Pediatric Gynecology

An Illustrated Guide for Surgeons

Ahmed H. Al-Salem

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Preface

The word "gynecology" comes from the Greek γυνή (*gyne*), "woman," and *-logia*, "study."

Pediatric gynecology is the medical specialty dealing with the medical and surgical abnormalities of the vulva, vagina, uterus, and ovaries of infants, children, and adolescents. This includes a number of pediatric gynecologic conditions that include both benign and malignant conditions. Disorders of the breast, disorders of sexual development, and precocious puberty are also included.

The specialty of pediatric gynecology is evolving rapidly and has witnessed several advancements during the last 20 years including minimal invasive surgery. This book is written in a simple and easy-to-read way. It covers most areas in the field of pediatric gynecology with an emphasis on the most important areas relevant to the patient's presentation, diagnosis, and management. This book is well illustrated and includes clinical, operative, pathological, radiological, and hand-drawn illustrations. This book should prove valuable to all involved in the care of these patients. This book will be useful to consultant pediatric surgeons, specialists, fellows, and residents. The book should be also useful to general surgeons, accident and emergency doctors, pediatricians, neonatologists, pediatric endocrinologist, gynecologists, general practitioners, trainees, medical students, and nurses.

Saihat, Saudi Arabia — Ahmed H. Al-Salem

Acknowledgments

I would like to express special thanks of gratitude to my family who supported me and made this project possible. I would also like to thank all my patients and their families and my colleagues and friends who supported and encouraged me.

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Chapter 1
Development of the Female Reproductive System

Ahmed H. Al-Salem

1.1 Introduction

- The male and female reproductive systems develop initially embryonically "indifferent". This is known as the indifferent stage.
- In this stage of gonadal development, it is impossible to distinguish between the male and female gonad.
- It is the product of the Y chromosome SRY gene that makes the "difference" and directs the development of the indifferent gonad into a male gonad (Testes) or female gonad (Ovaries).
- The presence of the Y chromosome SRY gene directs the gonad to develop into testes.
- The development of the indifferent gonads begin as a pair of longitudinal genital ridges which are derived from intermediate mesoderm and overlying epithelium.
- They initially do not contain any germ cells.
- The germ cells develop subsequently around the fourth week of intrauterine life.
- They begin to migrate from the endoderm lining of the yolk sac to the genital ridges, via the dorsal mesentery of the hindgut.
- The germ cells reach the genital ridges around the sixth week of intrauterine development.
- The epithelium of the genital ridges proliferates and penetrates the intermediate mesoderm to form the primitive sex cords.
- The indifferent gonads are composed of germ cells and primitive sex cords.

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- The indifferent gonads subsequently develop into the testes or ovaries.
- In a female embryo (46, XX chromosomes):
  - The absence of Y chromosome SRY gene influence degeneration of the primitive sex cords and do not form the testis cords.
  - The epithelium of the gonad continues to proliferate, producing cortical cords.
  - These cortical cords break up into clusters, surrounding each germ cell with a layer of epithelial follicular cells, forming a primordial follicle.
- The ovaries initially develop on the posterior abdominal wall and migrate caudally in a similar fashion to the testes reaching their final position just within the true pelvis.
- The gubernaculum becomes the ovarian ligament and round ligament of the uterus.
- In the first weeks of urogenital development, each embryo has two pairs of ducts, both ending at the cloaca.
  - The Mesonephric (Wolffian) ducts
  - The Paramesonephric (Mullerian) ducts
- In a female embryo (46, XX chromosomes):
  - The absence of Leydig cells which produce testosterone leads to degeneration of the mesonephric ducts leaving behind a vestigial remnant called Gartner's duct.
  - The absence of anti-Mullerian hormone which is normally secreted by Sertoli cells of testes allows for development of the paramesonephric ducts.
  - The Mullerian ducts develop into:

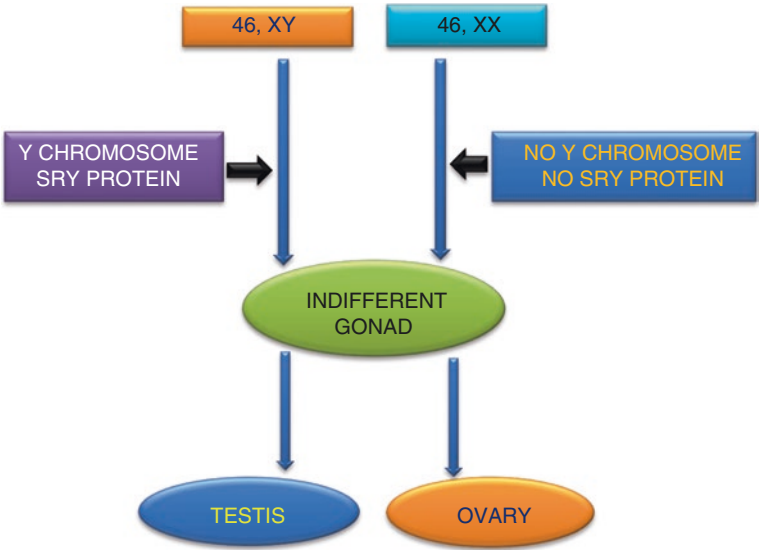
    The Fallopian tubes
    The uterus and cervix
    The upper 2/3 of the vagina

  - The lower 1/3 of the vagina is formed by sinovaginal bulbs (derived from the pelvic part of the urogenital sinus).
- The development of the external genitalia begins in the third week of intrauterine life.
- In females, this is under the influence of estrogens.
  - Mesenchymal cells from the primitive streak migrate to the cloacal membrane to form a pair of cloacal folds.
  - Cranially, these folds fuse to form the genital tubercle.
  - Caudally, they divide into the urethral folds (anterior) and anal folds (posterior).
  - Genital swellings develop on either side of the urethral folds.
  - The genital tubercle elongates slightly to form the clitoris.
  - The urethral folds and genital swellings do not fuse, but instead form the labia minora and labia majora respectively.
  - The urogenital groove remains open, forming the vestibule into which the urethra and vagina open.

1.2 Gonadal and Internal Genital System Development

- In females the reproductive system or genital organs comprise of:
  - Two gonads (ovaries)
  - The reproductive organs (Uterus and Fallopian tubes)
  - The external genitalia (labia mjora, labia minora, clitoris and vagina)
- The genotype and chromosomal sex of a fetus is determined at the time of conception.
- The phenotype of the fetus depends on the presence of sex chromosomes and the prevailing biochemical and hormonal milieu.
- A male fetus will develop in the presence of:
  - A Y-chromosome which encodes the SRY protein.
  - The SRY protein enables differentiation of the indifferent gonads into a testis.
  - Testicular differentiation of the indifferent gonad will result in the production of androgens including testosterone.
  - In addition to the SRY protein and androgens, testicular differentiation of the indifferent gonad produces a third factor, anti-Müllerian hormone (AMH).
  - AMH prevents female genital ductal differentiation as it leads to regression of the Mullerian ducts.
- Gonadal development begins in the fifth week of intrauterine life.
- The gonads develop on the posterior abdominal wall on either side of the spine.
- Until the seventh week of intrauterine life, the gonads are similar in both male and female fetuses.
- These are called indifferent gonads and initially, they develop as urogenital (gonadal) ridges from the mesothelium medial to the mesonephros (the developing kidney).
- The primitive or primordial germ cells develop around the fourth week of intrauterine life and migrate from the yolk sac of the embryo along the dorsal mesentery of the hindgut to the mesenchyme of the gonadal ridges by the sixth week and incorporate into the primary sex cords.
- The primary sex cords are not well developed in the female embryo and they regress by the eighth week of intrauterine life.
- The presence of two X-chromosomes in a female fetus and absence of the Y chromosome leads to the development of a female fetus.
  - The undifferentiated gonads will develop into ovaries.
  - The absence of AMH which is secreted by the Sertoli cells of testes will result in further development and maturation of the Mullerian ducts.
  - The Mullerian ducts will develop into the uterus, Fallopian tubes and upper two thirds of the vagina.
  - Further development and maturation of the female external genitalia is under the influence of estrogen secreted by the ovary.

- Gonadal differentiation takes place in the second month of intrauterine life.
- The first step is primitive germ cells differentiation.
  - This is under the influence of placental gonadotropins.
  - The germ cells migrating from the endoderm lining of the yolk sac to the genital ridge.
  - The germ cells undergo successive mitotic divisions differentiating into several million oogonia.
- The primitive follicles organize within the fetal ovarian cortex and by 5–6 months of intrauterine life the ovaries contain 6–7 million primordial follicles.
- These primordial follicles subsequently become enveloped by a layer of epithelial cells, and are referred to as primary oocytes.
- The vast majority of oocytes eventually degenerate over time.
- The remaining oogonia enter a dormant state referred to as meiotic arrest (first phase of meiosis).
- First phase meiosis will not complete until the onset of ovulation.
- Ovulatory follicles complete meiotic differentiation.
- It is estimated that at birth, between 2 and 4 million follicles remain and around 400,000 follicles are present at menarche.
- Ovarian follicles undergo varying rates of maturation and involution.
- The vast majority remains quiescent and eventually involutes by apoptosis, but can remain dormant for decades.
- The maturing ovaries descend into the pelvis at around the third month of intrauterine life.
- This descend of the ovary into the pelvis is guided by the gubernaculum and facilitated by the marked growth of the upper abdomen relative to the pelvis.



- The gubernaculum is a peritoneal fold which attaches the caudal aspect of the ovary to the uterus.
- The gubernaculum eventually forms the uteroovarian ligment and round uterine ligaments.
- Embryologically, there are two paramesonephric (Müllerian) ducts which arise from the mesoderm lateral to the mesonephric ducts.
- The Müllerian ducts in females and in the absence of AMH which is secreted by the Sertoli cells of testes mature and differentiate and give rise to:
  - The uterus
  - The fallopian tubes
  - The cervix
  - The upper 2/3 of the vagina.
- The paramesonephric ducts fuse to form a confluence.
- This occurs between the seventh and ninth weeks when the lower segments of the paramesonephric ducts fuse.
- The cranial end of the fused paramesonephric ducts yields the future uterus which contains mesoderm that will form the uterine endometrium and myometrium. At this stage, a midline septum is present in the uterine cavity; this usually regresses and disappears at around 20 weeks of intrauterine life.
- The unfused cranial ends of the paramesonephric ducts assume a funnel shaped configuration and remain open to the future peritoneal cavity as the fimbrial portions of the fallopian tubes (Figs. 1.1 and 1.2a–c).
- The caudal end of the fused ducts will form the upper two-thirds of the vagina.
- The lower third of the vagina is formed as the sinovaginal node (bulb) canalizes.
- The sinovaginal node inserts into the urogenital sinus at Müller's tubercle.
- The development of the lower abdominal wall is important to the development of the lower urogenital system.
- The lower abdominal wall is formed from the cloacal membrane and the proliferating adjacent mesenchyme.

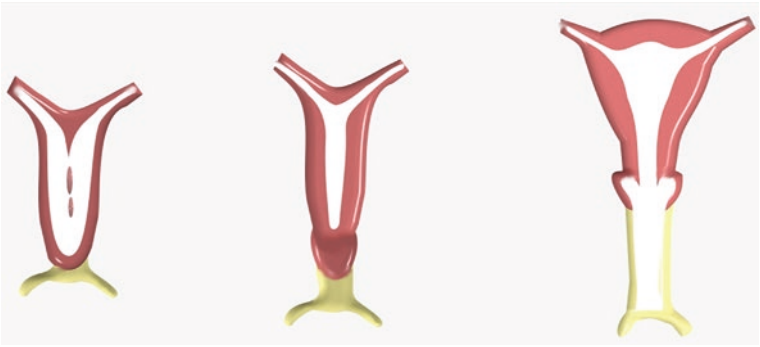


Fig. 1.1 An illustration showing the development of the uterus and vagina. Note that the upper two-thirds of the vagina are formed from the caudal end of the fused paramesonephric ducts. The lower third of the vagina is formed from canalization of the sinovaginal node

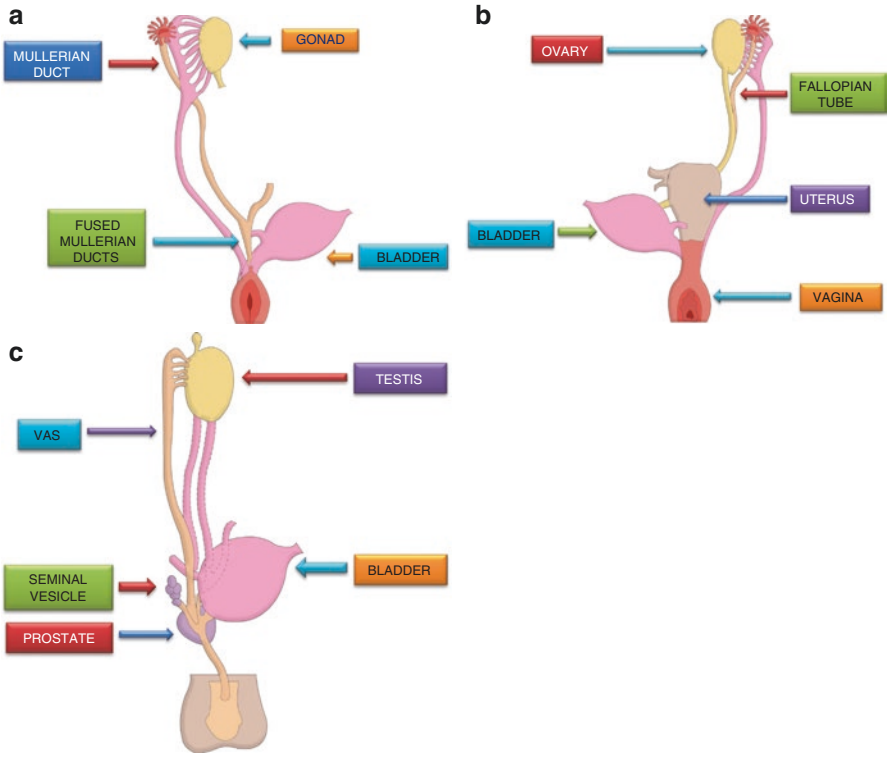
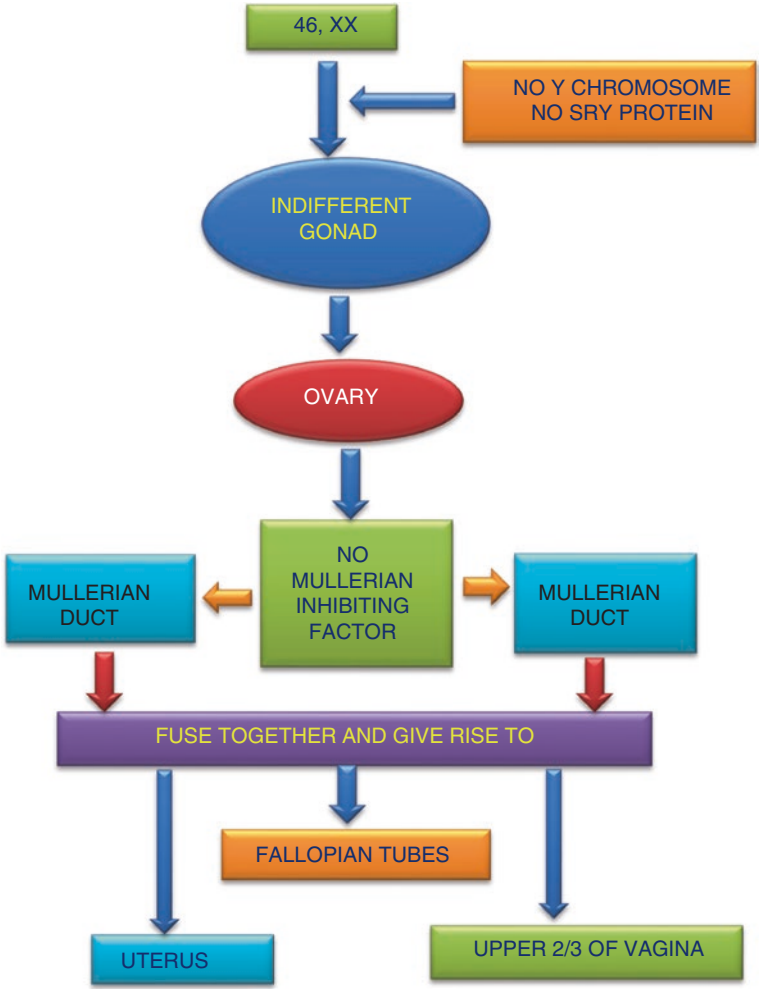


Fig. 1.2 (**a**–**c**) Illustrated diagrams showing the development of the female and male genital system

- The cloacal folds fuse anteriorly to give rise to the genital tubercle.
- During the seventh week of intrauterine life, the urorectal septum fuses to the inner surface of the cloacal membrane dividing it into two parts:
  - The anterior (ventral) urogenital membrane
  - The posterior anal membrane
- This will divide the rectum proper from the urogenital tract.
- The urogenital membrane subsequently perforates creating free communication between the amniotic cavity and the primary urogenital sinus.
- The folds surrounding the urogenital membrane are now referred to as the urethral folds and those around the anus the anal folds.
- The primary urogenital sinus develops into the definitive urogenital sinus (UGS).
  - The UGS consists of a caudal phallic portion and a pelvic portion.
  - The urethral groove and phallic (distal) portion of the UGS enlarge to form the vaginal introitus (vestibule).
  - This is closed off externally by the urogenital membrane which perforates in the seventh week.
  - The narrow pelvic (proximal) segment of the definitive urogenital sinus contributes to the short distal female urethra and lower third of the vagina.

1.3 Development of the External Genitalia

- The external genitalia remain sexually undifferentiated until around the seventh week of intrauterine life.
- Complete differentiation of the female external genitalia occurs around the twelfth week of intrauterine life.
- The genital tubercle develops around the fourth week of intrauterine life from mesenchymal proliferation.
- A protophallus develops ventral to the cloacal membrane.
- During the sixth week, the urethral groove and anal pit form resulting in focal depressions along the cloacal membrane.
- The primary urethral (urogenital) folds surround the primary urethral groove.



- The genital or labioscrotal swellings form lateral to the urethral folds.
- In the seventh week, the cloacal membrane involutes and the primary urethral groove becomes continuous with the definitive urogenital sinus.
- The secondary urethral groove forms as a result of deepening and widening the primary urethral groove in the eighth week.
- The external genitalia begin display sexual differentiation during the tenth week.
- In developing females:
  - The unfused parts of the labioscrotal (genital) swellings give rise to the labia majora.
  - These folds fuse anteriorly to form the mons pubis and anterior labial commissure, and posteriorly the posterior labial commissure.
  - The urethral folds fuse posteriorly to form the frenulum of the labia minora.
  - The unfused urethral (urogenital) folds give rise to the labia minora.
  - The unfused genital swellings enable the urogenital sinus to open into the anterior (urethral) part of the vagina and the vaginal vestibule.
  - The genital tubercle becomes the clitoris.
- The accessory urethral glands including the paraurethral glands (Skene) and urethral glands arise from the urogenital sinus from endodermal (epithelial) buds growing into the urethral mesenchyme.
- The paired greater vestibular glands (Bartholin) form in the 12th week and empty into the vaginal vestibule.
- The mesonephric (Wollfian) ducts regress in a female, but remnants of the mesonephric duct typically persist.
  - The Gartner's ducts are paired remnants of the mesonephric duct that may give rise to Gartner's duct cysts and are typically located in the broad ligament.
- The canal of Nuck is a virtual space and is the female analogue of the processus vaginalis in the male; if patent it is abnormal and forms a pouch of peritoneum in the labia majora.
- The epoophoron is the most cranial part of the mesonephric duct remnant. It is situated in the lateral portion of the broad ligament and may communicate with the Gartner's ducts more inferiorly in the broad ligament.
- It is homologous to the epididymis in males.
- The paraoophoron is also a mesonephric remnant analogous to the paradidymis in males. It is usually positioned medially in each broad ligament.

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Chapter 2
Delayed Puberty in Girls

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2.1 Introduction

- Puberty changes occur when the body starts making sex hormones. These changes normally begin to appear in girls between ages 8–14 years old.
- Puberty refers to the phase of development between childhood and adulthood in which complete functional maturation of the reproductive glands and external genitalia occurs.
- The other processes that characterize this transitional phase are the development of secondary sex characteristics, growth spurts, and psychosocial changes.
- Delayed puberty is defined clinically as the absence of the first signs of pubertal development beyond the normal range for the population.
- However, there are clear racial and ethnic variations in the timing of puberty, such as earlier onset of puberty in African American girls compared with Caucasian counterparts.
- In the United States, delayed puberty means the absence of breast development by age 12 years in girls.
- Delayed pubertal development with the absence of breast development by age 13 is strongly associated with impaired reproductive potential and should prompt an assessment to rule out ovarian failure with abnormal karyotype or other potentially irreversible problems.
- The stages of development during puberty are classified according to the Tanner stages.
- Although there is considerable variation between individuals, on average puberty begins at the age of 11 in girls and 13 in boys.

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- Puberty that begins abnormally early is referred to as precocious puberty and can be due to a peripheral cause (peripheral precocious puberty) or a central cause involving the hypothalamo-hypophyseal axis (central precocious puberty, or CPP).
- Traditionally, precocious puberty has been defined as any pubertal development occurring before age 8. Other authors define precocious puberty as pubertal development before age 7 in whites and age 6 in African Americans.
- At the other end of the spectrum, puberty may be delayed or absent. This delay can be constitutional, secondary to underlying conditions, or due to hypogonadism.
- Delayed puberty in girls occurs when breasts don't develop by age 13 or menstrual periods do not begin by age 16.
- Delayed puberty is more common in boys than in girls.
- The most common cause of delayed puberty is a functional defect in production of gonadotropin-releasing hormone (GnRH) from the hypothalamus.
- This may be due to physiologic individual variation, known as constitutional delay of growth and puberty, or other functional defects, such as undernutrition or chronic illness.
- The GnRH deficiency leads to defective secretion of gonadotropins (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) from the anterior pituitary, which results in inadequate steroid secretion by the ovaries.
- Other causes of delayed puberty include a variety of hypothalamic, pituitary, and gonadal disorders.

2.2 Tanner Stages

- Tanner stage 1:
  - Tanner stage 1 represents the girl's appearance before any physical signs of puberty appear. There are no noticeable physical changes for girls at this stage.
  - Toward the end of stage 1, the brain starts to send signals to prepare the body for changes.
  - The hypothalamus begins to release gonadotropin-releasing hormone (GnRH).
  - GnRH stimulates the pituitary gland to release two other hormones: luteinizing hormone (LH) and follicle-stimulating hormone (FSH).
  - These early signals typically start after a girl's eighth birthday.
- Tanner stage 2:
  - Stage 2 marks the beginning of physical development.
  - Puberty usually starts between ages 9 and 11 years.
  - The first signs of breasts development is called "buds".
  - This starts to form under the nipple. They may be itchy or tender, which is normal.
  - It is also common for breasts to differ in size and growth rate.
  - It is normal if one bud appears larger than the other.
  - The areola of the breast will also expand.
  - The uterus begins to get larger, and small amounts of pubic hair start growing.
- Tanner stage 3:

  - The physical changes become more obvious at this stage.
  - Physical changes in girls usually start after age 12.
  - Breasts "buds" continue to grow and expand.
  - Pubic hair gets thicker and curlier.
  - Hair starts forming under the armpits.
  - The first signs of acne may appear on the face and back.
  - The highest growth rate for height begins (around 3.2 inches per year).
  - Hips and thighs start to build up fat.

- Tanner stage 4:
  - Puberty is in full swing during stage 4.
  - In girls, stage 4 usually starts around age 13.
  - Breasts take on a fuller shape, passing the bud stage.
  - Many girls get their first period, typically between ages of 12 and 14, but it can happen earlier.
  - Height growth will slow down to about 2–3 inches per year.
  - Pubic hair gets thicker.

- Tanner stage 5:
  - This final phase marks the end of the child's physical maturation.
  - In girls, stage 5 usually happens around age 15.
  - Breasts reach approximate adult size and shape, though breasts can continue to change through age 18.
  - Periods become regular after 6 months to 2 years.
  - Girls reach adult height 1–2 years after their first period.
  - Pubic hair fills out to reach the inner thighs.
  - Reproductive organs and genitals are fully developed.
  - Hips, thighs, and buttocks fill out in shape.

Tanner stages	Age at the start	Changes
Stage 1	After the eighth birthday	None
Stage 2	From age 9 to 11	Breast "buds" start to form; pubic hair starts to form
Stage 3	After age 12	Acne first appears; armpit hair forms; height increases at its fastest rate
Stage 4	Around age 13	First period arrives
Stage 5	Around age 15	Reproductive organs and genitals are fully developed

2.3 Normal Puberty and Causes of Delayed Puberty

- Normal puberty is a phase of development between childhood and adulthood which manifest as complete, functional maturation of the reproductive glands and external genitalia.

- The start of sexual maturation (puberty) takes place when the hypothalamus gland begins to secrete gonadotropin-releasing hormone.
- The pituitary gland responds to this by releasing gonadotropins (FSH and LH) which stimulate the growth of the ovaries.
- The ovaries secrete the sex hormone (estrogen). These hormones cause the development of secondary sex characteristics, including breasts developments in girls, and pubic and underarm hair and sexual desire (libido).
- Some adolescents do not start their sexual development at the usual age (Fig. 2.1).

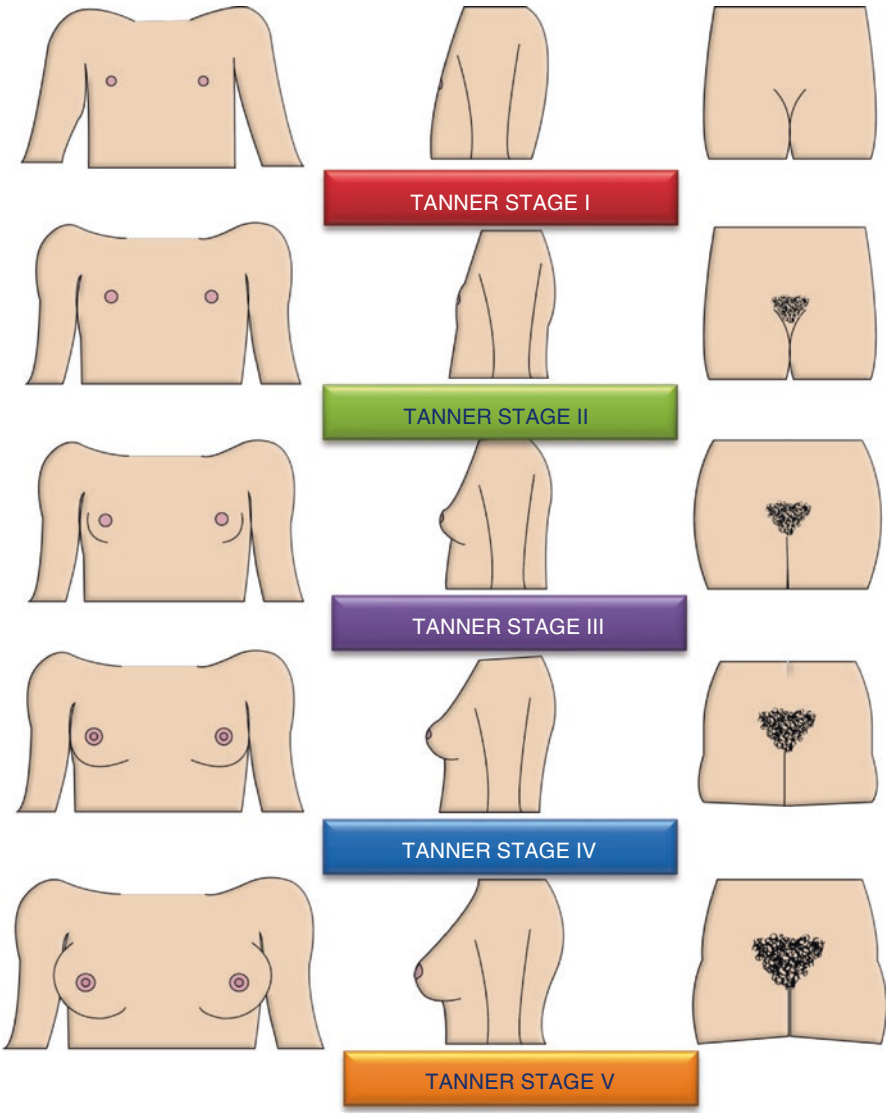
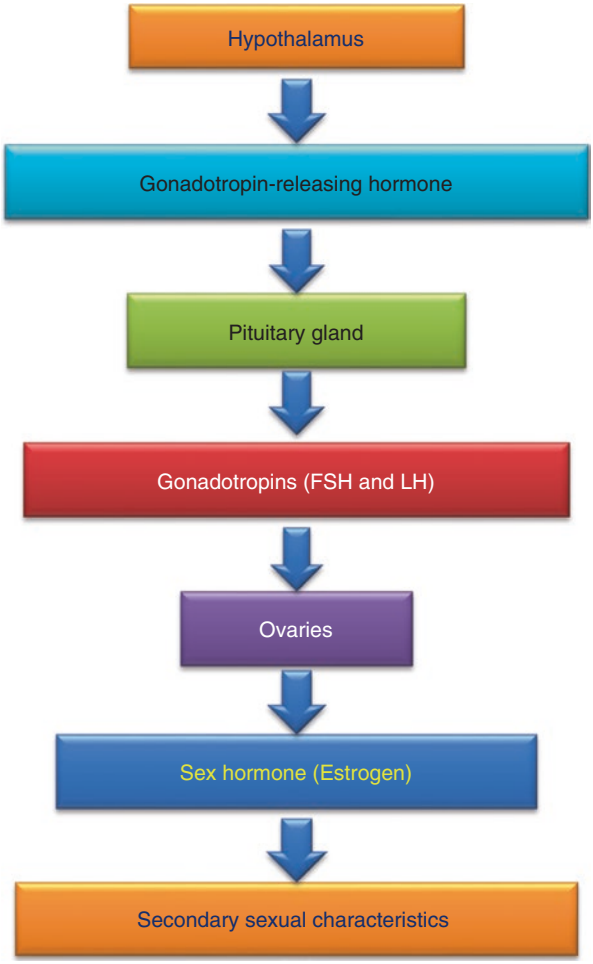


Fig. 2.1 Diagrammatic representation of Tanner stages

- In girls, delayed puberty is defined as:
  - No breast development by age 13 years.
  - A time lapse of more than 5 years from the beginning of breast growth to the first menstrual period.
  - No menstruation (amenorrhea) by age 16.



- There are several phases of normal pubertal changes:
  - Gonadarche: The activation of reproductive glands by the pituitary hormones follicular stimulating hormone and lutenizing hormone (FSH and LH).
  - Adrenarche: The activation of production and secretion of adrenal androgens.
  - Thelarche: The onset of breast development (age of onset 8–11 years).
  - Pubarche: The onset of pubic hair growth (mean age of onset 12 years).

  - Menarche: The onset of menstrual bleeding (age of onset 10–16 years; mean age: 13 years).
  - Anovulatory cycle: The menstrual cycle may be irregular in adolescents during the first few months/years after menarche. This is not pathological.

- Puberty starts when the pituitary gland begins to produce two hormones, luteinizing hormone (LH) and follicle-stimulating hormone (FSH).
- These hormones cause the ovaries to enlarge and begin producing estrogens.
- The growth spurt starts shortly after breasts begin to develop.
- The first menstrual cycle begins about 2–3 years later.
- A girl who has not started to have breast development by the age of 13 is considered to be delayed.
- There are also several factors that influence puberty:

  - General health including nutritional state and body weight
  - Genetics factors
  - Social environment (e.g. family stress)

- Delayed puberty is defined as lack of secondary sexual characteristics from the age of 13 years in females.
- CNS abnormalities result in hypogonadotrophic hypogonadism.
- Gonadal failure causes hypergonadotrophic hypogonadism.
- There are many possible causes of delayed puberty, some of which affect both genders and some of which are gender-specific.
- The causes of delayed puberty are divided into two broad categories:

  - Central causes
  - Peripheral causes

- Central causes may affect both genders and stem from the hypothalamic-pituitary axis or other areas of the body that are not specific to a gender.
- Peripheral causes, on the other hand, are gender specific and linked to the sexual organs of the individual.
- The most common cause of delayed puberty in both boys and girls is constitutional delay. However, a diagnosis of constitutional delay can only be made when other possible causes have been excluded.
- Central Causes of delayed puberty:

  - These are similar in males and females.
  - Many central causes are related to impaired structure or function of the hypothalamic-pituitary axis.
  - The causes for this include:

    A tumor near the hypothalamic-pituitary axis:

    - Astrocytoma
    - Craniopharyngioma
    - Germinomas
    - Optic glioma
    - Pituitary tumor

Physical trauma to the head secondary to head injury or surgery.
Radiation therapy directed towards the hypothalamic-pituitary axis.
Congenital abnormality of the hypothalamic-pituitary axis.
Abnormal hormone levels (e.g. low gonadotropin and sex steroid concentration).

– There are also several central causes that are not associated with abnormal structure and function of the hypothalamic-pituitary axis. These include:

Health conditions:

- Kidney disease
- Crohn's disease
- Cystic fibrosis
- Hypothyroidism

Medications (e.g. steroid therapy)
Malnutrition:

- Coeliac disease
- Anorexia nervosa

Excessive physical exertion (e.g. professional athletes and gymnasts)
Psychosocial deprivation

- Peripheral Causes of delayed puberty
  - These are gender specific and linked to the sexual organs of the individual.
  - Peripheral causes that may lead to delayed puberty in girls include:

Health conditions:

- Turner syndrome
- Prader-Willi syndrome
- Bardet-Biedl syndrome
- Swyer syndrome
- Polycystic ovary syndrome

Medications (e.g. cyclophosphamide, busulfan).
Radiation therapy directed to the abdominal and pelvic region.
Sexual disorders:

- Androgen insensitivity syndrome
- Congenital adrenal hyperplasia

Thalassaemia secondary to iron overload.

- It is important to establish the cause of delayed puberty, as it provides valuable information about the most appropriate therapy options.
- It is also important to establish a detailed patient's and family history including:
  - Growth pattern
  - General health
  - History of other medical conditions

  - Family history of similar symptoms
  - Psychosocial symptoms

- The diagnosis of delayed puberty is usually made based on the medical and family history of the individual and a physical examination to assess changes expected according to the age of the individual.
- The physical examination should include signs of growth, such as height and weight, and development of sexual characteristics, such as breast and the growth of pubic hair. It is also helpful to test for an abnormal sense of smell, which is a characteristic symptom of Kallmann's syndrome.

2.4 Management

- The initial evaluation of delayed puberty should consist of a complete history and physical examination to evaluate pubertal development, nutritional status, and growth.
- Take x-rays of one or more bones to see the level of bone maturity (a bone age x-ray).
- Some girls with delayed puberty are simply late to mature, but once they start, puberty will progress normally.
- This is called constitutional delayed puberty and is more common in boys than girls. These adolescents have a normal growth rate and are otherwise healthy. Although the growth spurt and puberty are delayed, they eventually proceed normally.
- Constitutional delayed puberty is often familial inherited from the parents, so it is more likely to occur if the mother started her periods after age 14.
- In girls with constitutional delayed puberty, breast development will eventually start on its own.
- The treatment for delayed puberty depends on its cause. When an underlying disorder is the cause of delayed puberty, puberty usually proceeds once the disorder has been treated.
- In many individuals with delayed puberty, medical treatment is not required and patients should be reassured that the body will have the expected sexual changes in time.
- However, short courses of sex hormones (estrogen) may be used to allow individuals to catch up with their peers and prevent psychological and emotional sequelae.
- This can be useful to prevent psychological and emotional consequences associated with a delay.
- Some authors advocate giving estrogens for 4–6 months hoping this will help get things started sooner.
- It is important to identify and treat any cause of delayed puberty.
- It is also important for these patients to have a counselor or psychological support. Counselling with respect to sexual function and fertility as appropriate.

- Pubertal induction followed by ongoing hormone replacement. Subsequent estrogen production may be adequate and ongoing hormone treatment unnecessary.
- Treat the underlying cause if possible; induction of puberty and hormone treatment may be required.
- In those with severe congenital hypogonadism, early gonadotrophins in the neonatal period or infancy may be indicated.
- Estrogen replacement should be gradual to avoid premature fusion of the epiphyses and prevent overdevelopment of the areolae of the breasts.
- Induction of puberty usually starts around age 10. Gradually increased doses of oral ethinylestradiol or transdermal estradiol are used, with cyclical progesterone therapy once adequate estrogen levels have been achieved or if breakthrough bleeding occurs. If growth hormone is also needed, estrogen therapy is usually delayed until age 12 years.
- Transdermal estradiol is thought to be more effective and have a better safety profile.
- A low-dose combined oral contraceptive pill can then be used.
- Decreased body fat is a major cause of pubertal delay in girls.
  - It can be seen in girls who are very athletic, particularly in gymnasts, ballet dancers, and competitive swimmers.
  - It can also be seen in girls with anorexia nervosa, who fear becoming too fat even when they are abnormally thin.
  - It can be seen in a number of chronic illnesses in which body fat is often decreased.
- For girls with delayed puberty secondary to decreased body fat, dietary manipulations and gaining weight will help get puberty started.
- Other causes of delayed puberty include:
  - Primary ovarian insufficiency
  - Turner syndrome
  - The major acquired cause of ovarian insufficiency is damage to the ovaries as a result of radiation therapy, usually to treat leukemia.
- For girls with primary ovarian insufficiency or a permanent deficiency of gonadotropins:
  - Long-term estrogen replacement is needed and can be given either in the form of a daily tablet of estradiol or as a patch that needs to be applied to the skin twice a week.
  - Some authors advocate starting these patients on a low dose and often increase the dose about every 6 months.
  - After 12–18 months, a progestin (for example, Provera) is to be added. This will, after a few months, result in a period, usually within a day or two of stopping the progestin.
- Various disorders, such as diabetes mellitus, inflammatory bowel disease, kidney disease, cystic fibrosis, and anemia, can delay or prevent sexual development. These should be identified and treated accordingly.

- Development may be delayed or absent in adolescents receiving radiation therapy or cancer chemotherapy.
- Puberty may also be delayed by autoimmune disorders such as Hashimoto thyroiditis, Addison disease (primary adrenocortical insufficiency), and some disorders that directly affect the ovaries).
- A tumor that damages the pituitary gland or the hypothalamus can lower the levels of gonadotropins or stop production of the hormones altogether.
- Genetic disorders cannot be cured, but hormone therapy may help sex characteristics develop.

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Chapter 3
Precocious Puberty

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3.1 Introduction

- Premature thelarche is the development of breast tissue in young girls in the absence of other signs of precocious puberty.
- Premature thelarche is also characterized by the lack of thickening and pigmentation of the nipples and the areola which is commonly seen in girls with precocious puberty.
- Premature thelarche is typically seen in girls aged 3 years or younger.
- In some of these cases, small ovarian cysts can be found and these transiently produce estrogens which may be responsible for premature thelarche.
- Premature pubarche on the other hand refers to the early appearance of pubic hair, axillary hair, or both in children without other signs of puberty. These patients will have adult-type axillary body odor.
- Premature pubarche refers to appearance of pubic hair and or axillary hair without other signs of puberty in girls younger than 7–8 years.
- Premature pubarche and premature thelarche are 2 common, benign, normal variant conditions that can resemble precocious puberty but are nonprogressive or very slowly progressive.
- Precocious puberty can be classified based upon the underlying pathologic process.
  - Central precocious puberty

    Central precocious puberty is also known as gonadotropin-dependent precocious puberty or true precocious puberty.
    It is caused by early maturation of the hypothalamic-pituitary-gonadal axis.

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It is characterized by sequential maturation of breasts and pubic hair in girls.
The sexual characteristics are appropriate for the child's gender (isosexual).
Central precocious puberty is idiopathic in 80–90% of cases in girls.

– Peripheral precocity

Peripheral precocious puberty is also known as gonadotropin-independent precocious puberty or peripheral precocious puberty.
Some authors use term peripheral precocity instead of peripheral puberty because puberty implies activation of the hypothalamic-pituitary-gonadal axis, as occurs in central precocious puberty.
Precocity refers only to the secondary sexual characteristics.
Peripheral precocity is most commonly either isosexual (concordant with the child's gender), or contrasexual (with virilization of girls and feminization of boys), but can also present with both virilizing and feminizing features in rare cases.
It is caused by:

- Excess secretion of sex hormones (estrogens or androgens) derived either from the gonads or adrenal glands.
- Exogenous sources of sex steroids.
- Ectopic production of gonadotropins from a germ cell tumor (e.g., human chorionic gonadotropin, hCG).

- Severe androgen excess should prompt further investigation to exclude a rare virilizing tumor or a variant form of congenital adrenal hyperplasia. This will manifest as:
  - Clitoral enlargement
  - Growth acceleration
  - Severe acne
- The etiology of premature pubarche is an earlier-than-usual increase in the secretion of weak androgens by the adrenal glands.
- This is also called premature adrenarche.
- Puberty can be normal, precocious or delayed.
- Precocious puberty is defines as puberty occurring at an unusually early age.
- Precocious puberty is considered when normal puberty occurs before 8 years of age in girls.
- This is opposite to delayed puberty.
- This comes from the Latin term *Pubertas praecox* which was used by physicians in the nineteenth century.
- For many years, puberty was considered precocious when it occurs in girls younger than 8 years; however, recent studies indicate that signs of early puberty are often present in girls aged 6–8 years.
- Physiologically, precocious puberty represents a variation of normal development that occurred at unusually early age.

- Precocious puberty (early pubic hair appearance, breast development, or genital development) may result from natural early maturation or from several other conditions.
- Rarely, precious puberty is triggered by a disease such as a tumor or injury of the brain.
- Precocious puberty is known to be associated with adverse effects on social behavior and psychological development.
- Precocious puberty is broadly classified into central and peripheral.
- Central precocious puberty is gonadotropin-dependent and represents the early maturation of the entire hypothalamic-pituitary-gonadal (HPG) axis.
- Precocious pseudopuberty is much less common and results from increased production of sex steroids and it is gonadotropin-independent.
- It is important to differentiate the two and correct diagnosis of the etiology of precocious puberty is important, because evaluation and treatment of patients with precocious pseudopuberty is quite different than that for patients with central precocious puberty.
- Central precocious puberty can be treated by suppressing the pituitary hormones that induce sex steroid production.
- Secondary sexual development induced by sex steroids from other abnormal sources is referred to as peripheral precocious puberty or precocious pseudopuberty.
- Symptoms in these children are usually secondary to adrenal insufficiency.
  - This results from 21-hydroxylase deficiency or 11-beta hydroxylase deficiency.
  - This will result in:

    Hypertension
    Hypotension
    Electrolyte abnormalities
    Ambiguous genitalia in females
    Signs of virilization in females
    Blood tests will typically reveal high level of androgens with low levels of cortisol.

- Precocious puberty is associated with advancement in bone age, which leads to early fusion of epiphyses, thus resulting in reduced final height and short stature.
- One of the sequels of precocious puberty is that a child can be fertile.
- The youngest mother was Lina Medina, who gave birth at the age of 5 years, 7 months and 17 days, in one report and at 6 years 5 months in another.
- Precocious puberty can cause several problems.
  - The early growth spurt initially can cause tall stature, but rapid bone maturation can cause linear growth to cease too early and can result in short adult stature.
  - The early appearance of breasts or menses in girls and increased libido in can cause emotional distress for some children.

3.2 Regulation of Normal Puberty

- For many years there were a lot of controversies over the issues of the timing and mechanism of normal puberty.
- Normally, the average age at thelarche was commonly believed to be 10.5 years.
- Eight years was the traditionally accepted lower limit of normal for thelarche and pubarche in girls.
- Currently, these figures are not accurate and several factors must be taken in consideration. These include:
  - The socioeconomic status
  - The color
  - The race
  - The dietary habits
- Recently, it was found that breast development was present in 15% of African American girls and 5% of white girls at age 7 years.
- The average age at thelarche was 10 years for white girls and 8.9 years for African American girls (Fig. 3.1a–e).
- It was also found that:
  - Between their seventh and eighth birthdays, 10% of white girls, 23% of African American girls, and 15% of Hispanic girls had breast development of at least Tanner stage 2.
  - An average age at breast Tanner stage 2 of 9.9 years for white girls and 9.1 years for African American girls.
- With a larger number of female children entering puberty at an earlier age, it is important to distinguish the early-normal maturing patient from the one with pathologically precocious puberty.
- This calls for a thorough history and clinical evaluation, assessment of the rate of maturation, and hormonal measurements.
- The mechanism of normal puberty was not fully understood.
- Over the last 10 years, there was a lot of advancement and understanding of the regulation of normal puberty.
- One important contributing factor is the discovery of kisspeptin and its receptor.
- Kisspeptin which is produced by hypothalamic neurons promotes GnRH secretion.
- Kisspeptin-producing hypothalamic neurons are located in the arcuate nucleus (ARC) and anteroventral periventricular area.
- These neurons also coproduce neurokinin B and dynorphin.
- Neurokinin B has local stimulatory effect on kisspeptin release.
- Dynorphin on the other hand has a repressive action on kisspeptin release.
- These neurons are also known as KNDy (Kisspeptin, Neurokinin B, Dynorphin) neurons.

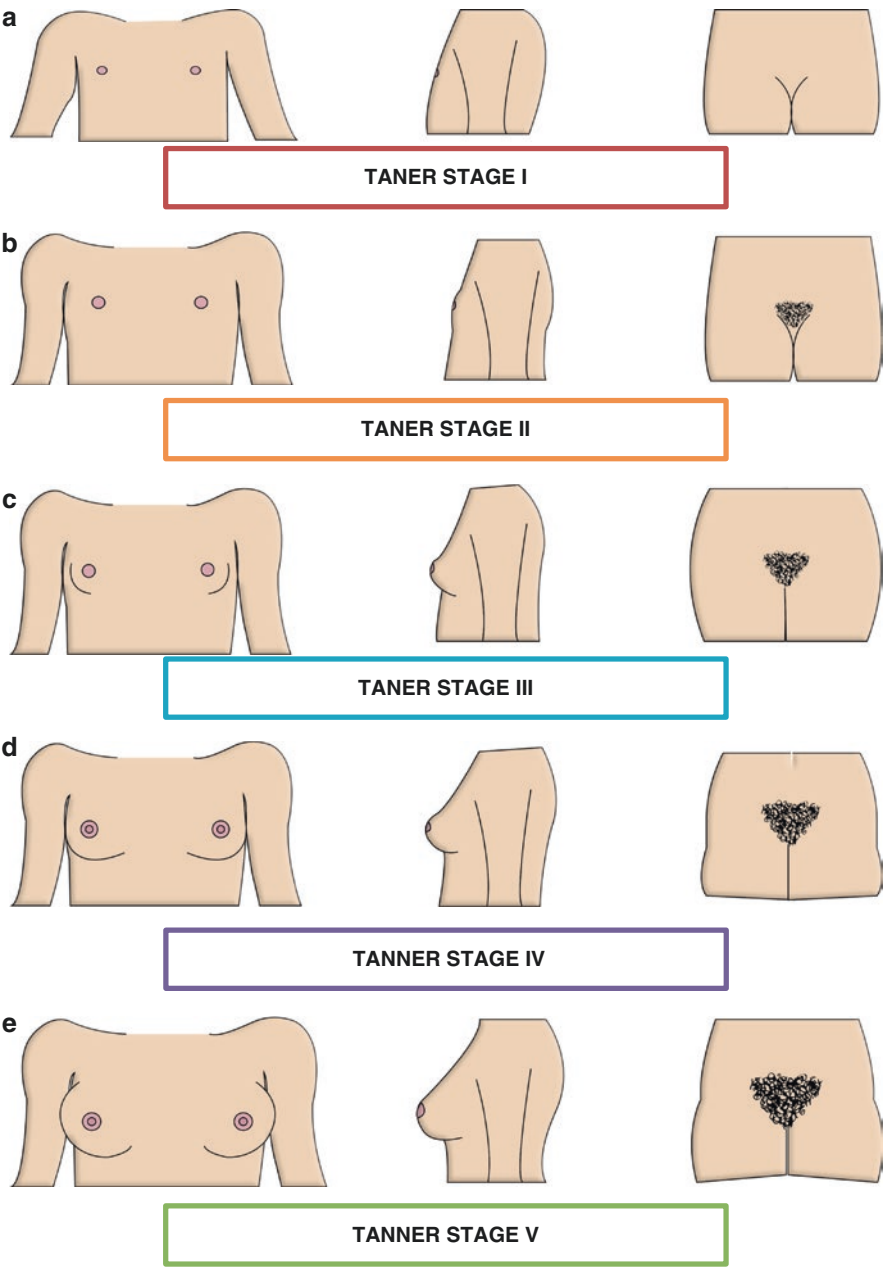

Fig. 3.1 (**a**–**e**) Diagramatic representations of Tanner stages of development

- This overlapping autocrine feedback allows for fine control of kisspeptin secretion.
- Additionally, KNDy neurons may be a site of action for the negative feedback effects of estradiol, and decreases in the intensity of this negative feedback occur as puberty begins.
- In reproductively mature females, regulation of hypothalamic reproductive capacity is influenced by the energy status of the organism, with peripheral energy stores being signaled to the brain by leptin and ghrelin.
- Leptin:
  - This is produced in adipose tissue and directly related to stored energy.
  - It acts through its receptor to stimulate kisspeptin secretion in the ARC.
- Ghrelin:
  - Ghrelin appears to suppress kisspeptin secretion in the ARC and anteroventral periventricular area.
  - Ghrelin secretion varies over the short term with food intake but also is influenced in the long term by energy stores.
- Additional signals of energy balance that may influence kisspeptin secretion include neuropeptide Y and proopiomelanocortin.
- These mechanisms are important for maintenance of ovarian function, but their role in the initiation of puberty is not known.
- Activating mutations of the genes for kisspeptin and its receptor have been found in girls with precocious puberty.
- It was also found that the regulation of puberty and reproductive function is also influenced by hypothalamic astrocytes and other neuroglial cells.
  - Neuroglial cells influence GnRH neurons in at least 2 ways.
  - Hypothalamic astrocytes secrete a host of growth factors, such as TGF-β, basic fibroblast growth factor, and epidermal growth factor-like peptides.
  - These growth factors act via specific receptors on GnRH neurons to increase neuronal growth and function.
  - Additionally, glial cells are directly opposed to GnRH neurons in a dynamic fashion.
  - Increases in levels of apposition are associated with greater GnRH secretion.
  - The apposition is negatively influenced by estradiol, and this may be a mechanism by which negative feedback occurs.
- Collections of neuroglial cells forming hypothalamic hamartomas are commonly associated with precocious puberty.
- Although this form of precocious puberty has been attributed to an ectopic source of GnRH pulsatility within the hamartoma, there is evidence that neuroglial effects on hypothalamic GnRH neurons may play a role.

3.3 Epidemiology

- The average age of thelarche was found to be around 11 years.
- Precocious puberty in girls is diagnosed when it starts before age 8 years.
- It was estimated that approximately 8% of white and 25% of black girls in the United States exhibited evidence of sexual precocity.
- Others considered precocious puberty only when breast development or pubic hair appear before age 7 years in white girls and age 6 years in black girls.
- It is important to note that in certain parts of the world, a decline in the age of puberty in girls has been noted.
- It was also found that black girls in the United States have onset of precocious puberty about 1 year earlier than white girls.

3.4 Classification and Etiology

- Precocious puberty is classified into central and peripheral.
- Central precocious puberty is also called complete or true precocious puberty.
- Central precocious puberty is considered if its cause can be traced to the hypothalamus or pituitary.
- The causes of central precocious puberty include:
  - Idiopathic or constitutional when no cause can be identified.
  - Damage to the inhibitory system of the brain. This can be secondary to:
    - Infection
    - Trauma
    - Irradiation
  - Hypothalamic hamartoma: This can produce pulsatile gonadotropin-releasing hormone (GnRH)
  - Langerhans cell histiocytosis
  - McCune–Albright syndrome
  - Intracranial neoplasm
  - Infection of the central nervous system most commonly tuberculosis
  - Trauma
  - Hydrocephalus
  - Angelman syndrome
  - Suprasellar arachnoid cysts
  - Slipped capital femoral epiphysis occurs in patients with central precocious puberty because of rapid growth and changes of growth hormone secretion.

- The causes of peripheral precocious puberty include:
  - Endogenous sources

    gonadal tumors (such as arrhenoblastoma)
    Adrenal tumors
    Germ cell tumor
    Congenital adrenal hyperplasia
    McCune–Albright syndrome
  - Exogenous hormones

    Environmental exogenous hormones
    Secondary to treatment for another condition
- Isosexual precocious puberty
  - This is seen in patients with precocious puberty who develop phenotypically appropriate secondary sexual characteristics.
- Heterosexual precocious puberty
  - This is also called heterosexual precocious puberty.
  - This is seen in patients with precocious puberty who develop phenotypically inappropriate secondary sexual characteristics.
  - A female may develop a deepened voice and facial hair.
  - This is a very rare condition.
  - It can be seen in children with a very rare genetic condition called aromatase excess syndrome in which exceptionally high circulating levels of estrogen are present.
  - Patients with this syndrome are hyperfeminized.
- Girls who have a high-fat diet and are not physically active or are obese are more likely to physically mature earlier.
- Exposure to chemicals that mimic estrogen (known as xenoestrogens) is a possible cause of early puberty in girls.
- Bisphenol A, a xenoestrogen found in hard plastics, has been shown to affect sexual development.
- Genetic and/or environmental factors.
- There is a higher prevalence of early puberty in black versus white girls.
- A pineal gland tumor (a chorionic gonadotropin secreting pineal tumor) with high levels of beta-hCG in serum and cerebrospinal fluid.
- Elevated melatonin could be responsible for some cases of precocious puberty.
- Familial cases of idiopathic central precocious puberty.
- Mutations in genes such as LIN28, and LEP and LEPR, which encode leptin and the leptin receptor, have been associated with precocious puberty.
- Mutations in the kisspeptin (KISS1) and its receptor, KISS1R (also known as GPR54), involved in GnRH secretion and puberty onset.

- The gene MKRN3 (Zinc finger protein 127) which is located on human chromosome 15 on the long arm in the Prader-Willi syndrome critical region2 was identified as a cause of premature sexual development with early breast and testes development, increased bone aging and elevated hormone levels of GnRH and LH.

3.5 Pathophysiology

- Normally, the onset of puberty is caused by the secretion of high-amplitude pulses of gonadotropin-releasing hormone (GnRH) by the hypothalamus.
- High-amplitude pulses of GnRH causes pulsatile increases in the pituitary gonadotropin-luteinizing hormone (LH) and follicle-stimulating hormone (FSH).
- Increased LH levels stimulate production of sex steroids by ovarian granulosa cells.
- Most girls suspected of having central precocious puberty, are otherwise healthy children whose pubertal maturation begins at an earlier age (6–8 years old).
- Pubertal levels of androgens or estrogens cause the physical changes of puberty, including breast development in girls.
- These levels also mediate the pubertal growth spurt.
- Increased FSH levels cause enlargement of the gonads and eventually promote follicular maturation in girls.
- The timing of puberty has a genetic component.
  - Precocious puberty was found to be familial in one fourth of cases.
  - The mode of inheritance was autosomal dominant.
- An increased body mass index (BMI) has been associated with early puberty.
  - This association is stronger in white girls than in black girls.
  - Body weight and fat mass are among the factors that may influence puberty onset in girls.
  - Increased BMI at age 3 years and the rate of increase in BMI from age 3–6 years were both positively associated with an earlier onset of puberty.
- These girls are otherwise healthy with no CNS structural abnormalities.
- CNS abnormalities associated are found in a small number of these children with precocious puberty and include the following:
  - Tumors of the CNS:

    Astrocytomas
    Gliomas
    Germ cell tumors secreting human chorionic gonadotropin (HCG).
  - Hypothalamic hamartomas

– Acquired CNS injury caused by:

  Inflammation
  Surgery
  Trauma
  Radiotherapy
  Brain abscess

– Congenital anomalies including:

  Hydrocephalus
  Arachnoid cysts
  Suprasellar cysts

3.6 Clinical Features, Morbidity and Mortality

- Breast enlargement is the first and most obvious sign of early precocious puberty in girls.
- Breast enlargement may initially be unilateral.
- The most reliable sign of precocious puberty as a result of increased estrogen production is breast enlargement.
- Initially, breast budding may be unilateral or asymmetric.
- Gradually, the breast diameter increases, the areola darkens and thickens, and the nipple becomes more prominent.
- This differentiates precocious puberty from premature thelarche where there is lack of thickening and pigmentation of the nipples and the areola.
- It is also important to distinguish enlargement of glandular breast tissue from fat as this can mimic true breast tissue.
- Pubic and axillary hair may appear before, at about the same time, or well after breast enlargement.
- These patients have axillary odor similar to adults and this usually starts about the same time as the appearance of pubic hair.
- Menarche occurs late usually 2–3 years after onset of breast enlargement.
- The pubertal growth spurt occurs early in females.
- Genital examination may or may not reveal pubic hair.
- Enlargement of the clitoris indicate significant androgen excess and this must be promptly evaluated.
- The vaginal mucosa has normally a deep-red color in prepubertal girls but in girls with precocious puberty it takes on a moist pastel-pink appearance as estrogen exposure increases.
- Mild acne may be normal in early puberty, but rapid onset of severe acne should increase suspicion of an androgen-excess disorder.
- Exposure to exogenous sex hormones is an occasional cause of early precocious puberty.

  - This can result from inadvertent exposure to androgens through contact with adult males who use topical androgens such as Androgel.

- Isolated sexual precocity of unknown etiology carries no increased risk of mortality.
- Children with a CNS, adrenal, or ovarian tumor may be at risk for tumor-related complications.
- Some studies have found an association between early puberty in girls and a higher risk of developing breast cancer as adults.
- Children with precocious puberty may be stressed because of physical and hormonal changes which may not be easy for them to cope with. These young girls will need support in order to understand.

  - They may be teased by their peers because of their physical difference.
  - Girls who reach menarche before age 9–10 may become withdrawn.
  - They may have difficulty adjusting to their environment.
  - They may have difficulties wearing and changing pads.
  - Girls with precocious puberty may have behavioral problems and are less socially competent than age-matched peers.
  - These emotional problems may persist into adulthood.
  - Girls with precocious puberty are at higher risk of sexual abuse because they have developed secondary sex characteristics.
  - Girls with precocious puberty are at a higher risk for socio-psychological problems.

- To overcome the distress associated with precocious puberty and early menses, parents should be encouraged to prepare their daughters for this event when they reach stage III–IV of breast development.
- Girls with precocious puberty may have increases in libido leading to increased masturbation or inappropriate sexual behaviors at a young age.
- Girls with precocious puberty have a slightly earlier age of initiation of sexual activity.
- Precocious puberty accelerates growth of the child.

  - These children may initially be considerably taller than their peers.
  - Because bone maturation is also accelerated, growth may be completed at an unusually early age.
  - This may result in short stature at the end.
  - This short stature is more likely if precocious puberty starts very early, before age 6 years than if it begins around 6–8 years.
  - There are several studies which showed that most untreated girls with idiopathic central precocious puberty reach an adult height within the reference range.
  - Determination of bone age can be used to predict adult height and to select patients with high risk for short stature if left untreated.
  - Most girls with precocious puberty who are aged 6–8 years at the onset of puberty achieve an adult height within the reference range.

  - Treatment with GnRH analogues such as Lupron is usually associated with only a modest gain in final height in this age group.

- Several authors advocate that treatment should be considered following an initial evaluation for girls who have predicted heights less than 4 ft 11 in or who are well below their target height.
  - Average of parents' heights, less 2.5 in.
  - Or when the patient also has very advanced bone age, a height below the 25th percentile, or both.
- The benefit of treatment which aims at increasing adult height is the greatest in patients who are diagnosed with central precocious puberty and started on GnRH analogues at younger ages.
- Normal adult height can be achieved in most cases if treatment is started before bone maturation is too advanced (>12 year in girls) and if good gonadal suppression is maintained for several years.
- Treatment allows growth to continue while dramatically slowing the rate of bone maturation.
- Girls with central precocious puberty are at increased risk for psychosocial problems and also significant behavior problems such as;
  - Poor self-esteem
  - Higher anxiety
  - Irritability
  - Withdrawal

3.7 Investigations and Diagnosis

- There is no defined age that separates normal from abnormal puberty development.
- The followings are indicative for evaluation:
  - The development of pubic hair (pubarche) before 8 years.
  - Breast development (thelarche) in girls with onset before 7 years.
  - The appearance of menstruation (menarche) in girls before 10 years of age.
- Early precocious puberty warrants evaluation for the following reasons:
  - Precocious puberty induce early bone maturation and reduce eventual adult height.
  - Precocious puberty may indicate the presence of a tumor or other serious medical problem.
  - Precocious puberty may help recognize the few children with serious conditions.
  - Precocious puberty cause a girl to become an object of adult sexual interest.
  - Precocious puberty cause social and psychological problems for both the child and parents.

- For girls, estradiol measurements are less reliable indicators of the stage of puberty.
  - Estradiol levels that exceed 20 pg/mL usually indicate puberty, but some girls who are clearly pubertal may have levels of less than 20 pg/mL.
  - In addition, estradiol levels may fluctuate from week to week.
  - Girls who have ovarian tumors or ovarian cysts often have estradiol levels that exceed 100 pg/mL.
- Levels of adrenal androgens (e.g., dehydroepiandrosterone [DHEA], dehydroepiandrosterone sulfate [DHEAS]) are usually elevated in girls with premature pubarche.
  - DHEA-S, the storage form of DHEA, is the preferred steroid to measure because its levels are much higher and vary much less during the day.
  - In most children with premature pubarche, DHEA-S levels are 20–100 mcg/dL, whereas in rare patients with virilizing adrenal tumors, levels may exceed 500 mcg/dL.
  - A 17-OH progesterone serum level should be done if mild or nonclassic congenital adrenal hyperplasia is suspected.
  - If a basal serum level of 17-OH is below 200 ng/dL, the diagnosis of nonclassic congenital adrenal hyperplasia can be excluded.
  - If the random 17-OH progesterone serum level is elevated, a corticotropin (i.e., Cortrosyn)–stimulation test should be done.
  - This is more valuable and provides the greatest diagnostic accuracy.
  - A post corticotropin 17-hydroxyprogesterone greater than 1000 ng/dL is diagnostic.
- The random LH serum level is now the best screening test for central precocious puberty (CPP).
  - The immunochemiluminometric (ICMA) method for LH is more specific than the immunofluorometric (IFMA) method.
  - An LH level of less than 0.1 IU/L is generally prepubertal.
  - Random follicle-stimulating hormone (FSH) levels do not discriminate between prepubertal and pubertal children.
  - Suppressed levels of LH and FSH accompanied by highly elevated testosterone or estradiol levels suggest precocious pseudopuberty rather than central precocious puberty.
  - A definitive diagnosis of central precocious puberty may be confirmed by measuring LH and FSH levels 30–60 min after stimulation with gonadotropin-releasing hormone (GnRH) at 100 mcg or with a GnRH analogue.
  - Most centers are using the analogue leuprolide (aqueous form) at a dose of 20 mcg/kg, up to a maximum of 500 mcg because native GnRH is no longer available.
  - An increase in FSH levels much greater than the increase in LH levels suggests that the child is prepubertal.

- Some studies suggest that an increase in LH levels to more than 8 IU/L is diagnostic of central precocious puberty, but this depends on the specific LH assay used.

  It was found that a peak LH level measured by ICMA that defined CPP was found to be 3.3 IU/L in girls.
  It was found that when the baseline LH level is prepubertal, an increase in LH level to 5 IU/L or more after leuprolide correlates well with progression of pubertal signs during a 6-month period of observation.
  It was found that no increase in LH and FSH levels after the infusion of GnRH suggests precocious pseudopuberty.

- It was also found that serum anti-Müllerian hormone and inhibin B offer markers for differentiating progressive central precocious puberty from slowly progressive central precocious puberty.
  - It was found that anti-Müllerian hormone levels are lower and inhibin B levels are higher in girls with the progressive form of central precocious puberty.
- Radiography of the hand and wrist is used to determine bone age.
  - If bone age is within 1 year of chronological age, puberty has not started.

    A 2-year-old girl with premature thelarche.
    Or the duration of the pubertal process has been relatively brief.
  - If bone age is advanced by 2 years or more, puberty likely has been present for a year or more or is progressing more rapidly.
- Head MRI:
  - MRI is indicated for those suspected to have a tumor or a hamartoma after hormonal studies indicate a diagnosis of central precocious puberty.
  - A high-resolution study that focuses on the hypothalamic-pituitary area is important.
  - For healthy girls aged 6–8 years with no signs or symptoms of CNS disease, the likelihood of finding a tumor or hamartoma is only about 2%.
  - The younger the child with central precocious puberty, the greater the chance of finding CNS pathology.
- Pelvic ultrasonography:
  - Ultrasonography is unnecessary for girls with a definite diagnosis of central precocious puberty.
  - In girls with central precocious puberty, ultrasonography usually reveals bilaterally enlarged ovaries, often with multiple small follicular cysts, and an enlarged uterus with an endometrial stripe.
  - Pelvic ultrasonography is essential when precocious pseudopuberty is suspected in girls because an ovarian tumor or cyst may be detected.

- If central precocious puberty is caused by a tumor in the hypothalamic-pituitary area, the histology of the tumor is important to the patient's prognosis.
  - Gliomas tend to grow more rapidly than astrocytomas.
  - Hamartomas are benign.
  - Treatment of precocious puberty associated with a hamartoma suppresses gonadotropin production by the pituitary without effect on the hamartoma itself.

3.8 Treatment

- Precocious puberty is a common problem affecting up to 29 per 100,000 girls per year.
- Precocious puberty is traditionally defined as the onset of secondary sexual development before the age of 8 years in girls.
- Because of trends towards earlier pubertal development, some healthy girls will have breast or pubic hair development before this age, and extensive evaluation and treatment may not be required.
- If the clinical evaluation and investigations leads to a diagnosis of progressive precocious puberty, treatment should be considered.
- The reasons for treatment include:
  - Preservation of adult height potential.

    This is especially so for girls under 6 years old.
    These girls have the greatest potential to achieve adult height with treatment.
  - Psychosocial difficulties with early puberty and menarche.
- Non-continuous usage of GnRH agonists stimulates the pituitary gland to release follicle stimulating hormone (FSH) and luteinizing hormone (LH).
- However, when used regularly, GnRH agonists cause a decreased release of FSH and LH.
- Continuous administration of LHRH and GnRH agonists provides negative feedback and results in decreased levels of LH and FSH 2–4 weeks after initiating treatment.
- The mainstay of treatment for central precocious puberty is GnRH analogs (GnRHa).
- These drugs provide constant serum levels of GnRH activity and thus override the pulsatility of endogenous GnRH.
- In the past, the 1-month formulation of leuprolide, called Lupron-Depot, was the mainstay of therapy.
- In 2011, 3-month formulations of Lupron-Depot 11.25 mg and 30 mg, were approved for children with precocious puberty.

