target tissues). ~26 million people w/ DM, ~79 million prediabetes, & 1.9 million new cases of DM diagnosed in 2010 (National Diabetes Fact Sheet, www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf)

Pathophysiology

- Periph insulin resistance → ↑ insulin secretion → Pancr failure → defective insulin secretion in resp to ↑ gluc → increased liver gluconeogenesis → hyperglycemia

Clinical Manifestation

- **Classical sx:** Polyuria, polydypsia, polyphagia, fatigue, weakness, muscle cramps, blurred vision, nausea, abdominal pain, changes in bowel mvmt. Most are asx.

Diagnostic Workup

- Criteria for diagnosing T2DM outside of Preg: Hgb A1c ≥6.5%, fasting gluc ≥126 mg/dL, 2-h 75 g OGTT plasma gluc ≥200 mg/dL, or a random plasma gluc ≥200 mg/dL in a pt w/ classic sx or in hyperglycemic crisis

Treatment and Medications

- Goal of rx is to achieve & maintain HbA1c levels of <7%. See also for Preg, below.
- **At dx:** Lifestyle changes (weight loss, exercise) may ↓ HbA1c 1–2%
- Bariatric Surg consideration for adults w/ T2DM & BMI >35 kg/m^2
- See appendix for oral hypoglycemic agent meds. See Ch. 1 for well-woman mgmt.

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HYPEROSMOLAR HYPERGLYCEMIC STATE

Etiology and Pathophysiology *(Emerg Med Clin North Am 2005;23:629)*

- Extreme hyperglycemia + hyperosmolality, w/o ketoacidosis
- Infxn causing about 60% of cases → physiologic stress → ↓ effectiveness of circulating insulin → ↑ counter regulatory hormones (glucagon, catecholamines, cortisol, GH) → ↑ periph resistance → gluconeogenesis → hyperglycemia → glycosuria → hypertonic osmotic diuresis (dehyd) → unable to maintain adequate fluid intake (2/2 acute illness) → sev hyperosmolality & intracellular dehyd, renal failure

Diagnostic Workup

- Plasma gluc level of ≥600 mg/dL, serum osmolality of ≥320 mOsm/kg, ↑ serum urea nitrogen (BUN): Cr ratio, pH >7.3, small ketonuria, absent to low ketonemia, bicarbonate >15 mEq/L

Treatment

- Treat the underlying cause. Mgmt very similar to DKA (above).
- 1st-line therapy is aggressive IV hydration, fluid deficit may be 8–12 L. Replace 1/2 of the fluid deficit in the 1st 12 h, & the remainder in the next 12–24 h w/ NS.
- Insulin infusion when potassium is ≥3.3 mEq/L. Regular insulin started at 0.1 U/kg/h w/ or w/o a 0.15 U/kg bolus.
- Once the serum gluc ≤300 mg/dL, D5 should be added & the insulin infusion ↓ to 0.05 U/kg/h
- If serum potassium level is <3.3 mEq/L → replete w/ KCl at a rate of up to 40 mEq/L/h until levels are above 3.3 mEq/L. 20 mEq/L KCl can then be added to each 1 L of IV fluid. Goal is to maintain nml serum K levels. Check K every 1–2 h.

DIABETES IN PREGNANCY

Epidemiology

- Pregestational diabetes in ~1% of all pregnancies, mostly type II.
- 90% of diabetes in Preg is GDM (see GDM, below)

Clinical Manifestation

- Type I usually known prior to Preg. Type II may have been unrecognized, but if gluc intolerance before 20 w, consider pregestational. Goal preconception HgA1c <6.5%. Consider hospital admission for very poor control during organogenesis.
- Fetal malformation rate in a nml Preg is 2–3% vs. 6–12% in pregnancies c/b diabetes *(Obstet Gynecol 2003;102:857)*. Rate of fetal malformations w/ Hgb A1c 7–8.9 = 5–10%; Hbg A1c 9–10.9 = 10–20%, HbgA1c >11 = >20%
- "Usual" defects include cardiac, renal, neural tube. Esp double outlet RV, truncus arteriosus, & caudal regression syn/sacral agenesis (considered pathognomonic).
- **Risks of DM in Preg:** ↑ malformations, ↑ SAB, ↑ IUGR, ↑ progression of nephropathy, retinopathy, cardiovascular dz, ↑ polyhydramnios, ↑ preeclampsia, ↑ labor dystocia & C/S deliv, ↑ fetal macrosomia, ↑ lacerations, ↑ shoulder dystocia, ↑ neonat RDS/hypoglycemia.

White classification of diabetes mellitus

Gestational class	DM existing only during Preg. Consider also unrecognized type II DM.		
A1	Diet controlled, no meds to control bld sugar		
A2	Requires medication (oral, or injected insulin) for control		
Pregestational class	**Onset age (y)**	**Duration (y)**	**Complications**
B	≥20	<10	None
C	10–19	10–19	None
D	Before 10 yo	>20	± benign retinopathy, other vascular complications
F	Any	Any	Nephropathy
H	Any	Any	Heart
R	Any	Any	Proliferative retinopathy
T	Any	Any	Renal xplant

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Screening for DM in Pregnancy

- **Univ GDM screening** std. Screen early if risk factors. Consider no screening by criteria.
- On **50 g oral gluc challenge test,** serum gluc ≥140 mg/dL identifies 80% GDM; ≥130 mg/dL identifies 90% GDM. Serum gluc ≥200 mg/dL → GDM w/o other testing. Positive screening test → 3 h fasting gluc challenge (100 g test; diagnostic table, below).
- **3-h OGTT:** Consume ≥150 g of carbohydrate per day for 3 d, then fasting. 100 g oral gluc challenge → fasting + 1-, 2-, 3-h post challenge bld gluc. 1 abn value = gluc intolerance (a/w fetal macrosomia). Dx of GDM made ≥2 abn values.
- New Endo one step Guideline differs from ACOG (*J Clin Endo Metab* 2013;98:4227)
  Universal DM testing before 13w gest, repeat if abnormal on different day to confirm.
  8–14hr Fasting gluc ≥126 mg/dL, untimed ≥200mg/dL, or HbA1C ≥6.5% = overt DM; Fasting 92-125 mg/dL = GDM
  24-28w screen if not prev dx, w/ 75g OGTT (after 8hr fast)
  Fasting gluc >126mg/dL or 2hr >200 mg/dL = overt DM;
  Fasting 92–125 mg/dL or 1hr >180 mg/dL or 2hr 153–199 mg/dL = GDM

Gestational diabetes risk assessment
Low risk
Age younger than 25 yo
Not a member of an ethnic group with increased risk for type 2 DM (Hispanic, African, Native American, South or East Asian, or Pacific Islander ancestry)
BMI <25; normal weight at birth
No h/o abnormal glucose tolerance
No h/o poor obstetric outcomes
No 1st degree relatives with DM
High risk
Severe obesity
Strong FHx of type 2 diabetes
Previous h/o GDM, impaired glucose metabolism, or glucosuria
Patients who meet all low-risk criteria and have no high-risk factors may forgo oral glucose challenge testing if appropriate.
From Metzger BE, Buchanan TA, Coustan DR, et al. Summary and Recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus. *Diabetes Care.* 2007;30(2):S251.

Criteria for diagnosis of gestational diabetes from oral glucose tolerance testing		
Time since 100-g glucose load (h)	**Modified O'Sullivan scale**	**Carpenter and Coustan scale**
Fasting	≥105	≥95
1	≥190	≥180
2	≥165	≥155
3	≥145	≥140
Values are plasma glucose levels in mg/dL.		
From O'Sullivan JB, Mahan CM. Criteria for the oral glucose tolerance test in pregnancy. *Diabetes.* 1964;13:278–285 and Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. *Am J Obstet Gynecol.* 1982;144:768–773.		

Management of DM in Pregnancy

- **GDM**
  Nutrition advice, diet/exercise, & 4×/d bld gluc testing (fasting + 1- or 2-h postprandial)
  If inadeq control → oral hypoglycemic agents (glyburide), if inadeq w/ max dose → insulin
  GDM-A1 no monitoring, no early deliv (routine induction at 41–42 or for OB indications)
  GDM-A2 antenatal testing (NST/BPP from 32–34 w) & deliver by 40 w

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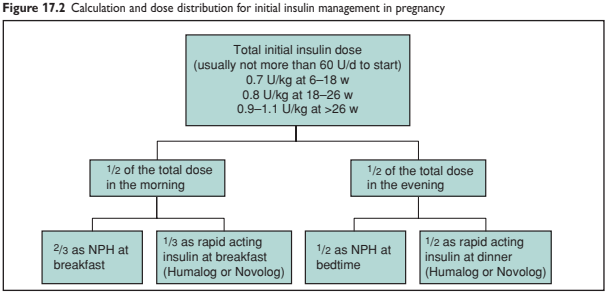
Goals for glycemic control in pregnancy	
Goal blood sugar values	
Fasting	60–90 mg/dL
Premeal	<100 mg/dL
1 h postprandial	<140 mg/dL
2 h postprandial	<120 mg/dL
Bedtime	<120 mg/dL
2–6 AM	60–90 mg/dL

From Metzger BE, et al. Summary and Recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus. *Diabetes Care*. 2007;30(2):S251.

- **Pregestational diabetes**
  Diet: 1800–2400 kcal daily, w/ 20% prot, 60% carbs, & 20% fat.
  The American Diabetes Association recommends insulin for pregnant women w/ type I or II DM. NPH & rapid-acting insulin combination used (see Table with insulin types, above). Type I DM usually ↑ insulin 50–100%. Type II DM often ↑ >200% in Preg. Consider baseline HELLP labs, thyroid testing (40% type I DM – thyroid d/o) & 24-h urine prot early Preg.
  Eye exam in 1st trimester, & baseline ECG (age >30 y or hypertensive).
  Pregestational DM obtain early sonogram, confirm viability, offer mat serum AFP for NT defects, US for anatomy & fetal echocardiography.
  1–2×/w fetal NST/AFI from 32–34 w or earlier. Serial fetal growth scans every 4–6 w to eval for IUGR or macrosomia. Deliv not later than 39–40 w, depending on gluc control in Preg.

Figure 17.2 Calculation and dose distribution for initial insulin management in pregnancy



(From Gabbe SG. Management of diabetes mellitus complicating pregnancy. *Obstet Gynecol* 2003;102(4):857)

Labor and Delivery for Diabetics

- Consider cesarean deliv for EFW >4500 g for pts w/ diabetes (>5000 g for nondiabetic)
- **Insulin mgmt during labor:** Usual intermediate insulin at bedtime. Morning dose insulin withheld. W/ active labor or gluc <70 mg/dL start D5NS IVF. Check bld gluc hourly in labor. Usually pregestational DM → IV insulin drip & titrate. Tight gluc control to avoid neonat hypoglycemia.
- Fetal lung maturity may be delayed in DM, even with reassuring FLM result.

Postpartum Management

- Usually insulin-dependent pregestational DM → resume prepregnancy regimen, or ½ of end Preg dose. GDM can stop rx, unless suspected DM 2. GDM resolves w/ deliv.
- Postpartum 75 g gluc tol test to identify nongestational DM for all GDM pts.

Postpartum glucose tolerance test			
	No DM	**Impaired glucose tolerance**	**Overt DM**
8 h fasting	<100	100–125	≥126
2 h after 75 g glucose load	<140	140–199	≥200

Values are plasma glucose levels in mg/dL.
From Metzger BE, et al. Summary and Recommendations of the Fifth International Workshop-Conference on Gestational Diabetes Mellitus. *Diabetes Care*. 2007;30(2):S251 and American Diabetes Association Standards of Medical Care in Diabetes—2010. *Diabetes Care*. 2010;33:S11–S61.

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GESTATIONAL DIABETES (GDM)

Definitions, Epidemiology, and Pathophysiology

- GDM is carbohydrate intolerance w/ onset or 1st recognition during Preg
- **Classification:** A1GDM is diet controlled; A2GDM requires pharmacologic intervention
- GDM in ~5–10% of pregnancies. 20–50% will → nongestational DM in 10 y; 30–50% → recurrent GDM.
- ↑ human placental lactogen/cortisol/progesterone/estrogen → ↓ periph insulin sens → impaired gluc resp → hyperglycemia. Screening per above, under Diabetes in Pregnancy.

Treatment and Medications

- See mgmt in Diabetes in Pregnancy, above.
- Oral hypoglycemics considered if dietary mgmt fails. Glyburide equiv to insulin for gluc control (starting dose: 1.25–2.5 mg twice daily → ↑ 2.5 mg as needed; max 10 mg BID). Insulin needs ↑ markedly btw 28 & 32 w gest *(Obstet Gynecol* 2003;102(4):857). See starting insulin schematic, above. Consider lower dose for insulin naive pt.

HYPOTHYROIDISM

Definition and Epidemiology

- Inadeq thyroid hormone to meet the requirements of periph tissues.
- **Primary hypothyroidism:** Hashimoto's thyroiditis, surgical removal, radioactive ablation, invasive fibrous thyroiditis, iodine deficiency. **Secondary hypothyroidism:** Pituitary/hypothalamic neoplasm, trauma, ischemic necrosis (Sheehan's syn), infxn.
- **Subclinical hypothyroidism:** Chronic autoimmune thyroiditis, partial thyroidectomy, radioactive iodine therapy for rx of hyperthyroidism, infiltrative disorders, drugs impairing thyroid fxn, inadeq replacement therapy for overt hypothyroidism, iodine deficiency
- 3.7% of the US pop. Females > males.

Etiology

- In women, most common cause (95%) is autoimmune (Hashimoto's thyroiditis).
- **Hashimoto's thyroiditis:** Lymphocytic thyroid infiltration → gland atrophy & fibrosis
- **Subclinical hypothyroidism:** Elevated TSH w/o overt hypothyroidism or low T_3/T_4. Early, mild thyroid failure. ~60–80% have ⊕ antithyroid peroxidase or antithyroglobulin Abs. Progression to overt hypothyroidism in women is about 4%/y. No need to treat TSH <10 mU/L & asx.

Clinical Manifestations and Diagnosis

- Weakness, dry skin, cold intolerance, hair loss, constip, weight gain, poor appetite, dyspnea, hoarse voice, menorrhagia, paresthesias, impaired hearing
- ↑ TSH, ↓ free T_4, ⊕ anti-TPO & other thyroid Abs. May also see HoNa, hypercholesterolemia, anemia, & elevated serum Cr kinase.

Treatment

- Daily levothyroxine 2 μg/kg body weight (typically 100–150 μg; start at 50–100 μg depending on severity). Adjust q4w 12.5–25 μg by TSH levels. Annual TSH levels recommended for nonpregnant.

Hypothyroidism in Pregnancy *(Lancet* 2012;379(9821):1142)

- Similar causes as nonpregnant. Also postpartum thyroiditis (autoimmune inflammation) → thyrotoxicosis → hypothyroidism. W/i 1-y postpartum.
- Mat hypothyroidism can ↑ SAB, placental abruption, preterm deliv, preeclampsia, mat HTN, postpartum hemorrhage, low birth weight, stillbirth, & ↓ intellectual & psychomotor dev of the fetus.
- Difficult to assess in early Preg: Total T_3/T_4 ↑ due to hCG cross reaction and stimulation of the TSH receptor & also ↑ TBG. In 1st trimester total T_4 ↑ & TSH ↓, w/ no real hypo or hyperthyroidism.
- ACOG does not recommend routine screening of asx pregnant pts. Test if on therapy, goiter, nodularity, h/o thyroid d/o/neck irradiation, prior infant w/ thyroid dysfxn, type I DM, FHx.
- Rx similar to nonpregnant pts. Preg may ↑ thyroid hormone requirements; monit TSH & adjust.
- Treat subclinical hypothyroid → improved obstetrical outcome, but did not modify long-term neurologic dev in the fetus. Maintain TSH <2.5 mU/L in 1st trimester & <3 mU/L thereafter.

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Thyroid function test results in pregnancy compared with nonpregnant hyperthyroid and hypothyroid conditions

Test	Normal pregnancy	Hyperthyroidism	Hypothyroidism
Thyroid-stimulating hormone (TSH)	No change	Decreased	Increased
Thyroxine-binding globulin (TBG)	Increased	No change	No change
Total T_4 (T_4)	Increased	Increased	Decreased
Free T_4 (fT_4) or free T_4 index (FTI)	No change	Increased	Decreased
Total triiodothyronine (T_3)	Increased	Increased or no change	Decreased or no change
Free T_3 (fT_3)	No change	Increased or no change	Decreased or no change
T_3 resin uptake (T_3RU)	Decreased	Increased	Decreased
Iodine uptake	Increased	Increased or no change	Decreased or no change

From American College of Obstetricians and Gynecologists. Thyroid disease in pregnancy. ACOG Practice Bulletin No. 37. *Obstet Gynecol.* 2002 (reaffirmed 2008);100:387–396 and Rashid M, Rashid MH. Obstetric management of thyroid disease. *Obstet Gynecol Surv.* 2007;62(10):680–688.

HYPERTHYROIDISM

Definition, Epidemiology, and Etiology (*Endocr Pract* 2011;17(3):456)

- Hyperthyroidism is caused by excess synthesis & secretion of thyroid hormone
- The prevalence of hyperthyroidism is 1.2% (0.5% overt & 0.7% subclinical)
- The most common causes are:
  - **Graves dz** (80%): Autoimmune TRAbs → bind TSH-R → ↑ TSH. Accounts for 95% of hyperthyroidism in Preg. ♀ 5–10× more than ♂.
  - **Thyroiditis** (10%): Painless inflammation of thyroid due to viral infxn or postpartum inflammation → release of preformed thyroid hormone. May resolve and → hypothyroid.
  - **Toxic adenomas:** Single or multinodular, autonomously functioning, secrete thyroid hormone. More common in setting of iodine deficiency.
  - **Other:** Amiodarone, struma ovarii (ovarian dermoid), TSH secreting pituitary adenoma, gestational trophoblastic dz, follicular cell carcinoma, iodine-induced, thyrotoxicosis factitia.

Clinical Manifestation and Physical Exam (*Lancet* 2003;362(9382):459)

- Nervousness, anxiety, heat intolerance, tremor, palps, weight loss, oligomenorrhea, tachy, exophthalmos, thyromegaly. Thyrotoxicosis in 1 of 500 pregnancies → ↑ preeclampsia, thyroid storm, CHF, IUGR, preterm deliv, stillbirth.
- Tachy (&/or arrhythmias), HTN, warm/moist/smooth skin, lid lag, goiter, tremors
- **Thyroid storm:** Medical emergency, extreme hypermetabolism → seizures, arrhythmia, stupor, shock, coma. Do not delay therapy while FT_4, FT_3, TSH pending.

Diagnostic Workup (*Endocr Pract* 2011;17(3):456)

- **Graves dz:** ↓ TSH, ↑ FT_4, ↑ FT_3, ±antithyroid peroxidase Ab (TPO), ⊕TSI, ⊕TRAb, other antithyroid Abs poss.
  When clinical presentation is not diagnostic, RAIU is performed (*J Fam Pract* 2011; 60(7):388): Diffuse, homogeneous = Graves dz; diffuse, heterogeneous = toxic multinodular goiter; focal = adenoma; no uptake = thyroiditis. IgG crosses placenta → fetal Graves
- **Subclinical hyperthyroidism:** ↓ TSH; nml FT_4 & FT_3. Asx.

Treatment (*Endocr Pract* 2011;17(3):456)

- **Symptom mgmt:** β-blocker to control tachy (propranolol also blocks T_4 conversion to T_3)
- **ATDs:** PTU is 1st-line drug during the 1st trimester; blocks both iodide organification & periph $T_4 \rightarrow T_3$ conversion; monit liver fxn. Methimazole okay in 2nd trimester. Titrate meds to fT_4 q2–4w.

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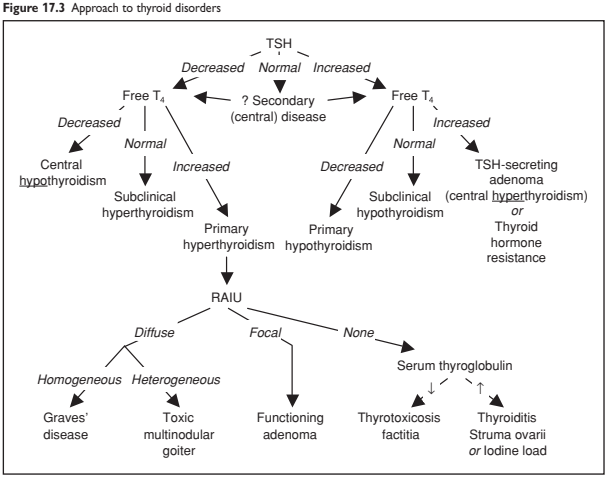
- **RAI:** Started for pts w/ contraindications to ATD use. Pretreat w/ methimazole prior to RAI to prevent worsening of hyperthyroidism. Contraindicated in Preg.
- **Surg:** For symptomatic compression, large goiter, low uptake, documented or suspected malig
- **Thyroid storm:** PTU 600–800 mg oral load, then 150–200 mg q4–6h. + 2–5 drops saturated potassium iodide solution q8h. Also, dexamethasone 2 mg IV or IM q6h for 4 doses, propranolol 20–80 mg PO q4–6h, & Phenobarb 30–60 mg PO q6–8h PRN restlessness.

Figure 17.3 Approach to thyroid disorders



(From Sabatine MS. *Pocket Medicine*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011)

ADRENAL DISORDERS

Adrenal Hormones

- **Adrenal cortex: Zona glomerulosa** = Mineralocort (aldosterone) → conserve sodium in nephron distal tubule & collecting duct → maintain BP; **zona fasciculata** = glucocorticoids (deoxycorticosterone, corticosterone, & cortisol) → ↑ bld sugar, suppress immune system, regulate metabolism; **zona reticularis** = androgens (DHEA, DHEA-S, & androstenedione) → estrogen precursors, other.
- **Adrenal medulla** = catecholamines (epinephrine, norepinephrine, dopamine), in resp to autonomic (sympathetic) nervous stimulation.

Cushing's Syndrome

- **Etiology:** Cushing's dz (65–70%), ectopic ACTH secretion by nonpituitary tumors (10–15%), adrenocortical tumors (18–20%), ectopic CRH secretion by nonhypothalamic tumors causing pituitary hypersecretion of ACTH (<1%).

Disorders of cortisol production		
	↑ cortisol	**↓ cortisol**
↑ ACTH	*Secondary hypercortisolism* Cushing's dz (cortisol excess)	*Primary hypocortisolism* Addison's dz
↓ ACTH	*Primary hypercortisolism* Cushing's syn (pituitary ACTH overproduction)	*Secondary hypocortisolism* Sheehan's syn

- **Clinical manifestations:** Progressive central obesity w/ sparing of extremities, moon facies, buffalo hump, skin striae, easy bruising, hyperpigmentation (if ↑ ACTH), fungal infections, gluc intolerance, HTN, osteoporosis, hypokalemia, psychosis. ♀ →

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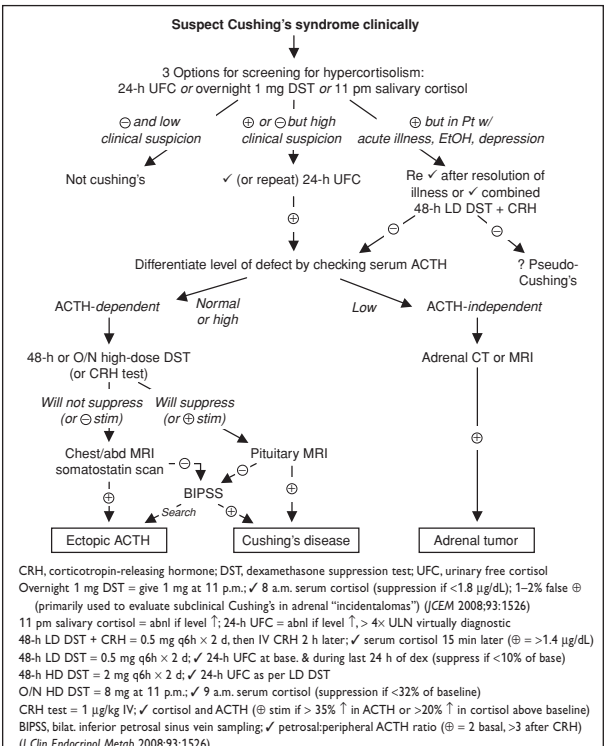
menstrual irregularities (33% amenorrhea, 31% oligomenorrhea, 36% other) (*J Clin Endocrinol Metab* 1998;83:3083). Androgen excess → adrenal glands are the major source of androgens in ♀ → hirsutism, thinning scalp hair, oily skin, increased libido.

Figure 17.4 Approach to suspected Cushing's syndrome



CRH, corticotropin-releasing hormone; DST, dexamethasone suppression test; UFC, urinary free cortisol
Overnight 1 mg DST = give 1 mg at 11 p.m.; ✓ 8 a.m. serum cortisol (suppression if <1.8 μg/dL); 1–2% false ⊕ (primarily used to evaluate subclinical Cushing's in adrenal "incidentalomas") (*JCEM* 2008;93:1526)
11 pm salivary cortisol = abnl if level ↑; 24-h UFC = abnl if level ↑, > 4× ULN virtually diagnostic
48-h LD DST + CRH = 0.5 mg q6h × 2 d, then IV CRH 2 h later; ✓ serum cortisol 15 min later (⊕ = >1.4 μg/dL)
48-h LD DST = 0.5 mg q6h × 2 d; ✓ 24-h UFC at base. & during last 24 h of dex (suppress if <10% of base)
48-h HD DST = 2 mg q6h × 2 d; ✓ 24-h UFC as per LD DST
O/N HD DST = 8 mg at 11 p.m.; ✓ 9 a.m. serum cortisol (suppression if <32% of baseline)
CRH test = 1 μg/kg IV; ✓ cortisol and ACTH (⊕ stim if > 35% ↑ in ACTH or >20% ↑ in cortisol above baseline)
BIPSS, bilat. inferior petrosal sinus vein sampling; ✓ petrosal:peripheral ACTH ratio (⊕ = 2 basal, >3 after CRH)
(*J Clin Endocrinol Metab* 2008;93:1526)

(From Findling JW, Raff H. Screening and diagnosis of Cushing's syndrome. *Endocrinol Metab Clin North Am.* 2005;34(2):385–402, ix–x)

- **Rx:** Surgical resxn of pituitary adenoma, adrenal tumor or ectopic ACTH-secreting tumor is gold std. Secondary options = pituitary XRT, bilateral adrenalectomy. Inhibitors for hypercortisolism if needed (ketoconazole, metyrapone, etomidate)

Adrenal Insufficiency

- **Definition:** Primary = adrenocortical insufficiency (Addison's dz). Secondary = ACTH ↓.
- **Etiologies:** Autoimmune (most common in industrialized nations; isolated vs. polyglandular autoimmune syn); infectious (most common in developing nations; TB, CMV, histoplasmosis); vascular (hemorrhage, thrombosis, trauma); drugs (ketoconazole, rifampin, anticonvulsants); deposition dz (hemochromatosis, amyloid, sarcoid); metastatic dz.
  Primary or secondary hypopituitarism; rapidly terminated glucocorticoid therapy (≥2 w at ≥10 mg/d) → HPA suppression; Megestrol (progest w/ glucocorticoid activity)
- **Clinical manifestations:** Fatigue, weakness, anorexia, orthostatic HoTN, nausea, vomiting, HoNa, hyperK, hyperpigmentation. ± manifestations of hypopituitarism. Consider AI w/ sev hyperemesis gravidarum.
- **Adrenal crisis:** All primary sx + sev abdominal or leg pain, syncope, dehyd, psychosis, seizures, lethargy, fever, hypoglycemia.

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- **Dx:**
  Early am cortisol <3 μg/dL = adrenal insufficiency. ≥18–20 μg/dL nml/ruled out.
  High-dose ACTH test: 1st-line test for most pts. Check serum cortisol → inject 250 μg cosyntropin (synthetic ACTH) → check cortisol at 60 min. Tests cortisol release.
  Low-dose (1 μg) ACTH test: Check serum cortisol → inject 1 μg cosyntropin → check cortisol at 30 min. Used if recent onset ACTH deficiency suspected.
  Serum ACTH: ↑ in primary, low–normal or ↓ in secondary
  Imaging if needed for pituitary or adrenal eval (MRI or CT).
- **Rx:**
  Acute adrenal insufficiency
  Rapid IV fluid hydration w/ isotonic saline
  4 mg dexamethasone IV q12h (dexamethasone does not interfere w/ serum cortisol level)
  Chronic adrenal insufficiency
  Hydrocortisone 20–30 mg PO daily in BID or TID divided doses (eg, 10/5/2.5 mg), or prednisone 2.5–7.5 mg PO daily. ↑ dose 2–3× for up to 3 d during acute illness.
  Fludrocortisone (not necessary in secondary adrenal insufficiency) 0.1 mg/d
  Preg: If adequately treated beforehand, most have Uncomp Preg, labor, & deliv. During labor, consider "stress dose steroids." Hydrate w/ IVFs & give hydrocortisone 25 mg IV q6h. At deliv, ↑ dose to 100 mg. After deliv, taper dose rapidly to maint dosing w/i 3 d. Only needed for >5 mg × >3 w of exog steroid.

Pheochromocytoma

- **Definition:** Rare catecholamine secreting chromaffin cell tumor originating from adrenal medulla (90%) & sympathetic ganglia (10%).
- **Epidemiology:** 0.8 per 100000 person years incid. <0.2% of pts w/ HTN. Rule of 10's: 10% extra-adrenal, 10% in children, 10% multi/bilateral, 10% recurrence, 10% malig, 10% familial.
- **Etiology:** MEN 2A/2B (2A = pheo/MTC/parathyroid hyperplasia; 2B = pheo/MTC/mucosal neuromas), von Hippel–Lindau, neurofibromatosis-1, familial paraganglioma.
- **Clinical manifestations:** HTN most common (sustained or paroxysmal), HA, sweating, palps, palor. Can be triggered by stress, abdominal manipulation, maybe IV contrast.
- In Preg → paradoxical supine HTN
- **Dx:**
  High risk (familial syndromes, personal Hx): Plasma free metanephrines (99% sens/89% spec)
  Low risk (all other): 24-h urine fractionated metanephrines & catecholamines (99% sens/98% spec). False + w/ sev illness, renal failure, OSA, labetalol, TCAs, sympathomimetics.
  Imaging after biochemical confirmation = CT/MRI abd/pelvis (98–100% sensitive). Consider MIBG scintigraphy if CT/MRI neg w/ + clinical/biochem. Also, consider genetic testing.
- **Rx:** α-adrenergic blockade (phenoxybenzamine) ± β blockade (propranolol) → Surg. In Preg → same as above. Laparoscopic resxn if previable fetus. C/S + tumor resxn at deliv.

HYPERANDROGENISM

Adrenal Hyperandrogenism

- **Definition:** ↑ primary adrenal androgens (DHEA & DHEA-S). Converted to androstenedione → testosterone (& also to estrogen). ♀ adrenarche = DHEA + DHEA-S ↑ → pubic hair dev. Can have ± hyperaldo, ± Cushing's syn.
- **Etiology:** Adrenal tumors (adenoma, carcinoma, bilateral macronodular adrenal hyperplasia), CAH (ACTH hypersecretion). Also in diff: Exogenous androgens, hyperprolactinemia, placental aromatase deficiency, PCOS. See also Ch. 6 (CAH) & Ch. 8 (PCOS).
- **Dx:** Clinical exam (hirsutism, androgenic alopecia, oily skin, acne, muscle hypertrophy, clitoromegaly, virilization, acanthosis nigricans)
  Labs: serum testosterone, DHEA-S (>500 μg/dL in ♀ sugg adrenal tumor), 17-OHP (nml 100–300 ng/dL), prolactin (nml <20 ng/mL; prolactin acting on receptors in adrenal → ↑ DHEA-S), thyroid fxn tests, gluc tol testing (fasting +2-h OGTT). Fasting gluc:insulin ratio <4.5 sugg insulin resistance.
  Imaging: MRI or CT
- **Rx:** Depends on etiology; Surg is recommended for adrenal tumors

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Polycystic Ovary Syndrome (See Ch. 8)

Ovarian Hyperthecosis

- **Definition:** Ovarian interstitial cells differentiate into islands of luteinized theca cells → ↑ steroid production. ↑ periph conversion to estrogen → ↑ endometrial hyperplasia.
- **Dx:** Menstrual irregularities, obesity, hyperandrogenism. Can be postmenopausal ♀ (unlike PCOS only in younger).
- **Rx:** Combination OCPs, weight loss, GnRH agonist (øLH secretion), surgical resxn.
- **Other ovarian tumors:** See Ch. 21 for other sex hormone producing tumors (teratoma, gonadoblastoma, granulosa cell, Sertoli-Leydig cell)

HIRSUTISM

Definition, Pathophysiology, and Epidemiology

- Excessive male pattern growth of coarse terminal hair in women.
- Conversion of testosterone to DHT by 5α-reductase → irreversible conversion of soft, vellus hair to coarse terminal hair.
- Ethnicity-related trends in hair follicle conc & thus propensity toward hirsutism; distinguish hypertrichosis from hirsutism. Mediterranean descent > northern Europeans > Asians.
- Overall 5–10% of reproductive age ♀. Typical onset in adolescence to early 20's.

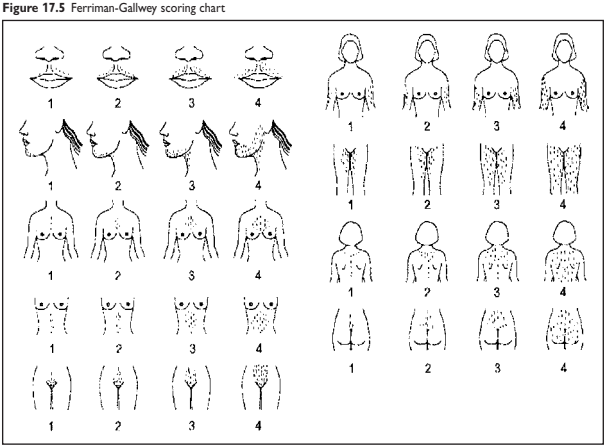
Etiology

- PCOS (70–80%), meds (anabolic steroids, danazol, progestins, metoclopramide, methyldopa), idiopathic, nonclassical 21-OH CAH, adrenal tumors, hyperthecosis, ovarian tumors, Cushing's syn, hyperprolactinemia

Clinical Presentation

- Terminal hair on lip, chin, chest, abd, arms, legs, back. Ferriman–Gallwey score to grade (95% of ♀ are nml w/ score <8; score >8, consider androgen-excess).

Figure 17.5 Ferriman-Gallwey scoring chart



Modified Ferriman–Gallwey scale for assessing hirsutism. Score nine body areas and sum. If no excess terminal hair, score is zero (Modified from Hatch, et al. Hirsutism: Implications, etiology, and management. *Am J Obstet Gynecol.* 1981;140:815–830)

Diagnosis – See Hyperandrogen/PCOS Workup (Chap. 8)

Treatment

- Combined OCPs 1st line (use lower androgenic progest products) → other treatments as for hyperandrogenism. Mechanical hair removal (shaving, waxing, laser).
- Antiandrogens effective but only monotherapy in reproductive aged ♀ w/ contraception. Spironolactone (also aldosterone receptor antag), flutamide, cyproterone, drospirenone (very weak antiandrogen, only available in combined OCP).

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PARATHYROID DISORDERS

Parathyroid Function

- **PTH** is the primary regulator of Ca & phosphorus (PO_4) levels. Regulated by negative feedback via parathyroid calcium sensing. Secreted by chief cells.
- PTH → ↑ Ca release from bone, ↓ renal excretion, ↑ 1–25 Vit D → ↑ serum calcium
- PTH → ↑ renal PO_4 excretion, ↑ intestinal Absorp (w/ Ca), ↑ release from bone (w/ Ca) → on balance ↓ phosphorus.
- **PTHrP** similar to PTH, synthesized in many tissues. Levels gradually ↑ in Preg & lactation. High conc in human breast milk. Pathologically ↑ in some cancers causing humoral HyperCa of malig (eg, squamous cell lung cancer)

Primary Hyperparathyroidism (PTH-related Hypercalcemia)

- ↑ PTH due to a d/o of the parathyroid tissue (gland production). Usually age >60. ~85% adenoma, ~15% hyperplasia, 1% carcinoma, drugs (thiazides, lithium).
- **Dx:** ↑ PTH or an inappropriately high-nml PTH in pt w/ ↑ Ca; exclude FHH, below.
- **Clinical manifestation:** Usually asx HyperCa (80%). Also a/w nausea, vomiting, constip, abdominal pain, nephrolithiasis (sx of high Ca). Osteitis fibrosa cystica = demineralization of bone, subperiosteal resorption, bone cysts, osteoclastomas/"brown tumors," & pathologic fractures.
- **Dx:** Total & free serum Ca. Decreased PO_4. High serum PTH for Ca level. Consider: PTHrP, 25-OH Vit D, urinary calcium, SPEP, UPEP, ACE, CXR/CT, mammogram. Neck sono eval & localize.
- **Rx:** HPTH has risk for mother & fetus: If Ca <12 mg/dL close monitoring, furosemide can be used for calciuresis. If Ca >12 mg/dL, parathyroidectomy better than medical mgmt, Surg ideally during 2nd trimester. ~50% of neonates of ♀ w/ HPTH have low Ca/tetany, at risk for IUGR, LBW, IUFD as a result of fetal PTH suppression.