- A study comparing the 1-month 7.5 mg leuprolide with the 11.25-mg 3-month leuprolide found that both preparations resulted in prompt and effective suppression of puberty, but LH and FSH levels were slightly higher with the 3-month dosing, which has the advantage of being more convenient for the family.
- Potent, long-acting synthetic derivatives of native GnRH, such as natrelin, suppress pituitary production of gonadotropins because they provide constant stimulus, whereas the pituitary responds only to pulsatile GnRH stimulation.
- Histrelin acetate (Supprelin LA), triptorelin or leuprolide, any GnRH agonists, may be used.
- There are many different GnRH analogs.
  - The primary analog used is depot intramuscular injections of leuprolide acetate.
  - This is administered every 4 weeks.
  - Depot leuprolide acetate injections require relatively frequent painful intramuscular injections.
  - Minor adverse effects include pain and/or bruising at the insertion site.
  - To overcome these:

    A longer-acting form was used.
    Early reports of the 11.25-mg every 3 months formulation indicated that it was highly effective, suppressing stimulated LH levels to under 3 U/L in 95% of patients.
    This showed clinical suppression in all patients.
    Subsequently, 2 different monthly doses (3.75 and 7.5 mg) in conjunction with the 11.25-mg every 3 months dose were used.
    These demonstrated a statistically higher mean stimulated LH concentration in the 3-month group compared to both the 3.75- and 7.5-mg monthly groups.

  - The GnRHa histrelin has been incorporated into a subdermal hydrogel implant.
  - After 1 year in place, the implants may become relatively brittle, and breakage of the device at removal is common.
  - In 5–10% of patients, ultrasonography may be required to locate fragments of the implant.
- For patients with precocious puberty treated with gonadotropin-releasing hormone (GnRH) agonists:
  - Follow up every 4–6 months to ensure that progression of puberty has been arrested.
  - Favorable signs include;

    Normalization of accelerated growth
    Reduction or no increase in size of breasts
    Suppression of gonadotropin levels after a challenge of GnRH.

- A GnRH test is performed about 4 months after starting treatment to confirm suppression and then yearly, as long as clinical indicators suggest that the drug is working as intended.
- Monitor bone age yearly to confirm that the rapid advancement seen in the untreated state has slowed.

- Some authors suggested that in girls with idiopathic central precocious puberty, treatment with a combination of GnRH analogue and growth hormone leads to better height results than does therapy with GnRH analogue alone.
  - The addition of recombinant human growth hormone to GnRH agonist therapy resulted in significant height increase, as well as increases in predicted adult height and height standard deviation for bone age, in children with central precocious puberty.
  - Efficacy was greater in patients whose initial treatment began prior to age 10 years or whose therapy lasted more than 12 months.
  - Treatment of central precocious puberty with GnRH agonists is just as effective in girls with obesity as in those who are not obese.

- Gonadotropin-Releasing Hormone Agonists
  - Leuprolide acetate (Lupron, Lupron Depot-Ped, Lupron Depot 3 month)

    It suppresses ovarian and testicular steroidogenesis by decreasing LH and FSH levels.
    Available in a monthly depot formulation in 7.5-, 11.25-, and 15-mg dose
  - Triptorelin (Triptodur, Trelstar, Trelstar Depot)

    This is indicated for central precocious puberty in pediatric patients aged 2 years or older.
    Triptorelin suppresses gonadotropin secretion via GnRH receptor desensitization and down-regulation.
    This reduces gonadal steroids to prepubertal levels.
  - Nafarelin (Synarel)

    Analogue of GnRH that is approximately 200 times more potent than natural endogenous GnRH.
    It suppresses gonadotrope responsiveness to endogenous GnRH, thereby reducing secretion of LH and FSH, which in turn reduces ovarian and testicular steroid production.
    It is administered intranasally to induce gonadotropin suppression.
    It is considered as second-line drug if leuprolide proves difficult to administer.
    Patient's adherence to a bid intranasal drug administration regimen may be difficult to achieve.
    Available as nasal spray; 200 mcg/spray.
    One 10 mL bottle contains 7-day supply for daily dose of 1600 mcg.

– Histrelin (Supprelin LA)

  This is an LHRH agonist that is a potent inhibitor of gonadotropin secretion.
  It desensitizes responsiveness of pituitary gonadotropin.
  Circulating LH and FSH levels initially increase following administration, leading to transient increase in concentration of gonadal steroids (testosterone and dihydrotestosterone in males and estrone and estradiol in premenopausal females).
  However, long-term administration decreases LH and FSH levels.
  Implant can provide continuous subcutaneous release of histrelin at nominal rate of 50–65 mcg/d over 12 months.

– Progestin

  This was used before availability of GnRH agonists.
  Progestins were the mainstay of therapy.
  Progestins work by providing feedback suppression of pituitary gonadotropin secretion.
  They lack significant androgenic or estrogenic activity.

– Medroxyprogesterone (Depo-Provera)

  This inhibits secretion of pituitary gonadotropin.
  Inhibits effect of LH.
  It is much less used now due to its relative ineffectiveness in reversing rapid advancement of skeletal maturation seen in central precocious puberty.
  It is effective at slowing breast growth and preventing or stopping menses when administered every 3 months.
  It is relatively inexpensive.
  It can be used when leuprolide cost is a factor and when adult height prediction is close to reference range or is not a major concern.

- Prolonged use has a risk of causing osteoporosis.
- After stopping GnRH agonists, pubertal changes resume within 3–12 months.
- When central precocious puberty (CPP) is caused by a CNS tumor other than a hamartoma, a resection should be attempted to the extent possible without impinging on vital structures such as the optic nerves.
- Radiation therapy is often indicated if surgical resection is incomplete. Unfortunately, removal of the tumor rarely causes regression of precocious puberty.
- The treatment of peripheral precocious puberty depends on the cause.

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Chapter 4
Breast Disorders in Female Children and Adolescents

Ahmed H. Al-Salem

4.1 Introduction

- A wide variety of breast disorders occurs in children (Fig. 4.1a, b).
- Breast disorders occurring in children range from:
  - Congenital conditions
  - Infections
  - Benign disorders
  - Malignant tumors

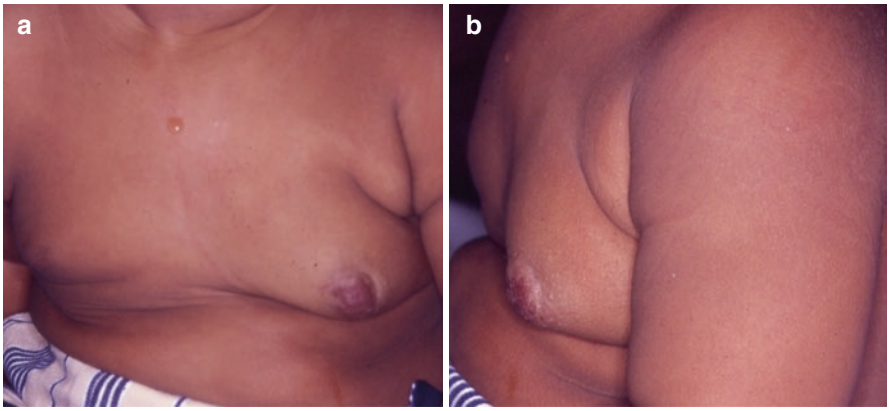

Fig. 4.1 (**a** and **b**) Clinical photographs showing a female child with breast hemangioma

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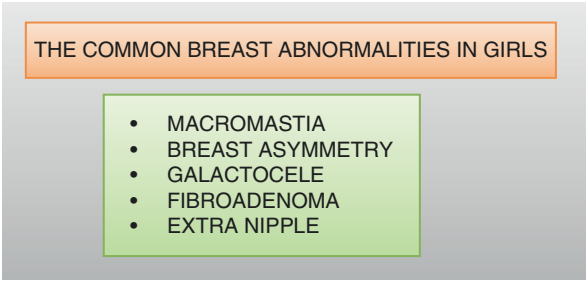
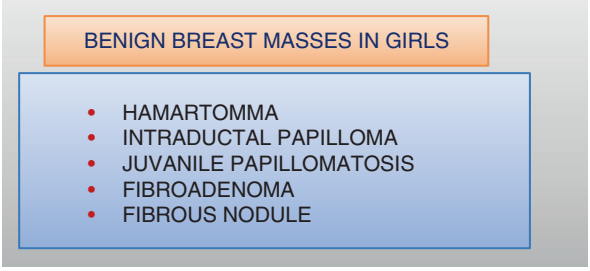
- Commonly one breast develops earlier than the other and the most common breast abnormality seen is asymmetrical breast development.
- The relatively high prevalence of breast cancer in adult females makes parents worry about children with breast complaints.
- Breast cancer is extremely rare in children.
- The reported prevalence of breast cancer in females under the age of 20 is less than 0.1 per 100,000.
- Ultrasound is the primary imaging modality used in assessing breast lesions in children, given its diagnostic specificity and lack of ionizing radiation.
- Mammography is seldom used, but is the modality of choice to visualize calcifications in select cases.
- CT or MR is usually reserved for evaluation of disease extent.
- The vast majority of pediatric breast complaints are of benign etiology.
- Normal anatomic structures can mimic breast masses.
- Non-neoplastic benign conditions in the pediatric breast include cyst, hematoma, mastitis with or without abscess, and galactocele.
- The most common benign solid mass in the pediatric breast is a fibroadenoma.
- The common breast abnormalities in girls include:
  - Macromastia
  - Breast asymmetry
  - Galactoceles
  - Fibroadenomas
  - Extra nipples
- A 2–3 cm mass on ultrasound in a child without atypical features or rapid enlargement is rarely malignant. This can be treated conservatively and follow up.
- A large mass that is larger than 4–5 cm or undergoing rapid enlargement need to be biopsied to exclude the possibility of a phyllodes tumor.
- Benign masses in the breast of a female girl include:
  - A hamartoma
  - Intraductal papilloma
  - Juvenile papillomatosis
  - A fibrous nodule
  - Fibroadenoma
- Malignant masses in the breast of a female girl are exceedingly rare.
- These are more commonly metastatic disease to the breast and rarely primary breast malignancy.
- Phyllodes tumor is the most common primary breast malignancy seen in female children.



- Invasive ductal carcinoma is rare in children, of which the secretory subtype is the most common.
- The presence of a breast mass in a girl with the following factors calls for a biopsy to exclude malignancy regardless of the imaging appearance of the breast lesion.
  - A strong family history of breast cancer
  - History of extramammary malignancy in other parts of the body
  - Genetic mutations
  - History of prior irradiation
  - A large mass or a rapidly growing mass



- Most breast conditions arising in female children are benign, and most cases can be treated conservatively.
- Diagnosis and treatment must be focused on avoiding damage to developing breast tissue.

4.2 Normal Breast Development

- The mammary glands start to develop when solid ectodermal cells invaginate and extend into the deeper mesenchyme from the axilla to the inguinal regions.
- This forms the mammary ridges or milk lines.

- The milk lines extend symmetrically along the anterior torso from the axillae to the groin.
- Normal breast development starts during the 5–6th week of fetal gestation.
- Subsequently, these ridges (milk lines) disappear, except in the pectoral area at the level of the 4th intercostal space, where the normal mammary gland develops.
- If normal involution is incomplete, ectopic or accessory nipples and/or breast tissue may form anywhere along these milk lines.
- The primary breast buds at the 4th intercostal space evolve into secondary buds and further branch into lactiferous ducts within the breast parenchyma.
- The nipple on the other hand develops during the perinatal period.
- Overlying the breast bud at the skin surface, a small depression or mammary pit forms which subsequently evolves into the nipple–areolar complex.
- The nipple develops as a result of proliferation of the mesenchyme underlying the areola.
- At birth, the nipples are poorly developed and are often depressed.
- Soon after birth, the nipples are raised from the shallow mammary pits by proliferation of the surrounding connective tissue.
- Prior to puberty, the breast is composed of epithelium lined lactiferous ducts supported by stromal connective tissue.
- Enlargement of these ducts are a common cause of self-limited bilateral palpable sub areolar nodules in the first 6–12 months of life due to maternal hormonal influence.
- These small nodules may cause concern for the parents and must be reassured.
- Normal thelarche:
  - The term thelarche refers to the onset of normal pubertal phase of breast development in females.
- Estrogen stimulates ductal growth and progesterone promotes lobular and alveolar differentiation, completing the terminal duct lobular unit.
- Budding of the breasts, or thelarche, usually occurs at approximately age 10–11 years in females.
- Premature thelarche:
  - This is defined as early onset of breast development in prepubertal girls, typically before age 7–8 years.
- Delayed thelarche:
  - This is defined as delayed onset of breast development that occurs after 12 years of age.
- Idiopathic premature thelarche generally occurs in younger children between ages 1–3, and is unusual after age 4.
- Idiopathic premature thelarche is benign and generally self-limited.
- This can be confirmed by ultrasound confirming the presence of normal developing breast tissue and absence of a discrete breast mass.

- Premature thelarche can also occur in conjunction with precocious puberty.
- In these patients it is important to exclude hormonally active adrenal or gonadal neoplasms as potential causes for precocious puberty.
- This developmental change, along with adrenarche (i.e., appearance of dark hair over the mons veneris), signifies entry into Tanner stage II of development.
- From this stage, complete maturation to Tanner stage V usually takes more than 4 years.
- Breast maturation in girls extends over a period as short as 18 months or as long as 9 years.
- There are five Tanner stages of normal pubertal breast development based on the clinical appearance of the developing breast.
- Tanner stages 1 (Fig. 4.2):
  - The breast appears as mildly heterogeneous retroareolar tissue.
- Tanner stage 2 (Fig. 4.3):
  - The breast appears as a hyperechoic nodule with central linear or stellate areas of hypoechogenicity which represent evolving hypertrophy, or occasionally from relative loss of soft tissue surrounding a lymph node (for example, weight loss), causing it to become clinically more prominent.

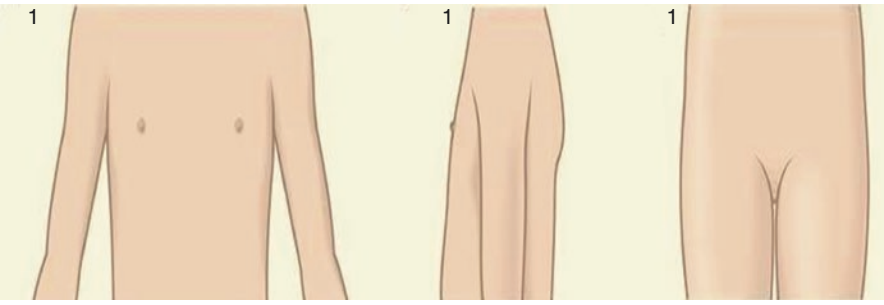


Fig. 4.2 A diagrammatic representation of Tanner stage I

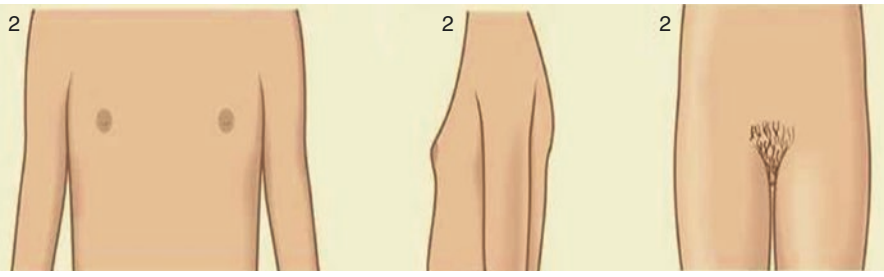


Fig. 4.3 A diagrammatic representation of Tanner stage II

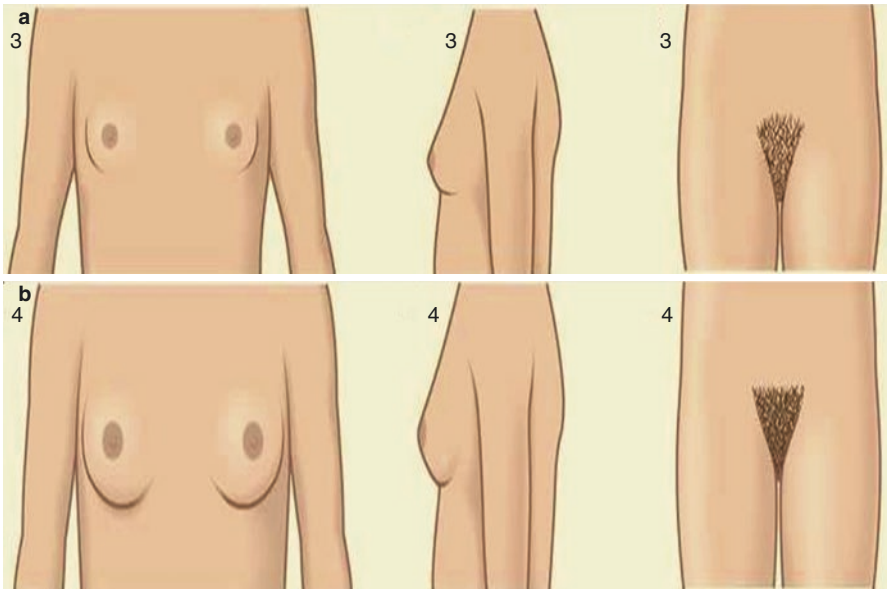


Fig. 4.4 (**a** and **b**) A diagrammatic representation of Tanner stage III and IV

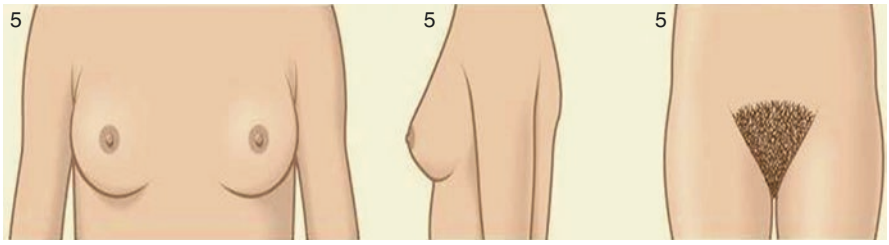
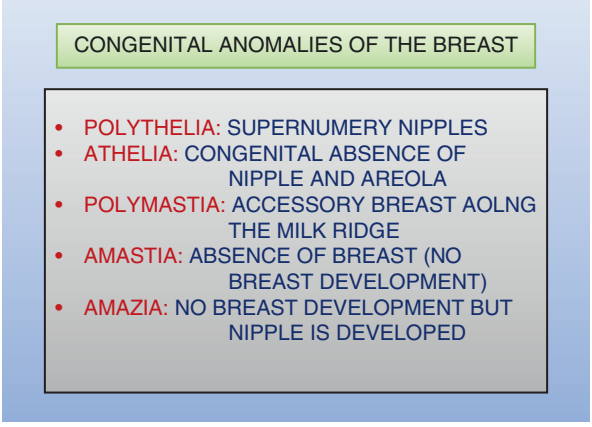


Fig. 4.5 A diagrammatic representation of Tanner stage V

- Tanner stage 3 and 4 (Fig. 4.4a, b):
  - The breast tissues demonstrate appearance of further expansion of the hyperechoic fibro glandular elements, with the central retro areolar hypoechoic regions evolving into more branching and eventually nodular configurations.
- Tanner stage 5 (Fig. 4.5):
  - The breast shows the appearance of mature echogenic breast tissue without central hypoechogenicity, as seen in the adult breast.

4.3 Congenital Breast Abnormalities

- Congenital abnormalities of the breast cover a wide range of abnormalities from aplasia, asymmetry, underdeveloped breasts and abnormal shapes to accessory breasts/nipples.



- The treatment timing is crucial, and many of the surgical corrective procedures require more than one operative procedure.
- It is important to keep in mind that the psychological consequences of these abnormalities can be serious in adolescent patients.
- The majority of these patients are young, healthy individuals, and the psychological and social impact of these conditions is significant.
- These patients can experience:
  - Embarrassment
  - Social isolation
  - Complexities in relationships
  - Complexities in sexual development
- Congenital abnormalities of the breast can be corrected at a single surgical setting.
- A multidisciplinary approach and staged treatment is required for more complex breast development abnormalities.
- Timing of the corrective procedures is crucial as the development of these patients continues.
- There are several breast abnormalities that occur during fetal development.
- These are rare and may be found in newborn infants.

- They may occur on both sides or only on one.
- It is important to be familiar with these abnormalities, as recognition and correct diagnosis obviate the need for intervention, particularly in children and adolescents.
- Athelia:
  - Complete absence of nipple and areola is termed as athelia.
  - This may be unilateral or bilateral.
  - Athelia can be familial, inherited as autosomal dominant.
  - It is seen in association with amastia (absence of breast tissue).
  - It may be associated with rare syndromes such as:

    Scalp-ear-nipple syndrome
    SEN syndrome (scalp nodules and ear malformation)
    Al-Awadi/Rass-Roths child syndrome
    Poland's syndrome

  - A thorough investigation to rule out any other associated ectodermal abnormalities is required.
  - Nipple and areola reconstruction can be carried out using small tissue flaps along with tattooing of a new areola in the absence of any other deformity.
  - Skin grafts could also be used to create areola.
- Amastia:
  - The total absence of breast tissue and nipple–areola complex is called amastia.
  - The absence of breast tissue only is called amasia.
  - In amastia, the mammary ridge disappears completely or fails to develop.
  - Amastia may be associated with other ectodermal defects such as:

    Cleft palate
    Isolated pectoral muscle
    Upper limb deformities
    Urological abnormalities
    Poland's syndrome

  - Amastia may be familial inherited as an autosomal dominant trait.
  - Amastia in girls can be treated with expanders and implants (augmentation mammoplasty).
  - New breasts in girls can also be reconstructed using myocutaneous flaps such as the latissimus dorsi myocutaneous flap.
- Polythelia (Accessory Nipples) and Polymastia (Accessory breast tissue):
  - The presence of extra breast is called polymastia (Fig. 4.6a, b).
  - The presence of extra nipple is called polythelia.
  - In approximately 1% of the population, an extra breast (polymastia) or extra nipple (polythelia) occurs.
  - Accessory nipples are seen in 1–5% of the general population.

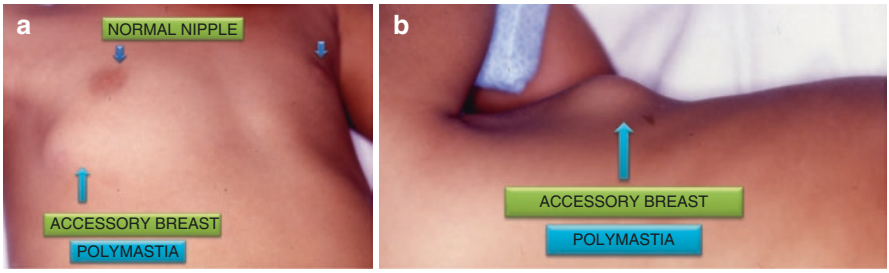


Fig. 4.6 (**a** and **b**) Clinical photographs showing accessory breast. Note the normal looking nipples and areola

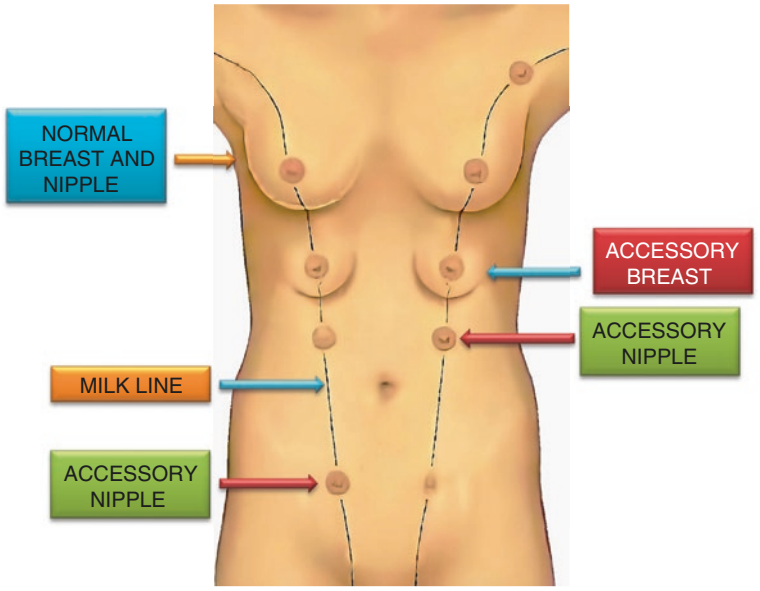


Fig. 4.7 A diagrammatic representation showing the nippleline, accessory breast and sites of accessory nipples

  - There are differences in the incidence of accessory nipples among ethnic groups.
  - Accessory nipples occur with the same incidence in male and females (Figs. 4.7 and 4.8).

- Accessory nipples develop along the milk line and more than 90% are seen in the inframammary region.
- There is some evidence that polythelia may be familial (inherited) and may be associated with urological (ectodermal) abnormalities.
- Some authors suggested urological workup to rule out associated urological abnormalities, but many think this is not necessary as accessory nipples are common, whereas urological abnormalities are rare.

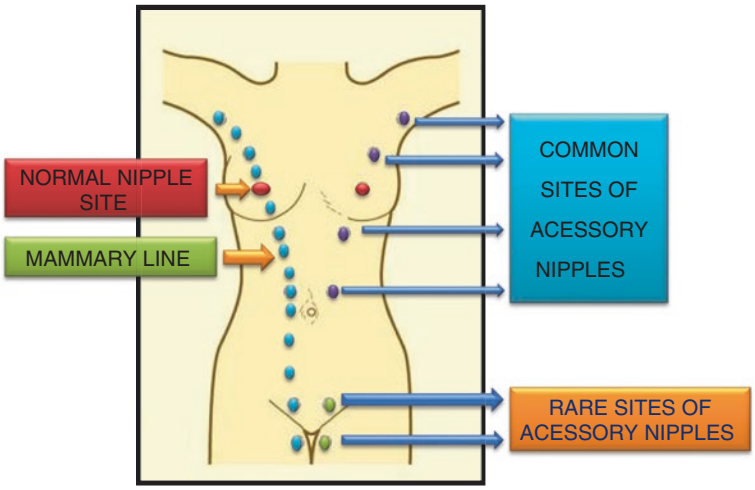


Fig. 4.8 Diagrammatic representation of the milk line and site of accessory

- The extra nipples are slightly more common in males than in females.
- The presence of these two conditions in girls may cause pain and discomfort during a menstrual cycle as a result of hormonal stimulation.
- These accessory nipples can be unilateral or bilateral.

- Clinically, they are well developed with surrounding areola seen in some patients.
- They are prone to the same diseases as normal nipples.
- Accessory nipples require no treatment unless the nipple causes irritation.
- Accessory nipples can be excised for cosmetic reasons.
- Ectopic or accessory breast tissue refers to breast tissue located somewhere other than the expected location of the normal breast in the 4th intercostal space.
- Accessory breasts are usually seen along the mammary ridge or milk line, which extends from the axilla to the vulva.
- The ectopic breast tissue represents incomplete involution of the ectodermal mammary ridge (embryonic progenitors to breast tissue).
- Ectopic breast tissue may contain some or all of the components of the mammary gland, including glandular tissue, areola, and nipple.

- Polymastia (Accessory breast tissue) or supernumerary breasts are seen in approximately 1–2% of the general population, but figures as high as 6% have been reported.
- Polymastia is more common in females and it may be familial.
- In approximately one third of patients there are multiple accessory breasts.
- The most common site for accessory breasts is the axilla.
- Axillary accessory breast tissue can have its own nipple–areola complex.
- Polymastia is usually diagnosed at puberty or during pregnancy when the accessory breast tissue develops along with the normal breasts.

- Accessory breasts are mostly asymptomatic, but can cause discomfort.
- For some patients, polymasia are seen as cosmetically unacceptable.
- Accessory breast tissue is susceptible to all the normal changes and disease spectrum seen in the normal breast.
- Both benign and malignant breast masses arising from ectopic breast tissue have been described in the literature.
- Because ectopic breast tissue is responsive to hormonal influence as much as normal breast tissue, it can cause swelling and discomfort in children and adolescents.
- Breast cancer cases have been reported in accessory breast tissue.
- Treatment of accessory breasts:
  - Accessory breasts are treated conservatively and surgery should be avoided as it may cause unsightly scars which are not accepted cosmetically.
  - Surgical excision is also known to be associated with postoperative complications.
  - Liposuction is a useful alternative for the fatty element of accessory breasts.
  - A combination of surgery for the glandular element and liposuction of the fatty element has been suggested.
  - Excess overlying skin should be excised in cases of large accessory breasts.
  - Postoperative complications include:

    Seroma formation
    Incomplete excision
    Damage to intercostal-brachial nerves
    Painful scar
    Deformity due to excess removal of tissue

- Abnormalities of the Shape of the Breast:
  - Breasts asymmetry is common.
  - Some degree of breast asymmetry is common.
  - Asymmetry of the breasts can be part of Poland's Syndrome or the breasts may develop with differing shapes or amounts of breast tissue.
  - One breast can developmentally be hypoplastic or absent (aplasia).
  - This can be unilateral or bilateral and can occur in isolation or in association with a defect in one or both pectoral muscles.
  - This 'true asymmetry' can be treated with various treatment options, including:

    Augmentation of the smaller breast with an implant.
    Reduction and mastopexy of the larger breast.
    A combination of both these options.
    This may necessitate the use of tissue expanders prior to implants insertion and more than one operation may be required.
    To get true symmetry, there is usually a need to operate on both breasts.

The best age to perform this type of surgery is when the breasts have fully developed, usually approximately at age 17 or 18 years.
Some hypoplastic breasts can also have a tubular element.
Lipofilling may be used to provide implant cover and improve contour to obtain a high degree of symmetry.

- An unusual cause of breast asymmetry is a giant fibroadenoma.
- Tubular Breasts:

  Tubular breasts are characterized by normal function/physiology of the breast tissue, but abnormal anatomical shape.
  It can be unilateral or bilateral.
  The classical features include:

  - Lack of breast skin
  - Breast hypoplasia and asymmetry
  - Conical breasts
  - Herniated nipple–areolar complex
  - A large areola and a constricted breast base

  Treatment:

  - The first correction technique for tuberous breasts was described by Rees and Aston in 1976.
  - They suggested widening of the constricted ring at the base of the breast tissue by radial scoring, essentially making cuts at the base of the breast from the centre, similar to the hands of a clock.
  - Several similar techniques to expand the base width have been described since.
  - Standard treatment includes placement of expanders through an inframammary fold incision following radial scoring and later replacement with implants.
  - These procedures do not correct the 'herniated nipple and areola complex', and a second procedure is often required to correct this deformity, such as reducing the size by circular periareolar round block mastopexy.
  - The dual plane technique differs from the subglandular position, in that the implant is placed in the subpectoral plane. The upper two thirds of the implant are covered by muscle and the lower third is covered by breast tissue.
  - Lipofilling in the periphery of the breast helps to achieve a final better contour and adds volume along with the expander.
  - The long-term outcome from surgery is not always satisfactory.
  - This may lead to loss of sensation, scar issues and asymmetry.

- Congenital Nipple Inversion
  - A congenital inverted nipple was first described by Sir Ashley Cooper in 1840.
  - It is seen in 2% of the general population.

- There is a family history of such a condition in 50% of patients.
- This may develop secondary to tethering and shortening of breast ducts, and development of fibrous bands behind the nipples during intrauterine life.
- This may result in breast feeding difficulties but the changes that occur in the breast during pregnancy may overcome such a difficulty.
- Treatment:

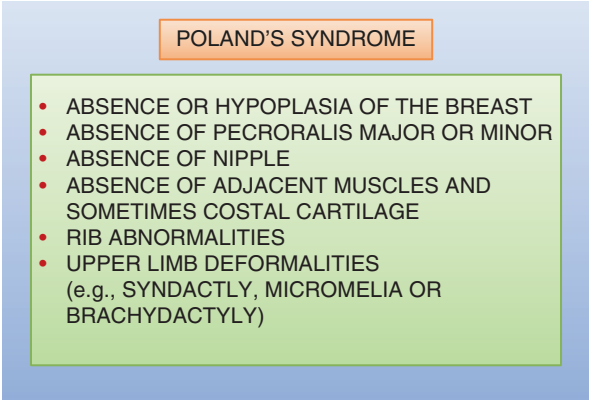
  Tightening of the areolar edge circumferentially.
  The use of adjacent dermal flaps to augment the nipple.
  Most of the procedures involve short circumareolar incision or an incision at the base of the nipple.
  The tight bands are stretched, but it is often required to divide the ducts.
  A stitch can be placed at the base of nipple when it is everted, but this is not recommended.
  These procedures may lead to loss of sensation and inability to breast feed.
  A suction device called a Niplette™ is available and when used regularly it may be successful in everting the nipple.

• Poland's Syndrome:

- Pectus excavatum and Poland's syndrome that include defects of the chest wall are the commonest forms of congenital chest wall defects.
- Poland's syndrome was first described by Alfred Poland from Guys Hospital London in 1841.
- It was later named Poland's syndrome by Clarkson in 1962.
- He reported three patients with breast and hand deformities and noted Poland had described a similar case earlier.
- Poland's syndrome consists of unilateral chest wall hypoplasia with ipsilateral upper limb deformity.
- The incidence of Poland's syndrome is variable and reported as one in 7000 to one in 1,000,000 in the general population.
- Poland's syndrome is three-times more common in males than females.
- Familial cases have been reported also.
- Poland's syndrome consists of some or all of the followings:
- Absence or hypoplasia of the breast
- Absence of pectoralis major or minor
- Absence of nipple
- Absence of adjacent muscles and sometimes costal cartilage
- Rib abnormalities
- Upper limb deformities (e.g., syndactyly, micromelia or brachydactyly).
- The exact cause of Poland's syndrome is not known but hypoplasia of the subclavian artery and its branches is thought to interrupt blood supply to the day 46 embryo and result in Poland's syndrome.
- There is a correlation between Poland's syndrome and carcinoma of underdeveloped breast and leukemia.

– Treatment:

The aim of the treatment should be to achieve symmetry.
The management of these patients requires a multidisciplinary team approach, including pediatrician and plastic surgeon, to decide the optimum age for reconstruction.
The future growth of the child should be considered in treatment planning.
It is recommended that repair should be done as a single-stage procedure in adults and two stages in children.



The best time for operation is in the late teens, but operations can be performed from 11–12 years onwards to help with self-esteem and normal psychological, social and sexual growth.
Aplastic ribs can be reconstructed using bone grafts or prosthetic mesh.
Muscle flaps and breast implants can be used to correct muscle and breast hypoplasia.
Surgical procedures usually involve a combination of replaceable expanders and autologous muscle flaps such as latissimus dorsi flaps.
The replaceable expanders are subsequently replaced by permanent implants.
Becker expander/prostheses implants can be used and placed in a dual plane if the pectoral muscle is normal.
The latissimus dorsi flap harvest can be performed endoscopically.
The other more complicated procedures of autologous tissue reconstruction include:

- Abdominal (i.e., transverse rectus abdominis myocutaneous and deep inferior epigastric perforators) flaps.
- Buttock (i.e., superior gluteal artery perforator or inferior gluteal artery perforator) flaps.
- These are usually reserved for more challenging cases.

- Another option is to use rectus abdominus transverse rectus abdominis myocutaneous flap (free or pedicled).
- A two-flap technique including free and pedicled transverse rectus abdominis myocutaneous flaps for chest and breast reconstruction has been described.

Use of lipofilling and contralateral reduction/mastopexy improves long-term cosmetic results.

- Macromastia
  - Macromastia is characterized by breasts that are disproportionately large.
  - Macromastia that occurs over weeks or months at the very onset of puberty is called virginal hypertrophy.
  - Treatment:

The treatment is initially conservative including weight loss if the patient is overweight and physiotherapy to improve posture and symptoms of neck and back strain.
If symptoms persist, the breasts can be made smaller by a reduction mammoplasty.
Reduction mammoplasty can be done as outpatients under general anesthesia.
Surgery should be deferred until the breasts mature and the patient is close to her adult height.
Typically, this is two to three years after menses have begun and after shoe size stops changing.

4.4 Non-neoplastic Breast Lesions

- Breast Abscess
  - Influx of maternal hormones through the placenta into the fetal circulation often causes the newborn's breasts to be enlarged.
  - In addition, some secretion (i.e., witch's milk) may be evident.
  - These changes disappear with time.
  - Breast abscess, although more commonly encountered in lactating women, mastitis and abscess can occur in childhood.
  - Mastitis occurs most frequently in infants (age <2 months; i.e. mastitis neonatorum) and later childhood (age 8–17), and is thought to be related to skin infection and or ductal obstruction.
  - Breast abscesses may occur in adolescent women, particularly if they are lactating.

These are managed with antibiotics.
Drainage under ultrasound guidance.
Surgical incision and drainage.

- Mastitis in nonlactating adolescent girls may occur.
- Staphylococcus aureus is the usual causative organism.
- Mastitis is usually treated with antibiotics but incision and drainage may be required.
- Prepubertal girls may develop breast abscesses.

  The abscess manifests as a tender and erythematous mass.
  The most common organism causing breast abscesses is Staphylococcus aureus.
  Recently, an increased number of skin and soft tissue abscesses caused by community-acquired methicillin-resistant S aureus (MRSA) have occurred in children.

- Treatment involves antibiotics, needle aspiration, or surgical drainage.
- The decision for surgical drainage should be carefully made because future breast deformation may occur.

• Mastitis neonatorum (Fig. 4.9a–c):

- Infections of the breast tissue may occur during the newborn period.

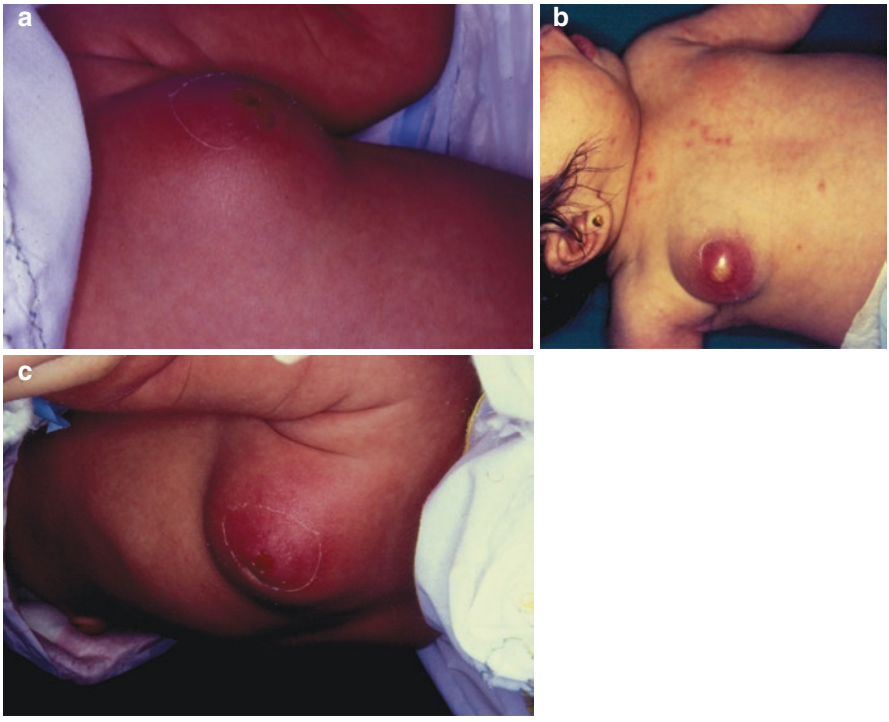


Fig. 4.9 (**a–c**) Clinical photographs showing breast abscess in female infants. Note the neglected abscess in the second patient

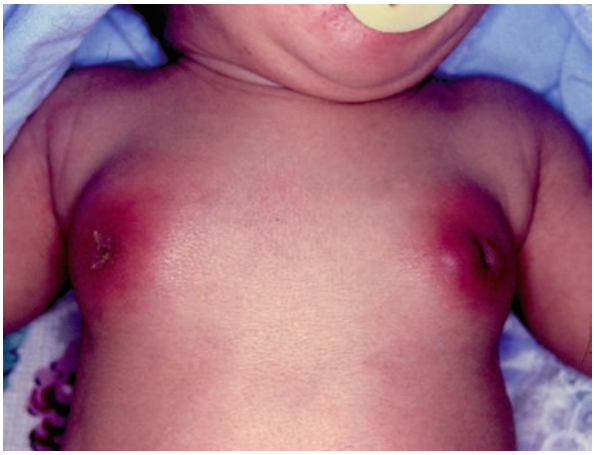


Fig. 4.10 A clinical photograph showing bilateral breast abscess in a girl (Bilateral Mastitis Neonatorum)

  - This can be unilateral or bilateral (Fig. 4.10).
  - Treatment:

    Antibiotics should be started early.
    Antibiotics may be enough in the stage of infection with cellulitis.
    If an abscess occurs, needle aspiration should be performed.
    Surgical drainage should be considered only when needle aspiration is unsuccessful.
    Surgery should be avoided as much as possible because an operation may damage the breast bud and result in reduction of adult breast size.

- There is bimodal distribution of breast abscess in girls with most cases presenting younger than 2 months or 8–17 years.
- Typically, suppurative mastitis presents with edema and erythema, occasionally with fever and leukocytosis.
- Ongoing mastitis can lead to the development of phlegmon and abscess.
- The most common pathogen is *Staphylococcus aureus*, followed by Streptococcus and less commonly Enterococcus species.
- The most common causative pathogens of breast abscess are:
  - *S. aureus* (>75% of cases)
  - Gram-negative bacilli
  - Group A Streptococcus
  - Enterococcus
- Ultrasound should be performed in patients with clinical symptoms of infection to exclude presence of a drainable abscess collection.
- The ultrasound typically shows skin thickening and hyperechoic indurated breast tissue associated with hyperemia (mastitis).
- Occasionally, a hypoechoic complex mass (phlegmon or developing abscess), or an organized thick walled complex fluid collection is present (frank abscess).

- Treatment includes:
  - Antibiotic therapy.
  - Ultrasound guided drainage.
  - This helps facilitate healing and also provides a sample for culture and sensitivity.
  - Surgical drainage in non-responsive cases.
- Piercing-associated breast infection
  - Body piercings in general have become more common.
  - This include nipple piercings.
  - Nipple piercing can cause local infection and disfiguration.
  - Staphylococcus and Streptococcus species are the common causative organisms.
  - Mycobacterium infection of the breast as a result of nipple piercings is extremely rare.
  - Treatment includes appropriate antibiotics and removal of the foreign body.
  - Aspiration under ultrasound guidance may be necessary in non-responding cases.

4.5 Fibrocystic Disease

- Cysts in the breast are most commonly seen in women between ages 35–50.
- They can also occur in children and adolescents but they are more common in the adolescent girls.
- Etiology:
  - The exact etiology of these cysts is not known.
  - These cysts may arise from dilatation of the lobular acini possibly due to imbalance of fluid secretion and resorption.
  - They may develop as a result of obstruction of the duct leading to the lobule.
- In children, these cysts are more commonly solitary.
- They often present as a palpable abnormality in the breast.
- Some girls notice breast tenderness and a feeling of "heaviness," especially before their menstrual periods.
- Physical findings may include a solitary breast lump or occasionally many small lumps throughout.
- These cysts can become infected and become tender.
- Ultrasound is the investigation of choice.
  - On ultrasound, if a simple cyst is demonstrated as an anechoic structure with imperceptible wall and posterior acoustic enhancement, benign diagnosis is confirmed and no further imaging or intervention is indicated.

  - If the cyst appears to be thick walled and or contains internal echoes, diagnostic considerations should include a complicated cyst, an abscess, a galactocele, or focal duct ectasia.

- Treatment:
  - Treatment is conservative.
  - Antibiotics are given when infection is suspected.

4.6 Breast Hematoma

- A hematoma is an area of localized hemorrhage.
- In children and adolescents, hematomas in the breast are often seen in conjunction with sports injuries, iatrogenic trauma, or activity related injuries such as bike handle bar injury.
- A clear history of trauma and signs of superficial bruising over the breast help confirm the diagnosis.
- Breast ultrasound:
  - On ultrasound, a hematoma can appear as a solid or complex cystic mass.
  - The sonographic appearance of a hematoma varies depending on the age of the hematoma.
  - A hematoma appears hyperechoic. It becomes progressively more anechoic as it regresses over time.
  - Because blood products can incite reactive changes, a hematoma can have irregular or even spiculated margins, mimicking malignancy.
- Treatment:
  - Treatment is conservative.
  - Follow up by ultrasound is recommended to ensure resolution.
  - Hematomas can become infected and antibiotics or sometimes incision and drainage may be necessary.

4.7 Galactocele

- Galactoceles are considered as retention milky cysts.
- They are most commonly seen in pregnant, lactating, or early post lactational women.
- Galactoceles can occasionally present in children and young infants with or without endocrinopathy.
- A galactocele results from occlusion of a lactiferous duct.

- Histologically they represent a cyst with walls lined by cuboidal to columnar epithelium.
- Galactoceles can persist up to several years post lactation.
- A galactocele on ultrasound appears as a complex cystic mass with variable internal echotexture depending on the relative milk (hyperechoic) versus water (hypoechoic/anechoic) contents.
- Occasionally, a fat-fluid level may be present, which is visualized on ultrasound as well as on mammography.
- This is diagnostic of a galactocele.
- The diagnosis of a galactocele depends on clinical history and imaging appearance.
- Once the diagnosis is confirmed, the treatment is conservative.
- Aspiration of milky fluid confirms the diagnosis of a galactocele if in doubt and provides symptomatic relief.

4.8 Benign Premature Thelarche

- Benign premature thelarche is defined as isolated breast development in females aged 6 months to 9 years (Figs. 4.11a, b and 4.12a–c).
- Physical examination should look for other signs of puberty:
  - Development of pubic hair
  - Thickening of the vaginal mucosa
  - Accelerated bone growth

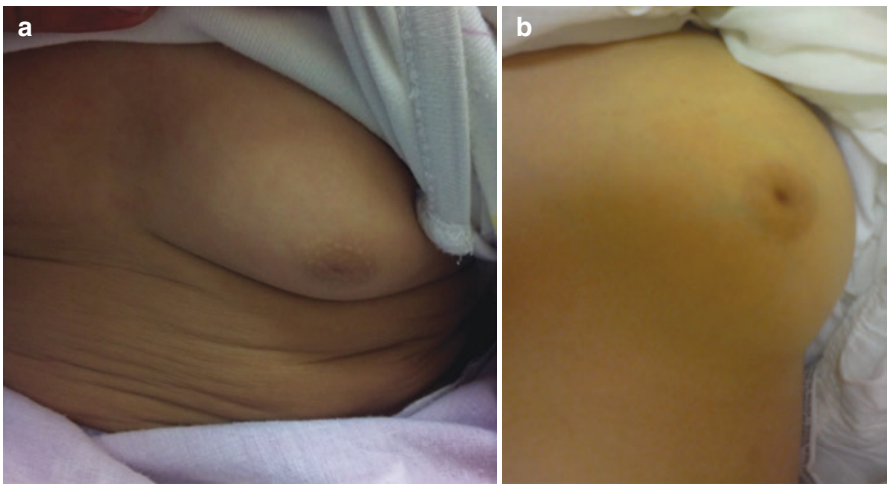


Fig. 4.11 (**a** and **b**) Clinical photographs showing two patients with premature breast development

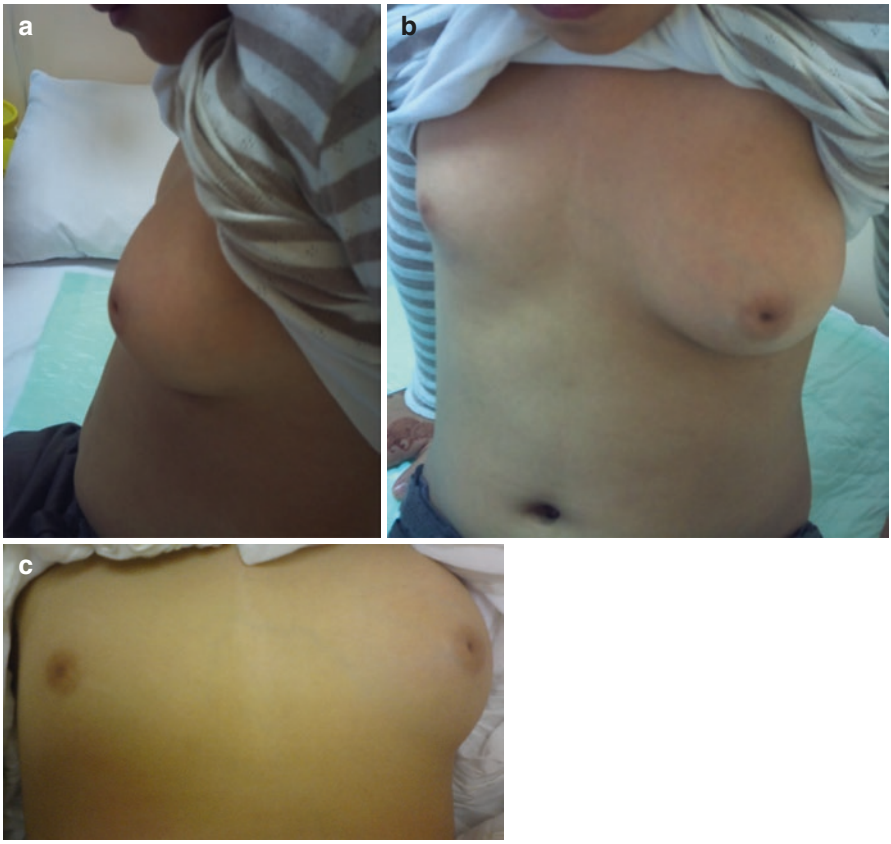


Fig. 4.12 (**a**–**c**) Clinical photographs showing premature breast development. This can be unilateral or bilateral. Note the unilateral normal looking and developed breasts in very young girls

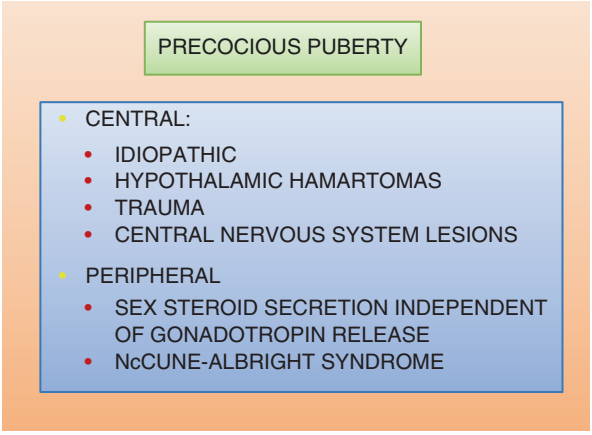
- If no other signs of puberty are present, reassure the patient and family that this is a benign condition.
- Examine the child every 6–12 months.
- If other signs of puberty are evident, precocious puberty should be considered as the diagnosis.

4.9 Precocious Puberty

- Early onset of puberty is more common in girls than in boys.
- It is predominantly mediated by premature activation of the hypothalamic-pituitary-gonadal axis.
- Central precocious puberty may be caused by:

  - It is most commonly idiopathic
  - Hypothalamic hamartomas
  - Trauma
  - Central nervous system (CNS) lesions

- Treatment involves continuous administration of exogenous gonadotropins.



- Peripheral precocious puberty is due to:

  - Sex steroid secretion independent of gonadotropin release
  - McCune-Albright syndrome

- When precocious puberty is suspected, tests for luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), thyroxine (T4), testosterone, and estradiol should be performed.

4.10 Mammary Duct Ectasia

- Mammary duct ectasia is a benign condition of the breast.
- Mammary duct ectasia is characterized by the followings:

  - Dilation of the mammary ducts
  - Periductal fibrosis
  - Inflammation

- Mammary duct ectasia has been described in infants, prepubertal boys and girls, and adult men and women.
- Clinical features include:

  - The usual presentation is with nipple discharge.
  - The nipple discharge may be bloody.

  - In children and adolescents, the lesion is usually unilateral.
  - The etiology of mammary duct ectasia is not known but infectious and inflammatory causes have been implicated in the etiology of mammary duct ectasia.
- Ultrasonographic findings:
  - These are usually suggestive of mammary duct ectasia.
  - The findings include dilated mammary ducts radially located around the nipple.
- Management:
  - Mammary duct ectasia is usually self-limited.
  - Surgery is usually not recommended if the diagnosis is certain.

4.11 Trauma

- Trauma to the breast can be iatrogenic or blunt.
- One of the causes of a palpable breast mass is trauma to the breast.
- The trauma causes fat necrosis, or breakdown of the adipose tissue.
- It is also important to remember that the history of trauma may be forgotten and while examining a traumatized breast, a mass may be discovered that was present prior to the event.
- In a traumatized breast, the clinically palpable mass is sometimes indistinguishable from a tumor.
- Ultrasonography, mammography, and even magnetic resonance imaging (MRI) of the breast may not be able to differentiate between these.
- A biopsy should be performed when there is doubt.
- The following features are seen in fat necrosis of the breast:
  - Peripheral calcifications
  - Fibrotic scar
  - Echogenic internal bands
- These features may also be consistent with breast cancer.
- Findings of lipid cysts or ultrasonographic evidence of fat necrosis may assist in the decision to monitor a palpable abnormality or perform a biopsy.

4.12 Fibrocystic Changes

- Fibrocystic changes of the breast are very common in the adolescent girls.
- They present as discrete breast cysts or diffuse, small lumps throughout the breast.
- This may be associated with breast tenderness and heaviness, especially before her menstrual period.

- Management:
  - Analgesia to control pain.
  - The patient is advised to avoid caffeine.
  - Evening primrose oil (1 tablespoon at bedtime) may be used to alleviate breast pain associated with fibrocystic changes of the breast.
  - A single dominant lump that is present for several months requires excisional biopsy.
  - Single dominant cysts may be aspirated.
  - Cytopathologic examination should be performed if the fluid is bloody.
  - Fibrocystic changes are histologically classified into the following three categories:

    Nonproliferative changes
    Proliferative changes without atypia
    Proliferative changes with atypia

  - Patients with proliferative changes and/or atypia have a higher risk for future malignancies.
  - Proliferative fibrocystic disease (described histologically as moderate or florid hyperplasia, sclerosing adenosis, or papilloma with a fibrovascular core) has been associated with a 1.5- to 2-fold increased risk of developing breast cancer.
  - The most substantial increase in risk of breast cancer is observed in patients with atypical or lobular hyperplasia.
  - This is associated with a 4.4-fold increase in cancer risk, which increases to 9-fold with a positive family history.
- Screening guidelines for patients with a history of atypia on breast biopsy findings include yearly physician examinations and yearly mammography.

4.13 Benign and Malignant Breast Tumors in Children and Adolescents

- It is important to stress that ultrasound is not useful in predicting histopathologic diagnosis, and so lesions that are suspicious for malignancy warrant a fine needle aspiration (FNA) and possible biopsy.

4.14 Fibroadenoma

- Breast masses in adolescent girls are infrequent and the majorities are benign.
- Fibroadenoma is the most common discrete breast mass.

- It accounts for 70–90% of breast masses seen in adolescent girls.
- Fibroadenomas are usually single but as many as 15% of patients may have multiple fibroadenomas.
- Fibroadenomas are benign fibroepithelial tumors and are the most common solid breast masses found in adolescent girls.
- Fibroadenomas arise from proliferation of specialized connective tissue stroma surrounding breast lobules.
- Fibroadenomas are estrogen sensitive tumors and may grow rapidly during puberty and pregnancy.
- The classic clinical presentation of a typical fibroadenoma is:
  - A nontender palpable mass
  - It is smooth and round
  - It is mobile rubbery
  - It is usually 2–3 cm in size
- They may occasionally become larger just before the patient's menstrual period.
- Risk factors for development of benign breast disease include:
  - High BMI
  - High-fat diet
  - Alcohol consumption during adolescence
- Ultrasonography is often used to help confirm the diagnosis.
- Mammography is not indicated and does not play a role in diagnosis due to the increased density of young breast tissue, and the risks of radiation exposure.
- At Ultrasonography:
  - Fibroadenomas are usually circumscribed, oval hypoechoic masses.
  - They may exhibit macro lobulations and become irregular in shape as they grow into larger masses.
  - A pseudo capsule may be seen in certain cases.
  - The internal echotexture of fibroadenomas can be either homogeneous or heterogeneous.
  - Posterior acoustic features vary.
- Complex fibroadenoma:
  - Rarely, a “complex fibroadenoma” has been described.
  - It appears less homogeneous on ultrasound.
  - Histologically, it contains foci of:

    Sclerosis
    Adenosis
    Papillary apocrine metaplasia, cyst, or calcifications

  - When present in children, complex fibroadenomas are associated with a minimally increased risk of developing breast cancer later in life.

- Management:
  - Breast masses with the characteristics of fibroadenoma may be serially monitored (every 1–3 months) with a careful physical examination.
  - An excisional biopsy may be performed if the patient and family are worried about it.
  - In the past most, palpable solid breast masses underwent biopsy despite benign features, but currently short-term follow-up of solid masses with probably benign sonographic features is a safe alternative to biopsy in the absence of atypical features or rapid enlargement.
  - A palpable breast mass meeting the criteria for a probably benign lesion at ultrasound has less than 1% chance of being malignant for all age groups, and the chance of such a lesion being malignant in a pediatric patient is even lower.
  - In a developing pediatric breast which is prone to iatrogenic injury, biopsy of a mass with typically benign sonographic features should be avoided.
  - Surgical excision remains indicated as follows:

    In a rapidly enlarging or symptomatic breast mass in children and adolescents regardless of benign sonographic features or initially benign pathology at biopsy, because a phyllodes tumor cannot be excluded.
    A probably benign appearing mass on ultrasound at initial presentation in children with a personal history of malignancy, prior local radiation, or genetic mutations known to increase risk of breast cancer such as BRCA1 or 2 mutations.
    The presence of any malignant features such as spiculation, microlobulation, angular margin, marked hypoechogenicity, or shadowing.
    Rarely, a "complex fibroadenoma" has been described, which appears less homogeneous on ultrasound and contains foci of sclerosis, adenosis, papillary apocrine metaplasia, cyst, or calcifications histologically.

- Juvenile, or giant, fibroadenoma:
  - An uncommon variant of breast fibroadenoma that is seen more commonly in African-American populations.
  - These are unusually large (>5 cm).
  - These can start small in size comparable in size to classic fibroadenomas, but often undergo rapid enlargement. When growth reaches greater than 5–10 cm, these lesions are referred to as juvenile giant fibroadenomas.
  - They usually display rapid growth but are in most cases benign.
  - Histologically, juvenile fibroadenomas have more cellularity than typical fibroadenomas. This is the reason they are also called cellular fibroadenoma.
  - Histologic features include stromal hypercellularity accompanied by intraductal epithelial hyperplasia.
  - They should be differentiated from phyllodes tumor (cystosarcoma phyllodes).
  - On ultrasonography, juvenile fibroadenomas appear similar to classic fibroadenomas, but demonstrate progressive growth and strikingly large size.
  - Management:

Given their frequent large size and rapid progressive growth, surgical excision is indicated.
This is also to exclude the possibility of a phyllodes tumor.
Definitive diagnosis of phyllodes tumors may be difficult in a core biopsy, often necessitating surgical excision for complete pathologic evaluation.

4.15 Pseudoangiomatous Stromal Hyperplasia (PASH)

- This is a benign proliferation of breast stroma with channels lined by thin spindle cells.
- The exact cause of this is not known.
- It is thought to be secondary to an exaggerated response from estrogen-primed breast tissue to progesterone.
- The management is conservative with close follow up and serial ultrasound evaluation.

4.16 Breast Hamartoma

- Hamartomas are benign tumors composed of disorganized mature breast tissue elements.
- Hamartomas are relatively common lesions seen in the adult breast, but they are rare in children and adolescents.
- Breast hamartomas may develop in patients with Cowden syndrome or may be an isolated finding in the adolescent patient.
- Hamartomas can grow to be very large in size (>10 cm) and this can be confused with a juvenile giant fibroadenoma.
- A hamartoma is a benign breast mass and there is no increased risk of developing later breast cancer.
- The clinical presentation is usually a painless mass, similar to that of the more common fibroadenoma.
- On ultrasound:
  - Hamartomas appear as well circumscribed oval or round masses.
  - They can be hypoechoic, isoechoic, or heterogeneous in echotexture,
  - Their ultrasound appearance mimics the appearance of the more common fibroadenoma.
- Mammography:
  - This is seldom used in children.
  - Mammography often shows a classic “breast within breast” appearance in hamartoma.

  - This is due to interspersed areas of radio dense fibro glandular components and radiolucent fatty components within an encapsulated mass.

- Histology:
  - Hamartomas appear as disorganized lobules and adipose tissue.
  - Hamartomas are made up of densely packed, enlarged lobules in a fibrous stroma.
  - There is usually a well-defined boundary between the lesion and normal surrounding breast tissue.
  - Hamartomas can be easily differentiated from fibroadenomas when representative tissue is available from core biopsy sampling.
  - Fibroadenomas are histologically characterized by proliferation of specialized stroma around lobules. Lobules and fat are usually not present in a fibroadenoma.
  - Occasionally however, hamartomas may be difficult to distinguish from fibroepithelial lesions at core needle biopsy, as hamartomatous elements can mimic normal background breast tissue, particularly if tissue sample is inadequate.
- Management:
  - Hamartomas should be included in the differential diagnosis of a probably benign appearing breast mass on ultrasound.
  - Breast hamartomas are to be treated conservatively and it is safe to follow them up in children and adolescents.
  - Surgical excision is indicated if the lesion undergoes rapid progressive growth.
  - It is important to remember that hamartomas can recur if excision is incomplete.

4.17 Intraductal Papilloma (Solitary Central Papilloma)

- Intraductal papilloma represents a mass within a lactiferous duct as a result of epithelial proliferation.
- Intraductal papillomas are very rare in children.
- They are usually solitary.
- Commonly, they are located in a subareolar duct.
- Histology:
  - A papilloma is a mass made up of multiple papillary structures, each defined by a fibrovascular core made up of connective tissue and small blood vessels, and lined by benign epithelium.
- They often cause post obstructive ductal dilatation.
- The clinical presentation is usually spontaneous serous or serosanguinous nipple discharge.

- On ultrasonography:
  - Intraductal papilloma appears as a solid intraductal mass.
  - The mass is seen within a dilated duct filled with anechoic fluid.
  - Occasionally, there is associated increased vascularity.
- Treatment:
  - Surgical excision is the treatment of choice.
  - This is also to exclude rarely associated malignancy.

4.18 Juvenile Papillomatosis (Multiple Peripheral Papillomas)

- Juvenile papillomatosis is a very rare condition.
- Juvenile papillomatosis is a localized proliferative process in the breast, in which multiple peripheral papillomas are present in peripheral ducts.
- This is distinct from intraductal papilloma, in which a solitary central intraductal papilloma is present in a central subareolar duct.
- Juvenile papillomatosis is considered a marker for familial breast cancer.
- These patients present similarly to fibroadenoma.
- They can be differentiated from fibroadenoma by ultrasonography.
- Histology:
  - Juvenile papillomatosis lacks the fibrovascular core which is typical in the central papilloma.
- On ultrasonography:
  - Papillomatosis may appear as ill-defined irregular hypoechoic tissue or masses, occasionally containing cystic spaces.
  - These lesions are heterogenous with a “Swiss cheese” like appearance.
  - There may be associated clustered microcalcifications.
- On MRI:
  - Papillomatosis presents as lobulated masses with cystic spaces well seen on T2 weighted sequences which enhance with gadolinium.
- Treatment:
  - Juvenile papillomatosis is a benign condition but is associated with carcinoma in up to 15% of the cases; therefore adequate surgical resection should be done to prevent recurrence.
  - A disproportionate number of patients with juvenile papillomatosis have family history of breast cancer (up to 58%) and these patients should be closely monitored due to increased risk of developing breast cancer later in life.

4.19 Fibrous Nodule

- Fibrous nodules are benign breast lesions.
- They are made up of focally dense collagenous stroma surrounding atrophic epithelial elements.
- They most commonly present as firm palpable masses in premenopausal women, but rarely may be seen in the pediatric population.
- Other names synonymous with fibrous nodule include:
  - Focal fibrosis
  - Fibrous disease
  - Fibrous mastopathy
  - Fibrosis of the breast
  - Fibrous tumor
- They appear as small noncalcified lesions usually 0.6–3.5 cm in size.
- They are seen on ultrasound as solid hypoechoic masses with circumscribed or indistinct, and occasionally irregular margins.
- Histology:
  - These lesions are made up of dense fibroconnective tissue similar to that in adjacent breast tissue with scant or absent adipose tissue.
  - Absence of features of other stromal lesions such as pseudoangiomatous stromal hyperplasia, fibroadenoma, lymphocytic or diabetic mastopathy, nodular fasciitis, fibromatosis, or myofibroblastoma.
- Management:
  - The treatment is conservative.
  - Periodic imaging surveillance.
  - If there are any imaging features suspicious for malignancy, excisional biopsy should be considered.

4.20 Phyllodes Tumor (Cystosarcoma Phyllodes)

- This is the most common breast malignancy in adolescents.
- Phyllodes tumors are rare, but nevertheless represent the most common primary breast malignancy in children and adolescents.
- Phyllodes tumors are rare fibroepithelial lesions which arise from the specialized connective tissues around mammary lobules.
- Phyllodes tumors were previously termed cystosarcoma phyllodes due to their cystic appearance and sarcoma-like characteristics including a propensity for hematogenous spread, therefore metastasizing to the lung rather than axillary lymph nodes.
- Like fibroadenomas, Phyllodes tumors arise from the lobular tissue.

- Ultrasonography cannot usually be used to distinguish between a fibroadenoma and a phyllodes tumor.
- The differentiation between a fibroadenoma and a phyllodes tumor lies in histologic examination.
- Phyllodes tumors have a more cellular stroma with nuclear atypia and mitotic figures.
- As many as 25% of phyllodes tumors are considered malignant.
- The degree of malignancy can be predicted by:
  - The presence of sarcomatous elements
  - The presence of infiltrative margins
  - The presence of stromal cell atypia
- For Phyllodes tumor, radiological investigations and FNA are not accurate and do not distinguish between benign and malignant forms and ultrasound-guided core needle biopsy is indicated in the management of these patients.
- The usual presentation of Phyllodes tumor is:
  - A painless breast mass.
  - The patient may give a history of sudden enlargement of a previously stable breast mass.
  - The mass may reach a large size with thinning of overlying skin.
  - There may be an increased vascularity of the area.
  - Phyllodes tumors tend to be large (>6 cm) at clinical presentation.
  - They appear as circumscribed, oval or round masses.
  - On ultrasound, they are hypoechoic or heterogeneous, often with posterior acoustic enhancement.
- Histology:
  - Phyllodes tumors are histologically categorized into:

    Low-grade
    Intermediate-grade
    High-grade (malignant)

  - All of which may recur.
  - They rarely, metastasize.
  - Classification of Phyllodes tumors into benign and malignant lesions is occasionally used.
  - There is significant clinical, imaging, and histologic overlap between phyllodes tumors and juvenile fibroadenomas.
  - Any rapidly enlarging breast mass should be biopsied to exclude phyllodes tumor.
  - Phyllodes tumors exhibit an overall variegated architecture and consist of fronds (cellular stromal tissue lined by epithelium), allowing for cystic or cleft-like spaces between abutting fronds on ultrasound.
  - The presence of intralesional cysts and clefts are highly suggestive of the diagnosis, although these may also be present in juvenile fibroadenomas.

- Management:
  - Ultrasound guided biopsy is indicated in any large or rapidly enlarging breast mass in children.
  - Surgical excision with wide margins is required for all phyllodes tumors.
  - Low grade phyllodes tumors are generally associated with lower rate of recurrence.
  - In children, recurrence rate of phyllodes tumor is even lower, estimated at approximately 10%.
  - Local recurrence does not alter prognosis.
  - Histologic features of phyllodes tumors include increased stromal cellularity, cellular atypia, stromal overgrowth, and presence of sarcomatous elements, the latter of which used to define the malignant type.
  - The management of a benign or malignant phyllodes tumor involves wide excision with a margin of normal breast tissue.
  - Malignant phyllodes tumors metastasize to the lungs and rarely metastasize to the axillary lymph nodes.
  - Axillary dissections are indicated for patients with palpable lymph nodes.

4.21 Metastatic Breast Tumors

- Metastases to the breast in children and adolescence girls are more common than primary breast cancers.
- Primary breast carcinoma is extremely rare in children and adolescence girls.
- The average American female has an 11% lifetime risk of developing breast cancer.
- The risk in a first-degree relative (i.e., mother, sister, daughter) of a breast cancer patient is 2- to 3-fold greater.
- This risk increases to 9-fold when the patient has bilateral premenopausal breast cancer.
- Other primary malignancies of the breast include rhabdomyosarcoma and Hodgkin disease.
- Metastatic breast disease in children is more often from a rhabdomyosarcoma.
- The following malignancies are the most common primary tumors that metastasize to the breast:
  - Lymphoma
  - Leukemia
  - Rhabdomyosarcoma
  - Neuroblastoma
  - Ewing sarcoma
  - Melanoma
  - Renal cell carcinoma

- An enlarging breast mass in a child with a known history of primary malignancy should be biopsied even if probably benign on ultrasonographic appearance.
- Metastatic disease in the breast can be solitary or multiple masses, involving one or both breasts.
- Radiology:
  - Imaging appearances of metastatic lesions in the breast are variable.
  - Ultrasound may show a circumscribed mass or a mass with irregular margins which is heterogeneous or hypoechoic in echotexture.
  - Mammography is less relevant in the pediatric population, but can show a circumscribed, partially obscured mass.
- Hematologic malignancy, cutaneous T-cell lymphoma, Lymphoma and leukemia are among the most common malignancies to metastasize to the breast secondarily.
- Primary breast lymphoma
  - This is extremely rare and usually manifests as non-Hodgkin's lymphoma.
  - Of the primary breast lymphomas, the majority are of B-cell type (Burkitt's).
  - T-cell lymphomas are exceedingly rare.
  - Cutaneous T-cell lymphomas are an uncommon subgroup of non-Hodgkin's lymphoma that arises primarily in the skin and can rarely present as a breast mass with or without involvement of axillary lymph nodes.
  - Cutaneous T-cell lymphomas account for about 4% of all cases of non-Hodgkin's lymphoma.
  - The age-adjusted annual incidence of cutaneous T-cell lymphoma is approximately six cases per million.
  - Cutaneous T-cell lymphomas increase in incidence with age and primarily affect adults, but can affect people of all ages, including children.
  - More indolent subtypes of Cutaneous T-cell lymphomas include:

    Mycosis fungoides
    Primary cutaneous anaplastic large cell lymphoma
    Lymphomatoid papulosis
    Subcutaneous panniculitis-like T cell lymphoma
    Primary cutaneous CD4+ small/medium pleomorphic T cellymphoma

  - Aggressive subtypes of Cutaneous T-cell lymphomas include:

    Sézary syndrome
    Primary cutaneous CD8+ aggressive epidermotropic T cell lymphoma
    Primary cutaneous gamma/delta T cell lymphoma
    Extranodal natural killer/T cell lymphoma.

  - Clinical features:

    Physical exam may show palpable masses or persistent papular rash involving the skin.

Comprehensive physical examination including a thorough skin examination is indicated to assess for multifocal disease.
These masses are hypervascular and often appear hypoechoic/anechoic but may appear hyperechoic on ultrasound.
They also enhance on MRI and are FDG avid on PET CT.
Mammography plays a minor role in children, but Cutaneous T-cell lymphomas appears as multiple and occasionally solitary superficial irregular masses.

– Treatment:

Systemic and topical therapy.
Stem cell transplantation is reserved for refractory, progressive cases.

4.22 Primary Breast Carcinoma

- It is important to understand that the spectrum of pediatric breast disease differs from that of the adult breast.
- Knowledge of common and uncommon benign and malignant pediatric breast lesions and their appearances clinically and on imaging is important for the proper diagnosis and management.
- When a patient presents with a breast mass, it is very important to document the followings:
  - Family history of breast and ovarian malignancies
  - Family history of *BRCA1* or *BRCA2* mutations
  - Previous history of malignancy
  - Previous chest irradiation
  - History of trauma
  - History of other breast masses
- It is important to document the following clinical features of the breast masses:
  - The size.
  - The contour, whether smooth or irregular.
  - Changes in the overlying skin including dimpling, edema and erythema.
  - Fixation of the mass.
  - The presence of axillary, infraclavicular, supraclavicular enlarged lymph nodes.
- Adolescent females who carry *BRCA1* or *BRCA2* gene mutations should begin routine clinical breast evaluation and screening at age 20 years.
- Ultrasonography:
  - The breast tissue in young children is very dense and because of this mammography is not usually very helpful.

  - Ultrasonography is more effective at delineating masses within the immature breast.
  - Color Doppler ultrasonography may increase the specificity of the diagnosis:

    Cysts are avascular.
    Fibroadenomas are hypovascular.
    Abscesses show increased peripheral flow.

  - Ultrasonographic findings alone may guide management in most cystic and solid-cystic lesions.
  - Fine-needle aspiration under ultrasound guidance may be performed to manage breast cysts.

- Magnetic Resonance Imaging:

  - Magnetic resonance imaging (MRI) with gadolinium-based enhancement is a new investigation for studying breast disease.
  - In women with a high risk of breast cancer, breast MRI has high sensitivity (88%) but only moderate specificity (67%).
  - In patients aged 25 years or older, guidelines recommend annual MRI as an adjunct to mammography in women at high risk, including the following:

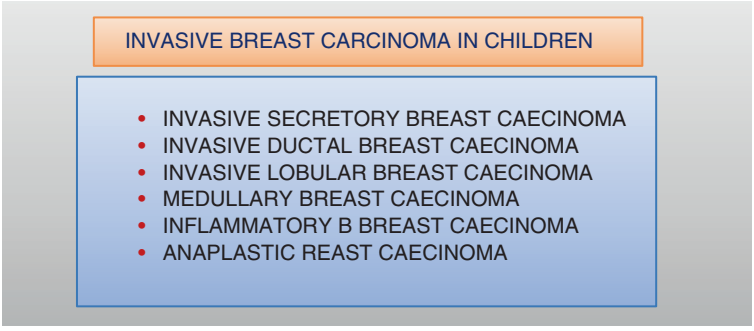
    Women with a *BRCA* mutation.
    First-degree relatives of a *BRCA* carrier.
    Women with a lifetime risk of 20–25%.
    Women who received radiation to the chest between ages 10 and 30 years.
    Women with Li-Fraumeni syndrome, Cowden syndrome, or Bannayan-Riley-Ruvalcaba syndrome or first-degree relatives of individuals with those syndromes.

- Biopsy:

  - In very young and preadolescent children, a biopsy should be considered with extreme caution because the developing breast bud may be irreparably damaged, even with a needle aspirate.
  - Discrete masses should almost always be removed in postpubertal girls.
  - Excisional biopsies are usually performed via a circumareolar incision.
  - If the mass is located away from the areola, an incision directly overlying the mass may be used.

- Primary breast carcinomas are exceedingly rare in the pediatric and adolescence breast.
- Metastatic disease is more common than primary breast malignancy.
- Primary breast carcinoma comprises <1% of childhood breast cancers.
- These are usually secretory, which are less invasive than ductal breast carcinoma.
- The exact incidence of primary breast cancer is not known but the estimated incidence is approximately 0.1 cases per million in females younger than 20 years of age.

- There are different types of invasive breast carcinoma in children.
- These include:
  - Invasive secretory breast carcinoma
  - Invasive ductal breast carcinoma
  - Invasive lobular breast carcinoma
  - Medullary breast carcinoma
  - Inflammatory breast carcinoma
  - Anaplastic breast carcinomas
- The most common subtype of invasive breast carcinoma in children is invasive secretory breast carcinoma.
- This carries a more favorable prognosis as compared to the less common subtypes of breast cancer seen in children which include:
  - Invasive ductal
  - Invasive lobular
  - Medullary, inflammatory, and anaplastic carcinomas
- Secretory breast carcinomas present as a painless palpable small circumscribed mass (usually <3 cm).
- Ultrasonography:
  - They typically appear as circumscribed or partially microlobulated hypoechoic masses with heterogeneous internal echotexture.
- Histology:
  - Secretory breast carcinoma contains bubbles of secretory components or cytoplasmic vacuoles on histology, which are characteristically positive by PAS stain.



- Treatment
  - Treatment includes surgical excision
  - Sentinel lymph node biopsy
  - Systemic adjuvant therapy depending on the disease extent

  - Initial surgical options for infiltrating lobular or intraductal carcinoma in adolescents include breast-sparing surgery (i.e., lumpectomy with axillary node dissection and irradiation) and modified radical mastectomy.
  - Younger women tend to have more aggressive disease.
  - Systemic adjuvant chemotherapy is strongly advised in all young women with breast carcinoma.

- Post radiation breast cancer:
  - Children who receive high dose radiotherapy for Hodgkin's disease are at significantly increased risk for developing breast cancer later in life.
  - It is estimated that these children have a cumulative incidence of breast cancer of 12–20% by about age 40.
  - This is comparable to that in the BRCA (breast cancer susceptibility) gene mutation which carriers a 10–19% risk.
  - This is in contrast to the general population of women of the same age group who have a cumulative incidence of breast cancer of 1%.
  - Young women at the greatest risk are those treated with radiotherapy between ages 10–16. These patients are at risk of developing tumors in the radiation field.
  - The risk of breast cancer in these patients increases with years post irradiation.
  - It is important for these patients to be followed up with routine screening.

    The American College of Radiology guidelines.
    Screening includes annual mammogram with adjunctive MRI in young women at least 25 years of age, 8–10 years following completion of radiotherapy.
    The imaging appearance of breast cancer arising after radiotherapy is not different from other primary breast cancers.

  - Exposure to ionizing radiation has been shown to increase breast cancer risk.
  - The patient's age during radiotherapy exposure is correlated to the risk.
  - The highest risk is posed to the adolescent.
  - Radiotherapy exposure for women older than 40 years only minimally increases the risk.
  - Women aged 25 years or older who were exposed to radiotherapy before age 30 years should be examined by a physician twice a year and should undergo annual mammography and magnetic resonance imaging (MRI) beginning 8 years after radiation exposure.
  - The lag of 8 years is because of the long latency period of radiation damage to tissue.
  - Because mammography has limited use in evaluating dense breast tissue, only twice-yearly physician examinations are recommended in patients younger than 25 years.

- Hereditary breast cancer/Cowden syndrome:
  - Approximately 10% breast cancers are hereditary.

- There are known associated factors which include:

  BRCA1 and BRCA2 mutations
  TP53 mutations in LiFraumeni syndrome
  STK11 mutations in Peutz-Jeghers syndrome
  PTEN mutations in Cowden syndrome

- The hallmark of hereditary breast cancer is early onset of disease.
- This highlights the importance of early screening for these patients.
- Cowden syndrome is also known as multiple hamartoma syndrome.
- The spectrum of hamartomatous overgrowth syndromes which include the Bannayan-Riley-Ruvalcaba syndrome and Cowden syndrome are associated with germ line mutations in the tumor suppressor PTEN gene which is located on 10q23.3 and inherited as an autosomal dominant inheritance.
- It is important to note that not all patients with clinical diagnosis of Cowden syndrome have an identifiable PTEN mutation.
- PTEN mutation carriers are at significantly increased risks for developing:

  Breast carcinoma
  Thyroid carcinoma
  Endometrial carcinoma
  Renal cell carcinomas

- Patients with Cowden syndrome carry a cumulative breast cancer risk of 77% by age 70.
- This markedly elevated risks for breast cancer in these patients calls for clinical breast examination and screening breast ultrasound at age 25, and starting screening mammogram and MRI at age 30 or 5 years before earliest known breast cancer in the family.

4.23 Genetics

- It is estimated that only 5% of all breast cancer patients have true hereditary breast cancer.
- Families with hereditary breast cancer have the following characteristics:
  - Early onset of breast cancer—Usually before age 45 years.
  - Increased incidence of bilateral breast cancer.
  - Autosomal dominant inheritance for breast cancer.
  - Increased frequency of multiple primary cancers.
- Adolescents of a parent with hereditary breast cancer have a 50% chance of inheriting the causative gene.
- Current recommendations suggest that mature young women consider genetic testing for the purposes of family and life planning.

- Genetic testing may be delayed until childbearing is complete or until age 35 years or older.
- Two breast cancer susceptibility genes have been mapped:
  - BRCA1 has linkage with breast, ovarian, and prostate cancers.
  - The BRCA1 gene confers an 83% breast cancer risk and a 63% ovarian cancer risk by age 70 years.
  - BRCA2 has linkage with male and female breast cancers.
  - Overall, the lifetime risk of developing breast cancer in known BRCA1 and BRCA2 carriers is 60–80%.
- Li-Fraumeni syndrome:
  - Patients with Li-Fraumeni syndrome are known to have an increased susceptibility to breast cancer.
  - Families with Li-Fraumeni syndrome have *p53* mutations, which are associated with an increased risk for:

    Sarcomas
    Breast cancer
    Lung cancer
    Laryngeal cancer
    Leukemia
    Adrenal cortical carcinoma

  - The pattern of inheritance is autosomal dominant.
  - Breast cancer develops in 77% of women with Li-Fraumeni syndrome between age 22 and 45 years, with 25% developing bilateral disease.
  - Rarely, breast cancer may develop in the teenaged patient.
- Cowden disease:
  - Cowden disease is characterized by:

    Multiple benign keratoses located at the mucocutaneous sites on the face, hands, feet, and forearms
    Goiter
    Lipomas
    Uterine leiomyomas
    Infiltrating breast ductal carcinoma of the breast may develop in 30% of these women
    Bilateral infiltrating breast ductal carcinomas may develop in one third of these patients
- Ataxia-telangiectasia:
  - Ataxia-telangiectasia syndrome is characterized by:

    Multiple telangiectasias
    Immune dysfunction

Sensitivity to ionizing radiation due to chromosomal fragility
Progressive neuromuscular deterioration
Heterozygotic individuals have a 5-fold greater risk of developing breast cancer

- Mutations of genes associated with inherited forms of colon cancer (i.e., MSH2, MLH1) are associated with multiple skin malignancies, gastrointestinal malignancies, and breast cancer.

4.24 Screening

- Screening recommendations for families with hereditary breast cancer (i.e., BRCA1, BRCA2, Li-Fraumeni) include:
  - Examination by a physician twice a year.
  - Screening mammography should be performed once or twice yearly beginning when the patient is aged 10 years younger than the youngest affected relative or no older than age 35 years.
  - Patients who have positive test findings for the BRCA1 or BRCA2 genes may opt to undergo prophylactic bilateral mastectomies, which is associated with an approximately 90% reduction in the risk of breast cancer.
  - Depending on the age at diagnosis in the first-degree relative, prophylactic mastectomies may be delayed until age 35 years or until childbearing is complete.

4.25 Chest Wall Malignancies

- Chest wall malignancies in children may occasionally involve the breast via contiguous growth or locoregional metastasis (Fig. 4.13a–c).
- The most frequent chest wall malignancies in children are the:
  - Malignant small round cell tumors (Ewing's sarcoma, PNET/Primitive Neuroectodermal Tumor)
  - Rhabdomyosarcoma
  - Osteosarcoma
  - Chondrosarcoma

- The diagnosis depends on cross sectional imaging such as CT, MR, or FDG PET.
- Treatment:
  - Local surgical resection and adjuvant chemotherapy.

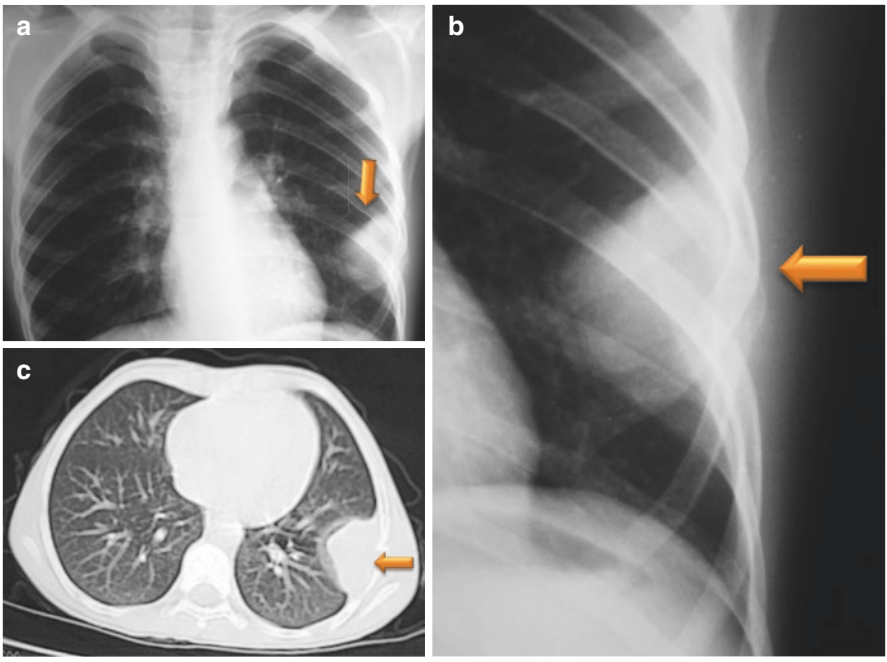


Fig. 4.13 (**a**–**c**) Chest x-rays and CT-Scan showing Askin's tumor of the chest wall (Askin's tumor is a primitive neuroectodermal tumor developing from the soft tissues of the chest wall)

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Chapter 5
Fused Labia (Labial Adhesions)

Ahmed H. Al-Salem

5.1 Introduction

- Labial fusion is a medical condition of the female genital anatomy where the labia minora become fused together (Fig. 5.1a, b).
- It is also called labial adhesion or fused labia, labial synechiae, labial agglutination, labial adherence, gynatresia, vulvar fusion, and vulvar synechi.
- Labial fusion is a relatively common condition that can cause significant distress to parents because of worries regarding the normality of their daughter's genitalia.
- Labial fusion is never present at birth, but rather acquired later in infancy.
  - This is typically seen in girls between the ages of 3 months and 6 years old.
  - The highest incidence of labial fusion is between the ages of 13 and 23 months.
- The exact etiology is not known. It is caused by insufficient exposure to estrogen.
  - Fused labia occur when estrogen levels are low and are therefore extremely rare in the first 3 months of life when maternal estrogens are still abundant in the infant's circulation.
- The condition is self-limiting and corrects itself naturally in early puberty when the endogenous production of estrogen starts.
- Labial adhesions can partially or completely block the opening to the vagina and rarely the opening of the urethra.
- Most of the time, labial adhesions do not cause any symptoms and may be noticed by the mother while cleaning or bathing the child.
- Labial adhesions do not cause long term issues and most of the time adhesions do not require any treatment.

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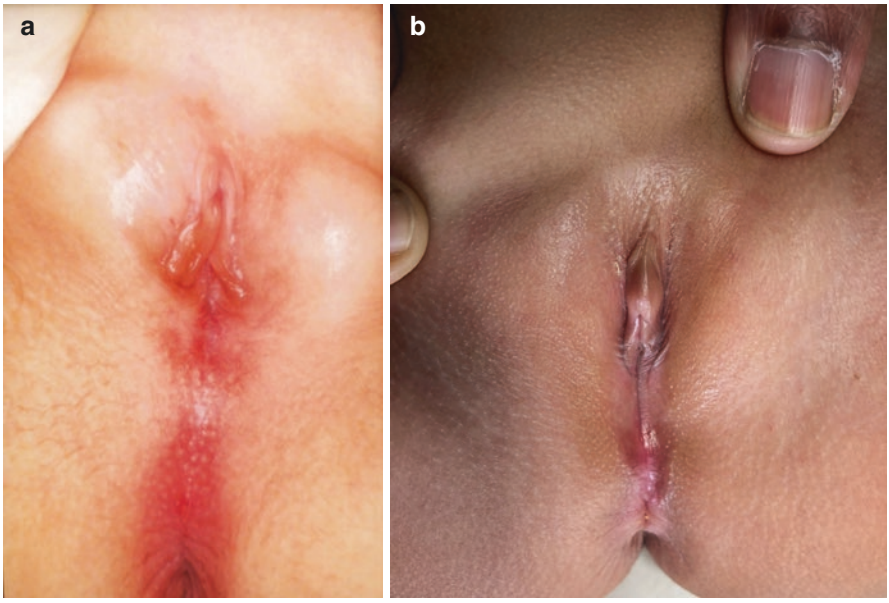


Fig. 5.1 (**a** and **b**) Clinical photographs showing labial adhesions (Fused labia). Note the almost completely closed vaginal opening. These girls pass urine from a small opening just below the clitoris

- Rarely patients may complain of the followings:
  - Changes in the urine stream
  - Post-void dribbling of urine
  - Dysuria and urinary frequency
  - Vaginal discharge
  - Urinary tract infection
  - In severe cases, labial adhesions can cause complete obstruction of the urethra, leading to urinary retention

5.2 Incidence

- The exact incidence of labial adhesions is not known.
- They are much more common than many might realize and it is estimated that about 2 out of every 1000 girls will develop labial adhesions before they reach puberty.
- Others estimate that labial fusion occurs in 1.8% of all prepubertal girls.

5.3 Etiology

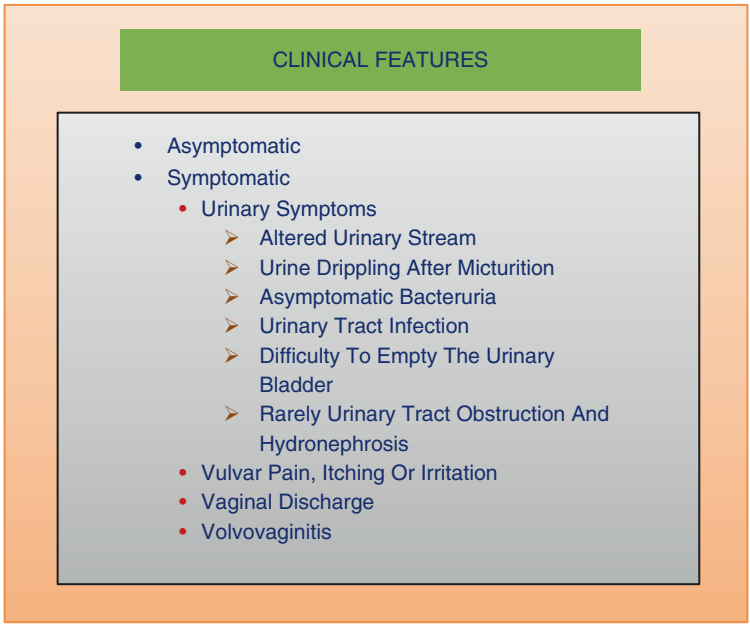
- The exact etiology of labial adhesions is not known.
- It is believed that labial adhesions develop from a combination of inflammation, trauma or infection that occurs in a low estrogen environment.
  - Normally, newborns have estrogen in their bodies from their mothers.
  - This estrogen level can take several months to decrease.
  - Labial adhesions are most likely to first appear between the ages of 13 and 23 months.

    This is the time when the estrogen from the mother has disappeared and also the time when babies are becoming more physically active.
  - So trauma or infection in the presence of a low estrogen influences the development of labial adhesions.
- The fusion typically begins at the posterior frenulum of the labia minora and continues anteriorly.
- This usually leaves an anterior opening below the clitoris where the child passes urine through.
- Labial adhesions have been associated with lichen sclerosus; in which adhesions are characteristically dense and difficult to treat and can persist into puberty and adulthood.

5.4 Clinical Features

- Most children with labial adhesions are asymptomatic.
- The labial adhesions are usually discovered by the mother while cleaning, changing the diaper or bathing the baby.
- Sometimes adhesions are discovered by a physician during routine clinical evaluation.
- Sometimes, labial adhesions become symptomatic depending on the degree of adhesions.
- These children may complain of:
  - Vulvar pain, itching or irritation
  - Difficulty to empty the urinary bladder
  - Urine dribbling well after they have finished passing urine
  - Recurrent urinary tract infections
  - Vaginal discharge

- Clinical evaluation reveals that the inner lips of the labia (labia minora) are stuck together.
- The extent of these adhesions is variable.



5.5 Treatment

- Asymptomatic labial adhesions can be treated conservatively.
- These adhesions may unstick on their own while waiting or during puberty when the child starts to produce her own estrogen.
- Symptomatic adhesions can be treated locally with estrogen or steroid cream.
- The standard method of treatment for labial fusion is the application of topical estrogen cream onto the areas of adhesion such as estriol 0.1% cream.
- This is effective in 90% of patients (50–100%) depending mostly on the density of the adhesions, the duration of estrogen application and whether or not there has been prior treatment and recurrence.
- Estrogen can have side effects and only a tiny amount of the cream is used, and for a short time (no longer than 6 weeks).
- Side effects such as breast budding, uterine bleeding and local skin discoloration or erythema have been reported. All of these effects regress promptly after discontinuation of the medication.
- Parents can be instructed to apply gentle pressure to the adhesion while applying the cream to help the labia become unstuck.

- In severe cases where the labia minora are entirely fused, causing urinary outflow obstruction or vaginal obstruction, the labia should be separated surgically (Figs. 5.2a, b, 5.3a, b, 5.4a, b).
- Recurrence after treatment is common but is thought to be prevented by good hygiene practices.

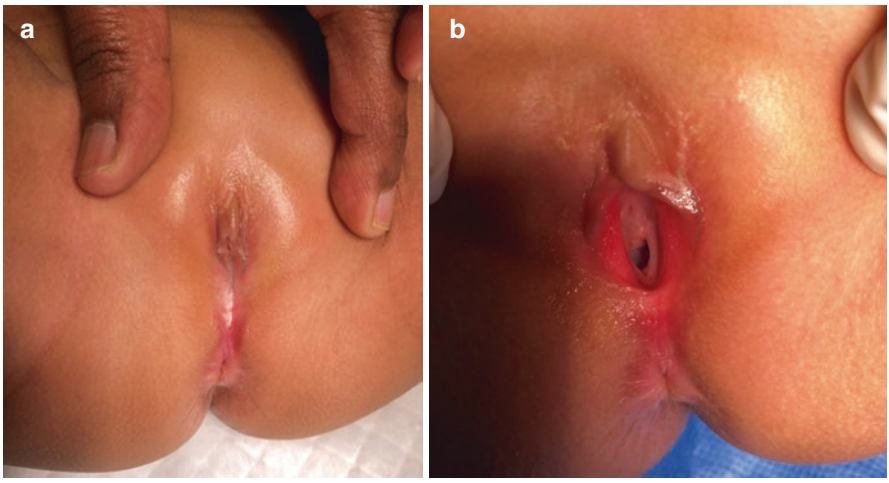


Fig. 5.2 (**a** and **b**) Clinical photographs showing a girl with fused labia that was separated manually under general anesthesia. Note the almost closed vaginal introitous and the normal looking hymen and vaginal introtous following separation

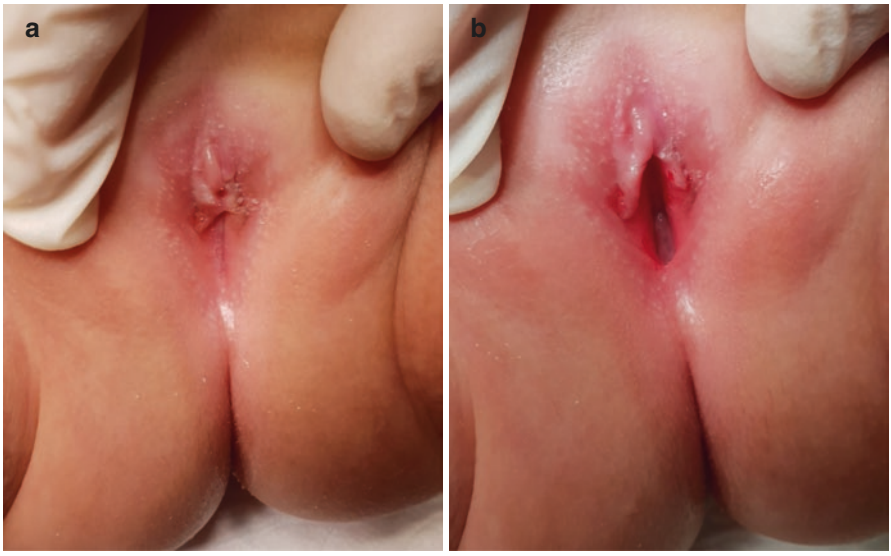


Fig. 5.3 (**a** and **b**) Clinical photographs showing a girl with fused labia that was separated manually. Note the almost closed vaginal introitous

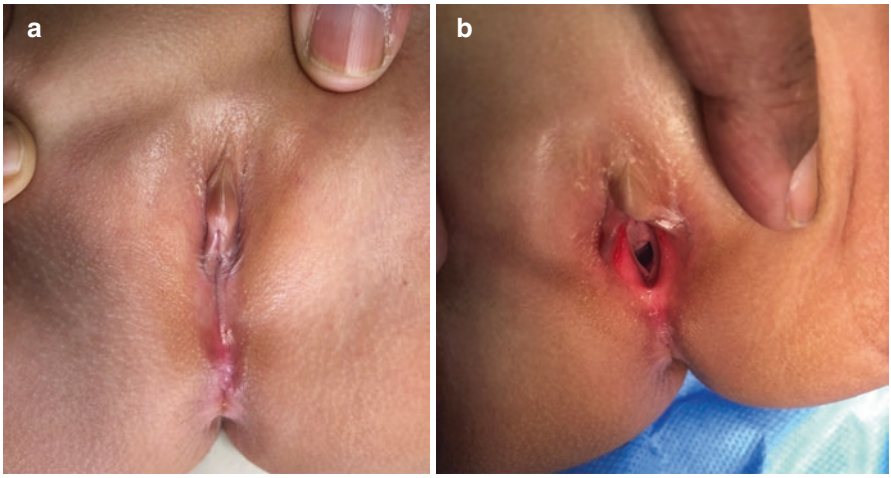


Fig. 5.4 (**a** and **b**) Clinical photographs showing a girl with fused labia that were separated manually

- Many physicians will also instruct the parents to apply estrogen cream after manual separation to prevent recurrence.
- Others advocate using betamethasone which may be more effective than estrogen cream in preventing recurrence, with fewer side effects.
- Severe labial adhesions can be separated manually under local or general anesthesia. This is especially for older children.
- Separation using local anesthesia is painful and traumatizing to the child and a brief general anesthesia is preferable.
- The adhesions are divided by using gentle labial traction or by running a sound along the line of fusion. There is usually no or minimal blood loss and suturing is not usually necessary.
- Recurrence is a common problem in labial adhesions after both application of estrogen cream and surgical separation.
- Recurrence rates range between 10–16%, depending on the method of treatment.
- Where vulvovaginitis or urinary tract infection coexists, a swab should be taken from the introitus and urine for culture and, if a pathogen is isolated, appropriate antibiotic treatment should be instituted.
- Lichen sclerosus leads to a typical appearance of the vulva, with parchment-like areas and foci of inflammation that look like ‘blood blisters’. Initial treatment will usually include local potent steroid cream application.

Further Reading

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Chapter 6
Imperforate Hymen

Ahmed H. Al-Salem

6.1 Introduction

- Most females are born with a hymen, which is a solid membrane located at the entrance of the vaginal opening.
- The hymen generally has a ring-like appearance with a small opening.
- Most girls have a small crescent- or donut-shaped opening in their hymen (Fig. 6.1a, b).
- An imperforate hymen is a congenital anomaly caused by a failure of the hymen to perforate during fetal development leading to complete obstruction of the vagina.
- This was first described by Ambroise Pare in 1633.
- Embryologically and as a consequence of normal development sometimes the central portion of the hymenal membrane is absent and persistence of the intact hymenal membrane results in imperforate hymen.
- Imperforate hymen is the most common and most distal form of vaginal outflow obstruction.
- The exact incidence of imperforate hymen is not known as many of these patients become symptomatic at adolescence when they begin their menstrual period.
- It has been estimated that approximately 1 in 1000 girls are born with an imperforate hymen.
- An imperforate hymen is most often diagnosed in adolescent girls after the age of menarche with otherwise normal genital development.

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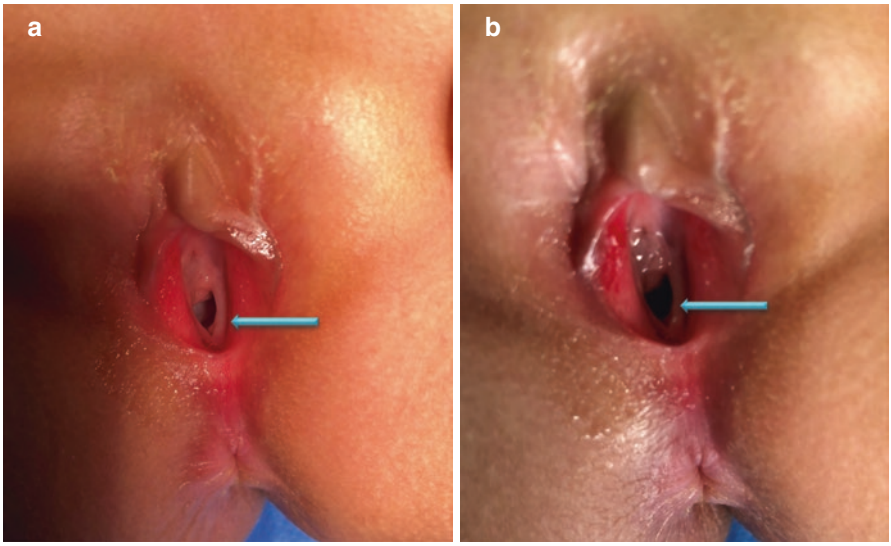


Fig. 6.1 (**a** and **b**) Clinical photographs of two girls showing a normal looking hymen

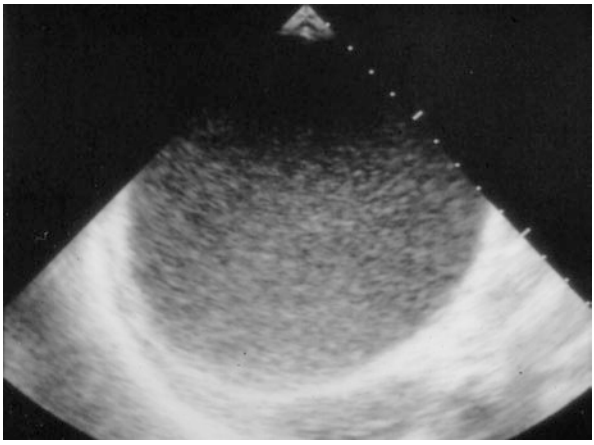


Fig. 6.2 An abdominal and pelvic ultrasound showing hydrcolpos in a girl with imperforate hymen

  - The usual presentation in these is amenorrhea and cyclic pelvic pain, indicative of hematocolpos secondary to vaginal outflow obstruction.
  - Vaginal atresia and a transverse vaginal septum must be excluded.

- An imperforate hymen can also be diagnosed in newborn babies.
  - The diagnosis of imperforate hymen is occasionally made on antenatal ultrasound scans of the fetus during pregnancy.
  - In newborns the diagnosis of imperforate hymen is based on the findings of:

    An abdominal or pelvic mass (Figs. 6.2 and 6.3).
    A bulging hymen. This is indicative of hydrocolpos or mucocolpos (Fig. 6.4).

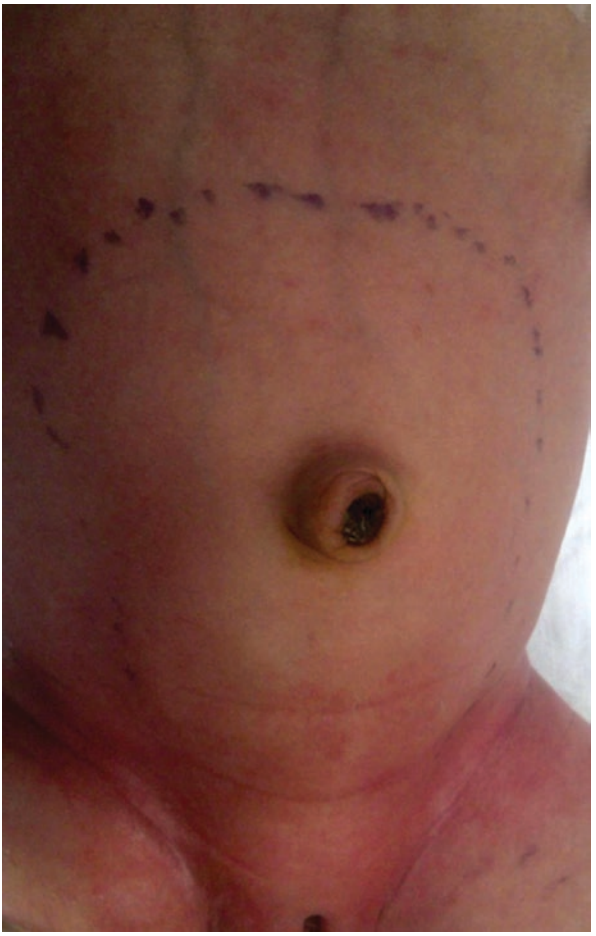


Fig. 6.3 A clinical photograph showing a female newborn with lower abdominal mass secondary to distended vagina with secretion due to imperforate hymen

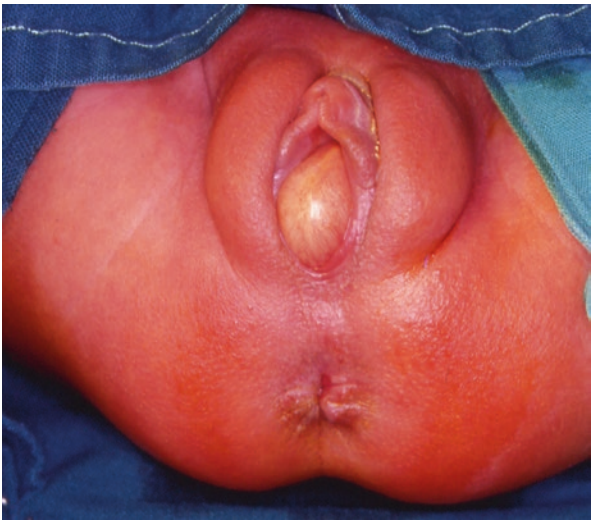


Fig. 6.4 A clinical photograph showing a newborn with imperforate hymen. Note the bulging hymen secondary to accumulation of secretions and distension of the vagina

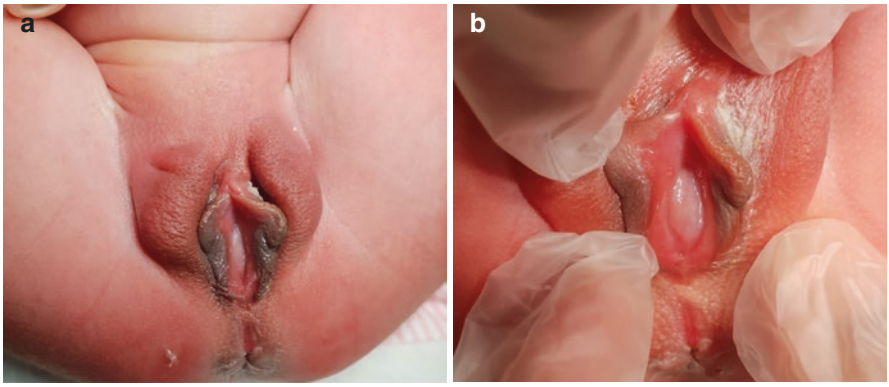


Fig. 6.5 (**a** and **b**) Clinical photographs showing a newborn with imperforate hymen. Note the mildly bulging hymen secondary to accumulation of secretions and distension of the vagina

- Sometimes the buldge of the hymen is not marked (Fig. 6.5a, b)
- Thorough genitourinary examination is essential in girls of all ages and once other causes of vaginal outflow obstruction are excluded, management of imperforate hymen is straightforward, and the long-term complications are minimal.
- Surgical treatment of the imperforate hymen is hymenotomy which typically involves making cruciate incisions of the hymen, excising segments of hymen from their bases, and draining the vaginal canal and uterus.

6.2 Embryology

- The genital tract develops during embryogenesis, from 3 weeks' gestation to the second trimester.
- The initial development of both the male and female genital tracts is identical and is referred to as the indifferent stage of development.
- There are paired Wolffian (mesonephric) ducts which connect the mesonephric kidney to the cloaca and paired Müllerian (paramesonephric) ducts which lie lateral to the Wolffian ducts.
- During the seventh week of gestation, the urorectal septum develops and separates the rectum from the urogenital sinus.
- In females and because of absence of testosterone which is produced by the testis, the Wolffian ducts regress and disappear.
- By the ninth week, the Müllerian ducts move caudally to reach the urogenital sinus and by the 12th week, the paired Müllerian ducts fuse into a single tube called the uterovaginal canal which insert into the urogenital sinus.
- Subsequently, two solid invaginations from the distal aspect of the Müllerian tubercle form the sinovaginal bulbs or vaginal plate.
- The cephalad portion of the Müllerian ducts forms the fimbria and fallopian tubes; the more distal segment forms the uterus and upper two thirds of the vagina.

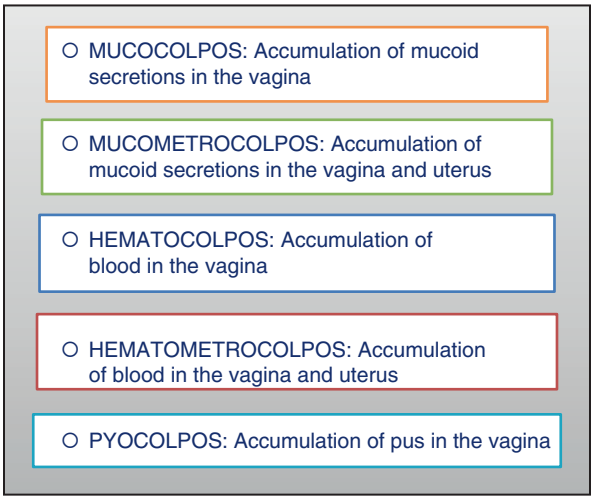
- The canalization of the paramesonephric ducts and/or upper vagina joins with the vaginal plate, which canalizes beginning caudally and creates the lower one third of the vagina and by the fifth month of gestation, the canalization of the vagina is complete.
- The hymen itself is formed from the proliferation of the sinovaginal bulbs, becoming perforate before or shortly after birth.
- Histologically, the hymen is a composite of vaginal epithelium and epithelium of the urogenital sinus interposed by mesoderm.
- Once the hymen becomes perforated or forms a central canal, it establishes a communication between the upper vaginal tract and the vestibule of the vagina.
- An imperforate hymen results when this "sheet" of tissue fails to completely canalize.
- In some patients, perforations do not become confluent, and a cribriform pattern with multiple small perforations may be observed.
- There are different normal variants in hymenal configuration. These variations range from the common annular, to crescentic, to navicular ("boatlike" with an anteriorly displaced hymenal orifice).
- Hymenal variations are rarely clinically significant before menarche.
- In the case of a navicular configuration, urinary complaints (e.g., dribbling, retention, urinary tract infections) may occasionally result.
- Sometimes, a cribriform (fenestrated), septate, or navicular configuration to the hymen can be associated with retention of vaginal secretions and prolongation of the common condition of a mixed bacterial vulvovaginitis.
- Occasionally, a hymenal tag will protrude from the vaginal vestibule, leading to concerns about a tumor or other significant pathology. These hymenal tags are of no clinical significance, and they do not require therapy.
- The most common hymnal form is the annular hymen with one central opening. However, there are several other variations such as:
  - The microperforate hymen
  - Septate hymen
  - Hymen with multiple perforations: In some patients, perforations do not become confluent, and a cribriform pattern with multiple small perforations may be observed
  - Anterior displacement of the hymen
  - Differences in rigidity and/or elasticity of the hymenal tissue
- This must be differentiated from vaginal atresia and a transverse vaginal septum.

6.3 Incidence

- Imperforate hymen is the most common vaginal obstruction of congenital origin.
- Estimates of the frequency of imperforate hymen vary from 1 in 1000 to 1 in 10,000 females.
- A population-based study estimated the frequency at 0.5 cases per 1000 women (95% confidence interval, 0.3–0.7).

6.4 Pathophysiology

- An imperforate hymen will result in obstruction of the vaginal outlet.
- This obstruction of the vaginal tract during the prenatal, perinatal, or adolescent period results in the entrapment and accumulation of vaginal and uterine secretions.
- Since the obstruction is at the level of the introitus of the vagina it will become evident when the distensible membrane bulges between the labia as a result of accumulation of these secretions.
- Various terms are used clinically depending on the nature of secretions accumulated:
  - Mucocolpos: Accumulation of mucoid secretions in the vagina.
  - Mucometrocolpos: Accumulation of mucoid secretions in the vagina and uterus.
  - Hematocolpos: Accumulation of blood in the vagina.
  - Hematometrocolpos: Accumulation of blood in the vagina and uterus.
  - Pyocolpos: Accumulation of pus in the vagina. This results from infection of an already present mucocolpos.
- In fetal development and in the immediate perinatal period, mucoid secretions from the uterovaginal tract result in mucocolpos under the influence of maternal estrogens. These secretions are commonly from the cervical glands. This will result in distension and bulging of the imperforate hymen.



- When the diagnosis is made in adolescence, the retained secretions consist of menstrual products (Hematocolpos).
- In adolescence, reflux of the endometrial tissue through the fallopian tubes as a result of hematometrocolpos and hematosalpinx may result in secondary endometriosis.

- Pyocolpos result from accumulation of infected secretions within the vaginal cavity and may result from an infection that is ascending through micro perforations in the hymenal membrane.

6.5 Clinical Features

- The clinical presentations of imperforate hymen are variable and range from an incidental finding on physical examination of an asymptomatic patient to findings discovered on clinical evaluation.
- Imperforate hymen can be diagnosed in adolescent girls or in the neonatal period.
- Imperforate hymen in adolescent girls:
  - Imperforate hymen is most often diagnosed in adolescent girls when they start menstruation and menstrual blood accumulates in the vagina and sometimes also in the uterus.
  - In adolescent females, the most common symptoms of an imperforate hymen are:

    Primary amenorrhea
    Abdominal or back pain
    Cyclical pelvic pain
    Urinary retention
    Constipation
    Nausea and diarrhea
    Urinary tract infection
    Urinary retention may be so severe, even in infants that it can lead to bilateral hydronephrosis or life-threatening renal failure.

  - If untreated or unrecognized before puberty, an imperforate hymen can lead to peritonitis or endometriosis due to retrograde bleeding.
  - In the symptomatic female adolescent, genital examination typically reveals a bulging bluish membrane across the vaginal vestibule, which represents the hematocolpos. If bulging is not noted in the resting state, it may be elicited by having the patient perform a Valsalva maneuver (Figs. 6.6 and 6.7).

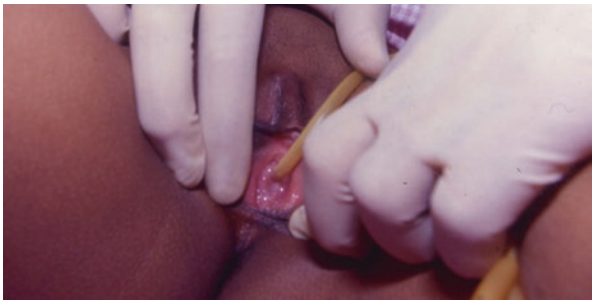


Fig. 6.6 A clinical photograph of an adolescent girl with imperforate hymen. Note the absence of a buldge at the time of clinical evaluation

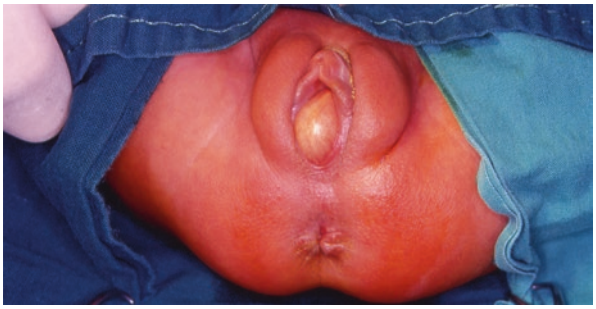
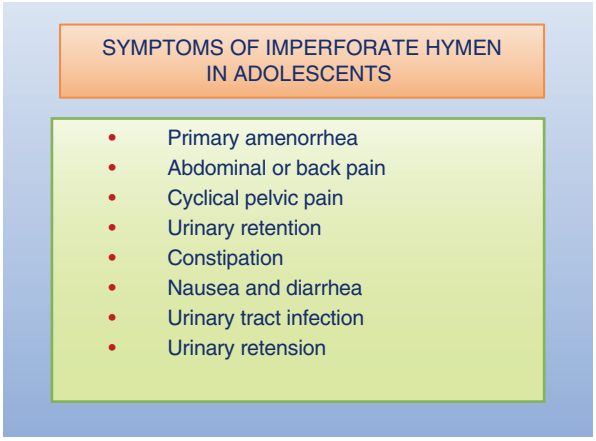


Fig. 6.7 A clinical photograph of a newborn female with imperforate hymen. Note the bulging hymen. The buldge is secondary to accumulation of secretions in the vagina which is obstructed by the imperforate hymen. These secretions are from the cervical glands and under the influence of maternal hormones



– If hematocolpos is present, a mass is often palpable on abdominal or rectal examination.
– The diagnosis of an imperforate hymen is usually made based purely on the physical exam, although if necessary the diagnosis can be confirmed by transabdominal, transperineal or transrectal ultrasound.

- Imperforate hymen in newborns:
  – An imperforate hymen can also be diagnosed in newborn babies and it is occasionally detected on antenatal ultrasound scans during pregnancy.
  – In newborns the diagnosis is based on the findings of an abdominal or pelvic mass or a bulging hymen (Fig. 6.7).
  – In the newborn with an imperforate hymen, the hymenal membrane is often seen bulging between the labia because of retained mucoid secretions in the vagina (mucocolpos or hydrocolpos) (Fig. 6.8).

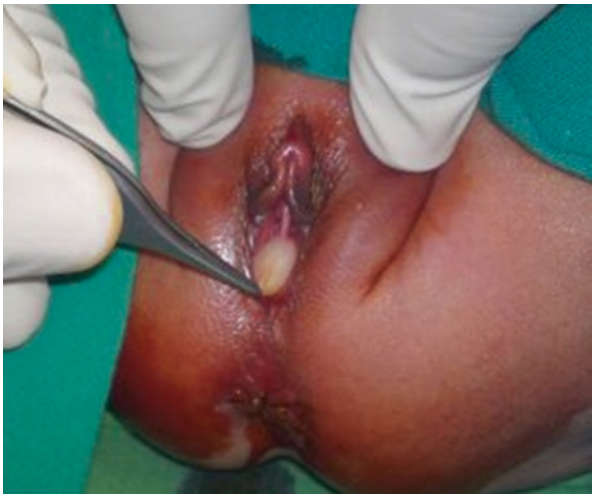


Fig. 6.8 A clinical intraoperative photograph showing a female newborn with imperforate hymen. Note the mucoid secretions distending the vagina and causing buldging of the imperforate hymen

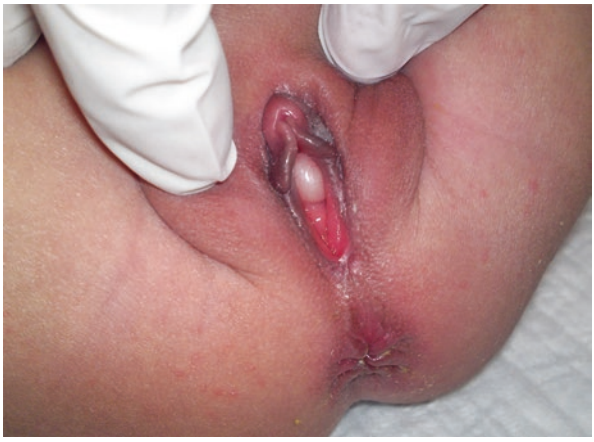


Fig. 6.9 A clinical photograph showing a ewborn girl with a vaginal cyst. This must be distinguished from an imperforate hymen. Note the cyst which fills the introitus but this is attached to only one vaginal aspect

- The membrane may be white because it is distended from trapped mucoid material secreted as a result of stimulation by maternal estrogen.
- One must distinguish imperforate hymen from a vaginal cyst, which fills the introitus but this is attached to only one vaginal aspect (Fig. 6.9).
- In severe cases, the distention extends proximally into the uterus (mucometrocolpos or hydrometrocolpos).
- A lower abdominal midline mass may be evident on physical examination because the shallow pelvis of a neonate allows the distended vagina and uterus to be palpated above the pubis symphysis.
- This mucocolpos can also lead to urinary tract infections or bladder outlet obstruction.

6.6 Diagnosis and Management

- In adolescent girls, the diagnosis of imperforate hymen is often established during examination when a distended bluish membrane is observed at the introitus. In the absence of this finding, only imaging findings can establish the diagnosis and level of obstruction.
- Other diagnoses of uterovaginal obstruction such as a transverse vaginal septum or complete vaginal agenesis, which may be associated with other developmental anomalies (e.g., Rokitansky-Küster-Maier-Hauser syndrome) must be kept in mind and excluded.
- In neonates, the diagnosis of imperforate hymen maybe suspected during routine antenatal ultrasound as early as 25 weeks' gestation.
  - This will appear as a thin bulging membrane separating the labia in association with a distended vagina.
  - These findings are usually noted during a routine antenatal ultrasound or during an evaluation for fetal ascites which result from distal urinary tract obstruction by a distended vagina and uterus. The ascites can also result from reflux of vaginal and uterine contents through the fallopian tubes.
- In neonates, the diagnosis of imperforate hymen can be made postnatally because of a bulging membrane at the vaginal introitus which may be associated with a palpable lower abdominal mass.
- The diagnosis can be confirmed by abdominal and pelvic ultrasonography or magnetic resonance imaging (MRI). This will also determine the extent of the vaginal outflow obstruction and to diagnose other associated anomalies.
- The treatment of imperforate hymen is surgical hymenotomy.
- This is to relieve the obstruction and reduce the risk of secondary endometriosis in adolescent females.
- Surgical hymenotomy typically involves making cruciate incisions of the hymen, excising segments of hymen from their bases, and draining the vaginal canal and uterus.
- An alternative to surgical hymenotomy is CO_2 laser therapy.
- Surgical Therapy:
  - Two techniques are most commonly advocated to treat imperforate hymen:

    Simple incision of the hymenal membrane
    Small excision of the hymenal membrane

  - Simple incision of the hymen is not the method of choice as this may be associated with postoperative stenosis with strictures.
  - The use of an X-shaped incision is the method of choice.
  - An elliptical excision of the membrane is performed close to the hymenal ring, using needle-tip cautery, followed by evacuation of the obstructed material.
  - This technique is considered to be most effective in definitive treatment.

  - To prevent recurrence, absorbable sutures are used to perform formal marsupialization by anchoring the incised membrane to the vaginal wall in several locations.
  - Incomplete drainage and failure of marsupialization may result in recurrent obstruction and, potentially, an ascending pelvic infection.

- Potential complications include:
  - Endometritis
  - Salpingitis
  - Tubo-ovarian abscess which may affect fertility in the future

- Secondary endometriosis:
  - This result from retrograde menstruation as a result of distension of the vagina, uterus and Fallopian tubes by menstruation blood is a potential complication.
  - Compared with primary endometriosis, secondary endometriosis generally does not become a chronic condition that impairs fertility. Retrograde menstruation can occur with secondary endometriosis as a result of vaginal outflow obstruction. However, this condition is believed to be self-limited after the primary condition is corrected.

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Chapter 7
Labial and Inter-Labial Masses

Ahmed H. Al-Salem

7.1 Introduction

- Many gynecologic diseases mimic urologic or general surgical conditions and it is important to be able to differentiate between these conditions for proper management.
- A variety of developmental and acquired disorders of the female genital tract can appear as a labial or inter labial mass.
- It is important to understand the variations in the normal anatomy and developmental changes of the external genitalia from birth to adolescence.
- Common gynecologic problems found in children and adolescents presenting as labial or/and inter-labial abnormalities include:
  - Imperforate hymen
  - Urethral prolapse
  - Paraurethral cyst
  - Hemangiomas
  - Benign and Malignant tumors
  - Dermoid cyst
  - Labial abscess
  - Inguinal hernia
  - Prolapsing uretrocele
- Introital masses are most commonly epithelial inclusion cysts of the hymen or lower vagina.
- These masses resolve spontaneously.
- Embryonic rhabdomyosarcoma, a rare malignant primary tumor of the vagina.
  - It appears as a grape-like masses protruding from the vagina.

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- Other possibilities include:
  - Condylomata acuminate
  - Ectopic ureter
  - Imperforated hymen
  - Congenital paraurethral cyst
  - Occasionally, the Bartholin gland or periurethral gland may occlude or form an abscess, leading to an acquired lateral mass.
- Imperforate hymen is the most commonly diagnosed obstructive anomaly, but has an incidence of less than 1%.
- Congenital paraurethral cysts are self-limited and benign with spontaneous resolution observed days to weeks after birth. However, the treatment of congenital paraurethral cysts remains controversial.

7.2 Normal Genital Anatomy

- The external genitalia of female newborns undergo several morphologic changes from infancy through childhood and adolescence.
- These changes are initially under the influence of maternal circulating estrogens.
- At birth:
  - The labia majora are anteriorly placed and appear edematous.
  - They are generally thickened and because of their edematous shape, they cover the introital opening.
  - The clitoris is also relatively large in size.
  - The vestibule and hymen are pale.
  - The hymen tends to occlude the vestibule and vaginal opening.
  - The vagina is rugated and moist and vaginal secretions may be present.
- During early childhood:
  - The vulva undergoes changes with thinning and attenuation of the labia majora and minora.
  - The vestibule becomes erythematous with prominent vascular markings.
  - The hymen becomes easily visualized and is thin, often translucent, and inelastic.
  - As a result of these changes, the vestibule becomes more apparent.
  - This allows easy visualization of the vaginal orifice with minimal retraction.
  - There are normal variations in the shape of the hymen.
  - The vagina has an erythematous appearance without rogues and normally, the pH is mildly basic and a mixture of bacterial flora is present.

- At puberty:
  - The hymen thickens and becomes elastic and redundant.
  - The vestibule begins to lose its erythematous appearance.
  - The vagina grows in length and develops rogues.
- The vulva represents the external female genitalia that surround the vaginal opening.
- The vulva is represented by (Fig. 7.1):
  - The labia majora
  - The labia minora
  - The clitoris
  - The vestibule of the vagina, bulb of the vestibule, and the glands of Bartholin.
- The labia majora:
  - These are two thick folds of skin running from the mons pubis to the anus.
  - The outer sides of the labia are covered with pigmented skin, sebaceous (oil-secreting) glands, and after puberty, coarse hair.
  - The inner sides are smooth and hairless, with some sweat glands.
  - Beneath the skin layer, there is mostly fatty tissue with some ligaments, smooth muscle fibres, nerves, and blood and lymphatic vessels.
  - The labia majora correspond to the scrotum in the male.
- The clitoris
  - Directly beneath the mons pubis and between the labia majora is a small structure of erectile tissue known as the clitoris.

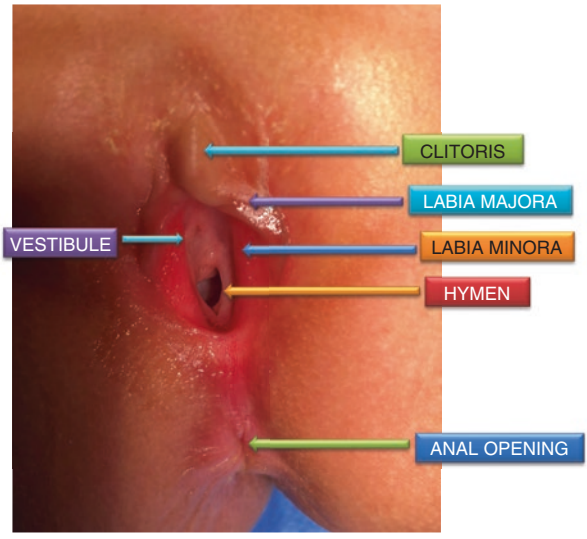


Fig. 7.1 A clinical photograph showing normal anatomy of the female external genitalia

  - It is capable of some enlargement caused by increased blood pressure during sexual excitement and is considered homologous (comparable in structure) to the male penis, only on a much smaller scale.
  - Unlike the penis, the clitoris does not contain the urethra for excretion of urine; it does have a rounded elevation of tissue at the tip known as the glans clitoridis.

- The labia minora
  - Surrounding the glans clitoridis on two sides are the beginning folds of the labia minora.
  - These folds are known as the prepuce (or foreskin) of the clitoris.
  - Like the glans penis, the glans clitoridis contains nerveendings and is highly sensitive to tactile stimulation.
  - The labia minora, two smaller folds of skin between the labia majora, surround the vestibule of the vagina; they have neither fat nor hairs. The skin is smooth, moist, and pink and has sebaceous and sweat glands.

- The vestibule
  - The vestibule of the vagina begins below the clitoris and contains the openings of the urethra, the vagina, and the ducts of the two glands of Bartholin.
  - The urethral opening is a small slit located closest to the clitoris; through this opening urine is excreted.
  - Below the urethral opening is the larger, vaginal orifice.
  - The two Bartholin ducts open on each side of the vaginal orifice; these glands secrete mucus (a thick protein compound) and frequently are sites of infection.
  - Each gland is about 1 cm (0.4 inch) in diameter; after the 30th year, they gradually diminish in size.
  - The vaginal orifice is surrounded or somewhat covered by a membranous fold of skin known as the hymen; any of a variety of activities can cause the hymen to stretch or tear.
  - Running along the sides of the vestibule are two elongated bodies of erectile tissue known as the bulb of the vestibule.
  - Many mucous glands are also present in the vestibular region.
  - Both the labia minora and labia majora tend to cover the vestibule.

7.3 Vulvar Abnormalities and Labial Adhesions

- Vulvar pruritus, pain, and discharge are common complaints in children.
- Labial adhesions occur frequently in prepubescent girls.
- The etiology of labial adhesions is not known.

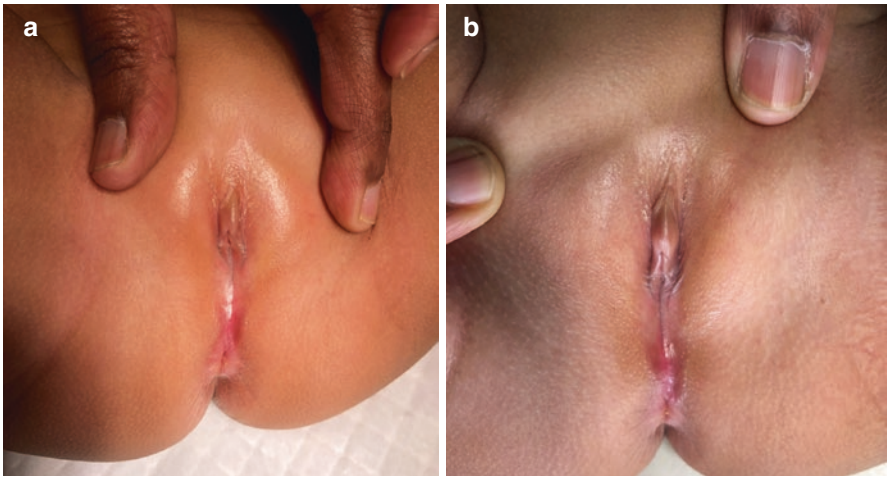


Fig. 7.2 (**a** and **b**) Clinical photographs showing labial adhesions in two girls. Note the almost covered vestibule as if there is no vaginal opening

- Adhesions are thought to develop because of local irritation or trauma to the unestrogenized labia (Fig. 7.2a, b).
- Labia adhesions are usually asymptomatic but they can present because of:
  - Urinary tract infections
  - Perineal wetness
  - Difficulty in passing urine
  - Symptomatic vulvitis
  - Parental anxiety as parents may confuse it with disorders of sexual developments or absent vagina.

- Treatment (Fig. 7.3a, b):
  - The treatment is usually conservative.
  - When symptomatic, labial adhesions are treated with estrogen-based cream applied under slight pressure to the labia.
  - Betamethasone cream may have equal efficacy.
  - Adhesiolysis is indicated in the following conditions:

    Failed conservative treatment
    Unusually dense adhesions
    Recurrent urinary tract infection and urinary retention

  - Manual separation of the labial adhesions can be done in the clinic without anesthesia using Xylocaine or EMLA cream.
  - Manual separation of labial adhesions can be done under general anesthesia if the adhesions are thick or if the child is very anxious.

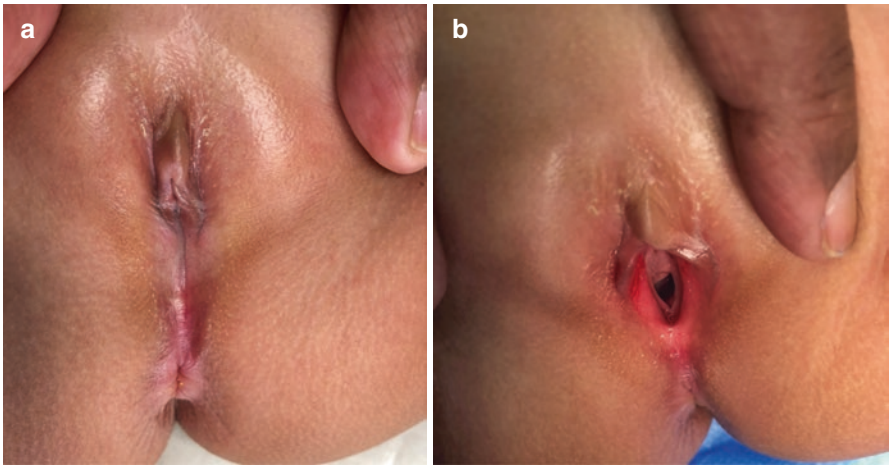


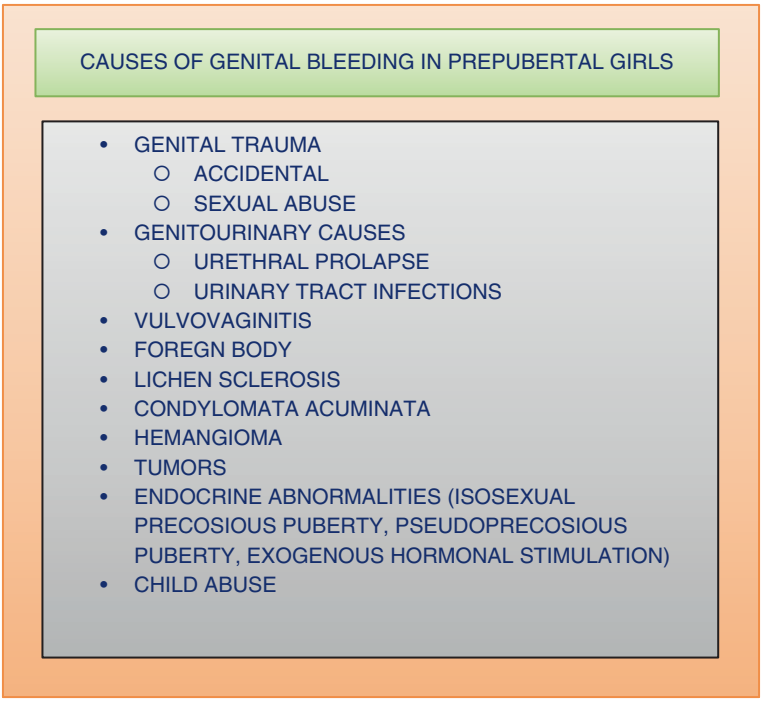
Fig. 7.3 (**a** and **b**) Clinical photographs showing labial adhesions before and after separation. Note the normal looking external genitalia after separation of these adhesions

  - There is a high risk of recurrence following manual separation and estrogen or other creams can be used for 4 weeks post seperation to keep the labial apart and reduce the recurrence rate.