  Nonpregnant → surgical mgmt for symptomatic pts or for asx pts w/:
  - Ca >1 mg/dL above the UL of nml (*J Clin Endocrinol Metab* 2009;94(2):335)
  - CrCl <60 mL/min
  - Bone T score <–2.5 &/or prev fragility fx
  - Age <50 y

Secondary Hyperparathyroidism in Renal Disease

- ↑ PTH due to appropriate resp to HypoCa
- When GFR <~40 mL/min → ↓ calcitriol & ↑ phosphorus → HypoCa & ↑ PTH
- Ca binds w/ PO_4 & can deposit in tissues
- Outside of Preg, treat w/ PO_4 binders, Vit D

Familial Hypocalciuric Hypercalcemia (FHH)

- Autosomal dominant mut in Ca sensing receptor causes shift in set point for Ca
- Critical to differentiate from PTH problem, as a benign condition
- Ca ↑, but usually <12; PTH inappropriately nml or mild ↑
- Urine Ca <200 mg/24 h, & Ca/CrCl <0.01 (24-h $U_{ca} \times S_{cr}/S_{ca} \times$ 24-h U_{cr}) supports dx
- ↑ Ca always recurs after Surg unless total parathyroidectomy, rx rarely indicated
- In Preg, neonate at risk for HypoCa/tetany unless inherits gene & then asx
- Father w/ FHH → neonate at risk for HyperCa postpartum

Hypoparathyroidism

- **Acq:** Neck Surg w/ incidental removal of parathroid glands (most commonly for HPTH), hypomagnesemia. Hereditary (rare): DiGeorge, polyglandular autoimmune type I. Dx is made w/ ↓ PTH in setting of ↓ calcium
- **Pseudohypoparathyroidism** (resistant to PTH due to mut) dx: ↑ PTH in setting of ↓ Ca
- **2° hypoparathyroidism** (appropriate ↓ PTH due to ↑ Ca) dx: ↓ PTH in setting of ↑ Ca
- **In Preg:** Avoid mat HypoCa → precipitates neonat HPTH → bone fractures
- **Postpartum:** May develop HyperCa, monit Ca postpartum & stop Vit D if develops
- **Rx:** Calcitriol + elemental Ca 1 g/d, titrate calcitriol weekly to low nml serum Ca level
- Treated pts are at risk for nephrolithiasis. If 24-h U_{ca} >300 mg/d → ↓ Vit D, can add thiazide diuretic to ↓ urinary calcium excretion

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Hypocalcemia
- **Sx:** Carpopedal spasm, oral paresthesias, Trousseau + Chvostek sign. Confirm w/ ionized Ca (preferred) or corrected calcium level for albumin. Corrected Ca (mg/dL) = measured total Ca (mg/dL) + 0.8 (4 – serum albumin [g/dL]).
- **Etiology:** Measure PTH, Vit D
  Low PTH: ↓ magnesium, neck Surg
  Nml PTH: Calcium sensor defect
  High PTH: Vit D deficiency, rhabdo, tumor lysis syn, pseudohyperparathyroidism, meds, pancreatitis, hydrofluoric acid exposure.
- **Rx:** Calcium (& treat hypomagnesemia)
  Asx or mild: Oral calcium 0.5–1 g elemental BID
  Sev: IV Ca-gluconate (preferred due to less tissue necrosis) or Ca-chloride. Treat Vit D deficiency also.

Hypercalcemia
- Confirm w/ ionized Ca (preferred) or corrected calcium level for albumin (see above for correction)
- **Clinical manifestations:** Renal stones, abdominal pain, polyuria, depression, fatigue
- **Rx:** Indicated for pts w/ total calcium >14 mg/dL or mod/sev sx
  Simultaneous hydration w/ isotonic saline, bisphosphonate ± calcitonin
  Bisphosphonate onset of action is 1–2 d
  Calcitonin works in hours, but tachyphylaxis occurs after ~24 h
  Zolendric acid more effective than pamidronate in malig (*J Clin Oncol* 2001;19(2):558)

PITUITARY DISORDERS

Definitions
- **Anter pituitary:** GH, TSH, ACTH, prolactin, LH, FSH, MSH
- **Post pituitary:** Oxytocin, ADH

Panhypopituitarism
- **Etiology:** Primary – Surg, tumors, ischemia (Sheehan syn → postpartum pituitary necrosis due to hypovolemic shock after deliv, watershed effect), radiation, infxn, autoimmune (lymphocytic hypophysitis). Secondary (hypothalamic) – Surg, tumors, infxn, trauma, autoimmune.
- **Clinical manifestations:** Based on specific hormones. Can include HoTN, weakness, inability to lactate, sexual dysfxn, loss of pubic & axillary hair, lethargy, polyuria, polydipsia. Also tumor mass effect: HA, visual changes, cranial nerve palsies.
- **Dx:** Hormone levels → low if chronic, nml if acute. Imaging by pituitary MRI.
- **Rx:**
  ACTH deficiency: Hydrocortisone 15–25 mg/d – may also consider prednisone or dexamethasone
  Mineralocort replacement unnecessary (regulated by angiotensin II & potassium)
  LH/FSH deficiency: Estrogen/progest therapy to simulate nml physiology; estradiol on cycle days 1–25 + progesterone days 16–25. Ovulation induction w/ gonadotropins for fertility.
  GH deficiency: Recombinant human growth hormone 2–5 mcg/kg/d. Monit w/ serum IGF-1.

Hyperprolactinemia
- **Etiology:** 50% of adenomas cause hyperprolactinemia (prolactin → stimulates lactation → ↓ GnRH → ↓ FSH + LH → can ↓ menses); drugs (SSRIs, estrogen, methyldopa, verapamil, morphine, dopamine receptor agonists [metoclopramide, domperidone, haloperidol, risperidone]); Preg, hypothyroidism, liver dz, kidney dz.
- **Clinical manifestations:** Amenorrhea, galactorrhea, infertility, ↓ libido, visual changes (bitemporal visual field losses w/ large adenomas)
- **Dx:** Serum prolactin. Brain MRI.
- **Rx:**
  Asx + microadenoma (≤10 mm) → follow w/ MRI. <2% progress to macroadenoma.
  Symptomatic ± microadenoma → dopamine agonist (bromocriptine 2.5 mg QD, or cabergoline 0.25 mg 2×/w). Side effects = N/V, orthostasis. Surgical: Transsphenoidal Surg. Radiation 3rd line.

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In Preg, microadema unlikely to grow. Macroadenoma (>10 mm) = 23% w/ sign if enlargement during Preg if no prior Surg or radiation; 5% if + prev Surg/radiation. Dopamine agonist before Preg to shrink adenoma. Monit at least q3mo. Serum prolactin <400 ng/mL reassuring. Consider MRI if visual changes or headaches. Breastfeeding does not ↑ growth

Prolactinoma & fertility: Dopamine agonist → lower serum prolactin → ovulation induction

Galactorrhea

- **Definition:** Physiologic nipple discharge (milky white, brown or green, elicited after manual expression from milk ducts). Pathologic discharge is bloody, serous, spont.
- **Etiology:** Preg, postpartum, nipple stimulation, pituitary adenoma (prolactinoma), hypothyroidism, craniopharyngioma, Cushing dz, acromegaly, neoplastic processes (breast, renal adenoCa, lymphoma), hydatidiform mole. See diff dx for hyperprolactinemia also.
- **Clinical manifestations:** Breast exam to elicit nipple discharge & for mass. Multi ducts/expressed manually/bilateral → more likely physiologic.
- **Dx:** Occult bld testing & microscopy. Diagnostic mammography, mammary ductography.

Gigantism and Acromegaly

- **Definitions:** Gigantism → elevated GH & IGF-1 before fusion of the epiphyseal plates → extremely tall stature. Acromegaly (10% adenomas) → elevated GH + IGF-1 after fusion of the epiphyseal plates. May be seen in familial syndromes such as MEN-1 & McCune–Albright syn.
- **Clinical manifestations:** Large hands & feet, coarsening of facial features, macroglossia, HA, OSA, acanthosis nigricans, arthralgias, carpal tunnel syn, jaw enlargement, hoarseness, extremely tall stature (gigantism), may coexist w/ amenorrhea & or galactorrhea in adol girls.
- **Dx:** Serum IGF-1 is single best test. OGTT: Serum GH should be <1 ng/mL 2 h after ingesting 75 g gluc load. In pts w/ acromegaly, postingestion serum GH >2 ng/mL in >85% cases (*JCEM* 2001;86(9):4364). Random serum GH not appropriate given pulsatile secretion. Brain MRI to look for pituitary tumor.
- **Rx:** Transsphenoidal resxn for pituitary tumor. Octreotide (mimics somatostatin → more potent inhib of GH & insulin than natural hormone), bromocriptine (dopamine agonist), XRT (rarely used in children).

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HEADACHE (HA)

Epidemiology (*Headache* 2006;46:365; *Lancet Neurol* 2013;12:175)

- 1 y HA prevalence is high (40–90%), may be increasing. Most are brief & do not prompt physician visit. Common neuro referral topic. ♀ > ♂, slightly. Decreases w/ age.
- 75% of primary HA will ↓ in Preg. ~40% PP → HA, esp 1st w.

Pathogenesis

- 90% are tension-type, migraine, or cluster HA. In ♀, 70% are a/w menses, but <20% are pure menstrual migraine.
- Multifactorial initiation. Nociceptor activation/sensitization can → central sensitization, ↑ pain transmission, ↓ pain threshold. Minor role for genetics.

Differential Diagnosis

- ***Primary* (most common):** Migraine, tension-type HA, cluster, orgasmic HA (elevated estrogen, prolactin, oxytocin)
- ***Secondary:*** Ischemic stroke, hemorrhagic stroke (SAH, AVM, HTN), venous sinus thrombosis, carotid or vertebral artery dissection, vasculitides, reversible cerebral vasoconstriction syndromes (Call-Fleming syn [reversible cerebral vasoconstriction], PRES)
- ***Other:*** Preeclampsia/eclampsia, benign intracranial HTN, sinusitis, overmedication, PDPH, tumor, estrogen withdrawal, brain tumor
- ***Primary care:*** Meningitis, pseudotumor cerebri, trigeminal neuralgia, TMJ syn, temporal arteritis

Diagnostic Workup

- **Hx:** Age, aura, prodrome, frequency, intensity, duration, timing, quality, radiation, assoc sx, FHx, precipitating/relieving factors, changes w/ activity/food/EtOH, resp to rx, visual changes, h/o trauma, change in sleep pattern/exercise/weight/diet/contraceptives, environmental toxins/exposures, menstrual Hx

Approach to HA by history

Question	Poss cause	Test to confirm/rx	Comments
Postural? Tinnitus?	Dural puncture	Typically by H&P only MRI + gadolinium for meningeal enhancement LP CT myelogram (most sensitive for leak) Analgesics, bld patch	Worse when upright. Incid 1.5%. Can occur days to weeks postprocedure.
H/o similar HA?	Migraine	Triptans or ergots	⅓–½ of ♀ w/ migraine Hx will have PP HA
Unilateral? Daily for limited time?	Cluster	100% oxygen CCBs, triptans, ergots, steroids	Assoc ipsilateral miosis, ptosis, conjunctival irritation, lacrimation
Sudden onset?	SAH Cerebral venous thrombosis	Plain CT, LP for hemorrhage If negative, MRI/MRA	Thunderclap HA
Elevated BPs, proteinuria, seizures?	Preeclampsia or eclampsia	Assess & monit for proteinuria, HTN, & hyperreflexia	HA can precede other signs of sev preeclampsia
Vasoconstrictive meds? Focal neuro deficits?	Reversible cerebral vasoconstrictive syndromes	See "sudden onset" category	Look for SSRIs, ergots, pseudoephedrine, bromocriptine PRES a/w cortical blindness & seizures

From *Int J Obstet Anesth* 2010;19:422; *Can J Anaesth* 2002;49:49.

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- **Warning signs:** Thunderclap HA, autonomic sx, 1st/worst HA of life, worsening, fever, change in mental status/personality, exercise assoc, very young or old age, h/o cancer/Lyme dz/HIV/Preg/PP, *focal neuro findings, *meningismus, *papilledema (* = imaging)
- **Physical exam:** BP, pulse, auscultation for bruits (neck, temporal), palpation (head, neck, spine), neuro exam w/ fundoscopy
- **Labs:** Usually not needed; TSH, ESR, CRP, toxicology screen, Lyme Ab, LP (if suspect SAH or infxn)
- **Imaging:** See warning signs. CT head/c-spine or MR ok. MRI/MRA head/neck if post fossa or vascular suspected.

Treatment and Medications

- **1st line:** Relaxation, ice packs, reassurance, acetaminophen, ibuprofen (not Preg). 2nd line: Add narcotics sparingly. 3rd line: Antiemetics (eg, chlorpromazine), IV magnesium. Avoid NSAIDs in 3rd trimester Preg (→ ductus arteriosus closure & oligohydramnios). Other treatments, see below.
- **Tension-type HAs:** Stress reduction, warm showers, massage, ice/heat packs, posture correction, physical therapy, prescription eyeglasses. NSAIDs, ASA, Tylenol, caffeine, muscle relaxants. Tricyclics for prevention.

MIGRAINE

Definition & Epidemiology

- Recurring syn of HA, nausea, vomiting, &/or other sx of neurologic dysfxn. Migraine w/ aura = visual sx occur/resolve w/ HA, risk factor for ischemic stroke.
- **Increases w/ age in ♀:** 22% at 20–24 yo; 28% at 25–29 yo; 33% at 30–34 yo; ~37% for 35–39 yo. Overall ↓ in Preg, but 8% of pregnant women (esp w/ h/o aura) have increased attack frequency.
- Risk for preeclampsia increased w/ HA (*Am J Hypertension* 2008;21(3):360). 2.4-fold ↑ w/ any HA Hx; 3.5-fold ↑ w/ migraine; 4-fold ↑ w/ migraines during Preg.
- **Status migrainosus:** >72 h → evaluate for secondary causes

Pathophysiology (*Headache* 2006;46:S49)

- Brain itself lacks pain receptors, but surrounding meningeal, muscle, skin, vessel, subcutaneous tissue, or mucous membrane inflammation/injury → HA pain
- Hormonal fluctuations in estrogen → menstrual migraine or PP migraine (withdrawal); ↓estrogen → increased in serotonergic tone
- **Migraine phases:** Prodrome → ± aura → main migraine pain → resolution

Treatment

- See conservative measures above. Narcotics not 1st line; abortive therapy needed early. Acute therapies used more than 2 d weekly can lead to rebound HA.
- Avoid combined OCPs if h/o migraine w/ aura or age >35 yo & no aura. D/c combination hormonal contraception if severity/frequency of HA increases or in setting of new onset migraine w/ aura.

Acute therapy for migraine

Class	Examples
Mild analgesic	Acetaminophen ASA Ibuprofen Naproxen Fioricet (butalbital, acetaminophen, caffeine)
Triptans[a]	Sumatriptan
Ergots[b]	Dihydroergotamine Ergotamine
BBs	Propanolol
Antidepressants	Amitriptyline Fluoxetine
CCBs	Verapamil, nifedipine

[a]Migraine ppx.
[b]Category X in Preg.
From MacGregor EA. Migraine in pregnancy and lactation: A clinical review. *J Fam Plann Reprod Health Care*. 2007;33(2):83–93.

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SEIZURE DISORDERS

Definition/Epidemiology

- Abn discharge of neurons in the CNS; 5–10% of pop affected
- Epilepsy – recurrent seizures, 0.5–1% of pop; 41 cases per 100000 women
- **Generalized seizures:** Start in both cerebral hemispheres at onset
- **Tonic–clonic:** 10–20-s tonic phase (constant muscle contraction) followed by 30-s clonic phase (intermittent muscle contraction)
- **Absence:** Transient lapse of consciousness – no loss of posture, muscle tone
- **Myoclonic:** Brief contraction, sudden onset
- **Atonic:** Brief loss of complete muscle tone (also called "drop attacks")
- **Partial/focal seizures:** Limited to 1 area of 1 cerebral hemisphere at onset
- **Simple:** Motor, sensory, or autonomic; no impairment of consciousness
- **Complex:** Impairment of consciousness + automatisms

Differential Diagnosis

- Syncope – no aura; motor manifestations <30 s; no postictal confusion; pt may have pallor & clamminess
- Psychogenic sz – asym limb movements, pelvic thrusting
- Other – metabolic (EtOH, hypoglycemia); migraine, TIA
- Eclampsia – generalized convulsions &/or coma in the setting of preeclampsia & w/o evid of other neurologic conditions. Preg assoc; pt often has elevated BPs, blurry vision, proteinuria, RUQ pain.

Pathophysiology/Etiology

- **A**lcohol withdrawal, ilicit drugs, meds (β-lactams, antidepressants, clozipine)
- **B**rain tumor; BP (a/w preeclampsia/eclampsia)
- **C**erebrovascular dz (subdural hematoma, hypertensive encephalopathy)
- **D**egen disorders (Alzheimer's)
- **E**lectrolyte imbalance (HoNa, hypoglycemia)

Antiepileptic drugs, side effects, and effect on pregnancy

Medication	Avg daily dose (max)	Systemic side effects	Preg side effects/ comments	FDA category
Phenytoin	300–400 mg (600 mg)	Gum hyperplasia, hypoCa, hyperK	Orofacial clefts, cardiac malfomations, genitourinary effects (*Neurol* 2005;64:961)	*D*
Carbamazepine	400–600 mg (1600 mg)	Aplastic anemia, leukopenia, hepatotoxicity, HoNa	NTDs; avoid if FHx of NTDs	*D*
Valproic acid	10–15 mg/kg/d (60 mg/kg)	Hepatotoxicity, increased NH_3, thrombocytopenia	AVOID during Preg; if necessary, high plasma levels should be <70 µg/mL & drug should be given in divided doses TID–QID A/w NTDs, ↓ in motor & mental developmental quotients – dose-resp relationship	*D*

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Medication	Avg daily dose (max)	Systemic side effects	Preg side effects/ comments	FDA category
Phenobarb	60–180 mg (300 mg)	Rash	Cardiac & orofacial malformations, genitourinary effects	*D*
Ethosuximide	20–30 mg/kg (1.5 g)	Rash, bone marrow suppression		*C*
Gabapentin	900–2400 mg (2400 mg)	GI upset	Limited data	*C*
Levetiracetam	1500–3000 mg (3000 mg)	GI upset (rare)	Limited data	*C*
Lamotrigine	400 mg (600 mg)		A/w left palate &/ or cleft lip in pts w/ 1st trimester exposure	*C*

From LaRoche SM, Helmers SL. The new antiepileptic drugs: Scientific review. *JAMA.* 2004;291(5):605–614.

Clinical Manifestations

- Aura – premonition, abn smells, tastes, oral automatism
- Postictal period – can last minutes to hours; slowly resolving period post sz. Pt may be confused, disoriented, lethargic.
- Status epilepticus – state of continuous seizures >30 min or repeated seizures w/o resolution of postictal periods. Assoc complications: Rhabdomyolosis, lactic acidosis, neuronal death.

Workup and Studies

- Obtain collateral Hx from witnesses as pt will often have amnesia of event
- Ask about loss of responsiveness, aura, unusual behavior, loss of autonomic control (urinary or fecal incontinence)
- Evaluate for etiology w/ h/o fever, illness, prev sz; in Preg, elevated BPs, prot in the urine, ext & facial swelling
- Exam to look for focal neurologic abnormalities or evid of injury from sz activity (oropharyngeal or musculoskeletal or secondary head injury & ecchymoses)
- **Labs:** CBC, CMP, LFTs, toxicology screen, medication levels
- **Preg:** Preeclampsia labs (CBC, LFTs, BUN/Cr, uric acid, LDH, proteinuria)

Pregnancy Care *(Neurol 2006;66:354)*

- 500000 WWE are of childbearing age; 3–5 births per 1000 will be to WWE *(Neurol 2000;55:S21)*. Preg w/ AEDs → ↑ IUGR & hypertensive disorders, ↑ CS *(Acta Obstet Gynecol Scan 2006;85:643)*. If sz free for 2 y, consider withdrawal of AEDs at least 6 mo prior to conception.

Management of WWE during pregnancy

Antepartum	Intrapartum	Postpartum
Drug conc should be established during Preg Perform serum conc every trimester, monthly for pts w/ breakthrough seizures & in those taking lamotrigine	Pt should take AED during labor No water labor Intravenous lorazepam or diazepam should be given if sz starts NOTE: Minimal variability can be expected for FHRT for 1 h	Mat plasma levels of AEDs may fluctuate until 8th w PP AED requirement is likely to fall in the puerperium (particularly lamotrigine & oxcarbazepine) PP sz risk elevated, in the setting of sleep depriv Most AEDs compatible w/ breastfeeding Consider relationship btw AEDs & contraception when counseling for PP birth control

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Contraception

- **Anticonvulsants that ↓ steroid levels:** Phenobarbitol, primidone, phenytoin, carbamezapine (to lesser extent w/ oxcarbazepine, felbamate, topiramate)
- If OCPs are deemed necessary, use 50 mcg of estrogen component or extended cycle treatments (3 cycles followed by 4-d break)
- **Emergency Contraception:** Levonorgestrel 1.5 mg separated by 12 h (doubled dose).
- **WHO recommends alternative form of contraception:** Levonorgestrel IUD, copper IUD, Depo-Provera (a/w decreased sz frequency)

ECLAMPSIA

Definition

- New onset seizures in a woman w/ preeclampsia, not attributable to other causes

Epidemiology

- Accounts for 12% of mat deaths, worldwide (developing countries > developed countries) (*Semin Perinatol* 2009;33:130). ~38% occur w/o preceding sx.
- 2% mortality; 23% will require ventilation; 35% have 1 major complication (pulm edema, renal failure, respiratory distress syn, dissem intravascular coagulation, stroke, cardiac arrest, acute respiratory distress syn)
- Seizures occur in 2–3% of pts w/ sev preeclampsia not receiving magnesium ppx; incid 1.6–10 cases per 10000 deliveries
- Distribution by GA:
  <20 w GA: Consider molar Preg or antiphospholipid Ab syn
  Antepartum: 38–55%
  Intrapartum: 13–16%
  Up to 48-h PP: 5–39%
  >48 h PP: 5–17%, think AVM, ruptured aneurysm, carotid artery dissection, or idiopathic sz d/o

Pathophysiology (*Am J Obstet Gynecol* 2004;190:714)

- Cerebral autoregulation in resp to high systemic BP → vasospasm of cerebral arteries, intracellular edema
- Loss of autoregulation of cerebral bld flow in resp to high systemic BP → hyperperfusion, endothelial damage, extracellular edema

Clinical Manifestations (*Obstet Gynecol* 2011;118:995)

- HA – cerebral edema (sens to predict eclampsia 0.98 [95% CI 0.87–1]) (*Acta Obstet Gynecol Scand* 2011;90:564)
- Vision changes – vasospasm of cerebral & retinal vessels
- Neurologic sx – most common premonitory sx (rates vary from 50–90%)
- Full PIERS model – odds ratio of 2.92 for predicting adverse outcomes in preeclampsia; calculator at: piers.cfri.ca/PIERSCalculatorH.aspx (*Lancet* 2011;377:219)
- Note: Presence of HTN & proteinuria are poor predictors of eclampsia, rare event. See also chaps. 11 and 12 for preeclampsia.

Treatment and Medication

- Drug of choice = magnesium sulfate (calcium channel antagonism) 4–6 g IV bolus then 1–2 g/h. If no IV → 5 g IM in each buttock (10 g total; rpt 3 g alternating buttock q4h). If seizing on magnesium, rebolus 2 g IV. Therapeutic level 4–6 mEq/L.
- **2nd line:** Phenytoin: Loading dose by weight (<50 kg = 1000 mg; 50–70 kg = 1250 mg; >70 kg = 1500 mg). Therapeutic level 12–20 mcg/mL. Check 2 h after loading → subseq dose; if <10 mcg/mL → 500 mg IV, if 10–12 mcg/mL → 250 mg. check level q12h.
- **3rd line:** Diazepam 5–10 mg IV bolus, rpt q10–15min prn, max 30 mg in 8 h
- Diazepam, phenytoin were a/w increased recurrence of seizures compared w/ magnesium sulfate (*Br J Obstet Gynaecol* 1998;105:300; *N Engl J Med* 1995;333)
- Fetal brady occurs during eclamptic sz. Recover mom; no need for urgent CS
- MagPIE trial: International RCT, >10000 ♀ w/ at least mild preeclampsia randomized to magnesium sulfate or placebo. Magnesium sulfate decreases relative risk of eclampsia by 58% (95% CI 40–71). No documented adverse effects on mom or baby in short-term or long-term period (*Lancet* 2002;359:1877; *British J Obstet Gynecol* 2006;114:300)

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Magnesium toxicity (approx levels)			
	Serum magnesium level		
	mmol/L	mEq/L	mg/dL
↓ patellar reflexes	4	8	10
Respiratory depression	6	12	14
Altered cardiac conduction	>7.5	>15	>18
Cardiac arrest	>12.5	>25	>30
Magnesium toxicity: Treat by stopping MgSO4, give Calcium gluconate 1 g IV, maintain airway, intubation if needed. Can use diuretics to remove excess magnesium.			

STROKE IN PREGNANCY

Epidemiology and Pathophysiology
- Stroke in Preg = 4–26/100000 (3–10/100000, nonpregnant women)
- Most common in 3rd trimester or puerperium, but also ↑ in PP (8.7× for ischemic stroke; 24× for hemorrhagic stroke). ~10% of all mat deaths.
- Most common cause of stroke in Preg is preeclampsia/eclampsia
- ↑ due to hypercoagulable state of Preg; cerebral endothelial dysfxn

Diagnosis (*Obstet Med* 2011;4:2)
- ***Acute***: Hx, PE (listen for murmurs, carotid & subclav bruits, & look for signs of periph emboli). Urgent CT, noncontrast, to rule out hemorrhage, followed by CT angio. MRI/MRA w/ gadolinium. Doppler scan of the LE → if negative, then MRV.
- ***Risk factors***: Hypercoagulable state: Lupus anticoagulant, anticardiolipin antibodies, anti-β2 glycoprotein, Factor V Leiden, prothrombin, prot C & S, antithrombin III. Peripartum cardiomyopathy.

Post Reversible Encephalopathy Syn (*Mayo Clin Proc* 2010;85:427)
- Related to cerebral autoregulation & endothelial dysfxn. Seen in preeclampsia.
- **Features:** HA, altered consciousness, visual disturbances (hemianopia, visual hallucinations), seizures (often presenting manifestation)
- **Radiology:** Symmetrical white matter edema in the post cerebral hemispheres, rarely seen on CT, but better depicted on MRI
- **Rx:** Lower BP, fully reversible w/i days to weeks

Postpartum Cerebral Angiopathy (*Am J Obstet Gynecol* 2004;191:375)
- Reversible cerebral vasoconstriction syndromes
- **Timeline:** Few days post deliv. Features: Thunderclap HA, vomiting, seizures.
- **Radiology:** Multifocal segmental narrowing of cerebral arteries, resolution in 4–6 w
- CSF nml

Cerebral Aneurysm Rupture and SAH (*N Engl J Med* 1996;335:768)
- Relative risk of intracerebral hemorrhage during Preg & up to 6 w PP is 5.6 times that of the nonpregnant pt
- Surgical rx after SAH during Preg improves mat & fetal outcomes
- Favor vaginal deliv unless aneurysm is diagnosed at term or there has been neurosurgical intervention w/i the week before deliv

CEREBRAL VENOUS THROMBOSIS

Definition and Epidemiology (*Stroke* 2011;42:1158)
- Thrombosis of the venous sinuses, cerebral veins, or jugular veins
- Represents 2% of all Preg-related strokes; 12/100000 deliveries (*Stroke* 2011;42:1158). Risk is highest during 3rd trimester & PP.

Etiology/Pathophysiology
- Dehyd, puerpurial & PP infxn, thrombophilia inherent to Preg
- Risk increased w/ use of OCPs (22.1-fold increased odds [95% CI 5.9–84.2%]); increased odds for pts w/ thrombophilia (eg, prothrombin gene mut)

Diagnostic WorkUp
- **Acute:** Brain CT &/or MRI, bubble study & vascular US of the venous sinuses, cerebral veins, or jugular veins–Best is MRI T2 + MRV – better visualization, good

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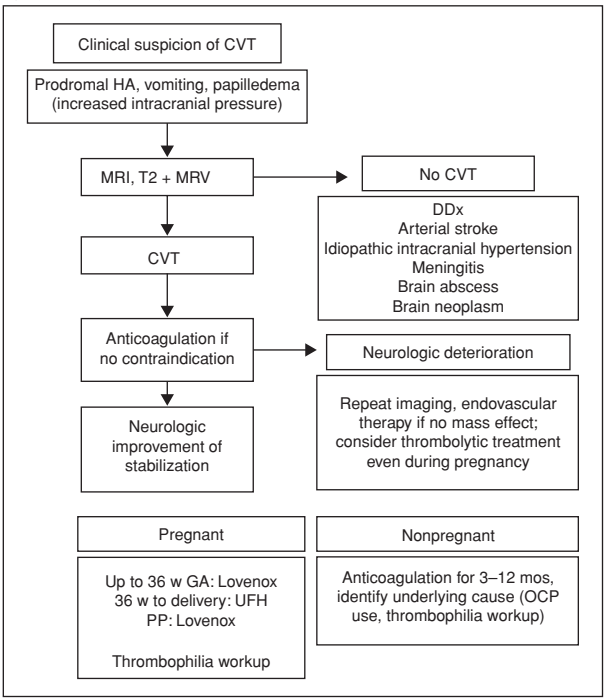
detection of brain parenchyma, no radiation. Can evaluate for both thrombosis & stroke (*Stroke* 2011;42:1158).
- A nml D-dimer, high negative predictive value, low probability of CVT
- Empty delta sign on contrast-enhanced CT (hyperdensity of cortical vein or dural sinus, filling defect) seen in 25–50% of cases
- Venous infarction is flame-shaped

Figure 18.1 Management of cerebral venous thrombosis



MULTIPLE SCLEROSIS IN PREGNANCY

Definition/Epidemiology

- Immune-mediated demyelinating neurologic condition, characterized by inflamm lesions affecting the brain & spinal cord & resulting in neurologic disability
- Dz classification:
  - ***Relapsing-remitting (RR):*** Manifestations develop in the context of clearly defined acute relapses followed by partial or complete recovery
  - ***Secondary progressive:*** Following an initial RR course, manifestations worsen gradually w/ or w/o superimposed acute relapses
  - ***Primary progressive:*** Manifestations gradually progress from onset w/o relapses
  - ***Progressive relapsing:*** Manifestations gradually progress from onset w/ subseq superimposed relapses
- Occurs in 3:2 ratio of females to males; peak incid of 30 y of age
- Effect of Preg on MS activity (PRIMS Study. *N Engl J Med* 1998;339:285; *Brain* 2004;127:1353)
- 70% reduction in relapse risk in the 3rd trimester of Preg in RRMS pts
- 72% relapse in 1st 3 mo PP – a/w relapse in prepregnancy year, relapse during Preg, no association w/ breastfeeding or epidural placement (*Brain* 2004;127:1353)

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- Long-term prog – increasing disability not related to Preg – fullterm Preg can lengthen time to secondarily progressive course (*N Engl J Med* 1998;339:285)

Diagnosis During Pregnancy and Postpartum

- Most common presenting sx are paresthesia in 1 or more ext, or 1 side of the face, weakness or clumsiness of leg or hand, or visual disturbances (eg, partial blindness, dimness of vision, or scotoma). Optic neuritis has been reported as the 1st symptom of MS in lactating women (*Obstet Gynecol* 2001;98:902).
- T2-weighted imaging remains the std tool for dx confirmation after 1st trimester

Rx During Preg

- **Acute flare:** 3–5-d course of high-dose corticosteroids administered IV
- Some corticosteroids cross the placenta. No association w/ prematurity, IUFD, or SABs
- DMT are offered to MS pt experiencing at least 1 relapse per year
- Interferon B–reduces relapse rates by ~30%; animal, human studies limited, but show no adverse fetal effects–not a/w increased risk of SAB (*Exp Cell Res* 2011;317:1301; *J Neurol* 2010;257:2020; *Neurol* 2010;75:1794)
- Natalizumab (monoclonal Ab against VCAM alpha-4-integrin) may be used for more aggressive dz; safety has not been established in Preg – pts should stop drug 3 mo prior to conception
- Fingolimod (modifies receptors involved in vascular genesis); no evid regarding safety in Preg – pts should stop drug 2 mo prior to conception
- IVIG – not licensed as std MS therapy, but beneficial effects reported w/ use during Preg

Treatment Postpartum

- 3–5-d course of high-dose corticosteroids (Solu Medrol 1000 mg QD) – protection from relapse for 4 w PP (*J Neurol* 2004;251:1133)
- DMT can be restarted but protective effects may be delayed for weeks

NEUROPATHIES IN PREGNANCY

Bell's Palsy (*Otolaryngol Head Neck Surg* 2007;137:858)

- **Definition:** Paralysis of the facial nerve – involving V1, V2, V3
- **PE:** Asym facial expression & unilateral weakness of eye closure
- **Epidemiology:** 2–4-fold ↑ during Preg, esp 3rd trimester or in 1st-w PP
- **Pathophysiology:** Increased perineural edema, hypercoagulability (thrombus of vasa-nervorum), relative immunosuppression in Preg
- Association w/ preeclampsia (*QJM* 2002;95:359)
- **Rx:** Cort taper; w/ exception of 1st 9 w of Preg

Meralgia Paresthetica

- **Definition:** Sensory neuropathy that occurs w/ compression of the lateral femoral cutaneous nerve as it penetrates the tensor fascia lata at the inguinal ligament
- **Pathophysiology:** Expanding abdominal wall & increased lumbar lordosis
- Rx rarely req

Postpartum Compression Neuropathies (*Obstet Gynecol* 2003;101:279)

- **Epidemiology:** Reported in 1–8/10000 deliveries
- **Femoral neuropathy:** Motor loss involving the quadriceps, w/ sparing of adduction; sensory loss involving the anter thigh & most of the medial thigh
- **Lateral femoral cutaneous neuropathy:** No motor fibers; lateral hip pain w/ paresthesias or hypesthesias over upper outer thigh
- **Peroneal neuropathy:** Foot drop caused by prolonged squatting sustained knee flexion, pres on the fibular head from stirrups or palmar pres during pushing
- **Obturator neuropathies:** Uncommon complication of deliv; pt p/w medial thigh pain & adductor weakness
- **Risk factors:** Fetal macrosomia, malpresentation, sensory blockade, prolonged lithotomy position, prolonged 2nd stage, improper use of leg stirrups & retractors

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Disease	Epidemiology	Clinical characteristics and physical exam	Treatment
Chloasma "Mask of Preg"	50–75% ↑ in Hispanics & those w/ dark complexions May fade w/i 1 y; persists in up to 30%	Onset in 1st–2nd trimester hormone-assoc facial hyperpigmentation in malar or central distribution Patchy macular facial hyperpigmentation Woods lamp	Avoid sun Sunscreen Bleaching: Hydroquinone, azelaic acid, tretinoin Chemical peel
Pruritic Urticarial Papules and Plaques of Pregnancy (PUPPP)	Most common gestational dermatosis Up to 1/300 ↑ in Caucasian, multi gestations, nulliparas	Onset in 3rd trimester. Typically resolves peripartum. Lesions may be target-like, wheals, or vesicles Intensely pruritic. Urticarial papules & plaques w/i abdominal striae. Thighs, arms, buttocks may be affected. Face, palms, soles, periumbilical region usually spared.	Symptom relief: Emollients, topical steroids, nonsedating antihistamine. Oral steroids for sev cases.
Impetigo herpetiformis "Pustular Psoriasis of Preg"	Rare, case reports only	Onset in 3rd trimester. Resolves slowly postpartum. Complications: Constitutional sx, mat sepsis, & placental insufficiency. Nonpruritic sterile pustules surrounding erythematous plaques in flexures → periph spread. Trunk, extremities, mucous membranes involved. Can become infected. Bx reveals spongiform pustule of Kogoj (neutrophil-containing pustule).	Oral steroids Cyclosporine Abx if bact superinfxn occurs Fetal surveillance
Herpes gestationis	1/10–50000 May occur w/ gestational trophoblastic dz. ↑ in Caucasian. >50% are HLA-DR3 or DR4+	Onset 2nd–3rd trimester Remits & recurs throughout Preg. Worse in subseq pregnancies. Placental insufficiency risk. Extreme pruritis. Erythematous papules → vesicles, bullae. Periumbilical → trunk + extremities. Mucous membrane & facial sparing. Neonat lesions in 10%. Bx shows immunofluorescent C3 deposit at basement membrane (distinguishes from PUPPP)	High potency topical steroids Nonsedating antihistamine Often requires oral steroids Fetal surveillance Avoid oral contraceptive agents for 6 mo postpartum (can precipitate flare in up to 50%)

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Disease	Epidemiology	Clinical characteristics and physical exam	Treatment
Prurigo gestationis	Up to 1/300	Onset 2nd–3rd trimester. Atopic eczema component. Resolves w/i 3 mo postpartum. Pruritic papules or plaques on trunk & extensor surfaces of extremities. Excoriated; "insect bite" appearance.	Emollients Topical steroids Nonsedating antihistamine
Folliculitis	Rare	Onset 2nd–3rd trimester Poss atopic component. Resolves w/i 2–3 w postpartum. Sterile papules or pustules arise from follicles on trunk. May spread to extremities.	Topical steroids. Benzoyl peroxide. Nonsedating antihistamine

From *Am Fam Physician* 2007;75:211; *J Am Acad Dermatol* 2006;54:395.

LICHEN SCLEROSUS

Epidemiology
- Prevalence unk (often asymptomatic, underreported) (*Obstet Gynecol Surv* 2012;67:55)
- Bimodal distribution: Prepubertal & postmenopausal females, w/ a mean age btw the 5th & 6th decade (*Obstet Gynecol* 2008;111:1243)
- Risk of malig transformation to squamous cell carcinoma

Pathology
- Atrophic epidermis ± hyperkeratinization (typically due to persistent scratching), homogeneous collagen layer w/ underlying lymphocytic infiltrate, blunting of rete ridges

Etiology
- Autoimmune component & genetic predisposition suspected
- Hormonal influences (low estrogen) & local inflamm responses may also play a role

Clinical Characteristics
- Vulvar pruritis is most common symptom
  May also present w/ vulvar irritation, pain, burning, dyspareunia
- **Ddx:** Psoriasis, lichen simplex chronicus, lichen planus, menopausal atrophy, candidiasis, autoimmune disorders such as vitiligo

Physical Exam (*Obstet Gynecol Surv* 2012;67:55)
- Exterior vulva thinned w/ a white plaque-like appearance, "cigarette paper"
- "Keyhole" distribution around vulva, introitus, & anus
- Excoriations & lichenification may be present due to persistent scratching
- Labia majora & minora may eventually lose distinction & fuse
- No vaginal involvement

Diagnostic Workup
- H&P exam
- Bx of affected area
- Rule out concurrent infxn

Treatment (*Obstet Gynecol* 2008;111:1243)
- Topical antihistamines for symptom relief
- High-dose topical steroids: Clobetasol 0.05% ointment nightly for 6–12 w, followed by maint 1–3×/w (1 of many rx regimens). See steroid chart, below.
- Topical retinoids for sev cases
- Topical tacrolimus, 0.1% ointment twice daily, or pimecrolimus 1% cream twice daily (do not use for extended periods)
- Triamcinolone injections: 2nd-line agents, indicated for persistent dz

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- Pts should return in 3-mo intervals during initial rx stages, until stable
- Lifetime surveillance in 6–12-mo intervals recommended

LICHEN SIMPLEX CHRONICUS

Epidemiology (*Dermatol Clin* 2010;28:669)
- Common cause of vulvar pruritis: Prevalence is unk
- Personal &/or FHx of atopy is common

Pathophysiology
- Vulvar irritation (caused by heat, sweat, clothing, contact dermatitis, topical products, atopic conditions, infxn) → intense & persistent scratching → lichenification

Clinical Manifestations
- Pruritis
- Sleep disturbances, often due to pruritis & intense scratching

Physical Exam
- Erythematous thickened epidermis & scaly vulvar plaques
- Vulvar skin may be hyperpigmented or hypopigmented, & appear leathery
- Excoriations may be present

Diagnostic Workup/Studies
- Bx shows chronic inflamm changes, hyperkeratinization, acanthosis

Treatment (*Obstet Gynecol* 2005;105:1451)
- Vulvar hygiene, sitz baths
- Rx of underlying d/o (ie, infxn)
- Avoidance of scratching: Gloves at night, barrier creams, occlusive dressing, cold pack
- Topical steroids: Hydrocortisone 1% applied to affected area daily for mild dz. Betamethasone 0.05% or clobetasol 0.05% applied daily for mod–sev dz.
- Antihistamines: Diphenhydramine or hydroxyzine 25–100 mg po q4–6h prn

LICHEN PLANUS

Epidemiology
- Prevalence of ~1% of women (*Obstet Gynecol* 2008;111:1243)
- Most common in the 5th–7th decade of life in females

Pathology
- Chronic inflamm changes, band-like dermal lymphocytic infiltrate, basal layer liquefactive necrosis, colloid bodies, acanthosis, hyperkeratinization
- Erosive lichen planus = most common form: Painful, desquamative, ulcerative lesions of vulva, vagina, & mucous membranes (including oral). Can form scar tissue, adhesions, or synechiae.
- Dev of squamous cell carcinoma is uncommon but poss

Etiology
- Presumed autoimmune process resulting in chronic inflammation

Clinical Manifestations (*Am Fam Physician* 2000;61:3319; *Obstet Gynecol* 2008;111:1243)
- **"P's":** Planar, Purple, Pruritic, Polygonal, Papules, & Plaques
- Pruritis is most common symptom
- May also present w/ vulvar or vaginal irritation, pain, burning, dyspareunia, discharge refrac to conventional rx

Physical Exam (*Obstet Gynecol* 2008;111:1243)
- Erythematous, shiny plaques of the vulva & occ the vagina
- May present w/ desquamation, ulcerations, & loss of architecture
- Wickham striae: White, lacy formation overlying papular lesions
- Bullae, ulceration, erosion in sev cases
- Oral & nongenital cutaneous lesions often coincide

Diagnostic Workup
- H&P exam

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- Bx of affected area:
  Immunofluorescence staining reveals basement membrane fibrinogen & IgM cytoids

Treatment (*Obstet Gynecol Surv* 2012;67:55)
- **Symptom relief:** Sitz baths, vulvar hygiene, barrier creams or petroleum jelly
- **High-dose topical steroids:** Clobetasol 0.05% cream applied nightly for 6–12 w, followed by maint 1–3×/w
- Topical tacrolimus, 0.1% ointment twice daily
- Triamcinolone injections
- **Oral steroids for sev erosive dz:** Prednisone 40 mg po daily × 1 w → taper
- **Immune mediators (after failure of other methods):** Methotrexate, azathioprine, cyclosporine, hydroxychloroquine
- **Surgical procedures for adhesions or synechiae:** Indicated when other treatments have failed
- Chronic condition, w/ relapsing-remitting course depending on resp to rx
- Routine yearly surveillance, as dev of squamous cell carcinoma is poss

Topical corticosteroids

Classification	Steroid (brand name)	Strength (%)
Class I (Super-high potency)	Clobetasol propionate (Temovate) Betamethasone dipropionate (Diprolene) Halobetasol propionate (Ultravate)	0.05 0.05 0.05
Class II (High potency)	Amcinonide (Amcort, Cyclocort) Desoximetasone (Topicort) Triamcinolone acetonide (Kenalog) Halcinonide (Halog) Fluocinonide (Lidex) Diflorasone diacetate (ApexiCon)	0.1 0.25 0.5 0.1 0.05 0.05
Class III (High potency)	Fluticasone propionate (Cutivate) Betamethasone valerate (Valisone) Triamcinolone acetonide (Kenalog, Triderm) Mometasone furoate (Elocon) Diflorasone diacetate (Florone)	0.005 0.1 0.5 0.1 0.05
Class IV (Mid potency)	Flurandrenolide (Cordran) Fluocinolone acetonide (Synalar)	0.05 0.025
Class V (Low-mid potency)	Prednicarbate (Dermatop) Desonide (DesOwen, Desonate) Hydrocortisone butyrate (Locoid, Cortizone-10) Hydrocortisone probutate (Pandel) Hydrocortisone valerate (Westcort) Triamcinolone acetonide (Kenalog)	0.1 0.05 0.1 0.1 0.2 0.025
Class VI (Low potency)	Betamethasone valerate (Beta-Val) Alclometasone dipropionate (Aclovate)	0.1 0.05
Class VII (Lowest potency)	Hydrocortisone (many brand names & OTC preparations)	0.5–2.5

SEBORRHEIC DERMATITIS

Epidemiology
- Overall prevalence unk
- Higher prevalence in immunocomp
- Most common in 3rd–4th decade of life

Etiology
- Lipophilic fungi of genus *Malassezia* implicated as potential pathogens
  Grow in sebaceous glands
  May be related to impaired immune resp

Clinical Characteristics and Physical Exam
- May present as asymptomatic plaques, as dandruff, or as pruritic, inflamed lesions where sebaceous glands are present
- Erythematous, yellow, oily scaly plaques in areas of sebaceous glands: Scalp, face, eyebrows, nasal folds, auricular surfaces, chest, back, body creases, vulva

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Treatment (*NEJM* 2009;360:387)
- **Antifungal meds:** Ketoconazole 2% shampoo/foam/gel/cream BID for 4 w (evid is based on rx of scalp seborrheic dermatitis)
- **Topical steroids to control itching, erythema:** Hydrocortisone 1% daily or BID for 4 w, clobetasol 17-butyrate 0.05% cream daily or BID for 4 w, betamethasone dipropionate 0.05% lotion daily or BID for 4 w
- **Calcineurin inhib:** Pimecrolimus 1% cream BID for 4 w
- **Recurrent dermatitis:** Maint rx once or twice weekly
- Oral steroids or isotretinoin in sev cases; usually in the immunocomp or for refract dz

HIDRADENITIS SUPPURATIVA

Epidemiology (*NEJM* 2012;366:158)
- Prevalence 1–4%
- Most common in the 2nd–3rd decade of life
- 3 times more common in women

Etiology
- Often related to hormonal changes (hyperandrogenism), obesity, smoking, & meds

Pathophysiology
- Abn shedding of keratinocytes → terminal follicles in areas w/ apocrine glands become occluded & rupture → chronic inflammation, abscesses, sinus tract formation

Clinical Characteristics and Physical Exam (*NEJM* 2012;366:158)
- P/w erythematous, painful, nodular lesions, hyperhidrosis, odor
- Axilla & perineal regions most common, in addition to inguinal, perianal, & vulvar regions
- Less commonly p/w strictures, fistulae, lymphedema, osteomyelitis
- Nodular lesions form abscesses → resultant drainage causes sinus tracts & scarring
- Depression, decreased quality of life
- **Hurley staging:** Stage 1 – localized nodules or abscesses w/o scarring or tract formation, Stage 2 – recurrent nodules or abscesses w/ scarring or tract formation, Stage 3 – widespread nodules or abscesses w/ scarring & tracts

Treatment (*Am Fam Physician* 2005;72:1547)
- **Initial treatments:** Proper hygiene, use of neutral soaps, warm compresses, lightweight loose-fitting clothing, weight loss, smoking cessation
- Anti-inflamm meds
- Antiandrogen meds (spironolactone, drospirenone, finasteride)
- Topical Abx (tetracycline, clindamycin), oral Abx for more sev cases (clindamycin, rifampin)
- Retinoids (isotretinoin)
- Intralesional or oral steroids
- Immune mediators (infliximab, cyclosporine)
- **Surgical treatments:** Incision & drainage, wide local excision, laser excision, unroofing or debridement. Usually reserved for widespread & sev dz.

FOX-FORDYCE DISEASE

Epidemiology
- Infrequent; <1%
- Most common in 2nd–4th decade of life
- Predominance in females (female to male ratio 9:1)

Etiology
- Keratotic occlusion of apocrine glands → gland rupture & papular eruption → pruritis & chronic inflammation
- Apocrine gland involvement is necessary for dx
- Often related to humidity, obesity, hormones, stress

Clinical Characteristics
- May be asymptomatic, but most often p/w intense pruritis
- Affects the axilla, areolar, perineum, & pubic regions

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- Multi small, darkened or flesh-colored papules
- May be a/w anhidrosis
- Acanthosis, or thickened skin, may be present

Treatment (*J Pediatr Adolesc Gyn* 2011;24:108)
- Combination OCP
- Topical steroids (0.05% desonide or 2.5% hydrocortisone once to twice daily)
- Topical or oral retinoids (0.025% tretinoin cream once daily)
- Topical or oral Abx
- Surgical excision of apocrine glands or liposuction curettage in sev cases

GYN-DERM CYSTS

Vaginal and perineal cysts

Cyst type	Clinical characteristics	Physical exam	Treatment
Epidermoid cyst Epidermal proliferation due to disruption of dermis Lined by keratinized epidermal cells	Commonly asymptomatic, may cause discomfort, altered cosmetic appearance, discharge	Mobile cyst commonly filled w/ white or clear fluid upon incision Located at vulva & perineum	Observation Excision
Gartner duct cyst Remnant of mesonephric duct	Dyspareunia, difficulty inserting tampons, feeling a bulge/mass	Cystic mass commonly found in the posterolateral vagina	Marsupialization Excision
Skene duct cyst Obst of Skene duct Lined by squamous epithelial cells	Commonly asymptomatic, dyspareunia, pain, urethral obst, UTI	Cystic mass in inferolateral periurethral region	Observation Excision
Bartholin gland cyst Obst of Bartholin gland	Dyspareunia, pain, drainage, may form abscess	Cystic mass in medial labia majora (at 5 or 7 o'clock, relative to the introitus)	Incision & drainage Word catheter placement Marsupialization Excision (Chap. 5)
Sebaceous gland cyst Obst of sebaceous gland	Commonly asymptomatic; may cause discomfort, altered cosmetic appearance	Mobile cyst filled w/ thick yellow material upon incision, often multi cysts Located at vulva & perineum	Observation Excision

From Hoffman BL, Schorge JO, Schaffer JI, et al. Benign disorders of the lower reproductive tract. In: Hoffman BL, Schorge JO, Schaffer JI, et al, eds. *Williams Gynecology*. 2nd ed. New York, NY: McGraw-Hill; 2012; Black M, Mckay M, Braude P, et al., eds. *Obstetric and Gynecologic Dermatology*. 2nd ed. Philadelphia, PA: Mosby; 2002.

COMMON DERMATOLOGIC MANIFESTATIONS OF SYSTEMIC DISEASE

Crohn's Disease
- Approximately 30% of pts w/ Crohn's dz have gyn-derm complications. See Ch. 15.
  Findings: Vulvar edema, ulcerations, inflammation, granulomas, "knife cut" lesions or fissures. Inflammation, granulomas of the ovary & fallopian tube. Sinus tracts, enteric fistulae to the female reproductive tract.
  Rx: Topical steroids, topical metronidazole, intralesion steroid injections, surgical correction of fistulae

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Autoimmune Disorders (*Obstet Gynecol* 2008;111:1243)
- Thyroid dz, vitiligo, pernicious anemia, SLE, atopic dermatitis, & alopecia areata have been a/w lichen simplex chronicus, lichen sclerosus, & lichen planus

Behçet Disease
- **Diagnostic criteria:** Recurrent oral ulcers & 2 or more of the following: Recurrent genital ulceration, ocular lesions (uveitis), skin lesions, or positive pathergy testing
- Rule out infxn as source of ulceration, such as HSV, syphilis, HIV, chancroid
- **Treatments:** Topical or intralesional steroids; may require systemic rx

Stevens–Johnson Syndrome
- Systemic hypersensitivity rxn causing edema, sloughing, &/or necrosis of mucous membranes, including lower genital tract
- Usually caused by meds; can also be secondary to infxn
- **Rx:** D/c medication, supportive care, Abx, wound care; systemic steroids & IVIG may be helpful

Drug Reaction
- Small, hyperpigmented lesions, erythematous plaques or bullae
- Genital, oral, & facial lesions are most common
- Local rxn to systemic or local administration of some meds, most commonly: Tetracycline, phenolphthalein, sulfa medications, NSAIDs & ASA
- Resolves w/ discontinuation of the drug

Erythema Multiforme
- Small, cutaneous target-like lesions
- Bullae & erosions of the genital, oral, & ocular mucous membranes
- May be a/w infxn (HSV most common) or due to drug rxn
- Rule out infectious source (ie, HSV, syphilis, mycoplasma PNA)
- **Rx:** Withdrawal of causative agent, oral antihistamines, topical steroids, wound care, rx of infxn if present

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Definition & Epidemiology

- **AIDS:** HIV infxn w/ or w/o sx + CD4 count <200/mm^3 or AIDS-indicator condition (OI or AIDS-related malig).
- Caused by infxn w/ HIV-1 or HIV-2 retroviruses. Female infxn in US = 23% of cases (*PLoS ONE* 2011;6:e17502). 2/3 heterosexual transmission. Risk factors: Minority ethnicity (AA → 10× ↑ infxn, & leading cause of death for AA ♀ 25–34 yo); low socioeconomic status; urban location (*JAMA* 2001;285:1186).

Pathophysiology

- HIV RNA virus targets CD4 receptor on T-lymphocytes
- Destruction & impairment of CD4 cells → immunodeficiency → OIs thrive
- Monit dz progression & resp to rx w/ CD4 count & viral RNA-load
- Potentiation of transmission by other STIs. Infxn w/ STI ↑ HIV risk 2–5× due to ↑ viral shedding, genital mucosal disruption, & local recruitment of inflamm cells (*Curr Opin HIV/AIDS* 2010;5:305); includes HSV, BV, trichomonas, gonorrhea/chlamydia & HPV

Gynecologic Care (*Obstet Gynecol* 2010;116:1492)

- **HIV screening recommended:** IV drug use, HIV+ sex partner, STI dx, prostitution, multi sex partners, Preg
- 1st-step screening by ELISA → Western blot for band specific confirmation
- HIV+ → ↑ number & severity of vaginal infections → screen frequently for other STIs
- Clinical course differs w/ HIV coinfection. HSV → ↑ frequency, pain, duration; use HSV suppression ppx. Syphilis → ↑ neurosyphilis & rx failure; re-evaluate clinically & w/ serologic titers at 3, 6, 9, 12, & 24 mo after therapy (*CDC MMWR* 2010;59:No.RR-12)
- Latex condoms are the only contraceptive that reduces HIV transmission; spermicides do NOT reduce transmission.
- HAART recommended for all HIV-infected individuals
- ↓ OCP efficacy w/ PIs & NNRTIs. Long-acting reversible contraception (IUD, implant) safe & effective.
- HIV+ ♀ 6× greater odds of ↓ bone mineral density & 4× ↑ odds of osteoporosis
- ↑ **incid of abn cervical cytology.** 4–6× ↑ risk for CIN. HPV infxn = 65% in HIV+ women vs. 30% seronegative (*JAMA* 2000;283:1031; *Glob Libr Women's Med* 2009;10:3843) w/ ↑ HPV persistence & progression. Incid of CIN correlates w/ ↓ CD4 count & ↑ HIV RNA levels. Routine colposcopy not recommended.
- Cervical cancer ↑ due to behavioral (less screening, IV drug use) & biologic factors (immunosuppression). More likely to present at advanced clinical stage.
- VIN, VAIN, & AIN also ↑ in HIV+ women (*Obstet Gynecol* 2006;107:1023)
- HAART a/w ↓ prevalence, ↓ incid & ↑ clearance of SIL (*J Inf Dis* 2010;201:681)

HIV in Pregnancy (http://aidsinfo.nih.gov/guidelines)

- **Univ routine testing (opt-out)** for all pregnant women at initial prenatal visit. Women who present in labor w/o prenatal care should get rapid HIV test; intrapartum AZT ↓ perinatal transmission. HIV a/w SGA, preterm deliv.
- Due to Preg plasma vol changes, CD4 count ↓ but no change on CD4 percentage. Dz progression unusual Preg (*J infect Dis* 1992;165:1116)
- HIV+ women should get pneumococcal, influenza, hepatitis A (if nonimmune), & hepatitis B vaccines + other std Preg vaccination. Screen for hepatitis C, given high rates of coinfection (*MMWR Recomm Rep* 2009;58:1).
- Transmission can occur transplacentally (related to mat viral load), during deliv, & w/ breastfeeding (*N Engl J Med* 1999;341:1698). HAART can ↓ perinatal transmission to <1% (untreated 15–25%) (*N Engl J Med* 1994:331:1173). Start HAART during Preg to suppress viral load, continue ppx at deliv, & provide neonat ppx to the infant.
- **Transmission rates:** HAART < dual therapy < AZT monotherapy << no therapy
  - **Antepartum:** All women should receive HAART during Preg – generally a combination from at least 2 classes of drugs. Recommended regimen is Zidovudine/Lamivudine/Ritonavir/Lopinavir. Efavirenz (NNRTI) category D: A/w increased neural tube defects. Some women may opt to start HAART after 1st trimester & organogenesis.
  - **Intrapartum AZT mgmt:** AZT at onset of labor 2 mg/kg loading dose followed by 1 mg/kg/h until deliv. Optional for women on HAART w/ HIV viral load <400 copies/mL. Continue oral HAART intrapartum. Avoid artificial rupture of membranes & instrumentation (scalp electrodes, operative deliv) if poss.
  - **Postpartum:** Infants should receive AZT for 6 w. Infants born to mothers not on HAART should receive 3 doses of nevirapine. Mat HAART continuation is essent given high rates of nonadherence & subseq mortality postpartum.

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Mode of deliv: CD ↓ transmission rates in women NOT receiving HAART & zidovudine monotherapy (2–4×). No signif difference in transmission rates btw CD & VD in women on HAART. CD indicated if viral load >1000 copies/mL. 3 h of AZT should be administered prior to operation if poss. Duration of ROM a/w transmission in women w/ unsuppressed viral load → best to perform CCD prior to ROM or active labor.

Breastfeeding not recommended in developed countries even when mother on HAART, due to postnatal transmission risk (*MMWR Morb Mortal Wkly Rep* 1985;34:721). Rate of HIV transmission ~10% from breastfeeding, but varies based on mat CD4 count, HIV viral load, & HAART use. In developing world, *do* recommend breastfeeding b/c infant mortality from HIV offset by increased diarrheal & PNA illness in formula-fed infants (*JAMA* 2006; 296:794).

TORCH INFECTIONS

- ***T***-oxoplasmosis, ***O***-ther (Syphilis, Varicella, Parvo), ***R***-ubella, ***C***-ytomegalovirus, ***H***-erpes simplex virus
- Infections classically transmitted uteroplacetentally or during deliv
- **General rule:** ↑ gestational age @ time of infxn = ↑ transmission rate
- Rubella & syphilis routinely screened in Preg, others if indicated by Hx/risk factors
- Most carry risk of IUFD, prematurity, growth restriction in addition to congen defects

Toxoplasmosis (*Clin Infect Dis* 1994:18:853; *Clin Infect Dis* 2008;47:554)

- **Epidemiology:** ~38% of women have immunity. Incident infxn during Preg is 0.2–1%. Congen infxn due to re-infection rare. Congen toxoplasmosis incid 1–2 cases out of 100000.
- **Microbiology:** *Toxoplasmosis gondii:* A ubiquitous protozoan parasite. Life cycle: Cat (definitive host of parasite) intestines produce oocysts which produce sporozoites → passed in feces → animals eat sporozoites → cysts form in bone & muscle → humans eat raw, undercooked meat, consume the tissue → infxn. OR, humans ingest oocysts while handling cat litter or soil.
- Maternal–fetal transmission occurs during **active phase of new infxn.** Transmission rate btw around 30%. Likelihood of **transmission ↑ w/ gestational age – 15% at 13 w, 44% at 26 w, 71% at 36 w.** Severity of congen infections peaks during transmission around 24–30 w.
- **Clinical manifestations:** Mat usually subclinical or nonspecific (fever, malaise, LAD, myalgia). Fetal classic triad of **chorioretinitis, hydrocephalus, intracranial calcifications.** Also seizures, jaundice, HSM, anemia. Late manifestations, ocular, & neurologic (developmental delay). Subclinical dz more common – only 10% show signs of congen infxn.
- **Dx/screening:** No univ screening. Dx by mat serology. A **single bld test does not distinguish btw acute & chronic infxn.** Nor does IgM vs. IgG distinguish, as both persist in chronic infxn. *Rising* titers demonstrate new infxn → 4× ↑ or greater done at least 2 w apart (stable titers = chronic infxn which poses no risk to fetus). Once new infxn documented: PCR of amniotic fluid. US surveillance of fetal dev & manifestations of infxn.
- **Rx** (*Lancet* 2004;363:1965): **Spiramycin** (1 g TID) or **pyrimethamine & sulfadiazine w/ leucovorin** (teratogenic risk in 1st trimester w/ latter combo). Rx reduces serious neurologic sequelae. Unclear if rx prevents transmission & ocular sequelae.
- **Prevention:** Hand hygiene, avoiding uncooked meats, cats, unfiltered water, & travel to less developed countries

Syphilis (see below)

Varicella virus (VZV) (*BJOG* 2011;118:1155)

- **Epidemiology:** 90% of women are infected (chickenpox) before adulthood. VZV incid in Preg ~5/10000.
- **Microbiology:** Herpes virus responsible for **1° infxn known as VZV (chickenpox) w/ subseq reactivations known as zoster.** Mat zoster (shingles) rarely a/w congen VZV syn.
- Clinical manifestations (*Obstet Gynecol* 1987;69:214): Mat VZV infxn can be sev. VZV PNA = common complication (10–20%) w/ 20–40% mortality w/o antiviral therapy. Congen syn rare <2%. Transplacental transmission <20 w gestation characterized by limb hypoplasia, cutaneous scars, neurologic abnormalities, ocular abnormalities, high mortality. After 20 w transmission, neonat dz 1° infxn near term (w/i 5 d of deliv) neonat mortality as high as 30%. Infxn >5 d from deliv, mat Ab xfer → more benign neonat infxn.

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- **Dx/screening:** Mother: Characteristic vesicular papules in different stages of progression. Culture or immunofluorescence studies. Serology early in infxn can confirm mat nonimmunity. PCR testing of amniotic fluid + US to detect fetal infxn.
- **Rx:** 1° chickenpox or exposed & VZV IgG negative: Antiviral therapy w/i 24 h of rash appearance. Acyclovir 800 mg 5× daily or Valacyclovir 1 g TID for 7 d. VZV zoster secondary infxn: Ig w/i 72 h of exposure. May be effective up to 10 d after exposure. Pregnant women w/ varicella PNA should be admitted & treated w/ IV acyclovir.

Parvovirus (*N Engl J Med* 1987;316:183; *Prenat Diagn* 2011;31:419)

- **Epidemiology:** Incid of acute parvovirus in Preg = 3%. By adulthood 30–60% of women have had infxn.
- **Microbiology** (*Rev Med Virol* 2003;13:347): Risk of vertical transmission to fetus ~33%. Virus affects fetal erythroid progenitor cells.
- **Clinical manifestations:** Children & adults → erythema infectiosum: Lace-like rash often on face "slapped check," arthropy, aplastic anemia. Fetal infxn: **Hydrops & stillbirth <24 w;** >24 w, persistent risk of hydrops, but ↓ likelihood of sev infxn & death. Hydrops from anemia → reduced survival of fetal red cells → high-output CHF.
- **Dx/screening:** Exposed women should be tested w/ serology: **+ IgM w/o IgG =** acute infxn. PCR amniotic fluid + US to confirm dx
- **Rx:** W/ confirmed infxn → **surveillance for** up to 12 w. **Weekly US & MCA dopplers** to look for fetal anemia. Intrauterine xfusion can be done to correct fetal anemia & ↓ fetal mortality.

Rubella (*Lancet* 1982;2:781; *Glob Libr Women's Med* 2012)

- **Epidemiology:** Rare in the US given immunization programs. ~90% of pop immune
- Congen rubella extremely rare – <1 case/y in US recently
- **Microbiology:** Self-limited viral infxn transmitted in droplets or nasopharyngeal secretions from infected persons, commonly from contact w/ infected child. Congen infxn occurs via hematogenous spread across placenta. **Earlier transmission = higher likelihood of sev defects.**
- **Clinical manifestations:** Mat often subclinical: Fever, desc maculopapular rash, LAD (post auricular), URI-like, nonspecific sx. Infxn in 1st trimester usually results in miscarriage. Infxn **after 20 w unlikely to result in neonat manifestations.** Classic fetal syn: Growth restriction, cataracts, cardiac defects, hearing defects, hepatosplenomegaly. Late manifestations: DM, thyroid disorders, panencephalitis.
- **Dx/screening:** Univ screening at initial prenatal visit → nonimmune pts vaccinated postpartum. Dx by serology titer immediately following exposure. If Ab + → woman likely immune, no risk to fetus. Conversion of (–)Ab or 4× ↑ titer indicates acute infxn (rpt titers 2–4 w apart). Confirm by IgM or direct PCR of fetal bld.
- **Rx/prevention:** Mat supportive measures. No rx exists for preventing transmission or for fetal infxn. Nonimmune mothers should be vaccinated postpartum. MMR vaccine should not be administered to pregnant women b/c of theoretical risk of transmission from live virus. Advised to avoid conception for 1 mo following vaccine

Cytomegalovirus (CMV) (*Infect Dis Obstet Gynecol* 2011;2011:1)

- **Epidemiology:** Most common congen infxn. Birth prevalence ~0.5%. Seropositivity in childbearing women ~58% in US. Risk factors: Low socioeconomic status (near 100%), non-White, multiparous. Most common infectious cause of sensorineural hearing loss.
- **Microbiology:** Herpes virus family, latent in numerous organs following infxn. Transmitted by close interpersonal contact including sexual contact & breastfeeding. Congen CMV: Transplacental transmission. Peripartum transmission does not harm dev of neonate.
- **Transmission** (*Obstet Gynecol Surv* 2010;65:736): 1° mat infxn, ~35% transmission. More likely to cause fetal infxn & sequelae. Reactivation of latent virus: 1–2% transmission rate. Reinfection w/ different strain poss.
- **Clinical manifestations:** 1° CMV – asx or a/w a mononucleosis-like syn. Fetal infxn & sequelae more common at <20 w gestation. 90% are asx; 5–10% overtly symptomatic w/ 5% mortality; 50–60% w/ sev neurologic morbidity: **Microcephaly, ventriculomegaly, chorioretinitis, HSM, sensorineural hearing loss.** Late infxns a/w hepatitis, PNA, purpura, & thrombocytopenia.
- **Dx/screening:** Routine screening not currently recommended in US. Dx by seroconversion during Preg. IgM helpful for reactivated infxn. Low IgG avidity

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indicative of primary infxn (can perform avidity testing). Viral culture can be performed, but does not distinguish btw new & recurrent. US screening for anomalies should be performed in suspected case. If CMV infxn present → amniocentesis to detect fetal infxn.

- **Prevention:** Hygienic precautions: Washing hands, avoidance of close contact
- **Rx:** High-titer CMV Ig may ↓ transmission & fetal/neonat morbidity

Herpes Simplex Virus (HSV) *(N Engl J Med* 1997;337:509)

- **Epidemiology:** HSV-1 or HSV-2 seroprevalence in pregnant females up to 72%. Congen HSV very rare, 1 in 5000–20000. Seroconversion during Preg = 3.7% in women seronegative to both types.
- **Microbiology:** 50–70% of genital HSV caused by HSV-2. Genital HSV-1 ↑ due to oral–genital practices. Transmission can occur transplacentally (rare) or through **contact w/ mother's genital tract during labor/deliv.** Mat **1° infxn (0.1% incid)** a/w **higher transmission rates at deliv** than recurrent infxn (mat antibodies are protective).
- **Clinical manifestations:** 1° infxn: Fever, malaise, dysuria, tender inguinal, LAD, painful genital ulcers. Many pts have mild or **subclinical presentation. Vesicles** → crusting ulcers. Recurrent episodes vary in frequency, usually milder & shorter than 1° episode. Latency: Dorsal nerve roots btw episodes. Neonat HSV: Mucocutaneous involvement (~45%), CNS dz (~33%), dissem dz w/ multiorgan involvement (~25%). Congen infxn extremely rare, can cause systemic dz w/ mortality >50%. Late trimester mat infections correlated w/ increased rates of preterm labor, preterm birth, & IUGR.
- **Dx/screening:** Univ screening not recommended. Dx by culture or PCR if lesion present. Serology can distinguish HSV type; IgM indicative of acute infxn.
- **Rx** (*MMWR Recomm Rep* 2010;59:1): 1° infxn: **Acyclovir** 400 mg TID × 7–10 d or Valacyclovir 1 g BID × 7–10 d. Recurrent infxn: Acyclovir 400 mg TID × 5 d or Valacyclovir 500 mg BID × 3 d. Suppressive therapy recommended for women w/ **recurrent** genital HSV from 36 w until deliv: Acyclovir 400 mg TID or Valacyclovir 500 mg BID. At time of deliv, **careful exam of woman's genital tract** should be performed. Women w/ active lesions of vulva, vagina, or cervix **should be offered CD.** Lesions on buttocks, mons, thighs, or anus can be covered during deliv.

OTHER INFECTIONS IN PREGNANCY

Influenza *(Obstet Gynecol* 2010;115:717) See also Chap 13.

- **Epidemiology:** During flu pandemics (including 2009 H1N1), pregnant women ↑ mortality rate, ↑ hospitalization, ↑ ICU admission, & ↑ deaths
- **Clinical manifestations:** Influenza → critical illness in Preg & carries much higher mortality rate. Physiologic changes of Preg → **less cardiopulmonary reserve** & **altered immune system.** Transplacental transmission rare & insig. Mat illness may lead to premature deliv.
- **Dx/screening:** Rapid flu testing available in 15 min or less, but sens is fairly poor ~63%. In pregnant & recently (<2 w) postpartum women, **rx should be administered clinically. Do not await diagnostic results.**
- **Rx:** Neuraminidase inhibitors. Ppx for exposed: Oseltamivir 75 mg daily × 10 d or Zanamivir 10 mg daily × 10 d. Rx: Oseltamivir 75 mg BID × 5 d or Zanamivir 10 mg BID × 5 d.
- **Prevention:** All pregnant women should receive inactivated influenza vaccination regardless of gestational age, & preferably by the beginning of flu season.

Hepatitis B Virus (HBV) And see Chap 15.

- **Epidemiology:** Prevalence ~1% US & 15–20% endemic areas (SE Asia, China, sub-Saharan Africa). Major source of morbidity from hepatitis, cirrhosis, & HCC. 5–10% of acutely infected will become chronic carriers. In endemic areas, perinatal is primary form of transmission.
- **Microbiology** (*JAMA* 1985;253:1740): Maternal–fetal transmission primarily during deliv. Transmission 40–90% w/o ppx, much higher if HBeAg +. CD does not prevent transmission. Breastfeeding does NOT ↑ rate of transmission (*Obstet Gynecol* 2002;99:1049).
- **Clinical manifestations:** Mat 1° infxn: Abdominal pain, fever, N/V, jaundice. Almost all infected infants become chronic carriers, although infxn generally asx. Infected newborns have risk for liver dz later in life.

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- **Dx/screening:** Dx by + surface Ag (HBsAg). Immunity is indicative of loss of HBsAg & appearance of HBsAb (Ab). IgM anti-HBc is indicative of primary infxn; sometimes only sign of infxn btw loss of HbsAg & rise of HBsAb. HBeAg a marker of high infectivity, carries high vertical transmission rates. Chronic infxn is determined by persistence of HBsAg >6 mo. ACOG recommends univ screening by checking HBsAg in prenatal panel.
- **Rx:** Vaccination universally recommended if serologically negative. Lamivudine during 3rd trimester may ↓ rate of transmission (*Obstet Gynecol* 2010;116:147). HepBIg & HBV vaccine recommended as ppx for neonates of HbsAg+ women. ↓ rate of transmission by almost 90% (*JAMA* 1985;253:1740).

Hepatitis C Virus (HCV) (*Hepatology* 2001;34:223; *Am Fam Physician* 2010;82:1225) See Chap 15.
- **Epidemiology:** 1.8% of noninstitutionalized persons carry HCV antibodies
- **Microbiology:** Vertical transmission ~2% – primarily during deliv. Risk factors for increased transmission include increased viral load, HIV coinfection, mat drug use, prolonged ROM, procedures during labor (fetal scalp electrode, operative vaginal deliv). CD does not appear to lower rates (*Arch Gynecol Obstet* 2011;283:255). Breastfeeding does not to appear to ↑ transmission. Infected infants are generally asx, sometimes w/ temporary transaminitis.
- **Dx/screening:** Hepatitis C screening is not univ; based on risk factors. HCV Ab + → obtain viral load, genotype. HCV by RIBA if concern for false-positive.
- **Rx:** Std – combined pegylated interferon alfa-2a & ribavirin. Not safe rx during Preg, ribavirin = teratogenic. Vaccinate for HBV if not infected or immune.