7.4 Genital Bleeding

- Vaginal bleeding can be seen in newborn females as a sign of withdrawal from the effect of maternal hormones.
- Bleeding from the genital area in a prepubescent girl should always be considered abnormal.
- Bleeding is most commonly extragenital and can be caused by:
  - Hematuria
  - Anal fissures
  - Vulvar irritation
- Other causes include:
  - Prolapse of the urethra
  - Trauma
  - A foreign body
  - Infection
  - Tumors
  - Child abuse
- Vaginal bleeding can be associated with precocious puberty or autonomous production, or with exogenous sources of hormonal stimulation.

- Vaginoscopy should be performed to exclude a foreign body, trauma, or rarely, primary and metastatic tumors of the lower genital tract.
- Acute genital bleeding in children requires immediate evaluation for the presence of serious injury or sexual abuse.



- Vaginoscopy is indicated for the followings:
  - If the source of bleeding is not apparent.
  - If the entire lesion cannot be identified for proper assessment.
  - If the patient is anxious and not tolerant of the examination.
- Vaginoscopy can be done under sedation or under general anesthesia.
- Straddle injuries are common during childhood from accidental falls onto blunt objects, resulting in soft tissue trauma from striking the perineum.
- Straddle injuries usually involve the mons, clitoris, and labia, sparing the vaginal ring or perineal body.
- They may result in a hematoma, linear lacerations, or abrasions.
- Management of genital trauma:
  - Vulvar hematomas are self-limited and should be managed conservatively.
  - Small or moderate hematomas can be managed conservatively with bed rest, ice packs, and analgesia for pain control.

  - Extremely large hematomas causing distortion of the midline pelvic structures can be evacuated to facilitate recovery.
  - Evacuation with debridement should be performed under general anesthesia.
- The possibility of sexual abuse must always be considered.

7.5 Congenital Paraurethral Cysts

- Normally the paraurethral glands provide lubrication of the urethral meatus.
- Congenital paraurethral cysts are derived from the paraurethral (Skene) gland ducts.
- Congenital paraurethral cysts are rare interlabial masses seen in newborn infants.
- The reported incidence ranges from 1 in 500 to 1 in 7000 births of female infants.
- The exact mechanism of development of congenital paraurethral cysts from these glands is not known.
- There are several factors that may be responsible for the development of paraurethral cysts.
- These factors include:
  - Exposure to maternal estrogen.
  - Obstruction of the paraurethral glands.
  - Displacement of tissue from the urogenital sinus transitional epithelium.
  - Paraurethral cysts can be lined with transitional, cuboidal, or columnar epithelial cells.
- Clinical features (Fig. 7.4):
  - Paraurethral cysts are usually non-tender.
  - They appear as white or yellowish with smooth borders.
  - Delicate blood vessels are usually prominent on the surface.
  - The cyst is filled with a white fluid.

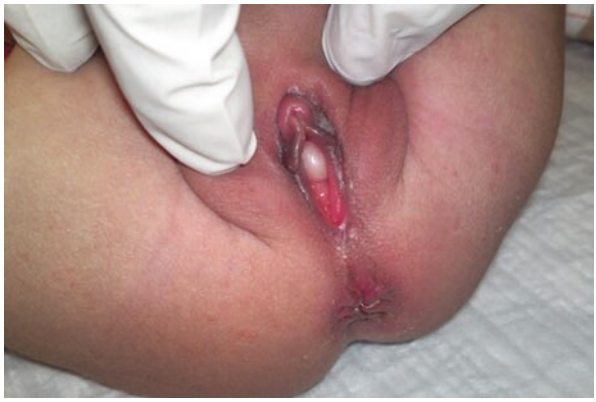


Fig. 7.4 A clinical photograph showing a newborn female with a congenital paraurethral cyst

- The cyst can displace the urethral meatus or deviates the urinary stream without causing urinary obstruction.
- The differential diagnosis for an interlabial mass in newborn female infants include:

  Hymenal cyst
  Sarcoma botyroides
  Urethral prolapse
  Prolapsed ectopic ureterocele
  Imperforate hymen with congenital hydrocolpos

- Hymenal cysts:

  These are the most common diagnosis associated with neonatal interlabial masses.
  They appear as solitary, fleshcolored masses that protrude directly from the hymen at the vaginal opening.
  They are most commonly found at the six o'clock position.
  The urethral meatus is not affected and remains visible with no urinary obstruction.
  Hymenal cysts are lined by stratified squamous epithelium.

- Sarcoma botyroides:

  These usually appear as a dull red mass resembling a "cluster of grapes" protruding from the vagina.
  The clinical presentation includes vaginal bleeding and vaginal discharge.

- Urethral prolapse:

  The masses of urethral prolapse are typically red or cyanotic in color with friable tissue.
  The prolapsed tissue surrounds the urethral meatus and is more common in older girls.

- Ectopic uretrocele (Fig. 7.5):

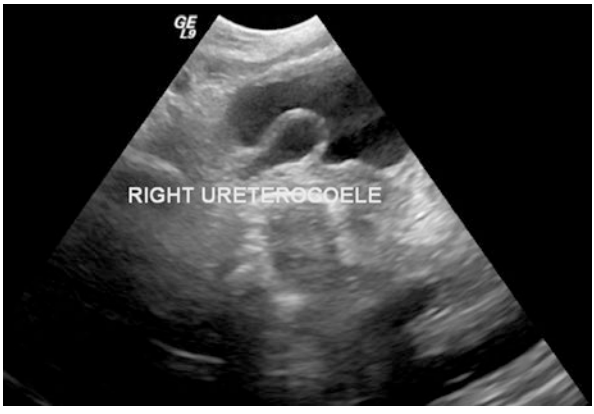


Fig. 7.5 A pelvic ultrasound showing a right uretrocele protruding into the urinary bladder. This can prolapse and appear as an interlabial mass

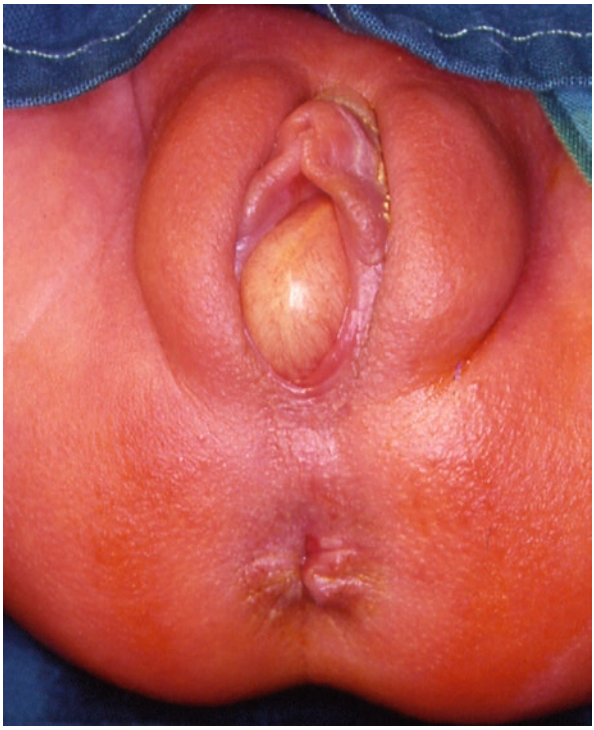


Fig. 7.6 A clinical phograph showing a hydrocolpos with imperforated hymen. Note the protruding introitus mass representing the distended hymen secondary to fluid accumulation in the vagina (hydrocolpos)

An ectopic ureterocele is red or purple in color and protrudes from the urethral meatus, without surrounding it.
Ureteroceles are often identified through antenatal ultrasound.
They are frequently associated with duplicated ureters.

– Congenital hydrocolpos (Fig. 7.6):

  Congenital hydrocolpos is characterized by an oval, bulging, blue or white-colored imperforate hymen.
  In these cases, the urethral meatus remains in the normal position, but significant distention of the vaginal cavity or abdomen can also be present.

– Congenital paraurethral cysts are generally asymptomatic.
– They are self-limited, and benign.
– Ultrasound can be used to rule out upper urinary tract anomalies if urinary obstruction develops.
– Spontaneous resolution of the cysts commonly occurs within days to weeks of birth.
– Paraurethral cysts that persist require surgical interventions:

  Aspiration
  Unroofing
  Marsupialization

7.6 Inguinal Hernia

- Inguinal hernias are found commonly in infancy and childhood.
- They are more common in boys than girls.
- Inguinal hernias are more common in premature infants with a reported incidence as high as 30%.
- The occurrence of an inguinal hernia in females is usually due to an incomplete closure of the processus vaginalis of the peritoneum.
- In girls, hydrocele of the canal of Nuck can be confused with an inguinal hernia.
- In female patients, the incidence of hernia sac containing ovary and fallopian tube has been reported to range from 2.9% to 15–20%.
- The presence of an ovary in hernia sac usually present as a firm mass in inguinal area and in neglected cases the blood supply of the ovary may be compromised leading to gangrene and loss of the ovary (Fig. 7.7).
- Small bowel can also herniate into an inguinal hernia and present as an inguinal mass.

- This can become irreducible and the blood supply of the intestine may be compromised (Fig. 7.8).
- This calls for early diagnosis and surgical repair.

7.7 Urethral Polyps

- Inter-labial mass may be of urethral, vaginal or labial origin.
- Urethral polyps are a rare in children1.
- In young girls these are much rarer.
- Histologically, these are fibroepithelial polys.

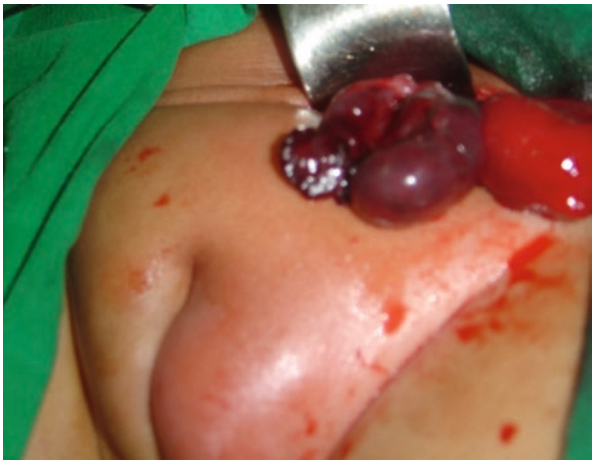


Fig. 7.7 A clinical photograph of a female child with a neglected left inguinal hernia containing the ovary. Note the already necrotic ovary

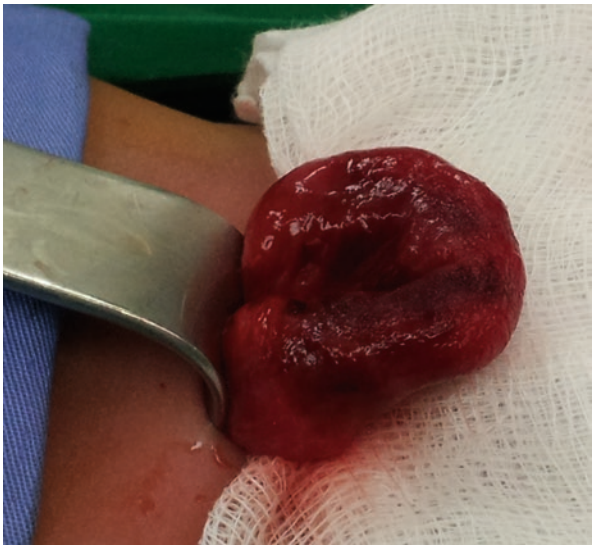


Fig. 7.8 A clinical intraoperative photograph showing an irreducible inguinal hernia. Note the change in the color of the intestine as a result of blood supply compromise

- In males urethral polyps presentation include:
  - A protruding mass through the urethral meatus
  - Painless hematuria
  - Obstructive voiding symptoms
- In girls urethral polyps presentation include:
  - Vaginal bleeding
  - An inter-labial mass
- Investigations like ultrasonography or urography are needed to exclude other urinary tract anomalies.
- Treatment is endoscopic or transurethral resection.

7.8 Imperforate Hymen

- Imperforate hymen presents as a bulging membrane between the labia minora.
- Imperforate hymen may also be familial.
- Hydrocolpos (mucocolpos) develops behind an imperforate hymen as a result of vaginal secretions from the cervical glands (Fig. 7.9a, b).
- These secretions are produced in response to maternal estrogens.
- These secretions can result in a rather sizable abdominal mass which represent a distended vagina and or uterus (hydrometrocolpos).
- The hydrocolpos can rarely obstruct the urethra and rectum and rarely the venous return from the lower extremities.

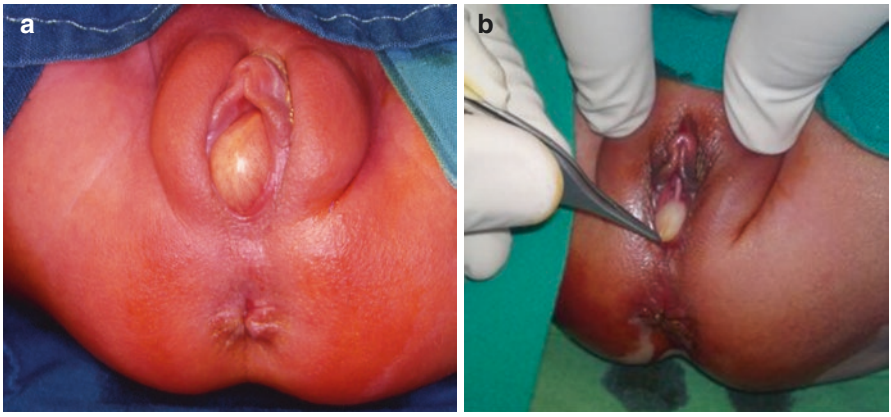


Fig. 7.9 (**a** and **b**) Clinical photographs showing imperforated hymen in two newborn girls. Note the accumulated fluid in the vagina as a result of stimulation of the cervical glands by maternal hormones

- A considerable hydrocolpos can also cause obstructive uropathy.
- Treatment:
  - Incision of the imperforate hymen and drainage of the fluid.

7.9 Ureterocele

- Ureterocele is a rare cause of urinary obstruction which is commonly associated with significant urinary tract anomalies.
- Ureterocele is a cystic dilatation of the ureter, which can involve the intravesical or extravesical part of the ureter (Figs. 7.10a, b and 7.11).
- Very rarely, the intravesical ureterocele can prolapse and present as mass protruding from the vagina.
- This can be confused with:
  - Epidermal inclusion cyst
  - Skene's duct cyst
  - Paraurethral cyst
  - Hidradenoma papilliferum
  - Mucocolpos
- The estimated incidence of ureterocele is 1/5000 to 1/12000.
- Prolapsing ectopic ureterocele account for less than 5% of the total intritous masses.
- It is associated with duplex renal system in 95% of female cases and with the presence of vesicoureteric reflux, especially with the extravesical form (Figs. 7.12a, b and 7.13).

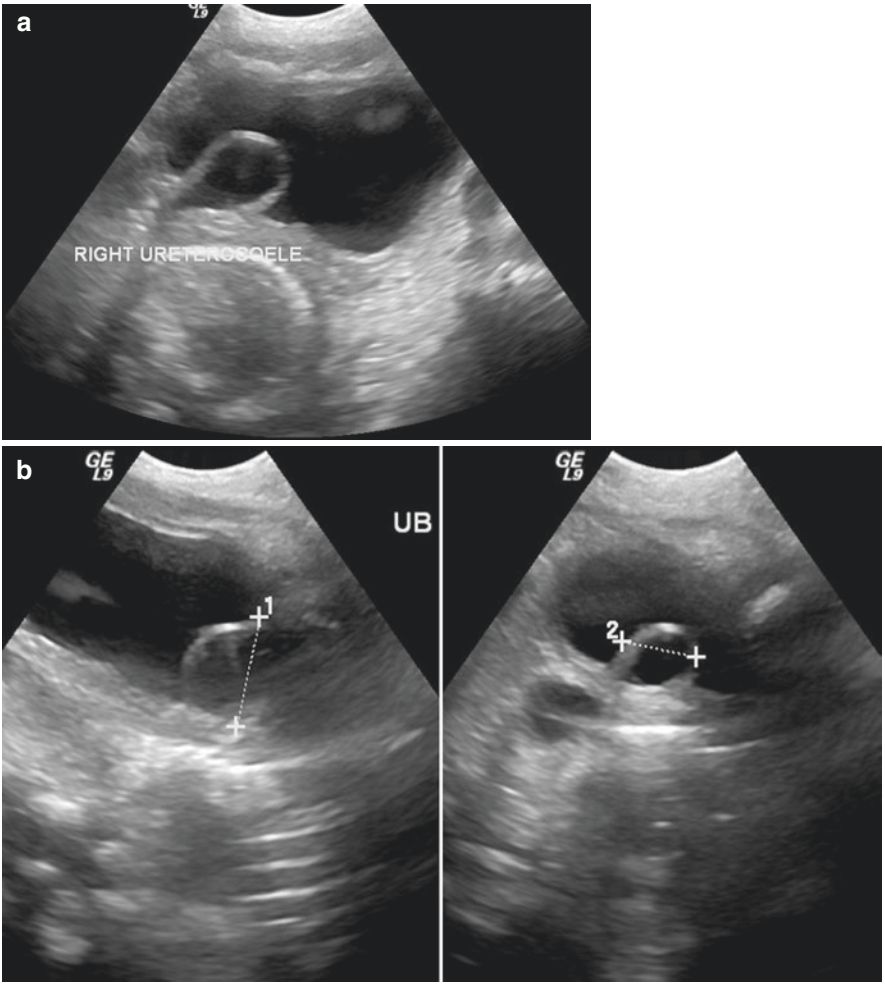


Fig. 7.10 (**a** and **b**) Ultrasound showing an intravesical uretrocele. This can prolapse and present as an introitus mass

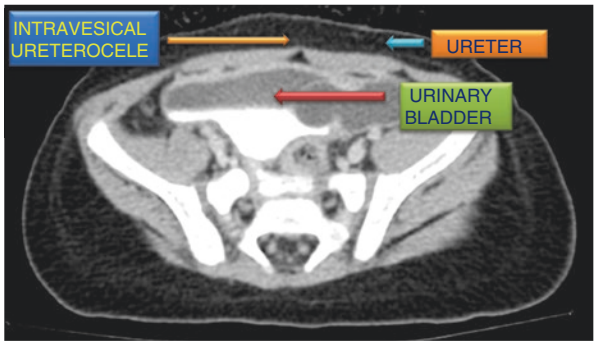


Fig. 7.11 Pelvic CT-scan showing an intravesical uretrocele

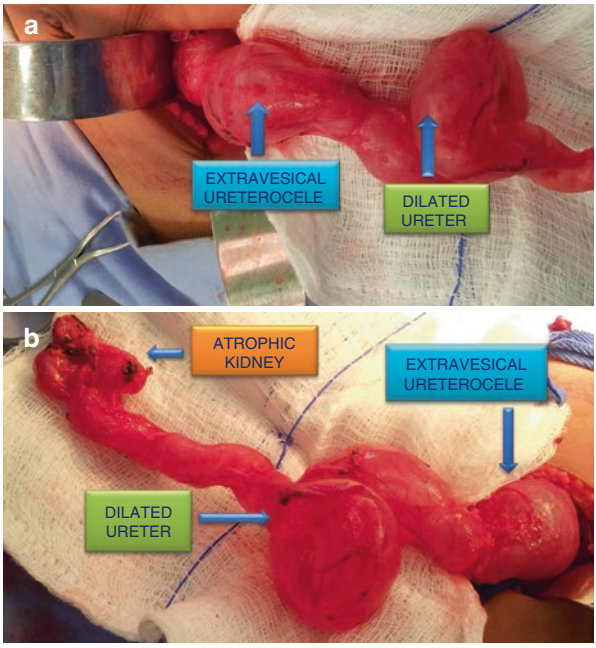


Fig. 7.12 (**a** and **b**) Clinical intraoperative photographs showing extravesical ureterocele causing hydroureter and progressive nephropathy with renal atrophy

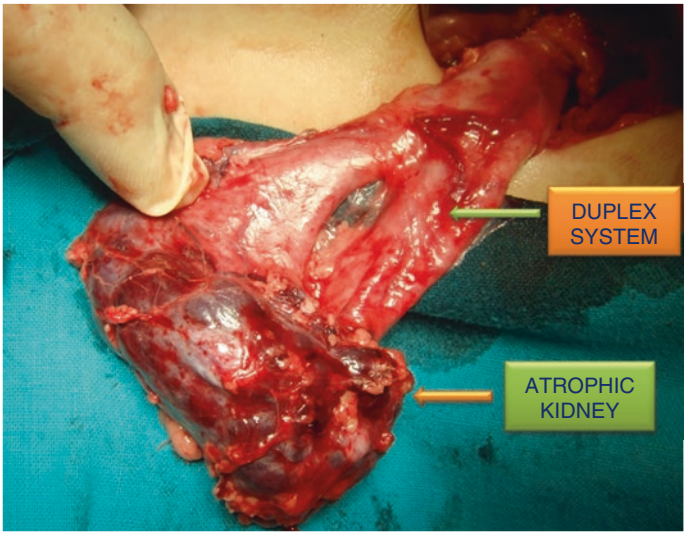


Fig. 7.13 An intraoperative photograph showing duplex system in a patient with ureterocele. Note the abnormal atrophic kidney as a result of reflux nephropathy

- It can be asymptomatic and incidentally diagnosed during workup for urinary tract infection or rarely present as urinary retention.
- It is important to diagnose uretroceles early as surgical decompression soon after diagnosis and further investigations are important to prevent renal complications.
- Diagnostic workup entails evaluation for associated renal duplex system and presence of vesicoureteric reflux.
- A prolapsing ureterocele presents as a mass protruding from vagina.
- The mass is firm and irreducible with no associated tenderness.
- The mass is not associated with vaginal discharge or bleeding.
- Treatment:
  - Decompression of the ureterocele should be done once diagnosed.
  - Decompression should be followed by further evaluation.
  - Decompression of a ureterocele can be done endoscopically or surgically.
  - The baby should be covered with prophylactic antibiotics, pending exclusion of vesicoureteric reflux.

7.10 Vulvar Abscess

- A wide variety of lesions occur on the vulva.
- Some of the disorders causing these lesions are limited to the vulva, while others also involve skin or mucocutaneous membranes elsewhere on the body.
- Swelling around the vaginal region (vulva) may involve the vaginal lips, labia minora, or the labia majora.
- Swelling in the vulvar region may be generalized or may be confined to one or more structures.
- It may be unilateral or bilateral.
- The causes are variable depending on the specific presentation.
- Localized vulvar swelling could be due to cysts, abscesses, or hernia (Figs. 7.14a, b, 7.15a, b and 7.16).
- Generalized vulvar swelling is more likely due to infectious, edematous, or allergic causes.
- Vulvar abscess is one of the gynecologic problems in girls.
- A neglected vulvar abscess can lead to serious and severe illness.
- These abscesses typically originate as simple infection in the vulvar skin or subcutaneous tissues.
- Commonly it starts as cellulitis and progress to form an abscess (Fig. 7.17).
- Spread of infection and abscess formation in the vulvar area is facilitated by the loose areolar tissue in the subcutaneous layers and the contiguity of the vulvar fascial planes with the groin and anterior abdominal wall.

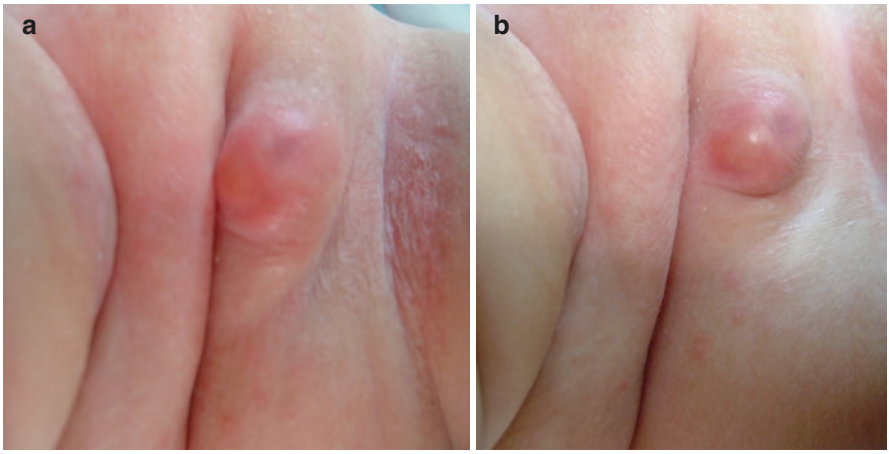


Fig. 7.14 (**a** and **b**) Clinical photographs showing labial cysts. These can become infected and form a labial abscess

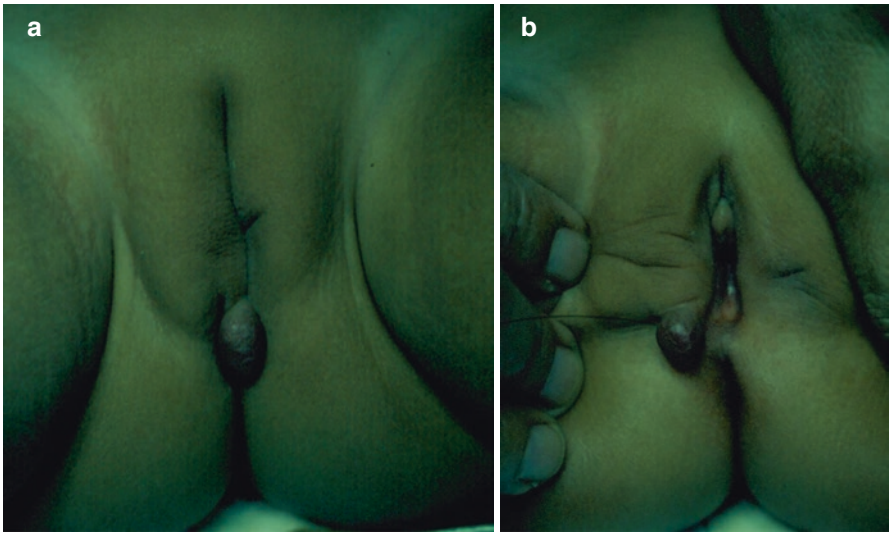


Fig. 7.15 (**a** and **b**) Clinical photographs showing a girl with a labial dermoid cyst

- Vulvar infection and abscess formation starts in the vulvar skin and originates in:
  - Hair follicles
  - Sweat glands
  - Sebaceous glands
- Hair follicles and sebaceous glands of the skin along with vulvar glands such as Bartholin's and Skene's can be sites for abscess formation.

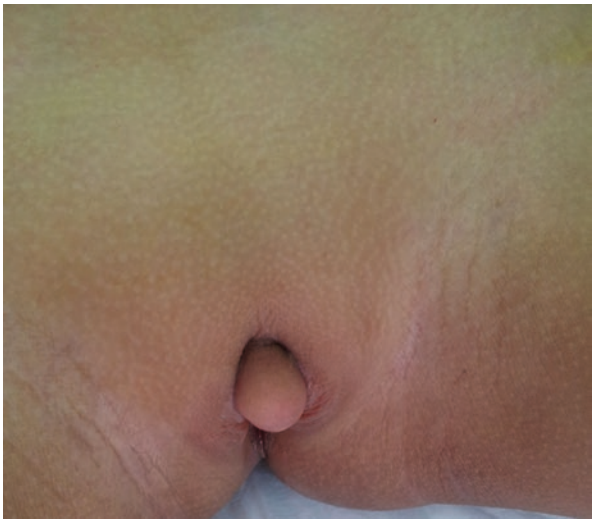


Fig. 7.16 A clinical photograph showing a clitoral dermoid cyst

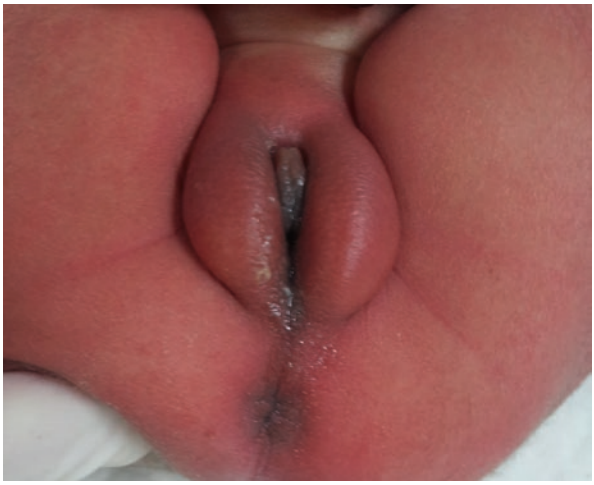
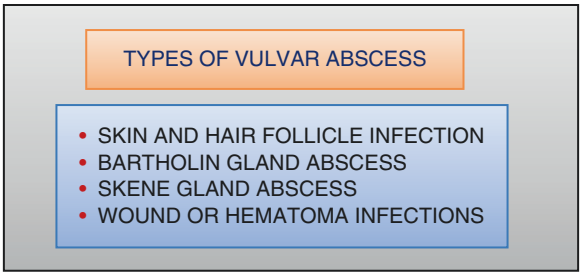


Fig. 7.17 A clinical photograph showing a female with cellulitis of the labia. Note the redness and edema of both labia. This suggests a vulvar infection with cellulitis that can progress to form an abscess. Early diagnosis and prompt treatment is important to avoid any complications

- The mons and labia majora are covered with hair, while the labia minora are not.
- Two major vulvar glands underlie the vestibule; these are:
  - The Bartholin glands (also referred to as the greater vestibular gland)
  - The paraurethral (Skene) glands
- There are two Bartholin's glands, each about the size of a pea.
- The glands are located on either side of the opening of the vagina.

- They provide lubrication to the vaginal mucosa.
- The Bartholin glands drain through the Bartholin ducts, located bilaterally in the vestibule at approximately the four and eight o'clock positions with respect to the vaginal introitus.
- Bacteria, such as *E. coli*, *Staphylococcus aureus* and sexually transmitted diseases (STDs), such as chlamydia or gonorrhea, may cause the infections that can lead to a Bartholin's abscess.
- It usually only occurs on one side of the vagina at a time.
- The paraurethral glands empty through Skene's ducts, which are located bilaterally just inferior and lateral to the urethral meatus.



- Clinical features and treatment.
  - Patients present with a painful tender vulvar mass.
  - This is usually associated with surrounding cellulitis (Fig. 7.18a, b).
  - Vulvar cellulitis and small abscess formation can be treated conservatively with antibiotics.
  - Methicillin-resistant *Staphylococcus aureus* is the commonest organism causing vulvar abscess.

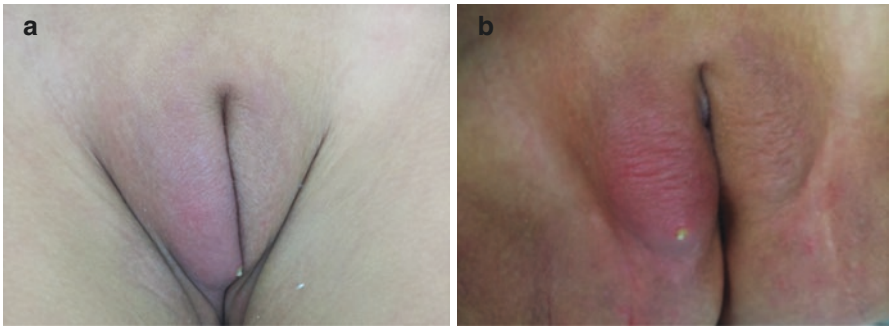
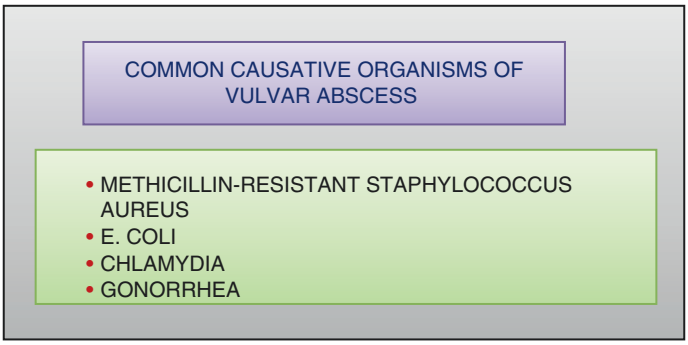


Fig. 7.18 (**a** and **b**) Clinical intraoperative photographs showing a female girl with vulvar abscess



– If the cyst becomes infected, it can lead to a Bartholin's abscess.
– Most people with a Bartholin's abscess completely recover, in some cases the cyst will return and become infected again.
– Abscesses of the Bartholin's gland can be treated with incision and drainage or marsupialization.
– Skene's duct abscess is rarely seen in adolescence, but should be recognized and treated appropriately.
– Hidradenitis suppurativa is another cause of vulvar abscesses in adolescents and may be treated both medically and surgically.

7.11 Sarcoma Botryoides

- Sarcoma botryoides is a term that is used to include certain neoplasms of the lower genitourinary tract which occur predominantly in children.
- The word "botryoid," was derived from a Greek term meaning "like a bunch of grapes."
- This refers to the gross appearance of Sarcoma botryoides which is characterized by the formation of fleshy, polypoid or grapelike masses.
- Rhabdomyosarcoma is a malignant tumor which arises from embryonic muscle cells.
- It is the most common soft tissue sarcoma in childhood and young adulthood, and accounts for 4–6% of all malignancies in this age group.
- Sarcoma botryoides is a rare tumor but it is considered the most common lower-urogenital sarcoma found in younger age groups.
- It occurs most often in female infants and young children.
- Sarcoma botryoides normally is found in children less than 8 years of age.
- Commonly, the onset of symptoms occurs at age 3 years (38.3 months) on average.
- In boys, Sarcoma botryoides arises in the:
  - Bladder
  - Urethra
  - Prostate

- In girls, Sarcoma botryoides arises in the:
  - Bladder
  - Cervix
  - Vagina
- These tumors resemble each other grossly but they vary in their histopathologic findings.
  - Many of these sarcomas are only indeterminately spindle-celled, and resemble embryonal connective tissue.
  - Others contain heterologous mesenchymal elements that most often resemble immature striated muscle cells, and only occasionally resemble cartilage.
- On the basis of these histologic variations, these neoplasms have been classified by terms such as:
  - Embryonal sarcoma
  - Rhabdomyosarcoma
  - Malignant mesenchymoma
- Clinical features of Sarcoma botryoides of the vagina include:
  - Vaginal bleeding is the most common presentation.
  - Vaginal discharge.
  - Obstructive symptoms or urinary retention.
  - Occasionally grape-like clusters may be seen protruding from the urethra or vagina.
  - The tumor appears as a polypoid mass, somewhat yellow in color and is friable.
  - These tumor masses may break off, leading to vaginal bleeding or infections.
- Histologically these tumors are made up of:
  - Rhabdomyoblasts that may contain cross-striations.
  - The tumor cells are crowded in a distinct layer beneath the vaginal epithelium (cambium layer).
  - These cells that are desmin positive.
- Treatment and prognosis.
  - The disease used to be uniformly fatal, with a 5-year survival rate between 10 and 35%.
  - As a result, treatment was radical surgery.
  - New multidrug chemotherapy regimens with or without radiation therapy are now used in combination with less radical surgery with good results.
  - An important point is a higher survival rate and better prognosis of vaginal sarcoma botryoides.
  - Currently, the survival rate of vaginal and cervical sarcoma botryoides have been reported to be of 96% and 60%, respectively.

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Chapter 8
Pediatric Vulvovaginal Disorders and Vulvovaginitis

Ahmed H. Al-Salem

8.1 Introduction

- Vulvovaginal complaints are common in prepubertal girls.
- These complaints include:
  - Vulvovaginal itching
  - Irritation
  - Skin rash
  - Localized pain
  - Bleeding
- Vulvovaginal complaints can be caused by several conditions including:
  - Vulvovaginitis
  - Lichen sclerosus
  - Urethral prolapse
  - Genital ulcers
  - Labial fusion (adhesions)
- Some of the vulvovaginal complaints can be mistaken for sexual abuse which must be kept in mind.
- Sexual trauma should be considered in prepubertal girls presenting with bleeding and hymenal lacerations.
- The possibility of irritants such as bath soaps, feminine hygiene products, baking soda, and bleach baths must be considered in girls with vulvovaginitis who present with generalized itching, irritation, discharge, and dysuria.

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- Bloody or purulent discharge may signify precocious puberty or indicate the presence of a foreign body.
- Vulvovaginitis is divided into nonspecific or specific, secondary to a specific pathogen.
- Specific vulvovaginitis is divided into infectious or noninfectious.
- Nonspecific vulvovaginitis is far more common than specific vulvovaginitis.
- Specific vulvovaginitis typically presents as an acute episode and treatment should be initiated only after a positive vaginal culture.
- Discharge that is copious and watery should hint to the possibility of vulvovaginitis secondary to a specific pathogen, such as *Streptococcus pyogene*.
- *Streptococcus pyogene* is one of the more common infections in prepubertal girls.
- Vulvovaginal streptococcal infection is often associated with a nasopharyngeal infection.
- Recurrent episodes of vulvovaginitis may require further investigation and other possibilities must be kept in mind including:
  - Foreign bodies
  - Congenital malformations
  - Tumors
  - Trauma
  - Skin diseases
- Pinworm is a known cause of itching in young girls
- Candida vulvovaginitis is more commonly seen in:
  - Infants in diapers
  - After prolonged antibiotic use
  - Patients with diabetes mellitus
  - Patients with immunosupression

8.2 Anatomy of the Pediatric Vulva

- Anatomically and histologically, the pediatric vulva is different from that of adults.
- These differences are due in part to the lack of estrogen.
- The anatomy and lack of estrogenization makes the pediatric vulva more susceptible to irritants and trauma.
- The maternal estrogens have a transient effect in newborn females and this effect gradually resolves within the first 6 months of life.
- The pediatric vulva is characterized by the following features:
  - It is hairless.
  - Has very little subcutaneous fat under the lateral aspects of the mons pubis and labia majora.

  - The labia minora lack pigmentation and have an atrophic appearance.
  - The distance from the anus to the vestibule is comparatively short, leaving the pediatric vulva more prone to irritation and inflammation.
  - The vulva is covered by keratinized, stratified squamous epithelium.

- The vestibule:
  - It is composed of squamous epithelium resembling vaginal mucosa, which is not glycogenated.
  - The linea vestibularis is a white streak in the midline of the posterior vestibule.
  - The linea vestibularis may be seen in up to 25% of newborn females.
  - This can be misinterpreted as a scar secondary to sexual abuse.
  - The fossa navicularis (the shelf-like area in the vestibule leading up to the hymen) and the lateral vestibular sulci are densely vascular and in most children will have an erythematous appearance.
  - There are apocrine glands present in the labia majora, prepuce, posterior vestibule, and perineal body but these are not active until puberty.
  - The eccrine sweat glands on the other hand do function prior to puberty.
  - Milaria related to obstruction of the eccrine sweat glands is common in neonates.

- The labia minora:
  - It does not contain glandular elements but may have sebaceous glands near the interlabial sulcus.

- The clitoris:
  - This may appear relatively more prominent in children nearing puberty than in adults.
  - This is in part due to the flat appearance of the labia majora and minora.
  - The size of the clitoris in a newborn is <0.9 cm when fully stretched.

- The hymen (Fig. 8.1):
  - This is a fold of vascularized mucous membrane that lies within the vaginal orifice.
  - The hymen separates the vagina from the vestibule.
  - The hymen is variable in term of thickness, size, and shape.
  - Normal diameters of the opening can be up to 1 cm.
  - There are different types of the hymen:

    The crescentic hymen is the commonest type.
    It starts in the periurethral area at 1 o'clock and extends around to the 11 o'clock position.
    The circumferential (annular) hymen extends full circle.

  - The hymen is originally a solid membrane that opens during the fetal period.

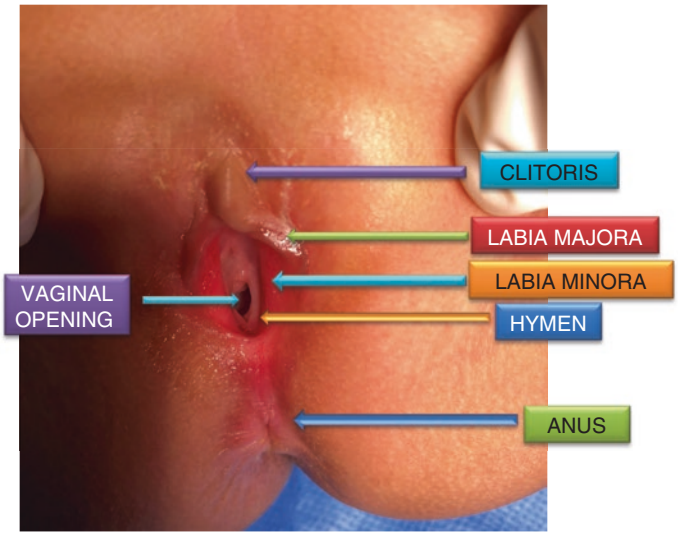


Fig. 8.1 A clinical photograph showing normal anatomy of the vulva in a young girl

– Abnormalities in this process can result in variations including:

Imperforate hymen has no opening
Microperforate hymen has a single small opening
Cribriform hymen has multiple small openings
Septate hymen has a residual band, usually in the anteroposterior diameter.

8.3 Lichen Sclerosus

- Lichen sclerosus is a chronic skin disorder of unknown etiology.
- The estimated prevalence of Lichen sclerosus is about 1 in 900–1000 in premenarchal girls.
- It is estimated that 7–15% of all vulvar lichen sclerosus is found in prepubertal girls.
- The mean age at diagnosis in children is 5.5–6.7 years.
- The exact cause of Lichen sclerosus is unknown but several factors may contribute to the etiology including;
  - Genetic factors
  - Autoimmune factors
  - Local irritation
- There is a genetic tendency for Lichen sclerosus as familial cases have been reported.

- Lichen sclerosus was also found to be associated with other autoimmune diseases such as:
  - Vitiligo
  - Thyroid disease
  - Alopecia areata
  - Rheumatoid arthritis
  - Diabetes mellitus
- Lichen sclerosus is also associated with HLA class II DQ7.
- It has been postulated that genital carriage of human papillomavirus in prepubertal girls may be a trigger for the development of LS.
- Lichen sclerosus is seen most frequently in adult women, but 10–15% of cases arise during childhood.
- The presentation of Lichen sclerosus include:
  - Pruritus
  - Soreness
  - Erosions and fissures
  - Papules and lumps
  - Papules and lichenification usually involve the labia and anal area without affecting the hymenal structures
  - Erythema
  - Purpura
  - Bleeding
  - Dysuria
  - Constipation
  - Painful defecation
  - Clinically it appears as a sharply demarcated white figure-of-eight encircling the vulva and anus.
  - There is lightening and thinning of the skin, sometimes associated with small tears, bruises, or bleeding due to subepithelial hemorrhages.
  - There are ivory-colored, flat-topped polygonal papules, which coalesce into plaques.
  - Over time, it leads to fusion and resorption of the labia minora and introital narrowing.
  - Progressive disease may cause scarring and loss of normal architecture, resulting in distorted-appearing anatomy.
- Treatment
  - Good perineal hygiene and reduction of scratching of the involved area.
  - Lichen sclerosus is best treated with a short course of high potency topical corticosteroid two to three times daily for to 6–12 weeks.
  - This includes 0.05% betamethasone dipropionate and 0.05% clobetasol proprionate ointments.

- Some authors advocate continuing 1% hydrocortisone ointment daily or 0.1% triamcinolone following resolution for an additional 3 months.
- Clinical improvement has been reported in 93–100% of pediatric patients.
- Recurrences are common and reported to be as high as 60%.
- Although symptoms may improve, hypopigmentation of the skin may persist.
- Side effects of treatment include:

  Steroid-induced atrophy
  Telangiectasias
  Erythema

8.4 Lichen Planus

- Lichen planus is very rare in pediatric patients and extremely rare to involve the vulva.
- Lichen planus is characterized by the followings:
  - Angular, violaceous demarcated flap papules.
  - Koebner's phenomenon:

    This results in a striking linear distribution along sites that are traumatized by scratching.
    The more common sites are in the flexor surfaces of the wrists, the forearms, and the inner thighs.

  - Vulvar lesions are less distinctive and may resemble leukoplakia, with a variable degree of excoriation, maceration, or verrucous thickening.
  - The buccal mucosa may exhibit a lacy pattern of minute white papules.
  - The diagnosis of lichen planus is made by a biopsy of the lesion.
  - Treatment is with topical and intralesional corticosteroid as well as antihistamines.
- Long-standing hypertrophic vulvar lichen planus may be complicated by squamous cell carcinoma.

8.5 Labial Adhesions (Labial Fusion)

- Labial adhesions are also known as labial agglutination or labial fusion.
- Labial fusion is an acquired condition in which the labia are adherent and fused in the midline.
- It is a common condition in prepubertal girls with an estimated incidence of 0.6–3%.
- Etiology:

  - The exact etiology of labial adhesions is not known.
  - This prepubertal age group is most susceptible to labial adhesions due to lack of systemic estrogen,
  - It is hypothesized that irritants denude the thin, non-estrogenized epithelium of the labia which lead to the formation of adhesions and subsequent reepithe-liazation forming an avascular connection between the two labia.

- It is seen commonly in girls between 6 months and 6 years of age.
- Presentation include:
  - Vulvovaginal irritation
  - Postvoid urinary dribbling
  - abnormal-appearing anatomy and absence of the vaginal introitus
  - Urinary tract infections
  - Urinary retention is uncommon
- It is not uncommon for these patients to be diagnosed mistakenly as congenital absence of the vagina, ambiguous genitalia, or imperforate hymen.
- Clinically (Fig. 8.2a, b):
  - Physical exam reveals thin, filmy adhesions visualized between labia minora.
  - It is possible for the adhesions to cover the vaginal introitus and sometimes the entire urethra.
  - A small pinpoint opening just below the clitoris is characteristic.
- Treatment (Fig. 8.3a, b):
  - The treatment of labial adhesions is controversial.
  - Conservative treatments as all labial adhesions were reported to resolve without treatment within 18 months.
  - This is based on the fact that once the young girls begin endogenous estrogen production, the adhesions will resolve spontaneously.

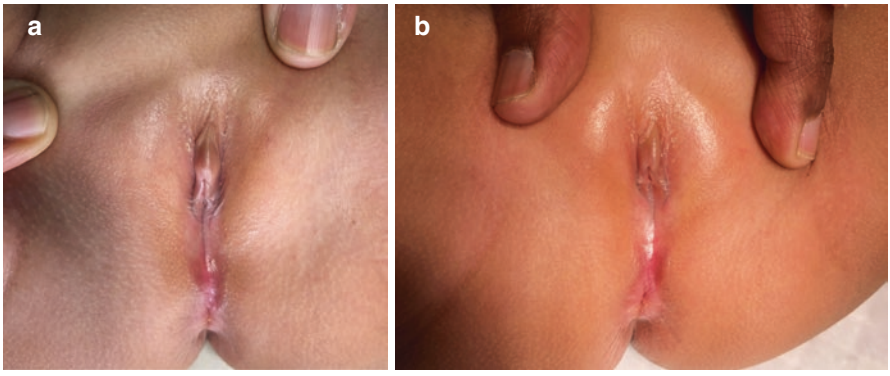


Fig. 8.2 (**a** and **b**) Clinical photographs showing fused labia. Note the almost closed intoitus with adherent labia in the midline

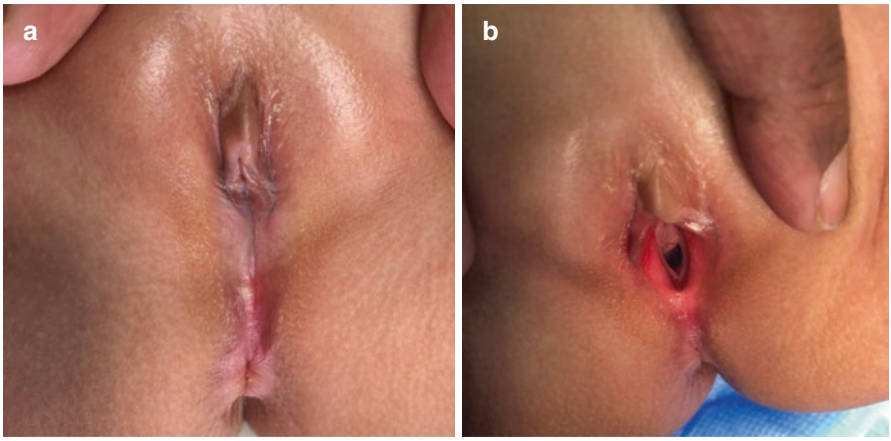


Fig. 8.3 (**a** and **b**) Clinical photographs showing fused labia before and after seperation. Note the normal looking vaginal intoitus and the normal looking hymen

- Many authors suggest using hygiene measures with or without some form of cream (e.g., petroleum jelly or vitamin A + D ointment).
- The use of these creams will protect the labial epithelium from irritants, thereby discouraging adhesions.
- The hygiene measures consist of removal of all potential vulvovaginal irritants (soaps, bubble baths, restrictive clothing) and daily sitz baths.
- The use of estrogen cream was advocated for symptomatic labial adhesions or for those with significant agglutination.
- Estrogen cream is used once or twice daily for 2–6 weeks.
- Estrogen cream should be applied with a gentle amount of pressure to the line of fusion only, either with a finger or cotton swab. The pressure itself may aid in resolving the adhesions.
- The efficacy of estrogen cream ranges from 50% to 91%.
- Side effects can include:

  Local irritation (erythema or burning)
  Vulvar pigmentation
  Rarely, pubertal changes (breast buds). The breasts changes usually regress following cessation of treatments.

- Following successful treatment with estrogen, the risk of recurrence may be minimized by daily application of a barrier cream (e.g., petroleum jelly).
- Topical betamethasone is an alternative for girls with a contraindication or intolerance to topical estrogen.

- Manual separation:

  This should be reserved for patients with acute urinary retention (complete agglutination) or failed medical treatment.

This can be done in the clinic using topical anaesthesia (e.g., EMLA cream or xylocaine)
Or using awake sedation (e.g., midazolam), with minimal discomfort and high success.
General anesthesia can be used for older girls or if the child is very anxious or the adhesions are thick.
There is a significant recurrence rate following manual separation, which may be as high as 40% and to reduce this daily application of a barrier cream (e.g., petroleum jelly) should be used for a minimum period of 4–6 weeks.

8.6 Genital Ulcers

- Genital ulcers are relatively rare in girls and young women without a history of sexual activity.
- In developed countries, the causes of genital ulcers are:
  - Herpes (30%)
  - Non-specific ulcer of unknown etiology (55%)
- In African and Asian countries, the causes of genital ulcers are:
  - Chancroid (45%)
  - Syphilis (25%)
- Genital ulcers in children and adolescents can present a complex diagnostic dilemma.
- It is important to differentiate between a blister and an ulcer.
  - A blister is a fluid-filled vesicle that can rupture to leave erosion, involving only the epidermis.
  - An ulcer affects both the dermis and epidermis.
- The differential diagnosis of solitary ulcers should include:
  - Syphilis (Treponema pallidum)
  - Chancroid (Hemophilus ducreyi)
  - Crohn's disease
  - Pyoderma gangrenosum
  - Ulcerative vulvitis (bacterial pathogen or trauma)
  - Cancer (basal or squamous cell carcinoma)
- Multiple ulcers are more commonly seen with:
  - Herpes
  - Chicken pox or shingles (VZV)
  - Mononucleosis (EBV)

  - Secondary syphilis
  - Candidiasis
  - Scabies
  - Behçet's syndrome
  - Aphthous ulcers
  - Fixed drug reactions

- Acute ulcers should be cultured for bacterial, viral, and fungal infections.
- Ulcers commonly appear following a prodromal viral illness, such as a gastrointestinal, upper respiratory, or nonspecific febrile illness.
- A biopsy may be performed, particularly if the ulcers are unexplained and chronic or recurrent.

  - The biopsy should be done at the edge of the lesion, not at the base.
  - The biopsy should include normal skin.
  - Serology may be helpful (HSV, VDRL, EBV).

- Herpes simplex virus infection:

  - Patients with herpes simplex presents with painful, multiple, vesicular, or ulcerative lesions.
  - The incubation period is 2–7 days.
  - During the first episode, 50–75% have systemic symptoms including fever, malaise, headache, myalgias, and bilateral tender inguinal lymphadenopathy.
  - The majority of genital lesions are caused by HSV-2.
  - Auto-inoculation from HSV-1 can occur, and it often has less frequent recurrences.
  - The virus is usually shed from active lesions, but asymptomatic shedding can occur.
  - The inactive virus resides in the dorsal root sacral ganglia.
  - The diagnosis is made by virus isolation from tissue culture.
  - Treatment include:

    Analgesics
    Oral antiviral medication (such as acyclovir).
    Antibiotics to treat secondary infection if present.
    Intravenous therapy may be required for severe disease.

- Infectious mononucleosis:

  - This is caused by Epstein Barr virus.
  - Patients typically present with flu-like symptoms and a sore throat.
  - Some patients present also with vulvar ulcers.
  - The ulcers are typically described as painful, punched-out lesions with irregular borders.
  - Diagnosis;

    The monospot heterophile antibody test may not be reliable.
    EBV titres will confirm the diagnosis.

- Treatment:

  These are usually self-limited.
  They may last a few weeks.
  Treatment is supportive and includes sitz baths and topical or oral analgesics.

- Aphthous ulcers:
  - These are known as canker sores when they affect the oral mucosa.
  - They can also be seen in the genital area.
  - They are painful, shallow ulcers involving mucosal surfaces.
  - They are non-infectious and possibly immune-mediated.
  - Treatment is symptomatic.
- Behçet's syndrome:
  - This is a chronic, relapsing systemic vasculitis.
  - The exact etiology is unknown.
  - It is more prevalent in individuals of Japanese or Mediterranean origin.
  - Presentation:

    Recurrent, painful oral or genital ulcers (or both).
    The ulcers may be single or multiple, shallow or deep, round to oval in shape.
    The ulcers usually have a yellowish necrotic base.

  - The International Study Group for Behçet's suggests that the diagnosis include:

    The presence of oral aphthous ulcers recurring at least three times a year.
    Plus at least two of the following:

    - Recurrent genital ulcers
    - Uveitis
    - Retinal vasculitis
    - Skin involvement such as erythema nodosum, or a positive pathergy test

  - Treatment:

    Treatment is primarily symptomatic.
    Corticosteroids and other drugs (e.g., colchicine, methotrexate) have been used also.

- Crohn's disease:
  - This is an inflammatory bowel disease.
  - It may have vulvar manifestations including linear ulcers with prominent edema, fissures, or fistulas.
  - Occasionally vulvar ulcers may precede gastrointestinal symptoms.

- Fixed drug eruptions:
  - These can also involve the genitalia.
  - The ulcers are usually recurrent, occurring in the same location each time the drug is ingested.
  - Possible implicated medications include:

    NSAIDs
    Acetaminophen
    Metronidazole
    Sulfonamides
    Tetracycline
    Phenytoin
    Oral contraceptives
    Barbiturates

8.7 Urethral Prolapse

- Urethral prolapse is very rare in prepubertal girls.
- It is more common in black female children than in white.
- It is characterized by protrusion of the urethral mucosa beyond the urethral meatus, forming a beefy, red, friable, congested mass.
- Urethral prolapse typically presents as painless vaginal bleeding, commonly in girls aged 5–8 years.
- Physical exam will reveal a circular red or blue protrusion typically arising from or obscuring the vaginal introitus.
- Etiology:
  - The exact etiology of urethral prolapse is not known.
  - Urethral prolapse is often precipitated by a history of repeated Valsalva, such as would occur with chronic constipation, chronic cough, or a urinary tract infection with the constant sensation of needing to strain.
  - It was proposed that hypo-estrogenic state in young females predisposes the child to urethral prolapse. The patient may be referred with urinary tract symptoms (hematuria, dysuria), blood staining in the diaper or undergarments, a vaginal mass, or concerns about abuse.
- Treatment:
  - This is controversial
  - Some authors advocate surgery as first line therapy
  - Others advocate conservative treatment.
  - Conservative treatment includes:

    Topical estrogen cream
    Topical estrogen cream can be applied to the affected area twice daily for 2–4 weeks.

Soothing tub soaks
Analgesics
Sitz baths
Topical povidone
The child may need to void in a tub bath to reduce the discomfort.
Treating the Valsalva-related precipitant is paramount.

– Surgery:

Surgery is indicated when conservative measures fail or in those with recurrent urethral prolapse.
Surgery involves excision of the prolapsed distal mucosa with re-anastomosis of the proximal urethral mucosa to the vestibule using a fine absorbable suture.
Surgical complications include:

- Bleeding
- Urethral stenosis
- Recurrence

8.8 Atopic Dermatitis

- Atopic dermatitis is one of the most common skin disorders seen in infants and children.
- It affects 10–15% of the children.
- It is a chronic disorder that is often seen with allergies and asthma.
- Etiology:
  - Atopic dermatitis results most likely from a primary immunologic abnormality.
  - The defect is altered T-cell immune function.
  - Add to this a coexisting structural abnormality of the skin, leaving a compromised barrier against external irritants.
- Classification:
  - Atopic dermatitis is classified based on the age of the patient.
  - In children atopic dermatitis is classified as follows:

The infantile atopic dermatitis:

- This is seen commonly in infants 2–6 months of age.
- It is characterized by erythema, papules, vesicles, and intense pruritus on the face, trunk, or extremities.
- Infantile atopic dermatitis usually spares the diaper area because of its moist nature.

Childhood atopic dermatitis:

- This occurs in the prepubertal years.
- Commonly it affects the wrists, ankles, and antecubital and popliteal fossas.
- The lesions are usually drier and can eventually become lichenified.
- The patients can also have "wet" lesions that can be erythematous, edematous, oozing, and weepy.
- When the vulva is involved, pruritus is common.
- There is an increased chance of secondary infections in these patients with bacteria or with fungus.

- Treatment:
  - Control of possible offending allergic agents, such as food or environmental allergens.
  - Lubricants should be used frequently to moisten and rehydrate dry areas.
  - Wet compresses with Burrow's solution can also be used to soothe acutely inflamed skin.
  - To reduce the chance of secondary infection, parents should be instructed to keep the child's fingernails short and clean.
  - Systemic antihistamines can be used to treat severe pruritus.
  - Topical corticosteroids are used to treat atopic dermatitis but should be used with extreme caution in the genital.
  - Topical corticosteroids can be associated with side effects which include:

    Immune suppression

    - Telangiectasias
    - Striae
    - Pigment changes

    These side effects depend on the duration, potency, and location of use of topical corticosteroids, especially in intertriginous areas.
    Tacrolimus (also known as FK506) is a nonsteroidal topical preparation that is also used to treat atopic dermatitis.
    Tacrolimus was shown to be the safe and effective in treating atopic dermatitis.
    Patients with severe or refractory atopic dermatitis should be referred to a dermatologist.

8.9 Seborrheic Dermatitis

- Seborrheic dermatitis is a relatively common condition characterized by:
  - Erythematous, scaly, crusting, or greasy-appearing eruptions.
  - It occurs in places that have high concentrations of sebaceous glands, mainly the scalp, face, neck, axillae, and intertriginous areas.

- Infantile seborrheic dermatitis is seen in infants as early as the second week.
- It may persist up to 12 months of age and resolves spontaneously.
- Seborrheic dermatitis can be complicated by bacterial infections especially when it occurs in the groin area.
- The following features differentiates seborrheic dermatitis from atopic dermatitis:
  - Its early onset
  - Greasy, scalelike appearance
  - Predilection for the scalp and intertriginous areas
  - Absence of pruritus
- Treatment:
  - Seborrhea is treated with softening of the scales with selenium sulfide preparations, lubricants, and antifungal agents.
  - Refractory cases should be referred to a dermatologist.

8.10 Lichen Simplex

- Lichen simplex is a thickening of the skin in response to scratching.
- The skin becomes "lichenified" and thus is thickened in response to repeated irritation.
- There may also be an element of psoriasis, eczema, or lichen sclerosus.
- The lesions clinically appear as pale with increased skin margin markings.
- Histologically, the skin is hyperkeratotic and acanthotic, with dermal inflammation.
- Treatment:
  - Lichen simplex is treated with topical corticosteroids (1–2% hydrocortisone) until the underlying factors causing the problem are eliminated.
  - Antihistamines are also useful.

8.11 Psoriasis

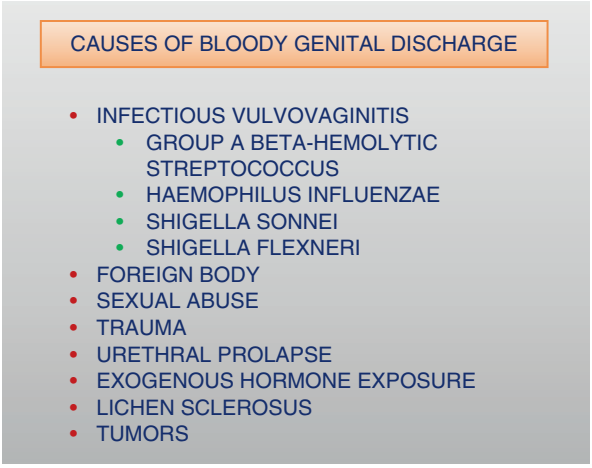
- Psoriasis is a papulosquamous skin disease caused in part by a marked increase in epidermal cell turnover, with excessive cell proliferation.
- Psoriasis affects adults mainly.
- It can be inherited, with up to one third of patients having a family member with the disease.
- In the pediatric age group:
  - 2% of patients with psoriasis were diagnosed as infants
  - 8% of patients with psoriasis were diagnosed as children
  - 25% of patients with psoriasis were diagnosed as adolescents.

- In 17% of patients with psoriasis the vulvar is affected.
- Psoriasis results from a T-cell lymphocyte immune response that stimulates cytokines and other mediators to produce inflammation.
- Psoriasis most frequently affects:
  - The scalp
  - Extensor surfaces of the limbs (elbows and knees)
  - The sacral region
  - In the genital area, the vulva, perineum, and anus may be involved, sparing the labia minora and vagina.
- Psoriasis is characterized by:
  - Psoriatic lesions appear as well-demarcated erythematous papules or plaques that have adherent silvery or gray scales.
  - Arthritis is an associated finding in up to 5–7% of patients and occurs up to 2 years after the onset of skin findings.
  - The lesions of the genital region are not scaly.
  - The lesions may have a glazed appearance with or without superficial erosions and fissuring deep in folds (flexural psoriasis).
  - Nail pitting or the presence of scalp or postauricular erythema and scaling may be subtle signs to help confirm the diagnosis.
  - In rare instances, the vulva may be the only site of disease.
  - As psoriasis is primarily a process that involves the epidermis, scarring is rare.
  - Removal of scales produces the characteristic punctate bleeding points known as the Auspitz sign, resulting from the rupture of capillaries high in the papillary dermis.
  - Another phenomenon characteristic of psoriatic lesions is the Koebner phenomenon, an abnormal reaction of the skin in which local injury or trauma produces an extension of the lesion.
  - Koebner's phenomenon appears 3–30 days post injury.
- Stress, cutaneous injury, and upper respiratory streptococcal infections may trigger exacerbations.
- Treatment:
  - Avoidance of skin injury
  - Good vulvar hygiene
  - Emollients and moisturizers may be helpful
  - Treatment of concurrent infections with antibiotics and antifungals
  - Streptococcal vulvovaginitis may be seen in conjunction with psoriasis and this should be treated.
  - Topical steroids are commonly used for initial control (fluorinated ointments are recommended to be used two to three times daily).
  - Topical corticosteroids can produce dramatic results even at low potencies.
  - Topical corticosteroids should be used cautiously, especially in the genital area, because of the increased potential for side effects.
  - Low potency steroids can be used for maintenance with or without weak tar preparations.

- The use methotrexate or retinoids, should be considered as second line agents and should be avoided as much as possible for children with vulvar psoriasis.
- Patients with complicated and extensive involvement should be referral to a dermatologist.

8.12 Straddle Injury

- There are several causes for vaginal bleeding in the prepubertal girl which include:
  - Trauma
  - Vulvar dermatologic abnormality
  - Precocious puberty
  - Foreign body
  - Urethral prolapse
  - Occasionally withdrawal bleeding occurs shortly after birth due to the withdrawal of maternal estrogens.
  - The condition usually ceases within 5–6 days but rarely vaginoscopy may be necessary to rule out a vaginal tumor.
- Straddle injury usually refers to a genital injury resulting from inadvertent trauma to the perineum.
  - Falling on to the cross-bar of a bicycle.
  - Slipping off a diving board.
  - Mishaps related to monkey bars or jungle gyms.
- Most injuries are minor lacerations or abrasions of the labia minora and posterior fourchette, accompanied by bruising of the labia majora and mons.
- The labial fat pads of the vulva may act as a barrier protecting the hymen and lower vagina.



- The labia minora can be severed leading to persistent bleeding.
- External bruising, which may not be noted until the following day, is a common finding.
- Injuries to the urethra and bladder are uncommon in females unless the injury is severe and associated with pelvic bones fractures.
- The treatment is conservative and examination under anaesthesia is indicated in the following situations:
  - Inability to void or concern about urethral injury
  - Continuous bleeding requiring suture or hemostasis
  - A large or expanding hematoma that needs to be evacuated
  - Suspected anal sphincter injury
  - Penetrating injury necessitating inspection of the upper vagina
- Conservative management includes:
  - Analgesics.
  - Intermittent ice packs to reduce swelling.
  - If the child develops urinary retention, a temporary urethral catheter may be inserted.
  - Sitz baths.
- Hymenal, vaginal, or perianal lacerations suggest a penetrating genital injury and are suspicious for sexual assault or abuse.
- Signs of other injuries elsewhere on the body may raise suspicion of abuse.

8.13 Pediatric Vulvovaginitis

- Vulvovaginitis is one of the most common gynecologic problems in premenarchal girls.
- It accounts for approximately 80–90% of outpatient visits by children to gynecology offices.
- Vulvovaginitis usually occurs in the 2–6 year old age group.
- Vulvovaginitis may result from multiple causes including:
  - Infection
  - Irritation
  - Foreign body
  - Allergy
  - Systemic diseases
  - Sexual abuse
- Vulvovaginitis may have a nonspecific etiology or may be due to known pathogens.
- Non-specific vulvovaginitis is probably the most common pediatric gynecological problem seen.