Tuberculosis (TB) (*Chest* 1992;101:1114)
- **Epidemiology:** Same in Preg as general pop. Btw 5–10% of reproductive women have reactive tuberculin skin test. Worldwide TB = **leading infectious dz cause of mat mortality.** Risk factors in US: Low socioeconomic status, urban area, IV drug use, homelessness, immigrant from underdeveloped country, & incarceration.
- **Clinical manifestations:** 3–4% develop active TB during 1st year. 5–15% will later develop an active infxn. Active TB: **Cough, fever, hemoptysis, weight loss, fatigue, night sweats.** Untreated active infxn has a 50% mortality rate at 5 y. Active TB → congen infxn through transplacental transmission. Extremely rare & a/w miliary TB.
- **Dx/screening:** Screening should occur in women w/ risk of progression from latent to active. **TST or interferon gamma release assay.** Those w/ positive testing should undergo CXR.

Classification of TST reaction

TST size (mm)	Group in which this is considered positive
≥5	HIV +, close contact w/ cases, abn CXR, immunosuppressed pts (chemo, glucocorticoids)
≥10	Persons at risk of reactivation, chronic renal failure, DM, malignancies, children <4 yo, foreign born from TB prevalent countries, residents & employees of high-risk settings
≥15	Healthy individuals w/ low likelihood of true TB infxn

From Jensen PA, Lambert LA, Iademarco MF, et al. Guidelines for preventing the transmission of Mycobacterium tuberculosis in health-care settings, 2005. *MMWR Recomm Rep.* 2005;54(RR-17):1–141.

- **Rx** (*MMWR* 2000;49:1):
  Latent TB: 9 mo INH 5 mg/kg/d. Can delay rx of latent TB until 2–3 mo PP unless high risk of progression to active dz (HIV+, recent contacts)
  Active TB: INH, rifampin, ethambutol ± pyrazinamide × 9 mo minimum. Streptomycin should be avoided in Preg (congen deafness). Breastfeeding not contraindicated during rx. Infant should be given pyridoxine (B6) if mother is on INH.

HUMAN PAPILLOMA VIRUS (HPV)

Epidemiology
- Most common sexually transmitted virus worldwide
- Most common viral cause of cancer worldwide (5% of all cancers)
- Worldwide prevalence around 10% although 80% of sexually active adults will acquire an HPV infxn in their lifetime (*Am J Epidemiology* 2000;151:1158)

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- Prevalence highest in teenagers & young women shortly after sexual debut (*JAMA* 2007;297:813)
- **Risk factors:** Young age, early age at 1st intercourse, number of sexual partners, other STIs (HIV, HSV, chlamydia), smoking, low education, minority race

Microbiology

- DsDNA virus. ~40 strains of HPV infect the anogenital tract & can be a/w anogenital warts & cancer including **cervical, vaginal, vulvar, oropharyngeal, anorectal, & penile.** High-risk HPV types cause cancer: HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68. Types 16 & 18 account for 70% of cancer cases (*N Engl J Med* 2003;348:518). Low-risk HPV types cause warts: HPV6, 11, 42, 43, 44.
- Transmission usually through intercourse, but can occur through close personal contact.
- Warts esp contagious → infectivity up to 60%. Vertical transmission may be as high as 55% during vaginal deliv. Infxn generally **transient** → 90% cleared by 24 mo (*Vaccine* 2006;24:S42).
- Risk factors for persistence/progression of HPV to precancerous lesions: Older age, immunosuppression, cigarette smoking, high-risk genotypes (*Vaccine* 2006;24:42).
- HPV's carcinogenic potential related to (*J Virol* 1989;63:4417)
  E6 gene a/w inactivation of p53 (tumor suppressor prot)
  E7 gene a/w inactivation of the Rb apoptotic pathway

Clinical Manifestations

- Based on strain & site of infxn. Include genital & nongenital warts (condyloma acuminatum), Bowen's dz (squamous carcinoma in situ), giant condyloma, & intraepithelial neoplasia.
- **Cervical dysplasia:** HPV infxn leading to cellular atypia & progression from low-grade to high-grade histology is the basis for cervical cancer (*J Pathol* 1999;189:12) See also Chaps 1 (screening) and 21 (cancer).
- **Genital warts (condylomata acuminata):** Caused by low-risk HPV 6 & 11 (90%) (*MMWR Recomm Rep* 2010;59:1). Usually asx papillomatous growths, commonly appear around introitus. Vary in appearance: Hyperpigmented, papilliform, flat, papular, pedunculated (in contrast to **condylomata lata** of syphilis which is flat & velvety). Regression occurs ~20–50% of cases. Persistence a/w immunocomp status & dev of squamous cell carcinoma. Lesions a/w HPV 6 & 11 are almost 100% benign. 30% of flat condylomas a/w high-risk types & have oncogenic potential.

Diagnostic Studies

- **HPV testing:** Current testing exists in either a binary (± high-risk HPV) form or specific genotyping that can detect presence of specific strains (HPV16, HPV18). See Ch. 1 and 21.
- **Genital warts:** Dx of **condyloma** made by inspection. 5% acetic acid solution → causes acetowhite change for easier identification. Bx considered if dx uncertain, lesion does not respond to rx or worsens w/ therapy, pt immunocomp, warts are pigmented, indurated, fixed, bleeding, or ulcerated.

Treatment (*MMWR Recomm Rep* 2010;59:1)

- Rx goal for **genital warts** is amelioration of sx & cosmetic improv
- CDC recommended regimens:
  Patient-administered:
  Podofilox 0.5% gel applied BID × 3 d followed by 4 d off, up to 4 cycles
  Imiquimod 5% cream applied qhs 3 × a week for up to 16 w
  Sinecatechins 15% ointment TID for up to 16 w
  5-fluorouracil 5% cream applied BID × 5 d followed by 9 d off, up to 4 cycles
  (Safety of all of these therapies in Preg is unk & should not be used)
  Provider-administered: Cryotherapy, trichloroacetic acid 85%, surgical removal (excision, laser, electrosurgery, infrared coagulation)
- Ppx (*CDC-ACIP* 2011)
  Bivalent (*Cervarix)* & quadrivalent (*Gardasil*) vaccine. Quadrivalent includes HPV 16, 18 as well "low-risk" strains HPV 6, 11. Vaccination recommended in females & males 11–26 yo. Bivalent effective against HPV 16, 18.

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SYPHILIS

Epidemiology *(MMWR 2003;52:1117)*

- Once highly prevalent dz now uncommon in US & developed countries.
- Increasingly common in MSM populations. Up to 25% coinfection rate w/ HIV – most prevalent in Africa, India, SE Asia, & the Caribbean.

Microbiology

- **Caused by the spirochete: *Treponema pallidum.*** Sexually transmitted through microabrasions of intercourse or vertical transmission. Following infxn, the organisms invade LN to disseminate to other organs.
- Sexual transmission occurs during both primary & secondary infxn. Rate ~30%. Requires open lesions w/ organisms present

Clinical Manifestations

- Primary syphilis
  - **Chancre** at site of inoculation. Ulcer is usually single, **painless,** indurated, a/w LAD. Most common location in women: Labia majora + minora, fourchette, cervix, perineum. Generally heal w/o rx secondary to natural immune resp.
- Secondary syphilis
  - Weeks to months after primary infxn. ~25% develop systemic illness.
  - **Rash** (typically palms & soles), up to 90% of pts. 0.5–2 cm in diameter often referred to as copper pennies.
  - **Condyloma lata:** 10–15% pts. Large raised white lesions usually near chancre
  - Highly infectious – not to be confused w/ condyloma acuminatum (HPV/warts)!
  - **Systemic sx:** Fever, HA, malaise, LAD.
  - Immunocomp can develop ocular dz, ulcerative lesions
- Latent syphilis
  - **Asx w/ + serologic testing.** If pt never had sx = **latent of unk duration.** Early/late distinction is <1 y (**early latent**) vs. >1 y (**late latent**) from sx. Pts >1 y from sx are relatively noninfectious.
- Tertiary syphilis (late)
  - Develops after latent period of 1–30 y after primary infxn. Most common manifestations: CNS (neurosyphilis), CV (aortitis), Gummatous (on skin & bones)
  - **Neurosyphilis:** Syphilitic meningitis (syphilis in CSF), meningovascular syphilis (ischemia/infarction of CNS), parenchymal syphilis (tabes dorsalis, general paresis)
- Congen syphilis
  - Preg does not change course of mat dz. Fetal manifestations depend on time of transmission. Early infxn → high rates of SAB. Late infxn → placental involvement, hydrops, IUGR, stillbirth. **Transmission ↑ w/ GA, but severity ↓.**
  - **Vertical transmission highest w/ 1° or 2° syphilis (50%).** Rx lowers risk of transmission to 1–2%. Congen syphilis is classified as **early** or **late. Early: Sx prior to 2 yo:** Rhinitis (snuffles), rash, PNA, HSM, osteochondritis (similar to adults). **Late: Sx after 2 yo:** Saddle nose, Hutchinson's teeth (peg-shaped incisors), keratitis, deafness, gumma, skeletal & CNS malformations.

Diagnostic Studies

- Organism cannot be cultured. Definitive dx made by direct visualization of organisms w/ either dark field microscopy (gold std), direct fluorescent Ab, or PCR.
- **Serologic testing:** Nontreponemal (VDRL, RPR) vs. treponemal (FTA-ABS, TPA)
  - Nontreponemal tests – used for pop screening (Preg, MSM). Low cost, widely available. Use titers to monit resp to rx. 4-fold change in titer necessary to demonstrate resp to rx. False positives a/w Preg, autoimmune dz, IV drug use, TB, rickettsial infxn, hepatitis, malig. Sensitivities can be poor esp during primary & late stages (70–80%).
  - Treponemal tests – more specific, generally used for confirmatory testing. Cannot be used alone to diagnose rpt infxn as antibodies may stay positive following successful rx. False positives a/w lupus, Lyme's, leptospirosis.
- **Preg:** Screening at the 1st prenatal visit w/ nontreponemal test followed by rpt testing in 3rd trimester & at deliv if pt is high risk.
- Lumbar puncture w/ signs of tertiary/neurosyphilis, or HIV+ & latent syphilis

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Treatment

Treatment regimens for syphilis		
Adult recommended regimens	**PCN G**	**PCN allergic**
Primary or secondary syphilis	2.4 million units IM in single dose	Doxycycline 100 mg BID × 14 d + Tetracycline 500 mg QID × 14 d
Early latent syphilis	2.4 million units IM in single dose	Doxycycline 100 mg BID × 28 d + Tetracycline 500 mg QID × 28 d
Late latent or latent of unk duration	2.4 million units IM QW × 3 doses	Doxycycline 100 mg BID × 28 d + Tetracycline 500 mg QID × 28 d
Tertiary syphilis	2.4 million units IM QW × 3 doses	Consult ID
Neurosyphilis	Aqueous crystalline PCN G 18–24 U IV daily × 10–14 d OR PCN 2.4 IM daily + Probenecid 500 mg QID × 10–14 d	CTX 2 g IM or IV daily ×10–14 d OR Consult ID
Pregnant women	PCN G per stage of infxn	No proven alternatives. Desensitization.

- **Jarisch–Herxheimer rxn:** Febrile rxn w/i 24 h of rx → release of inflamm proteins from dead or dying organisms. Can induce preterm labor or cause fetal distress in pregnant women.
- Eval should be made at 6 & 12 mo after rx (24 if latent dz or worse). Serologic testing should show decline by 4 fold. Failure of decline = re-evaluation for HIV, CSF exam should be considered. Retreatment involves 2.4 million units IM for 3 w.
- Partners exposed w/i 90 d of dx & partners of pts w/ syphilis of unk duration & high nontreponemal titers (>1:32) should be treated presumptively (*MMWR Recomm Rep* 2010;59:1).

MOLLUSCUM CONTAGIOSUM

Epidemiology (*J Am Acad Dermatol* 2006; 54:47)

- Common worldwide. A/w childhood, immunodeficiency (including HIV) & atopic dermatitis. Seropositivity up to 25% in general pop.

Microbiology

- **Pox virus** spread through direct skin-to-skin contact or through fomites
- Considered a sexually transmitted infxn when found in genital region

Clinical Manifestations

- Firm dome-shaped papules on skin w/ shiny surface & central umbilication
  Appear anywhere except palms & soles, but generally localized. Commonly in skin folds – axilla, popliteal folds. Sexually transmitted areas include groin, genitals, thighs, & lower abd. Dermatitis can occur around the lesion – erythema & pruritus.
- Widespread, large >15 mm lesions should raise suspicion for HIV+.
- Natural Hx in immunocompetent person: Spont resolution in months
  Lesions can last years (*Int J Dermatol* 2006;45:93)

Diagnosis

- Clinical – based on appearance of lesion. Histology: H&E reveals **Henderson-Patterson Bodies:** keratinocytes w/ cytoplasmic inclusion bodies

Treatment

- No clear evid for rx given lesions are self-limiting. Rx of sexually transmitted lesions indicated to avoid transmission of dz. **Perform comprehensive body exam** to locate all lesions for rx.

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- **Cyrotherapy:** Liquid nitrogen applied 6–10 s (can cause hypopigmentation)
- **Other 1st-line options:** Curettage, cantharidin, podophyllotoxin (*Cochrane Database Syst Rev* 2009)

CHANCROID

Epidemiology
- Uncommon in US & developed countries. Major cause of genital ulcers in developing countries. In US: Minority pop, female prostitutes, drug users. **Up to 10% have concurrent syphilis infxn.**

Microbiology
- ***Haemophilus ducreyi*** – gram negative rod (school of fish appearance). Extremely infectious. Incubation 3–10 d, reliant on break in skin. Cytotoxin secreted causes cellular damage & ulcer dev.

Clinical Manifestations
- **Erythematous papule,** 1–2 cm diameter → pustular & ulcerates. Distinguished from syphilis as it is painful, sometimes purulent & base is red & granular. Typically found on fourchette, vestibule, clitoris & labia (*Clin Infect Dis* 1997;25(2):292). Often single lesion but can be multi & bleeds.
- LAD present in ½ cases & can become fluctuant & painful.

Diagnosis (*MMWR Recomm Rep* 1990;39:1)
- Difficult lab dx due to need for culture on special media (sens <20%)
  Special PCR test exists by private clinical labs. "Probable" dx based on clinical sx & negative testing for syphilis & HSV.

Treatment (*MMWR Recomm Rep* 2010;59:1)
- **CDC recommendation:** Azithromycin 1 g PO or CTX 250 mg IM or Ciprofloxacin 500 mg PO BID × 3 d. Ciprofloxacin contraindicated in pregnant & lactating women.
- Pt should be re-examined at 3–7 d after initiation of therapy. Lack of clinical improv w/i 7 d, consider incorrect dx, coinfection, HIV+, nonadherence, drugs resistance. Healing is slower for immunocompromised (HIV), uncirc men. LAD might require needle aspiration or drainage

PUBIC LICE

Epidemiology
- Generally transmitted sexually. Less commonly transmitted by fomites on clothing & bedding. Most commonly affected are teens, young adults.

Etiology
- **Phthirus pubis or "crab louse**" is primary organism. Crab-like claws attach to human hair, feeding on human bld, laying eggs. Eggs incubate for 6–8 d before hatching.

Clinical Manifestations
- **Pruritus** from attachment & biting
- **Maculopapular lesion may develop** (lower abd, prox thighs, buttocks)
- Manifestations can occur in any hairy area, but pubic area is often involved

Diagnostic Studies
- Demonstration of louse or nits (eggs) under microscopic exam
- Dx should trigger eval of family members, sexual contacts, & for other STIs.

Treatment (*MMWR Recomm Rep* 2010;59(RR-12):1)
- Pediculicides kill both lice & eggs
- **CDC rec: Permethrin 1%** cream or Pyrethrins w/ piperonyl butoxide (washed off after 10 min). Alternative: Malathion 0.5% (8–12 h) or Ivermectin (250 ug/kg) (for rx failure). Permethrin, Pyrethrin safe in pregnant & lactating women.
- Re-evaluate after 7–10 d of rx. Bedding or clothing should be bagged or washed. Lice will die 48 h after removal from host or temperature >125°C.

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GENITAL ULCERS

Ulcerative lesions of the genital tract

	Syphilis	Herpes	Chancroid	Lympho-granuloma venereum	Granuloma inguinale/ Donovanosis
Organism	Treponema pallidum	Herpes simplex I or II	Haemophilus ducreyi	*Chlamydia trachomatis* Serovars L1, L2, L3. More prevalent in Africa, India, SE Asia, Caribbean	*Klebsiella granulomatis* (gram neg encapsulated bacterium). Needs rpt exposure, long incubation.
Lesion characteristic	Single painless indurated ulcer w/ rolled edges	Painful fluid-filled vesicles w/ erythematous base	One or more painful ulcers varying in size	Single ulcer or papule; can be painful or painless. Infected lymph tissue → necrosis in nodes → abscess.	Painless nodules → ulcerative lesions that bleed easily on contact; can become sclerotic & very large. Usually on genitalia, cervix. Resemble keloids.
LAD	Bilateral, nontender	Uni- or bilateral, tender	Unilateral, tender, suppurative, often fluctuant	Unilateral tender, can suppurate or mat together. Stages: Ulcer →healed →LAD →fibrosis/ strictures (*Clin Infect Dis* 2006;42:186).	None
Dx	Dark field microscopy, serology w/ treponemal test confirmation	Culture or PCR of lesions	Culture or special PCR testing	Chlamydia serology correlated w/ presentation, PCR testing. IgG >1:64. Low success w/ cx. PCR testing exists.	Donovan bodies on microscopy (safety pin appearance) on Wright–Giemsa stain.
Rx	Benzathine PCN G. See section for algorithm based on stage of presentation.	Acyclovir or Val-acyclovir. See section for specific dosing.	Azithromycin 1 g PO or CTX 250 mg IM or Ciprofloxacin 500 mg PO BID × 3 d or Erythromycin 500 mg PO TID × 7 d	Doxycycline 100 mg PO BID × 3 w (nonpregnant) Alt: Erythromycin 500 mg QID × 3 w or Azithromycin 1 g weekly × 3 w. Aspirate buboe to prevent rupture. Check & treat <60 d sexual contacts. (*MMWR Recomm Rep* 2010;59:1)	Doxycycline 100 mg BID × 3+ weeks & resolution of lesions Alt: Azithromycin 1 g weekly; Ciprofloxacin 750 mg BID; Erythromycin 500 mg QID (preferred for Preg) or Bactrim BID, all × 3+ weeks & resolution of lesions Add aminoglycoside if no resp.

From Workowski KA, Berman S. Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep*. 2010;59(RR-12):1–110 and Holmes K, Sparling P, Stamm W. *Sexually Transmitted Diseases*. 4th ed. New York, NY: McGraw-Hill; 2008.

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TYPES OF HYSTERECTOMY

Simple (Extrafascial) Hysterectomy

- Only uterus (& cervix) removed. For nonmalignant diagnoses or stage IA1 cervical cancer.

Radical Hysterectomy

- Uterus removed en bloc w/ parametrium (round, broad, cardinal, & uterosacral ligaments) & upper vagina. Ovaries can be preserved; bilateral pelvic LND usually included. For cervical cancer greater than stage IA1 or endometrial cancer involving cervix.
- **Piver–Rutledge–Smith classification (1974):** 5 classes of hysterectomy (I–V)
  - **I:** Simple extrafascial hysterectomy: Uterus & cervix only
  - **II:** Modified radical hysterectomy (Wertheim's): Uterus, cervix, prox vaginal (1/3), parametrium/paracervix & uterine artery transected medial to ureter
  - **III:** Radical hysterectomy (Meigs–Wertheim): Uterus, cervix, prox vagina (1/3), uterine artery ligated at origin
  - **IV:** Extended radical hysterectomy: Uterus, cervix, 3/4 of vagina, superior vesical artery
  - **V:** Partial exenteration w/ removal of distal ureter &/or bladder

  Complications of radical hysterectomy (*Gynecol Oncol* 2009;114:75): Bladder/bowel dysfxn (up to 85%); lymphocyst requiring drainage (3%); vesicovaginal (1%) or ureterovaginal (2%) fistula; PE or deep vein thrombosis (1–3%).

Querleu–Morrow classification of radical hysterectomy

4 types of radical hysterectomy (A–D, below) based on lateral extent of resection. Applies to fertility preserving surgery and laparoscopic/robotic surgery.

Type	Description	Surgical considerations	Indication
A	Minimal resxn of paracervix	Paracervix transected medial to ureter but lateral to cervix. Uterosacral & cardinal ligaments transected close to uterus. Vaginal resxn (<10 mm).	Early invasive cervical cancer (<2 cm), advanced cervical cancer after chemoradiation
B	Transection of paracervix at level of ureter	Partial resxn of uterosacral & cardinal ligaments. Ureter unroofed & mobilized laterally. Vaginal resxn (10 mm).	Early cervical cancer (stage 1A)
C1	Transection of paracervix at junction w/ internal iliac artery (w/ nerve preservation)	Uterosacral ligament transected at rectum, cardinal ligament transected at bladder. Ureter mobilized. 15–20 mm of vagina resected. Hypogastric nerves identified, preserved.	Stages IB–IIA cervical cancer
C2	Transection of paracervix at junction w/ internal iliac artery (w/o nerve preservation)	Paracervix completely transected. Hypogastric nerves not isolated or preserved.	Stages IB–IIA cervical cancer
D1	Laterally extended endopelvic resxn	Resxn of entire paracervix (at pelvic sidewall) & hypogastric vessels	Pelvic exenteration
D2	Laterally extended endopelvic resxn	D1 + resxn of entire paracervix, hypogastric vessels, & adj fascial or musc structures	Pelvic exenteration

From Querleu D, Morrow CP. Classification of radical hysterectomy. *Lancet Oncol.* 2008;9(3):297–303. doi:10.1016/S1470-2045(08)70074-3.

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CERVICAL CANCER

Epidemiology (*CA Cancer J Clin* 2011;61:212)
- 2nd most common cancer in women worldwide
- **Mean age at dx:** 40–59 y; bimodal distribution peaks 35–39 y & 60–64 y
- 60% women w/ cervical cancer in developed countries were never screened or were not screened in past 5 y

Pathology (*J Clin Pathol* 1998;51:96)
- **Squamous cell carcinoma:** 80% of invasive cervical cancer
- **AdenoCa:** 20–25% of invasive cervical cancer. In 15%, lesion not visible (located w/i endocervical canal)
  Mucinous adenoCa: Most common type (well differentiated)
  Endometrioid carcinoma: 30% of cervical adenocarcinomas
  Clear cell carcinoma: 4% of adenocarcinomas. DES exposure ↑ risk
- **Adenosquamous carcinoma:** Benign & malig glandular & squamous elements. More aggressive than adenoCa.
- **Small cell carcinoma:** Neuroendocrine tumors. Clinically aggressive; ↑ propensity for metastases; a/w HPV18; CD56 marker often positive

Etiology (*J Pathol* 1999;189(1):1)
- Risk factors (*Int J Cancer* 2007;120:885)
  Lack of cervical cancer screening. Cigarette smoking: 2–3 fold ↑ risk in current & former smokers. Multi sexual partners (more than 6 partners significantly ↑ risk). HPV infxn.
  H/o STIs. Early age of sexual activity. ↑ parity. Long-term combined OCP use (higher hormone levels make cells vulnerable to mut). Immunosuppression (esp HIV). Low socioeconomic status. DES exposure in utero. No known racial predilection but mortality rate for black > white.

Role of HPV
- HPV detected in 99% of cervical cancer
- HPV types 16, 18, 31, 33, & 45 → high-risk types. Most common HPV 16 & 18.
  E1–E7 (early oncoproteins in cervical cancer) expressed in HPV positive cases (E1 & E2 → viral replication; E6 & E7 → viral transformation). E6 & E7 form complexes w/ p53 & pRB (tumor suppressor genes); E6 inactivates p53; E7 inactivates Rb.
- **CIN:** Precursor lesion. Cervical cancer may take >10 y.
  CIN 1: 57% spontaneously regress; 1% progress to carcinoma
  CIN 2: 43% spontaneously regress; 5% progress to carcinoma
  CIN 3: 30% spontaneously regress; 12% progress to carcinoma

Clinical Manifestations (*J Clin Pathol* 1998;51:96)
- Abn uterine bleeding or postcoital bleeding. Vaginal discharge (serosanguinous or yellow, foul smelling). Hematometra: Pelvic pain, difficulty w/ urination or defecation. Metastatic dz: Back pain, leg swelling (usually unilateral), & neuropathic pain.
- **Exam:** Firm barrel-shaped cervix; necrotic or friable lesion on cervix, poss extension into parametrium, vagina pelvic sidewall, & uterosacral ligament

Diagnostic Workup and Staging (see Table)
- Cervical Cytology Screening Guidelines (American Society for Colposcopy and Cervical Pathology (ASCCP), American Cancer Society (ACS), and U.S. Preventive Services Task Force (USPSTF)). See Ch. 1.
- Clinically staged. Advanced imaging does not influence staging dx.
- Inspection, palpation, CXR, colposcopy, cystoscopy, proctoscopy, IVP, bx of exophytic cervical lesions; cervical conization
- Preoperative imaging may guide mgmt. PET superior to CT & MRI for imaging of nodal dz: PET sens = 84%.

Treatment (see Table) (*Gynecol Oncol* 1980;9:90; *Gynecol Oncol* 1980;32:135)
- **Surg:** An option for stages IIA or less
- **Chemo & RT:** An option for stages IA2–IVB
- **Recurrent cervical carcinoma:** Evaluated w/ PET scan to exclude distant metastases
  Localized recurrence after Surg → RT or chemoradiation or Surg
  Central recurrences after definitive Surg or adjuvant RT: Pelvic exenteration. Rpt RT considered in selected pts.

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- **Fertility sparing Surg:**
  Radical trachelectomy (pts w/ up to stage IB1; tumor size <2 cm) similar recurrence rates to radical hysterectomy in carefully selected pts.
  Cervical conization in stage IA1 cancers

Posttreatment Surveillance

- Cancer detected w/i the 1st 6 mo after rx = persistent cancer
- F/u exam w/ pap q3mo × 2 y, then q6mo × 3 y, then annually

International Federation of Gynecology and Obstetrics (FIGO) staging for cervical cancer, 2009	
Stage I	Tumor confined to the cervix
IA	Microscopically invasive cancer
IA1	Stromal invasion of ≤3 mm in depth, extension of ≤7 mm
IA2	Stromal invasion of >3 mm but ≤5 mm, extension ≤7 mm
IB	Clinically visible lesion limited to cervix
IB1	Lesion ≤4 cm in greatest dimension
IB2	Lesion >4 cm in greatest dimension
Stage II	Tumor invades beyond the uterus; not to pelvic wall
IIA	Upper 2/3 vagina w/o parametrial invasion
IIA1	Lesion ≤4 cm in greatest dimension
IIA2	Lesion >4 cm in greatest dimension
IIB	Obvious parametrial invasion – no pelvic sidewall involvement
Stage III	Tumor extends to pelvic sidewall or lower 1/3 vagina &/or causes hydronephrosis
IIIA	Tumor invades lower 1/3 vagina, no extension to pelvic sidewall
IIIB	Tumor extends to pelvic sidewall &/or causes hydronephrosis
Stage IV	Tumor extends beyond the true pelvis or involves the bladder or rectal mucosa (bx proven)
IVA	Spread to adj organs
IVB	Spread to distant organs

From Current FIGO staging for cancer of the vagina, fallopian tube, ovary, and gestational trophoblastic neoplasia. *Int J Gynaecol Obstet.* 2009;105(1):3–4.

Management of cervical cancer by stage	
Stage IA1 – (fertility conservation desired)	Cold knife conization Postconization f/u: Pap smear, colposcopy, ECC every 3 mo AIS: 25% risk of residual dz in hysterectomy specimens after cervical conization w/ negative margins, 50% w/ positive margins: Every 4-mo f/u needed
Stage IA1 – (fertility not desired)	Simple hysterectomy
Stages IA2–IB2	Radical hysterectomy & pelvic LND Primary chemoradiation therapy (RT) equivalent to Surg (esp in medically unfit pts)
Stages II–IV	Chemoradiation Cisplatin = agent of choice for chemoradiation: Radiosensitizer, ↓ risk of progression of dz & local recurrence
Stage IVB	Single or combination chemo. Cisplatin resp rate: 20–25%. Combination chemo may have ↑ resp rates. Local radiation may be combined w/ chemo

Cervical Carcinoma in Pregnancy *(Best Pract Res Clin Obstet Gynaecol* 2005;19:611)

- **Stage IA1:** Follow w/ colposcopy each trimester; surgical rx after vaginal deliv if invasion <3 mm & no LVSI. Risk of hemorrhage at deliv ↑. Or C-section + simple hysterectomy (stage IA1) if childbearing complete.
- **Stage IA2** (Tumors >3–5-mm invasion): Can be followed until term; modified radical hysterectomy + pelvic lymphadenectomy at deliv or 6 w postpartum. Vaginal deliv acceptable; C-section necessary for stage IB & above.
- **Stages IB1–IIA dz:** Delay of rx can impact survival; if dx made after 20 w, rx can be postponed→ classical C-section; modified radical hysterectomy + pelvic/paraaortic LND. RT is as effective as Surg.

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- **Invasive cancer:** If at or near term, immediate deliv & definitive rx is recommended. At gestational age <20 w, termination of Preg & definitive rx is an option.
- Neoadjuvant chemo in Preg may be an option for stages IB2–IIB after appropriate counseling

UTERINE CANCER

Epidemiology (*Obstet Gynecol*; 2005;104:65:413; *J Natl Med Assoc* 2006;98:1930; *Cancer Control* 2009;16:53)
- Most common gynecologic malig; 4th most common cancer in females
- 8th leading cause of cancer-related death among women in US
- **Lifetime incid:** 2.6%; White > Black > Hispanic > Asian. Mortality: Black > White.
- **Median age at dx:** 67 y (5% <40 y; 90% >50 y)
- Tumors confined to the uterus in 75% of cases

Endometrial Hyperplasia (EH) (*Cancer* 1985;56:403)
- Precursor lesion of endometrioid EC. From continuous estrogen stimulation & relative progestin deficiency. Classification based on architecture (simple vs. complex) & cytologic features.
  Simple EH (w/o atypia): ↑ gland proliferation; abundant stroma; no nuclear atypia
  Complex EH (w/o atypia): ↑ gland:stroma ratio; crowded irreg glands; no nuclear atypia
  Simple EH w/ atypia: ↑ gland:stroma ratio; simple appearing glands; glands lined by atypical nuclei
  Complex EH w/ atypia: Markedly ↑ gland:stroma ratio, severely crowded glands; nuclear atypia
- D&C req prior to rx to rule out occult carcinoma. 43% have EC diagnosed at the time of hysterectomy for hyperplasia (*Cancer* 2006;106:1012)

Outcomes by type of endometrial hyperplasia

Pathology	Progression to cancer (%)	Regression (%)	Persistence (%)
Simple EH, w/o atypia	1	80	19
Complex EH, w/o atypia	3	80	17
Simple EH w/ atypia	8	69	23
Complex EH w/ atypia	29	57	14

From *Cancer*. 1985;56:403; *Hum Reprod*. 1999;14:479.

- **Rx of EH w/o atypia:**
  Progestins (cyclic or continuous); eg, MDPA 10 mg/d for 12–14 d for 3–6 mo or local progestogen (LNG IUD) or OCPs. Postmenopausal women: MDPA; D&C for f/u
  F/u: Rpt endometrial sampling if abn bleeding recurs
- **Rx of EH w/ atypia:**
  Hysterectomy. For fertility preservation or poor surgical candidates: LNG IUD or continuous progestins: Megestrol acetate (40–60 mg 2–4 times/d for 6 mo) → 94% regression rate. **F/u:** Endometrial bx or D&C q3mo for at least 1 y; if regression does not occur, progesterone dosage should be increased or hysterectomy considered.

Pathology (*J Clin Oncol* 2006;24:4783; *Am J Surg Pathol* 1994;18:687)
- **Grading:** Based degree of solid components, nuclear features, & architectural pattern
  Grade 1: 5% or less nonsquamous or nonmorular solid growth pattern
  Grade 2: 6–50% nonsquamous or nonmorular solid growth pattern
  Grade 3: >50% nonsquamous or nonmorular solid growth pattern
- **Epithelial tumors**
  Endometrioid adenoCa: 75–80% of EC; most common
  UPSC: 10% of EC; closely resembles tumors of the ovary and fallopian tube. More than 50% of pts w/ stage I UPSC have extrauterine dz. Poor prog; high risk of recurrence. EIC: Poss precursor of UPSC.
  Clear cell: 3–4% of EC. Poor prog; 20–65% 5-y survival
  Others: *Mucinous, secretory, squamous*
- **Mesenchymal tumors** (sarcomas): 2–5% of EC

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Epithelial endometrial cancer types	
Type I (90%)	**Type II (10%)**
Low-grade nuclei	High-grade nuclei
Endometrioid histology; background of EH	Papillary serous & clear cell histology
Estrogen-associated	Atrophic background/polyps
Good prog, younger age	Worse prog, early metastasis
PTEN, K-ras, DNA mismatch repair mutations	P53 mutations

From Bokhman JV. Two pathogenetic types of endometrial carcinoma. *Gynecol Oncol.* 1983;15(1):10–17.

Etiology *(Obstet Gynecol 2005;104:413)*

- ↑ unopposed estrogen → EH → EC
- **Microsatellite instability:** Germ-line mut in DNA mismatch repair genes (MLH1, MSH2, MSH6, PMS2) → Lynch II syn: 25–30% of all EC; 40–60% lifetime risk of EC
- **Risk factors for EC:** Prolonged unopposed estrogen (RR 10); chronic anovulation (eg, PCOS); BMI >30 (RR 2–5); diabetes & HTN (independent risk factors); Tamoxifen (RR 3–7); older age (RR 2–3); nulliparity (RR 3); early menarche, late menopause (1.5–3)
- **Protective factors for EC:** Smoking (RR 0.5); OCPs: ↓ EC risk by 40% up to 15 y after discontinuation; 12 y of use ↓ risk by 72%

Clinical Manifestations and Physical Exam *(Obstet Gynecol 2005;106:413)*

- **Presentation:** Abn uterine bleeding (10% postmenopausal bleeding is EC); chronic anovulation; abn pap smear 30–50%; asymptomatic 5%; leukorrhea 10%; hematometra due to cervical stenosis
- **Ddx:** Atropic vaginitis, fibroids, endometrial polyps, cervical carcinoma, CIN

Diagnostic Workup

- **Office endometrial sampling:** Least invasive approach
- **Pelvic US** (not diagnostic but may help triage pts): ET <5 mm = 99% NPV *(NEJM 1997;227:1792)*
- **Fractional D&C:** Office endometrial bx results correlate well w/ uterine curettage & ET up to 6 mm *(Acta Obst Gynecol Scand 2001;80:959)*
- Cervical conization if cervical involvement suspected to rule out primary cervical carcinoma
- **CA125:** Elevated in women w/ advanced stage dz & UPSC. Not routinely performed.
- **Chest radiograph, CT/MRI:** If extrauterine dz suspected or CA125 elevated.

FIGO staging for endometrial cancer, 2009			
		2-y survival (%)	**5-y survival (%)**
Stage I	Tumor confined to uterus		
IA	No or <50% myometrial invasion	IA: 97	IA: 91
IB	≥50% myometrial invasion	IB: 94–97	IB: 85–91
Stage II	Tumor invades the cervical stroma	II: 85–93	II: 74–83
Stage III	Local &/or regional spread		
IIIA	Invasion of uterine serosa ± adnexa	IIIA: 80	IIIA: 66
IIIB	Vaginal ± parametrial invasion	IIIB: 62	IIIB: 50
IIIC	Metastases to pelvic ± para-aortic nodes	IIIC: 75	IIIC: 57
IIIC1	Positive pelvic nodes		
IIIC2	Positive para-aortic nodes ± positive pelvic nodes		
Stage IV	Tumor invades the bladder ± bowel ± distant metastases		
IVA	Invasion of bladder or bowel mucosa	IVA: 47	IVA: 26
IVB	Distant metastases including intra-abdominal ± inguinal nodes	IVB: 37	IVB: 20

From *Int J Gynecol Obstet.* 2009;105:3; *Int J Gynaecol Obstet.* 2006;95:S105.