- The symptoms of vulvovaginitis include:
  - Local discomfort
  - Irritation and pruritus
  - Dysuria
  - Local erythema
  - bleeding
  - Vaginal discharge which may be purulent
- Associated urinary tract infections may be caused by reflux. The urinalysis is often contaminated, so culture of a catheterized specimen may be required.
- If there is a foul odor with discharge, a foreign body should be suspected.
- The possibility of sexual abuse should be considered and cultures taken to rule out specific infections such as gonorrhea.
- Most cases will respond to sitz baths and ointments such as Mycolog.
- Resistant cases may require a short course of estrogen cream.
- The incidence of recurrence is high.

8.14 Etiology

- Nonspecific vulvovaginitis accounts for 50–75% of vulvovaginitis cases in girls.
- This is attributed to several factors including:
  - Small labia minora
  - Absence of labial fat pads
  - Absence of pubic hair
  - Diminished protection of the introitus by the labia majora
  - The proximity of the anus to the vagina (Fig. 8.4a, b)
  - Prepubertal girls are hypoestrogenic and therefore have thin vaginal epithelium which is susceptible to irritation and inflammation

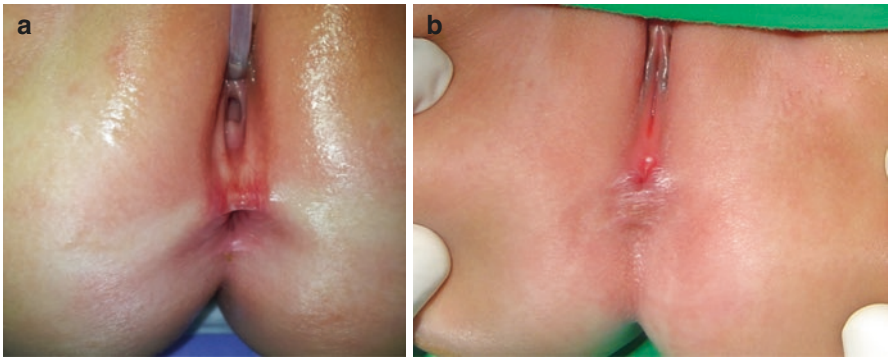


Fig. 8.4 (**a** and **b**) A clinical photographs showing a child with anterior ectopic anus. Note the proximity of the anus to the vagina

  - The vagina lacks lactobacilli, which may increase susceptibility to bacterial growth
  - Poor perineal hygiene
  - The use of tight-fitting
  - The use of nonabsorbent clothing
  - Exposure to chemicals such as bubble bath, shampoos, and deodorant soaps
  - Sexual abuse and frequent masturbation

- Infectious vulvovaginitis in prepubertal girls is often secondary to respiratory, enteric, and, less frequently, sexually transmitted organisms.
- The following are known causative organisms of vulvovaginitis:

  - Group A streptococcus
  - *Staphylococcus aureus*
  - Haemophilus influenza
  - *Streptococcus pneumoniae*
  - Neiserria meningitides
  - Shigella
  - Yersinia
  - Candida species
  - Gardnerella vaginalis
  - Neiserria gonorrhea
  - Chlamydia trachomatis
  - Human papillomavirus

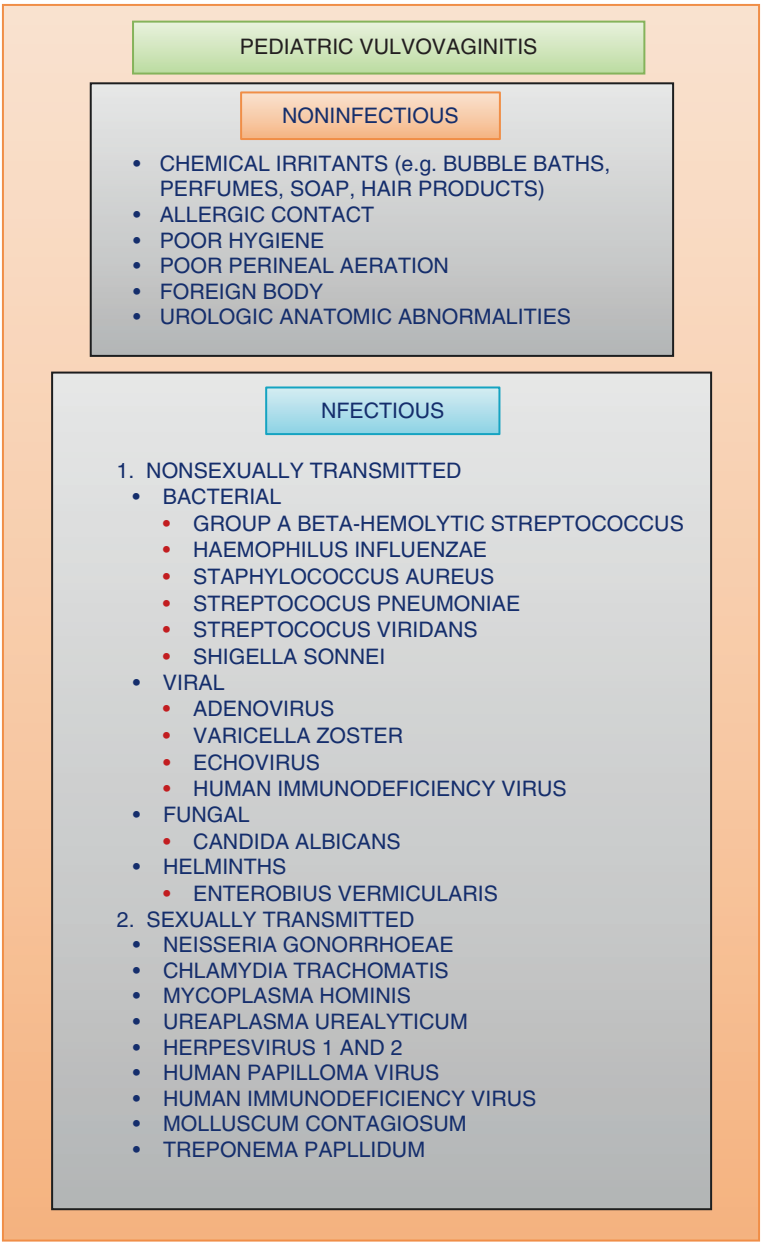
- Recurrent vulvar/perianal pruritis, especially at night, is suspicious for a parasitic infection such as pinworms (*Enterobius vermicularis*).
- Other rare noninfectious causes of vulvovaginitis:

  - Foreign bodies
  - Vaginal polyps
  - Tumors
  - Systemic illnesses
  - Ectopic ureters
  - Urethral prolapse

8.15 Diagnosis

- The evaluation of vulvovaginal region may reveal a markedly mottled erythematous appearance.
- In patients with vulvovaginitis, it is important to differentiate between infectious and noninfectious causes.
- In the pediatric age group there is overlap between normal flora and potential pathogens which makes it difficult to differentiate between infectious and noninfectious causes of vulvovaginitis.

- The presence of purulent vaginal discharge suggests an infectious cause and calls for microbial investigation.
- A diagnosis of nonspecific vulvovaginitis should be made if vaginal cultures grow normal flora and no other etiology is known for the vulvovaginitis.
- Diagnostic tests include a wet prep, smear for Gram stain, and aerobic culture.



- A pinworm test in suspected cases.
- Chlamydia/gonorrhea cultures should be done if sexual abuse is suspected.

8.16 Noninfectious Vulvovaginitis

- This is also called nonspecific vulvovaginitis.
- One of the most common causes of noninfectious vulvovaginitis is poor perineal hygiene.
- Another common cause of vulvovaginitis is excessive or prolonged exposure to moisture combined with poor aeration of the perineal tissues. This is predisposed to by several factors including:
  - Obesity
  - Wearing tight or synthetic undergarments
  - Exposure to long periods of wet undergarments
  - Enuresis
- Vaginal foreign bodies can also present as nonspecific vulvovaginitis.
  - These patients usually present with profuse, persistent, foul-smelling vaginal discharge that may be blood stained.
- Patients with nonspecific vulvovaginitis may show nonspecific inflammation to severe excoriation, which may be associated with secondary bacterial infections, most commonly due to *Staphylococcus aureus*.
- Allergic vulvovaginitis or contact dermatitis:
  - These patients may present with pruritus.
  - Offending agents include topical creams, lotions, perfumed soaps, toilet paper, and poison ivy.
  - With chronic exposure, the vulva may develop cracks or fissures and eventually a lichenified appearance.
  - Eosinophils in the vaginal fluid may be found in cases resulting from allergic reactions.
  - Chemical irritants from bubble baths, laundry detergents, soaps, and fabric softeners produce a similar clinical picture.
- Anatomic disorders are rare causes that can present as vulvovaginitis.
- These anatomic disorders include;
  - Ectopic ureter
  - Urethral prolapse
  - Vesicovaginal fistula
  - Rectovaginal fistula
- Patients with ectopic ureter typically present with a history of incontinence and a constantly wet perineum.

- These patients can be easily misdiagnosed as having primary enuresis or stress incontinence.
- A voiding cystourethrogram confirms the diagnosis.
- Patients with vesicovaginal fistulas present with a constantly wet perineum and nonspecific vulvovaginitis and excoriation.
- The presence of feculent vaginal discharge suggests a rectovaginal fistula.
- Patients with urethral prolapse usually present with blood staining on their underwear, vaginal bleeding with accompanying vulvar pain or dysuria. Examination reveals an everted, red, circular mass at the external urethral meatus.
- Treatment:
  - Attention should be paid to perineal hygiene.
  - Undergarments should be 100% cotton, loose fitting, and cleaned or rinsed thoroughly with mild hypoallergenic detergent without fabric softener.
  - Acute nonspecific vulvovaginitis can be treated symptomatically with frequent sitz baths containing baking soda or colloidal oatmeal or with wet compresses of Burrow's solution.
  - Severe cases can be treated with a 1% hydrocortisone cream once or twice a day for up to 2 weeks.
  - Estrogen cream can be used to facilitate healing.
  - Antibiotics can be used to treat superinfection.
  - Recurrent symptoms requiring repeated trials of medication might warrant examination under general anesthesia and vaginoscopy to rule out a foreign body.

8.17 Infectious Vulvovaginitis, Nonsexually Transmitted

- Vaginal discharge is a more prominent finding associated with infectious causes of vulvovaginitis than with noninfectious causes.
- The diagnosis of infectious vulvovaginitis is based on a positive culture of vaginal discharge.
- Group A beta-hemolytic streptococci (GAS), *Streptococcus pneumoniae*, and Hae-mophilus influenzae can cause a purulent vaginal discharge.
- The vaginal discharge in vulvovaginitis can be accompanied with other symptoms such as:
  - Vulvovaginal erythema
  - Edema
- Viral vulvovaginitis can be caused by:
  - Adenovirus
  - Varicella
  - Echovirus

  - Epstein-Barr virus
  - Herpesvirus 1 and 2

- Viral vulvovaginitis usually present as ulcerative lesions in the vaginal area.
- The diagnosis can be confirmed by a special viral culture medium and treatment with acyclovir may be initiated while awaiting cultures.
- Gastrointestinal pathogens such as Shigella can produce an acute or chronic vaginal discharge that is bloody, purulent, and foul-smelling, with associated vulvovaginal erythema. It is sometimes associated with diarrhea.
- Culture of the vaginal discharge is diagnostic, and appropriate systemic antibiotics can be administered.
- *Enterobius vermicularis* (pinworms) usually causes perianal itching and sometimes vulvovaginitis (vaginal discharge, nonspecific inflammation, and excoriation from scratching).
- The diagnosis is confirmed by observation of pinworm ova and/or adults with a saline wet mount or with Scotch tape testing, which is best done when the patient is asleep during the night, when the worms emerge to feed.
- Patients are treated with mebendazole.
- Candidal vulvovaginitis is extremely rare in healthy prepubertal children.
- Predisposing factors for Candidal vulvovaginitis include:

  - Recent antibiotic use
  - Poor perineal aeration
  - Inflammatory skin conditions such as seborrheic dermatitis
  - Diabetes mellitus
  - Immunodeficiency syndromes

- The presentation of these patients include:

  - Pruritus
  - Dysuria
  - Diffuse vulvar erythema
  - Thick cheesy vaginal discharge
  - Excoriation from scratching
  - The presence of white plaques on the vaginal mucosa. “Satellite lesions”.
  - Erythematous prominences in the creases are characteristic of candidal rashes, especially in those who wear diapers.

- A patient with a candidal infection will have a low vaginal pH, and budding yeast and pseudohyphae can be seen with a saline wet mount and KOH preparation.
- Treatment consists of topical or oral antifungal agents such as fluconazole.
- The area should be kept as dry as possible.
- Persistent candidal vulvovaginitis especially in the prepubertal child, should prompt investigation for the presence of diabetes or HIV or other immunodeficiency syndromes.

8.18 Infectious Vulvovaginitis, Sexually Transmitted

- The possibility of sexual abuse must be kept in mind when evaluating prepubertal girls with sexually transmitted vulvovaginitis.
- When sexual abuse is confirmed, these patients should be referred to a child abuse specialist to ensure proper and complete care.
- Cultures should always be obtained for gonorrhea and chlamydia before treatment.
- The clinical features include:
  - Pruritus
  - Dysuria
  - Vaginal discharge, and odor
- Vulvovaginitis, secondary to infection with *Neisseria gonorrhoeae* is associated with a purulent thick yellow discharge along with vulvar erythema, edema, and excoriation and inguinal lymphadenopathy.
  - This is indicative of sexual abuse.
  - Diagnosis is confirmed with a culture and the patient is treated with antibiotics.
- Chlamydia trachomatis can cause vulvovaginitis with pruritus and a vaginal discharge.
  - The presence of *C. trachomatis* is also indicative of sexual abuse, but it can also be acquired perinatally.
  - Culture of the vaginal discharge confirms the diagnosis.
  - The patient should be treated with azithromycin or doxycycline.
- Trichomonas is diagnosed by observing the organisms with a saline wet mount and can be recognized by the presence of a fishy odor (positive "whiff") when potassium hydroxide is added to the sample of vaginal discharge.
  - It is treated with metronidazole.
- Bacterial vulvovaginitis is predominantly associated with sexual abuse but has been reported in normal patients.
  - It is diagnosed by the presence of a positive "whiff," a higher-than-normal pH, and the presence of "clue cells" with a saline wet mount.
  - Treatment is with metronidazole.
- Herpes simplex virus (HSV) produces vesicular lesions with a resultant ulcerative vulvovaginitis.
  - It is usually associated with inguinal lymphadenopathy and systemic symptoms.
  - HSV can be treated with acyclovir.

- Human papilloma virus (HPV):
  - This causes condyloma acuminate.
  - It is characterized by painless, soft, moist, granular, and friable lesions.
  - These lesions are seen predominately in the vaginal vestibule and perianal area.
  - The lesions can become secondarily infected and produce pruritus, pain, and discharge.
  - Treatment consists of cryotherapy or serial applications of TCA.
- Molluscum contagiosum are waxy, centrally umbilicated lesions 2–5 mm in diameter.
  - Treatment can include imiquimod cream or curettage.
- Vulvovaginitis from syphilis is usually due to the manifestation of secondary syphilis, which includes a rash over the perineum and inner thighs and development of condyloma lata on the vulva and anus.

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Chapter 9
Inguinal and Femoral Hernias in Girls

Ahmed H. Al-Salem and Osama A. Bawazir

9.1 Introduction

- Hippocrates was the first to use the Greek term *hernios* for bud or bulge to describe abdominal wall hernias.
- Abdominal wall hernias are defined as protrusions of abdominal contents through a defect or weakness in the abdominal wall.
- Abdominal wall hernias are among the most common surgical problems seen in infants and children.
- There are several different types of abdominal wall hernias in infants and children.
- These including (Fig. 9.1):
  - Inguinal hernia
  - Umbilical hernia
  - Paraumbilical hernia
  - Epigastric hernia
  - Femoral hernia
  - Spigelian hernia
  - Lumbar hernia
  - Incisional hernia
  - Other rare hernias

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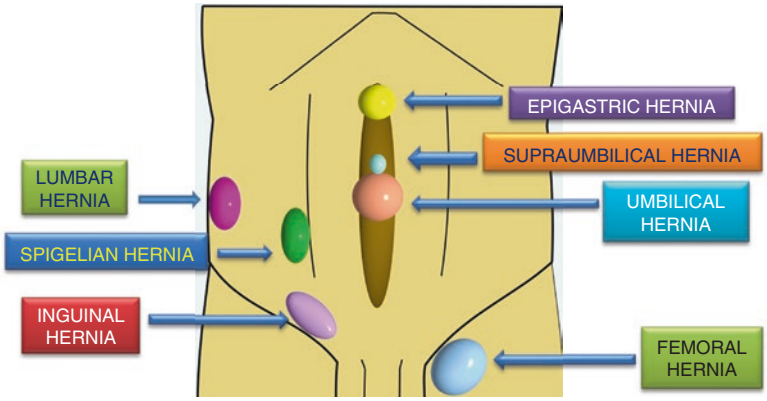

Fig. 9.1 Diagrammatic representation of the different types of abdominal wall hernias and their sites of occurrence

- The incidence of these hernias in infants and children is also variable.
- The frequency of the different types of these hernias among males and females is also different.
- The management of abdominal wall hernias is different and depends on the type of hernia, age of the patient and mode of presentation.

9.2 Inguinal Hernia

- The exact incidence of indirect inguinal hernia in infants and children is unknown.
- The incidence of hernias is about 10–20 per 1000 live births and is much more common in premature infants.
- Indirect inguinal hernias are more common on the right side and about 60% of hernias occur on the right side.
- Premature infants are at increased risk for inguinal hernia, with incidence rates of 2% in females and 7–30% in males.
- Approximately 5% of all males develop a hernia during their lifetime.
- Inguinal hernias are much more common in males than in females.
- The male-to-female ratio is estimated to be 4–8:1 (Figs. 9.2a, b and 9.3).
- Moreover, the risk of incarceration of inguinal hernia is more than 60% in premature infants.
- Inguinal hernias:
  - 60% on the right side
  - 30% on the left side
  - 10% are bilateral

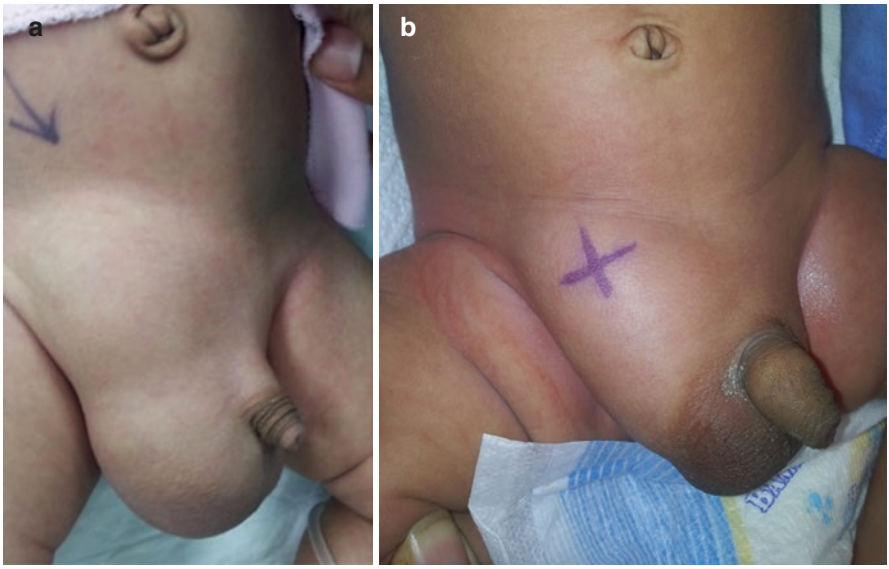

Fig. 9.2 (**a** and **b**) Clinical photographs showing a large right side inguinal hernia in two infants

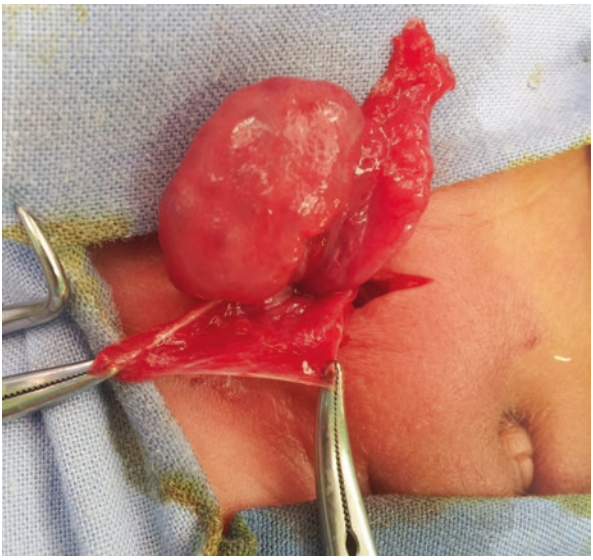

Fig. 9.3 A clinical photograph showing a right inguinal hernia in a girl. Note the ovary in the hernia sac

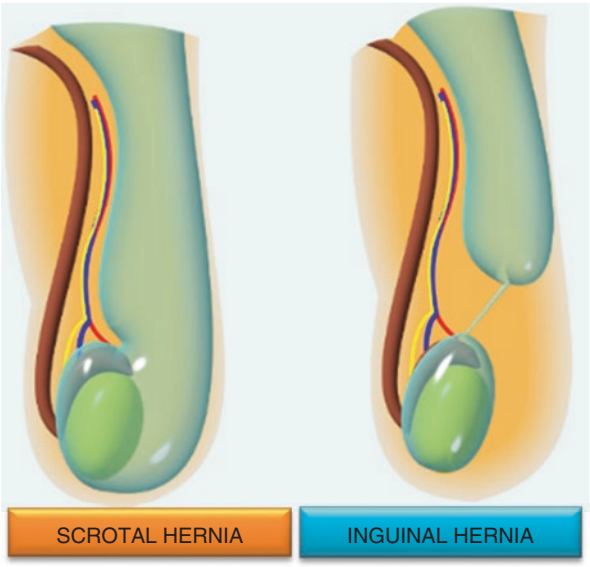

Fig. 9.4 Diagrammatic representation of the classic inguinal hernia and inguinal hernia extending into the scrotum (scrotal hernia)

- Anatomically speaking, indirect and direct inguinal hernias differ in that the direct hernia bulges through the inguinal floor medial to the inferior epigastric vessels and the indirect hernia arises lateral to the inferior epigastric vessels.
- Inguinal hernia can be:
  - Complete: Where the whole sac descends into the scrotum and surrounds the tesis (Scrotal hernia).
  - Incomplete: Where the hernial sac ends up in the inguinal canal above the testis (Inguinal hernia) (Fig. 9.4).

9.3 Etiology

- Inguinal hernias are congenital.
- Embryologically, the processus vaginalis is an outpouching of peritoneum attached to the testicle that trails behind as it descends retroperitoneally into the scrotum.
- Normally, the processus vaginalis obliterates.
- When obliteration of the processus vaginalis fails to occur, inguinal hernia results.
- Increased intra-abdominal pressure is seen in a variety of conditions and contributes to the appearance of inguinal hernia.
- Increased intra-abdominal pressure is seen associated with the following conditions:

  - Chronic cough
  - Ascites
  - Increased peritoneal fluid from biliary atresia, peritoneal dialysis or ventriculoperitoneal shunts
  - Intraperitoneal masses
  - Organomegaly
  - Constipation

- Other conditions associated with increased incidence of inguinal hernias are:
  - Extrophy of bladder
  - Neonatal intraventricular hemorrhage
  - Myelomeningocele
  - Undescended testes

- The following conditions are associated with an increased risk of inguinal hernia:
  - Prematurity and low birth weight
  - Urologic conditions:

    Cryptorchidism
    Hypospadias
    Epispadias
    Exstrophy of the bladder
    Ambiguous genitalia
    Cloacal exstrophy

  - Patent processus vaginalis, which may be present because of increased intraabdominal pressure due to ventriculoperitoneal shunts, peritoneal dialysis, or ascites
  - Abdominal wall defects

    Gastroschisis
    Omphalocele

  - Family history

    Meconium peritonitis
    Cystic fibrosis
    Connective tissue disease
    Mucopolysaccharidosis
    Congenital dislocation of the hip
    Ehlers-Danlos syndrome
    Marfan syndrome
    Fetal hydrops
    Liver disease with ascites
    Ventriculoperitoneal shunting for hydrocephalus

9.4 Clinical Features

- The parents of infants and children with an inguinal hernia present to the hospital or clinic with a history of a swelling that is commonly intermittent, in the inguinal or inguino-scrotal region in boys and inguinal or inguino-labial region in girls.
- The swelling commonly comes and goes.
- The swelling commonly occurs after crying or straining.
- Sometimes, they present with an obvious swelling at the inguinal region or sometimes within the scrotum in boys.
- The swelling is painless and reducible in a simple inguinal hernia.
- The presence of a painful swelling suggests an incarcerated inguinal hernia (Fig. 9.5).
- Patients with an incarcerated hernia generally present with a tender firm mass in the inguinal canal or scrotum that is irreducible.
- Silk sign: When the hernia sac is palpated over the cord structures, the sensation may be similar to that of rubbing two layers of silk together. This finding is known as the silk sign and is highly suggestive of an inguinal hernia.
- Patients with testicular feminizing syndrome may present as unilateral or bilateral inguinal hernias in agentically males and phenotypically females.
  - During inguinal herniotomy these patients will have normal looking testes in the hernial sacs (Fig. 9.5a–c)

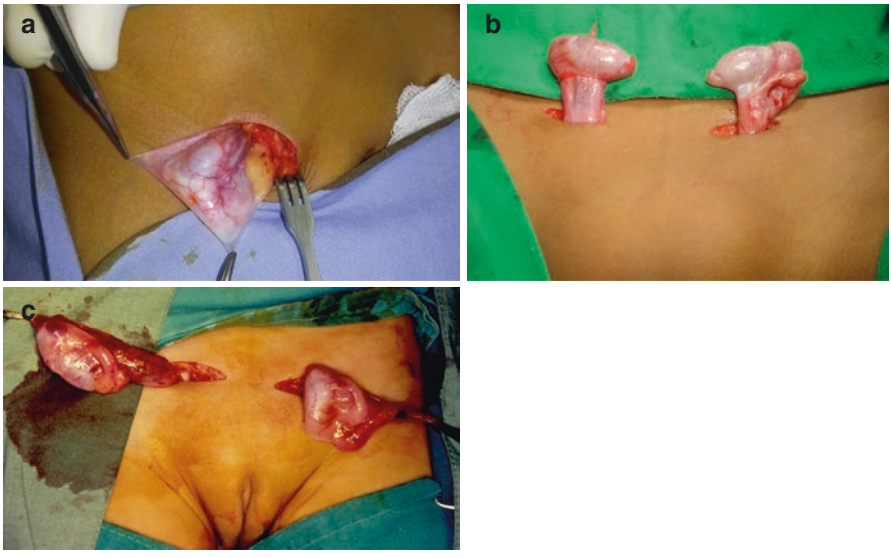

Fig. 9.5 (**a–c**) Clinical intraoperative photographs showing girls with testicular feminizing syndrome. Note the normal female external genitalia and the presence of normal looking testes in the inguinal hernial sacs

9.5 Complications of Inguinal Hernias

1. Incarceration (Fig. 9.6):
   - The herniated bowel in inguinal hernia can become swollen, edematous and engorged within the hernia sac.
   - The hernia becomes irreducible and causes intestinal obstruction in infants and children.
   - Every attempt should be made to reduce it manually.
   - Incarceration occurs in 17% of right-sided hernias and 7% of left-sided hernias.
   - More than 50% of cases of incarceration occur within the first 6 months of life; the risk gradually decreases after age 1 year.
   - Premature infants have twice the risk of incarceration than the general pediatric population.
   - More than two thirds of all incarcerations occur in children younger than 1 year.
   - Girls are more likely to develop incarceration of an inguinal hernia; the incidence in girls is 17.2%, whereas the incidence in boys is 12% (Fig. 9.7).

2. Strangulation:
   - Once the vascular supply of the herniated contents becomes compromised, the hernia becomes strangulated.
   - This may lead to ischemic necrosis and intestinal perforation.
   - This is an indication for emergency surgical exploration (Fig. 9.8a, b).

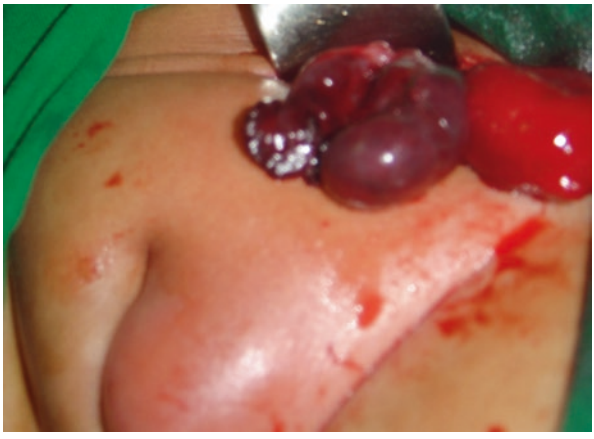

Fig. 9.6 A clinical photograph showing left inguinal hernia containing the ovary that was irreducible and became necrotic

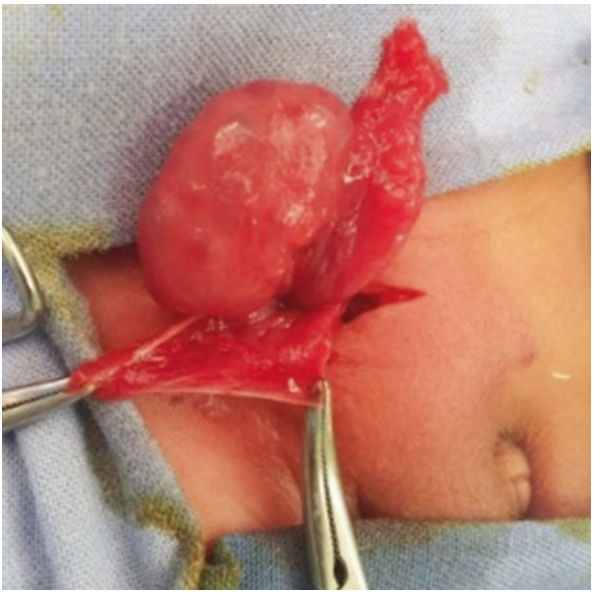

Fig. 9.7 An intraoperative photograph showing irreducible hernia containing the ovary which was swollen

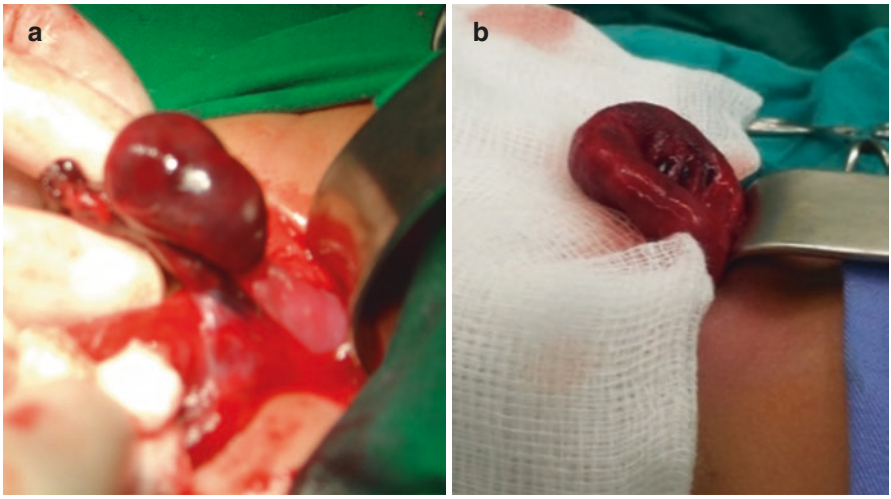

Fig. 9.8 (**a** and **b**) Clinical photographs showing a strangulated inguinal hernia. Note the necrotic ovary and the colour of the intestne as a result of strangulation

9.6 Treatment

- All pediatric inguinal hernias require operative treatment to prevent the development of complications, such as incarceration or strangulation.
- Most inguinal herniatomies are performed as a day case surgery.

- Laparoscopic hernia repair in children is not performed as commonly as in adults.
- Contralateral inguinal hernia exploration:
  - There is controversy about whether the contralateral groin should be explored.
  - Today, most surgeons do not routinely perform a contralateral exploration unless a contralateral inguinal hernia or patent processus vaginalis can be demonstrated either by preoperative ultrasonography or intraoperative laparoscopy.
  - A hernia develops in the other side of the groin in up to 30% of children who have had hernia surgery. This is more so if the initial hernia was on the left side.
  - When an inguinal hernia is present, some pediatric surgeons perform a contralateral groin exploration.
  - This is to detect an occult patent processus vaginalis that may lead to a hernia on the opposite side (metachronous contralateral hernia). This is present in less than 5% of cases.
  - The Goldstein test:

    This can be used to determine when to perform a contralateral groin exploration.
    In this test, the abdomen is insufflated with gas through the already open hernia sac.
    Crepitus in the opposite groin is a positive test result, suggesting a contralateral patent processus vaginalis and warranting a contralateral exploration.
    This test may not be conclusive.

  - An alternative approach is laparoscopy which can be used to detect an occult contralateral patent processus vaginalis. This can be done through a separate incision at the umbilicus or through the already opened hernia sac. This allows inspection of the contralateral inguinal ring and assessment of its patency.

9.7 Hydrocele of the Canal of Nuck

- During fetal development, the testicle develops below the kidney, within the peritoneal cavity.
- Subsequently, the testicle descends down and through the inguinal canal and finally into the scrotum.
- During its descent, it is accompanied by an extension of peritoneum (the processus vaginalis).
- Normally, the processus vaginalis obliterates and becomes a fibrous cord.
- The distal part of the processus vaginalis forms the tunica vaginalis. In postnatal life, this is a potential space that should not communicate with the peritoneal cavity of the abdomen.
- If the processus vaginalis does not close, it is referred to as a patent processus vaginalis.

- If the patent processus vaginalis is small in caliber and allow fluid to pass from the abdomen, the condition is referred to as a communicating hydrocele.
- If the patent processus vaginalis is larger, allowing ovary, intestine, omentum, or other abdominal contents to protrude, the condition is referred to as inguinal hernia.
- A hydrocele usually transilluminates on examination. However, gas-filled intestines also transilluminate. This must be considered during evaluation.
- An important point differentiating a hydrocele from an inguinal hernia is that you can get above a hydrocele but you cannot get above an inguinal hernia. The only exception to this is an abdomino-scrotal hydrocele.
- Hydrocele of the canal of Nuck:
  - This occurs in girls when fluid accumulates within the processus vaginalis in the inguinal canal.
  - Clinically it present as an inguinal swelling.
  - This is rare and must be differentiated from an inguinal hernia.
- Treatment:
  - Unlike hernias, many newborn hydroceles resolve because of spontaneous closure of the patent processus vaginalis.
  - Hydroceles can also attain a large size and size is not an indication for surgery.
  - The noncommunicating hydrocele:

    The fluid in the hydrocele is usually reabsorbed before the infant reaches age 1 year.
    Hydroceles in infants are to be observed.
    In 95% of congenital hydroceles, the natural history is one of gradual and complete resolution by 1 year of age.
    For those lasting longer than 1 year or for those non-communicating hydroceles that manifest after the first year, surgical repair is indicated since these rarely resolve spontaneously.
  - Indications for hydrocele repair:

    Congenital hydroceles that fail to resolve by age 2 years.
    Non-communicating hydroceles that manifest after I year of age.
    Continued discomfort and enlargement of hydrocele.
    Secondary infection (very rare)

9.8 Femoral Hernia

- Femoral hernia is rare in infants and children.
- Femoral hernias are a relatively uncommon type, accounting for only 3% of all abdominal wall hernias.

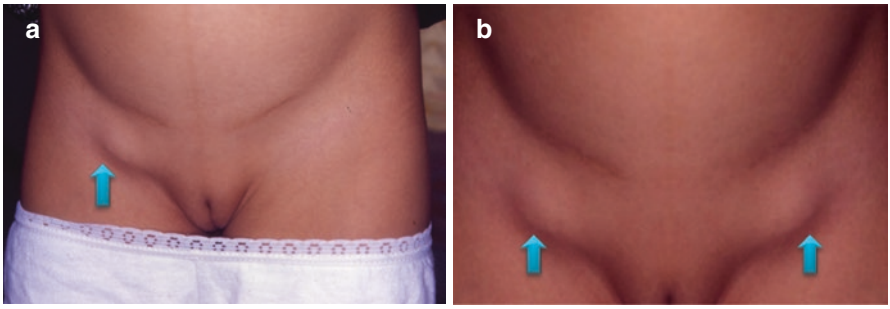

Fig. 9.9 (**a** and **b**) Clinical photographs showing unilateral and bilateral femoral hernia in two girls. Both girls were diagnosed as bilateral inguinal hernia and underwent bilateral inguinal herniotomy. Note the scars from the previous operation. Note also the position of the hernias, below the inguinal ligament and lateral to the pubic tubercle. This is important and must be kept in mind when diagnosing inguinal hernias in girls

- They form about 0.4–1.1% of all groin hernias.
- The majority, 70% of femoral hernias occur in infants under the age of 1 year.
- The first femoral hernia in children was described by Sir Astley Cooper in 1827. He described a femoral hernia in two girls.
- Femoral hernias are more common in adults than in children.
- Femoral hernias are most common in the 5–10 year age group, and unlike adults there is a similar sex incidence.
- Femoral hernia (Fig. 9.9a, b):
  - 58% on the right side.
  - 29% on the left side.
  - 13% are bilateral.

- Cooper's hernia: A femoral hernia with two sacs, the first being in the femoral canal, and the second passing through a defect in the superficial fascia and appearing almost immediately beneath the skin.
- Strangulation can happen in all hernias, but is more common in femoral and inguinal hernias due to their narrow "necks".
- The incidence of strangulation in femoral hernias is high. A 15–20% incidence of incarceration or strangulation among children with femoral hernias calls for early diagnosis and repair.

9.9 Etiology

- The exact etiology of femoral hernia is not known.
- Several factors have been cited as important predisposing factors in adults. These include:

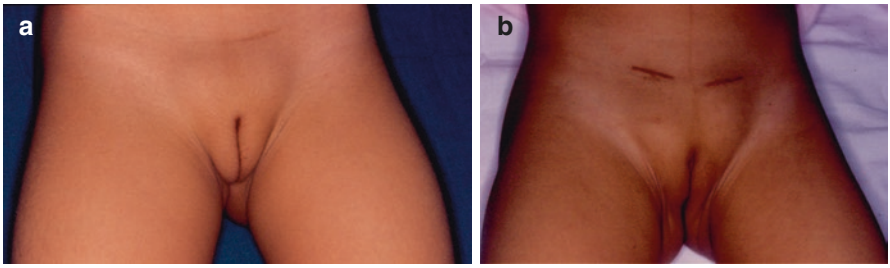

Fig. 9.10 (**a** and **b**) Clinical photographs of two girls who presented with femoral hernias but had surgery for inguinal hernia. One had unilateral inguinal herniotomy while the second one underwent bilateral inguinal herniotomy

  - Parity
  - Increased intra-abdominal pressure
  - Previous inguinal surgery

- This however is not the case in children, where femoral hernia is considered congenital.
- This is supported by its occurrence in infants and twins.
- Previous inguinal herniotomy has been incriminated as an etiological factor for femoral hernia in children. This however has not gained much support and others consider it a misdiagnosis with a coincidental inguinal hernia, which is common among children with femoral hernia (Fig. 9.10a, b).
- A correct preoperative diagnosis is made in only 43% of children with femoral hernia and because of this it is not rare for some of these children to have more than one operation for recurrent inguinal hernia before the correct diagnosis of femoral hernia is made.
- This is attributed to its rarity and lack of awareness among physicians caring for these children.

9.10 Diagnosis

- Femoral hernias occur just below the inguinal ligament, when abdominal contents pass through a naturally occurring weakness called the femoral canal.
- While femoral hernias can occur in both males and females, almost all of them develop in women because of the wider bone structure of the female pelvis.
- The femoral canal:
  - This is located below the inguinal ligament on the lateral aspect of the pubic tubercle.
  - It is bounded by the inguinal ligament anteriorly, pectineal ligament posteriorly, lacunar ligament medially, and the femoral vein laterally.

  - It normally contains a few lymphatics, loose areolar tissue and occasionally a lymph node called Cloquet's node.
  - The function of this canal appears to be to allow the femoral vein to expand when necessary to accommodate increased venous return from the leg during periods of activity.

- Femoral hernias are more common in females than in males.
- They typically present when standing erect as a groin lump or bulge.
- The bulk of a femoral hernia lies below an imaginary line drawn between the anterior superior iliac spine and the pubic tubercle (which essentially represents the inguinal ligament) whereas an inguinal hernia starts above this line.
- A 15–20% incidence of incarceration or strangulation among children with femoral hernias calls for early diagnosis and repair.

9.11 Treatment

- Several operative approaches have been described for femoral hernia repair in children.
- Simple ligation and excision of the hernia sac is insufficient, and in order to obviate recurrence this must be supplemented with repair of the femoral canal.
- Either open or minimally invasive surgery may be performed.
- Three approaches have been described for open surgery.
  - Lockwood's infra-inguinal approach.
  - Lotheissen's trans-inguinal approach.
  - McEvedy's high approach.
- The infra-inguinal approach is the preferred method for elective repair.
- The trans-inguinal approach involves dissecting through the inguinal canal and carries the risk of weakening the inguinal canal.
- McEvedy's approach is preferred in the emergency setting when strangulation is suspected. This allows better access to and visualization of bowel for possible resection.
- In any approach, care should be taken to avoid injury to the urinary bladder which is often a part of the medial part of the hernia sac.

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Chapter 10
Persistent Mullerian Duct Syndrome

Ahmed H. Al-Salem and Moustafa Hamchou

10.1 Introduction

- Persistent Müllerian duct syndrome is a rare disorder of sexual development that affects males.
- It was first described by Nilson in 1939.
- Males with this disorder have normal male reproductive organs, though they also have a uterus and fallopian tubes, and upper part of the vagina.
- This is a rare condition and results from a complete failure of the testes to produce Mullerian Inhibiting Hormone or substance (MIH, MIS).
- The Müllerian duct usually breaks down during early development in males but as a result of this failure, the Mullerian system of ducts will persist and develop into a uterus, Fallopian tubes and upper part of the vagina.
- Persistent Müllerian duct syndrome is a rare disorder; however, the prevalence of the condition is unknown.
- The affected individuals have the normal chromosomes of a male (46, XY) and normal external male genitalia.
- They usually present with undescended testes (cryptorchidism) or inguinal hernia. The undescended testes are usually bilateral and impalpable. The uterus and fallopian tubes are typically discovered at the time of orchidopexy or inguinal herniotomy (Fig. 10.1a, b).
- The most common presentation is a phenotypic male with an inguinal hernia on one side and an impalpable contralateral undescended testis.

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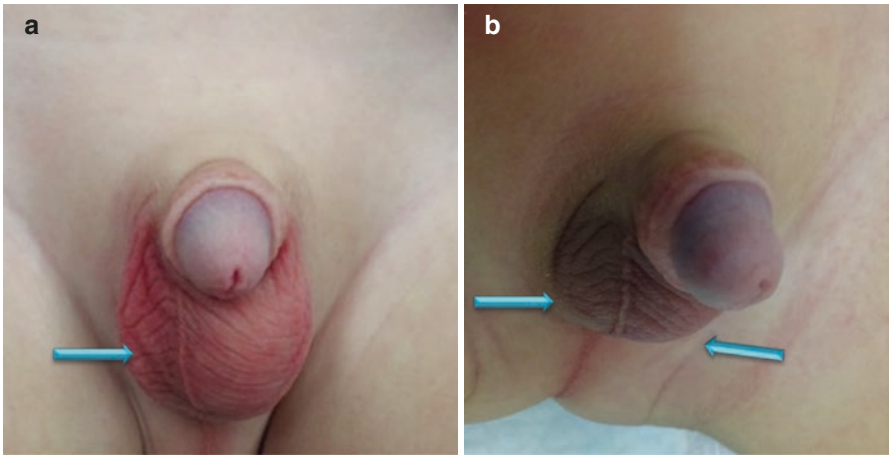

Fig. 10.1 (**a** and **b**) Clinical photographs of a patient with normal looking external genitalia and undescended right testis and another with bilateral undescended testes

- Occasionally, both testes are undescended (bilateral cryptorchidism) and the uterus and Fallopian tubes are found in the pelvis.
- Sometimes, the descended testis pulls the fallopian tube and uterus into the track through which it has descended. This creates a condition called hernia uteri inguinalis, a rare form of inguinal hernia.
- In other cases, the undescended testis from the other side of the body is also pulled into the same track, forming an inguinal hernia. This condition, called transverse testicular ectopia, is common in people with persistent Müllerian duct syndrome.
- A vas deferens is presents bilaterally, usually running close to the uterus.
- To avoid damage to the vas, care must be taken at the time of Müllerian remnants excision.
- Rarely, the vas deferens ends blindly.
- Other effects of persistent Müllerian duct syndrome may include the inability to father children (infertility) or blood in the semen (hematospermia). Also, the undescended testes may break down (degenerate) or develop cancer if left untreated.

10.2 Embryology and Etiology

- In a human fetus the Mullerian and Wolffian ducts are both present at 7 weeks of gestation.
- In a male fetus, the testis differentiates by the end of the seventh gestational week.
- Normal sex differentiation is controlled by testosterone, dihydrotestosterone, and MIF.

- Sertoli cells secrete MIF, which leads to regression of the Mullerian ducts.
- Testosterone has a direct effect on the Wolffian ducts, and promotes their differentiation into the epididymis, vas deferens, and seminal vesicles.
- Dihydrotestosterone induces male differentiation of external genitalia.
- PMDS patients have both Wolffian and Mullerian duct structures due to a deficiency of MIF.
- Persistent Müllerian duct syndrome is caused by mutations in the *AMH* gene or the *AMHR2* gene.
- The *AMH* gene provides instructions for making a protein called anti-Müllerian hormone (AMH).
- The *AMHR2* gene provides instructions for making a protein called AMH receptor type 2.
- The AMH protein and AMH receptor type 2 proteins are involved in male sex differentiation.
- All fetuses have a pair of the Müllerian duct, the precursor to female reproductive organs (uterus, Fallopian tubes, and upper vagina).
- During development of a male fetus, these two proteins work together to induce breakdown and regression of the Müllerian duct.
- Mutations in the *AMH* and *AMHR2* genes lead to nonfunctional proteins that cannot signal for regression of the Müllerian duct.
- As a result of these mutations, the Müllerian duct persists and goes on to form a uterus, Fallopian tubes and upper vagina.
- Approximately 45% of cases of persistent Müllerian duct syndrome are caused by mutations in the *AMH* gene and are called persistent Müllerian duct syndrome type 1.
- Approximately 40% of cases of persistent Müllerian duct syndrome are caused by mutations in the *AMHR2* gene and are called persistent Müllerian duct syndrome type 2.
- In the remaining 15% of cases, no mutations in the *AMH* and *AMHR2* genes have been identified, and the genes involved in causing the condition are unknown.
- Persistent Müllerian duct syndrome is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations.
- The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.
- Persistent Müllerian duct syndrome affects only males.
- Females with two mutated copies of the gene do not show signs and symptoms of the condition.
- Two anatomic variants of PMDS have been described, the male type and the female type.
- The most common variant is the male form, encountered in 80–90% of cases and characterized by unilateral cryptorchidism with a contralateral inguinal hernia.
- The male form of PMDS can be of two types.

  - The first type is hernia uteri inguinalis, which is usually characterized by a descended testis and herniation of the ipsilateral corner of the uterus and the ipsilateral fallopian tube into the inguinal canal.
  - The second type is crossed testicular ectopia, which is characterized by herniation of both testes and the entire uterus and both fallopian tubes.

- The second anatomic variant of PMDS, the female form, is seen in only 10–20% of cases and is characterized by bilateral cryptorchidism, with the testes fixed within the round ligaments in an 'ovarian position' with respect to the uterus. The gonads are fixed within the pelvis.
- The mobility of Mullerian structures is an important factor that determines the clinical presentation.
- If the uterus and fallopian tubes are mobile, they may descend into the inguinal canal during testicular descent.
- On the other hand, if the Mullerian structures are relatively immobile, testicular descent may be impeded.

10.3 Clinical Features

- PMDS is characterized by the presence of derivatives of the Mullerian duct (i.e., fallopian tubes, uterus, and the upper part of the vagina) in a normal genotypically and phenotypically male.
- PMDS patients have normal development of external genitalia and secondary sexual characteristics.
- Patients with persistent Müllerian duct syndrome (PMDS) usually present with undescended testes (cryptorchidism) or inguinal hernias.
- The diagnosis is discovered at the time of orchidopexy or inguinal hernia repair where the uterus and fallopian tubes are found in the hernia sac.
- Adults with persistent Mullerian duct syndrome may present with ignored cryptorchidism or inguinal hernia or present with hematuria due to hormonal imbalances.
- In the majority of children the usual presentation is with unilateral undescended testis and a contralateral inguinal hernia.
- Some patients present with bilateral undescended testes.
- In other cases, the descended testicle pulls the fallopian tube and uterus into the canal through which it descended. These patients present with an inguinal hernia with a sac containing the uterus and Fallopian tubes. This type of inguinal hernia is called hernia uteri inguinalis,
- It is also possible for the undescended testicle from the other side of the body to be pulled into the same side of the descended testis. This condition is called transverse testicular ectopia and is common in males with PMDS.
- Other signs and symptoms of PMDS may include:
  - Infertility
  - Blood in the semen (hematospermia)

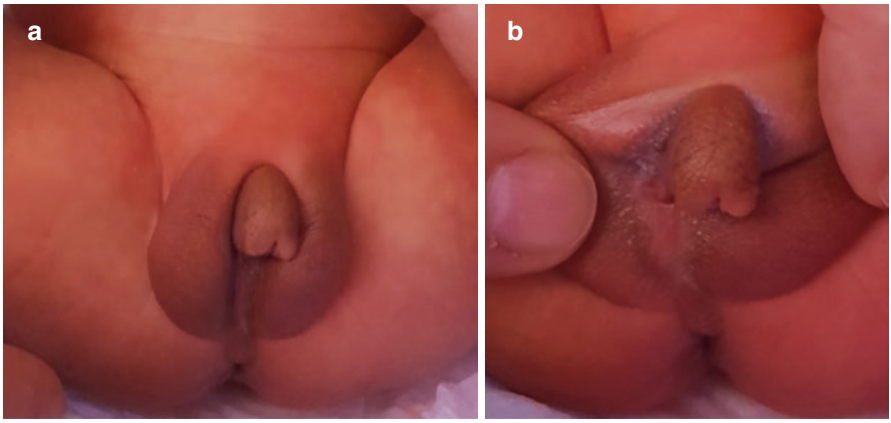

Fig. 10.2 (**a** and **b**) Clinical photographs showing a male patient with hypospadias. He was found to have persistant Mullerian Duct syndrome

  - Hematuria
  - Intestinal defects and kidney abnormalities
  - Hypospadias (Fig. 10.2a, b)
- Patients with PMDS have an increased risk of cancer.
  - Cancer may develop in an undescended testicle that is not treated.
  - Cancer may develop in Mullerian structures that have not been removed.

10.4 Diagnosis and Surgical Management

- Ultrasonography (US), MRI and multi-detector CT are useful invstigations to diagnose PMDS (Fig. 10.3).
- Laparoscopy is by far the most accurate diagnostic method for the impalpable testis.
- The association of cryptorchidism and PMDS makes laparoscopy the method of choice for both the diagnosis and treatment (Figs. 10.4 and 10.5a, b).
- The treatment for persistent Mullerian duct syndrome (PMDS) is surgery.
- The aim of treatment is to prevent the two main complications:
  - Malignant transformation
  - Avoid infertility
- This consists of (Figs. 10.6, 10.7, 10.8a, b and 10.9a, b):
  - Orchidopexy for the undescended testis
  - Inguinal herniotomy if the patient present with an inguinal hernia
  - Excision of Müllerian structures.

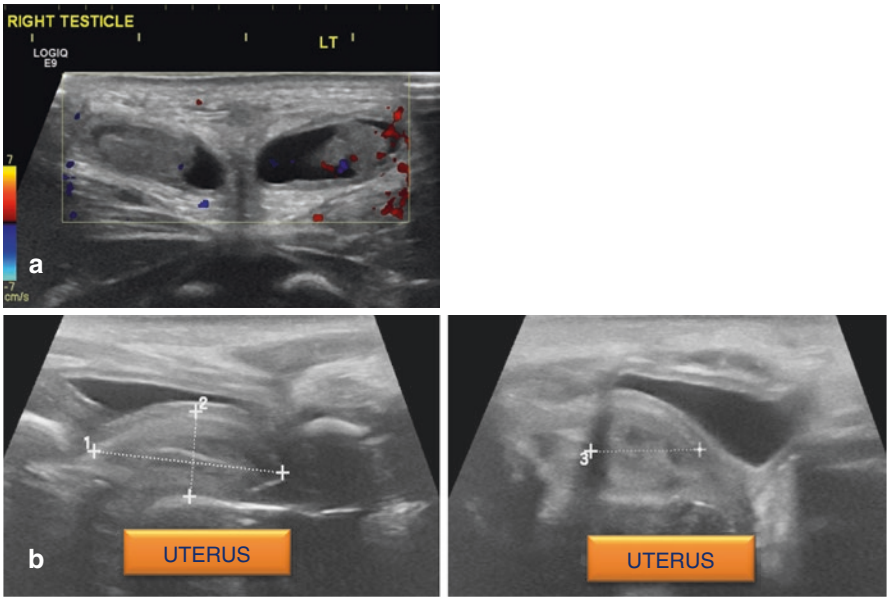

Fig. 10.3 (**a** and **b**) Abdominal and pelvic ultrasound showing bilateral testes and a uterus in a child with persistant mullerian duct syndrome

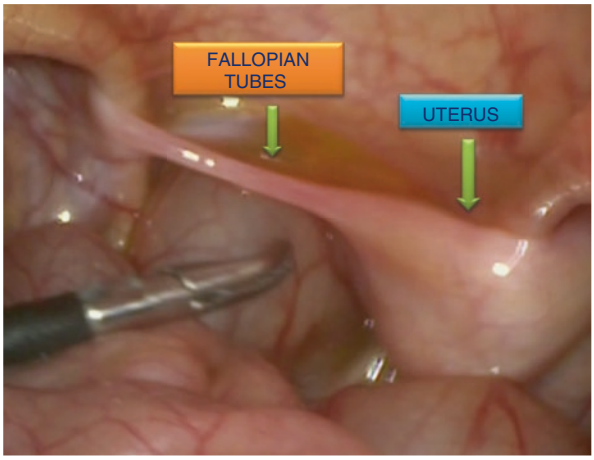

Fig. 10.4 Intraoperative photograph during laparoscopy for a patient with persistant mullerian duct syndrome. Note the uterus and Fallopian tube

- Excision of Müllerian structures is controversial.
- Currently, the recommendation is to remove the Müllerian structures due to increasing reports of cancer, and because they can also cause discomfort and hematuria.
- It has been suggested that surgery should be done between the ages of 1 and 2 years.

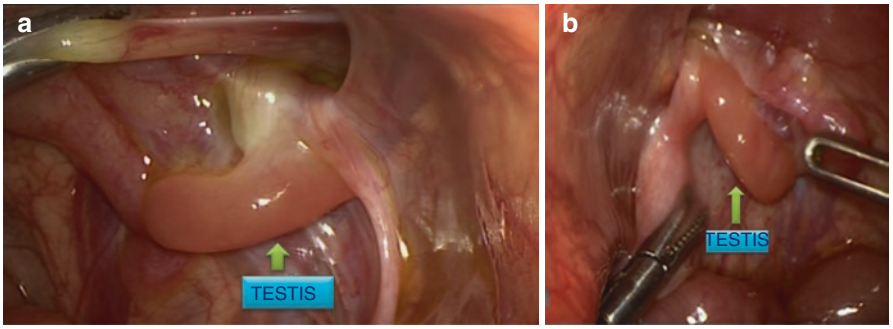

Fig. 10.5 (**a** and **b**) Intraoperative photograph during laparoscopy for a patient with persistant mullerian duct syndrome. Note the presence of testes, one on each side. This patient was also found during laparoscopy to have a uterus and fallopian tubes. The uterus was small in size

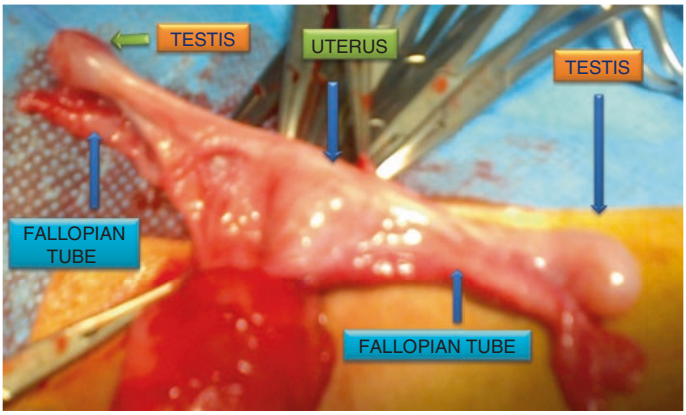

Fig. 10.6 Intraoperative photograph of a patient with persistent Mullerian duct syndrome. This patient was operated on for undescended testis and intraoperatively was found to have persistant mullerian duct syndrome. Note the presence of a uterus, two fallopian tubes and two testes but no ovaries. This results from deficiency of MIS

- Orchidopexy and removal of Mullerian structures should be done at the same time or as a staged procedure if needed.
- Infertile males can be helped by sperm extraction from the testes and assisted reproductive technology.
- Orchidopexy:
  - This may necessitates division of the uterus to lengthen the vas.
  - A transverse testicular ectopia may be associated with this condition.
  - In this, both testes are found on the same side.
- Excision of Mullerian remnants
  - This is not a simple procedure and care should be taken to avoid injury to the vas.

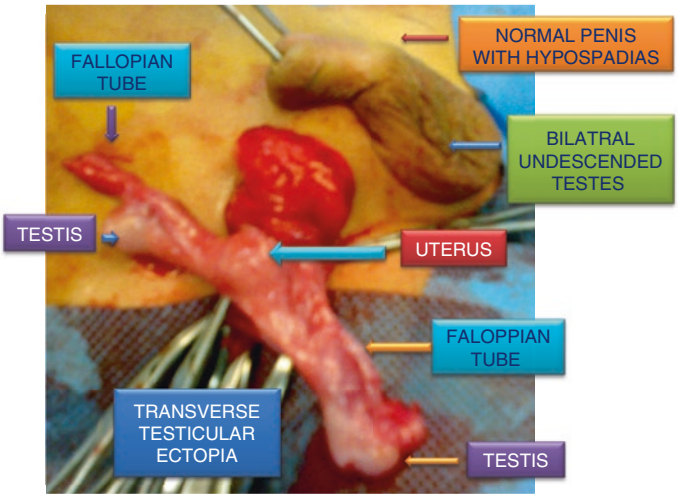

Fig. 10.7 Intraoperative photograph of a patient with persistent Mullerian duct syndrome. Note the presence of a uterus, two fallopian tubes and two testes but no ovaries. This results from deficiency of MIS. Note also the normal penis, bilateral undescended testes and transverse testicular ectopia

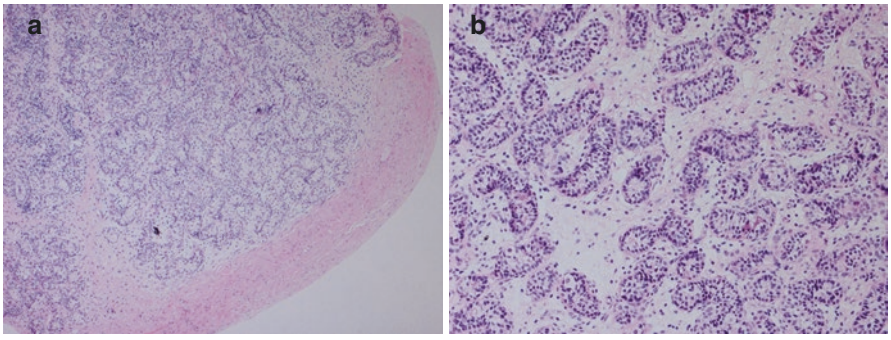

Fig. 10.8 (**a** and **b**) Histological photographs of a testicular biopsy from a patient with persistent Mullerian duct syndrome. Note the presence of normal testicular tissue

  - Currently, removal of Müllerian remnants is necessary, since the remnants may produce symptoms and are known to be associated with an increased risk of subsequent malignancy.

- The risk of malignancy in an ectopic testis in a case of PMDS is similar to that in a cryptorchid testis in a healthy male.
- Germ cell tumors have been reported in the testis, whereas tumors of the Mullerian duct derivatives are very rare.

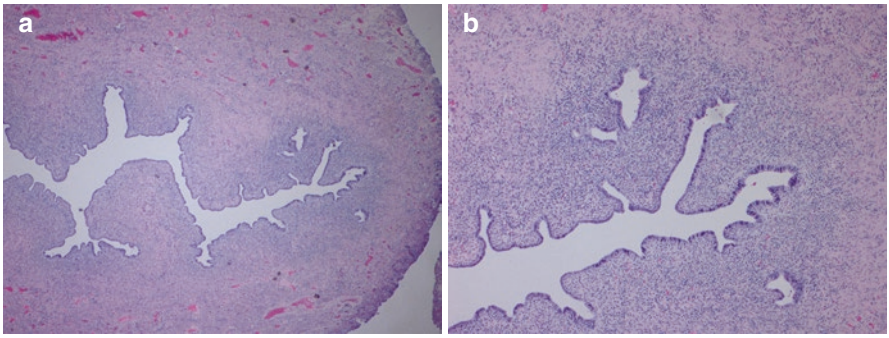

Fig. 10.9 (**a** and **b**) Histological photographs of an excised uterus from a patient with persistent Mullerian duct syndrome. Note the presence of a rudemanrty uterus

Further Reading

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Chapter 11
Vaginal Atresia, Agenesis and Vaginal Septum

Ahmed H. Al-Salem

11.1 Introduction

- Vaginal atresia is a congenital developmental defect leading to utero-vaginal outflow tract obstruction.
- Vaginal atresia is estimated to occur in 1 in 5000–10,000 live female births.
- Transverse vaginal septum, formerly called partial vaginal agenesis, is relatively uncommon, with a reported incidence of 1 in 70,000 females.
- Congenital vaginal obstruction commonly presents after puberty and presentation in infancy is uncommon.
- The anomaly is often undetected until adolescence, when primary amenorrhea or abdominal pain due to an obstructed uterovaginal tract prompts a diagnostic evaluation.
- Vaginal atresia is reported to be the second most common cause of primary amenorrhea in tertiary care centers.
- The exact cause for vaginal atresia is unknown.
- The development of the vaginal canal is normally completed within the fetus by the 20th week of gestation.
- Vaginal atresia develops when the caudal portion of the vagina, contributed by the urogenital sinus, fails to form and as a result this caudal portion of the vagina is replaced with fibrous tissue which causes obstruction of the vaginal outflow.
- Vagina atresia and agenesis may occur as:
  - An isolated developmental defect
  - As part of a complex of anomalies

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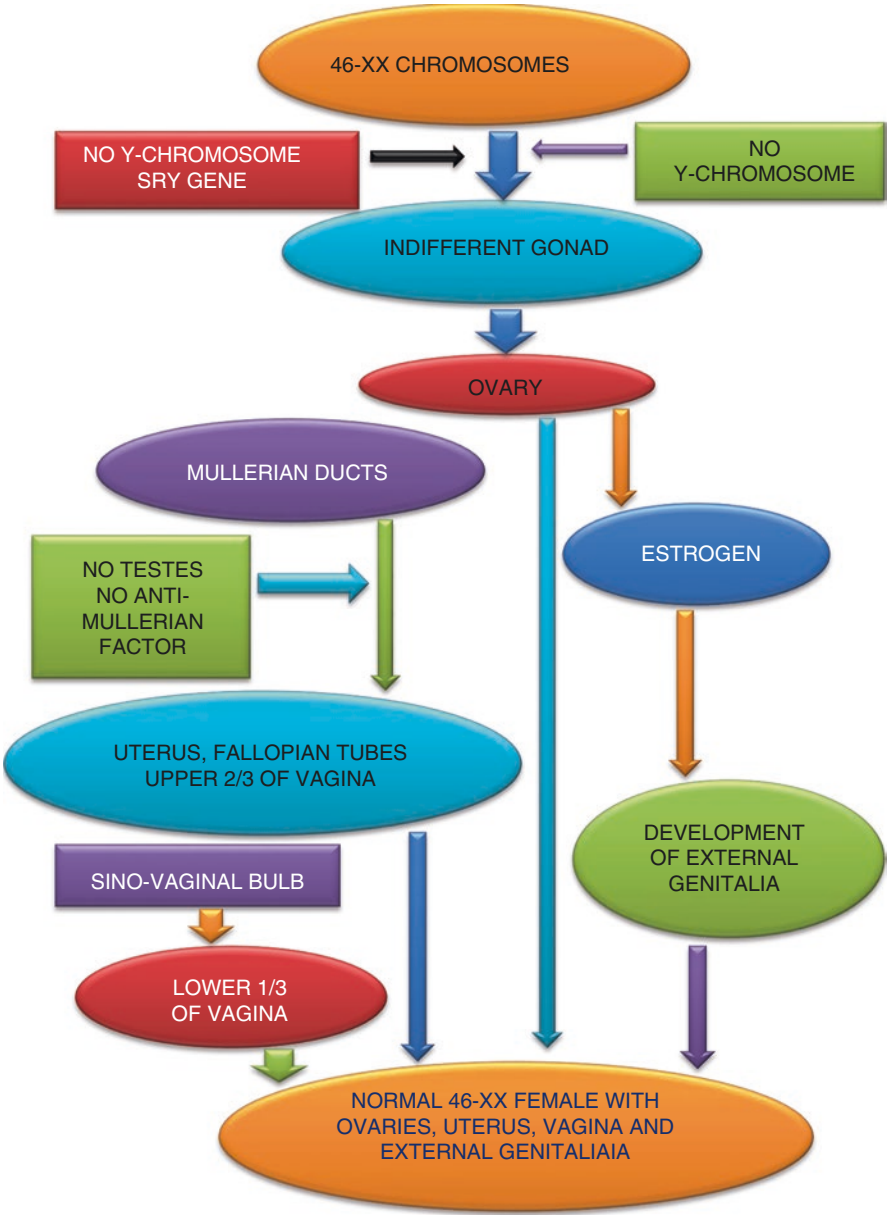
- These complex anomalies include:
  - Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome
  - Bardet-Biedl syndrome
  - Kaufman-McKusick syndrome
  - Fraser syndrome
  - Winters syndrome
- In 1998, the American Society for Reproductive Medicine classified the uterine anatomic types as müllerian anomalies or vaginal anomalies.
- According to this classification system, vaginal atresia is an anomaly classified as type I.
- Renal anomalies occur in 30% of patients with Rokitansky-Mayer-Küster-Hauser (MRKH) syndrome. These anomalies include:
  - Unilateral agenesis of the kidney
  - Ectopic kidneys
  - Horseshoe kidney
  - Crossed-fused ectopia
- Associated skeletal anomalies include:
  - Fused vertebrae or other variants
  - Anomalies of the ribs and limbs

11.2 Embryology

- Normal reproductive organ development in females requires the timely coordination of the following three discrete but interdependent systems:
  - Gonadal structures
  - Internal ductal system
  - External genitalia
- In the female embryo, the absence of testes and the consequent absence of both androgens and müllerian-inhibiting substance (MIS) allow ongoing development and differentiation of the müllerian duct system with regression of the wolffian ducts.
- The female reproductive tract develops from a pair of Müllerian ducts.
- The Müllerian ducts give rise to the following structures:
  - Fallopian tubes
  - Uterus
  - Cervix
  - Upper two-thirds of the vagina



- The lower third of the vagina develops from the sinovaginal bulb.
- The normal development of the Müllerian ducts depends on the completion of three phases:

– Organogenesis

  This is characterized by the formation of the two Müllerian ducts.
  Failure of this stage will result in uterine agenesis/hypoplasia or a unicornuate uterus.