Management *(Obstet Gynecol 2005;106:413; Int J Gynaecol Obstet 2000;70:209)*

- Surg depends on stage:
  All stages: Hysterectomy & BSO (std rx)

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All stages: LND (pelvic & para-aortic) & staging→ allows assessment of the extent of dz to tailor adjuvant therapy. Therapeutic value in stage I dz is unk (*Obstet Gynecol* 2012;120:383)
Stage II → radical hysterectomy & lymphadenectomy + adjuvant therapy based on pathology
Stages III–IV → optimal cytoreductive Surg
Laparoscopic or robotic Surg not inferior to open Surg

- **Radiation therapy (RT):**
  PORTEC trial → pelvic radiation decreases local recurrence (4.2% vs. 13.7%) but overall survival unchanged
  Vaginal brachytherapy → for risk for recurrence or pts who have vaginal recurrence → 60–75% survival
  Whole pelvic (external beam) *adjuvant* radiation may prevent vaginal/local recurrence
  In poor surgical candidates, *primary* RT may be considered
  Survival rate for pts treated w/ *primary* RT w/o Surg: 50% at 5 y
- **Adjuvant chemo:**
  Rx of choice in pts w/ metastatic or recurrent endometrial cancer
  Combination chemo (carboplatin & paclitaxel) → improved resp rate
  Serous & clear cell cancers: Carboplatin & paclitaxel = resp rate 60–70%
- **Hormonal therapy:**
  Occ used in rx of stage I, grade 1 dz in women who wish to maintain fertility or in poor surgical candidates; resp rates 58–100%
  In pts w/ recurrent dz, overall resp rate 25%
  Regular histologic (eg, endometrial bx) monitoring necessary

Posttreatment Surveillance

- Exam q3–6mo × 2 y, then q6mo for 3 y, then annually. If CA-125 elevated at the time of dx, it can be followed at each visit. Most recurrences diagnosed w/i the 1st 2 y; 10% recur >5 y after original dx. Routine chest radiographs or pap smears do NOT improve survival or outcome.

Uterine Sarcomas (*Pathology* 2007;39:55; *Oncol* 1993;50:105)

- Uncommon, arise from mesenchymal (stromal) component of uterus
  Carcinosarcoma (previously called MMMT)
  Present w/ postmenopausal bleeding; median age 65 y; h/o exposure to radiation; more common in AA women; lymphatic route of spread; ↑ potential for extrauterine metastasis
  Adenosarcoma:
  Variable in size. Locally invasive
  Endometrial stromal sarcoma
  Abn uterine bleeding or asymptomatic uterine enlargement. Indolent course, may recur late. 70% are stage I or stage II at dx.

FIGO staging for carcinosarcomas, 2009	
Stage I	Tumor confined to the uterus
IA	Tumor 5 cm or less in greatest dimension
IB	Tumor more than 5 cm
Stage II	Tumor extends beyond the uterus w/i the pelvis
IIA	Tumor invades adnexa
IIB	Tumor involves other pelvic tissue
Stage III	Tumor infiltrates abdominal tissues
IIIA	1 site of involvement (abdominal)
IIIB	More than 1 site of involvement
Stage IV	
IVA	Tumor invades bladder or rectum
IVB	Distant metastasis

From Prat J. FIGO staging for uterine sarcomas. *Int J Gynaecol Obstet.* 2009;104(3):177–178.

Leiomyosarcoma
Median age at dx: 55 y. Menorrhagia & pelvic mass. Hematogenous route of spread. **Primary sites of recurrence:** Lung (41%), pelvis (13%).

- **Rx of carcinosarcoma:**
  Surg – hysterectomy, BSO, removal of metastatic dz
  LND preferred in carcinosarcomas, controversial in leiomyosarcomas & other sarcomas
  Adjuvant chemo & RT recommended

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EPITHELIAL OVARIAN CANCER (EOC)

Definitions and Epidemiology (http://seer.cancer.gov/csr/1975_2008, accessed December 1, 2012)
- EOC is derived from surface epithelium of ovary. Incid: 12.8/100000 women/y
- 5th leading cause of cancer death in US. 90% of all ovarian cancers.
- **Lifetime risk:** 1.5%. Risk of death: 1%.
- **Presentation red flag sx:** Incidental abdominal pain, abdominal distension, loss of appetite, rectal bleeding, postmenopausal bleeding, weight loss

Pathology (*Human Pathology* 2009;40:1213)
- **Serous tumors:** Low & high grade
- 40–50% of EOC; most common type of EOC. 60% bilateral. Psammoma bodies seen in low-grade tumors. Most common in BRCA carriers & in pts w/ Lynch syn
- Mucinous tumors (*Int J Gynecol Cancer* 2008;18:209)
- 10% of EOC. 8–10% bilateral
- Endometrioid adenoCa
- 10% of all ovarian cancers. 28% bilateral. 42% a/w endometriosis; 15–20% a/w endometrial carcinoma
- Clear cell cystadenocarcinoma
- 10% of all ovarian cancers. 40% bilateral. A/w endometriosis & HyperCa.
- Brenner/transitional cell carcinoma
- Rare, poorly differentiated similar to high-grade transitional cell carcinoma of bladder
- Carcinosarcoma
- 1–4% of all ovarian neoplasms. Carcinomatous & sarcomatous elements. Often stage III or stage IV at dx. Poor overall survival.
- Metastatic tumors
- **Krukenberg tumor:** Signet ring cell, GI tumor. Colonic adenoCa. Pancr adenoCa. Breast cancer: Accounts for 6–40% of metastatic tumors to ovary; often bilateral. Renal cell carcinoma. Burkitt's lymphoma. Low malig potential (borderline) tumor: Mucinous or serous.

Etiology (*Gynecol Oncol* 2010;119:7)
- **Risk factors:** Nulliparity, FHx, early menarche, late menopause, white race, increasing age, residence in North America or Northern Europe, personal h/o breast cancer, European Jewish, Icelandic or Hispanic ethnicity, talc exposure
- **Protective factors:** Long-term OCP use, tubal ligation, hysterectomy, breastfeeding
- **Hypothesis of etiology:** Incessant ovulation, gonadotropin/hormone/inflammation stimulation
- Hereditary breast & ovarian cancer (& see Ch. 1, screening)
- 10% of all ovarian cancers. BRCA1, BRCA2, & Lynch syn. Autosomal dominant.
- **Lifetime risk w/ mut:** 28–44%; higher w/ BRCA1. Cancer occurs 10 y earlier.

Diagnostic Workup
- **Pelvic US:** Complex adnexal mass (septations &/or solid components, size, wall loculation, papillary projections)
- **Abdominopelvic CT or MRI:** Complex adnexal mass, omental caking, ascites, peritoneal studding, perihepatic diaphragmatic implants, CA-125 ↑ esp w/ serous tumors
- Refer to gynecologic oncologist if complex adnexal mass, elevated CA-125, ascites, significantly elevated CA-125 in premenopausal (>200 U/mL) or postmenopausal (>35 U/mL) women, FHx of breast or ovarian cancer in 1st-degree relative (*Obstet Gynecol* 2007;110:201)

Management
- Preventative. BRCA1/BRCA2 carriers: Risk reducing BSO by age 40 or completion of child bearing
- **Surgery**
  - Stage I: TAH, BSO, omentectomy, peritoneal biopsies, pelvic & para-aortic LND, pelvic washings
  - Stage I w/ desired fertility: Fertility sparing Surg w/ unilateral salpingo-oophorectomy, peritoneal biopsies, omentectomy, pelvic & para-aortic LND, pelvic washings
  - Stages II–IV: TAH, BSO, omentectomy, debulking of gross dz; optimal reduction to residual dz <1 cm
- **Adjuvant chemo:** Grade III or stage IC or higher: Postsurgical systemic chemo w/ platinum & paclitaxel.

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- **Neoadjuvant chemo:** Used for pts who are not initial surgical candidates. Adjuvant RT not recommended.
- **Recurrent/persistent dz** (*Clin Obstet Gynecol* 2012;55:114)
  Carboplatin + paclitaxel for platinum sensitive dz (recurrence >6 mo from rx). Single-agent rx w/ alternative chemo agent (eg, topotecan, paclitaxel, docetaxel, gemcitabine) for platinum resistant (recurrence <6 mo from rx) or platinum refrac dz (progression during rx).
- **Carcinosarcoma/MMMT:** Surg + platinum-based chemo + paclitaxel or ifosfamide; role of radiation unk.

Posttreatment Surveillance (*Am J Obstet Gynecol* 2011;204:466)
- Exam ± CA-125 q3mo for 3 y, then q6mo for 2 y, then yearly
- CT &/or PET, CA-125 if recurrence suspected

FIGO staging for ovarian cancer, 2009

		5-y survival (%)
Stage I	Tumor confined to ovaries	89
IA	1 ovary; capsule intact	IA: 94
IB	Both ovaries; capsule intact	IB: 91
IC	Surface of 1 or both ovaries; capsule rupture; malig ascites, or positive peritoneal washings	IC: 80
Stage II	Tumor in 1 or both ovaries w/ extension to pelvis	II: 66
IIA	Extension to uterus or fallopian tubes	IIA: 76
IIB	Extension to other pelvic tissues	IIB: 67
IIC	Stage IIA or IIB w/ capsule rupture, malig ascites, or positive pelvic washings	IIC: 57
Stage III	Peritoneal implants or positive pelvic LNs	III: 34
IIIA	Tumor limited to pelvis w/ negative LNs, but microscopic seeding of the abdominal peritoneal surfaces, or extensions to small bowel or mesentery	IIIA: 45
IIIB	Peritoneal implants or metastasis not exceeding 2 cm in diameter; negative LNs	IIIB: 39
IIIC	Peritoneal metastasis outside of pelvis & >2 cm in diameter; positive LNs	IIIC: 35
Stage IV	Distant metastasis; malig pleural effusion; parenchymal liver metastasis	IV: 18

From *Int J Gynaecol Obstet* 2009;105:3; National Cancer Institute-SEER survival data 1998–2001.

GERM CELL TUMORS

Definitions and Epidemiology (*Cancer Treat Rev* 2008;34:427)
- Cancer derived from primordial germ cells. 1–2% of all ovarian malignancies
- 58% of all ovarian tumors in women <20 yo. Incid: 0.41/100000 women/y

Pathology (*Int J Gynecol Path* 2006;25:305)
- **Dysgerminomas**
  1–2% all of ovarian tumors; 32% of malig germ cell tumors. Adolescents/young adults.
  10–15% bilateral. Monophasic proliferation of primitive germ cells w/ infiltrating T cells.
  Testicular seminoma equivalent; OCT4 positive & CD30 positive staining
  Lymphatic spread common; humoral HyperCa common; rapid enlargement
  High cure rate w/ rx (88.6%)
- **Endodermal sinus tumor (yolk sac tumor)**
  14–20% of malig germ cell tumors. Young girls/young women; 1/3 premenarchal
  Schiller–Duval bodies (microscopic feature w/ central capillary surrounded by flattened parietal cells). AFP, cytokeratin, & PLAP positive staining.
  Unilateral, aggressive tumor
- **Embryonal carcinoma**
  4% of malig germ cell tumors. Avg age: 15 yo.
  Cohesive groups of large primitive cells w/ overlapping nuclei, indistinct borders, syncytiotrophoblastic giant cells. hCG production leads to isosexual pseudoprecocity. Staining positive for OCT3, OCT4, & CD30.

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- **Polyembryoma**
  Young girls. Numerous embryoid bodies resembling presomite embryos. hCG/AFP may be elevated.
- **Nongestational choriocarcinoma**
  2% of malig germ cell tumors. Cytotrophoblasts & intermediate trophoblasts capped w/ syncytiotrophoblasts in plexiform pattern. hCG, hPL, inhibin, & cytokeratin positive.
  Early hematogenous spread to distant sites. Relatively chemoresistant.
- **Mixed germ cell tumor**
  5% of all malig germ cell tumors. 2 or more malig germ cell elements w/ at least 1 primitive. Dysgerminoma most common component.
- **Immature teratoma**
  Embryonic tissue; predominantly neuroepithelial. Grade 1, 2, or 3 based on quantity of neuroepithelial tissue. Unilateral.
- **Mature teratoma**
  Solid, cystic (dermoid, 95%), or fetiform. Composed of fetal or adult structures, no embryonal components. Most common ovarian tumor. 46XX karyotype.
  Only 1–2% malig; most common malignancy is squamous cell carcinoma.
- **Monodermal teratomas**
  Struma ovarii, carcinoid, central nervous center tumor, carcinoma group, sarcoma group, sebaceous tumor, pituitary-type tumor, retinal anlage tumor, others.

Clinical Manifestations

- Abdominal pain (55–80%), abdominal/pelvic mass, abdominal enlargement, fever (10–25%), ascites, ovarian torsion or rupture; abdominal distension (35%), vaginal bleeding (10%)
- Short duration of sx (2–4 w)
- 60–70% present at stage I or stage II, 20–30% stage III, stage IV uncommon. Metastasis by peritoneal or lymphatic spread; hematogenous spread more common than EOC.
- Dysgerminoma a/w primary amenorrhea/gonadal dysgenesis

Diagnostic Workup

- **Chest radiograph:** Eval for metastasis
- **Pelvic US:** Cystic lesion w/ densely echogenic tubercle (Rokitansky nodule for mature teratoma). CA-125 not useful.
- **Abdominal/pelvic CT:** Complex mass; fat attenuation in mature teratomas; calcification; speckled calcification in dysgerminomas (*Radiographics* 1998;18:1525)
- Karyotype if dysgerminoma suspected & h/o primary amenorrhea
- Staging same as for EOSs, above.

Germ cell serum tumor markers

	AFP	hCG	LDH	E2	Inhibin	Testosterone	Androgen	DHEA
Dysgerminoma	–	±	+	±	–	–	–	–
Yolk sac	±	+	±	±	–	–	–	–
Immature teratoma	±	–	±	±	–	–	–	±
Choriocarcinoma	–	+	±	–	–	–	–	–
Endodermal sinus	+	–	+	–	–	–	–	–
Polyembryoma	±	+	–	–	–	–	–	–
Mixed germ cell	±	±	±	–	–	–	–	–

Inhibin + for Granulosa cell, and +/– for Sertoli-Leydig and Gonadoblastoma. Testosterone/Androgen + for Sertoli-Leydig and +/– for Gonadoblastoma. See sex cord stromal tumors, below.
From Pectasides D, Pectasides E, Kassanos D. Germ cell tumors of the ovary. *Cancer Treat Rev.* 2008;34(5):427–441.

Management

- **Surg:** TAH, BSO, omentectomy, peritoneal biopsies, pelvic washings, pelvic & paraaortic LND, surgical debulking if not sparing fertility.
  Fertility sparing Surg poss if contralateral ovary appears nml; cystectomy may be poss. Bx contralateral ovary if dysgerminoma or if appears abn.
  Second-look Surg if residual mass postchemotherapy or residual teratoma
- **Adjuvant chemo:**
  BEP (bleomycin, etoposide, cisplatin) is gold std
  Recurrence treated w/ chemo again

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- **Primary surveillance:** Option for stage IA or IB
- **Adjuvant radiation (RT):** Alternative therapy for dysgerminomas

Posttreatment Surveillance (*Am J Obstet Gynecol* 2011:204:466)
- Exam & tumor marker(s) q2–4mo for 2 y, then yearly. Imaging w/ surveillance if no reliable tumor marker. CT & tumor marker(s) if recurrence suspected
- Overall prog based on stage, residual dz, histologic type, preop AFP & bhCG elevation; age not a factor

SEX CORD-STROMAL TUMORS

Epidemiology (*J Clin Oncol* 2007;25:294)
- 7% of all malig ovarian neoplasms. Indolent course w/ favorable prog.

Pathology (*J Clin Oncol* 2007;25:294)
- **Granulosa cell tumor (GCT):**
  70% of malig sex cord-stromal tumors. Incid: 0.4–1.7/100000 women. More common in nonwhite, obese women.
  3–5% of all ovarian neoplasms. Adult type-estrogen production w/ abn bleeding in 66%; EH 25–50%; endometrial cancer 5%.
  Juvenile type: 90% in prepubertal girls; 95% unilateral; excellent prog.
  Call–Exner bodies w/ eosinophilic material & nuclear debris, coffee bean nuclei. 95% unilateral. 78–91% stage I at dx; good prog.
- **Sertoli–Leydig cell tumors:**
  0.2% of all ovarian neoplasms. 98% unilateral. Avg age 20–30 y.
  90% stage I; 70–90% 5-y survival; may recur soon after dx/rx
  Tubules of epithelial cells are steroid secreting
- **Thecoma:**
  Benign. Postmenopausal women. Estrogen → EH (15%).
  Luteinized thecomas → virilization. Abundant lipid cytoplasm; solid, yellowish tumors.
- **Fibroma:**
  Benign. Most common sex cord-stromal tumor; 4% ovarian neoplasms.
  4–8% bilateral. Postmenopausal women. Whorled bundles of spindle-shaped fibroblasts & collagen. A/w Meigs syn & basal nevus syn.
- **Steroid cell tumors:** 0.1–0.2% of all ovarian tumors. Stromal luteomas, Leydig (hilus) cell tumor, & steroid cell tumor not otherwise specified.
- **Others:** Sclerosing stromal tumors, sex cord tumor w/ annular tubules, gynandroblastomas

Clinical Manifestations
- **Presentation:** Abn bleeding, abdominal distension, abdominal pain. Isosexual precocious puberty w/ juvenile GCTs. Virilization from androgens in Sertoli–Leydig. Meigs syn (fibroma, ascites, pleural effusions).

Diagnostic Workup (*Radiographics* 1998;18:1525)
- **Pelvic US/Pelvic CT:** Large, unilateral, multicystic w/ solid components; rare calcifications; carcinomatosis in GCTs (rare); well-defined hypoechoic mass for Sertoli–Leydig cell tumors; lack of papillary projections
- **Pelvic MRI:** High signal intensity due to tumor hemorrhage; GCTs w/ sponge-like appearance; Sertoli–Leydig cell tumors as solid mass; fibrothecomas w/ low signal intensity on T2
- Staging same as for EOSs, above

Sex cord-stromal tumor markers

	E2	Inhibin	Testosterone	Androgen	DHEA
Thecoma—fibroma	–	–	–	–	–
Granulosa	±	+	±	–	–
Sertoli–Leydig	±	±	±	±	±

From Pectasides D, Pectasides E, Kassanos D. Germ cell tumors of the ovary. *Cancer Treat Rev.* 2008;34(5):427–441. doi:10.1016/j.ctrv.2008.02.002. Epub 2008 Apr 18.

Management
- **Surg:** TAH, BSO, omentectomy, peritoneal biopsies, pelvic & para-aortic LND, pelvic washings. Fertility sparing Surg when poss & desired. Endometrial sampling w/ granulosa cell tumors, for hyperplasia. See tables.

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Posttreatment Surveillance (*Am J Obstet Gynecol* 2011;204:466)
- Exam & tumor marker(s) q2–4mo for 2 y, then q6mo for 3 y, then yearly
- CT & tumor marker(s) if recurrence suspected

Treatment of germ cell tumors	
Stage 1A	TAH, BSO, & staging (omentectomy, peritoneal biopsies, pelvic & para-aortic LND, pelvic washings). Fertility sparing Surg & staging if future fertility desired. Adjuvant chemo not indicated.
Stage IC, malig ascites, high mitotic activity, or Stage >1	TAH, BSO, staging, debulking Fertility sparing Surg & staging if future fertility desired Adjuvant chemo (BEP or platinum/taxane)
Recurrent dz or pelvic/intra-abdominal dz	Secondary debulking Surg when feasible Postoperative therapy based upon prev treatments: Platinum based chemo, radiation for localized dz, or hormone therapy
Distant recurrence	Platinum-based chemo, or hormonal rx in selected pts

VAGINAL CANCER

Epidemiology
- 1–2% of all gynecologic malignancies. Incid of VAIN: 0.2/100000 women
- **Mean age:** 70–90 y. 84% are metastases from other sites.

Pathology (*Curr Opin Obstet Gynecol* 2005;17:71)
- **VAIN** is precursor lesion. Upper 3rd of vagina most common. A/w CIN. Risk of transformation to invasive vaginal carcinoma 9–10%.
- **Squamous cell carcinoma**
  85% of vaginal cancer. Superficial spread, then invasion to paravaginal tissue. Metastasis to liver/lung.
- **AdenoCa:**
  15% of cases. Metastasis to lung, supraclavicular & pelvic LNs. Metastasis from other sites is more common than primary vaginal adenoCa.
- **Clear cell adenoCa:** DES exposure. Coexists w/ vaginal adenosis.
- **Melanoma:** <1–3% of vaginal malignancies. Pigmented or nonpigmented.
- **Sarcoma botryoides:** Multicentric; anter wall; grape like. More common in children.
- **Adenosquamous carcinoma:** 1–2% of vaginal cancer. Aggressive.
- **Secondary carcinomas:** Extension from cervix, endometrial metastasis, bowel/bladder local extension, gestational trophoblastic dz.

Etiology
- HPV 16 & 18 found in invasive cancer & VAIN. DES exposure. Endometriosis linked w/ adenoCa. Radiation exposure.

Clinical Manifestations
- Vaginal bleeding or bloody discharge usually indicates advanced lesions. Urinary sx.

Diagnostic Workup
- Bx for tissue dx; view by colposcopy w/ Lugol's solution (localized or skip lesions). Bx cervix & vulva as well.

Management
- **VAIN I:** Observation
- **VAIN II or III:** Wide local excision, partial or total vaginectomy, intravag 5-FU, trichloroacetic acid, 5% imiquimod, laser therapy (*Journal of Lower Genital Tract Disease* 2012;16:00)
- **Stage I SCC:** <0.5 cm thick: Intracavitary radiation, wide local excision, or total vaginectomy; >0.5 cm thick: Radical vaginectomy w/ pelvic LND & inguinal LND (if lower 3rd), radiation if lower 3rd to pelvic/inguinal LNs or poorly differentiated/infiltrating.

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- **Stage I adenoCa:** Total radical vaginectomy, hysterectomy, LND, vaginal reconstruction ± intracavitary/interstitial radiation
- **Stage II SCC/adenoCa:** Brachytherapy/EBRT or radical vaginectomy or pelvic exenteration ± radiation
- **Stages III & IVA SCC/adenoCa:** Interstitial, intracavitary, & EBRT
- **Stage IVB SCC/adenoCa:** Radiation ± chemo
- **Melanoma:** Wide local excision, radical excision w/ inguinofemoral LND, pelvic exenteration, radiation, chemo, or immunotherapy (*Int J Gynecol Cancer* 2004;14:687)
- **Local recurrence:** Pelvic exenteration or radiation
- **Distant recurrence:** Chemo
- **Prog:** 70% 5-y survival for stage I; 50% survival for advanced stage

FIGO staging for vaginal cancer, 2009	
Stage I	Tumor limited to vaginal wall
Stage II	Tumor involves the subvaginal tissue; not extended to the pelvic sidewall
Stage III	Tumor extends to the pelvic sidewall
Stage IV	Tumor extends beyond the true pelvis or has involved the mucosa of the bladder or rectum
IVA	Tumor invades bladder &/or rectal mucosa &/or direct extension beyond pelvis
IVB	Distant spread

From Current FIGO staging for cancer of the vagina, fallopian tube, ovary, and gestational trophoblastic neoplasia. *Int J Gynaecol Obstet.* 2009;105(1):3–4.

Posttreatment Surveillance (*Am J Obstet Gynecol* 2011;204:466)

- Exam (if low risk) q6mo × 2 y then yearly × 2 y; (if high risk) q3mo × 2 y, then q6mo × 2 y, then yearly. Pap smear yearly. CT or PET if recurrence.

VULVAR CANCER

Definitions and Epidemiology (*Hematol Oncol Clin N Am* 2012;26:45)

- **VIN:** Dysplasia confined to epithelium
- **Vulvar carcinoma:** Lesion invading through basement membrane
- **Incid:** Vulvar cancer 2.3/100000 women/y; VIN: 1.2–2.1/100000 women
- 4–7% of all gynecologic malignancies. Median age at dx: 68 y.
- **Lifetime risk:** 0.27%

Pathology

- **VIN usual type:** Warty, basaloid, mixed. HPV related.
- **VIN differentiated type:** A/w lichen sclerosus, squamous cell hyperplasia. NOT HPV related. Risk of developing keratinizing squamous cell carcinoma.
- **SCC:** 92% of vulvar cancer. Warty & basaloid type; keratinizing, nonkeratinizing, basaloid, verrucous, warty, & acantholytic type; invasive or superficial invasion. Most common sites: Labia majora (50%), labia minora (15–20%). HPV16 & 18; 40% of invasive cancers are HPV positive; 80% of VIN are HPV positive; vaccination may prevent.
- **Basal cell carcinoma:** 2–4% of vulvar malignancies. Infiltrating tumor w/ basal cells of the epidermis. Labia majora is the most common site. Basosquamous or metatypical basal cell carcinoma: Malig squamous component, found in 3–5% of basal cell carcinomas (treat as squamous carcinoma).
- **Bartholin's gland carcinoma:** 40% adenoCa; 40% squamous carcinoma; 15% adenoid cystic carcinoma. Bx any Bartholin's gland abscess in woman >35 y.
- **Sarcoma:** 1–2% vulvar malignancies. Leiomyosarcoma, liposarcoma, fibrosarcoma, neurofibrosarcoma, rhabdomyosarcoma, malig schwannoma, angiosarcoma, epithelioid sarcoma.
- **Verrucous carcinoma:** Rare. Cauliflower-like appearance. Slow growing & locally invasive (will even invade bone)
- **Malig melanoma:** 2nd most common vulvar malig. Labia minora or clitoris most common sites. Arise de novo; pigmented lesion, asymptomatic.
- **Paget's dz of vulva:** <1% of vulvar neoplasms. Concurrent w/ underlying adenoCa in 4–20%. 12% invasive; 35% recurrence rate. Large pale cells (Paget cells). Raised, velvety appearance. A/w adenoCa of other location (breast/colon): 30%.

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Clinical Manifestations

- **Presentation:** Vulvar itching & irritation, burning, pain, dysuria. Pigmented lesions, ulcerations, papules, nodules, or scar-like lesions. Persistent condyloma (30% w/ VIN 3).

Diagnostic Workup

- Bx flat, elevated, or pigmented lesions; bx genital warts in postmenopausal women or women who fail topical therapy. Colposcopy.

Management

- **VIN:** Wide local excision (low risk of recurrence if negative margins); laser ablation if cancer not suspected (colposcopy to delineate margins); topical 5% imiquimod
- **Vulvar squamous carcinoma**
  - **Stage I:** Wide local excision if microinvasive (<1 mm invasion), otherwise, radical local excision w/ complete unilateral LND (bilateral LND if lesion <1 cm from midline)
  - **Stage II:** Modified radical vulvectomy w/ bilateral inguinal LND & femoral LND: Radiation if margins <8 mm, lymphovascular invasion, or >5 mm thick
  - **Stage III:** Modified radical vulvectomy w/ bilateral inguinal/femoral LND w/ radiation
  - **Stage IV:** Radical vulvectomy followed by radiation
  - **Recurrence:** Depending on location & extent of recurrence, options include wide local excision, radical vulvectomy, pelvic exenteration, radiation, chemo
- **Basal cell carcinoma:** Radical local excision
- **Bartholin's gland carcinoma:** Radical local excision or hemivulvectomy, consider ipsilateral inguinal LND
- **Sarcoma:** Radical local excision
- **Verrucous carcinoma:** Radical local excision; radiation contraindicated (induces anaplastic transformation which may lead to metastasis)
- **Malig melanoma:** Radical local excision if <1 mm invasion; consider ipsilateral inguinal LND if >1 mm invasion
- **Paget's dz of vulva:** Wide local excision; modified radical vulvectomy if underlying adenoCa
- **Prog:** 5-y survival 72.7%; based on stage at dx; ↑ risk of metastasis if nodes positive, advanced stage, advanced age, increased stromal invasion, LVSI

Posttreatment Surveillance *(Am J Obstet Gynecol* 2011;204:466)

- Exam q3mo × 2 y, then q6mo × 3 y, then yearly.
  CT &/or PET if recurrence suspected. VIN surveillance: q6mo for 1 y, then annually; recurrence high (30–50%).

Clark, Breslow, and Chung staging for melanoma See also chapter 1

	Clark	Breslow	Chung
I	Confined to epithelium	0.75 mm or less	Confined to epithelium
II	Penetrate basement membrane; extend into papillary dermis	0.76–1.50 mm	Penetrates basement membrane; extends to 1 mm or less from granular layer
III	Fills papillary dermis	1.51–2.25 mm	Penetrates btw 1.1 and 2 mm from granular layer
IV	Invades deep reticular dermis	2.26–3 mm	Invades beyond 2 mm from granular layer
V	Invades subcutaneous adipose tissue	>3 mm	Invades into subcutaneous adipose tissue

From Jahnke A, Makovitzky J, Briese V. Primary melanoma of the female genital system: A report of 10 cases and review of the literature. *Anticancer Res*. 2005;25(3A):1567–1574.

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FIGO staging for vulvar cancer, 2009	
Stage I	Tumor limited to the vulva
IA	Lesion ≤2 cm in size, confined to the vulva or perineum & w/ stromal invasion ≤1 mm; no nodal metastasis
IB	Lesion >2 cm in size or w/ stromal invasion >1 mm; confined to perineum, w/ negative nodes
Stage II	Tumor of any size w/ extension to adj perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) w/ negative nodes
Stage III	Tumor of any size w/ or w/o extension to adj perineal structures w/ positive inguinofemoral LNs
IIIA	(i) 1 LN metastasis ≥5 mm (ii) 1–2 LN metastases <5 mm
IIIB	(i) 2 or more LN metastases ≥5 mm (ii) 3 or more LN metastases <5 mm
IIIC	Positive nodes w/ extracapsular spread
Stage IV	Tumor invades other regional structures (2/3 upper urethra, 2/3 upper vagina) or distant structures
IVA	(i) Tumor invades urethral &/or vaginal mucosa &/or bladder mucosa &/or rectal mucosa; fixed to pelvic bone (ii) Ulcerated or fixed inguinofemoral LNs
IVB	Distant metastasis including pelvic LNs

From Current FIGO staging for cancer of the vagina, fallopian tube, ovary, and gestational trophoblastic neoplasia. *Int J Gynaecol Obstet.* 2009;105(1):3–4.

GESTATIONAL TROPHOBLASTIC NEOPLASIA

Definition and Epidemiology

- Originates from abn proliferation of placental trophoblasts. Incid varies by geography (2/1000 in Japan, 0.6–1.1/1000 in Europe/North America) *(NEJM* 1996;335:1740)
- GTN includes 4 types of related tumors: Complete & partial hydatidiform mole, invasive mole, placental site trophoblastic tumor, & choriocarcinoma. Invasive GTN usually follows molar Preg, but can follow any gest.

Molar Pregnancy

Features of complete and partial hydatidiform moles		
Feature	**Complete mole**	**Partial mole**
Karyotype	46XX (90%), 46XY (10%)	69 XXY (90–93%)
Fetal or embryonic tissue	Absent	Present
Hydatidiform swelling of chorionic villi	Diffuse	Focal
Trophoblastic hyperplasia	Diffuse	Focal
Scalloping of chorionic villi	Absent	Present
Trophoblastic stromal inclusions	Absent	Present
Implantation-site trophoblast	Diffuse, marked atypia	Focal, mild atypia
Risks	Low dietary carotene. Vit A deficiency. Age >35 y. Prev SAB.	Prev SAB. Irreg menses. OCP use >4 y.

From Berkowitz RS, Goldstein DP. Chorionic tumors. *N Engl J Med.* 1996;335(23):1740–1748.

- **Clinical presentation** *(NEJM* 1996;335:1740)
  - **Complete hydatidiform mole:** Vaginal bleeding (89–97%); enlarged uterus for gestational age (38–51%); Theca lutein ovarian cysts (26–46%); hyperemesis gravidarum (20–26%); preeclampsia (12–27%); hyperthryoidism; respiratory distress (2–27%)
  - **Partial hydatidiform mole:** Signs & sx of incomplete or missed abortion; SGA or IUGR; less likely to present w/ medical complications
  - Diagnostic w/u pelvic US, serum hCG level, CBC, PT/PTT, renal & liver fxn studies, type & screen, pre-evacuation chest radiograph, if exhibiting sx of hyperthyroidism → TSH, T3/T4; hyperemesis → chemistry

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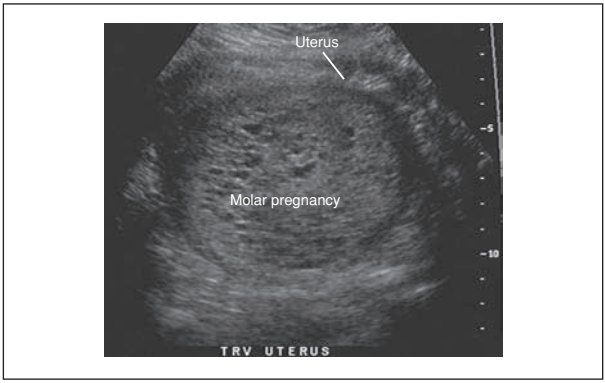
Figure 21.1 Transverse uterus ultrasound image of a molar pregnancy with characteristic snowstorm pattern



(Courtesy of Patricia Johnson, University of Virginia)

- **Rx**
  Suction curettage followed by sharp curettage if pt desires future fertility. Rh immune globulin for RhD-negative women. Hysterectomy an option if pt desires sterilization.
  Prophylactic chemo following molar Preg (*Obstet Gynecol* 1986;67:690) is controversial. Decreases postmolar GTN from 47–14% in high risk (WHO > 6; see below) complete moles. Can be used in high-risk moles or if f/u unreliable.
- **Post rx surveillance** (*Obstet Gynecol* 2004;103:1365)
  Serum hCG level w/i 48 h of evacuation
  Serum hCG levels every 1–2 w until normalized (<5)
  Serum hCG level monthly for 6 mo once negative
  Use of reliable hormonal contraception needed during surveillance

Invasive Mole (*Chemo Research and Practice* 2011;2011:1; *Obstet Gynecol* 2004;103:1365)

- Risk of developing persistent/invasive GTN: 15–20% after complete hydatidiform mole; 1–4% after partial hydatidiform mole.
- GTN diagnosed after molar gest if:
  ≥4 hCG values plateau (±10%) over at least 3 w
  ≥10% rise in hCG for ≥3 values over at least 2 w
  Presence of histologic choriocarcinoma
  Persistence of hCG 6 mo after molar evacuation (& rule out new Preg)
- Metastatic GTN seen in 4% after evacuation for complete mole (*Chemo Research and Practice* 2011;2011:1)
  Most common sites for metastases: Lung (80%), vagina (30%), brain (10%), & liver (10%)

Choriocarcinoma (*Obstet Gynecol* 2004;103:1365)

- Arises from cytotrophoblasts & syncytiotrophoblasts. Does not contain chorionic villi. 50% arise from complete hydatidiform mole, 25% from nml pregnancies, 25% from spont abortion/ectopic Preg. Most aggressive.

Placental Site Trophoblastic Disease

- Uncommon variant of choriocarcinoma. Predominantly composed of intermediate cytotrophoblasts. Tumor marker, HPL.
- Secrete small amounts of βhCG → tumor burden may be large before hCG levels detectable

Subseq Preg after GTN (*NEJM* 1996;335:1740)

- 1% subseq pregnancies result in molar gest; women w/ GTN in remission have nml Preg rates following GTN; no ↑ incid of spont abortion, congenital anomalies, C-section

Survival after GTN

- Prog depends on age, interval btw gest & dz, & serum bHCG
- **Low risk:** 84% stage I GTN & 87% low-risk stages II–III → complete remission w/ single-agent chemo (*J Reprod Med* 2006;51:835; *Semin Oncol* 1995;22:166; *J Reprod Med* 1992;37:461; *Obstet Gynecol* 1987;9:390; *Gynecol Oncol* 1994;54:76)

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- **High risk:** 80% pts w/ stage IV dz achieve remission w/ multiagent therapy
- **Risk of relapse:** 2% nonmetastatic GTN; 4% low-risk metastatic GTN; 13% pts high-risk metastatic GTN (*Cancer* 1996;66:978). Median time to relapse: 6.5 mo. Survival rate for relapsed GTN: 77.8% (*J Reprod Med* 2006;51:829).

FIGO staging of GTN, 2009	
Stage I	Dz confined to uterus
Stage II	GTN extends outside uterus but limited to genital structures (adnexae, vagina, broad ligament)
Stage III	GTN extends to lungs, w/ or w/o known genital tract involvement
Stage IV	All other metastatic sites (brain, liver)

From Current FIGO staging for cancer of the vagina, fallopian tube, ovary, and gestational trophoblastic neoplasia. *Int J Gynaecol Obstet.* 2009;105(1):3–4.