– Fusion of Müllerian ducts

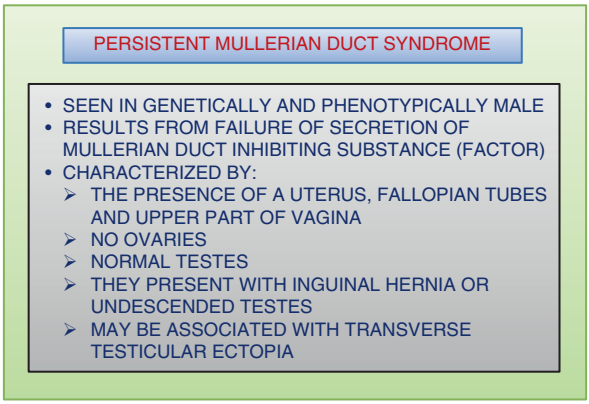
  This is characterized by fusion of the two Müllerian ducts to form the uterus, fallopian tubes and upper two thirds of vagina.

– Resorption of the septum between the two Müllerian ducts.

  This involves resorption of the central septum between the two already fused Müllerian ducts
  Failure of this stage will result in a septate or arcuate uterus.

- The müllerian duct is identifiable by 6 weeks' gestation in both male and female individuals.
- This duct elongates and reaches the urogenital sinus by 9 weeks' gestation, thus forming the uterovaginal canal.
- The two müllerian ducts proceed caudal to cephalad to the uterine fundus and fuse.
- Bilateral endodermal invaginations (i.e., sinovaginal bulbs) form as the müllerian tubercles regress.
- Cephalic growth of the sinovaginal bulb is completed at 15–26 weeks' gestation, and fusion of the sinovaginal bulb with the vaginal cord forms the vaginal plate.
- Although controversy surrounds the development of a patent genital tract, canalization of the uterovaginal canal is believed to occur from the caudal to the cephalic aspect, with an epithelial lining derived from the urogenital sinus.
- Vaginal development is completed by 5 months' gestation.
- Mesenchyme surrounding these structures develops into the musculature of the genital tract.
- Cephalic remnants of the müllerian ducts form the fallopian tubes.
- Given this developmental scheme, pathophysiologic events resulting in a septate uterus can be attributed to failure of the septum to regress between the fused müllerian ducts.
- Arcuate, bicornuate, or didelphic uteri can be attributed to incomplete fusion of the müllerian ducts.
- Uterovaginal atresia in patients with MRKH syndrome is best explained by the failure of the caudal development of the müllerian ducts.
- Failures at the level of the vaginal plate may explain the variants of transverse vaginal septum.
- Although the vagina is embryologically derived from structures of both the müllerian and urogenital sinuses, how much each anlage contributes to final normal development remains unclear.
- Vaginal atresia is found to occur when the urogenital sinus does not contribute to the formation of the lower portion of the vagina.

- Failure of this normal development at any stage can lead to genital abnormalites:



– Persistent Mullerian duct syndrome:

  This is seen in male children as a result of failure of secretion of MIS or failure of the receptors to respond to MIS.
  It is characterized by the presence of a uterus, upper part of vagina and fallopian tubes in a phenotypically and genetically normal male.

– A septate uterus:

  This results from failure of the septum between the 2 müllerian ducts to regress.

– Arcuate, bicornuate, or didelphic uteri:

  These result from incomplete fusion of the müllerian ducts.

– Uterovaginal atresia:

  This results from failure of the caudal development of the müllerian ducts.

– A transverse vaginal septum:

  This results from failures at the level of the vaginal plate.

– Vaginal atresia:

  This occurs when the caudal portion of the vagina, contributed by the urogenital sinus, fails to form.
  This caudal portion of the vagina is replaced with fibrous tissue.

– Lower vaginal atresia is a type of vagina atresia where the lower third of the vagina fails to develop.

  It is usually not considered a type of Mullerian duct anomaly.
  It occurs from a failure of recanalisation of the urogenital sinus.

- Patients with RMKH syndrome and vaginal atresia are phenotypically and genotypically female with a 46, XX karyotype. However, a familial association suggests autosomal dominant transmission of a mutant gene by male relatives.
- Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome is defined as Müllerian aplasia with vaginal agenesis and uterine remnants.

  It is commonly associated with renal and sometimes vertebral anomalies.
  The MRKH syndrome or distal vaginal atresia is sometimes associated with anorectal malformations.

- There are other syndromes that are found in conjunction with individuals with vaginal atresia.
- These syndromes include:

  - Rokitansky-Mayer-Küster-Hauser Syndrome

    Rokitansky-Mayer-Küster-Hauser syndrome is a disorder seen in females and characterized by absence or underdeveloped uterus and vagina.
    It is also called Müllerian agenesis.
    It is seen in genetic female with 46XX chromosomes.
    Kidney anomalies are seen in 30% of these patients.
    Vaginal agenesis or müllerian aplasia affects 1 in every 4000–5000 females.
    It may form part of a cloacal malformation.
    This disorder is caused by an implication in the WNT4 protein coding gene, which is found on the short arm (p) of chromosome 1.

    - A genetic mutation occurs causing a substitution of leucine to proline residue at position 12 on the amino acid in the WNT4 protein.
    - Essentially, this will cause a reduction in the intranuclear levels of β catenin.
    - Inhibition of steroidogenic enzymes such as 17α-hydroxylase and 3β-hydroxysteriod dehydrogenase because of this mutation, which leads to an excess amount to androgen in the system.
    - As WNT4 gene is essential for developing a protein that is essential for female sex development, the Müllerian duct is either absent or deformed when this gene is not present.
    - The development of the female reproductive system may be disrupted in the absence of the WNT4 protein's regulation.
    - Abnormal androgen production is also induced, eventually leading to hyperandrogenism and Müllerian aplasia.

  - Bardet-Biedl Syndrome

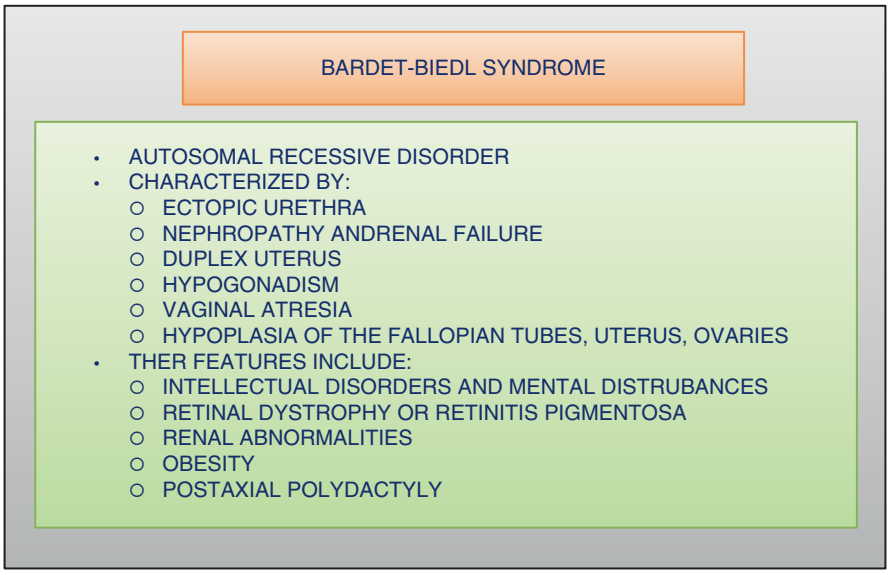
    Bardet-Biedl syndrome (BBS) is a ciliopathic human genetic disorder that can affect various parts of the body.
    This is a genetically heterogeneous group of autosomal recessive disorders.
    Parts of the urogenital system where the effects of BBS are seen include:

- Ectopic urethra
- Nephropathy and renal failure
- Duplex uterus
- Hypogonadism
- Vaginal atresia
- Hypoplasia of the fallopian tubes, uterus, ovaries
- Intellectual disorders and mental disturbances
- Loss of vision (Retinal dystrophy or retinitis pigmentosa appears at age 10–20 years)
- Renal abnormalities
- Obesity
- Postaxial polydactyly

ROKITANSKY-MAYER-HAUSER SYNDROME

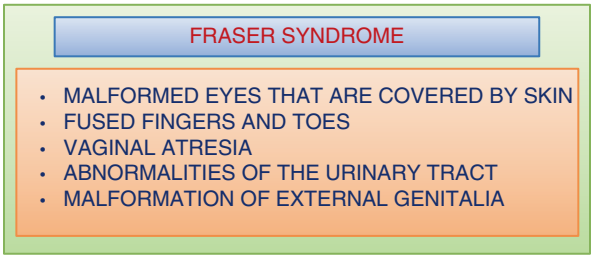
- SEEN IN GENETICALLY AND PHENOTYPICALLY FEMALES
- MAY FOR PART OF A CLOACAL MALFORMATION
- IT IS CAUSED BY AN IMPLICATION IN THE WNT4 PROTEIN CODING GENE WHICH IS FOUND ON THE SHORT ARM OF CHROMOSOME 1
- ABSENCE OF WNT4 GENE WILL LEAD TO INHIBITION OF STEROIDOGENIC ENZYMES AND INTERFER WITH THE DEVELOPMENT OF MULLERIAN DUCTS
- THE RESULT IS HYPERANDROGENISM AND MULLERIAN APLASIA
- IT IS CHARACTERIZED BY:
  - ABSENCE OR UNDERDEVELOPED UTERUS AND VAGINA
  - RENAL ANOMALIES IN 30%

- Other common features associated with this syndrome include:
  - The exact mechanism that causes BBS is still unclear.
  - Mutations in more than 20 genes can cause BBS.
  - It is inherited as an autosomal recessive condition.
- The majority of the genes that are related to BBS encode proteins which are called cilia and basal bodies, which are related structures.
- The gene mutations that occur in BBS are:
  - BBS1, BBS2, ARL6, (BBS3), BBS4, BBS5, MKKS (BBS6), BBS7, TTC8 (BBS8), BBS9, BBS10, TRIM32 (BBS11), BBS12, MKS1 (BBS13), CEP290 (BBS14), WDPCP (BBS15), SDCCAG8 (BBS16), LZTFL1 (BBS17), BBIP1 (BBS18), IFT27 (BBS19), IFT72 (BBS20), and C8ORF37 (BBS21).
  - The majority of the genes that are related to BBS encode proteins which are called cilia and basal bodies, which are related structures.



– Fraser Syndrome

These infants often have eyes that are malformed and completely covered by skin.
These children are born with fingers and toes that are fused together
Abnormalities of the urinary tract
vaginal atresia
Infants born with Fraser syndrome have malformations of their genitals.

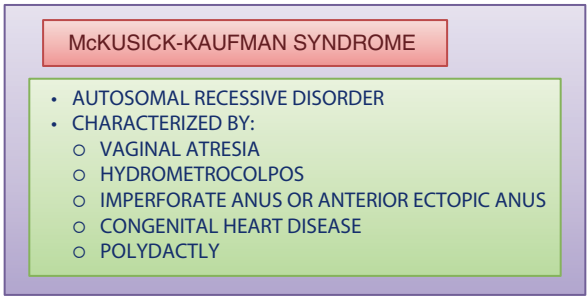


– McKusick-Kaufman syndrome

An autosomal recessive disorder

A female with McKusick-Kaufman syndrome has:

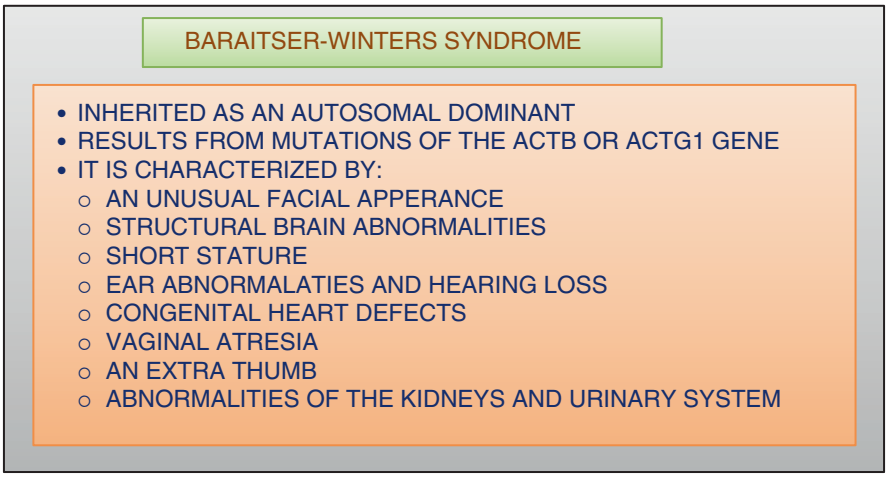
- Vaginal atresia
- Imperforate anus
- Congenital heart disease
- Hydrometrocolpos
- Polydactyly



– Winter's syndromes

This is also called Baraitser-Winter syndrome
Baraitser-Winter syndrome is a condition that affects the development of many parts of the body, particularly the face and the brain.
This condition is described as autosomal dominant.
The condition almost always results from new (de novo) mutations in the *ACTB* or *ACTG1* gene and occurs in people with no history of the disorder in their family.
It is characterized by:

- An unusual facial appearance that include widely spaced eyes (hypertelorism), large eyelid openings, droopy eyelids (ptosis), high-arched eyebrows, a broad nasal bridge and tip of the nose, a long space between the nose and upper lip (philtrum), full cheeks, and a pointed chin.
- Structural brain abnormalities
- The most frequent brain abnormality associated with Baraitser-Winter syndrome is pachygyria, which is an area of the brain that has an abnormally smooth surface with fewer folds and grooves.
- Short stature
- Ear abnormalities and hearing loss
- Congenital heart defects
- The presence of an extra (duplicated) thumb
- Abnormalities of the kidneys and urinary system
- Vaginal atresia



11.3 Classification

- The most widespread classification system is currently that produced by the American Society of Reproductive Medicine (formerly American Fertility Society—AFS) in 1998.
- Class I: Agenesis and hypoplasia
  - Early developmental failure of the Müllerian ducts, for unknown reasons at around 5 weeks' gestation, results in various degrees of agenesis or hypoplasia of the uterus, cervix and upper two-thirds of the vagina.

    In agenesis, a uterus is not identified or small rudimentary tissue without differentiation may be present.
    The most common form is the Mayer–Rokitansky–Kuster–Hauser syndrome.
    This consists of a combined agenesis of the uterus, cervix and upper portion of the vagina.
    Symptoms may manifest at puberty as primary amenorrhoea with normal secondary sexual characteristics, as ovarian function is preserved.
    These patients have normal female sexual development.
    In uterine hypoplasia, a small but fully differentiated organ is present.
- Class II: Unicurnate
  - This anomaly results from complete or near-complete arrested development of one of the Müllerian ducts.
  - Four possible subtypes can develop:

    Absent rudimentary horn
    Non-cavitary (non-functional) rudimentary horn

Cavitary communicating rudimentary horn
Cavitary non-communicating rudimentary horn

  - The last one may obstruct and present with abdominal pain, subsequently requiring surgical intervention.

- Class III: Didelyphs
  - This anomaly results from complete non-fusion of both Müllerian ducts.
  - The individual horns are fully developed and almost normal in size.
  - A deep fundal cleft and two cervices are present.
  - A longitudinal or transverse vaginal septum may be present
- Class IV: Bicornuate
  - This class is characterized by partial non-fusion of the Müllerian ducts.
  - This results in a central myometrium that may extend to the level of the internal cervical os (bicornuate unicollis) or external os (bicornuate bicollis), with a fundal cleft >1 cm deep.
  - The horns of the bicornuate uteri are not as fully developed and are smaller than those in the didelphys uteri.
- Class V: Septate
  - This class of anomaly occurs when the final fibrous septum between the two Müllerian ducts fails to resorb.
  - This results in the formation of a uterus that is completely or partially divided into two cavities.
  - The septum may be muscular (with similar signal intensity as the myometrium), fibrous or a combination of both.
  - This class is associated with the poorest obstetrical outcomes.
  - It is important to distinguish a fibrous septum from a muscular septum, as the former can be repaired by a hysteroscopic approach, whereas the latter may require a transabdominal surgical approach.
  - The fundal cleft is <1 cm deep and the intercornual distance is usually <4 cm.
  - The morphology of the outer fundal contour is the key to the diagnosis.
  - The differentiation between a septate and bicornuate uterus is important because they differ in their reproductive prognosis and treatment.
- Class VI: Arcuate
  - This group is characterized by mild indentation of the endometrium at the uterine fundus.
  - It is the result of near complete resorption of the uterovaginal septum.
  - Currently, no definitive depth has been established to differentiate the arcuate configuration from the septate.
  - This class is highly controversial, as it remains unclear whether this variant should be classified as a true anomaly or as an anatomic variant of normal.

ASRM CLASSIFICATION OF MULLERIAN ANOMALIES

CLASSIFICATION	ANOMALIES

- Class I: Uterine Agenesis / Uterine hypoplasia
  - Vaginal (Uterus: normal/ variety of abnormal forms)
  - Cervical
  - Fundal
  - Tubal
  - Combined anomalies
- Class II: Unicurnate Uterus/unicornis unicollis 15% (6-25%)
  - Communicating contralateral rudimentary horncontains endometrium
  - Non-communicating contralateral rudimentary horn contains endomerium
  - No cavity : Contralateral horn has no cavity
  - No horn
- Class III: Uterus Didelyphs 7.5% (5-11%)
- Class IV: Bicornuate Uterus 25% (10-39%)
  - Complete division, all the way down to the internal or external os
  - Partial division, not extending to the internal os (bicornate unicollis)
- Class V: Septate Uterus 45% (34-55%)
  - Compelete division, all the way down to the internal or external os
  - Incomplete division, involving the endometrial cavity but not the cervix
- Class VI: Arcuate 7%
- Class VII: DES related (In utero diethylstilbestrol (DES) exposure (T-shaped uterus)

ASRM: American Society of Reproductive Medicine . DES: Diethylsilbestrol

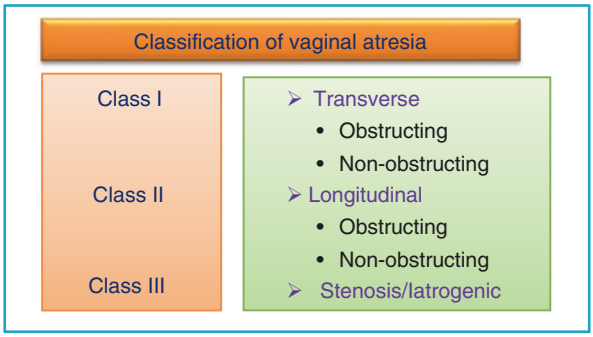
– Data regarding the reproductive outcome of patients in this category are extremely limited and conflicting.
– Currently, it is generally thought that an arcuate uterus is compatible with normal pregnancy and delivery.

- Class VII: Diethylstilbestrol related
  – Several million women were treated with diethylstilbestrol (DES), a non-steroidal estrogen, to prevent miscarriage between 1945 and 1970.
  – The drug was promptly removed from the market when it was found that up to 15% of newborn girls who were exposed to DES had uterine malformations and an increased risk of vaginal clear cell carcinoma.
  – The uterine abnormalities include hypoplasia and a T-shaped uterine cavity.
  – Patients may also have abnormal transverse ridges, hoods and stenosis of the cervix.
- Classification of vaginal atresia:
  – This classification is based on the presence or absence of the vagina and also the level of vaginal atresia.
  – Vaginal atresia is classified anatomically into three types:

    Vaginal agenesis

    - This is seen as part of the Mayer-Rokitansky-Küster-Hauser syndrome

    Proximal vaginal atresia
    Distal vaginal atresia



- The ESHRE/ESGE classification system of female genital anomalies
  – Congenital malformations of the female genital tract result from embryological maldevelopment of the Mullerian or paramesonephric ducts.
  – These malformations are common with a prevalence of 4–7%.

- Due to their prevalence and clinical importance, the ESHRE/ESGE classification system of female genital anomalies was developed.
- This is a reliable classification system which seems to be extremely useful for effective diagnosis and their management; as well as a better understanding of their pathogenesis.
- The European Society of Human Reproduction and Embryology (ESHRE) and the European Society for Gynaecological Endoscopy (ESGE), recognizing the clinical significance of female genital anomalies, have established a common working group under the name CONUTA (CONgenital UTerine Anomalies), with the goal of developing a new updated classification system.
- This new system is called, The European Society of Human Reproduction and Embryology (ESHRE) and the European Society for Gynaecological Endoscopy (ESGE) classification system (The ESHRE/ESGE classification system of female genital anomalies).

11.4 Associated Anomalies

- Vagina atresia and agenesis are congenital anomalies of genitourinary tract and may occur as:
- An isolated developmental defect
- Part of a complex of anomalies such as:
  - The Rokitansky-Mayer-Küster-Hauser syndrome
  - The Bardet-Biedl syndrome
  - The Kaufman-McKusick syndrome
  - The Fraser syndrome
  - The Winters syndrome
- Renal anomalies:
  - Occur in 30% of patients with RMKH syndrome.
  - These anomalies include:

    Unilateral agenesis of the kidney is the most commonly reported anomaly, occurring in 67% of cases.
    Ectopic kidneys
    Horseshoe kidney
    Crossed-fused renal ectopia
    Renal dysplasia
    Duplicated collecting system
- Skeletal anomalies:
  - Fused vertebrae
  - Anomalies of the ribs and limbs

GTA Classification-CONUTA (ESHRE/ESGE)

Grimbizis GF, Gordts S, Di Spiezio Sardo A, Brucker S, De Angelis C, Gergolet M, Li TC, Tanos V, Brolmann H, Gianaroli L, Campo R.
The ESHRE/ESGE consensus on the classification of female genital tract congenital anomalies.
Hum Reprod. 2013 Aug;28(8):2032-44.

ESHRE/ESGE classification
Female genital tract anomalies

	Uterine anomaly		Cervical/vaginal anomaly	
	Main class	*Sub-class*	*Co-existent class*	
U0	Normal uterus		C0	Normal cervix
U1	Dysmorphic uterus	a. T-shaped b. Infantilis c. Others	C1	Septate cervix
U2	Septate uterus	a. Partial b. Complete	C2	Double 'normal' cervix
U3	Bicorporeal uterus	a. Partial b. Complete b. Bicorporeal septate	C3	Unilateral cervical aplasia
U4	Hemi-uterus	a. With rudimentary cavity (communicating or not horn) b. Without rudimentary cavity (horn without cavity/no horn)	C4	Cervical aplasia
U5	Aplastic	a. With rudimentary cavity (bi-or unilateral horn) b. Without rudimentary cavity (bi-or unilateral uterine remnants/aplasia)	V0	Normal vagina
U6	Unclassified malformations		V1	Longitudinal non-obstructing vaginal septum
			V2	Longitudinal obstructing vaginal septum
			V3	Transverse vaginal septum and/or imperforate hymen
			V4	Vaginal aplasia
U			*C*	*V*

Associated anomalies of non-Müllerian origin:

SGUMGG USZ UZH © M. Bajka

GTA Classification-CONUTA (ESHRE/ESGE)

Grimbizis GF, Gordts S, Di Spiezio Sardo A, Brucker S, De Angelis C, Gergolet M, Li TC, Tanos V, Brolmann H, Gianaroli L, Campo R.
The ESHRE/ESGE consensus on the classification of female genital tract congenital anomalies.
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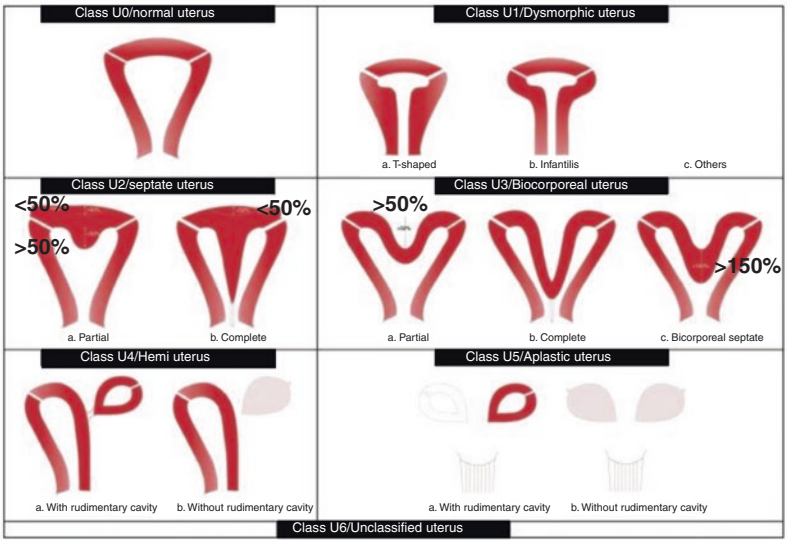

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11.5 Clinical Features

- The clinical presentation of vaginal atresia varies and is primarily related to its association with other anomalies of the genitourinary tract.
- The diagnosis of vaginal atresia can be made at any time between the perinatal period and adolescence.
- Hydrocolpos and hydrometrocolpos are clinical conditions resulting from accumulation of cervico-vaginal secretions in the vaginal and uterine cavities and caused by congenital malformations.
- These cervico-vaginal secretions are due to increased secretions by cervical mucous glands secondary to maternal hormone stimulation which gradually accumulates and expands the vagina and uterus due to vaginal outlet obstruction.
- It is a rare condition seen in female newborns and infants and much less often young girls.
- The clinical presentation is that of an abdominal mass associated with absence or abnormality of the vaginal opening.
- The presence of this abdominal mass which is made up of distended vagina and uterus (Hydrometrcolpos) may be complicated by pressure on the urinary badder and ureter leading to obstructive uropathy.
- Symptoms and signs in the newborn include (Fig. 11.1a–c):

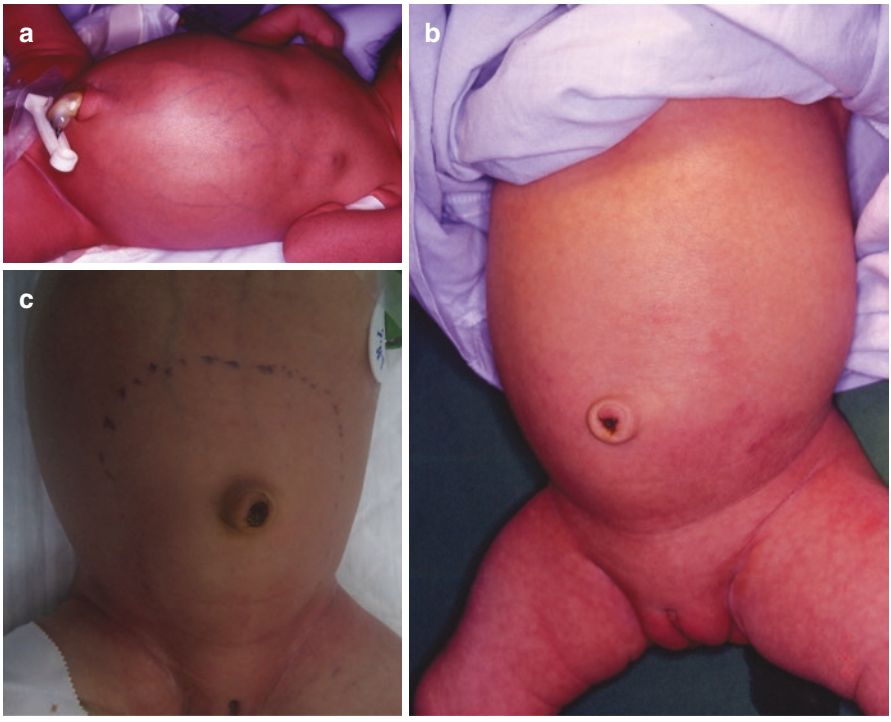

Fig. 11.1 (**a–c**) Clinical photographs of three newborns with vaginal atresia. Note the abdominal distension secondary to distended vagina and uterus (Hydrometrocolpos)

- Abdominal mass (Hydrometrocolpos)
- Respiratory distress

  This is secondary to distended abdomen secondary to hydrometrocolpos
  This leads to compression on the diaphragm and restriction of respiration

- Sepsis

  Hdrometrocolpos may be complicated with infection leading to pyometrocolpos
  This can lead to septicemia

- Vaginal atresia can sometimes be diagnosed by physical examination soon after birth.

  The presence of an abdominal mass in a female newborn should alert treating physician to the possibility of vaginal atresia.

- A child with vaginal atresia often has other congenital abnormalities.

- Perineal examination may reveal (Fig. 11.2a–d):
  - Normal looking external genitalia
  - No apparent vaginal orifice and no hymen can be seen upon closer perineal examination.
  - Development of secondary sex characteristics is normal in patients with vaginal atresia and these will be apparent in the adolescent.
  - An isolated vaginal dimple or a small vaginal pouch with a normal hymenal ring may be seen sometimes.
  - Normal urethral opening
  - Labial fusion may obscure the anatomy of some patients and this be confused with vaginal atresia.
  - The presence of posterior labial fusion and enlarged clitoris is suggestive of congenital adrenal hyperplasia.
  - Symptoms and signs of vaginal atresia or vaginal agenesis can often go unnoticed in females until they reach the age of menstruation.
  - At this age, they will have amenorrhea and hemocolpos.

- Symptoms in adolescence and adults include:
  - Cyclical abdominal pain
  - Difficulty passing urine
  - Backache
  - Amenorrhea
  - Difficulties with sexual intercourse
  - A small pouch or dimple where a vaginal opening should be
  - Pelvic and abdominal mass when the upper vagina becomes filled with menstrual blood

- Hydrocolpos can be associated with genitourinary anomalies including persistent urogenital sinus and cloacal malformation.

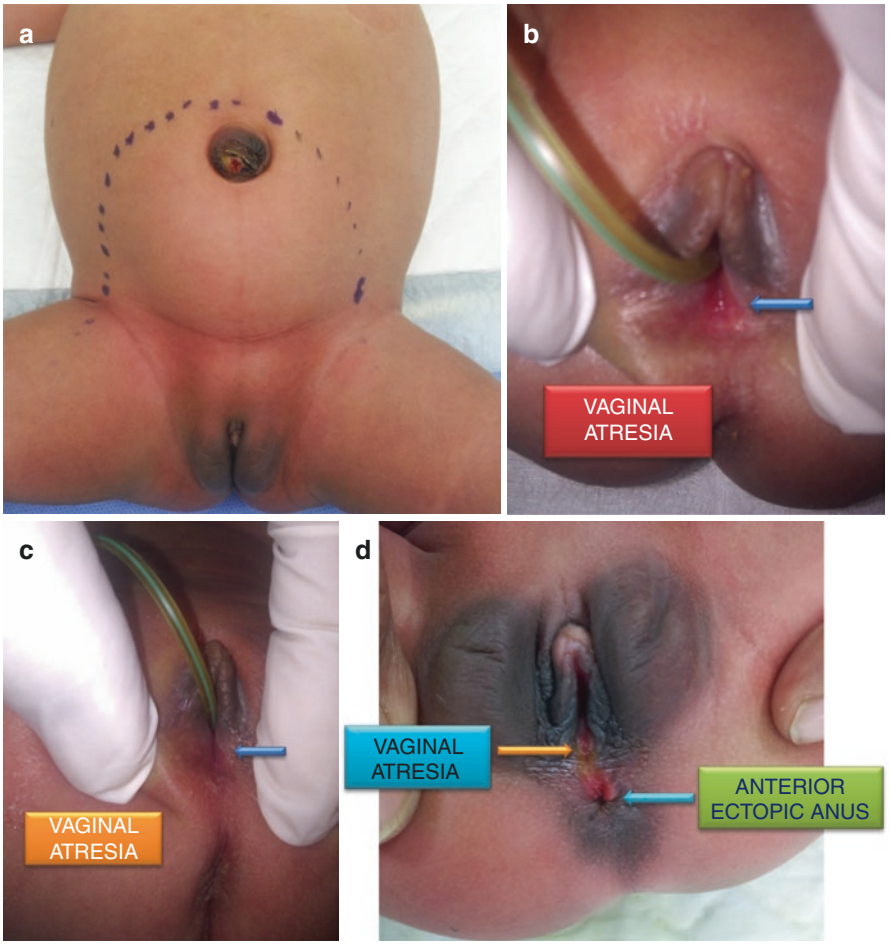

Fig. 11.2 (**a–d**) Clinical photographs of patients with vaginal atresia showing distended abdomenl and absence of a vaginal opening. There is a palpable lower abdominal mass which represents the distended obstructed vagina and uterus (hydrometrocolpos). Note also the associated anterior ectopic anus in the last photograph. Anterior ectopic anus or anorectal agenesis can be associated with vaginal atresia in patients with McKusick-Kaufman syndrome. These patients will also have congenital heart disease and polydactly

- Vaginal atresia can be associated with several syndromes like Mckusick-Kaufman syndrome and Bardet-Biedl syndrome.
- The most common complication of hydrocolpos is compression of the bladder and ureters, leading to hydronephrosis, which can ultimately cause kidney damage.
- Other complications including sepsis and pyocolpos.
- The presence of polydactly and congenital heart disease is suggestive of an associated syndrome (McKusick-Kaufman syndrome, Bardet-Biedl syndrome). The polydactly can affect either lower and upper limbs or only one limb (Fig. 11.3a–f).

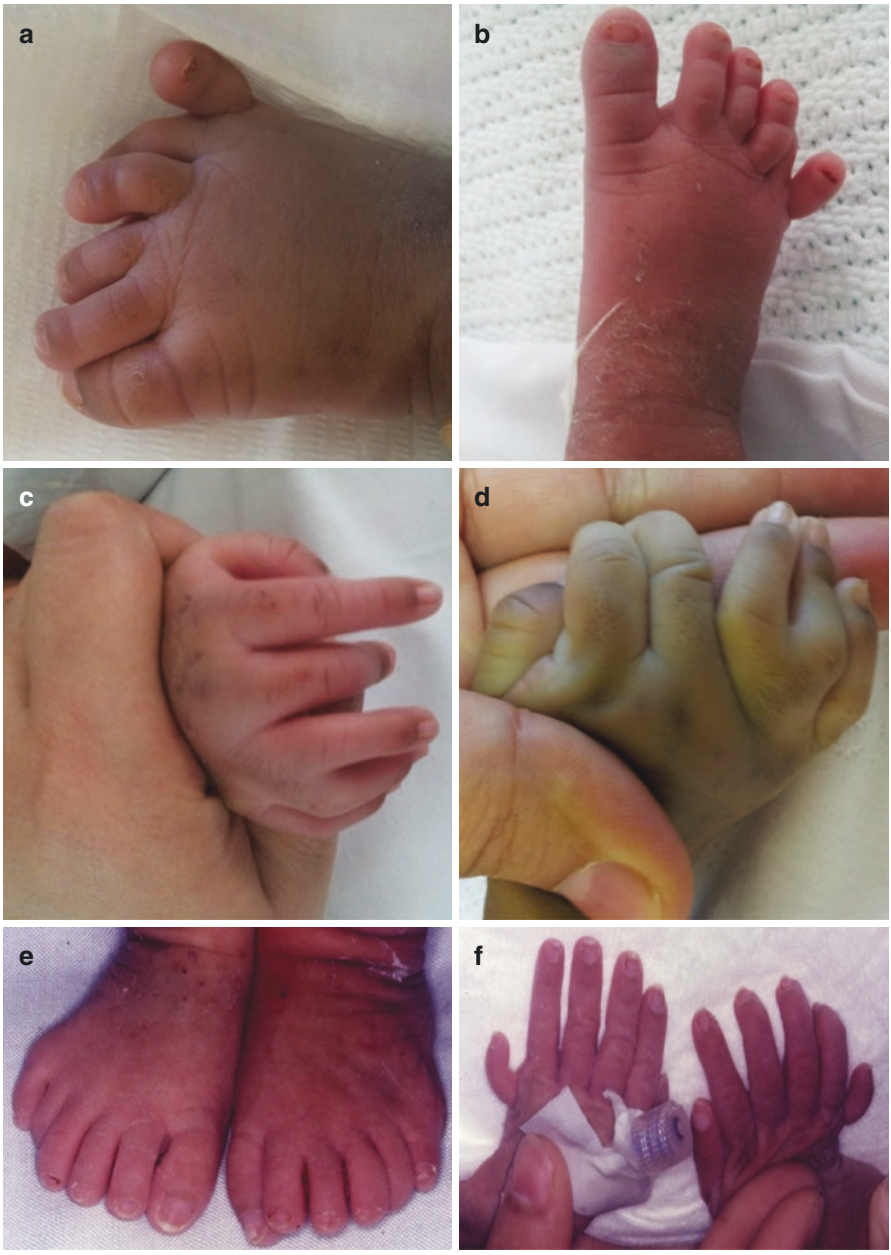

Fig. 11.3 (**a**–**f**) Clinical photographs showing polydactly in patients with Mckusick-Kaufman syndrome. The polydactly can affect the hands and feet

11.6 Investigations

- The diagnosis can be suspected from a detailed prenatal US.
- In newborns, it is important to define the anatomic abnormality leading to the hydrometrocolpos.
- Abdominal radiograph (Fig. 11.4a, b):
  - This may reveal a soft tissue density pushing the bowel to the side and upwards.
  - The soft tissue density is due to distended vagina and uterus forming a mass.
- Further confirmation can be provided by an early postnatal ultrasound or CT-scan (Figs. 11.5, 11.6a–g and 11.7a, b).
- Ultrasound, CT-scan or MRI is useful to evaluate the degree of obstructive uropathy.
- Ultrasound is the cornerstone of imaging in patients with suspected vaginal atresia.
- Abdominal and pelvic ultrasonography (Fig. 11.5):
  - This is a simple, non-invasive investigation for patients with vaginal atresia.
  - It is valuable to define the ovaries, uterus, and proximal vagina.
  - The presence of hydrocolpos or hydrometrocolpos can be detected with ultrasound.
  - It is also useful to evaluate the kidneys, ureter and urinary bladder and associated anomalies.

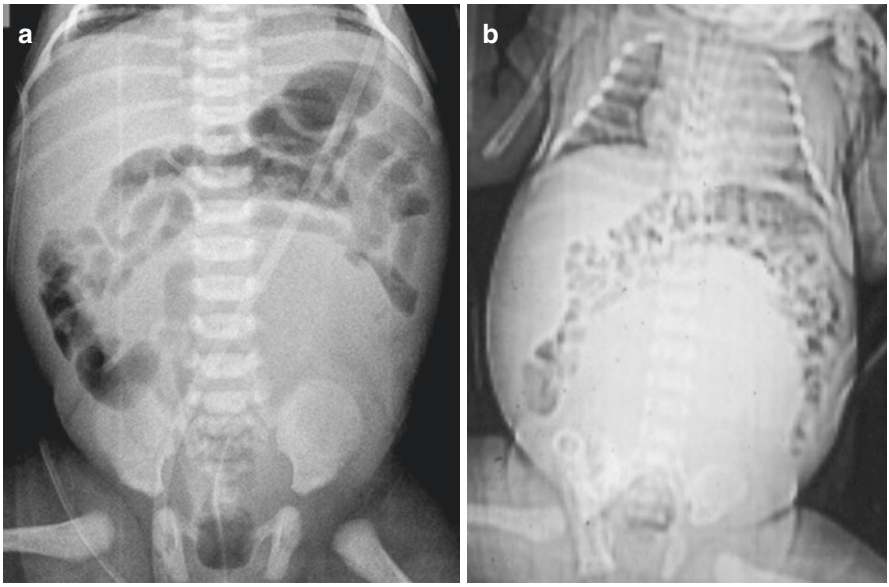

Fig. 11.4 (**a** and **b**) Abdominal radiograph showing a soft tissue density pushing the bowel upwards and to the sides. This soft tissue represents hydrometrocolpos secondary to vaginal atresia

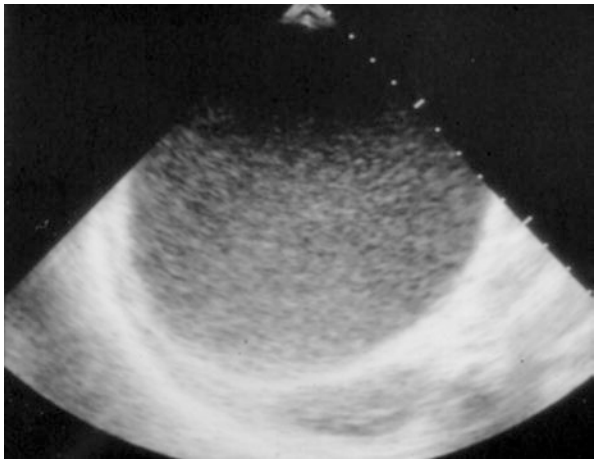

Fig. 11.5 Abdominal ultrasound showing hydrometrocolpos secondary to vaginal atresia

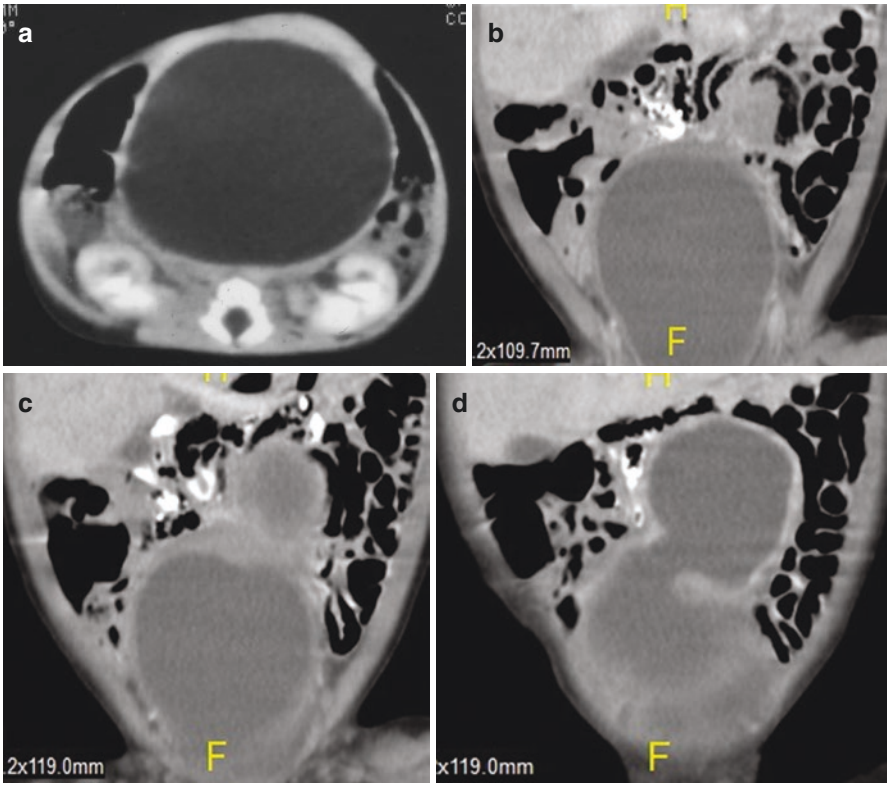

Fig. 11.6 (**a**–**g**) Abdominal CT-scan showing hydrometrocolpos secondary to vaginal atresia. Note the dilated vagina and uterus

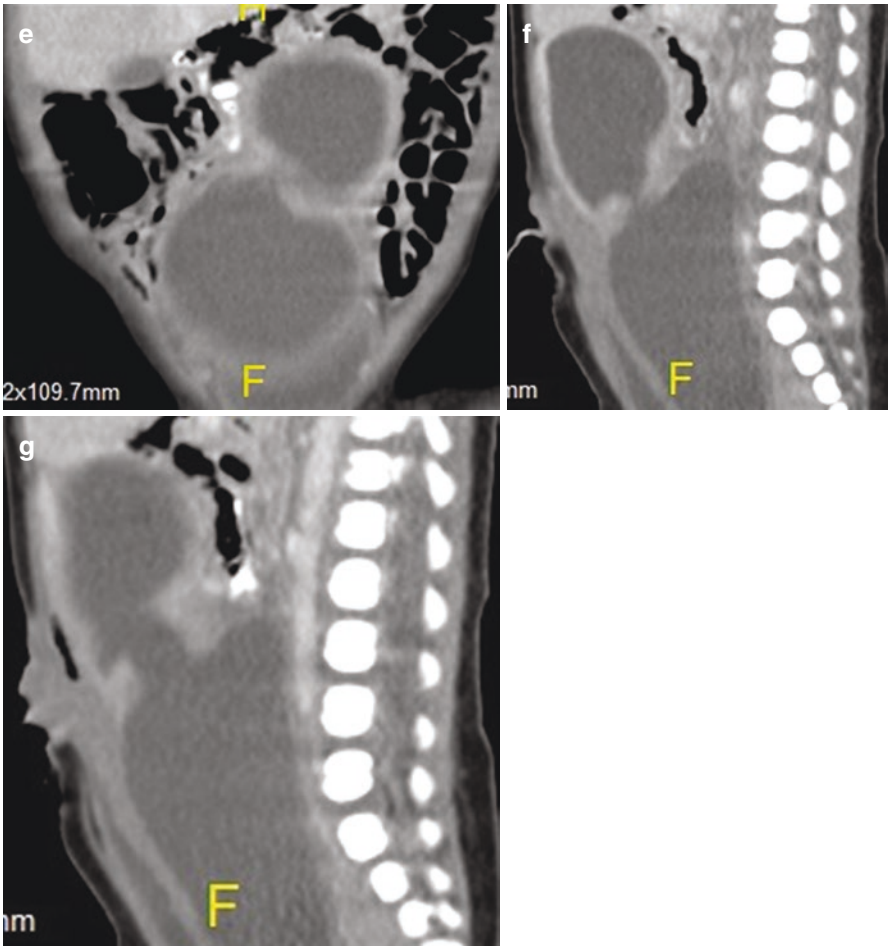

Fig. 11.6 (continued)

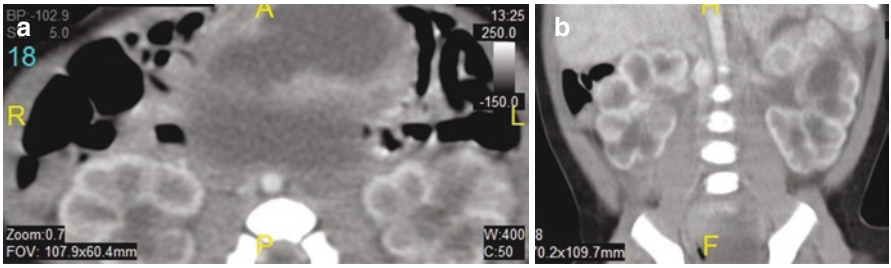

Fig. 11.7 (**a** and **b**) Abdominal CT-scan showing bilateral hydronephrosis secondary to pressure from hydrometrocolpos

  - Abdominal, pelvic, and transperineal sonograms depict the ovaries, uterus, and proximal vagina.
  - They enable evaluation of the urinary tract so that anomalies can be identified.

- Fetal MRI is useful in further differentiating pelvic mass.
- CT-scan gives more detailed information regarding the anatomy and etiology.

- Whereas imperforate hymen is clinically evident and simple to treat, vaginal atresia is more complex to define and manage.
- Although magnetic resonance imaging (MRI) is routinely obtained to further delineate the internal anatomy in patients with vaginal agenesis, MRI may be only 31% sensitive in depicting uterine structures in patients with vaginal agenesis.
- Reconstruction of three-dimensional images of the pelvis may facilitate the surgical procedure, particularly when a proximal vaginal pouch (e.g., in the transverse septum) is present or when duplication anomalies of the vaginal tract are present.

- MRI imaging provides additional anatomic details with excellent soft tissue contrast to determine the thickness of the transverse septum, length of the atresia, and the presence or absence of a cervix (Fig. 11.8a–h).

– A karyotype

  This is frequently obtained in the evaluation of complex anomalies.
  Patients with the most common presentation of vaginal atresia and those associated with The Rokitansky-Mayer-Küster-Hauser syndrome (MRKH) syndrome typically have a normal 46, XX karyotype.

– Genitography

  This is an unnecessary invasive investigation that may be harmful leading to secondary infection with subsequent pyometrocolpos.
  This must be kept in mind when evaluating hydrometrocolpos as there is a possibility of secondary infection and development of pyometrocolpos which is a serious complication (Figs. 11.9a–c and 11.10a, b).

– Laparoscopy

  This may be necessary to evaluate the uterus and adnexal structures if they are not clearly identified on ultrasonography or MRI.

11.7 Treatment

- The treatment of vaginal atresia is surgical.
- The goals of surgical management in patients with vaginal atresia are:
  - To relieve vaginal obstruction
  - To restore normal anatomy and a normal sex life
  - To preserve the patient's reproductive potential

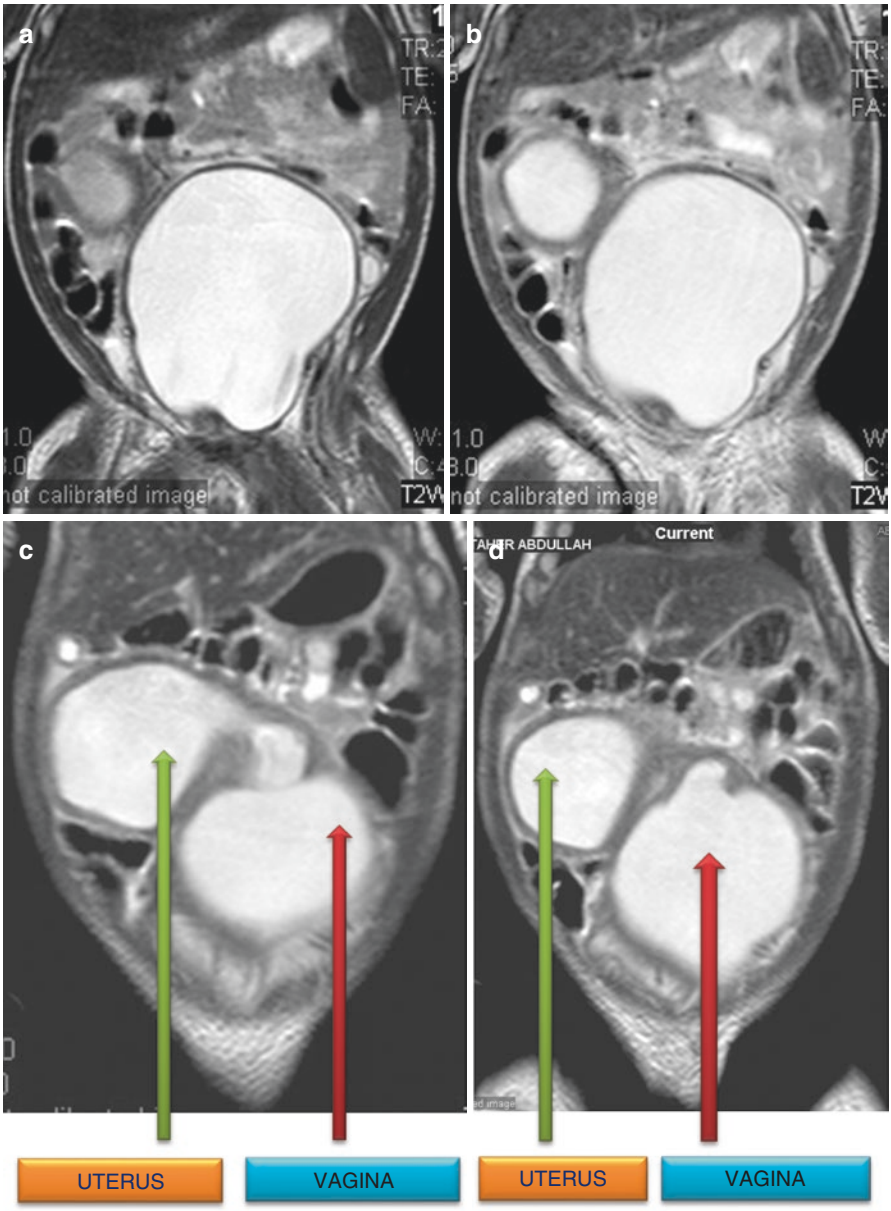

Fig. 11.8 (**a**–**h**) MRI showing hydrometrocolpos. Note the markedly dilated vagia and uterus. Note also the level of vaginal atresia

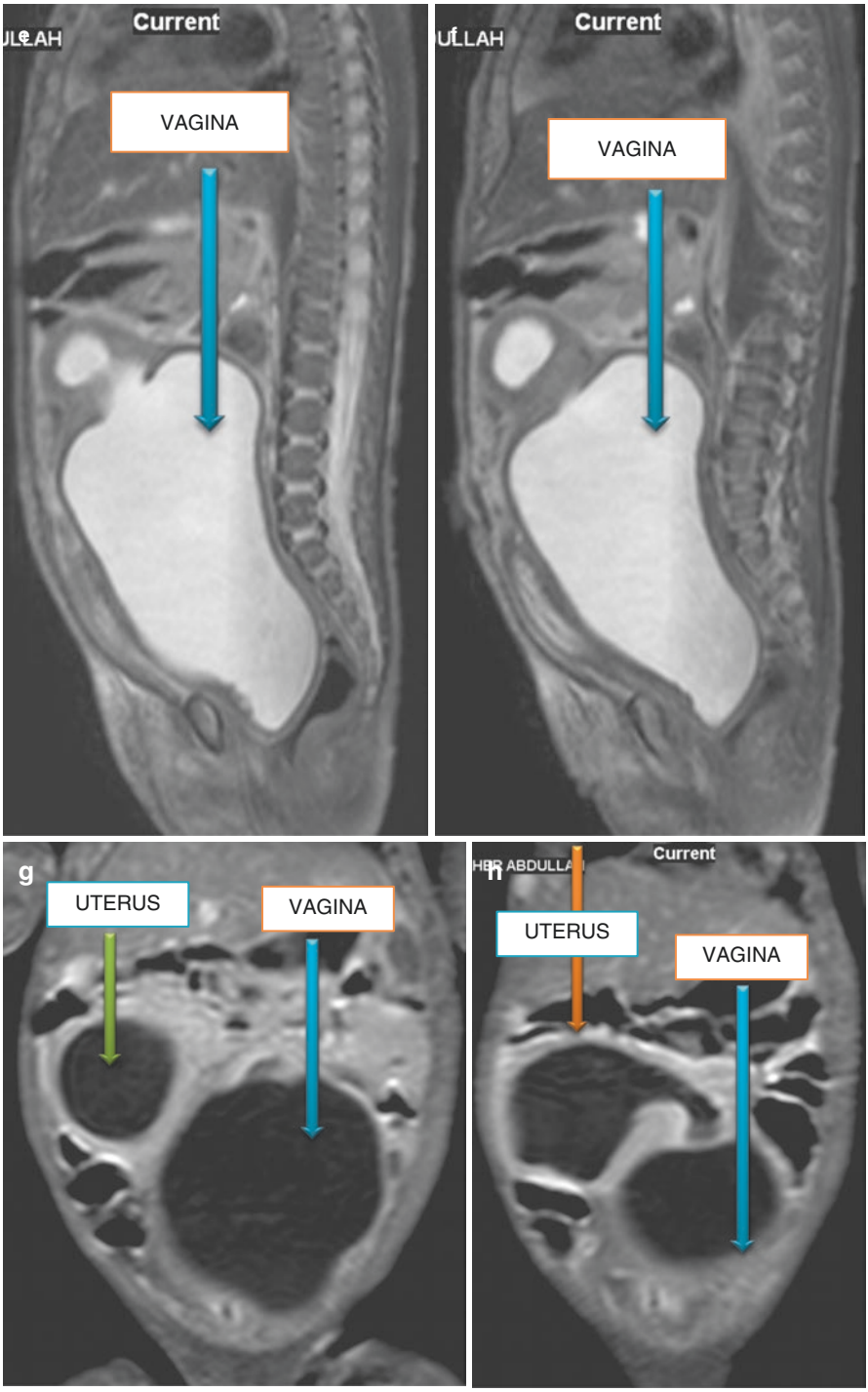

Fig. 11.8 (continued)

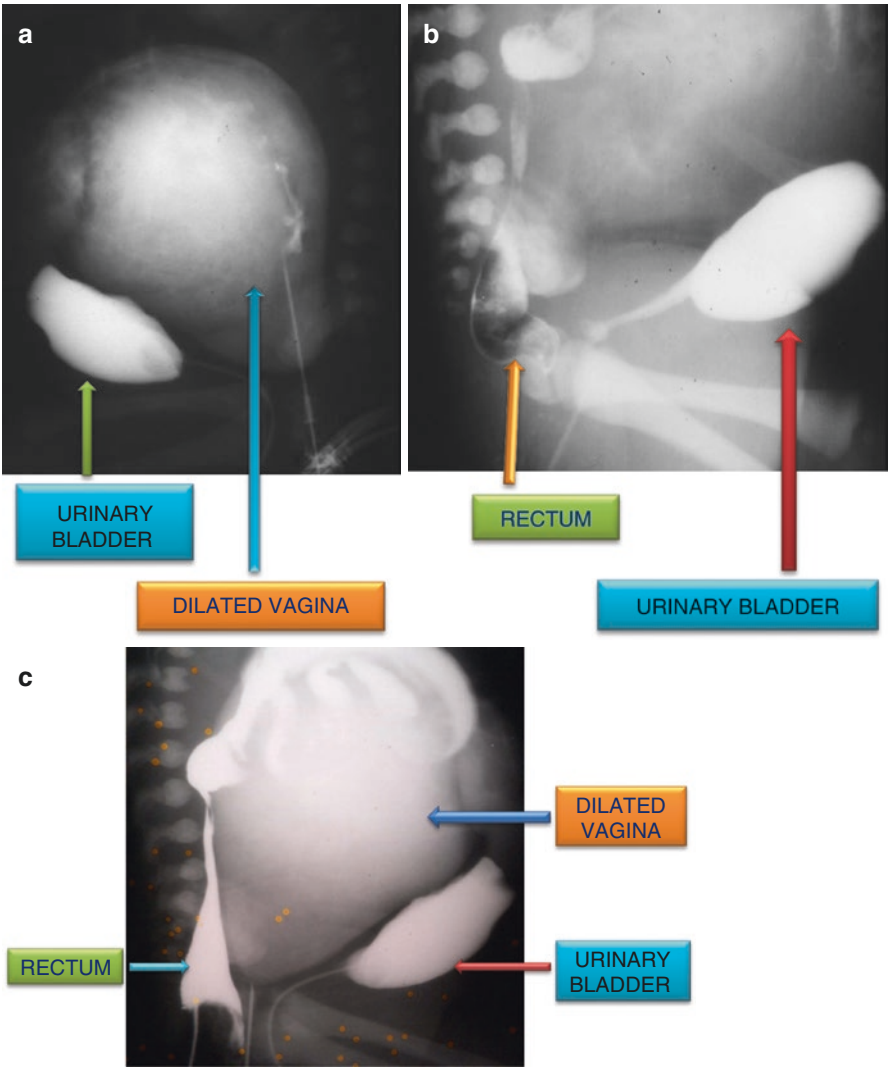

Fig. 11.9 (**a–c**) Contrast study (contrast injected into the distended vagina, rectum and urinary bladder) showing hydrocolpos compressing the colon posteriorly and the urinary bladder anteriorly

- Surgical intervention is usually delayed until the late teens so the patient is mature enough to comply with postoperative care.
- Surgical or medical intervention must be started sooner than this if a patient presents with vaginal outflow obstruction, abdominal or pelvic pain, or a risk for secondary endometriosis.
- The timing of surgery depends on the patient's anatomic configuration, the patient's presentation and on the presence or absence of functional endometrial tissue.

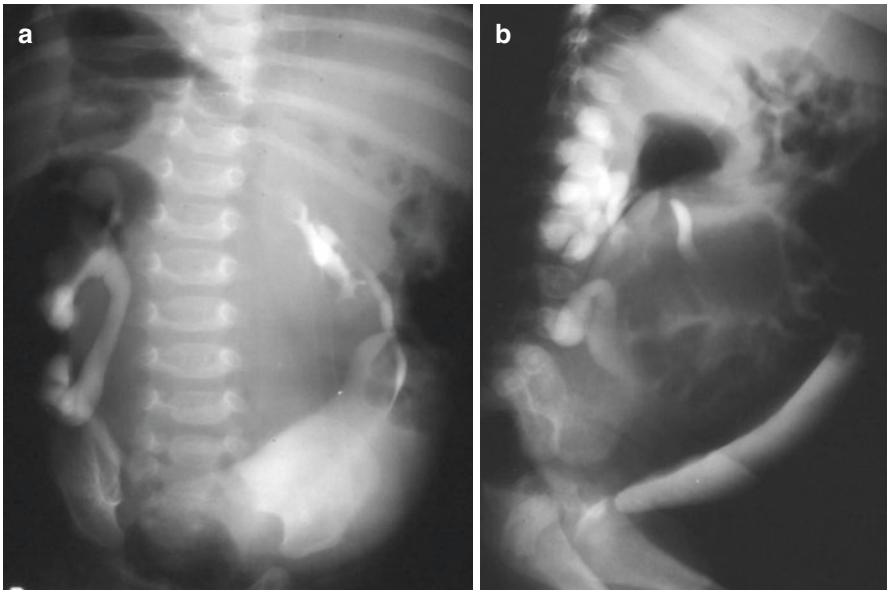

Fig. 11.10 (**a** and **b**) Intravenous urography showing dilated ureters and hydronephrosis secondary to pressure from hydrometrocolpos

- The decision to perform surgery to correct vaginal atresia must be made in the context of the patient's overall condition. If a patient has a lethal or complex congenital anomaly that might complicate anesthesia or surgical management, reconstruction of the uterovaginal outflow tract should be carefully considered. Alternative decompression or resection techniques may be preferable.
- Patients with clinically significant neurodevelopmental delay should be reevaluated for anatomic reconstruction within the context of future sexual maturation.
  - A complex perineal reconstruction that does not improve a patient's daily function and that requires the use of postoperative dilators could be imprudent because of physical and psychological trauma.
- In newborns with hydrocolpos, emergency drainage of the hydrocolpos should be done or more preferably, an abdomino-perinal vaginal pull-through can be done as a single stage:
  - A Foley's catheter is inserted.
  - Laparotomy is done through a lower transverse abdominal incision.
  - The hydrometrocolpos is defined and the anatomy is outlined (Fig. 11.11a, b).
  - The distended vagina is opened anteriorly and drained.
  - A new vaginal opening is created in the perineum using a semicircular or transverse incision at the hymenal ring.
  - Using blunt and sharp dissection from below toward the peritoneal cavity, a channel is created (Figs. 11.12a–c, 11.13a, b and 11.4a–f).

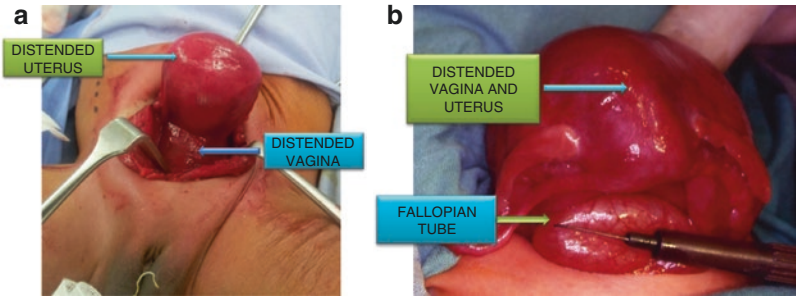

Fig. 11.11 (**a** and **b**) Clinical intra-operative photographs showing hydrometrocolpos secondary to vaginal atresia. Note the markedly distended vagina and uterus which form a mass arising from the pelvis. The mass will cause pressure effect on the urinary bladder and ureters causing hydronephrosis. The fluid accumulating in the vagina and uterus may drain into the peritoneal cavity via the Fallopian tubes causing ascites. The hydrocolpos may also become infected leading to pyocolpos

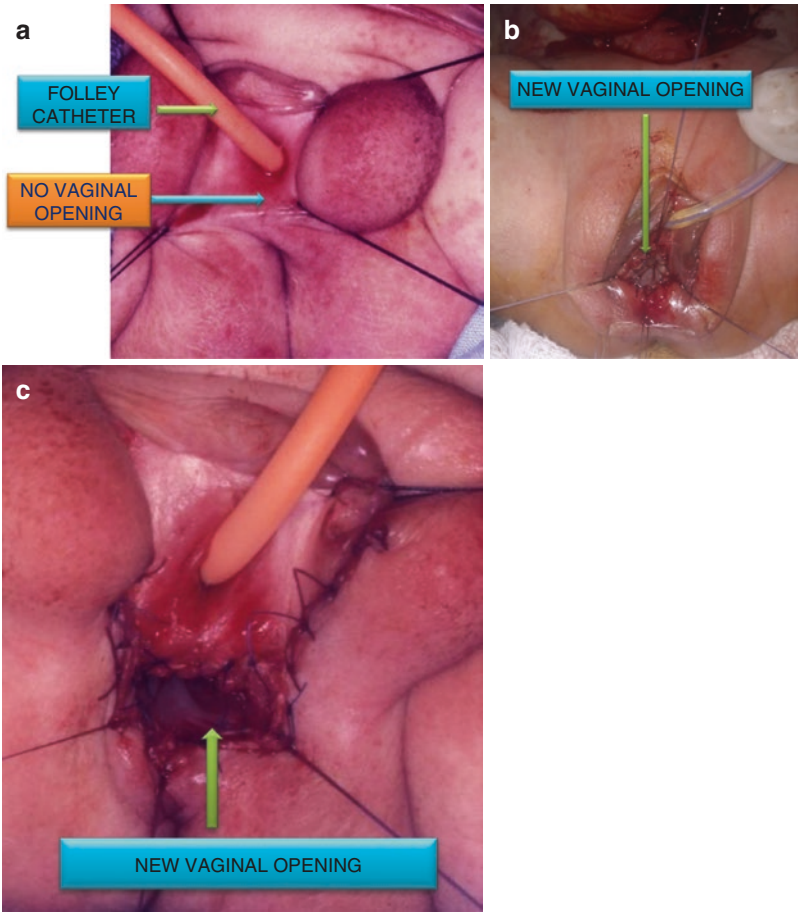

Fig. 11.12 (**a–c**) Clinical intra-operative photographs showing vagina atresia and abdominoperineal vaginal pull through. Note the Foley catheter in the urethra and absence of vaginal opening in the upper photograph. Note also the newly created vaginal opening

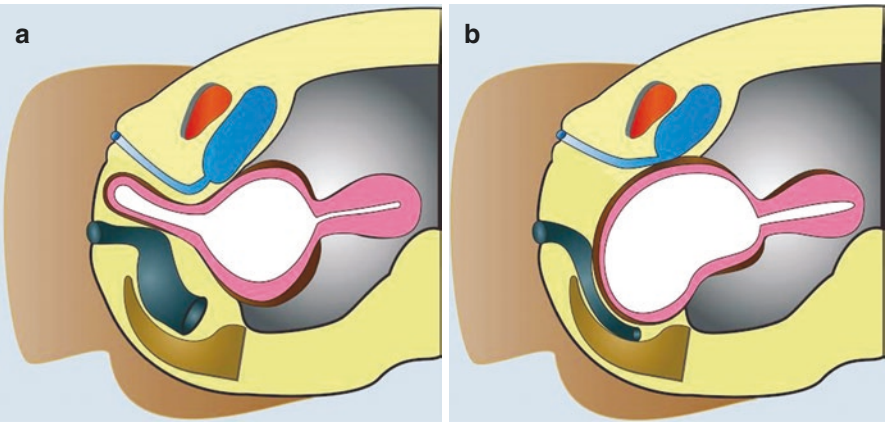

Fig. 11.13 (**a** and **b**) Diagrammatic representation of vaginal atresia. Note the markedly distended vagina and the variable distance between the vaginal atresia and the perineum. The distended vagina will cause compressing on the posteriorly placed rectum and also on the urinary bladder and ureters. Compression effects on the urinary bladder and ureters will lead to obstructive uropathy and hydronephrosis and hydroureters

  - At this stage, it is important to protect the rectum. The rectum is close and can be injured easily at this stage of dissection.
  - A Hegar dilator is passed into the distended vagina through the opening created in the anterior wall of the vagina and the posterior wall is pushed downwards till the newly created vaginal opening.
  - In those without hydrocolpos, vaginal reconstruction is delayed till late childhood or early adolescence.
  - There are several reconstruction procedures by using either extra-abdominal tissues or intra-abdominal tissues. There is however, no consensus regarding the ideal method for creating a functional vagina.