Modified WHO prognostic scoring system as adapted by FIGO				
Low risk, WHO score of 0–6; high risk, WHO score of ≥7				
Score	0	1	2	4
Age (yr)	<40	≥40	–	–
Antecedent Preg	Mole	Abortion	Term	–
Interval months from index Preg	<4	4–6	7–12	≥13
Pretreatment serum bhCG	$<10^3$	10^3–$<10^4$	10^4–$<10^5$	$\geq 10^5$
Largest tumor size	–	3–<5 cm	≥5 cm	–
Site of metastases	Lung	Spleen, kidney	GI	Liver, brain
Number of metastases	–	1–4	5–8	>8
Prev failed chemo drugs	–	–	1	≥2

Treatment regimens for GTN	
Protocol for low-risk GTN (stage I or low-risk stage II/III & WHO score ≤6)	
Initial therapy	Sequential methotrexate/actinomycin D Hysterectomy if finished w/ childbearing (w/ adjunctive single-agent chemo)
Resistant therapy	MAC EMACO, if MAC fails Hysterectomy (w/ adjunctive multiagent chemo) Local uterine resxn (to preserve fertility)
F/u	12 consecutive months of undetectable hCG levels Contraception for 12 mo
Protocol for high-risk GTN (stage II or stage III & WHO score ≥7)	
Initial therapy	EMACO or EMAEP (etoposide, methotrexate, actinomycin D, carboplatin)
Resistant therapy	VBP Surg, as indicated
F/u	12 consecutive months of undetectable hCG levels Contraception for 12 mo
Protocol for Stage IV GTN	
Initial therapy	EMACO; w/ brain mets → radiation, craniotomy for periph lesions; w/ liver mets → embolization, resxn to manage complications
Resistant therapy	EMAEP; VBP; experimental protocols; Surg, as indicated; hepatic artery infusion or embolization
F/u	Weekly hCG levels until undetectable for 3 w, then monthly hCG × 24 mo Contraception × 24 mo

From May T, Goldstein DP, Berkowitz RS. Current chemotherapeutic management of patients with gestational trophoblastic neoplasia. *Chemother Res Pract.* 2011;2011:806256.

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CHEMOTHERAPY

Tumor Biology *(Principles and Practice of Gynecologic Oncology. 5th ed. 2009:381)*

- 3 types of nml tissue growth explain chemo side effects
  - **Static:** Well-differentiated cells, rare division (neurons, oocytes)
  - **Expanding:** Normally quiescent, proliferate w/ stress (hepatocytes, vascular endothelium)
  - **Renewing:** Continuous proliferation (bone marrow, GI epithelium, epidermis)
- **Gompertzian growth:** Tumor growth exponential during initial division followed by exponential growth retardation → as tumor mass ↑, time to double tumor size also ↑; metastasis doubling time is faster than primary lesion. Rapidly proliferating cells have short G1 → these cells are the most chemosensitive.
- Prolonged survival & cure achieved when cell pop ↓ to 10^1–10^4 cells, which is microscopic dz → basis for adjuvant chemo following upfront surgical debulking

Figure 21.2 Illustration of host tumor interactions in the development and spread of cancer

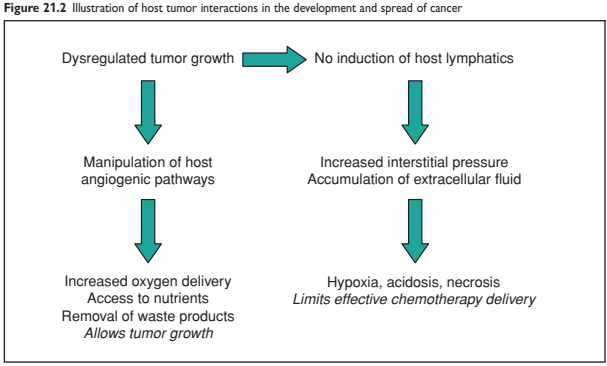
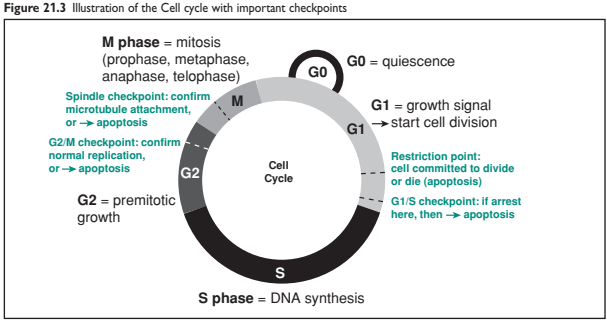


Figure 21.3 Illustration of the Cell cycle with important checkpoints



Types of Chemotherapy

- **Neoadjuvant chemo:** Prior to Surg or RT
- **Adjuvant chemo:** Following Surg or RT
- **Concurrent chemo:** Administered w/ radiation to sensitize tumor to radiation effects

Common Toxicities

- Graded using common terminology criteria for adverse events → Graded 1–4
- **Bone marrow tox**
  - Most common dose limiting side effect
  - Neutropenia → most common bone marrow tox. Occurs 7–14 d after rx.
  - Use of G-CSF & PEG-filgrastim does not improve long-term survival compared to dose reduction

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- **GI**
  - N/V most common
  - Anticipatory nausea: Occurs prior to administration of chemo
  - Acute onset nausea: Occurs w/i 1 h of chemo, lasts <24 h
  - Delayed onset nausea: Occurs >1 d following chemo & persists for several days
- **Alopecia**
  - Important psychological side effect, almost always reversible
- **Skin tox**
  - Allergic/hypersens rxn
  - Skin hyperpigmentation
  - Photosensitivity
  - PPE
  - Local extravasation necrosis
- **Neurotoxicity**
  - Periph neuropathy → most common
  - Highest rates seen w/ cisplatin, paclitaxel, docetaxel
  - Paresthesias → loss of vibratory & position sense → functional impairment
- **GU**
  - Cisplatin → renal tox from metabolites (carboplatin has little renal tox)
  - Ifosfamide & cyclophosphamide → hemorrhagic cystitis due to byproduct, acrolein
    - Mesna administered to bind & neutralize acrolein in the bladder
- **Hypersensitivity rxns**
  - Early rxn → paclitaxel
    - Occurs due to rxn to Cremophor EL (in which paclitaxel is compounded)
    - 80% reactions occur w/ 1st or 2nd cycle
  - Late rxn → carboplatin
    - Most common during 2nd course of chemo for recurrence (cycles 7–13)
    - Thought to be due to Ag recall

RADIATION THERAPY

External Beam Radiation (EBRT)

- Types of EBRT
  - 3-dimensional conformal RT
    - CT used to guide geometry of radiation rx → std of care for gynecologic cancers (*Gynecol Oncol* 1997;66:351)
  - Intensity-modulated radiation therapy (*Int J Radiat Oncol Biol Phys* 2002;52(5):1330)
    - Specialized 3-dimensional conformal RT
    - Allows dose modulation w/i each beam & dose escalation for tumor site w/ decreased dose to nml tissue (may be useful in extended field EBRT)
- **Definitions in EBRT**
  - **Borders of std pelvic fields** (*Principles and Practice of Gynecologic Oncology*. 5th ed. 2009:381)
    - Superior → S1–L5 interspace (early dz) or L4–5 (advanced dz)
    - AP-PA field 15 × 15 cm w/ lateral width of 8–9 cm
  - **Extended field EBRT** → includes para-aortic nodes in radiation field (T12–L1)
    - Useful in cervical cancer w/ para-aortic nodal dz, but ↑ side effects given inclusion of more nml tissue (bowel, kidneys)
  - **Midline block** → used to block tissue adj to planned brachytherapy during EBRT
  - **Parametrial boost** → given to pts w/ parametrial/sidewall involvement following EBRT
  - **Fractions** → total dose delivered in fractions (1.8–2 Gy) daily
    - Decreases dose to healthy tissue by allowing for sublethal DNA damage repair
- **Side effects:** Acute (≤3 mo after rx) or late onset (>3 mo after rx)
  - Skin → ulceration, necrosis; GI → diarrhea, fistula, perforation; GU → cystitis, fistula
  - Reproductive organs → premature menopause; bone marrow/pelvic bones → transient lymphopenia, fractures

Brachytherapy

- Highly concentrated radiation dose to immediately surrounding tissue
- **Interstitial brachytherapy** (vaginal/vulvar cancer): Radioactive sources temporarily loaded into hollow needles imbedded in tumor bed

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- **Intracavitary brachytherapy** (cervical & endometrial cancer): Radioactive sources placed in body cavities (*Principles and Practice of Gynecologic Oncology*. 5th ed. 2009:381)
  - Low-dose rate → uses Iridium or Cesium
    - 40–100 cGy/h
    - Requires 1–2 treatments that last 48–72 h each
    - Requires inpt hospitalization
  - High-dose rate → uses Iridium
    - 20–250 cGy/min
    - Requires 3–5 outpt treatments following insertion
  - Similar efficacy & late complications w/ HDR & LDR (*Cochrane Database Syst Rev* 2010;7:CD007563)
- **Anatomic landmarks for brachytherapy**
  - **Point A** → 2 cm superior & 2 cm lateral to the external cervical os (point of crossage of ureter & uterine artery)
  - **Point B** → 3 cm lateral to point A (location of obturator LNs)

Radiation treatment for gynecologic cancers

Cancer	Radiation type
Cervical (stages 1B–IV)	Definitive whole pelvic (± extended field) EBRT w/ cisplatin chemosensitization, ± parametrial boost, brachytherapy (LDR or HDR)
Endometrial	Adjuvant whole pelvic EBRT, adjuvant vaginal cuff brachytherapy
Vulvar (following resxn)	Adjuvant whole pelvic EBRT
Advanced dz	Chemo + EBRT
Vaginal	Whole pelvic EBRT ± boost, brachytherapy (*Int J Radiat Oncol Biol Phys* 2005;62:138)

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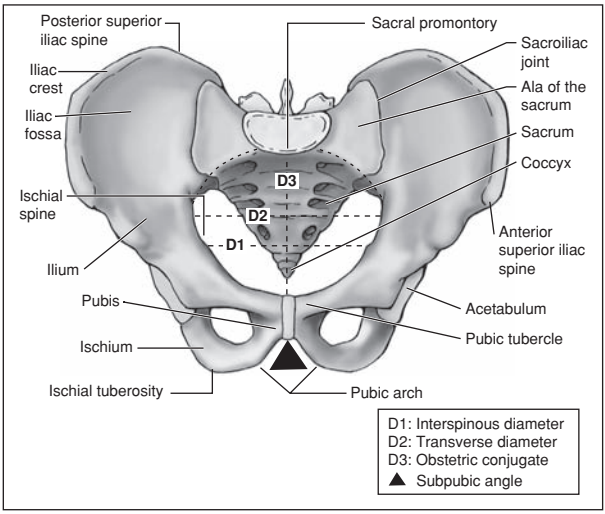
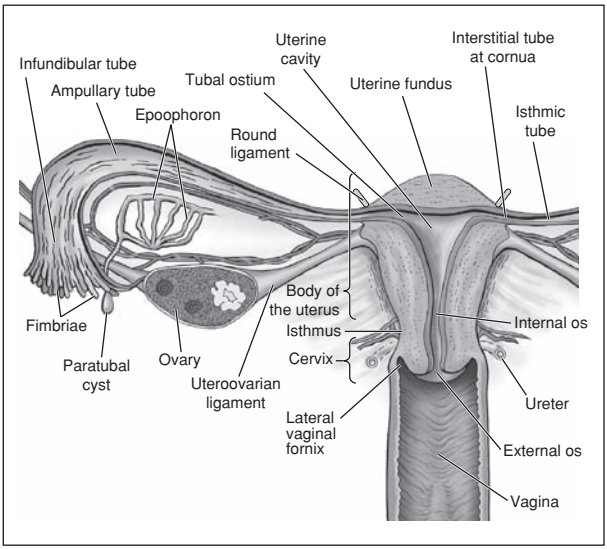
Figure APP-1-1 The female bony pelvis



(From Moore KL, Dalley AF. *Clinically Oriented Anatomy.* 5th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2006)

Figure APP-1-2 Internal female reproductive organs, posterior view



(From Moore KL, Dalley AF. *Clinically Oriented Anatomy.* 5th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2006)

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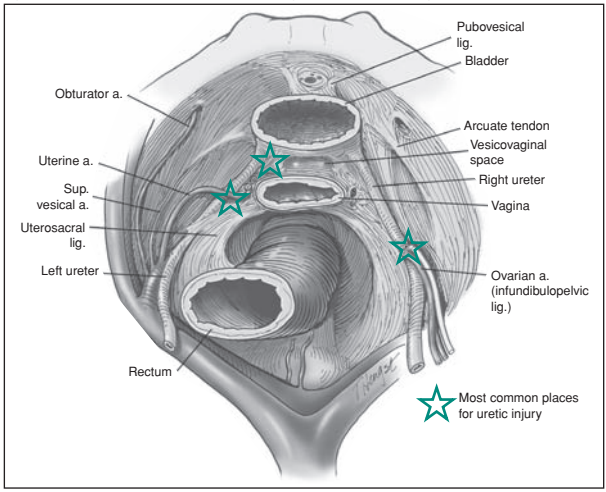
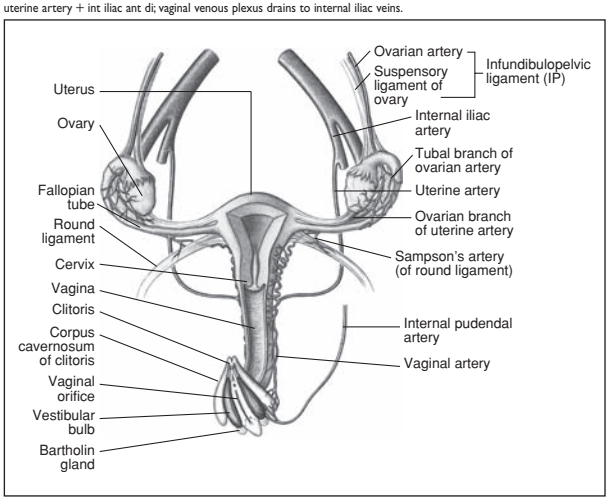
Figure APP-1-3 The course of the ureter and relationship to the sites of vulnerability



(From Berek DL. *Berek & Novak's Gynecology.* 15th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2012)

Figure APP-1-4 Blood supply of pelvic organs and external genitalia. Note ovarian art from anterior aorta between renal and inf mesenteric arteries; L ov vein drains to L renal V; R ov vein drains to inf vena cava; vaginal blood supply is uterine artery + int iliac ant di; vaginal venous plexus drains to internal iliac veins.



(From Rohen JW, Yokochi C, Lutjen-Drecoll. *Color Atlas of Anatomy.* 7th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2011)

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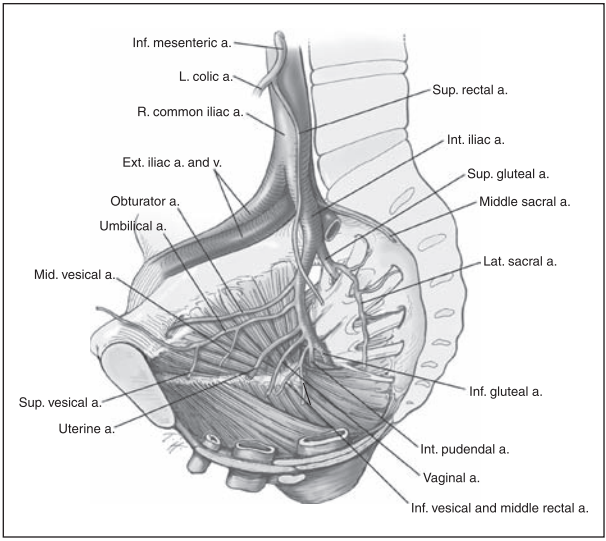
Figure APP-1-5 Pelvic arterial blood supply



(From Berek DL. *Berek & Novak's Gynecology.* 15th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2012)

Pelvic arterial blood supply, considerations		
Artery	**Branches**	**Surgical significance**
Common iliac	1. Internal iliac artery 2. External iliac artery	Ureter crosses bifurcation at the pelvic brim
External iliac	1. Inferior epigastric artery 2. Deep circumflex iliac artery 3. Femoral artery (origin of superficial epigastric artery)	IEA may be injured during laparoscopic entry; can give accessory obturator branch
Internal iliac	1. Anter division: Obturator artery Umbilical → superior vesical → obliterated Uterine artery Vaginal artery Inferior vesical artery Middle rectal artery Internal pudendal artery Inferior gluteal artery	Ligation of the anter division may be done to control uterine hemorrhage
	2. Post division: Iliolumbar artery (iliac & lumbar branches) Lateral sacral arteries Superior gluteal artery	Ligation → gluteal necrosis
Internal pudendal	1. Inferior rectal 2. Perineal artery 3. Post labial branches 4. Artery of the bulb of the vestibule 5. Dorsal artery of the clitoris 6. Deep artery of the clitoris	Exits pelvis through greater sciatic foramen to gluteal region → curves around the sacrospinous ligament to enter perineum through the lesser sciatic foramen (through the pudendal canal w/ vein & nerve)

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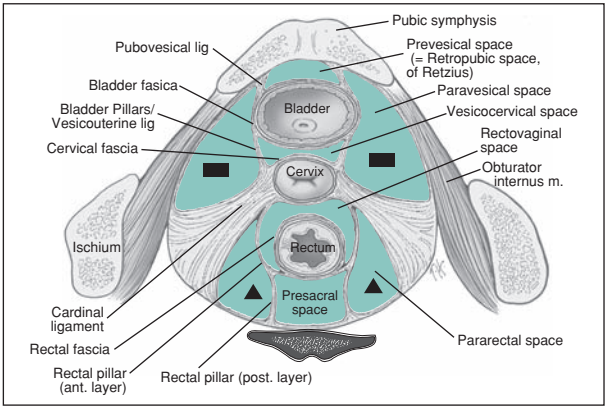
Figure APP-1-6 Avascular planes of the female pelvis



Avascular planes of the female pelvis, considerations		
	Description	**Surgical significance**
Retropubic space (Space of Retzius)	Boundaries: Pubic bone, anter abdominal wall muscles anteriorly; ATFP & ischial spine laterally Contents: Clitoral neurovascular bundle; obturator neurovascular bundle ± accessory obturator art from ext iliac	During a Burch retropubic colposuspension procedure, dissection of this space can lead to bleeding from the venous plexus of Santorini around the sides of the urethra
Vesicovaginal space	Central space Boundaries: Bladder anteriorly; bladder pillars laterally; vaginal adventitia posteriorly Contents: Loose areolar tissue	During abdominal hysterectomy sharp dissection in the midline to open the space; bleeding from bladder pillars laterally
Rectovaginal space	Central space Boundaries: Vagina anter; rectal pillars laterally; rectum posteriorly Contents: Loose areolar tissue	Need to open in difficult hysterectomy or in sacrocolpopexy to attach mesh to the post vagina
Presacral space	Central space Boundaries: Sigmoid & rectum & post cul de sac anteriorly; common iliac & internal iliac laterally; presacral periosteum posteriorly Contents: Loose areolar tissue & presacral vessels including the median & lateral sacrals, superior & middle rectal arteries can pass through the space	Need to open in sacrocolpopexy & presacral neurectomy
Paravesical spaces (■)	2 lateral spaces (■) Boundaries: Bladder anteriorly; bladder pillars medially; obturator internus, levator ani muscles, & pelvic side wall laterally; cardinal ligament complex posteriorly; medial umbilical artery (obliterated) superiorly; connects anteriorly to the Space of Retzius Contents: Loose areolar tissue, dorsal clitoral neurovascular bundle, accessory obturator artery	Need to open in Burch retropubic colposuspension, radical hysterectomy, or paravaginal defect repair
Pararectal spaces (▲)	2 lateral spaces (▲) Boundaries: Cardinal ligament anteriorly; rectum medially; sacrum posteriorly; internal iliac & pelvic side wall laterally Contents: Loose areolar tissue	Need to access if obliterated cul de sac; radical hysterectomy, & sacrospinous fixation Ureterolysis is a prerequisite

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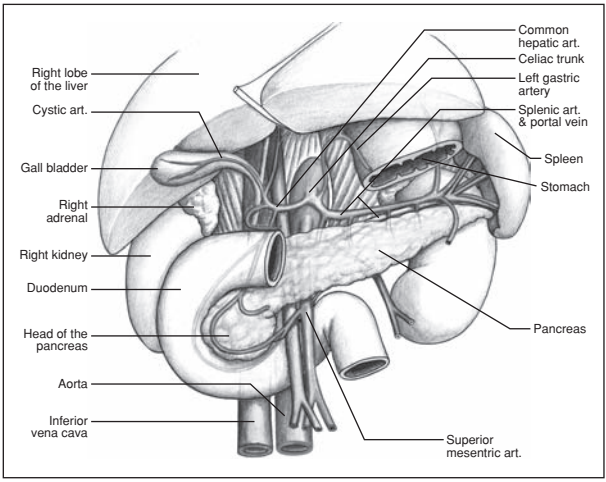
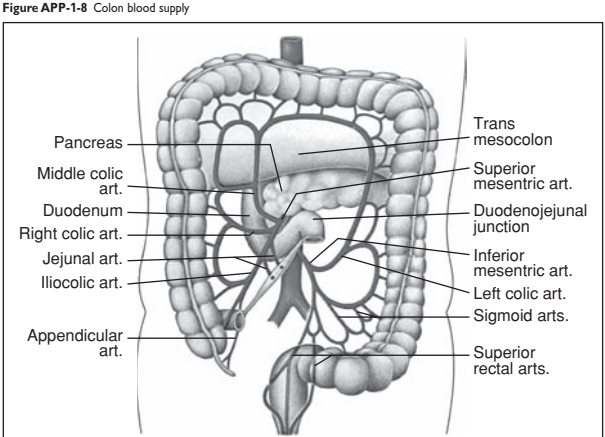
Figure APP-1-7 Upper abdominal blood supply



(From Rohen JW, Yokochi C, Lutjen-Drecoll. *Color Atlas of Anatomy.* 7th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2011)

Figure APP-1-8 Colon blood supply



(From Rohen JW, Yokochi C, Lutjen-Drecoll. *Color Atlas of Anatomy.* 7th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2011)

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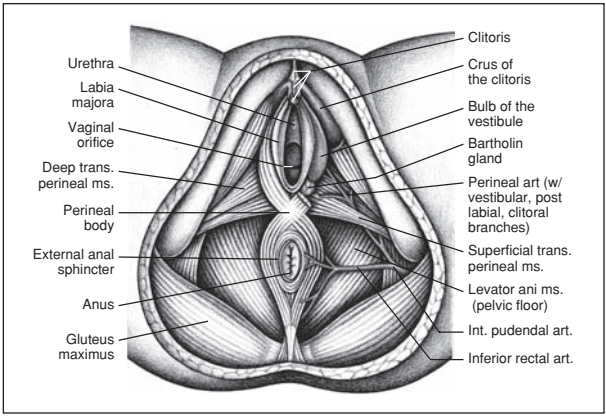
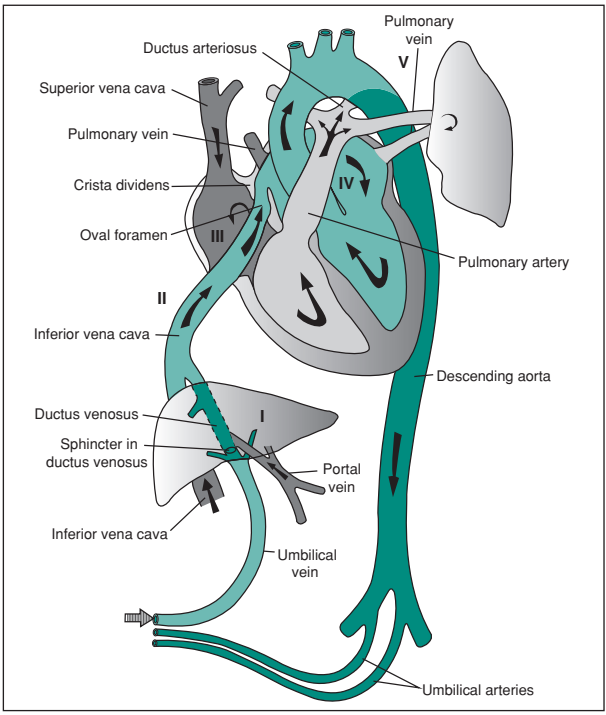
Figure APP-1-9 Urogenital triangle and pelvic floor



(From Rohen JW, Yokochi C, Lutjen-Drecoll. *Color Atlas of Anatomy.* 7th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2011)

Figure APP-1-10 Fetal circulation. *Arrows* = blood flow. Oxygenated and deoxygenated blood mix in liver (I), inferior vena cava (II), right atrium (III), left atrium (IV), and confluence of ductus arteriosus and descending aorta (V).



(From Sadler TW. *Langman's Medical Embryology.* 12th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2012)

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Levonorgestrel Intrauterine System (LNG-IUS) (Adapted from Bayer HealthCare Pharmaceuticals Inc., physician insert, 2009)

- **Timing:** Insert after Preg ruled out or after 1st trimester abortion or postpartum
- **Preparation:**
  - Informed consent, bimanual exam
  - Obtain cervical cx, cleanse cervix w/ an antiseptic solution
  - Consider paracervical block
  - Sound uterine cavity
- **Procedure (sterile):**
  - See http://www.mirena-us.com/hcp/placement-&-removal/precise-placement.jsp
  - Ensure slider on inserter is advanced all the way toward the device. Pull threads to draw device into insertion tube. Ensure arms are parallel to slider. Fix threads in the cleft at end of handle. Set flange to depth measured by uterine sound.
  - Hold the slider firmly. Apply gentle countertraction w/ tenaculum. Gently advance the insertion tube into the uterus until flange is 1.5–2 cm from external cervical os. While holding inserter, release device by pulling slider back until top of slider reaches mark. Advance inserter until flange touches cervix.
  - Release LNG-IUS by pulling the slider down all the way
  - Cut threads to 2–3 cm visible outside cervix
  - Consider US to verify position. Remove if not positioned appropriately. Do not reinsert same device.
  - String check ~4 w after placement of IUD

ParaGard (Copper T 380A IUD) (Adapted from Teva Women's Health, Inc., physician insert, 2010)

- **Timing:** Same as LNG-IUS. Can be used as emergency contraception w/i 5 d of unprotected intercourse.
- **Preparation:** Same as LNG-IUS
- **Procedure:**
  - See http://www.paragard.com/Pdf/ParaGard-PI.pdf
  - Load IUD into insertion tube by folding the 2 horizontal arms against the stem, & push tips of the arms securely into the inserter tube (<5 min from insertion)
  - Introduce white rod into the insertion tube until it touches the end of the IUD
  - Adjust the blue flange to the uterus cavity length. Advance insertion tube to uterine fundus (blue flange should be at external os).
  - Hold white rod steady & withdraw the insertion tube 1 cm to release IUD
  - Advance insertion tube to fundus
  - Hold the tube steady & withdrew rod
  - Withdraw tube completely. Trim threads to 3–4 cm.
  - Consider US to verify position. Remove if not positioned appropriately. Do not reinsert same device.
  - String check ~4 w after placement of IUD

SUBDERMAL DEVICE INSERTION

Etonogestrel implant (Implanon) insertion (Adapted from Merck & Co Inc., physician insert, 2012)

- **Timing:** Same as LNG-IUS
- **Preparation:** Informed consent
- **Procedure (sterile):**
  - Position arm flexed at the elbow & externally rotated so that wrist is parallel to ear or her hand is positioned next to her head
  - Identify insertion site at the inner side of the nondominant upper arm about 8–10 cm (3–4 in) above the medial epicondyle of the humerus
  - Insert just under skin to avoid large bld vessels & nerves deeper in the subcutaneous tissue btw triceps & biceps muscles
  - Mark the spot where implant will be inserted. Mark a spot a few centimeters prox to the 1st mark as a direction guide.
  - Clean insertion site w/ an antiseptic solution; anesthetize area along insertion path. Remove implant applicator from package. Ensure implant needle & rod are sterile.
  - Look for the etonogestrel implant rod, (white cylinder inside the needle tip)
  - Lower the IMPLANON rod back into the needle by tapping it back into the needle tip. Remove the needle shield while holding the applicator upright.

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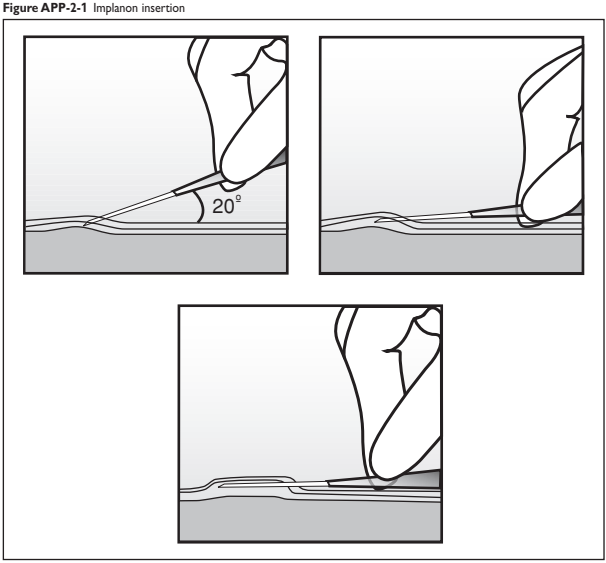
Stretch the skin around the insertion site w/ thumb & index finger
At <20-degree angle, insert tip of the needle w/ bevel up
Lower applicator to a horizontal position. Lift the skin up w/ the tip of the needle.
While "tenting" the skin, insert the needle to its full length parallel to skin surface
Press the obturator support, turn obturator 90 degrees
Hold obturator fixed & fully retract cannula. Confirm that the implant has been inserted by palpation. Grooved tip of the obturator should be visible.
Consider pres dressing to minimize bruising
If not palpable, implant can be located w/ high-frequency US or MRI

Figure APP-2-1 Implanon insertion



(From Speroff L, Darney PD. *A Clinical Guide for Contraception.* 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011)

BARTHOLIN ABSCESS INCISION AND DRAINAGE

- **Indication:** For rx of cystic enlargement or abscess formation. Will not prevent recurrence.
- **Preoperatively:**
  Identify incision point (inner surface of abscess. INSIDE hymenal ring).
  Obtain informed consent (risk of recurrence & poss need for additional procedures)
- **Steps:**
  Infiltrate skin w/ local anesthesia
  Incise using a scalpel w/ a no. 11 blade
  Explore the inside of the cyst/abscess & open any loculations
  A Word catheter can be used to reduce recurrence. Insert the deflated Word catheter into the cyst cavity & inject 2–3 mL of sterile saline through the catheter to inflate the balloon. Tuck end of Word catheter into the vagina.

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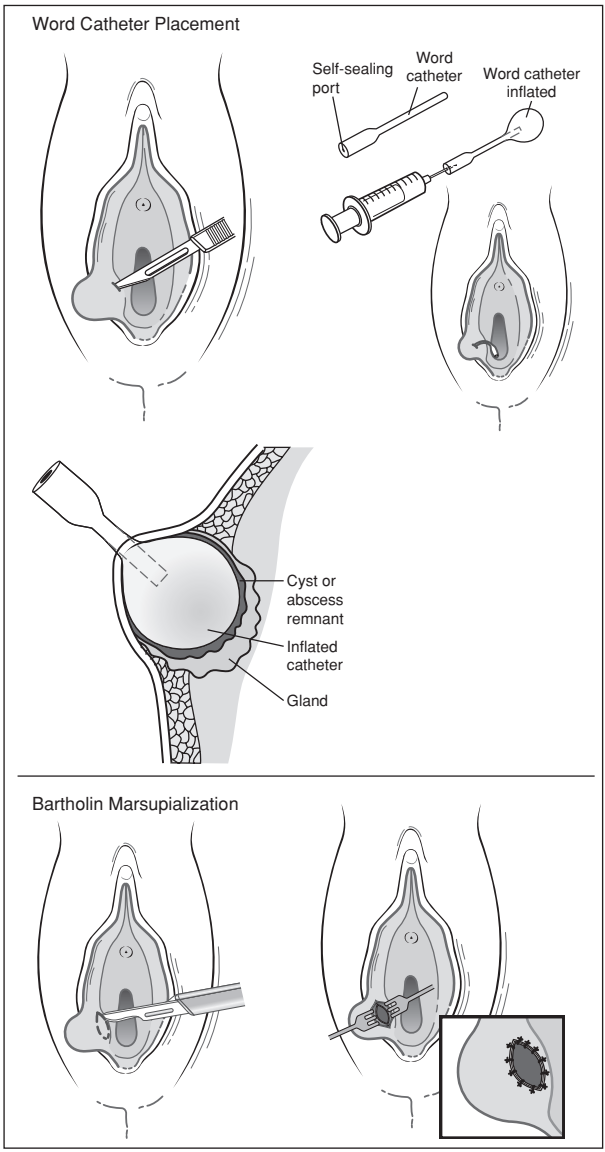
Figure APP-2-2 Word Catheter: After local anesthesia and preparation, use a stab incision to create a 1–1.5-cm deep opening in the cyst. Insert the tip of a Word catheter, and inflate the bulb with water or lubricating gel. Keep the catheter in place for 4 w. **Marsupialization:** Make a fusiform incision adjacent to the hymenal ring. Remove an oval wedge of vulvar skin and the underlying cyst wall. Suture the cyst wall to the adjacent vestibular skin.



(From Zuber TJ, Mayeaux EJ. *Atlas of Primary Care Procedures.* Philadelphia, PA: Lippincott Williams & Wilkins; 2004)

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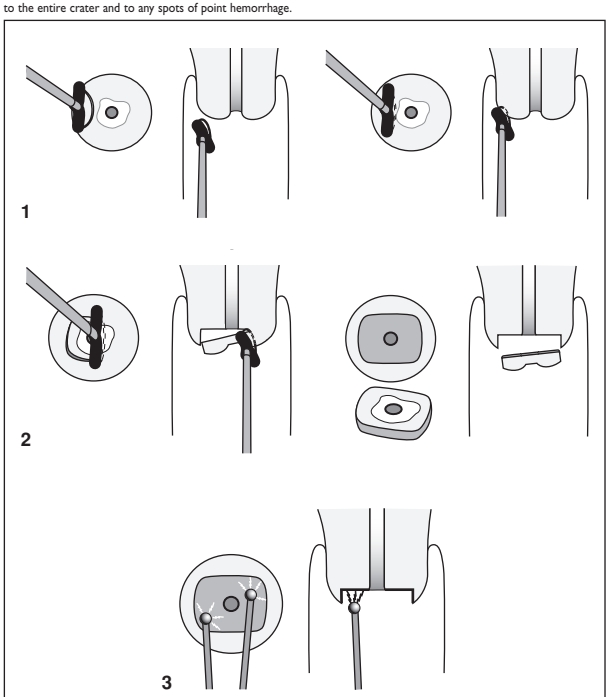
LOOP ELECTROSURGICAL EXCISION PROCEDURE (LEEP)

- **Indication:** To better characterize glandular or squamous lesions after unsatisfactory initial w/u, by excising the transformation zone of the cervix
- **Preoperatively:**
  Colposcopic exam & biopsies
  Exclude Preg (unless high suspicion of invasion), obtain informed consent
- **Steps:**
  Ground pt, insert insulated speculum w/ smoke evacuation tubing. Select appropriately sized loop to excise transformation zone.
  Use iodine or acetic acid to identify lesions
  Consider paracervical block
  Introduce loop 3–5 mm lateral to os at 90-degree angle to cervix. Activate current (cutting) prior to tissue contact.
  Draw loop parallel to surface until opposite side of os is reached. Withdraw at 90-degree angle. Stop electrical current.
  Perform an endocervical curettage or "top hat" excision
  Obtain hemostasis using electrocautery or Monsel solution. Apply pres.
  Tag specimen for orientation, & send to pathology

Figure APP-2-3 (1) To excise tissue, the loop is held just above the surface of the cervix and 2–5 mm lateral to the lesion, and current is applied before the loop contacts the cervix. (2) Draw the loop slowly through the tissue until the loop is 2–5 mm past the edge of the transformation zone on the opposite side. (3) Superficial fulguration is usually applied to the entire crater and to any spots of point hemorrhage.