- The Abbe-McIndoe operation:
  - In this procedure, a split-thickness skin graft is taken from the buttock and used to create the neovagina.
  - Girls who are offered the McIndoe operation require a certain level of psychological and sexual maturity to be motivated and compliant with the dilation (mold) regimens necessary for a successful outcome.

- Abbe-McIndoe operation
  - With the patient in the lithotomy position, an H- or Z-shaped incision is made on the perineum.
  - A Foley catheter is inserted into the urinary bladder.
  - Sharp and blunt dissection of the tissues interposed between the urinary tract and the rectum results in a cavity 10–12 cm in length.
  - During dissection care should be taken to avoid injury to the urethra and the Foley catheter in the urethra guides the dissection away from it.

– The proximity of the dissection to the rectum may result in injury to the rectum and this is best avoided by placing an examining finger or Hegar dilator in the rectum.
– A split-thickness skin graft is harvested from the inner thigh or buttocks prior to the perineal incision.
– Although a full-thickness graft tends to limit contraction, it transfers undesirable epithelial appendages.

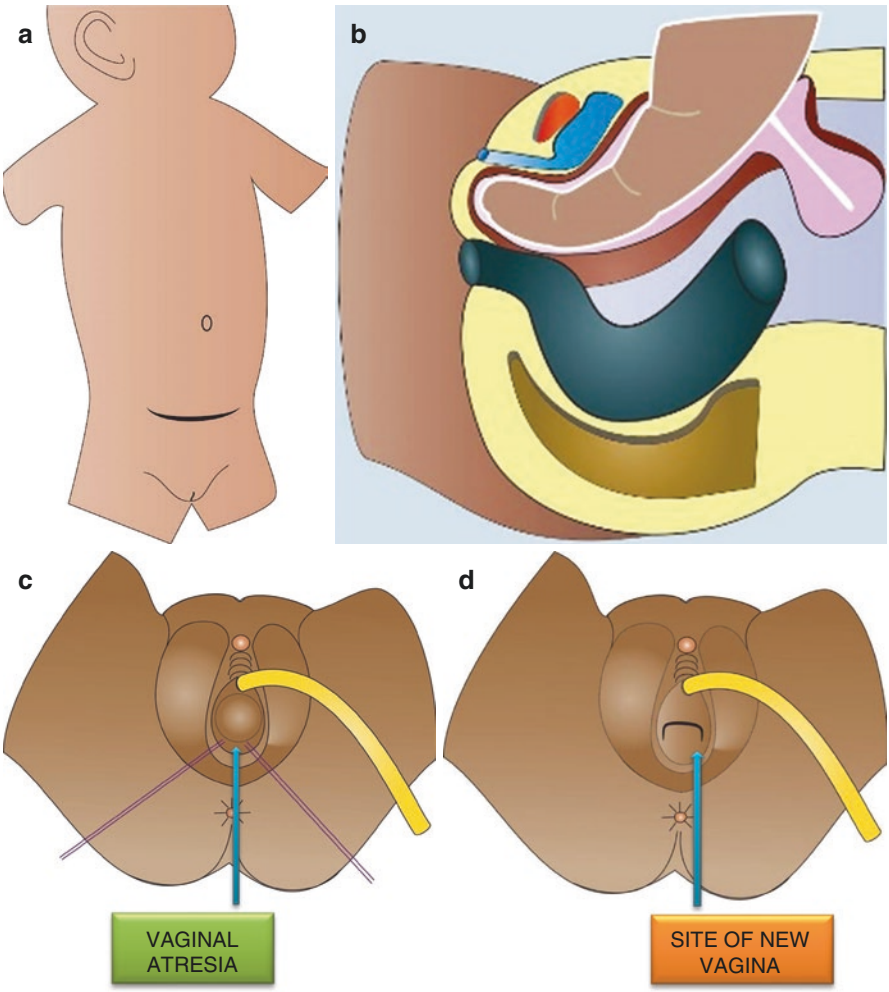

Fig. 11.14 (**a**–**f**) Diagrammatic photographs showing the perineal stage of the vaginoplasty and the incision used to create the opening to the peritoneal cavity. The vaginal wall is pulled through this opening, opened and sutured to the margins. Note the finally constructed vaginal opening

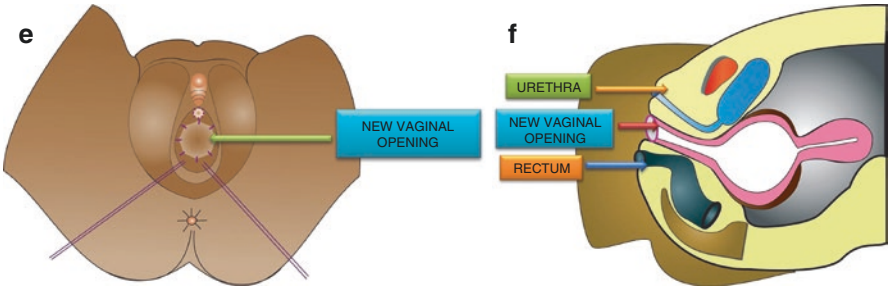

Fig. 11.14 (continued)

- A suitably shaped piece of polyethylene foam approximately 5 cm wide and 15 cm long serves as a mold for the neovagina.
- This is covered with adhesive plastic. Also used is a mentor mold, which is inflated with saline once, placed in the neovaginal space.
- The skin graft is sutured to the mold with Vicryl, with the skin surface facing the obturator.
- This construct is inserted into the soft-tissue pouch.
- The labia are sewn closed with silk sutures.
- The Foley catheter is left in place, and the patient is given stool softeners.
- Postoperatively, the patient is kept in the hospital for 1 week; the mold is then removed in the operating room.
- The neovagina is irrigated, and any areas of granulation tissue are cauterized.
- The patient is then discharged with a mold (e.g., a Young dilator), which is removed upon voiding and defecation.
- Advantages of this procedure are:

  Low morbidity and mortality

- Disadvantages include:

  Tendency to develop vaginal stenosis
  The lack of natural lubrication
  The possible development of fistulas
  The need for continuous mold placement if the vagina is not used.

• Musculocutaneous flaps using the rectus abdominis and gracilis muscles are rarely used to create the neovagina.

- Musculocutaneous flaps provide a reliable means of creating a neovagina.
- Although they provide a sensate surface, they are bulky.
- The rectus and gracilis muscles are the primary muscle groups used.
- As with fasciocutaneous and subcutaneous pedicled flaps, operations involving these flaps tend to cause scarring and use hair-bearing skin.

  - Bilateral flaps have been used to create a neovagina for vaginal atresia, but they are primarily reserved for reconstruction after ablative oncologic surgery.
  - A unilateral flap is often appropriate for reconstruction after repair of recto-neovaginal fistulas or urethral defects.

- Vulvovaginoplasty using tissue expanders
  - In vulvovaginoplasty, tissue expanders are used to increase the available skin from the labia.
  - This tissue is used to create a posteriorly directed pouch.
  - Functional assessment reportedly has yielded unsatisfactory results.
  - Several groups report the use of amnion as a homograft, without evident rejection. This technique maintains a vaginal space for future dissection, but it has not gained wide acceptance.

- Successful use of laparoscopic assisted biomaterial grafts for reconstruction of congenital atresia of the vagina and cervix has been reported.
- Intestinal segments, typically derived from the sigmoid colon may provide advantages over the skin grafts used in the Abbe-McIndoe operation, in that the former do not routinely require postoperative dilation.
- Sections of the ileum, cecum, and rectosigmoid colon have also been used.
- The advantages are:
  - Distensability
  - Self-lubricating nature of the conduit
  - Reduced natural contraction resulting in neovaginal stenosis, which allow the patient to avoid the discomfort of long-term use of dilators.

- Disadvantages are;
  - The potential complications encountered after laparotomy and bowel resection
  - The continuous production of mucous secretions that may require the use of an absorptive pad or tampon.

- The peritoneum has been used to maintain a cavity until the surfaces become epithelialized.
- Correction of vaginal atresia using tissue from intestine.
  - The patient is placed in a lithotomy position to afford access to the abdomen and perineum.
  - The abdomen is entered through a Pfannenstiel incision, and the status of the uterine remnant is evaluated.
  - For the patient with müllerian agenesis, rudimentary uterine horns may be present with remnant fallopian tubes.
  - The value of these structures, in terms of subsequent fertility, must be determined.
  - The ovaries are typically normal and undisturbed.
  - Patients with androgen insensitivity syndrome have male gonads, which are removed to prevent malignant transformation.

- A segment of the sigmoid colon is chosen, with a major vascular pedicle supplying the mesenteric arcade.
- This segment is divided, and the adjacent intestinal tract is placed in continuity.
- Then, whether the graft is moved to the perineum in an isoperistaltic or a reverse peristaltic manner is decided on the basis of the length of the mesenteric pedicle.
- The chosen proximal end of the sigmoid colon is closed in two layers.
- The perineal dissection requires a circular or cruciate incision at the hymenal ring.
- Then, blunt dissection from below toward the peritoneal reflection allows this incision to be opened and the sigmoid to be passed into the newly created tract.
- A single-layer anastomosis is created to the hymenal regions by using absorbable sutures.
- Attempts are made to extraperitonealize the sigmoid.
- A Vaseline pack is placed in the neovagina to maintain apposition to the dissected tissues.
- The use of closed-suction drains is optional.
- Intestinal segments typically derived from the sigmoid colon and rarely the ileum, cecum, and rectosigmoid colon.
- This procedure is known to be associated with complications, mainly:

  Excess mucous drainage
  The potential for prolapse

- Currently this procedure is done via the laparoscopic assisted approach which is associated with lower morbidity.

• Laparoscopic Vecchietti procedure:

- The aim of this procedure is to create a neovagina by invagination by using an acrylic olive that is placed against the vaginal dimple.
- The olive is attached to a traction device mounted on the abdomen with laparoscopically placed subperitoneal sutures.
- Traction is applied to the olive using an attraction device.
- Traction is applied to the olive to produce 1–1.5 cm of invagination per day, creating a neovagina in approximately 7–9 days.
- The vaginal wall is grasped with a Babcock, opened and a single-layer anastomosis is created between the edges and the hymenal regions by using absorbable sutures.
- Then, after the neovagina is created, active dilation is required until regular sexual activity is started.
- The laparoscopic Vecchietti procedure has gained a degree of acceptance in the management of vaginal atresia.
- One advantage of this technique over the Frank procedure is that uninterrupted traction is applied.

  - In addition, prolonged hospitalization is unnecessary because the traction can be completed on an outpatient basis.

- Another laparoscopic approach is an adaptation of the Davydov procedure.
  - This technique is characterized by a three-stage operation that includes:

    Dissection of the rectovesical space
    Abdominal mobilization of the peritoneum to create the vaginal fornices
    Attachment of the peritoneum to the introitus

  - With use of the laparoscopic approach, the abdominal end of the neovagina is closed with a purse-string suture.
  - This laparoscopically assisted operation lowers the rate of intraoperative complications, shortened operating time and hospital stays, and minimizes external scars.
  - After surgery, sexual function (composite score for desire, arousal, lubrication, orgasm, satisfaction, pain) approaches that of matched controls without gynecologic disorders.

- Robotic-assisted repair of vaginal atresia has been described.
- At present, no consensus has been reached regarding the ideal method for creating a functional vagina.
- At present, the most common operation is McIndoe vaginoplasty.
- In 1938, Frank described a nonsurgical technique developed especially for patients with Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome.
  - In this clinical situation, absence of the uterus and proximal vaginal tract obviates complex reconstructive operations.
  - The goal is to create a blind-ending vaginal pouch.
  - The technique involves forceful dilation of a shallow rudimentary vaginal pit with the sequential application of progressively wider and longer dilators.
  - Problems of stenosis, dyspareunia (20%), and decreased vaginal lubrication have made this option unattractive for many patients.

- Nonsurgical creation using Frank dilators is the best first-line approach for these patients.
  - Patients use the dilators, increasing in length and diameter, with spandex underwear as they sit on a stationary racing bicycle seat for 30–120 min/day.
  - This process uses pressure to create the vagina.
  - Care must be taken to avoid dilating the urethra.
  - If this treatment option fails, surgical intervention should be considered.
  - In the patient with functional ovarian tissue but an absent uterus and vagina, reconstruction of the genital tract is not medically urgent.
  - In the absence of ambiguous genitalia, gender assignment is not an issue, and involving the patient in the decisions regarding future surgery is important.

- Wharton-Sheares-George operation

- This method is suitable for a flat perineum with no pouch.
- Two dimples at the lower end of the vestigial müllerian ducts are identified in between the two labia just below the urethral orifice located within the normal hymen.
- Hegar dilators are gently pushed through the dimples with increasing size.
- The tunnels created along the vestigial müllerian ducts appear like double-barrel tunnels with a central septum.
- The central septum is then excised to form a neovagina.
- A vaginal mold is placed in the neovagina for 2 months with repeated washing and cleaning, after which patients are advised intermittent self-dilatation until active sexual function.

11.8 Complications

- Creation of a neovagina by using skin grafts requires long-term use of vaginal dilators, molds, or sexual activity to avoid stenosis.
- Dilator trauma places the posterior wall abutting the rectum at some risk for neovaginal-rectal ulcers and fistulas that may require additional surgery.
- The potential for malignant transformation of the neovaginal epithelium is always present.
- Complications related to the sigmoid neovagina tend to be related to excess mucous drainage and the potential for prolapse.

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Chapter 12
Cloacal Anomalies

Ahmed H. Al-Salem and Munther J. Haddad

12.1 Introduction

- A persistent cloaca is a complex congenital birth defect in which there is a confluence of the rectum, vagina, and urethra into a single common channel (Fig. 12.1).
- Cloacal anomalies are very rare and occur in 1 per 20,000–40,000 live newborn females.
- A persistent cloaca occurs exclusively in girls and is considered the most complex and technically challenging defect in the spectrum of anorectal malformations.
- A common error in the diagnosis of cloaca may occur during the neonatal period where physician may confuse it with high anorectal malformation with a rectovaginal fistula.
- Cloacae represent a spectrum of defects, but the common denominator is the presence of a single perineal orifice and the rectum, vagina, and urethra open into a single common channel.
- The length of this common channel is variable and ranges from 1 to 10 cm, with an average length of approximately 3 cm.
- The length of this common channel is important both for surgical reconstruction and also for prognosis.
- The goals of treatment include an anatomic reconstruction to achieve bowel and urinary control, as well as normal sexual function.

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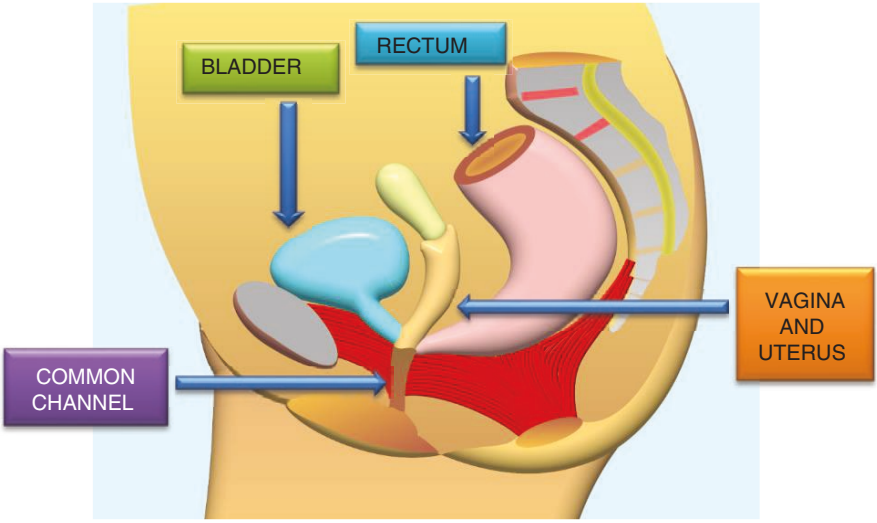

Fig. 12.1 A diagrammatic representation of cloaca. Note the urethra, vagina and rectum opening into a common channel. The length of the common channel is important for prognosis

- In 1982, Pena introduced the posterior sagittal approach to repair high anorectal malformation. This technique was also used to repair cloacal malformations.
- This technique is extended and used to repair the more complex cloacae and it is called the posterior sagittal anorectovaginourethroplasty (PSARVUP).
- This approach allowed for direct exposure to the complex anatomy and an excellent visualization and repair of the voluntary muscles of urinary and fecal continence.
- It is important to accurately diagnose persistent cloaca in the neonatal period because 90% of these patients have an associated urologic problem, and 40% of them may present also with an abdominal mass secondary to hydrocolpos.
- The hydrocolpos may produce two important complications:
  - It may compress the trigone of the urinary bladder, producing ureterovesical obstruction, megaureter, and hydronephrosis.
  - The hydrocolpos if left undrained may become infected, leading to a pyocolpos.
- Approximately 40% of patients with cloaca have a double Mullerian system consisting of two hemiuteri and two hemivaginas. This septation disorder may be partial or total and symmetric or asymmetric.
- It is important to recognize and document this for future follow-up of these patients.
- The urinary tract and the distended vagina (Hydrocolpos) may both need to be managed within the newborn period to avoid serious complications.
- Drainage of the distended vagina may lead to resolution of the secondary urological complications.

- The goals of management of cloaca include:
  - Early and accurate diagnosis of both cloaca and associated anomalies.
  - Immediate neonatal management including fecal, urinary and vaginal diversion depending on the presentation.
  - An anatomic reconstruction to achieve bowel and urinary control, as well as normal sexual function.

12.2 Associated Anomalies

- Associated anomalies are common in patients with cloaca.
- More than 80% of all patients with a cloaca have an associated urogenital anomaly. These include:
  - Absent kidney
  - Vesicoureteral reflux
  - Horseshoe kidney
  - Ectopic ureters
  - Double ureters
  - Hydronephrosis and megaureters as a result of vesicoureteral reflux or ureterovesical obstruction.
- A tethered spinal cord: An intravertebral fixation of the phylum terminale.
- Patients with anorectal malformations and tethered cord have a worse functional prognosis regarding bowel and urinary function.
- Sacrum and spine anomalies:
  - The sacrum is the most frequently affected bony structure.
  - Anomalies of the sacrum include hypodevelopment, sacral hemivertebrae, and hemisacra.
  - Hemivertebrae may also affect the lumbar and thoracic spine, leading to scoliosis.
  - Patients with cloaca may have spinal anomalies other than tethered cord, such as;

    Syringomyelia
    Myelomeningocele
- Genital anomalies:
- Approximately 50% of patients have various degrees of vaginal or uterine septation.
  - Absent vagina
  - 2 hemivagina
  - 2 hemiuteri

12.3 Classification

- Cloacae represent a wide spectrum of anomalies.
- In all, the rectum, vagina and urethra open together in a common channel.
- The length of this common channel is variable and ranges from 1 to 10 cm with an average of 3 cm.
- The length of this common channel is important both for management and prognosis.
- Based on the length of the common channel cloacae are divided into two main groups (Fig. 12.2a, b):

  1. Short common channel:
     - The length of the common channel is less than 3 cm.
  2. Long common channel:
     - The length of the common channel is more than 3 cm.

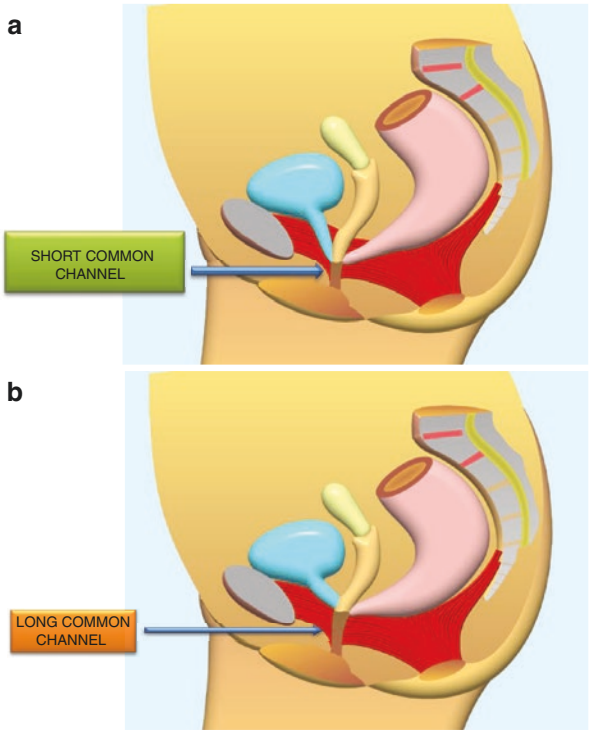

Fig. 12.2 (**a**, **b**) Diagrammatic representation of cloaca. Note the length of the common channel which is variable ranging from 1 to 10 cm but commonly around 3 cm. The cloaca is divided into two types, low and high based on the length of the common channel. It is a short common channel if the length of the common channel is less than 3 cm and long common channel if it is more than 3 cm

12.4 Clinical Features

- Persistent cloaca is a clinical diagnosis that is usually made in the neonatal period.
- The presence of a single perineal orifice provides clinical evidence of persistent cloaca.
- The external genitalia in these patients are usually not well developed and often appear small (Figs. 12.3 and 12.4).
- Some of these patients may present with abdominal distension and examination of the abdomen may reveal an abdominal mass, which likely represents a distended vagina (hydrocolpos) and is present in about 40% of patients with persistent cloaca (Fig. 12.5a, b).
- The distended vagina may also lead to distension of the uterus leading to hydrometrocolpos and sometimes the fluids distending the uterus may spill over to the peritoneal cavity via the Fallopian tubes leading to ascites.

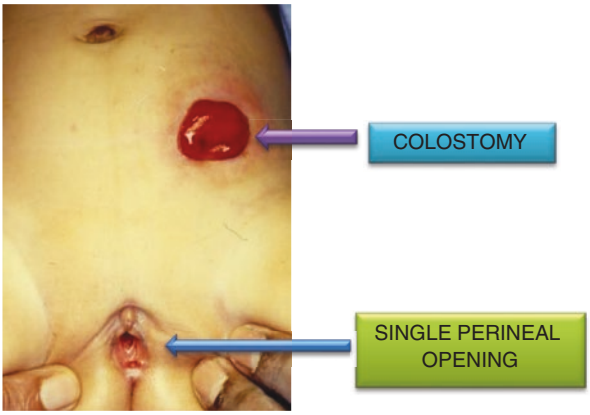

Fig. 12.3 A clinical photograph showing not well developed external genitalia in a patient with cloaca. Note also the colostomy which was done in the newborn period. Note also the presence of a single perineal opening

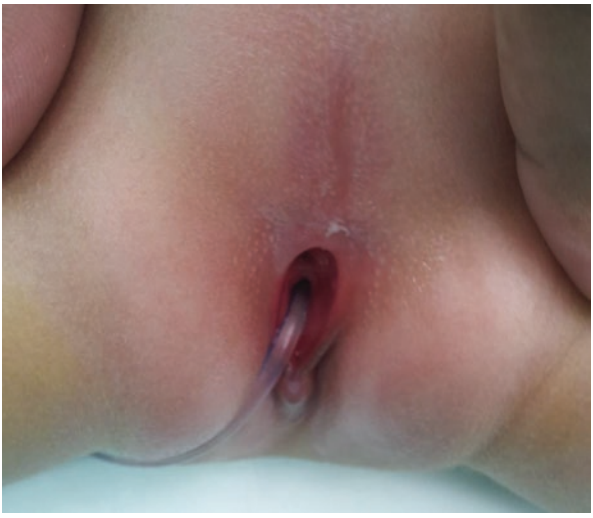

Fig. 12.4 A clinical photograph of a patient with cloaca. Note the catheter passed through a single perineal opening

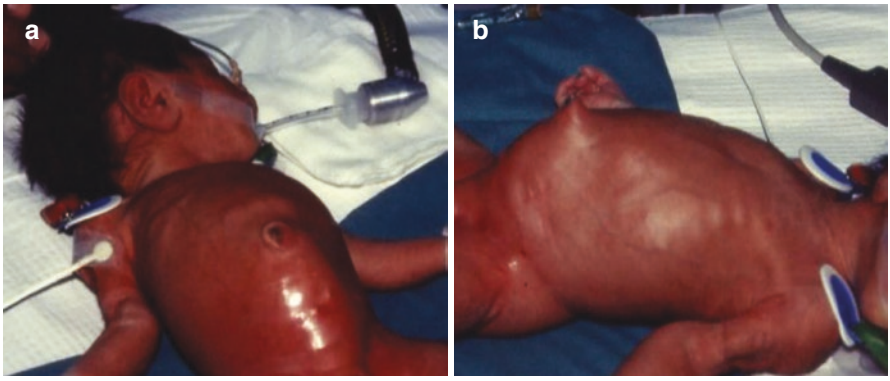

Fig. 12.5 (**a**, **b**) Clinical photographs of a newborn with cloaca showing abdominal distension secondary to hydrocolpos

- The distended vagina is also a common cause of an obstructed urinary tract because of its pressure on the trigone of the urinary bladder. This leads to obstruction of the uretro-vesical jnction leading to hydroureter and hydronephrosis. A severe hydronephrosis may lead to calcyeal rupture with urine extravasation either retroperitoneally or in the peritoneal cavity.
- It is important to decompress the distended vagina as soon as possible and once the vagina is decompressed, the urinary tract may no longer be obstructed and usually the hydroureter and hydronephrois resolve.
- If the hydrocolpos is not drained during the newborn period, it can become infected leading to pyocolpos. This is a serious condition which may lead to septicemia.
- A hemisacrum in these patients is almost always associated with a presacral mass, commonly teratomas, or anterior meningoceles.
- The Currarino triad includes:
  - An anorectal malformation
  - A hemisacrum
  - A presacral mass (teratoma, anterior meningocele)

12.5 Investigations

- Plain radiography of the spine:
  - This is to look for spinal anomalies, such as spina bifida and spinal hemivertebrae.
- Plain radiography of the sacrum:
  - This is to look for sacral anomalies, such as a hemisacrum and sacral hemivertebrae.

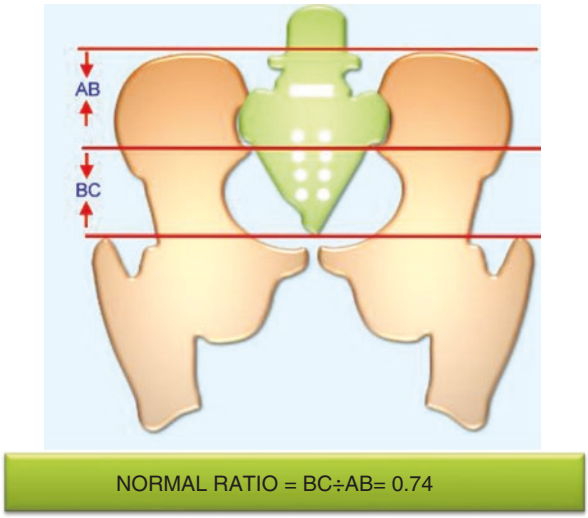

Fig. 12.6 Diagrammatic representation of calculating the sacral ratio

- The degree of sacral hypodevelopment can also be assessed.
- Traditionally, to evaluate the degree of sacral hypodevelopment, the number of sacral vertebral bodies was counted.
- A more objective assessment of the sacrum can be obtained by calculating the sacral ratio.
- To calculate the sacral ratio (Fig. 12.6):

  The distance from the coccyx to the sacroiliac joint is measured and divided by the distance from the sacroiliac joint to the top of the pelvis.
  To calculate the sacral ratio, a lateral radiography is more accurate than the anteroposterior view.
  The sacral ratio is important as this correlates with the patient's functional prognosis.
  The normal sacral ratio is greater than 0.7.
  Bowel control has rarely been observed in patients with a sacral ratio less than 0.3.

- A hemisacrum is almost always associated with a presacral mass, commonly:

  A teratoma
  An anterior meningoceles

- The Currarino triad should be excluded.
- The Currarino triad includes:

  An anorectal malformation
  A hemisacrum
  A presacral mass should be excluded.

• Abdominal ultrasonography to evaluate for urologic anomalies and a distended vagina (hydrocolpos).

- Spinal ultrasonography in the first 3 months of life is valuable.
- MRI is currently the procedure of choice to evaluate the anomalies of the cloaca, the presence of tethered cord, sacrum and spine (Fig. 12.7).
- Echocardiography to detect associated cardiac anomalies.
- A distal loopogram in those with a preliminary colostomy (Figs. 12.8 and 12.9)

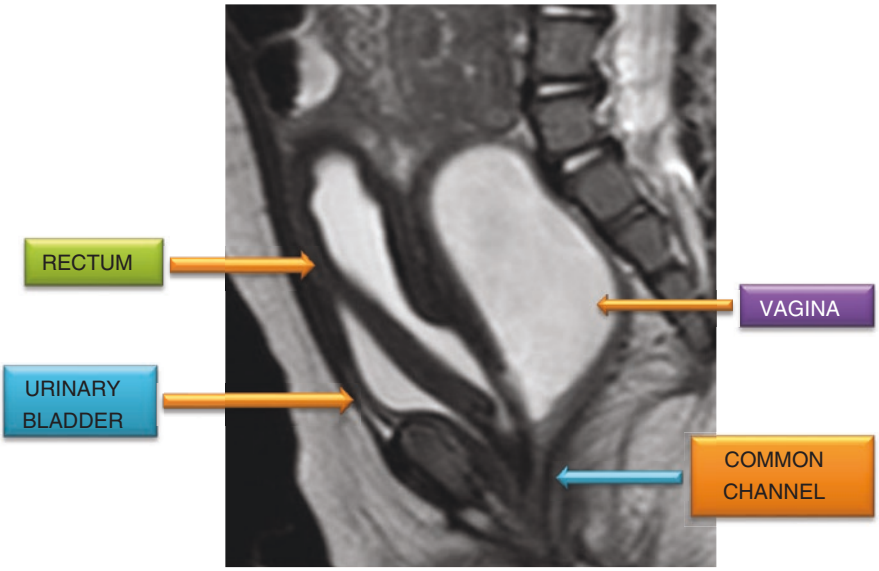

Fig. 12.7 MRI of a patient with cloaca showing the rectum, urethra and vagina joining distally together in a common channel. Note the abnormal position of the vagina which is located posteriorly and the rectum anteriorly

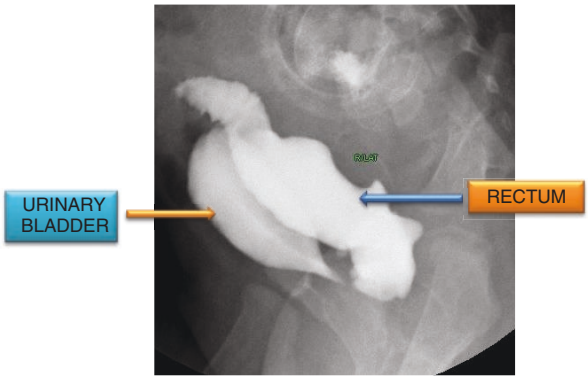

Fig. 12.8 A contrast study showing the urinary bladder and rectum in a patient with cloaca

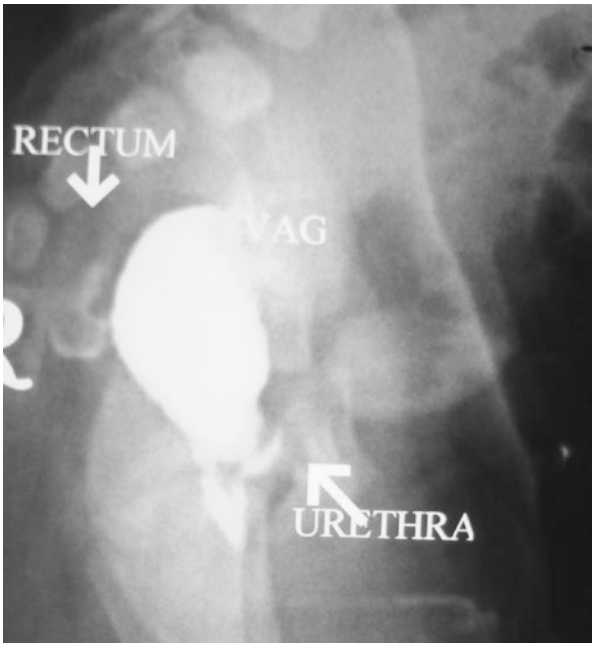

Fig. 12.9 A contrast study showing the vagina and rectum in a patient with cloaca

12.6 Management

- The goals of early management of cloaca are to (Fig. 12.10):
  - Detect associated anomalies.
  - Achieve satisfactory diversion of the gastrointestinal tract.
  - Drain associated hydrocolpos.
  - Divert the urinary tract when necessary.
  - To achieve bowel control, urinary control, and normal sexual function.
- The repair of persistent cloaca represents a technical challenge and should be performed in specialized centers by pediatric surgeons dedicated to the care of these patients.
- The management of cloaca is performed in stages.
- The first stage consists of fecal diversion and urinary and vaginal diversion if necessary (Figs. 12.11a–c and 12.12a, b).
- The definitive repair of cloaca is performed at a later date, followed by colostomy closure. This is done using the posterior sagittal anorectovaginourethroplasty (PSARVUP).
- It consists mainly of:
  - Separating the rectum from the urogenital tract.
  - Followed by separation of the vagina from the urethra and bladder.
  - Reconstruction of the common channel as a neo-urethra.

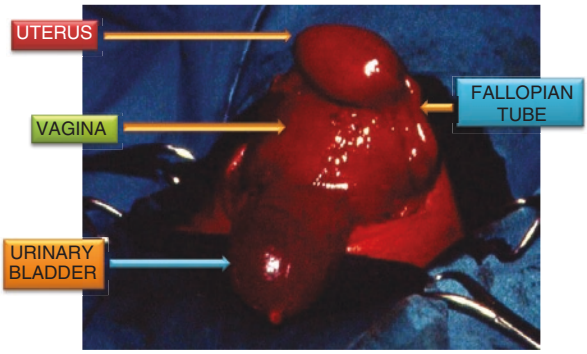

Fig. 12.10 An intraoperative photograph of a patient with cloaca who presented with hydrometrocolpos. Note the distended vagina and uterus

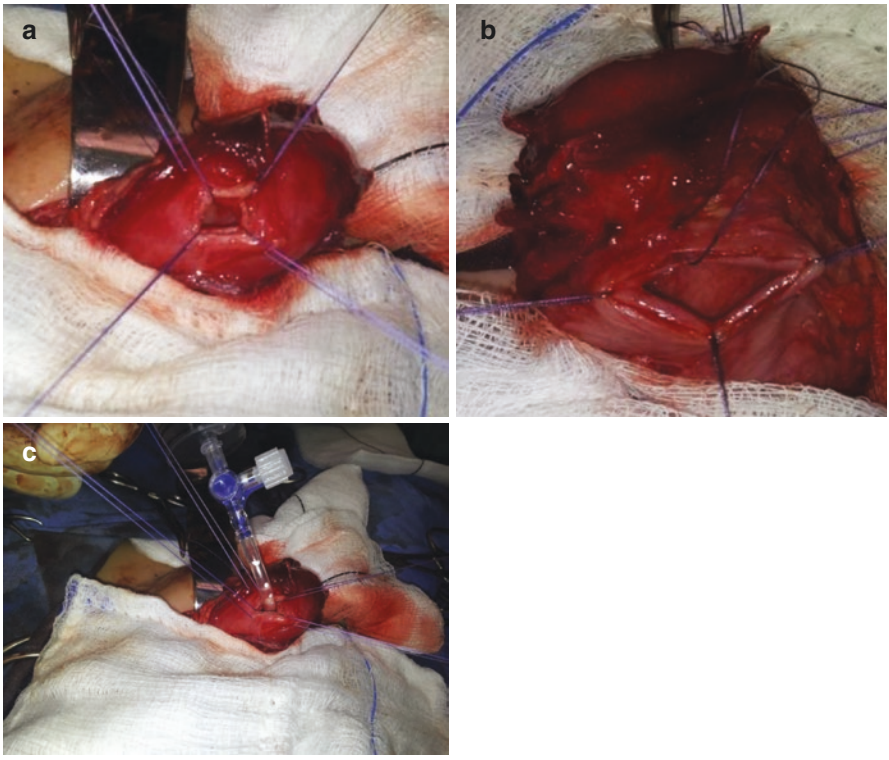

Fig. 12.11 (**a**, **b**, **c**) Intraoperative photographs of a patient with cloaca showing the already opened vagina which was distended secondary to hydrocolpos

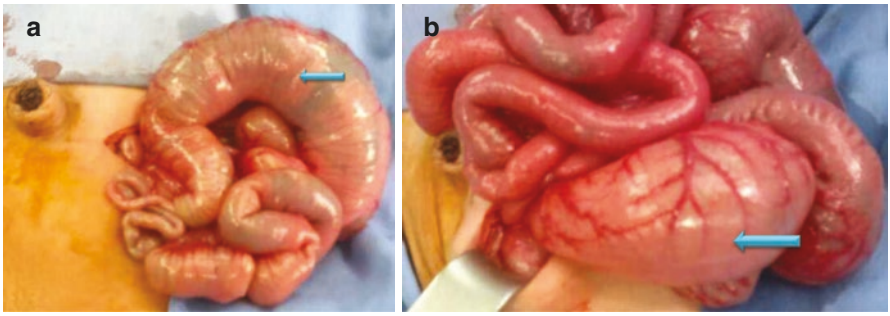

Fig. 12.12 (**a**, **b**) Intraoperative photograph showing dilated sigmoid colon in two patients with cloaca

  - Mobilization and dissection of the vagina so that it could be pulled down to be placed posterior to the urethra.
  - Performance of a pull-through of the rectum placing it within the limits of the sphincter.

- The repair can usually be performed using only the posterior sagittal approach.
- For more complex anomalies, an abdominal approach is added to mobilize a very high vagina or gain length on a very high rectum.
- If the common channel is shorter than 3 cm, the posterior sagittal approach can be used to repair the defect without an abdominal approach.
- For patients with a common channel longer than 3 cm, a laparotomy is usually required. Complex vaginal mobilizations are often required, and vaginal replacement (with colon or small intestine) is frequently necessary. Laparoscopy should be valuable in this regard.
- Total urogenital mobilization is a technique that allows mobilization of the urethra and vagina as one structure.
- If total urogenital mobilization does not adequately lengthen the vagina, the vagina and urethra must be separated, which is a technically challenging procedure.
- The pulled-through rectum is placed within the limits of the sphincter mechanism, which is determined with an electrical stimulator.
- Total diversion of the gastrointestinal tract is achieved with a colostomy (a double barrel colostomy) placed in the descending colon. This leaves a sufficient length of the colon for subsequent pull through.
- Total diversion of the fecal stream is necessary to avoid spillage and prevent urinary tract infections.
- The patient must be left with a good length of distal colon long enough for the future pull-through, and sometimes for a vaginal replacement if needed.

- The mucous fistula is also important for radiologic evaluation of the distal colon.
- Patients with cloaca have no contraindications to definitive surgery when future fecal or urinary incontinence is a concern.
- Even for patients with incontinence, a bowel management program is almost always successful in keeping a patient clean and dry.
- In patients in whom bowel management is unsuccessful (<3%), a permanent colostomy may be the best option to ensure good quality of life.
- In patients with urinary incontinence, many options are available for keeping a patient clean.
- Urinary diversions, such as the Mitrofanoff procedure and the use of intermittent catheterization, are usually successful in keeping the patient dry of urine.
- The repair of persistent cloaca represents a technical challenge and should be performed in specialized centers by pediatric surgeons dedicated to the care of these patients. This especially for cloaca with a long common channel.
- A distal colostogrphy through the mucous fistula is essential to outline the anatomy.
- Cystoscopy and vaginoscopy are essential components for better evaluation of the patient with persistent cloaca. This is important to define the anatomy and plan surgical reconstruction. It is important to determine the length of the common channel, the presence of vagina or a bifid vagina, the presence of one cervix or more and the site of rectal fistula. This is valuable and helps the surgeon to predict whether a laparotomy will be required in combination with the posterior sagittal approach. It is also important to stress the value of laparoscopy in the management of these patients especially those with long common channel.
- Prognostic factors include:
  - The quality of the sacrum and spine.
  - The quality of the sphincter muscles.
  - The length of the common channel.
- Approximately 50% of patients have various degrees of vaginal or uterine septation. These can be totally or partially repaired during the main operation.
- The Foley catheter remains in place for approximately 10–14 days.
- Anal calibration is performed 2 weeks after the operation, followed by a program of anal dilatations. Once the desired size is reached, the colostomy can be closed.
- Cystoscopy and vaginoscopy should be performed before colostomy closure to ensure that no urethrovaginal fistula is present, which would necessitate a reoperation and this should be done with the colostomy still in place.
- Dilatations are continued afterward according to a prescribed protocol. They are a vital part of the postoperative management to avoid a stricture at the anoplasty site.

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Chapter 13
Menstruation Disorders in Adolescents

Ahmed H. Al-Salem and Salah Radwan

13.1 Introduction

- In developed countries, the median age at menarche is between 12 years and 13 years.
- In the United States, the median age of menarche is 12.43 years, with only 10% of females menstruating at 11 years and 90% by 13.75 years.
- Menarche usually occur when females have Tanner stage IV breast and pubic hair development.
- Studies have shown that a higher gain in body mass index during childhood is related to an earlier onset of puberty.
- Other factors that may influence the onset of puberty include:
  - Environmental factors
  - Socioeconomic conditions
  - Nutrition
  - Access to preventive health care system
- The average interval from the development of breast buds to the onset of menarche is 2–3 years.
- Menarche typically occurs within 2–3 years after thelarche (breast budding), at Tanner stage IV breast development, and is rare before Tanner stage III development.
- By age 15 years, 98% of females will have had menarche.

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- In the first years after menarche, anovulatory cycles are more common and may constitute 50% of cycles. Nevertheless, most cycles are still between 21 and 45 days and last between 2 and 7 days (mean, 5 days).
- There is an association between the age of menarche and the length of time needed to achieve regular ovulatory cycles.
  - A younger age of menarche is associated with more than 50% ovulatory cycles after 1 year.
  - A later onset of menarche is not associated with fully ovulatory cycles for 8–12 years.

Tanner stages
• Stage 1: No palpable breast tissue
• Stage 2: Development of breast buds with elevation of the papilla
• Stage 3: Enlargement of the breast without separation of the areola
• Stage 4: Formation of a secondary mound, as the areola and papilla project above the breast
• Stage 5: Recession of the areola to the contour of the breast

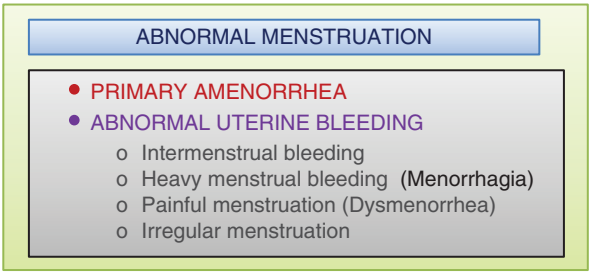
- It is estimated that normally, 30–40 mL of blood is lost in a normal menstrual cycle.
- Loss of more than 80 mL of blood or bleeding that persists for longer than 7 days is abnormal and should be considered an indication of abnormal menstrual cycle. It is difficult to measure this and menstrual flow requiring changes of menstrual products every 1–2 h is considered excessive, particularly when associated with flow that lasts more than 7 days at a time.
- Due to the relative immaturity of the hypothalamic-pituitary-ovary axis in the first 2 years following menarche, more than half of the menstrual cycles are anovulatory.
- This results in irregular cycles where cycle frequency can vary from less than 20 days to more than 90 days.
- After the first 1–2 years, the capacity for estrogen-positive feedback on the anterior pituitary develops with the subsequent mid-cycle LH surge and ovulation, resulting in regulation of the menstrual cycle.
- It is estimated that 55% of cycles are anovulatory cycles in the first year post menarche.
- Anovulatory cycles are often heavy and prolonged with some girls bleeding for several weeks at a time. This can lead to iron deficiency anemia, and in rare cases cardiovascular collapse requiring admission and blood transfusion.
- Initial anovulatory cycles tend to be pain-free, although heavy menstrual loss can result in an element of dysmenorrhea.
- When regular ovulatory cycles commence, the periods often become more painful due to the increased levels of circulating prostaglandins.

Normal menstrual cycles in adolescent girls	
Menarche (Median Age)	12.4 Years
Mean cycle interval	32 Days in the first year
Menstrual cycle interval	21–45 Days
Menstrual flow length	7 Days or less

- Bleeding disorders are a relatively common cause of menorrhagia, occurring in 10–47% of cases.
- An evaluation for primary amenorrhea should be considered for any adolescent who has not reached menarche by age 15 years or has not done so within 3 years of thelarche.
- Lack of breast development by age 13 years also should be evaluated.
- The duration of menses ranges from 2–7 days during their first menses.
- Immaturity of the hypothalamic–pituitary–ovarian axis during the early years after menarche often results in anovulation and cycles may be somewhat long; however, 90% of cycles will be within the range of 21–45 days.
- Short cycles of less than 20 days (polymenorrhea) and long cycles of more than 45 days (oligomenorrhea) may also occur but by the third year after menarche, 60–80% of menstrual cycles are 21–34 days long.
- Girls and adolescents with more than 3 months between periods should be evaluated.
- Menstrual dysfunction is a common complaint amongst adolescent girls.
- It is estimated that approximately 25% of girls have significant menstrual dysfunction which can affect their activities and result in school absence.
- The menstrual cycles can be:
  - Absent (Amenorrhea)
  - Irregular
  - Heavy (Menorrhagia)
  - Painful (Dysmenorrhoea)
- It is important to note that these symptoms improve with time and serious pathology is rare.

Menstrual abnormalities that require further evaluation
1. Menstrual periods that have not started within 3 years of thelarche
2. Menstrual periods that have not started by 14 years of age with a history or examination suggestive of excessive exercise or eating disorder
3. Menstrual periods that have not started with signs of hirsutism
4. Menstrual periods that have not started by 15 years of age
5. Menstrual periods that occur more frequently than every 21 days or less frequently than every 45 days
6. Menstrual periods that occur 90 days apart eve for one cycle
7. Menstrual periods that last more than 7 days
8. Menstrual periods that require frequent pad or tampon changes (more than 1–2 h)
9. Menstrual periods that are heavy and are associated with bleeding at other sites or a family history of a bleeding disorder

- Disorders of menstruation may present as abnormal uterine bleeding which includes the following:
  - Absence of bleeding (Amenorrhea)
  - Irregular bleeding
  - Abnormally heavy bleeding (Menorrhagia)
  - Bleeding in between periods
  - Painful periods (Dysmenorrhea)
- According to the International Federation of Gynecology and Obstetrics (FIGO) system, abnormal uterine bleeding is determined on the basis of four parameters:
  - Frequency
  - Regularity
  - Duration
  - Volume
- This was revised in 2018 to include intermenstrual bleeding.



- Amenorrhea, or absent menstruation, can be either primary or secondary.
- Primary amenorrhea is defined as either:
  - The lack of menstruation by the age of 15 years (or within 3 years of thelarche) with otherwise normal pubertal development.
  - The lack of secondary sexual characteristics by the age of 13 years.
- Secondary amenorrhea is defined as the lack of menstruation for 6 months, though it is uncommon even in adolescents to lack menstruation for more than 3 months.
- The causes of abnormal uterine bleeding are classified according to the PALM-COEIN system.
  - The acronym PALM represents structural causes:

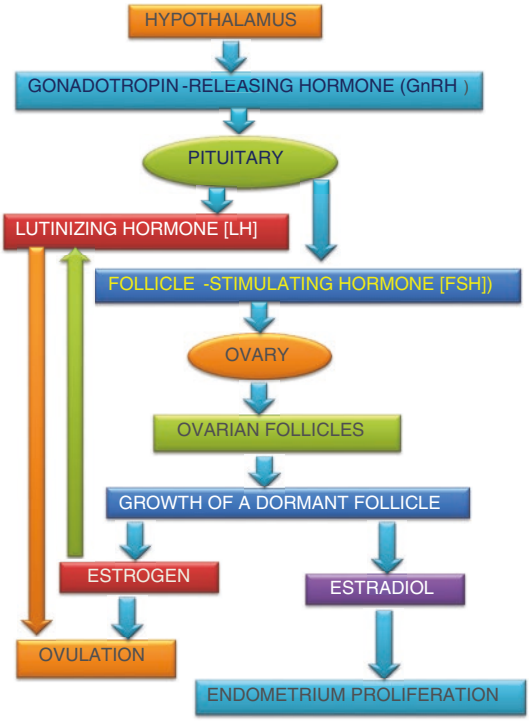
    Polyp
    Adenomyosis
    Leiomyoma
    Malignancy and hyperplasia

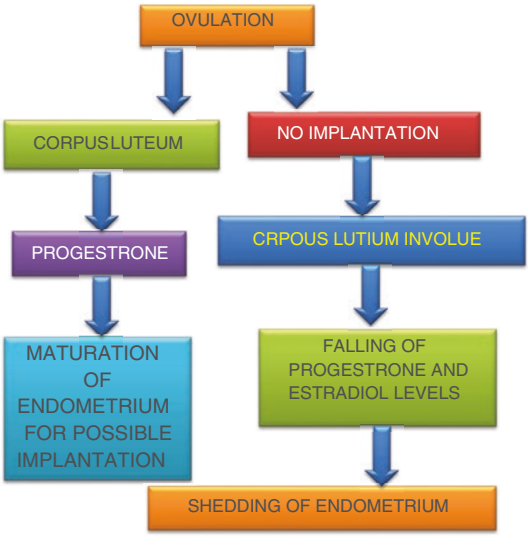
– The acronym COEIN represents nonstructural causes:

Coagulopathy
Ovulatory dysfunction
Endometrial
Iatrogenic
Not otherwise classified

13.2 Pathophysiology

- Puberty is a process that requires multiple steps and also involves the maturation of the neuroendocrine system.
- The hypothalamus begins to secrete gonadotropin-releasing hormone (GnRH).
- GnRH stimulates the pituitary gland to release luteinizing hormone [LH] and follicle-stimulating hormone [FSH] and as a result the ovarian follicles become more sensitive to stimulation.
- This stimulation eventually leads to selection of a dominant ovarian follicle.
- As the ovarian follicle grows, it produces estrogen, which in turn provides positive feedback on the gonadotropins to cause an LH surge and thus ovulation.
- The dominant follicle also secretes estradiol, which causes the endometrium to proliferate, and prepare for potential implantation.
- After ovulation, a corpus luteum develops as the granulosa cells become luteinized.





- The corpus luteum secretes progesterone, which affects the endometrium and promotes its development into a more stable environment for possible implantation.
- Failure of implantation of an embryo leads to involution of the corpus luteum.
- This involution leads to falling progesterone and estradiol levels and thus to shedding of the endometrium as it loses its blood supply.
- Disturbance in any of the above steps will result in abnormal menarche and menstruation.

13.3 Etiology and Classification

13.4 Primary Amenorrhea

- The most common causes of primary amenorrhea are:
  - Ovarian insufficiency
  - Müllerian agenesis
  - Hypogonadotopic hypogonadism
  - Pregnancy
- It is important to note that ovulation and intercourse can occur before the onset of menarche.
- Primary amenorrhea is also caused or associated with other etiologies such as ambiguous genitalia, hyperandrogenism, and Cushing syndrome.

General causes of primary amenorrhea
• Ovarian insufficiency
• Mullerian agenesis
• Hypogonadotropic hypogonadism

- Causes of primary amenorrhea:
  - Hypogonadotropic hypogonadism:

    Anorexia
    Stress- and exercise induced hypogonadism
    GnRH deficiency
    Hyperprolactinemia
    Hypopituitarism

  - Eugonadotropic eugonadism:

    Pregnancy
    Imperforate hymen
    Asherman syndrome
    Müllerian agenesis
    Polycystic ovary syndrome (PCOS)

  - Hypergonadotropic hypogonadism:

    Ovarian dysgenesis
    Ovarian insufficiency
    Complete androgen insensitivity syndrome
    Congenital adrenal hyperplasia

- Another way of classifying the causes of primary amenorrhea is on the basis of the absence or presence of breasts and a uterus, as follows:
  - Breasts present, uterus present:

    Hypothalamic dysfunction
    Pituitary lesion
    Polycystic ovary syndrome (PCOS)
    Ovarian insufficiency

  - Breasts present, uterus absent:

    Müllerian agenesis
    Complete androgen insensitivity

  - Breasts absent, uterus present:

    Hypogonadotropic hypogonadism
    Gonadal dysgenesis/agenesis

- Breasts absent, uterus absent:

  Enzyme deficiency (i.e., 17,20-desmolase deficiency)
  Agonadism

- The etiologies of primary amenorrhea can also be divided according to the components of the hypothalamic-pituitary-ovarian (HPO) axis as well as the uterus and other endocrine disorders as follows:

  - Anatomic defects:

    Müllerian agenesis (Mayer–Rokitansky–Kuster–Hauser syndrome)
    Complete androgen insensitivity syndrome
    Imperforate hymen
    Transverse vaginal septum

  - Primary hypogonadism:

    Gonadal dysgenesis

    - Turner syndrome (45,X)
    - Swyer syndrome (46,XY)

    Gonadal agenesis

- Hypothalamic causes:

  Dysfunctional

  - Stress
  - Exercise
  - Diet
  - Eating disorders

  Kallmann syndrome

- Pituitary causes:

  Tumors

  - Prolactinoma
  - Other hormone-secreting tumors

- Other endocrine gland disorders:

  Adrenal

  - Adult onset adrenal hyperplasia
  - Cushing syndrome

  Thyroid disease
  Ovarian tumors (e.g. granulosa cell tumor)

- Multifactorial/other causes:

  Polycystic ovary syndrome (PCOS)
  Constitutional delay

- Patients with primary amenorrhea should be evaluated if:
  - A female with normal secondary sexual characteristics has failed to menstruate by the age of 15 years or within 3 years of breast budding (thelarche).
  - There is lack of breast development by the age of 13 years.

- The evaluation should include:
  - A thorough history and physical examination to assess for any history of vaginal bleeding, development of other secondary sexual characteristics, or evidence of excess androgens, such as hirsutism or increased muscle mass.
  - Any changes in weight, stress or activity level, headaches, visual disturbances, or milk production.
  - History of childhood health and any chronic illness.
  - The use of any medications, including metoclopramide and antipsychotic agents.
  - Family history of delayed puberty or premature ovarian failure.

- Physical examination for primary amenorrhea include:
  - Measurement of height, weight, body mass index (BMI), and vital signs.
  - Evaluate for staging of thelarche and adrenarche
  - Signs of hyperandrogenism, including hirsutism, acne, and clitoromegaly.
  - Thelarche marks the beginning of breast development
  - Adrenarche indicates the activation of the adrenal cortex to produce androgens and it is associated with pubarche, or the development of pubic hair.
  - Physical features consistent with Turner syndrome, such as short stature, webbed neck, shield chest, and widely spaced nipples.
  - If feasible, a genital examination should be performed to evaluate for the presence of an imperforate hymen, absent or blind-ending vagina, or transverse vaginal septum, as well as the presence of a cervix, uterus and ovaries.
  - If this is not possible, imaging can be performed to evaluate for the presence of müllerian structures.

- The laboratory workup for patients with primary amenorrhea
  - This depends on the findings from the history and physical examination.
  - In the presence of a blind-ending vaginal pouch, measurement of testosterone level and karyotyping are indicated to differentiate between müllerian agenesis and complete androgen insensitivity syndrome.
  - If a uterus is present, laboratory evaluation includes:

    A pregnancy test
    Follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, thyroid-stimulating hormone (TSH), and prolactin levels.

If the FSH is high, primary hypogonadism is likely, and karyotyping should be performed to determine whether there is evidence of Turner syndrome (45,X or 45,X/46,XX mosaic) or Swyer syndrome (46,XY).
If the FSH is low or normal, the cause is likely hypothalamic, and further workup may include imaging of the head if no obvious cause (e.g., stress or exercise induced hypothalamic dysfunction) is identified.
If the fasting prolactin level is elevated, and there is no recent history medication intake such as psychotropic medications, magnetic resonance imaging (MRI) of the pituitary should be performed to evaluate for a pituitary microadenoma or an adenoma.

– Signs of hyperandrogenism calls for measurements of:

Serum testosterone
Dehydroepiandrosterone sulfate (DHEA-S)
17-hydroxyprogesterone (17-OHP)
These are important to rule out an ovarian or adrenal tumor or congenital adrenal hyperplasia.

13.5 Abnormal Uterine Bleeding

- The most common causes of abnormal uterine bleeding in adolescents are:
  - Ovulatory dysfunction, commonly due to immaturity of the hypothalamic-pituitary-ovarian (HPO) axis
  - Polycystic ovary syndrome (PCOS)
  - Coagulopathy
  - Pregnancy
  - Pelvic infections
  - Hypothyroidism
  - Hyperprolactinemia
  - Functional hypothalamic dysfunction
- Ovulatory dysfunction is the most common cause of abnormal uterine bleeding in adolescents.
- The most common cause of irregular menstrual cycles is immaturity of the HPO axis.

Causes of abnormal uterine bleeding in adolescent girls
1. Immaturity of the hypothalamic-pituitary-ovarian axis
2. Pregnancy
3. Coagulopathy
• Von Willebrand disease
• Platelet function disorders

Causes of abnormal uterine bleeding in adolescent girls
• Other bleeding disorders
• Hepatic failure
4. Hyperandrogenic anovulation
• Polycystic ovary syndrome
• Congenital adrenal hyperplasia
• Androgen producing tumors
5. Hypothalamic dysfunction
• Obesity
• Underweight
• Significant rapid weight loss
• Stress related hypothalamic dysfunction
6. Hyperprolactinemia
7. Thyroid disease
8. Primary pituitary disease
9. Primary ovarian insufficiency
10. Iatrogenic secondary to radiation or chemotherapy
11. Medications including hormonal contraceptives and anticoagulation therapy
12. Sexually transmitted infections
13. Malignancy
• Estrogen producing ovarian tumors
• Androgen producing tumors
• Rhabdomyosarcoma
14. Uterine lesions
15. Foreign body

- Vaginal foreign body can present with diverse symptoms. It should be considered in any young girl presenting with recurrent or persistent vaginal discharge and or bleeding.
- During anovulatory cycles, an oocyte is not released, and as a result of this no corpus luteum is formed and progesterone is not produced. The unopposed estrogen leads to endometrial proliferation with fragile blood vessels. The endometrium irregularly outgrows its blood supply, thus leading to unpredictable, and sometimes heavy and prolonged bleeding.
- Evaluation of patients with abnormal uterine bleeding (AUB) should include:
  - A thorough history including age of menarche, menstrual bleeding patterns (e.g., number of cycles over the past 12 months), duration and severity of menstrual flow, and pelvic pain associated with the cycle.
  - A history of current or previous sexual activity.
  - A history of any previous sexually transmitted infections (STIs) and any current vaginal discharge or dysuria.
  - A history of any medications including the use of anticoagulants, antipsychotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and hormonal contraceptives, which can all cause irregular menses.

  - History of All previous surgical procedures and any complications (e.g., post-operative bleeding).
  - A thorough family history for bleeding disorders, especially von Willebrand disease.

- Physical examination for abnormal uterine bleeding (AUB) should include:
  - Height, weight, BMI, and vital signs.
  - Signs of hyperandrogenism and also for indications of insulin resistance, which may suggest polycystic ovary syndrome (PCOS).
  - Inspection for petechiae, skin pallor, ecchymoses, and swollen joints.
  - The possibility of pelvic inflammatory disease calls for inspection for vaginal discharge, and endocervical samples should be collected for detection of gonorrhea or chlamydia.
  - Urine samples can also be tested with nucleic acid amplification if a vaginal examination is not feasible.
  - A bimanual examination assessing for cervical motion tenderness, uterine and adnexal tenderness is also important when there is concern about possible sexually transmitted disease.

- Laboratory evaluation for abnormal uterine bleeding (AUB) should include:
  - A pregnancy test
  - A complete blood count (CBC)
  - TSH levels
  - Testing for gonorrhea and chlamydia
  - Screening for bleeding disorders when indicated
  - High-risk patients should be tested for HIV, syphilis, and hepatitis B and C
  - For those with irregular bleeding patterns, measurement of hormone levels (e.g., estradiol, FSH, LH, and prolactin) may be indicated.
  - A 2-h glucose tolerance test, as well as fasting lipid levels are performed in those with suspected insulin resistance or metabolic abnormalities
  - In those with suspected androgen excess evaluation of free and total testosterone levels, DHEA-S, and 17-OHP should be considered.
  - Screening for bleeding disorders includes CBC with platelets; coagulation studies, and, if there is concern about possible von Willebrand disease, von Willebrand-ristocetin cofactor activity, von Willebrand factor antigen, and factor VIII level.

13.6 Polycystic Ovary Syndrome (PCOS)

- PCOS is one of the most common endocrine disorder, with a prevalence of 6–10%.
- It is also the most common cause of irregular menstrual bleeding, oligomenorrhea, or amenorrhea, associated with hyperandrogenism.
- Oligomenorrhea is defined as menstrual cycles occurring more than 35 days to 3 months apart.

- In adolescents, oligomenorrhea may be extended to cycles that last longer than 45 days until 2–3 years after menarche, though cycles extending past 35 days may be an early indicator of irregular menstrual cycles.
- Patients with PCOS often have few, irregular, and at times heavy cycles throughout the year.
- There are multiple diagnostic criteria for PCOS, including those of the National Institute of Health, the Rotterdam Consensus Criteria, and those of the Androgen Excess Society.
- They all include two of three different criteria in some combination, as follows:
  - Hyperandrogenism (either clinical or laboratory)
  - Oligoamenorrhea or amenorrhea
  - Polycystic ovaries on pelvic ultrasonography
- The diagnosis of PCOS may be more challenging to make in adolescents as anovulatory cycles and acne are more commonly seen among this age group. This makes it difficult to diagnose PCOS based on the above criteria.
- Consequently, some authors have recommended that all of the Rotterdam criteria to diagnose PCOS, including laboratory evidence of hyperandrogenism or progressive hirsutism, and not only acne must be present for a diagnosis of PCOS in adolescents.
- Obesity is also commonly associated with PCOS, because insulin resistance plays a role in the central pathophysiology of the disease, but as many as 20% of adults with PCOS are not obese.
- Metabolic syndrome is also common in PCOS adolescents, which places these individuals at increased risk for cardiovascular disease and diabetes.
- In an adolescent with hirsutism and irregular menstrual bleeding, it is important to exclude other causes including:
  - Congenital adrenal hyperplasia
  - Ovarian and adrenal tumors
- Endometrial adenocarcinoma although extremely rare in adolescents, it should be considered in the differential diagnosis of adolescents presenting with irregular menses.

13.7 Heavy Menstrual Bleeding

- Heavy menstrual bleeding (menorrhagia) is defined as blood loss exceeding 80 mL or bleeding that lasts longer than 7 days each menstrual cycle.
- The cause of heavy menstrual bleeding are:
  - Uterine structural causes

    Fibroids
    Adenomyosis

  - Systemic or iatrogenic causes
  - Bleeding disorders

    Von Willebrand disease
    Coagulation factor deficiencies
    Platelet abnormalities

- Von Willebrand disease:

  - This is an autosomal inherited bleeding disorder
  - The prevalence of Von Willebrand disease is 0.8–1.3% in the general population and 13–20% in those with menorrhagia
  - There are three types and various degrees of severity.
  - The most common form of von Willebrand disease, type 1, is autosomal recessive, accounts for 70% of cases, and presents with a milder bleeding tendency as compared with the other types.
  - It is due to either a quantitative or a qualitative deficiency in von Willebrand factor, a protein involved in platelet adhesion.
  - Heavy menstrual bleeding may be the presenting symptom in as many as 53% of patients with von Willebrand disease.
  - Patients with von Willebrand disease can also present with bleeding from other sites including epistaxis, bleeding following tooth extraction, joint bleeding and intraoperative and postoperative bleeding.
  - Patients with heavy menstrual bleeding should be investigated for von Willebrand disease.

13.8 Intermenstrual Bleeding

- Intermenstrual bleeding (IMB), previously referred to as metrorrhagia, is defined as bleeding in between periods.
- The causes of intermenstrual bleeding in adolescents include:

  - Pregnancy
  - Sexually transmitted infections (STIs)

    Chlamydia trachomatis
    Trichomonas vaginalis
    Herpes simplex virus (HSV)
    Human papillomavirus (HPV)
    Neisseria gonorrhoeae

  - Iatrogenic etiologies from administration of exogenous steroids, including oral contraceptive pills

- Sexually transmitted infections (STIs):

  - This is one of the causes of intermenstrual bleeding in adolescents.

  - STIs can also cause irregular vaginal bleeding due to inflammation of the genital tract, including the cervix and endometrium, which can be fragile and shed irregularly.
  - The risk factors for STI include:

    Age less than 25 years
    Multiple partners
    Early age of sexual activity
    Inconsistent condom use
    Alcohol or drug consumption

  - The symptoms of STIs include:

    Vaginal discharge
    Dysuria
    Genital lesions

- Exogenous hormone administration can cause intermenstrual and irregular bleeding patterns.
- Exogenous hormone administration can be given in the form of:
  - Combined estrogen-progestin contraceptives, administered orally or transdermally
  - Progestin-only contraceptives (e.g., depot medroxyprogesterone acetate, the etonogestrel implant, and the levonorgestrel-releasing intrauterine device [IUD]).
  - The levonorgestrel-releasing IUD is associated with irregular bleeding and spotting in the first 3–6 months after placement.
  - The nonhormonal copper IUD is associated with heavier periods and irregular bleeding during the first few months after placement, but the heavier bleeding improves over time, whereas the irregular bleeding generally does not.