(From Zuber TJ, Mayeaux EJ. *Atlas of Primary Care Procedures.* Philadelphia, PA: Lippincott Williams & Wilkins; 2004)

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ENDOMETRIAL BIOPSY

- **Indications:**
  Used to exclude endometrial cancer in high-risk pts w/ abn uterine bleeding (>35 y, obese, FHx, PCOS, etc.), as part of w/u for glandular abnormality on Pap smears, or f/u after conservative mgmt of endometrial hyperplasia
  Req before endometrial ablation, and often before hysterectomy
- **Preoperatively:** Exclude Preg, obtain informed consent
- **Steps:**
  Perform speculum exam
  Clean the cervix w/ Betadine. Consider tenaculum placement.
  Advance endometrial sampling Pipelle through the cervical canal to the uterine fundus
  Withdraw the stylet to apply suction; sample all 4 walls

AMNIOCENTESIS

- **Indications:**
  Detection of lung maturity, genetic dx, & to exclude infection
  Confirm rupture of membranes using the amnio-dye test ("tampon test")
  Relieve pres sx in polyhydramnios
- **Preoperatively:** Obtain informed consent
- **Steps:**
  Use US to identify large amniotic fluid pocket away from the fetus
  Advance spinal needle into amniotic fluid w/ sonographic guidance
  Withdraw stylet, attach syringe, & draw back to obtain a fluid sample

COMMON GYNECOLOGIC SURGERIES

Dilatation and Curettage (Evacuation)

- **Indications:** Before endometrial ablation, for definitive sampling of endometrium, termination of Preg, or to remove retained products of conception
- **Preoperatively:**
  Exclude Preg (unless for termination)
  Obtain informed consent
  Consider cervical softening w/ misoprostol
- **Steps:**
  Ensure adequate anesthesia (general, regional, local), empty bladder
  EUA for uterine position/size
  Insert a speculum, apply tenaculum to anter lip of the cervix
  Use dilators to gradually open the cervix. Optimal dilation depends on procedure.
  May perform curettage w/ suction device, or w/ a sharp curette. For suction curettage, the curette size usually corresponds to the gestational age/uterine size.
  Introduce the curette to fundus & sample all walls & fundus
  Consider forceps to remove larger tissue fragments, or US guidance for difficult procedures

Bartholin cyst marsupialization with or without excision

- **Indication:** Recurrent cyst formation. Objective is to open a new ductal orifice.
- **Preoperatively:** Obtain informed consent
- **Steps:**
  Start w/ 2–4-cm incision 1 cm lateral & parallel to hymenal ring near medial edge of labium minus
  Incise the cyst wall & use Allis clamps to grasp the skin & cyst wall edges
  Drain the cyst completely; open any loculations
  Use interrupted stitches to suture the cyst wall to the adj skin edge
  Consider cyst wall excision/bx for repeated recurrences or if high risk for malig

Cold Knife Conization (CKC)

- **Indication:**
  To better characterize glandular or squamous lesions after unsatisfactory initial w/u by excising the transformation zone of the cervix

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Generally reserved for more difficult cases & pts w/ recurrence after LEEP
A/w more obstetric complications compared to LEEP & Laser conization

- **Preoperatively:**
  Colposcopic exam & biopsies are req before Surg
  Exclude Preg (unless high suspicion for invasion)
  Obtain informed consent
- **Steps:**
  Adequate anesthesia, empty bladder
  Use iodine or acetic acid for identification of the lesions
  Inject vasopressin or dilute epi circumferentially into cervical stroma, lateral to line of resxn
  Place sutures at 3 & 9 o'clock to manipulate the cervix
  Make an incision that creates a 2–3-mm border around lesion. Ensure inclusion of the endocervical canal.
  Perform endocervical curettage
  Hemostasis w/ Monsel solution or electrocautery

Operative hysteroscopy

- **Indications:**
  Eval & rx of polyps, myomata, adhesions, septa. Also tubal sterilization, removal of retained IUD or FB.
- **Preoperatively:**
  Obtain informed consent, exclude Preg
  In premenopausal women, consider performing during the early proliferative phase of the menstrual cycle, or treating w/ progestins to induce endometrial atrophy
  In postmenopausal women, consider misoprostol if there is cervical stenosis
- **Steps:**
  Adequate anesthesia, empty bladder
  Perform EUA to determine uterine position/size
  Insert speculum, apply tenaculum to the anter lip of the cervix
  Use dilators to gradually open the cervix. Dilate to diameter of the hysteroscope.
  Introduce the hysteroscope into the uterine cavity, survey cavity
  Distention media include isotonic electrolyte (LR, NS) & nonelectrolyte (glycine, mannitol). Infusion pres should be ~45–80 mmHg
  Perform the indicated procedure
  Monit fluid deficit. Plan completion of the case if the deficit reaches 750 cc; stop if 1500 cc (nonelectrolyte), or 2500 cc (electrolyte).

Endometrial ablation

- **Indications:** Heavy menstrual bleeding
- **Preoperatively:**
  Exclude Preg
  Exclude malig & hyperplasia by endometrial bx
  Need to have a plan for contraception after ablation
  Obtain informed consent
- **Steps:**
  Adequate anesthesia, empty bladder, EUA
  Insert a speculum, apply a tenaculum to the anter lip of the cervix
  Sound the uterus
  Use dilators to gradually open the cervix. Dilation determined by diameter of ablative device.
  Consider hysteroscopic eval if concern for cavitary abnormalities (polyps, etc.)
  Perform indicated procedure (variations include resectoscope, rollerball, thermal balloon, hydrothermal, radiofrequency, microwave, & cryoablation)
  Monit fluid deficit if distending medium is used

Hysteroscopic tubal ligation

- **Indications:** Undesired fertility
- **Preoperatively:**
  Exclude Preg
  Best done during the proliferative phase of the cycle, or after rx w/ OCPs, DMPA, etc. to induce endometrial atrophy for visualization
  Obtain informed consent
- **Steps:**
  Adequate anesthesia, empty bladder, EUA
  Insert a speculum, apply tenaculum to the anter lip of the cervix, sound the uterus
  Use dilators to gradually open the cervix. Dilation determined by diameter of hysteroscope.

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Currently, only approved system is the microinsert (Essure)
Cannulate each tubal ostium w/ Essure device. Follow package insert to deploy insert.
Pt must use contraception until tubal occlusion is documented by HSG (at 3 mo)

Operative laparoscopy

- **Indications:** Minimally invasive access to abd
- **Preoperatively:**
  Decide entry point (eg, umbilical, LUQ) & method of entry (eg, Veress, open)
  Obtain informed consent
- **Steps:**
  General anesthesia w/ neuromuscular blockade, OG tube, Foley catheter, EUA
  Consider inserting a uterine manipulator
  Using a scalpel, make a skin incision large enough to accommodate the laparoscopic trocar
  Abdominal trocars can be inserted in several ways:
  Introduce the Veress needle into the abdominal cavity w/ the abdominal wall elevated. 2 "pops" can be felt as the needle passes through the fascia & peritoneum. Abdominal entry is confirmed by "saline drop test" or by measurement of entry pres; initial pres of <5 mmHg is reassuring. Insufflate abd w/ CO_2 to max pres of 10–12 mmHg. Remove Veress needle. A trocar can then be inserted into the peritoneal cavity.
  Direct trocar insertion – insert trocar directly w/o insufflation, w/ elevated abdominal wall
  Optical access trocar entry – direct visualization of abdominal wall through trocar during insertion
  Open entry (Hasson technique) – A 1–2-cm incision is made below the umbilicus. Dissect tissue to fascia, incise fascia, open peritoneum, & insert blunt trocar.
  Systematically inspect the abd & pelvis
  Perform procedure (hysterectomy, cystectomy, oophorectomy, etc.)
  Desufflate abd, close fascia for incisions 10 mm or greater. Close skin.

Laparoscopic tubal ligation

- **Indications:** Permanent sterilization
- **Preoperatively:**
  Informed consent
- **Steps:**
  Adequate anesthesia w/ muscle relaxation, EUA, OG tube, empty bladder
  Select the site & mode for laparoscopic entry
  Systematic eval of the abd
  Identify the tubes & follow them out to the fimbriated ends
  Ligation can be performed w/ clips, rings, cautery, or excision. Salpingectomy is the most effective method of tubal ligation. See chapter 1.

Total abdominal hysterectomy

- **Indications:** Heavy uterine bleeding, symptomatic fibroids, pelvic organ prolapse, Gynecologic malignancies
- **Preoperatively:**
  Obtain informed consent
  Endometrial bx (in setting of abn uterine bleeding), Pap smear
- **Steps:**
  General anesthesia, preop antibiotic, EUA, Foley catheter
  Abdominal entry through appropriate incision (midline, paramedian, Pfannenstiel, etc.)
  Consider abdominal wall retractor & abdominal packing
  Grasp the round ligaments, uteroovarian ligaments, & fallopian tubes w/ curved Kelly clamps to elevate the uterus & provide traction
  Divide the round ligament btw 2 transfixion sutures & extend the incision down to the broad ligament
  Dissect the broad ligament into anter & post leaves
  Identify the ureter
  Carry anter broad ligament incision inferomedially to the level of the vesicouterine fold. Open the post leaf toward the uterosacral ligaments.
  For oophorectomy: Open a window in the broad ligament to isolate the IP ligament. Clamp the IP w/ 2 Heaney clamps & transect the IP btw them. Suture ligate the distal pedicle w/ a free tie & transfixion suture & the prox pedicle w/ a single free tie.

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To preserve the ovaries: Isolate the fallopian tube & the uteroovarian ligament. Clamp across these 2 structures; cut, & suture ligate.
Rpt above steps on opposite side of uterus
Dissect the vesicouterine peritoneum off the anter uterus & cervix
Identify the uterine arteries & carefully dissect off the surrounding connective tissue. Use Heaney or Zeppelin clamps to come across the uterine vessels on either side; incorporate the vessel, not adj uterine or cervical tissue. Cut the vessels & doubly ligate.
Clamp cardinal ligament; transect, & doubly ligate
Pull uterus upward & clamp across uterosacral ligaments. Cut ligaments close to the uterus (avoiding ureters) & suture ligate.
Place 2, curved clamps immediately below the cervix. Cut above these clamps to remove the uterus & cervix.
Close vaginal cuff w/ figure-of-eight stitches. Incorporate uterosacral & cardinal ligaments into cuff repair for additional support.
Ensure hemostasis & close the abd

Vaginal hysterectomy

- **Indications:** See above
- **Preoperatively:**
  Informed consent & endometrial bx/Pap smear
- **Steps:**
  Adequate anesthesia, antibiotic. EUA, Foley catheter w/ pt in dorsal lithotomy.
  Place weighted speculum & use Deaver retractors to expose the cervix
  Grasp the anter & post lips of the cervix using 2 tenacula, or thyroid clamp
  Inject vasopressin or lidocaine/epi around the cervicovaginal junction
  Make an elliptical incision at the cervicovaginal junction
  W/ downward traction, dissect bladder off cervix until anter peritoneum comes into view
  Open the anter peritoneum & slide the anter Deaver into elevate bladder
  Using upward traction, open the post peritoneum into the Pouch of Douglas
  Pull the uterus outward & identify the uterosacral ligaments. Clamp ligaments; cut, & suture ligate.
  Clamp, cut, & suture ligate the cardinal ligaments, uterine arteries, uteroovarian ligaments & round ligaments. If oophorectomy is performed, the IP ligaments are identified, clamped, cut, & suture ligated in place of the uteroovarian ligaments.
  Ensure hemostasis. Close vaginal cuff using interrupted or running sutures. Incorporate uterosacral & cardinal ligaments into cuff repair for additional support.

COMMON OBSTETRIC SURGERIES

Cesarean section

- **Indication:** Need for immediate deliv, failure to progress in labor, or if pt not a candidate for labor/vaginal deliv (numerous indications)
- **Preoperatively:**
  CBC, type & screen, informed consent
- **Steps:**
  Adequate anesthesia (general, neuraxial, etc.)
  Foley catheter, prophylactic Abx, pt should be supine w/ leftward tilt
  Abdominal entry: Generally low, transverse, though sometimes vertical.
    Variations of low transverse incisions include:
    Pfannenstiel (most common)—3 cm above the pubic symphysis & slightly curved upward. Fascia is incised transversely & dissected off underlying rectus muscles. Rectus muscles separated in the midline.
    Maylard incision – 3–8 cm above the symphysis. Fascia incised transversely, inferior epigastric vessels are ligated, rectus muscles are divided transversely.
    Cohen incision – 3–4 cm above the symphysis. Fascia incised in the midline, extension of the fascial incision, separation of rectus, & entry to peritoneum done bluntly.
    Consider a bladder flap by incising the vesicouterine peritoneum in the midline, & extending the incision bilaterally. Use blunt or sharp dissection to expose the lower uterine segment.
  Hysterotomy: Generally transverse in lower uterine segment, 2 cm above the bladder margin. Can extend bluntly or w/ bandage scissors. Alternatives include low vertical incision or classical incision (vertical incision extends to upper uterus).

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Deliv: Slide hand below the infant's head & elevate it to the level of the incision. Apply fundal pres to facilitate deliv. If breech, deliver legs, rotate body to deliver shoulders & arms, deliver head.
Deliver placenta w/ uterine massage or manually. Clear uterus of clot & placental tissue.
Close hysterotomy in 1 or 2 layers. The 1st layer closure is performed w/ a running, locking stitch. An imbricating, running stitch may then be used.
Reapproximate fascia w/ a running, delayed-absorbable or permanent suture
Close subcutaneous layer if >2 cm thick; close skin w/ subcuticular suture or staples

Tubal ligation at time of C-section

- **Indication:** Undesired fertility
- **Preoperatively:**
  Obtain informed consent
  Contraceptive counseling
- **Steps:**
  Exteriorize uterus for easy identification of the tubes; follow tube out to fimbriated end
  Modified Pomeroy: Grasp the isthmic portion of the tube ~4 cm from the cornua w/ a Babcock clamp to elevate loop of the tube. Ligate the base of the loop w/ plain catgut. Divide the mesosalpinx in the center of the loop. The portion of the tube w/i the ligated loop is then excised.
  Parkland method: Use a Babcock forceps to hold a segment of the tube about 3–4 cm from the cornua. Create a window in an avascular area of the underlying mesosalpinx. Doubly ligate the tube at the prox & distal end. Excise the segment of tube.
  Irving method: Perform all steps of the Parkland method. Then, bury the prox end of the tube into a pocket created in the myometrium.
  Uchida method: Dissect mesosalpinx off the fallopian tube & excise a segment of the tube. Suture mesosalpinx closed; bury the prox stump of the fallopian tube w/i mesosalpinx. The distal stump is left exteriorized.
  Alternatively, total salpingectomy can be performed

Postpartum tubal ligation

- **Indication:** Undesired fertility
- **Preoperatively:** Obtain informed consent, including nonpermanent contraceptive options
- **Steps:**
  General, spinal or epidural anesthesia, insert Foley catheter
  Make small (2–4 cm), transverse, infraumbilical skin incision
  Carry down to the fascia, incise fascia transversely, & enter peritoneum
  Immediately postpartum, the uterine fundus sits just below the umbilicus. Identify fallopian tubes & follow out to fimbriated ends.
  Ligate tubes (see above for options)
  Ensure hemostasis
  Close the fascia, subcutaneous layer if >2-cm thick, & skin

Cervical cerclage

- **Indication:** Recurrent Preg loss a/w cervical insufficiency, or cervical insufficiency diagnosed early in current Preg
- **Preoperatively:** Obtain informed consent, confirm viability, confirm intact membranes, rule out intra-amniotic infection
- **Steps:**
  General, spinal, or epidural anesthesia
  Empty bladder, position in lithotomy, place weighted speculum, use retractors to expose the cervix
  Grasp the cervix w/ ring forceps
  Use Mersilene tape, Prolene, or Ethibond suture
  McDonald cerclage: W/ the suture, make a bite in the cervix from 12–10 o'clock as close to the junction w/ the rugated vaginal epithelium as poss. The next bites go from 8–6 o'clock, from 6–4, & from 2–12. Cinch tightly & tie. Leave a 2–3-cm tail so the stitch can be removed.
  Shirodkar cerclage: Open the vesicocervical space by making a small incision at the cervicovaginal junction. Push the bladder up w/ careful dissection. Open the posterior rectovaginal space similarly. Hydrodissection before incision is sometimes useful. Use right angle allis clamps to pull the vessels lateral. Suture

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through cervix anterior-posterior in U-shaped fashion (two bites). Consider closing the mucosal incision.
Ensure hemostasis

Repair of obstetrical laceration

- **Preoperatively:** Ensure proper equipment & instruments available, as well as a good light source. If unable to fully visualize the laceration or source of bleeding, move pt to the OR.
- **Steps:**
  Provide local anesthesia in the absence of an epidural
  Examine the cervix, vagina, labia, & periurethral area
  Rectal exam to evaluate for 3rd- & 4th-degree lacerations
  Examine the cervix systematically. Repair w/ interrupted absorbable sutures.
  Hemostatic 1st-degree lacerations do not require repair
  For 2nd-degree lacerations, anchor suture 1–2 cm above the apex. Close the laceration w/ a running, locked stitch until the hymenal ring.
  Pass the suture under the vaginal mucosa to the muscle layer of the perineal body
  Close the muscle layer w/ a running stitch
  Close the skin using subcuticular or interrupted sutures
  Perform a rectal exam to ensure no suture material is in the rectum

Pudendal nerve block (see Figure 4.3)

- **Indication:**
  To obtain analgesia necessary for deliv or repair of perineal lacerations
- **Preoperatively:**
  Appropriate equipment & good light source
- **Steps:**
  Use an Iowa trumpet & 20-gauge needle
  Prepare 10 cc of 1% lidocaine w/o epi
  Identify the spinous process of the ischium
  Inject 2.5 cc above & below the spinous process on each side
  Check for the anal reflex

Male circumcision

- **Indication:** Elective surgical procedure based on parental request
- **Preoperatively:**
  Examine the infant & ensure:
    Adequate shaft length (>1 cm)
    No congen anomalies
    No bleeding diathesis
  Obtain informed consent
- **Steps:** The 3 major methods employ the GOMCO clamp, Hollister Plastibell, & Mogen clamp. The GOMCO clamp is the most widely used, & is a/w the fewest complications.
  Provide local anesthesia & prep the skin
  Determine the size of the bell that will be needed (edge of bell should reach the frenulum & minimally extended over the corona)
  Apply 2 artery hemostats at 3 & 9 o'clock on the foreskin
  Use a 3rd hemostat to open the space btw the glans & the foreskin, avoiding the 5 & 7 o'clock positions
  The hemostat is then used to create a crush line on the dorsal aspect of the foreskin (>1 cm away from the coronal sulcus). Cut the crushed skin & retract the foreskin.
  Place the bell over the glans, inside the foreskin
  Inspect to make sure that the remaining shaft skin is symmetrical, & not under tension T
  Tighten clamp, cut foreskin, & remove residual tissues
  Wait for 5 min before opening the clamp
  Inspect for bleeding & apply pres if needed
  Use petroleum-soaked gauze around the edges of the foreskin
  Ensure infant is able to urinate before discharge home
  Dressing should remain for 12–24 h

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Antibiotics (selected; see also specific topics, and for UTI/pyelo see Chapter 14)

Drug	Mechanism of action	Pregnancy class (FDA) Breastfeeding (AAP/ Thompson)	Standard indication	Typical regimen	AE, CI
Ampicillin	β-lactam – inhibits cell wall synthesis	B Compatible w/ breastfeeding	GBS ppx	2 g IV then 1 g IV q4h	N/V, diarrhea
			Chorio (w/ gentamicin)	2 g IV q6h	
			Latency Abx (PPROM)	2 g IV q6h × 48 h, followed by amoxicillin	
Amoxicillin	β-lactam – inhibits cell wall synthesis	B Compatible	UTI (Preg), otitis, respiratory tract infxn	500–875 mg q12h × 7–10 d	N/V, diarrhea
			Latency Abx (PPROM)	250 mg TID × 5 d (s/p IV ampicillin course)	
Cefazolin (Ancef)	Cephalosporin (1st generation, β-lactam) – inhibits cell wall synthesis	B Compatible	Preop ppx	2 g IV × 1	N/V, diarrhea
			GBS ppx alternative	2 g IV × 1 then 1 g q6h	
Gentamicin	Aminoglycoside – inhibits prot synthesis by binding 30S ribosomal subunit	D Compatible	Chorio Endometritis	1.5 mg/kg IV q8h for both	Renal dysfxn requires dose adjustment, ototoxicity
Clindamycin	Inhibits prot synthesis by binding 50S ribosomal subunit	B Compatible	Preop ppx	600 or 900 mg IV × 1	*C. Difficile* colitis, N/V
			GBS ppx alternative	900 mg q8h	
			Endometritis (w/ gentamicin)	300–450 mg PO q6h × 7–14 d	
			Wound cellulitis, incl MRSA		
Ciprofloxacin (Cipro)	Fluoroquinolone – interferes w/ DNA synthesis	C Usually compatible	UTI, GI tract infxn, respiratory tract infxn	400 mg IV/PO for 7–14 d	Rash, diarrhea, *C. Difficile* colitis, N/V, tendon rupture, generally avoided in Preg – poss risks to fetal MSK dev
			Anthrax	500 mg BID PO × 60 d	
Trimethoprim-sulfamethoxazole (Bactrim)	Trimethoprim – interferes w/ tetrahydrofolic acid production & DNA formation Sulfonamide – blocks bact synthesis of dihydrofolic acid	C Usually compatible	UTI	160/800 mg BID PO × 3 d (7–14 d for complicated UTI)	Rash, N/V, diarrhea, hepatic dysfxn, CI w/ sulfa allergy Generally avoided in 1st & 3rd trimester of Preg

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Nitrofurantoin (Macrobid)	Inhibits prot synthesis	B Usually compatible	UTI (Preg)	100 mg BID PO × 5–7 d	N/V, hepatic dysfxn CI during labor/delivery, or when labor is imminent
Ceftriaxone (Rocephin)	Cephalosporin (3rd generation, β-lactam)	B Usually compatible	Pyelo	1 g IV q24h	Allergy/anaphylaxis, N/V, diarrhea
			Gonorrhea	250 mg IM × 1 dose	
Piperacillin/ tazobactam (Zosyn)	β-lactam + β-lactamase inhib	B Likely compatible	PID Bacteremia PNA	3.375–4.5 g IV q6h × 7–10 d	Rash, GI upset, leukopenia
Erythro	Macrolide – inhibits prot synthesis by binding 50S ribosomal subunit	B Usually compatible	Chlamydia	500 mg PO q4h	GI upset, rash
			Latency Abx (PPROM)	250 mg IV q6h × 48 h, then PO TID × 5 d	
Azithro (Zithromax)	Macrolide – inhibits prot synthesis by binding 50S ribosomal subunit	B Infant risk minimal	Chlamydia Respiratory tract infections Latency Abx (PPROM)	1 g PO × 1 dose 500 mg PO daily × 3–5 d (Also IV)	GI upset, hepatic dysfxn
Vanco	Inhibits bact cell wall synthesis	C Infant risk cannot be ruled out	MRSA skin infxn, bacteremia	15–20 mg/kg IV q12h	Red man syn, caution w/ renal dysfxn. Check serum trough levels.
			GBS ppx (if PCN allergy)	1 g IV q12h during labor	
			C. Difficile infxn	125 mg PO QID × 10–14 d	
PCN	β-lactam	B Usually compatible	GBS ppx	5 million units × 1 IV, then 2.5 million units q4h IV	Allergy/anaphylaxis, N/V, diarrhea
Cephalexin (Keflex)	Cephalosporin (1st generation, β-lactam) – inhibits cell wall synthesis	B Infant risk is minimal	Soft tissue infxn UTI	500 mg PO BID × 7–14 d	Allergy/anaphylaxis, N/V, diarrhea
Metronidazole (Flagyl)	Bact enzyme deactivation	B Unk, may be of concern	Bact vaginosis	500 mg PO BID × 7 d	N/V, rash, antabuse-type rxn w/ EtOH, CI in 1st trimester
			Trichomonas vaginalis	2 g PO × 1 dose	
			PID	500 mg PO BID × 14 d	
			C. Difficile colitis	500 mg PO TID × 10–14 d	
Doxycycline	Tetracycline – inhibits prot synthesis	D Avoid in breastfeeding	Chlamydia	100 mg BID × 7 d	N/V, photosensitivity, CI in Preg (tooth discoloration)
			PID	100 mg BID × 14 d	

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Antihypertensives/Medications for Preeclampsia (and see Chapter 12)

Alphamethyldopa (Aldomet)	Inhibits dopamine production → reduced levels of norepi & epinephrine; central α2 agonist → inhibits symp NS	B Compatible	HTN	250–500 mg PO TID	CI if concurrent MAOI therapy, caution w/ CHF
Hydralazine	Vasodilator	C Compatible	HTN	10–25 mg PO QID	Tachy
Labetalol	β-blocker	B Compatible	HTN (incl preeclampsia, hypertensive urgency)	HTN: 200 mg PO q12 up to 2400 mg daily HTN urgency: 20 mg IV, followed by 40 IV if nec (max 300)	Brady, CI w/ asthma
Magnesium	Nonspecific calcium channel blockade	A Compatible	Sz ppx in preeclampsia Eclamptic sz rx	4 g IV bolus, then 2 g/h 3–5 g IM × 2 (used if no IV access)	Flushing, HA, blurry vision, drowsiness Magnesium tox: Hyporeflexia, somnolence, pulm edema, resp depression
Nifedipine (Procardia)	CCB	C Compatible	HTN	Extended release formula: 30–60 mg daily	CI w/ magnesium therapy, HoTN Caution w/ hepatic dysfxn

Anticoagulants

Enoxaparin (Lovenox)	Antifactor Xa, antithrombin (LMWH)	B Indeterminate	DVT ppx	40 mg SQ daily	HIT, hypersensitivity Sev bld loss, CI w/ epidural anesthesia (risk for epidural hematoma)
			DVT rx	1 mg/kg q12h	
			Thrombophilia	Varies based on risk	
Heparin	Activates antithrombin III	C Compatible	Same	5000 U SQ q8h IV infusion 5000–10000 BID	Same as LMWH
Warfarin (Coumadin)	Inhibits synthesis of Vit K dependent clotting factors (2, 7, 9, 10, prot C & S)	X Usually compatible	Same	Varies – target INR 2–3	Bleeding, CI w/ epidural anesthesia (risk for epidural hematoma)

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Chemotherapies for Gynecologic Malignancy

Carboplatin	Alkylating agent	Ovarian cancer Endometrial cancer	BSA based	Myelosuppression (thrombocytopenia) Hypersensitivity, N/V
Cisplatin	Alkylating agent	Cervical cancer Germ cell tumors GTN	BSA based	Neuropathy, ototoxicity Nephrotoxicity, N/V
Paclitaxel (Taxol)	Stabilizes microtubules	Ovarian cancer Carcinosarcoma	BSA based	Alopecia, N/V, neuropathy, hypersensitivity rxn, myelosuppression
Docetaxel (Taxotere)	Stabilizes microtubules	Recurrent ovarian cancer	BSA based	Alopecia, edema, nail/skin changes, N/V, diarrhea, mucositis
Bevacizumab (Avastin)	Monoclonal IgG Ab binds VEGF → inhibition of angiogenesis	Ovarian cancer	Weight based	HTN, GI hemorrhage/perforation, proteinuria, arterial thromboembolism
Topotecan (Hycamtin)	Inhibits topoisomerase I	Recurrent ovarian cancer	BSA based	Alopecia, myelosuppression, N/V, fatigue
Gemcitabine (Gemzar)	Nucleoside analogue that inhibits DNA synthesis	Recurrent ovarian cancer	BSA based	N/V, myelosuppression, rash, stomatitis
Doxorubicin (Adriamycin)	Inhibits topoisomerase I	Recurrent ovarian cancer	BSA based	PPE, alopecia, myelosuppression (leukopenia), N/V, cardiotoxicity (requires MUGA before starting), mucositis
Bleomycin	Induces DNA strand breaks	GTN, germ cell tumors	BSA based	Pulm fibrosis, alopecia, hyperkeratosis, stomatitis, PPE
Etoposide	Inhibits topoisomerase II	GTN, germ cell tumors	BSA based	Alopecia, N/V, diarrhea, fever/malaise, AML, myelosuppression (leukopenia)
Methotrexate	Inhibits dihydrofolate reductase → decreased purine synthesis	GTN	15–30 mg PO/IM × 5 d	N/V, hepatotoxicity, photosensitivity, stomatitis, pulm fibrosis
		Ectopic Preg	50 mg/m^2 IM	
Actinomycin D	Binds to DNA, intercalating btw base pairs	GTN	Weight based	N/V, diarrhea, esophagitis, agranulocytosis
Ifosfamide	Alkylating agent	Recurrent cervical cancer, high-grade endometrial stromal sarcoma	BSA based	N/V, hemorrhagic cystitis (give w/ Mesna), encephalopathy, myelosuppression (leukopenia)
Cyclophosphamide (Cytoxan)	Alkylating agent	Recurrent ovarian cancer	Weight based	N/V, pulm fibrosis, cardiotoxicity, myeloid leukemia
Fluorouracil (5-FU)	Inhibits thymidylate synthetase	Cervical cancer, vaginal dysplasia	5% cream topically as directed	N/V, diarrhea, myelosuppression, coronary artery spasm

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Uterotonics (and see Chapter 11)

Oxytocin (Pitocin)	Stimulates uterine oxytocin receptors → increases uterine contractility	Postpartum hemorrhage, induction of labor	10–80 U in 1 L crystalloid 10 U IM (if no IV access)	N/V, emesis
Misoprostol (Cytotec)	Prostaglandin E_1 analog → stimulates uterine contractions	Postpartum hemorrhage; cervical ripening, 1st trimester abortion	600–1000 mcg PR or PO 25–50 mcg vaginally for cervical ripening	N/V, diarrhea, fever, chills
Methylergonovine (Methergine)	Ergot alkaloid → increases uterine contractility	Postpartum hemorrhage	0.2 mg IM, q2–4h up to 5 doses 0.2 mg PO q6h × 4 d	HoTN, N/V CI w/ HTN
Carboprost (Hemabate)	Prostaglandin $F_{2\alpha}$ → stimulates uterine contractions	Postpartum hemorrhage	0.25 mg IM	N/V, diarrhea, flushing, chills, CI w/ asthma
Dinoprostone (Cervidil, Prostin E_2)	Prostaglandin E_2 → stimulates uterine contractions	Postpartum hemorrhage	20 mg PR	N/V, diarrhea, fever, chills, HA, CI w/ asthma
		Cervical ripening	10 mg in vaginal fornix for cervical ripening	

Tocolytics

Nifedipine (Procardia)	CCB	C Compatible	Preterm labor (tocolysis)	20 mg PO q6–8	HoTN, tachy, dizziness, CI w/ magnesium
Magnesium	CCB (antagonizes procontractile effects of calcium)	A Compatible	Preterm labor (tocolysis) Neuroprotection for preterm labor	6 g IV loading dose, then 1–3 g/h 4 g IV loading dose, then 1g/h	Flushing, HA, blurry vision, drowsiness Magnesium tox: Hyporeflexia, somnolence, pulm edema, resp depression
Indomethacin (Indocin)	Prostaglandin synthetase inhib	C Compatible	Preterm labor (tocolysis)	100 mg PO loading dose, then 50 mg PO q6 × 8 doses	Oligohydramnios Premature closure of ductus arteriosus
Terbutaline	β-adrenergic agonist	B Compatible	Preterm contractions Tachysystole	0.25 mg SQ × 1 (may rpt if needed)	Tachy, nervousness, cardiac dysrhythmia. Black box warning against prolonged use b/c of mat cardiovascular effects.

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Selected Treatments for Diabetes

Metformin (Glucophage)	Suppresses hepatic gluconeogenesis, increases insulin sens, enhances periph gluc uptake	B Infant risk minimal	DM II PCOS	500 mg BID, titrated up to 2000 mg daily	GI upset, lactic acidosis, CI in renal insufficiency. Do not use w/ renal contrast
Sulfonylureas (glyburide, glipizide, glimepiride)	Closes K_{ATP} channels on β-cell plasma membranes → increased insulin secretion	C (glyburide most studied in Preg) Infant risk cannot be ruled out	DM II GDM A2 (glyburide)	Varies based on drug Glyburide: 2.5 mg PO w/ dinner, up to 5 mg PO BID	Weight gain, hypoglycemia, Sulfa allergy
Thiazolidinediones (pioglitazone, rosiglitazone)	Activates nuclear transcription factor PPAR-g	C Infant risk cannot be ruled out	DM II	Pioglitazone: 15–30 mg PO daily Rosiglitazone: 4–8 mg PO daily	Edema, weight gain, CI in heart failure
Insulin (multi forms) -Lispro (Humalog) -Regular (Novalin R) -NPH (Novalin N) -Lantus (Glargine)	Insulin receptor agonist Onset/peak/duration 15 min/30–90 min/3–5 h 30–60 min/50–120 min/5–8 h 1–3 h/8 h/20 h 1 h/no peak/24 h	B Compatible	DM I, DM II, GDM	Varies (SQ administration) Also IV insulin drip (regular)	Hypoglycemia

Antiemetics

Prochlorperazine (Compazine)	Depresses chemoreceptor trigger zone	C Infant risk cannot be ruled out	N/V	5–10 mg PO/PR q6–8h	Prolonged QT, tardive dyskinesia
Metoclopromide (Reglan)	Promotes GI motility; inhibits dopamine receptors	B Poss risk	N/V	10–20 mg PO/IV q8h	Tardive dyskinesia, neuroleptic malig syn
Ondansetron (Zofran)	Selective 5HT-3 receptor antag	B Infant risk cannot be ruled out	N/V	4–8 mg PO/IV q4–8h	Constip, prolonged QT
Promethazine HCl (Phenergan)	H1 receptor blocker	C Compatible	N/V	12.5–25 mg PO/PR/IV q6h	Sedation, IV dosing can cause tissue necrosis

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Analgesics (and see Chapter 4)

Acetaminophen (Tylenol)	Unk	B Compatible	Analgesic, antipyretic	325–500 mg q8h, not to exceed 4000 mg daily	Hepatic dysfxn
ASA	Inhibits prostaglandin synthesis (cyclooxygenase inhib); inhibits platelet aggregation	D Signif effects on some infants, use w/ caution	Analgesic, antiplatelet	81–325 mg PO daily	Allergy to NSAID, GI upset, CI w/ GI ulcers
Ibuprofen (Advil, Motrin)	NSAID, inhibits prostaglandin synthesis	C – 1st & 2nd trimester, D – 3rd trimester Compatible	Analgesic, anti-inflammatory	200–800 mg PO q6–8h	Allergy to NSAID, GI upset, CI w/ GI ulcers, caution w/ HTN
Fentanyl (Sublimaze)	Opioid receptor agonist	C Compatible	Analgesic (narcotic)	Dosage varies based on form: IV, transdermal, pt-controlled IV pump	N/V, respiratory depression, constip, pruritis
Hydromorphone (Dilaudid)	Opioid receptor agonist	C Infant risk is minimal	Analgesic (narcotic)	Dosage varies based on form: IV, IM, PO, pt-controlled IV pump	N/V, respiratory depression, constip, pruritis
Morphine	Opioid receptor agonist	C Compatible	Analgesic (narcotic)	Dosage varies based on form: IV, IM, PO, pt-controlled IV pump	N/V, respiratory depression, pruritis, CI w/ renal insufficiency
Oxycodone (Roxicodone, Percocet)	Opioid receptor agonist	B Poss infant risk	Analgesic	5–15 mg PO q4–8h	N/V, constip, respiratory depression
Hydrocodone (Vicodin)	Central acting analgesic	C May be of concern	Analgesic, antitussive	5–10 mg PO q4–8h	N/V, constip, respiratory depression

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Psychiatric/Substance Abuse Medications (selected)

Buprenorphine (Butrans)	Opioid receptor agonist/antag	C Infant risk has been demonstrated	Opioid dependence	10–30 mcg/h transdermal patch	Rash, GI upset
Bupropion (Wellbutrin)	Dopamine/norepi reuptake inhib	C May be of concern	Depression, smoking cessation	IR: 100 mg PO BID–TID XR: 150–300 mg PO daily	HTN, constip, N/V, lower sz threshold
Citalopram (Celexa)	SSRI	C Poss infant risk	Depression, anxiety	20–40 mg PO daily	GI upset, sexual dysfxn, prolonged QT
Disulfiram (Antabuse)	Inhibits aldehyde dehydrogenase (enzyme that metabolizes EtOH)	C May be of concern	Alcoholism	500 mg PO daily	Dermatitis. Can have fatal EtOH withdrawal rxn.
Fluoxetine (Prozac)	SSRI	C May be of concern	Depression, anxiety	20–80 mg PO daily	GI upset, HA, dizziness, fatigue, sexual dysfxn, serotonin syn, prolonged QT
Lithium	Unk	D Effects on newborns – use w/ caution	Bipolar d/o	Varies by formulation	Hypothyroidism, tox, renal dysfxn, GI upset, CV effects. Fetal CV defects.
Methadone	Opioid receptor agonist	C Compatible	Opioid dependence	80–120 mg PO daily for maint therapy	Cardiac dysrhythmia, prolonged QT, constip, dizziness
Sertraline (Zoloft)	SSRI	C May be of concern	Depression, anxiety	25–100 mg PO daily	GI upset, HA, dizziness, fatigue, sexual dysfxn, serotonin syn
Trazadone	Serotonin reuptake inhib & receptor antag	C May be of concern	Sleep aid, depression	50–150 mg PO nightly/daily	GI upset, drowsiness, prolonged QT, postural HoTN
Lorazepam (Ativan)	Benzodiazepine (binds GABA receptor)	D May be of concern	Anxiety, sleep aid, EtOH withdrawal	0.5–2 mg daily (divided doses) PO, IV	Drowsiness, dizziness, delirium, caution w/ respiratory insufficiency

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Medications for Urinary Incontinence (see Chapter 7)

Steroids (and for topical steroids, see Chapter 19)

Betamethasone (Celestone)	Anti-inflammatory – Accelerates prot production & production of surfactant	C Compatible	Fetal lung maturity	12.5 mg IM q24h × 2 doses (24–34 w gest)	Mat hyperglycemia, leukocytosis, fetal hypoglycemia
Dexamethasone	Anti-inflammatory	C Compatible	Fetal lung maturity	12 mg IM q12h × 2 doses (24–34 w gest)	Mat hyperglycemia, leukocytosis, fetal hypoglycemia
			Anti-inflammatory, rheumatologic conditions Thrombocytopenia	10 mg IV q12h	
Prednisone	Glucocorticoid analog	C Compatible	Anti-inflammatory, rheumatologic conditions	Varies based on indication, 5–60 mg daily PO	HTN, fluid retention, euphoria, Cushing syn, hyperglycemia

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Contraception

Medroxyprogesterone (Depo-Provera)	Suppresses ovulation, decreases tubal motility, causes endometrial atrophy, & thickens cervical mucus	X Compatible	Contraception, menorrhagia	150 mg IM every 3 mo	May cause irreg bleeding, weight gain, breast tenderness, HAs, reversible loss of bone density, delayed fertility. CI w/ sev HTN, stroke, liver dz, or breast cancer.
Mirena IUS (Levonorgestrol-releasing intrauterine system)	Thickens cervical mucus, thins the endometrium, decreases tubal motility, may suppress ovulation	X Compatible	Contraception, menorrhagia	Intrauterine device effective for 5 y	Risk of ectopic Preg if Preg does occur, irreg bleeding, uterine perforation/malposition, expulsion. CI w/ uterine anomaly. Do not insert if active cervical/uterine infxn or h/o infxn in last 3 mo.
Paragard IUD (Intrauterine Copper contraceptive)	Creates spermicidal environment	X Compatible	Contraception	Intrauterine device effective for 10 y	See above. May worsen dysmenorrhea or menorrhagia. CI w/ Wilson dz.
Subdermal Implant (Etonogestrel implant)	Suppresses ovulation, decreases tubal motility, thins the endometrium, & thickens cervical mucus	X Compatible	Contraception	Subdermal implant effective for 3 y	Unpredictable bleeding. CI w/ sev HTN, stroke, liver dz, or breast cancer.
Norethindrone (Micronor)	Thickens cervical mucus, prevents ovulation (~50% of the time), decreases tubal motility, & thins endometrium	X Compatible	Contraception, menorrhagia	5 mg PO daily	CI w/ sev HTN, stroke, liver dz, or breast cancer
Combined OCPs Low-dose (Alesse, Loestrin) Mid dose (Orthocyclen) High dose (Ovral) Multiphasic (Ortho Tri-Cyclen) Extended cycle (Seasonale, Seasonique)	Suppresses ovulation, thickens cervical mucus, decreases tubal motility, & thins endometrium	X Usually compatible	Contraception, menorrhagia, irreg menses, dysmenorrhea, acne	Low-dose: 20 mcg ethinyl estradiol Mid-dose: 30–35 mcg ethinyl estradiol High-dose: 50 mcg ethinyl estradiol Multi progest forms	May cause breast tenderness, HAs, nausea, breakthrough bleeding. Increased risk of thrombotic events (but lower risk than in Preg). CI if h/o DVT, vascular dz, breast cancer, migraines w/ aura, stroke, poorly controlled DM or HTN, smoker >35 yo, liver or gallbladder dz, or SLE
Nuva-Ring (Ethinyl estradiol/etonogestrel vaginal ring)	See above	X Usually compatible	Contraception, menorrhagia, irreg menses	1 ring placed vaginally for 3 w, remove for 1 w, rpt w/ new ring	See above. May cause vaginal irritation or discomfort.
Ortho Evra Patch (Norelgestomin/ethinyl estradiol transdermal system)	See above	X Usually compatible	Contraception, menorrhagia, irreg menses	Apply to lower abd, buttocks, upper torso (not breasts), or upper outer arm. Exchange weekly × 3 w & then leave off × 1 w.	See above. May cause skin irritation. Use w/ caution if wt >198 lbs

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Infertility

Clomiphene citrate (Clomid)	Interrupts estrogen's central negative feedback, increases FSH secretion → maturation of ovarian follicles	X Contraindicated	Ovulation induction	50 mg PO daily for 5 d, can ↑ by 50 mg increments to 250 mg	Hot flashes, mood swings, ovarian cysts, increased risk of multi gest
Letrozole (Femara)	Aromatase inhib, suppresses ovarian estradiol secretion, increases FSH secretion → maturation of ovarian follicles	X Contraindicated	Ovulation induction	2.5–5 mg PO daily for 5 d	Hot flashes, mood swings, joint pains, fatigue, increased risk of multi gest
Gonadotropins (Follstim, Fertinex, Gonal-f)	FSH/LH preparations	X Contraindicated	Stimulates ovarian follicle maturation	Start at 50–75 IU/d IM (protocols vary)	Ovarian hyperstimulation syn, increased risk of multi gest

Osteoporosis

Bisphosphonates -Alendronate (Fosamax) -Risedronate (Actonel) -Ibandronate (Boniva)	Inhibition of osteoclasts	Osteoporosis (rx & ppx), HyperCa of malig	Alendronate: 35 mg PO once weekly Risedronate: 35 mg PO once weekly Ibandronate: 150 mg PO monthly, 3 mg IV every 3 mo	Erosive esophagitis, osteonecrosis – caution w/ dental Surg, infxn. CI if renal dz.
SERM -Raloxifene	Binds to estrogen receptors (both activating & deactivating), reduces bone Absorp	Osteoporosis (rx & prevention) Breast cancer	60 mg PO daily	Stroke, VTE, CI in Preg, caution w/ coronary heart dz
Calcitonin	Reduces osteoclast number, increases osteoblast activity	HyperCa	4 μ/kg subq or IM every 12 h	May cause hypocalcemic tetany
		Osteoporosis	200 units intranasal daily	

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Hormone Replacement (Postmenopausal)

Estrogen -Oral (CEE, Premarin) -Patch (17β-Estradiol, Climara)	Systemic HRT	Menopausal/vasomotor sx	Oral: 0.3, 0.45, 0.65, 0.9, or 1.25 mg daily Patch: 0.0375, 0.5, 0.075, 0.1 mg/d, apply weekly	Increased risk of stroke, VTE, breast cancer. CI w/ h/o breast cancer, coagulopathy, smokers. Estrogen only preparations CI if pt has uterus (risk of endometrial hyperplasia).
Estrogen-progesterone -Oral (CEE + medroxyprogesterone acetate, Prempro) -Patch (17β-Estradiol + norethindrone acetate, Combipatch)	Systemic HRT	Menopausal/vasomotor sx in pts w/ uterus	0.3–0.625 mg CEE + 1.5 mg MDPA daily 0.05 mg/d E_2 + 0.14–0.25 mg/d NETA, apply patch twice weekly	Increased risk of stroke, VTE, breast cancer. CI w/ h/o breast cancer, coagulopathy, smokers.
Vaginal estrogen -CEE, Premarin -17β-Estradiol, Estrace	Local HRT	Vaginal atrophy	0.5 g vaginally daily for 2 w, then twice weekly 2 g vaginally daily for 2 w, then twice weekly	CI w/ h/o endometrial or breast cancer

Lipid and Cholesterol therapy see Chapter 1
Constipation therapies & stool softeners see Chapter 7
Antidiarrheal medications see Chapter 7
Iron supplements and formulations see Chapter 16
Types of insulin see Chapter 17
Anti seizure medications see Chapter 18

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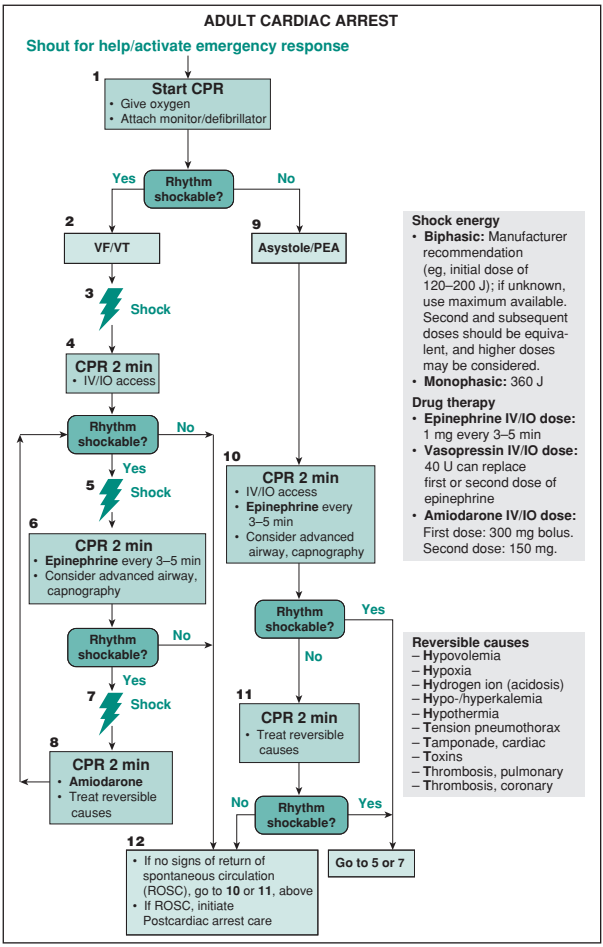
Figure APP-4-1 2010 VF/pulseless VT, asystole and PEA algorithms



(From *Circulation.* 2010;122:S729–S767.)

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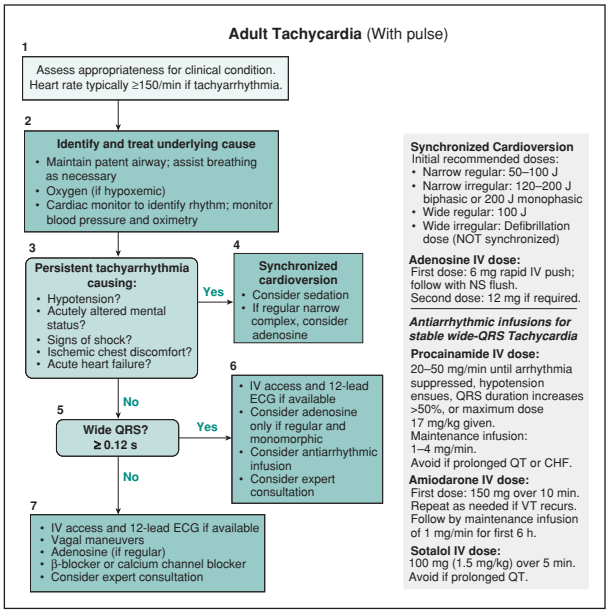
Figure APP-4-2 2010 ACLS tachycardia algorithm



(From *Circulation.* 2010;122:S729–S767.)

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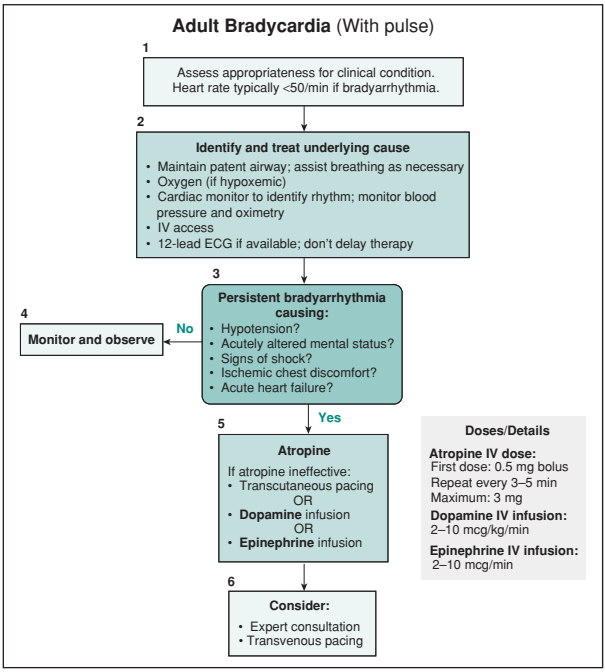
Figure APP-4-3 2010 ACLS bradycardia algorithm



(From *Circulation.* 2010;122:S729–S767.)

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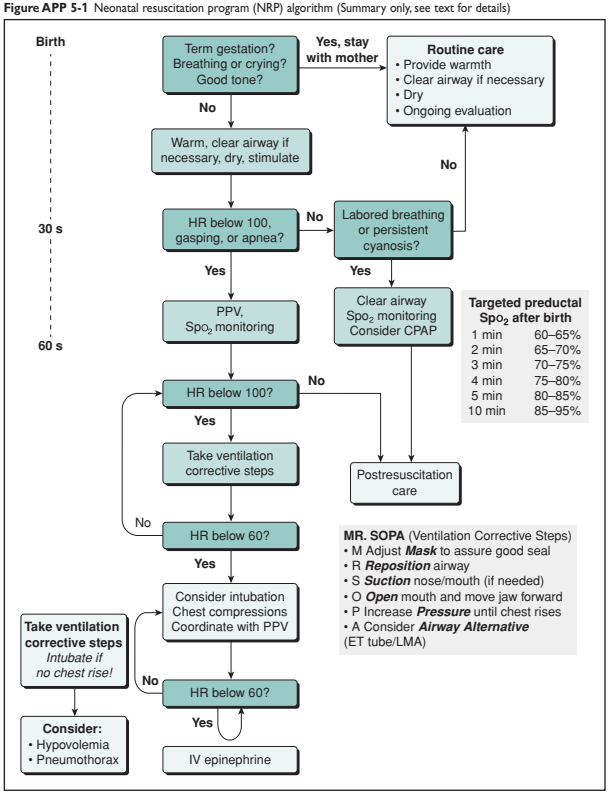
Figure APP 5-1 Neonatal resuscitation program (NRP) algorithm (Summary only, see text for details)



(From Kattwinkel J, Perlman JM, Aziz K, et al. Neonatal resuscitation: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Pediatrics.* 2010;126:e1400)

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ABBREVIATIONS

17-OHP	17-hydroxyprogesterone
AA	African American
AAP	American Academy of Pediatrics
Ab(s)	antibody(ies)
ABG	arterial blood gas
AC	abdominal circumference
ACEI	angiotensin-converting enzyme inhibitor
ACh	acetylcholine
aCL	anticardiolipin antibody
ACOG	American Congress /College of OB/GYN
ACS	acute coronary syndrome/ American Cancer Society
ACTH	adrenocorticotropic hormone
ADH	antidiuretic hormone
AE	adverse effects
AED	antiepileptic drug
AEDF	absent end diastolic flow
AF	amniotic fluid
AFC	antral follicle count
AFE	amniotic fluid embolism
AFI	amniotic fluid index
AFLP	acute fatty liver of pregnancy
AFP	alpha-fetoprotein
AFV	amniotic fluid volume
AG	anion gap
Ag	antigen
AI	active ingredient
AIDS	acquired immunodeficiency syndrome
AIHA	autoimmune hemolytic anemia
AIN	anal intraepithelial neoplasia
AIS	adenocarcinoma in situ/ androgen insensitivity syndrome
AKI	acute kidney injury
AMA	advanced maternal age
AMH	anti-Müllerian hormone
AML	acute myeloid leukemia
Amp	amplitude/ampicillin
AMS	altered mental status
Amy	amylase
ANA	antinuclear antibody
AP	angina pectoris/anteroposterior
aPa/APLA	antiphospholipid antibodies
APRN	advanced practice registered nurse
APS	APLA syndrome
aPTT	activated partial thromboplastin time
AR	absolute risk
ARB	angiotensin receptor blocker
ARDS	acute respiratory distress syndrome
ARF	acute renal failure
ARR	AR reduction
ART	antiretroviral therapy/assisted reproductive technology
AS	aortic stenosis
ASA	American Society of Anesthesiologists/aspirin
ASCAs	antisaccharomyces cerevisiae antibodies
ASCCP	American Society for Colposcopy and Cervical Pathology
ASD	atrial septal defect
ASIS	anterior-superior iliac spine
ASRM	American Society for Reproductive Medicine
AT-III	antithrombin III
ATD	antithyroid drug
ATFP	arcus tendineus fasciae pelvis
ATN	acute tubular necrosis
AUB	abnormal uterine bleeding
AVA	aortic valve area
AVF	arteriovenous fistula
AVM	arteriovenous malformation
AVSDs	atrioventricular septal defects
Azithro	azithromycin
AZT	zidovudine
BASE	brief abuse screen for the elderly
BB	beta blocker
BBT	basal body temperature
BC	bulbus cordis
BCC	basal cell carcinoma
BE	base excess
bhCG	beta-hCG
BiAsp	biphasic insulin aspart
BMD	bone mineral density
BPD	biparietal diameter
BPH	benign prostatic hyperplasia
BPP	biophysical profile
BSA	body surface area
BSO	bilateral salpingo-oophorectomy
BV	bacterial vaginosis
C	Caucasian
Ca	calcium
CAD	coronary artery disease
CAH	congenital adrenal hyperplasia
CAIS	complete androgen insensitivity
CAP	community-acquired pneumonia
CARPREG	Cardiac Disease in Pregnancy Score
c/b	complicated by
CCAM	congenital cystic adenomatoid malformation
CCB	calcium channel blocker
CD	cesarean delivery/Crohn's disease
CDC	Centers for Disease Control and Prevention

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CDH congenital diaphragmatic hernia
CEE conjugated equine estrogen
CF cystic fibrosis
CFU colony-forming units
CGH comparative genomic hybridization
CHD congenital heart disease
CHF congestive heart failure
chorio chorioamnionitis
CHTN chronic hypertension
CI confidence interval/contraindication
CIC clean intermittent self-catheterization
CIN cervical intraepithelial neoplasia
CIS carcinoma in situ
CKC Cold Knife Conization
CKD chronic kidney disease
CKI creatine kinase inhibitor
CK-MB creatine kinase-MB
CL cervical length
CM Certified Midwife
CMV cytomegalovirus
CNM Certified Nurse-Midwives
CO cardiac output
COC combined oral contraceptive
COH Controlled ovarian hyperstimulation
Const Del constitutional delay
COP colloid osmotic pressure
COPD chronic obstructive pulmonary disease
Cort corticosteroid
COX cyclooxygenase
CP cerebral palsy
CPCs choroid plexus cysts
CPD cephalopelvic disproportion
CPM Certified Professional Midwives
CPP chronic pelvic pain
CR cervical ripening
CrCl creatinine clearance
CRF chronic renal failure
CRH corticotropin-releasing hormone
CRL crown-rump length
CRP c-reactive protein
crypto cryptosporidiosis
CS cesarean section
CSII continuous subcutaneous insulin infusion
C&S culture & sensitivity
CSE combined spinal–epidural
CSF cerebrospinal fluid
CT computed tomography
CTA CT angiography
CTCAE common terminology criteria for adverse events
CTD connective tissue disease
CTS carpal tunnel syndrome/conflict tactics scale
CTV CT venography
CTX chest x-ray/contractions
CUS compression ultrasonography
CVA cerebrovascular accident
CVC central venous catheter
CVD cardiovascular disease
CVP central venous pressure
CVS Chorionic villus sampling
CVT cerebral venous thrombosis
CVVS continuous venovenous hemofiltration
c/w consistent with

DBP diastolic blood pressure
D&C dilatation and curettage
DCM dilated cardiomyopathy
DDx differential diagnosis
D&E dilation & evacuation
DEM Direct Entry Midwives
DES diethylstilbestrol
DEXA dual-energy x-ray absorptiometry
DHEA-S dehydroepiandrosterone sulfate
DHT dihydrotestosterone
DIC disseminated intravascular coagulation
dig digoxin
DKA diabetic ketoacidosis
DMPA depot medroxyprogesterone acetate
DMSO dimethyl sulfoxide
DMT disease-modifying treatments
DPG diphosphoglycerate
dsDNA double-stranded DNA
DV domestic violence

EAS external anal sphincter
EBL estimated blood loss
EBRT external beam radiation therapy
EC emergency contraception/endometrial carcinoma
ECC endocervical curettage
ECG electrocardiogram
EDD estimated date of delivery
EE ethinyl estradiol
EF ejection fraction
EFW estimated fetal weight
EGA estimated gestational age
EH endometrial hyperplasia
EIC endometrial intraepithelial carcinoma
EIF echogenic intracardiac focus
ELISA enzyme-linked immunosorbent assay
EMACO etoposide, methotrexate, actinomycin D, cytoxan, oncovin
EMBx endometrial biopsy
EMS emergency medical service/endometrial stripe
EOC epithelial ovarian cancer
EPDS Edinburgh postnatal depression scale
EPT expedited partner therapy

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ER emergency department/room
ERCD elective repeat cesarean delivery
ERCP endoscopic retrograde cholangiopancreatography
ERV expiratory reserve volume
Erythro erythromycin
ES elastic stockings
ESR erythrocyte sedimentation rate
ESRD end-stage renal disease
ET endometrial thickness/estrogen therapy
EUA examination under anesthesia
exp expiratory
FAST focused assessment sonography for trauma
FDA food drug administration
FDG fluorodeoxyglucose
FE_{Na} fractional excretion of sodium
FE_{urea} fractional excretion of urea
FEV forced expiratory volume
ffDNA free fetal DNA
fFN fetal fibronectin
FFP fresh frozen plasma
FH fundal height
FHH familial hypocalciuric hypercalcemia
FHM fetal heart motion
FHR fetal heart rate
FHRT FHR tracing
FHT fetal heart tones
FIGO Federation of Gynecology and Obstetrics
FISH fluorescence in situ hybridization
FL femur length
FLM fetal lung maturity
FM fetal movement
FMH fetomaternal hemorrhage
FMP final menstrual period
FNA fine-needle aspiration
FRC functional residual capacity
FSH follicle-stimulating hormone
FTA-ABS fluorescent treponemal antibody absorption
FTT failure to thrive
FVIII factor VIII
FVL factor V Leiden
FU fluorouracil
FVC forced vital capacity
fx fracture or function

GA general anesthesia
G20210A prothrombin G20210A
GABA gamma-aminobutyric acid
GAD glutamic acid decarboxylase
GBS group B *Streptococcus*
GC/CT Neisseria gonorrhoeae/Chlamydia trachomatis
G-CSF granulocyte colony-stimulating factor
GCT granulosa cell tumor
GDM gestational diabetes mellitus
GDPP gonadotropin-dependent (central) precocious puberty
GERD gastroesophageal reflux disease
GFR glomerular filtration rate
GGT γ-glutamyl transpeptidase
GH growth hormone
GHTN gestational hypertension
GLT glucose loading test
GnRH gonadotropin-releasing hormone
G6PD glucose-6-phosphate dehydrogenase
GS gestational sac
GTN gestational trophoblastic neoplasia
GTT glucose tolerance test
GVHD graft versus host disease

H Hispanic
HA headache/hemolytic anemia
HAART highly-active antiretroviral therapy
HAP hospital-acquired pneumonia
HAV hepatitis A virus
HbA hemoglobin A
HbA1c hemoglobin A1c
HBcAg hepatitis B core antigen
HbEP hemoglobin electrophoresis
HbF hemoglobin F
HbS hemoglobin S
HBV hepatitis B virus
HC head circumference
HCAP healthcare-associated pneumonia
hCG human chorionic gonadotropin
HCV hepatitis C virus
HDL high-density lipoprotein
HDR high-dose rate
HDV hepatitis D virus
HEAA hydroxyethoxyacetic acid
HEG hyperemesis gravidarum
HELLP Hemolysis, Elevated Liver enzymes, Low Platelets
HepBIg hepatitis B immune globulin
HEV hepatitis E virus
H/H hemoglobin and hematocrit
HIDA hepatobiliary iminodiacetic acid
HIT heparin-induced thrombocytopenia
HIV human immunodeficiency virus
HK hypokinesis
HL humerus length
HLA human leukocyte antigen
HLHS hypoplastic left heart syndrome
hMG human menopausal gonadotropin
HNPCC hereditary nonpolyposis colorectal cancer
HoNa hyponatremia
HoTN hypotension
HPA hypothalamic–pituitary–adrenal

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hPL	human placental lactogen
HPO	hypothalamic–pituitary–ovarian
HPV	human papilloma virus
HQOL	health-related QOL
HRT	hormone replacement therapy
HSDD	hypoactive sexual desire disorder
HSG	hysterosalpingogram
HSV	herpes simplex virus
HT	hormone therapy
HTLV	human T-cell lymphotropic virus
HUS	hemolytic uremic syndrome
hyperaldo	hyperaldosteronism
hyperK	hyperkalemia
HyperNa	hypernatremia
hyperphos	hyperphosphatemia
HypoCa	hypocalcemia
hypoK	hypokalemia
hypophos	hypophosphatemia
IAS	internal anal sphincter
IBD	inflammatory bowel disease
IC	inspiratory capacity/interstitial cystitis
ICP	intrahepatic cholestasis of pregnancy
ICSI	intracytoplasmic sperm injection
ICU	intensive care unit
I&D	incision & drainage
IEA	inferior epigastric artery
IFN	interferon
IGF	insulin-like growth factor
IMRT	intensity-modulated radiation therapy
INH	isoniazid
innomin	innominate
INR	international normalized ratio
intravag	intravaginal
I&O	input/output
IOL	induction of labor
IP	infundibulopelvic/intraperitoneal
IPCD	intermittent pneumatic compression devices
IPV	intimate partner violence
IR	immediate release
IRV	inspiratory reserve volume
ISD	intrinsic sphincteric deficiency
ITP	immune thrombocytopenia purpura
IUD	intrauterine device
IUFD	intrauterine fetal demise
IUGR	intrauterine growth restriction
IUI	intrauterine insemination
IUP	intrauterine pregnancy
IV	intravenous
IVC	inferior vena cava
IVDU	intravenous drug use
IVF	in vitro fertilization
IVH	intraventricular hemorrhage
IVIG	intravenous immunoglobulin
IVP	intravenous pyelogram
JVD	jugular venous distension
JVP	jugular venous pressure
K-B	Kleihauer–Betke
KUB	kidneys, ureters, bladder
LA	left atrium/lupus anticoagulant
LAD	lymphadenopathy
LAIV	live attenuated influenza vaccine
LBP	low back pain
LBW	lean body weight/low birth weight
LCIS	lobular carcinoma in situ
L&D	labor and delivery
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LDR	low-dose rate
LDUH	low-dose UFH
LE	lower extremity
LEEP	loop electrosurgical excision procedure
Levo	levofloxacin
LFT	liver function tests
LH	luteinizing hormone
LMP	last menstrual period
LMWH	low molecular weight heparin
LND	lymph node dissection
LNG IUD	levonorgestrel-releasing intrauterine device
LNG-IUS	levonorgestrel intrauterine system
LOF	leakage of fluid
LP	low pressure/lumbar puncture
LPP	leak point pressure
LPS	lipopolysaccharides
LPV	localized provoked vulvodynia
L/S	lecithin/sphingomyelin
LUNA	laparoscopic uterosacral nerve ablation
LVEF	left ventricular ejection fraction
LVSI	lymphovascular space involvement
MAC	methotrexate, actinomycin D, cytoxan
MAOI	monoamine oxidase inhibitor
MAP	mean arterial pressure
MCA	middle cerebral artery
MCV	mean corpuscular volume
MDCT	multidetector CT
MDD	major depressive disorder
MDI	metered dose inhaler/multiple daily injection
MDPA	medroxyprogesterone acetate
MDR	multidrug resistant
MDS	myelodysplastic syndrome
MEN	multiple endocrine neoplasia
MESA	microsurgical epididymal sperm aspiration

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MI myocardial infarction
MIBG metaiodobenzylguanidine
MIS Müllerian inhibiting substance
Mitoc mitochondrial
MIVF maintenance intravenous fluid
MMK Marshall–Marchetti–Krantz
MMP matrix metalloproteinase
MMR measles, mumps, rubella
MOA mechanism of action
MoM multiple of the median
MR mental retardation/mitral regurgitation
MRA magnetic resonance angiography
MRAT melanoma risk assessment tool
MRKH Mayer–Rokitansky–Kuster–Hauser
MRSA methicillin-resistant *Staph aureus*
MS mitral stenosis
MSAFP maternal serum AFP
MSD mean sac diameter
MSH melanocyte-stimulating hormone
MSK musculoskeletal
MSM male sex with men
MSSA methicillin-sensitive staphylococcus aureus
MTC medullary thyroid cancer
MTX methotrexate
MUCP maximal urethral closure pressure
MUGA multigated acquisition
MUI mixed urinary incontinence
MV mitral valve
MVI multivitamin
MVP maximum vertical pocket
MVU Montevideo Units

NAAT nucleic acid amplification test
NAIT neonatal alloimmune thrombocytopenia
NB nasal bone
NCAH nonclassical congenital adrenal hyperplasia
NCI National Cancer Institute
NE norepinephrine
NEC necrotizing enterocolitis
NETA Norethindrone acetate
NGT nasogastric tube
NICHD National Institute of Child Health and Human Development
NICU neonatal intensive care unit
NIH National Institute of Health
NIHF nonimmune hydrops fetalis
NNRTI nonnucleoside reverse transcriptase inhibitor
NNT number needed to treat
NPH neutral protamine Hagedorn
NRFHT nonreassuring fetal heart tracing
NS normal saline
NST nonstress test
NSTEMI non-ST segment elevation MI
NT neural tube
NT nuchal translucency
NTD neural tube defect
NVP nausea and vomiting of pregnancy
NYHA New York Heart Association

OAB overactive bladder
OC obstetric conjugate
OCP oral contraceptive pill
OGTT oral glucose tolerance test
OHSS ovarian hyperstimulation syndrome
OHVIRA obstructed hemivagina and ipsilateral renal anomaly
OI opportunistic infection
O&P ova and parasite
OR odds ratio/operating room
OSA obstructive sleep apnea
OTC over-the-counter

PA posterior–anterior/pulmonary artery
PA primitive atrium
PAC pulmonary artery catheter
PAIS partial/incomplete AIS
pANCAs perinuclear antineutrophil cytoplasmic antibodies
PAP pulmonary artery pressure
PAPP-A pregnancy-associated plasma protein A
PCA patient-controlled analgesia
PCEA patient-controlled epidural analgesia
PCI percutaneous coronary intervention
PCN penicillin
PCOS polycystic ovary syndrome
PCP primary care physician
PCr plasma creatinine
PCR polymerase chain reaction
PCWP pulmonary capillary wedge pressure
PD primary dysmenorrhea
PDA patent ductus arteriosus
PDPH postdural puncture headache
PE pulmonary embolism
PEC preeclampsia
PEFR peak expiratory flow rate
PET positron emission tomography
PFT pulmonary function test
PG phosphatidylglycerol/prostaglandins
PGD preimplantation genetic diagnosis
pheo pheochromocytoma
pHTN pulmonary hypertension
PHV peak height velocity
PI protease inhibitor
PID pelvic inflammatory disease
PIERS Preeclampsia Integrated Estimate of Risk
PJP Pneumocystis jirovecii pneumonia

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PLAP placental alkaline phosphatase
PMDD premenstrual dysphoric disorder
PMH past medical history
PMI point of maximal impulse
PMNC polymorphonuclear cell
PMP postmenopausal
PMS premenstrual syndrome
PNa plasma sodium
PNA pneumonia
POC products of conception
POI premature ovarian insufficiency
POP progestin-only pill/pelvic organ prolapse
POP-Q pelvic organ prolapse quantification
PORTEC postoperative radiation therapy in endometrial cancer
PP postpartum
PPD purified protein derivative
PPE palmar plantar erythrodysesthesia
PPH postpartum hemorrhage
PPI proton pump inhibitor
PPROM preterm premature rupture of membranes
PPV positive predictive value
ppx prophylaxis
PR per rectum/pulmonary regurgitation
PRAMS Pregnancy Risk Assessment Monitoring System
PRES posterior reversible encephalopathy syndrome
PRL prolactin
progest progestin
PROM premature rupture of membranes
PSI pneumonia severity index
PSV peak systolic velocity
PT prothrombin time
ptb preterm birth
PTD preterm delivery
PTH parathyroid hormone
PTHrP parathyroid hormone-related protein
PTL preterm labor
PTU propylthiouracil
PTX pneumothorax
PUBS periumbilical blood sampling
PUPPP Pruritic Urticarial Papules and Plaques of Pregnancy
PUVA psoralen and ultraviolet A
PV per vagina/primitive ventricle
PVA polyvinyl alcohol
PVD peripheral vascular disease
PVR postvoid residual/pulmonary vascular resistance
pyelo pyelonephritis
QOL quality of life
RA right atrium
RAI radioactive iodine
RAIR rectoanal inhibitory reflex
RAIU radioactive iodine uptake
Rb retinoblastoma
RBBB right bundle branch block
RBC red blood cell
RCRI revised cardiac risk index
RCT randomized control trial
RDS respiratory distress syndrome
RDW red cell distribution width
REDF reversed end diastolic flow
retic reticulocyte
RF(s) risk factor(s)
RhD Rhesus D
RI reticulocyte index
RIBA recombinant immunoblot assay
RN registered nurse
RNA ribonucleic acid
ROA right occiput anterior
ROM rupture of membranes
RPL recurrent pregnancy loss/retroperitoneal lymphadenectomy
RPR rapid plasma reagin
RR relative risk
RRMS relapsing remitting multiple sclerosis
RRT renal replacement therapy
RSV respiratory syncytial virus
RT radiation therapy
RUSB right upper sternal border
RV residual volume/right ventricle
SAB spontaneous abortion
SAH subarachnoid hemorrhage
SARS severe acute respiratory syndrome
SBE subacute bacterial endocarditis
SBO small bowel obstruction
SBP systolic blood pressure
SCC squamous cell carcinoma
SCD sequential compression device
SCID severe combined immunodeficiency disease
SD secondary dysmenorrhea
S/D systolic/diastolic
SDP single deepest pocket
SE profile side-effect profile
SERM selective estrogen receptor modulators
SGA small for gestational age
SIDS sudden infant death syndrome
SIRS systemic inflammatory response syndrome
SIS saline infusion sonography sonohysterography
SLE systemic lupus erythematosus
SMX sulfamethoxazole
SNRIs serotonin and norepinephrine reuptake inhibitors
SOB shortness of breath

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sPEC	severe preeclampsia
SPEP	serum protein electrophoresis
SQ	subcutaneous
SS	sliding scale
SSI	surgical site infection
SSRI	selective serotonin reuptake inhibitor
STEMI	ST segment elevation MI
STI	sexually transmitted infection/disease
SUI	stress urinary incontinence
SV	stroke volume
SVD	spontaneous vaginal delivery
SVR	systemic vascular resistance
SVT	supraventricular tachycardia
T	testosterone
TA	transabdominal
TAH	total abdominal hysterectomy
TBG	thyroxine-binding globulin
TC	transcervical
T&C	type and crossmatch
TCA	tricyclic antidepressant
TDaP	tetanus, diphtheria, acellular pertussis
T2DM	Type II Diabetes Mellitus
TE	tracheoesophageal
TENS	Transcutaneous electrical nerve stimulation
TESE	testicular sperm extraction
TG	triglycerides
thal	thalassemia
TIA	transient ischemic attack
TIBC	total iron-binding capacity
TLC	total lung capacity
TLH	total laparoscopic hysterectomy
TMJ	temporomandibular joint
TMP	trimethoprim
TNF	tumor necrosis factor
TNM	tumor, node, metastasis
TOA	tuboovarian abscess
TOLAC	trial of labor after prior cesarean
TOT	transobturator tape
tPA	tissue plasminogen activator
TPN	total parenteral nutrition
TPO	thyroid peroxidase
TR	tricuspid regurgitation
TRAb	TSH receptor antibody
TRALI	transfusion-related lung injury
T&S	type and screen
TSH-R	TSH receptor
TSI	TSH-stimulating immunoglobulin
TST	tuberculin skin test
TTE	transthoracic echocardiography
TTP–HUS	thrombotic thrombocytopenic purpura–hemolytic uremic syndrome
TTTS	twin-to-twin transfusion syndrome
TVL	total vaginal length
TVT	tension-free vaginal tape
TVUS	transvaginal ultrasound
UA	urinary albumin
UAE	uterine artery embolization
UC	ulcerative colitis
UCr	urine creatinine
uE3	unconjugated estriol
UFH	unfractionated heparin
UNa	urine sodium
uncirc	uncircumcised
UOP	urine output
UPEP	urine protein electrophoresis
UPSC	uterine papillary serous carcinoma
URI	upper respiratory infection
Uro	urology
US	ultrasound/ultrasonography
USPSTF	U.S. Preventive Services Task Force
UTI	urinary tract infection
UUI	urge urinary incontinence
VAIN	vaginal intraepithelial neoplasia
Vanco	vancomycin
VAP	ventilation-associated pneumonia
VB	vaginal birth/vaginal bleeding
VBAC	vaginal birth after cesarean
VBP	vinblastine, bleomycin, carboplatin
VCAM	vascular cell adhesion molecule
VDRL	venereal disease research laboratory
VEGF	vascular endothelial growth factor
VIN	vulvar epithelial neoplasia/ vulvar intraepithelial neoplasia
VSx	vasomotor symptoms
VSD	ventriculoseptal defect
VT	tidal volume
VTE	venous thromboembolism
VVF	vesicovaginal fistula
vWD	von Willebrand disease
vWF	von Willebrand factor
Vz/vac	vaccine
VZV	varicella zoster virus
WHI	Women's health initiative
WHO	World Health Organization
wnl	within normal limits
WWE	women with epilepsy
XR	extended release/x-ray
XRT	radiation therapy/ radiotherapy

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