13.9 Dysmenorrhea

- Dysmenorrhea is defined as painful menses.
- Dysmenorrhea may be either primary or secondary.
- Primary dysmenorrhea occurs in the absence of any identifiable pathology and is attributed to the production of prostaglandins during the menstrual cycle.
- Primary dysmenorrhea presents with painful menses and occasionally is accompanied by nausea, vomiting, diarrhea, fatigue, and headache.
- Secondary dysmenorrhea occurs when there is an identifiable pelvic or hormonal pathology causing pain.
- In secondary dysmenorrhea, the pain often precedes the onset of menses.
- The most common gynecologic causes of secondary dysmenorrhea are:
  - Endometriosis
  - Pelvic inflammatory disease (PID)

- Endometriosis occurs when endometrial glands and stroma implant outside of the uterus, most commonly in the peritoneal cavity but also in the gastrointestinal (GI) tract, urinary tract, and lung.
- Endometriosis may be asymptomatic but can also cause cyclic and acyclic pelvic pain, painful menses, dysuria, dyschezia and infertility.
- Endometriosis may be present in as many as 70% of adolescents who present with dysmenorrhea.
- Laparoscopy is valuable if endometriosis is suspected.
- Pelvic inflammatory disease (PID) is a polymicrobial infection that is 10 times more common in adolescents than in adults.
- Pelvic inflammatory disease (PID) can present with painful, irregular uterine bleeding or vaginal discharge.

13.10 Treatment Options

- The choice of treatment depends on symptoms as well as the known potential side effects.
- Oral progestogens are widely used as first-line treatment for adolescent menstrual problems and can be taken continuously to defer or delay menstruation, or cyclically to improve irregular and heavy periods.
- They are effective treatments for irregular menses and/or menorrhagia.
- The main risk of treatment with oral progestogens is the potential risk of developing venous thromboembolism.
- The progestin-only pills (POP) is also an oral progestogen but in much smaller doses.
  - They include Cerazette (desogestrel 75 μg), Micronor (NET 350 μg) and Norgeston (levonorgestrel 30 μg).
  - It works by thickening cervical mucus to prevent sperm penetration, and in some cases it inhibits ovulation.
  - The POP is of little use in the management of adolescent menstrual dysfunction but it can lead to:

    Amennorhoea in some girls
    Prolonged menses in up to 50%
    Breakthrough bleeding in 70%

- The combined oral contraceptive pill (COCP) (Microgynon 30 (ethinyl estradiol 30 μg with levonorgestrel 150 μg) inhibits the production of LH and FSH from the anterior pituitary, leading to inhibition of ovulation.
- It is an effective first-line treatment for irregular menses, menorrhagia and dysmenorrhoea.
- Adolescent girls with acne or hirsutism due to polycystic ovarian syndrome would benefit with a more anti-androgenic pill containing a third-generation progestogen such as desogestrel (Marvelon) or gestodene (Femodene).

- The side effects of COCP include breast tenderness, mood disturbance, deep vein thrombosis and nausea and vomiting.
- Girls with the following thrombophilias should not be give COCP:
  - Factor V Leiden deficiency
  - Protein C/S deficiency
  - Prothrombin gene mutation
  - Antithrombin III deficiency
  - Antiphospholipid syndrome
  - Systemic lupus erythematosus
  - Myeloproliferative disorders
- The use of the COCP with factor V Leiden is known to increase the risk of deep vein thrombosis 35-fold.
- COCP can be used to treat heavy menstrual bleeding associated with bleeding disorders such as idiopathic thrombocytopenic purpura, Von Willebrand's disease, platelet dysfunction, haemophilia carriers and rare factor deficiencies.
- The risk of breast cancer in current users of the COCP is 24% above the baseline risk. The younger the age that the COCP is started, the greater the risk and if the girl is known to be a carrier of BRCA1/2, then the COCP is contraindicated.
- Tranexamic acid is an antifibrinolytic which is effective at reducing menstrual loss by up to 50% and can be used in girls with bleeding disorders.
- Tranexamic acid can cause gastro-intestinal side effects and it is contraindicated in those with a personal or family history of thromboembolic disease.
- Mefenamic acid is a non-steroidal anti-inflammatory drug which acts by inhibiting prostaglandin synthetase.
  - It is effective for dysmenorrhoea, and can also help to reduce menstrual loss by up to 20%.
  - It should be avoided in girls with bronchial asthma, bleeding disorders or renal impairment.
  - Side effects include nausea, diarrhea and heartburn.
- The levonorgestrel intra-uterine system (Mirena) is a long-acting reversible contraceptive.
  - It is a T-shaped plastic frame with a rate-limiting membrane on the vertical stem which releases 20 μg levonorgestrel into the uterine cavity each day.
  - It prevents endometrial proliferation, thickens cervical mucus and in up to 25% inhibits ovulation.
  - It is effective for menorrhagia and dysmenorrhoea.
  - It can cause irregular and heavy bleeding for the first 3–6 months; however, at 1 year 65% have amenorrhoea or light bleeding.
  - Side effects include mood disturbance, acne and headache.
- Depo-Provera is a depot injection of MPA (medroxyprogestrone acetate) given every 12 weeks.

- It is a long-acting reversible contraceptive which works primarily by inhibiting ovulation.
- It is effective for menorrhagia with up to 70% becoming amenorrhoeic by 12 months.
- Depo-Provera can be associated with increased weight gain and has been shown to reduce bone mineral density in adolescents.
- It can also cause spotting of vaginal bleeding.

13.11 Management of Primary Amenorrhea

- The treatment of amenorrhea depends upon the cause.
- In cases of müllerian agenesis:
  - This should be discussed with the patient and the family including future fertility options and sexual relationships.
  - Treatment includes surgical creation of a neovagina
- In cases of androgen insensitivity syndrome:
  - Complete gonadectomy may be performed either early or after the patient has completed puberty to prevent gonadal neoplasia.
- Anatomic causes, such as imperforate hymen or transverse vaginal septum, are treated surgically to create a new vaginal opening.
- In cases of primary hypogonadism (premature ovarian failure), treatment should include hormone therapy, and testing for a premutation in the *FMR1* gene.
- In cases of functional hypothalamic amenorrhea, gaining weight and reducing exercise levels will likely result in resumption of menses.
- Treatment of Polycystic ovary syndrome
  - For patients who wish to conceive, clomiphene citrate is the first-line treatment, followed by gonadotropins
  - For patients who do not wish to conceive, a combined oral contraceptive pill (COCP) is usually the first line of treatment, provided that there are no contraindications.
  - A combined oral contraceptive pill is therapeutic for multiple reasons:

    It regulates menstrual cycles
    It suppresses ovarian and adrenal androgen production and increases circulating levels of sex hormone binding globulin, thus lowering the levels of free testosterone in the serum.

  - Overweight and obese patients should change their life style so as to decrease their risk for cardiovascular disease, diabetes, and metabolic syndrome.
  - Metformin may be used to delay the development of diabetes in those with impaired glucose tolerance, but is not as effective as lifestyle modifications.

- Patients with hirsutism are treated by combining cosmetic procedures with medications such as COCPs and antiandrogens (e.g., spironolactone, flutamide and finasteride).
- When antiandrogen medications are being used, it is important to use contraceptives as well because the antiandrogens are teratogenic.

13.12 Treatment of Heavy Menstrual Bleeding

- First-line therapy for heavy menstrual bleeding often includes nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, naproxen, and mefenamic acid.
- They decrease prostaglandin levels, which are increased in women with heavy menstrual bleeding.
- Other treatment options include:
  - Hormone therapy with COCPs
  - Progestin-only medications, including pills, injections or implants
  - Medroxyprogesterone acetate (MPA)
  - Etonogestrel implant (especially if there are contraindications for COCP therapy)
  - Another progestin-only option is the levonorgestrel-releasing intrauterine device (IUD)
  - The use of antifibrinolytic drugs, such as tranexamic acid however, these agents are not currently approved for use in adolescents.
- If a patient is diagnosed with von Willebrand disease:
  - Consult a hematologist in order to optimize the treatment regimen.
  - Medical treatment includes antifibrinolytic agents, COCPs, and progestin-only contraceptives.
  - Other treatment options include desmopressin acetate and recombinant factor VIII.
- Intermenstrual bleeding
  - If a patient is taking a short-acting hormone, bleeding during the first few months is common and it is important to counsel the patient about proper administration and consequences of the medication.
  - If a patient was recently started on contraceptives, unscheduled bleeding is common in the first 3 months, and all that is needed is reassurance.
  - If irregular bleeding persists and the adolescent is taking a low-dose COCP (e.g., <20 μg ethinyl estradiol), the intermenstrual bleeding (IMB) may resolve if the estrogen dose is increased.
  - She may also benefit from increasing either the progestin level or the estrogen in her formulation.

  - For patients who are taking progestin-only unscheduled bleeding can often be treated by administering NSAIDs or by providing brief estrogen supplementation with COCPs, provided that no contraindications exist.

- Primary dysmenorrhea
  - NSAIDs inhibit prostaglandin synthesis and lead to less vigorous uterine contractions.
  - They are more effective if regularly scheduled doses are given 1–2 days before anticipated menses.
  - If no improvement is seen after three menstrual cycles, a trial of oral contraceptive pills for three menstrual cycles may be offered.
- Secondary dysmenorrhea
  - Secondary dysmenorrhea is less likely to respond to NSAIDs than primary dysmenorrhea is.
- Endometriosis
  - NSAIDs are a common first-line treatment for endometriosis.
  - Oral contraceptives, progestins, androgens, and gonadotropin-releasing hormone (GnRH) agonists are the treatment of choice for endometriosis.
  - GnRH agonists do provide effective relief of endometriosis-related pain, but they have significant side effects, including osteopenia, vaginal dryness and hot flashes.
- Pelvic inflammatory disease
  - Treatment of pelvic inflammatory disease (PID) consists of antibiotics given orally or intravenously.
  - The development of an abscess requires surgical or percutaneous drainage.
  - Untreated PID is associated with significant morbidity. To avoid this, some authors advocate that all sexually active women presenting with lower abdominal or pelvic pain with no other identifiable etiology, or cervical motion, uterine or adnexal tenderness be empirically treated for PID.

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Chapter 14
Polycystic Ovarian Syndrome

Ahmed H. Al-Salem

14.1 Introduction

- Polycystic ovary syndrome is a relatively common condition.
- It is commonly seen in women but can be seen in adolescent girls also.
- Their main presentation include:
  - Hirsutism

    The excess body hair can be on the face, chin, neck, back, chest, breasts, or abdomen.
  - Severe acne
  - Menstrual irregularities

    Menstrual cycle irregularities can include absence of periods for months, heavy or long-lasting periods, or periods that happen too often.
  - Some girls, but not all, have also small cysts on their ovaries.
- The presence of polycystic ovaries is not essential for the diagnosis of polycystic ovarian syndrome.
- The diagnosis polycystic ovaries is made:
  - If 12 or more follicles measuring 2–9 mm diameter are present in at least one ovary.
  - If a total ovarian volume is greater than 10 cm^3.

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- About 60–70% of girls with polycystic ovary syndrome are overweight or obese, but some are normal weight or thin.
- Girls with polycystic ovary syndrome may have a family history of polycystic ovary syndrome affecting their mothers, aunts, or sisters.
- They may also have a family history of type 2 diabetes mellitus.
- Polycystic ovary syndrome may also be called "ovarian hyperandrogenism."
- This is because the ovaries produce too much androgen.
- The major features of polycystic ovarian syndrome include:
  - Menstrual dysfunction
    - Amenorrhea
    - Oligomenorrhea
  - Anovulation
  - Signs of hyperandrogenism

Ultrasound diagnosis of polycystic ovaries
• One or two ovaries can be affected
• If 12 or more follicles measuring 2–9 mm in diameter are present in at least one ovary
• If a total ovarian volume is greater than 10 cm^3

- Other clinical features include hirsutism and obesity
- Stein-Leventhal syndrome
  - This consist of the followings:
    - Polycystic ovaries
    - Hirsutism
    - Amenorrhea/Oligomenorrhea
    - Obesity
- The exact etiology of polycystic ovarian syndrome is not known.
  - Abnormal function of the hypothalamic-pituitary-ovarian axis was proposed as a possible etiology of polycystic ovarian syndrome.
  - This will result in inappropriate gonadotropin secretion.
- One of the most consistent biochemical features of polycystic ovarian syndrome is a raised plasma testosterone level.
- The clinical and biochemical presentation of polycystic ovarian syndrome is heterogeneous.
- Hyperandrogenemia is the most consistent biochemical abnormality.
- The diagnosis of polycystic ovarian syndrome remains controversial.
- It is based on various signs, symptoms, and/or laboratory findings.

- The 1990 National Institutes of Health (NIH) definition of polycystic ovarian syndrome requires the simultaneous presence of:
  - Hyperandrogenism (clinical and/or biochemical)
  - Menstrual dysfunction in the absence of other causes
  - Hyperandrogenism as an etiology

Polycystic ovarian syndrome
• Menstrual dysfunction
– Amenorrhea
– Oligomenorrhea
• Cutaneous signs of hyperandrogenism
– Acne
– Hirsutism
– Alopecia
• Obesity
• Disordered gonadotropin [luteinizing hormone (LH) and follicle-stimulating hormone (FSH)] secretion
• Polycystic ovaries by ultrasonography
• Defects in insulin action (Insulin resistance) and/or insulin secretion (Pancreatic β-cell dysfunction)

Risks associated with polycystic ovarian syndrome
• Infertility
• Dysfunctional uterine bleeding
• Endometrial carcinoma
• Depression
• Type 2 Diabetes
• Hypertension
• Dyslipidemia and metabolic syndrome, independent of insulin resistance

14.2 Epidemiology

- Polycystic ovarian syndrome is considered one of the most common endocrine disorders affecting women in their reproductive-age and also adolescence girls.
- Polycystic ovarian syndrome is common worldwide.
- The prevalence of polycystic ovarian syndrome was reported to be 4–12% in the United States of America.
- The prevalence of polycystic ovarian syndrome was reported to be 6.5–8% in Europe.

14.3 Definition of Polycystic Ovarian Syndrome

- The 2003 Rotterdam [European Society for Human Reproduction and Embryology and American Society for Reproductive Medicine (ESHRE/ASRM)] definition of polycystic ovarian syndrome requires only two of the following three criteria:
  - Hyperandrogenism (clinical and/or biochemical)
  - Ovulatory dysfunction (oligo- or anovulation)
  - Ultrasonographic evidence of polycystic ovaries in the absence of other causes.
  - The Rotterdam criteria broadened the polycystic ovarian syndrome phenotype to include women with ovulatory dysfunction and polycystic ovaries but without hyperandrogenism, and eumenorrheic women with hyperandrogenism and polycystic ovaries (often called "ovulatory" polycystic ovarian syndrome).
- The 2006 Androgen Excess Society (AES) definition reemphasized the importance of hyperandrogenism in the etiology of polycystic ovarian syndrome, requiring:
  - The absence of:

    Other hyperandrogen-causing disorders
    Syndromes of severe insulin resistance
    Thyroid dysfunction
    Hhyperprolactinemia
  - Hyperandrogenism (clinical and/or biochemical)
  - Ovulatory dysfunction (oligo- or anovulation)
  - Polycystic ovarian morphology.
- The 2009 Androgen Excess and Polycystic Ovary Syndrome Society's definition also emphasized:
  - The importance of hyperandrogenism in the syndrome's etiology
  - Hyperandrogenism (clinical and/or biochemical)
  - Ovarian dysfunction (oligo- or anovulation and/or polycystic ovaries)
  - The exclusion of other androgen excess or related disorders.
- All of the diagnostic criteria for polycystic ovarian syndrome require the exclusion of other disorders such as:
  - Nonclassical congenital adrenal hyperplasia
  - Cushing syndrome
  - Hyperprolactinemia
  - Hypothyroidism
  - Acromegaly
  - Premature ovarian failure
  - A virilizing adrenal or ovarian neoplasm
  - A drug related condition

- The ultrasound definition of polycystic ovarian syndrome include:
  - The presence of ≥12 follciles with a 2- to 9-mm diameter on the ovary.
  - An ovarian volume >10 mL.
  - Only one ovary consistent with polycystic ovarian morphology is sufficient for the diagnosis.
- The diagnosis of polycystic ovarian syndrome in children and adolescents girls is more difficult for the following reasons:
  - Using menstrual irregularity to diagnose polycystic ovarian syndrome is difficult.

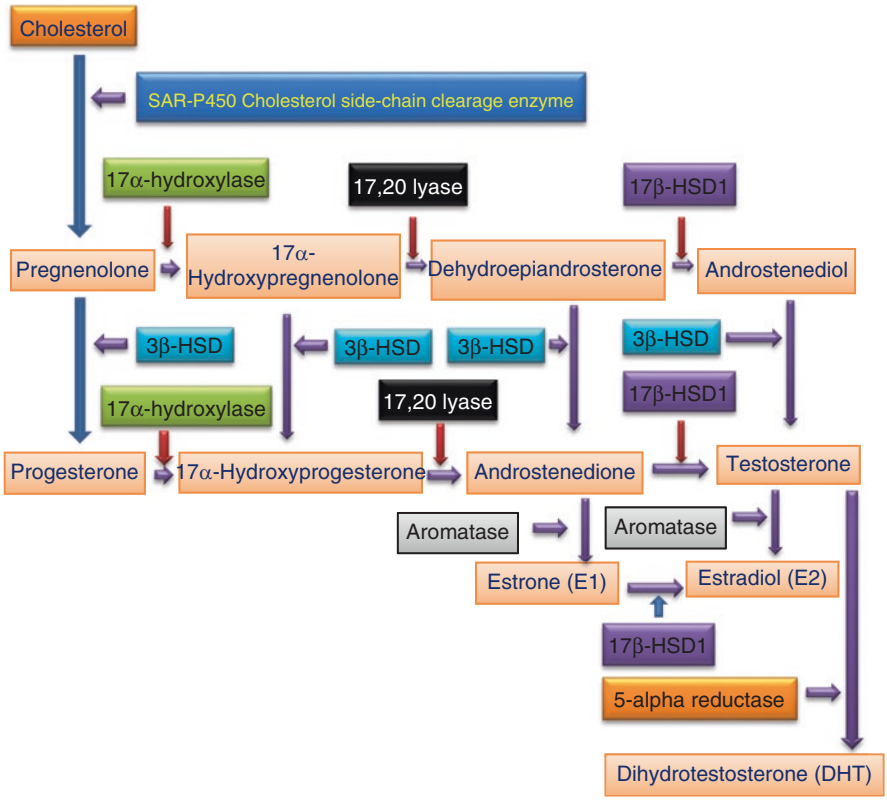
    More than 50% of menstrual cycles are anovulatory in the first 2 years after menarche.
    However, menstrual irregularity for more than 2 years after menarche is not considered physiological and is predictive of continued irregularity
  - Nonpathologic acne and mild hirsutism are common in the peripubertal years.
  - Children develop physiologic insulin resistance during puberty.
  - Limited normative data of androgen levels by body mass index (BMI) and pubertal stage exist.
  - Ovarian size appears to be maximal in the perimenarchal period; ≈25% of adolescent girls have multifollicular ovaries, and polycystic-type ovaries can occur in up to 20–30% of reproductive-age women and 10% of healthy, regularly menstruating girls, making the differentiation of "normal" versus "abnormal" ovaries difficult for even experienced specialists.
  - A transvaginal ultrasound is often inappropriate for pediatric patients, particularly virginal girls, and the use of a transabdominal ultrasound yields limited resolution of ovarian morphology and has been shown to underestimate the presence of the syndrome.
- An alternative method for diagnosing polycystic ovarian syndrome in adolescent girls has been advocated.

Five criteria for the diagnosis of polycystic ovarian syndrome in adolescent girls
• Oligo- or amenorrhea 2 years after menarche
• Clinical hyperandrogenism
– Hirsutism
– Acne
– Alopecia
• Biologic hyperandrogenism (An elevated testosterone concentration)
• Insulin resistance or hyperinsulinemia
– Acanthosis nigricans
– Abdominal obesity
– Glucose intolerance
• Polycystic ovaries

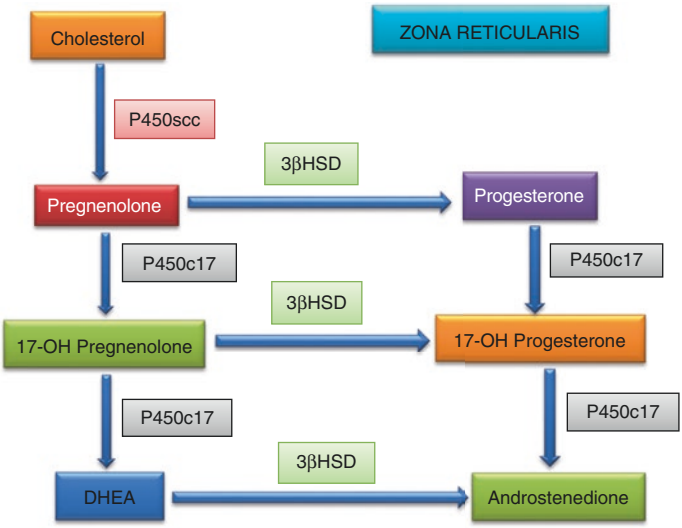
- The following five criteria are required for the diagnosis of polycystic ovarian syndrome in adolescent girls:
  - Oligo- or amenorrhea 2 years after menarche
  - Clinical hyperandrogenism (hirsutism, acne, and/or alopecia)
  - Biologic hyperandrogenism (an elevated testosterone concentration)
  - Insulin resistance or hyperinsulinemia (acanthosis nigricans, abdominal obesity, and/or glucose intolerance)
  - Polycystic ovaries

14.4 Pathogenesis of Polycystic Ovarian Syndrome

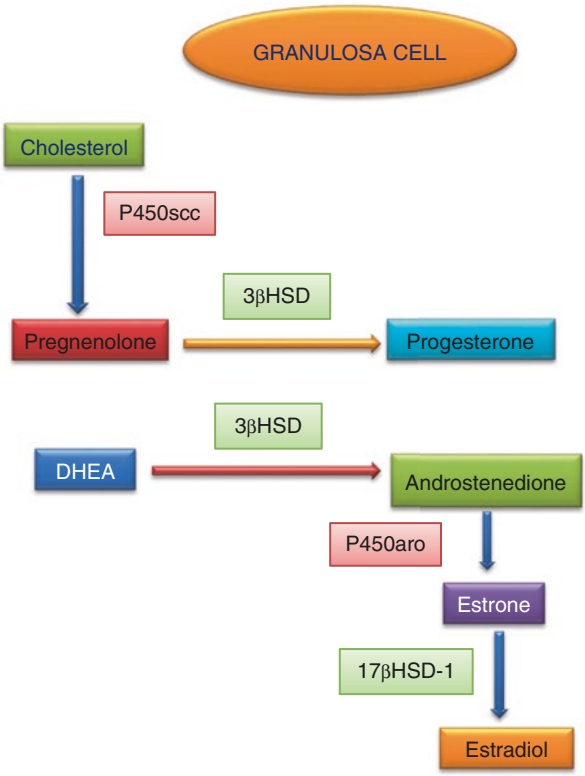
- The exact etiology and pathogenesis of polycystic ovarian syndrome is not known
- It is a complex multifactorial disorder



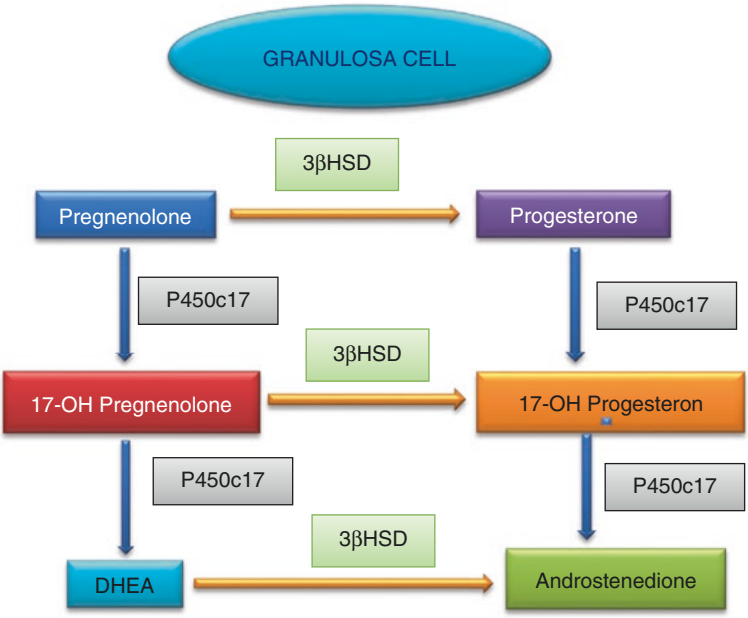
- There is evidence that polycystic ovarian syndrome may result from prenatal exposure to androgen excess in utero.
- The production of all steroid hormones, including androgens, begins with cholesterol.
- The type of steroid produced by a particular gland depends on the tissues of the gland, the steroidogenic enzymes and the availability of their substrates/cofactors.
- The major enzymes involved in adrenal and ovarian androgen production are shown below.



- It was interesting to note that hyperandrogenemia persists when ovarian steroidogenesis is suppressed with a long-acting gonadotropin-releasing hormone (GnRH) agonist and when adrenal steroidogenesis is suppressed with dexamethasone.
- This suggests that both glands play a role.
- In the adrenal gland:
  - Sex steroid synthesis occurs in the zona reticularis
  - Dehydroepiandrosterone (DHEA) and androstenedione are the principal androgen precursors androgen precursors produced in the adrenal gland.
  - 3βHSD (3β-hydroxysteroid dehydrogenase) is the principle enzyme as shown below.



- Sex steroid synthesis in the ovary occurs in both the granulosa and theca cells as shown below.
- P450c17, the "qualitative" regulator of steroidogenesis, is only expressed in the theca cell.
- Androstenedione is the principal androgen precursor produced in the ovary.
- Isozymes of 17β-hydroxsteroid dehyrogenase (17βHSD) can convert androstenedione to testosterone.
- Alternatively, aromatase (P450aro) can convert androstenedione to estrogens.



- In patients with polycystic ovarian syndrome, there is overexpression of steroidogenic enzymes (in particular, P450c17 and 3β-hydroxysteroid dehydrogenase) in theca cells of the ovary.
- The majority of patients with polycystic ovarian syndrome also have abnormal responses to GnRH agonists.
- Adrenal hyperresponsiveness to adrenocorticotropic hormone (ACTH) occurs in about 25% of patients with polycystic ovarian syndrome.
- This results in excess production of:
  - Dehydroepiandrosterone (DHEA)
  - DHEA-sulfate (DHEA-S)
  - Androstenedione
- The adrenal glands may be an even more important source of hyperandrogenism in nonobese subjects.
- Enhanced 5α-reductase activity in the liver and peripheral tissues (e.g., adipose tissue) may also increase conversion of testosterone to the biologically more potent androgen, dihydrotestosterone (DHT).
- The followings are the effects of increased androgens in patients with polycystic ovarian syndrome:
  - Insulin sensitivity and insulin resistance
  - Influence adipocyte function
  - Regulate lipolysis in adipose tissue depots

- Testosterone causes a dose-dependent AR-mediated decrease of catecholamine (β-adrenergic)-stimulated lipolysis in differentiated preadipocytes from abdominal subcutaneous fat depots but not from omental fat depots.
- Androgen-mediated lipogenesis and lipid deposition may be the major factors involved.
- Androgens mediate lipoprotein lipase (LPL), the key enzyme for the hydrolysis of triglycerides into free fatty acids and glycerol and subsequent lipid storage in adipose tissue.
- Androgens stimulate lipogenesis in visceral adipose tissue.
- Androgen excess is also associated with an atherogenic lipid profile in females.
- Testosterone lowers high-density lipoprotein cholesterol (HDL-C).
- Androgens promote endothelial dysfunction and accelerate atherosclerotic changes.
- Increased testosterone is associated with increased risk for hypertension.
- These effects are more expressed in obese patients.

• The followings are the effects of insulin in patients with polycystic ovarian syndrome:

- Hyperinsulinemia secondary to insulin resistance is common in polycystic ovarian syndrome.
- This occur independent of obesity or BMI.
- The degree of hyperinsulinemia also correlates with the severity of polycystic ovarian syndrome.
- Several factors suggest that hyperinsulinemia is the primary factor driving increased androgen production.
- Androgen excess can cause insulin resistance but the mechanism of this is unclear.
- Insulin has several direct and indirect effects in patients with polycystic ovarian syndrome that potentiate the hyperandrogenic state.

  Insulin may act alone to stimulate ovarian androgen secretion directly.
  Insulin may augment LH-stimulated androgen secretion.
  Insulin may act indirectly to:

  • Potentiate ACTH-mediated adrenal androgen production
  • Enhance the amplitude of GnRH-stimulated LH pulses
  • Decrease hepatic production of sex hormone binding globin (SHBG) (thereby increasing free testosterone levels)
  • Decrease production of IGFBP-1
  • This will increase the availability of free insulin and the availability of free IGF-1, which can also stimulate androgen production.
  • Insulin may contribute to mid-antral follicular arrest, a characteristic feature of the polycystic ovary.

- The "two-hit" hypothesis of polycystic ovarian syndrome
  - For the first "hit," one or more of a number of different mechanisms lead to increased androgen production.
  - These include:

    Primary adrenal, ovarian, and/or neuroendocrine abnormalities
    Insulin resistance and hyperinsulinemia
    Prenatal, immediate postnatal, and/or peripubertal androgen exposure

  - For the second "hit," the preexisting hyperandrogenism reduces the sensitivity of the GnRH pulse generator to progesterone-mediated slowing during pubertal maturation, thereby initiating a series of changes in the hypothalamus pituitary ovarian (HPO) axis that result in ovulatory dysfunction and sustained hyperandrogenism.
  - Thus, a cycle is established whereby the presence of hyperandrogenism, the final common pathway for the development of polycystic ovarian syndrome, begets more hyperandrogenism.
  - This "two-hit" hypothesis further reinforces the importance of diet and physical activity, and their effects on maintaining insulin sensitivity and appropriate body weight, on a woman's health.
- In patients with polycystic ovarian syndrome, environmental factors leading to obesity (diet and physical inactivity) may perpetuate not only the metabolic, but also the endocrine aberrations of this syndrome.

14.5 Etiology

- The exact etiology of polycystic ovarian syndrome is not known.
- Polycystic ovarian syndrome is known to be associated with abnormalities in the metabolism of androgens and estrogen and also in the control of androgen production.
- This manifests as high serum concentrations of androgenic hormones, such as:
  - Testosterone
  - Androstenedione
  - Dehydroepiandrosterone sulfate (DHEA-S)
- There are however variations and some patients with polycystic ovarian syndrome may have normal androgen levels.
- Polycystic ovarian syndrome is also associated with:
  - Peripheral insulin resistance
  - Hyperinsulinemia
  - Obesity

- Insulin resistance in polycystic ovarian syndrome can be secondary to a post binding defect in insulin receptor signaling pathways, and elevated insulin levels may have gonadotropin-augmenting effects on ovarian function.
- Hyperinsulinemia may also result in suppression of hepatic generation of sex hormone–binding globulin (SHBG), which in turn may increase androgenicity.
- Hyperinsulinemia is also responsible for dyslipidemia and for elevated levels of plasminogen activator inhibitor-1 (PAI-1) in patients with polycystic ovarian syndrome.
- Elevated PAI-1 levels are a risk factor for intravascular thrombosis.
- Insulin resistance in polycystic ovarian syndrome has been associated with adiponectin.
  - Adiponectin is a hormone secreted by adipocytes.
  - It regulates lipid metabolism and glucose levels.
  - Patients with polycystic ovarian syndrome whether lean or obese have lower adiponectin levels.
- Anovulation in patients with polycystic ovarian syndrome results from the following factors:
  - The anterior pituitary gland secrets luteinizing hormone (LH).
  - Luteinizing hormone effect on the ovarian theca cells is increased.
  - The ovarian theca cells, in turn, increase the production of androgens (e.g., testosterone, androstenedione).
  - As a result of the decreased level of follicle-stimulating hormone (FSH) relative to LH, the ovarian granulosa cells cannot aromatize the androgens to estrogens.
  - This will result in a decreased estrogen levels and ultimately anovulation.
  - Two other factors, growth hormone (GH) and insulin-like growth factor–1 (IGF-1) may also augment the effect on ovarian function.
- As a result of these changes, the ovaries in patients with polycystic ovarian syndrome:
  - Are enlarged bilaterally.
  - They have a smooth, thickened capsule that is avascular.
  - On cut sections, subcapsular follicles in various stages of atresia are seen in the peripheral part of the ovary.
  - The most striking ovarian feature of polycystic ovarian syndrome is hyperplasia of the theca stromal cells surrounding arrested follicles.
  - On microscopic examination, luteinized theca cells are seen.
- Some evidence suggests that patients with polycystic ovarian syndrome have a functional abnormality of cytochrome P450c17, the 17-hydroxylase, which is the rate-limiting enzyme in androgen biosynthesis.
- Polycystic ovarian syndrome is a genetically heterogeneous syndrome.

- Polycystic ovarian syndrome can be familial inherited as an autosomal dominant mode of inheritance.
- A family history of type 2 diabetes in a first-degree family member is associated with an increased risk of metabolic abnormality, impaired glucose tolerance, and type II diabetes.
- There is a genetic link between polycystic ovarian syndrome and obesity.
- A variant within the FTO gene (rs9939609, which has been shown to predispose to common obesity) was significantly associated with susceptibility to the development of polycystic ovarian syndrome.
- CYP17 promoter activity was found to be fourfold greater in cells of patients with polycystic ovarian syndrome.
- It was suggested that that the pathogenesis of polycystic ovarian syndrome may be in part related to the gene regulation of CYP17.

14.6 Clinical Features

- Polycystic ovary syndrome is a common disorder that commonly affects females of reproductive age.
- Polycystic ovary syndrome may also develop in older women, teens and young adults.
- Normally, the ovaries produce "female" (progesterone and estrogen) and "male" (androgen) sex hormones.
- In polycystic ovary syndrome, the ovaries produce excess amounts of the male (androgen) sex hormones.
- As a result of this, sometimes the ovarian cells fill up with fluid, the ovaries become enlarged and form cysts.
- These abnormal cysts can be detected by ultrasound.
- Patients with polycystic ovarian syndrome have abnormalities in the metabolism of androgens and estrogen and in the control of androgen production.
- Polycystic ovary syndrome can result from abnormal function of the hypothalamic-pituitary-ovarian axis.
- The followings are important points during the evaluation of patients with polycystic ovarian syndrome:
  - A complete medical history
  - A detailed family history
  - Detailed information on menarche and the nature of menstrual cycles
  - History of any predisposing factors to polycystic ovarian syndrome:

    Low birth weight with excessive catch-up growth
    Premature adrenarche/pubarche

  - A thorough physical examination
  - Clinical signs of hyperandrogenism and/or insulin resistance:

    Hirsutism
    Acne
    Alopecia
    Acanthosis nigricans
    Assessment of regional adiposity

- The major features of polycystic ovarian syndrome include:
  - Menstrual dysfunction which manifest as:

    Irregular periods
    Absent periods
    Heavy periods
    Frequent periods

  - Anovulation
  - Signs of hyperandrogenism
  - Other signs and symptoms of polycystic ovarian syndrome may include the following:

    Hirsutism and abnormal hair growth
    Infertility
    Acne
    Obesity and metabolic syndrome
    Diabetes
    Obstructive sleep apnea
    Baldness/thinning of head hair
    Acanthosis nigricans
    Hypertension

- The clinical features, evaluation and diagnosis of the polycystic ovarian syndrome should aim at excluding other causes of androgen excess and menstrual dysfunction.
- These include:
  - Late-onset congenital adrenal hyperplasia
  - Hyperprolactinemia
  - Thyroid dysfunction
  - Premature ovarian failure

- The evaluation of suspected polycystic ovarian syndrome in the pediatric age group require the following measurements:
  - FSH, LH
  - Prolactin
  - Thyroid stimulating hormone (TSH)

- 17-hydroxyprogesterone (17-OHP)
- Total and free testosterone
- Sex hormone binding globin (SHBG)
- A lipid panel
- A random blood glucose level
- A fasting glucose and insulin levels
- A 2-h oral glucose tolerance test (OGTT)
- A pelvic ultrasound (transabdominal if the girl is virginal) may be performed in a girl with high testosterone levels or rapidly progressive hirsutism or virilization
- If the evaluation suggests a potential adrenal tumor, a computed tomography (CT) scan or a magnetic resonance imaging (MRI) study should be performed.

14.7 Diagnosis and Diagnostic Criteria

- A 1990 expert conference sponsored by the National Institute of Child Health and Human Disease (NICHD) of the United States National Institutes of Health (NIH) proposed the following criteria for the diagnosis of polycystic ovarian syndrome:
  - Oligo-ovulation or anovulation manifested by oligomenorrhea or amenorrhea
  - Hyperandrogenism (clinical evidence of androgen excess) or hyperandrogenemia (biochemical evidence of androgen excess).
  - Exclusion of other disorders that can result in menstrual irregularity and hyperandrogenism.
- In 2003, the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) recommended that at least two of the following three features are required for the diagnosis of polycystic ovarian syndrome:
  - Oligo-ovulation or anovulation manifested as oligomenorrhea or amenorrhea
  - Hyperandrogenism (clinical evidence of androgen excess) or hyperandrogenemia (biochemical evidence of androgen excess)
  - Polycystic ovaries (as defined on ultrasonography)
- The Androgen Excess and polycystic ovarian syndrome Society (AE-PCOS) emphasized that, in the society's opinion, polycystic ovarian syndrome should be considered a disorder of androgen excess, as defined by the following:
  - Clinical/biochemical evidence of hyperandrogenism
  - Evidence of ovarian dysfunction (oligo-ovulation and/or polycystic ovaries)
  - Exclusion of related disorders

- The Society of Obstetricians and Gynaecologists of Canada (SOGC) indicated that a diagnosis of polycystic ovarian syndrome (PCOS) is made in the presence of at least two of the following three criteria, when congenital adrenal hyperplasia, androgen-secreting tumors, or Cushing syndrome have been excluded:
  - Oligo-ovulation or anovulation
  - Clinical/biochemical evidence of hyperandrogenism
  - Polycystic ovaries on ultrasonograms (>12 small follicles in an ovary)
- There are other disorders that can result in menstrual irregularity and hyperandrogenism.
- These must be excluded and include:
  - Adrenal or ovarian tumors
  - Thyroid dysfunction
  - Congenital adrenal hyperplasia
  - Hyperprolactinemia
  - Acromegaly
  - Cushing syndrome

The diagnostic criteria for polycystic ovarian syndrome regure the exclusion of the followings
• Nonclassical congenital adrenal hyperplasia
• Cushing syndrome
• Hyperprolactinemia
• Hypothyroidism
• Acromegaly
• A virilizing adrenal or ovarian tumors
• Premature ovarian failure
• A drug related condition

- Evaluation include the following investigations:
  - Thyroid function tests (TSH, free thyroxine)
  - Serum prolactin level
  - Total and free testosterone levels
  - Free androgen index
  - Serum hCG level
  - Cosyntropin stimulation test
  - Serum 17-hydroxyprogesterone (17-OHPG) level
  - Urinary free cortisol (UFC) and creatinine levels
  - Low-dose dexamethasone suppression test
  - Serum insulin-like growth factor (IGF)–1 level
  - Androstenedione level
  - FSH and LH levels
  - GnRH stimulation testing

  - Glucose level
  - Insulin level
  - Lipid panel

- Abdominal and pelvic ultrasonography
- A transvaginal ultrasonography is preferable if feasible
- Abdominal and pelvic CT scan or MRI to visualize the adrenals and ovaries
- An ovarian biopsy may be performed for histologic confirmation of polycystic ovarian syndrome.
- An endometrial biopsy may be obtained to evaluate for endometrial disease, such as malignancy.

14.8 Treatment and Outcome

- The treatment of polycystic ovarian syndrome is variable for each case and depends on the severity of symptoms.
- Specific treatments can include insulin-sensitizing drugs or oral contraceptives to regulate periods and control acne and unwanted hair growth.
- Combination oral contraceptives can also decrease endometrial cancer risk in teens.
- Weight loss for obese girls is important as excess weight affects insulin levels.
- A 5–10% weight loss in patients with polycystic ovarian syndrome has been shown to:

  - Decrease testosterone concentrations
  - Increase SHBG
  - Normalize menses
  - Improve fertility
  - attenuate insulin resistance and other metabolic aberrations

- Increased physical activity is important not only to reduce weight but it also decreases insulin resistance.
- Acne can be treated with:

  - Medication applied to the skin
  - Antibiotics
  - Estrogen and progesterone medication which also regulates periods
  - Spironolactone which blocks the androgens that causes the acne.
  - For acne, topical treatment with salicylic acid, benzoyl peroxide, clindamycin/benzoyl peroxide preparations, tretinoin, and clindamycin/tretinoin combinations can be used.
  - If topical therapies for acne are ineffective, oral isotretinoin can be used.
  - Isotretinoin and because of its teratogenicity, is typically only used in severe cases of acne and in combination with effective forms of contraception.

- Combined hormonal oral contraceptive pills containing both estrogen and progestin are the most common form of therapy in adolescents with polycystic ovarian syndrome.
- These improve:

  Hirsutism
  Acne
  Menstrual irregularity

- The estrogen component both suppresses LH secretion (and thus ovarian androgen production) and increases hepatic SHBG production (decreasing the amount of free testosterone); the progestin component protects the endometrium from unopposed estrogen.

- Hirsutism:
  - Hirsutism, the most common cutaneous sign of hyperandrogenism.
  - This can be progressive in patients with polycystic ovary syndrome.
  - Therefore, the sooner it is treated, the better the outcome.
  - This can be reduced with estrogen and progesterone medications and/or spironolactone.
  - Many girls also try different ways to get rid of unwanted hair using waxing, plucking, shaving, depilation, electrolysis, and laser hair removal.
  - Eflornithine cream (Vaniqa), an inhibitor of ornithine decarboxylase, is another option for the treatment of hirsutism.
  - Vaniqa can be applied twice a day to unwanted areas of hair to prevent new hair from growing.
  - This must be used every day, or the hair will grow back.
- Abnormal menstrual periods:
  - These can be treated with several different ways.
  - Oral contraceptive pills containing estrogen and progesterone can be used to regulate periods.
  - Other treatment options are:

    Progesterone given orally for 5–10 days every 1–3 months to bring on a period.
    An estrogen and progesterone patch
    An intrauterine device (IUD).

- Combined oral contraceptive pills also inhibit 5α-reductase in the skin, decreasing its exposure to dihydrotestesterone.
- The fourth-generation progestin drospirenone (Yasmin® [30 μg of ethinyl estradiol + 3 mg drospirenone] and Yaz® [20 μg of ethinyl estradiol + 3 mg drospirenone]) has been suggested as the ideal choice as it has direct antiandrogenic activity.
- Both high-dose (30–35 μg of ethinyl estradiol) and low-dose (20 μg of ethinyl estradiol) oral contraceptive pills appear comparable.

- OrthoEvra®, a transdermal contraceptive patch, is also a treatment option for girls with polycystic ovarian syndrome.
- This may be associated with an increased risk for venous thromboembolism.
- The NuvaRing®, a transvaginal contraceptive ring, is another option.
- Reducing insulin resistance may also improve the signs and symptoms of polycystic ovarian syndrome.
  - Physical activity and exercise
  - A healthy diet
  - Metformin helps reduce insulin resistance and can be associated with a small amount of weight loss.
- Letrozole or clomiphene citrate are used to induce ovulation when fertility is desired.
- The aim of antiandrogen treatment:
  - To block androgen binding to the androgen receptors
  - To inhibit 5α-reductase
- Inhibiting 5α-reductase limits the conversion of testosterone to the more biologically active dihydrotestosterone.
- The most commonly used antiandrogen is spironolactone.
- Spironolactone:
  - Act as a competitive androgen receptors antagonist
  - Inhibits 5α-reductase
  - Decreases testosterone production
- The recommended dosage of spironolactone is typically 100–200 mg/day in divided doses.
- Flutamide is another antiandrogen (androgen receptors inhibitor).
- The recommended dosage of flutamide is 250–500 mg/day.
- Flutamide has side effects which limit its use.
- These include:
  - Hepatotoxicity
  - Fetal abnormalities
- Finasteride, a 5α-reductase inhibitor, is another antiandrogen that is used for the treatment of hirsutism.
- The recommended dosage of finasteride is 5 mg/day.
- Insulin-sensitizing agents are also frequently used in the management of polycystic ovarian syndrome.
- Metformin is the most commonly used, particularly in adolescents with impaired glucose tolerance, insulin resistance, and/or obesity.
- Metformin:
  - Inhibits hepatic glucose production
  - Increases peripheral tissue insulin sensitivity

  - Improve insulin sensitivity
  - Improve insulin and androgen levels
  - Improve lipid parameters
  - Improve menstrual cycles
  - Reduce the incidence of diabetes in those at high risk
- The thiazolidinediones (TZDs) (troglitazone, rosiglitazone, and pioglitazone) are another class of insulin-sensitizing agents.
  - They act as agonists for the nuclear peroxisome proliferator-activated receptor γ (PPARγ).
  - They improve peripheral insulin sensitivity, androgen levels, and ovulatory function.
- Octreotide (Sandostatin®), an analog of somatostatin.
  - It has been used in patients with polycystic ovarian syndrome.
  - Somatostatin inhibits pancreatic insulin release.
  - It decreases pituitary GH secretion.
  - It blunts the LH response to GnRH.
  - Somatostatin is given parenterally and known to have extensive side-effect which limits its use to treat patients with polycystic ovarian syndrome.
- Combined therapy is commonly used now to treat patients with polycystic ovarian syndrome.
  - The combination of ethinyl estradiol/drospirenone-containing oral contraceptive pills (Yasmin® or Yaz®) with metformin.
  - The combination of ethinyl estradiol/drospirenone, metformin, and flutamide.

Medications used in the management of polycystic ovarian syndrome
• Oral contraceptive agents (e.g., ethinyl estradiol, medroxyprogesterone)
• Antiandrogens (e.g., spironolactone, leuprolide, finasteride)
• Hypoglycemic agents (e.g., metformin, insulin)
• Selective estrogen receptor modulators (e.g., clomiphene citrate)
• Topical hair-removal agents (e.g., eflornithine)
• Topical acne agents (e.g., benzoyl peroxide, tretinoin topical cream (0.02–0.1%)/gel (0.01–0.1%)/solution (0.05%), adapalene topical cream (0.1%)/gel (0.1%, 0.3%)/solution (0.1%), erythromycin topical 2%, clindamycin topical 1%, sodium sulfacetamide topical 10%)

- The aim of surgical management of polycystic ovarian syndrome is to restore ovulation.
- Various laparoscopic methods were used and include the following:
  - Electrocautery
  - Laser drilling
  - Multiple biopsy

14.9 Prognosis

- Patients with polycystic ovarian syndrome may be at increased risk for:
  - Cardiovascular disease
  - Cerebrovascular disease
  - Patients with hyperandrogenism have elevated serum lipoprotein levels.
  - Approximately 40% of patients with polycystic ovarian syndrome have insulin resistance that is independent of body weight.
  - These patients are at increased risk for type 2 diabetes mellitus and consequent cardiovascular complications.
  - Patients with polycystic ovarian syndrome are also at an increased risk for endometrial hyperplasia and carcinoma.
- It is important to note that a girl with polycystic ovarian syndrome can become pregnant, even if she is not having regular periods.

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Chapter 15
Endometriosis in Adolescent Girls

Ahmed H. Al-Salem

15.1 Introduction

- Endometriosis refers to the presence of endometrial glands and stroma outside the uterus cavity and uterine musculature.
- These ectopic endometrial implants are usually located in the pelvis, but can occur nearly anywhere in the body.
- Endometriosis is a common condition that affects women during the reproductive years.
- The prevalence and the severity of endometriosis significantly increase with age.
- The disease can be associated with many distressing and debilitating symptoms, or it may be asymptomatic discovered during exploration for other reasons.
- Endometriosis should be considered in adolescent girls presenting with chronic pelvic pain.
- The exact etiology of endometriosis is not known.
- Endometriosis is common in adolescent and young women who have dysmenorrhea and pelvic pain.
- WNT4 is a confirmed endometriosis susceptibility gene, thus representing a shared risk factor for endometriosis as well as uterine anomalies.
- Endometriosis is known to be associated with the existence of Müllerian duct malformations such as:
  - The septate uterus is the most common form of structural uterine anomalies
  - A complete septate uterus with cervical duplication
  - A complete transverse vaginal septum

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  - Imperforate hymen
  - Cervical agenesis

- It is important to note that there might be a genetic predisposition for endometriosis.
- A family history of endometriosis is correlated with a higher likelihood of endometriosis in the patient.
- Adolescent endometriosis is common and often severe but the presentation is not specific.
- As a result of this the diagnosis of endometriosis is often delayed.
- The reproductive potential and functional outcomes might decrease because of this delay in diagnosis.
- This must be kept in mind and the aims of early diagnosis and treatment include:
  - To resolve the pain
  - To prevent disease progression
  - To prevent organ damage
  - To preserve fertility

15.2 Etiology

- The exact etiology of endometriosis is not known.
- Several theories for the etiology of endometriosis have been proposed.
  - Sampson's theory:

    This suggests that endometriosis occurs in the pelvis by retrograde menstruation through the fallopian tubes.
    This theory is supported by the observation that implants occur most commonly in the dependent portions of the pelvis.

  - Meyer's theory:

    This suggests that undifferentiated cells of the peritoneal surface differentiate into endometrial tissue.

  - Halban's theory:

    This suggests that ectopic endometrial tissue develop as a result of spread through vascular or lymphatic channels.

  - Recently, it was proposed that endometriosis develops as a result of immunologic defects. The immunological defect allows ectopic endometrial tissue to proliferate and not be cleared by the immune system.
- There might be a genetic predisposition for endometriosis.
- A woman with a first-degree relative with endometriosis has a lifetime risk of the disease approximately 10 times that of a woman without an affected family member.

15.3 Incidence

- The exact incidence of endometriosis is not known.
- It is estimated that among adolescents with pelvic pain the incidence of endometriosis is 25–38%.
- The incidence of endometriosis in adolescents refractory to medical treatment for pelvic pain is 67% at laparoscopy.
- Endometriosis has been described in premenarchal girls.
- Endometriosis, when diagnosed in adolescent girls it is more likely to be associated with a Mullerian anomaly.
- It is estimated that Mullerian anomalies are seen in 11% of teenagers with endometriosis.

15.4 Clinical Features

- Chronic pelvic pain is the main presentation of endometriosis.
  - Chronic pelvic pain can be cyclic or acyclic pain.
  - In some patients there is an increase in pain intensity at mid-cycle and with menses.
  - Onset of pain usually precedes flow by a few days and begins to resolve 1–2 days into the menses.
  - Symptoms also usually improve during pregnancy and after menopause
  - They can recur postpartum or with postmenopausal hormone replacement therapy.
- Pelvic examination can reveal tender nodularity, a fixed and nonmobile uterus, or adnexal masses representing endometriomas.
- This is seen more commonly in adults as the disease is progressive.
- In adolescent girls, pelvic examination is more likely to reveal only mild-to-moderate tenderness.
- A pelvic ultrasound should be performed to rule out associated uterine anomaly, other pelvic pathology or the rare endometrioma.
- When the products of cyclic sloughing of endometriotic implants become entrapped by cyst formation, the resulting mass is referred to as an endometrioma.
- Endometriomas are uncommon in adolescent girls.
- These can occur in any location but are most commonly found involving one or both ovaries. These masses can become quite painful, and patients with rupture present with an acute surgical abdomen.
- Approximately one third of patients with endometriosis remain asymptomatic.
- It is important to note that the size of visible endometriosis has no correlation with the degree of pain or other complaints.

- The degree of pain does correlate with the depth of tissue infiltration by endometriosis.
- The pain in patients with endometriosis correlates with the degree of peritoneal inflammation rather than the volume of implants.
- Intrapelvic/intra-abdominal adhesions secondary to endometriosis are also important determinants of the degree of pain.
- In addition to pain, patients present with nonspecific symptoms of fatigue, generalized malaise, and sleep disturbances.
- Symptoms of endometriosis can be variable and include:
  - Dysmenorrhea
  - Heavy or irregular bleeding
  - Pelvic pain
  - Lower abdominal or back pain
  - Dyspareunia
  - Dyschezia (pain on defecation) often with cycles of diarrhea and constipation
  - Bloating, nausea, and vomiting
  - Inguinal pain
  - Pain on micturition and/or urinary frequency
  - Pain during exercise
- Endometriotic implants are commonly found on the:
  - Uterus
  - Ovaries
  - Rectosigmoid area
  - Urinary bladder
  - Posterior peritoneum
- The patient usually presents with a history of progressively increasing pelvic pain and/or secondary dysmenorrhea.
- Not uncommonly, these patients present with painful bowel movements, diarrhea, or hematochezia in association with their menses when endometriosis involves the rectosigmoid colon.
- These patients may also present with dysuria, flank pain, or hematuria if the bladder or ureters are involved by endometriosis.
- Cyclic pain is pain that accompanies bleeding at the time of menstruation.
  - This could involve the bladder (hematuria)
  - This could involve bowel (hematochezia and painful defecation)
  - Rarely, bleeding occurs at uncommon sites such as:

    The umbilicus
    Abdominal wall
    Perineum
    Occasionally, patients present with a cyclically painful expanding mass in a pelvic surgery scar secondary to a focus of endometriosis.

- Acute exacerbations can be caused by chemical peritonitis secondary to leakage of old blood from an endometriotic cyst.
- Secondary dysmenorrhea occurs twice as often in women with endometriosis as in controls and endometriosis should be considered in a patient presenting with significant dysmenorrhea.
- Uncommon cyclic symptoms include:
  - Hemoptysis secondary to pulmonary involvement
  - Catamenial seizures secondary to brain involvement
  - Umbilical bleeding secondary to implants in the umbilicus
- Endometriosis may be complicated by partial or complete bowel obstruction secondary to:
  - Adhesion formation.
  - Circumferential bowel involvement by endometriosis.
  - Extensive involvement of the rectum and other areas of the gastrointestinal tract may cause adhesions and obstruction.
- Ureteral obstruction and hydronephrosis may develop as a complication of endometriosis secondary to:
  - Endometrial implants on the ureter.
  - A mass effect from an endometrioma.
- Rupture of an ovarian endometrioma may present as an acute abdomen.

15.5 Staging of Endometriosis

- The American Society for Reproductive Medicine classification of endometriosis is currently the most widely used staging system.
- This staging system is based on surgical exploration.
- This is based on point scores which are assigned based on:
  - The number of lesions
  - Their bilaterality
  - Associated adhesion formation
  - Lesion size
- The patient's stage (i.e., 1–4, or minimal, mild, moderate, and severe) may be useful in determining her prognosis for subsequent reproduction.
- The staging system can also be used to monitor a patient's response to treatment.
- The four stages of endometriosis are evaluated using the following criteria:
  - Endometrial implants

    Location
    Extent

Depth

- Endometriomas

  Presence
  Size

- Adhesions

  Severity

- Stage 1 Endometriosis (Minimal)
  - This is characterized by superficial implants that are sometimes mistaken for cysts or ovarian cancer.
  - They resemble small, flat patches or flecks on the pelvic surface.
  - The presence of these implants causes irritation and inflammation in surrounding tissues, leading to the formation of adhesions.
  - These adhesions cause pain and dysfunction.
- Stage 2 Endometriosis (Mild)
  - This is characterized by superficial implants but more aggressively.
  - Black spots appear over the fibrous adhesions which have grown in intensity.
  - These cause irritation during ovulation and/or pelvic pain.
  - The lesions also appear in the recto-uterine pouch.
- Stage 3 Endometriosis (Moderate)
  - This is characterized by the presence of endometriomas which are sometimes called “chocolate cysts”.
  - Chocolate cysts get their name because after time, the blood inside of the cyst turns dark red and brown.
  - These cysts may ruptures and cause extreme abdominal pain and inflammation in the pelvic region.
  - Inflammation and infection, in turn, cause more adhesions.
  - These endometriomas have the tendency to increase in size and number and this will result in more adhesions that form in response.
- Stage 4 Endometriosis (Severe)
  - This is the most severe stage of endometriosis.
  - It is characterized by the presence of a large number of cysts and severe adhesions.
  - Endometriomas can grow very large, even as big as a grapefruit.
  - Endometriomas larger than 2 cm in size will likely need to be removed surgically.
  - Since many of the cysts are on the back wall of the uterus and the rectum, women with stage 4 may complain of painful bowel movements, constipation, nausea/vomiting and abdominal pain.
  - In addition, infertility is likely with stage 4 endometriosis.

- Endometriosis is one of the causes of subfertility.
  - This is secondary to peritubal and periovarian adhesions which can interfere mechanically with ovum transport and also tubal mobility.
  - Endometriosis may also cause more sperm binding to the ampullary epithelium, thereby affecting sperm-endosalpingeal interactions.

15.6 Investigations and Diagnosis

- Endometriosis is the underlying cause in 15% of women presenting with pelvic pain.
- Endometriosis should be considered in women with chronic pelvic pain who do not respond to standard nonsteroidal anti-inflammatory drugs (NSAIDs) or oral contraceptive therapy.
- The differential diagnosis in females with suspected endometriosis include:
  - Acute appendicitis
  - Chlamydial Genitourinary Infections
  - Urinary Tract Infection
  - Cystitis
  - Diverticulitis
  - Ectopic Pregnancy
  - Gonorrhea
  - Ovarian Cysts
  - Ovarian Torsion
  - Pelvic Inflammatory Disease
- Pelvic ultrasonography, computed tomography (CT) scanning, and magnetic resonance imaging (MRI) are indicated for patients with advanced disease.
- Transvaginal ultrasonography or endorectal ultrasonography can be used to assess endometriosis.
  - The ultrasonographic features of endometriomas vary from simple cysts to complex cysts with internal echoes to solid masses, usually devoid of vascularity.
  - Transvaginal ultrasonography is a useful method of identifying the classic chocolate cyst of the ovary.
  - The typical appearance is that of a cyst containing low-level homogenous internal echoes consistent with old blood.
- Magnetic resonance imaging (MRI)
  - This is useful in detecting rectal involvement.
  - It can also detect rectovaginal endometriosis, pelvic masses, bowel obstruction, hydronephrosis and cul-de-sac obliteration.
  - Endometriomas may appear as cystic masses.

- Intravenous pyelography and barium enema are indicated for patients with suspected ureter or colon involvement.
- A complete blood cell (CBC) count
- Urinalysis and urine culture
- Cervical Gram stain and cultures can be performed for those with suspected sexually transmitted diseases.
- Serum cancer antigen 125 (CA-125)
- Laparoscopy and biopsy is the procedure of choice to diagnose endometriosis.
- Laparoscopy and biopsy
  - Laparoscopy is considered the primary diagnostic modality for endometriosis.
  - The classic lesions are blue-black or have a powder-burned appearance
  - The lesions can also be red, white, or nonpigmented.
  - It is important to note that microscopic evidence of endometriosis may be found in normal-appearing peritoneum.
  - The most common sites of endometriosis found during laparoscopy are:

    Ovaries
    Posterior cul-de-sac
    Broad ligament
    Uterosacral ligament
    Rectosigmoid colon
    Bladder
    Distal ureter

- Histologic diagnosis of endometriosis depends on demonstrating both endometrial glands and stroma in biopsy specimens obtained from outside the uterine cavity.
- The presence of fibrosis in combination with hemosiderin-laden macrophages in symptomatic patients may be sufficient for a presumptive diagnosis.

15.7 Approach and Management Considerations

- The goals of treatment of endometriosis are:
  - To relive the pain
  - To stop progression of the endometriosis
  - To preserve fertility
- Medical management is the initial approach in the adolescent girls.
- Surgical therapy should be reserved for the patient with persistent pain despite medical treatment.

- Nonsteroidal anti-inflammatory drugs (NSAIDs):
  - These are the first-line treatment in adolescent girls.
  - They inhibit the cyclooxygenase enzyme pathway that produces prostaglandins and leukotrienes.
  - NSAIDs have been shown to decrease menstrual loss and significantly improve dysmenorrhea.
- Hormonal treatment:
  - The aim is to interrupt the normal cyclic production of reproductive hormones.
  - Medications currently used to treat endometriosis include:

    Gonadotropin-releasing hormone (GnRH) agonists
    Progestins
    Oral contraceptive pills
    Androgens

  - Adolescent girls with symptoms that do not respond to NSAIDs for three menstrual periods can be offered hormonal therapy.
  - These are used to suppress the proliferation of endometriotic implants that depend on ovarian steroids for growth.
  - Combination oral contraceptive pills (COCPs) act by ovarian suppression and continuous progestin administration.
  - Continuous oral contraceptive pills have been shown to suppress endometriosis.
  - Initially, a trial of continuous or cyclic combined oral contraceptive pills should be administered for 3 months. With pain relief, this treatment is continued for 6–12 months.
  - Continuous noncyclical administration of combined oral contraceptive pills, omitting the placebo menstrual tablets, for 3–4 months helps avoid any menstruation and associated pain.
  - Women with endometriosis are at increased risk of epithelial ovarian cancer, and combined oral contraceptive pills are believed to protect against this.
  - Cyclic oral contraceptive pills on the other hand are less effective in treating menstrual pain.
  - Side effects of continuous oral contraceptive pills include:

    Breakthrough bleeding, which decreases over time
    Nausea
    Breast tenderness

  - Oral contraceptive pills can be used concurrently with NSAIDs.
  - Continuous hormone therapy similar to oral contraceptive pills can be obtained using the transdermal patch (Ortho Evra®; norel-gestromin/ethinyl

estradiol transdermal system, Ortho—McNeil—Jannsen Pharmaceuticals, Inc., NJ, USA) or vaginal ring (Nuva Ring®; etonogestrel/ethinyl estradiol vaginal ring, Organon USA, NJ, USA).
- The combination of desogestrel and ethinyl estradiol reduces the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary by decreasing the amount of gonadotropin-releasing hormones (GnRHs).
- The combination of norgestimate and ethinyl estradiol reduces the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary by decreasing the amount of gonadotropin-releasing hormones (GnRHs).

- Progestational agents
  - All progestational agents act by decidualization and atrophy of the endometrium.

    A high-dose of these hormones is used to suppress the hypothalamus through negative feedback. This results in a hypoestrogenic state.

  - Norethindrone is a common progestin used in many of the oral contraceptive pills currently available.
  - Progestins stop endometrial cell proliferation, allowing organized sloughing of cells after withdrawal.

    Medroxyprogesterone is a common progestin available in both an oral (PO) and an intramuscular (IM) depo form.
    Megestrol produces results similar to those of medroxyprogesterone.

  - Medroxyprogesterone acetate is used to suppress pain in both the oral and injectable depot preparations.

    Oral doses of 10–20 mg/day can be administered continuously.
    Adverse effects include:

    - Weight gain
    - Fluid retention
    - Depression
    - Breakthrough bleeding

  - Megestrol acetate has been used in doses of 40 mg with similarly good results.
  - The levonorgestrel intrauterine system (LNG-IUS) has been shown to reduce endometriosis-associated pain.
  - When inserted at the time of laparoscopic surgery, it has been found to reduce the recurrence of dysmenorrhea by 35%.
  - Continuous progestins (norethindrone acetate 15 mg daily, medroxyprogesterone acetate 30–50 mg daily or medroxyprogesterone acetate 150 mg intramuscularly every 3 months) is also effective in reducing pain from endometriosis by inducing amenorrhea.

- Progestins can be used to treat patients who do not tolerate oral contraceptive pills, or in whom oral contraceptive pills is contraindicated.
- A levonorg-estrel-releasing IUD can be beneficial in suppressing menses and it is used as an alternative for adolescent girls.
- A levonorg-estrel-releasing IUD is safe and effective in adolescents, with no increased risk of pelvic inflammatory disease or ectopic pregnancy.
- Etonogestrel implants have been used successfully in adults to treat pain symptoms associated with endometriosis
- Side effects of continuous progestins include:

  Irregular menses
  Weight gain
  Bloating
  Acne
  Headaches

• Gonadotropin-releasing hormone analogues (agonists)

- They work by down-regulating the pituitary release of gonadotropins, which results in a hypoestrogenic state.
- A GnRH agonist is indicated in adolescent girls who do response to treatment with oral contraceptive pills and progestins.
- A 3.75 mg of depot leuprolide given intramuscularly every month was associated with improvement in dys-menorrhea, pelvic pain, deep dyspareunia, and pelvic tenderness.
- Surgical intervention by laparoscopy is indicated for those not responding to a 3 months GnRH therapy.
- Side effect of GnRH agonist therapy:

  Its negative effect on bone mineral density
  When GnRH agonists are used for 6 months, the trabecular bone loss is 7% and may not return to baseline levels following cessation of treatment.
  To combat this loss, daily add-back therapy with either estradiol (0.625 mg daily), norethindrone (5 mg daily) or medroxyproges-terone acetate (5 mg daily) has been shown to be effective in the adult population to help preserve BMD and not interfere with the effect of the GnRH agonist on relieving pelvic pain.
  The use of GnRH agonist therapy in adolescents is recommended for approximately 6 months followed by continuous oral contraceptive pills use.
  If GnRH therapy is prolonged for more than 9 months, BMD should be performed every 6 months, then every 2 years when stable.

- Gonadotropin-releasing hormone (GnRH) analogues produce a hypogonadotrophic-hypogonadic state by downregulation of the pituitary gland.

Goserelin and leuprolide acetate are commonly used agonists.
The GnRH analogues (agonists) supply constant stimulation of the pituitary receptors, leading to downregulation and eventual suspension of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secretion.
This suspension results in a profound hypoestrogenic state, similar to menopause.
GnRH agonists should be used with caution in adolescents younger than 16 years because of adverse effects on bone density.

- Goserelin and leuprolide acetate are the commonly used agonists.
- Goserelin suppresses ovarian and testicular steroidogenesis by decreasing luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels.

  Goserelin is administered monthly as a subcutaneous (SC) implant in the upper abdominal wall.

- Treatment is usually restricted to monthly injections for 6 months.
- Side effects include:

  Loss of trabecular bone density
  This is restored by 2 years after cessation of therapy.
  Other adverse effects include hot flashes and vaginal dryness.

- Leuprolide suppresses ovarian and testicular steroidogenesis by decreasing luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels.

  Leuprolide is given daily subcutaneously or monthly intramuscular as depo formulation.

- Nafarelin is an analogue of gonadotropin-releasing hormone (GnRH) that is approximately 200 times more potent than natural endogenous GnRH.

  Nafarelin suppresses gonadotrope responsiveness to endogenous GnRH, thereby reducing secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which in turn reduces ovarian and testicular steroid production.
  Nafarelin is available as a nasal solution (2 mg/mL) administered twice daily.

- Add-back therapy has been shown to prevent loss in bone density and to relieve vasomotor symptoms without reducing the efficacy of GnRH regimens.
  - GnRH agonists have been used for 12 months with norethindrone add-back therapy with good results.
  - GnRH therapy has also been proven to relieve the pain and bleeding associated with extrapelvic distant endometriosis.
- The use of Japanese acupuncture may be effective in the treatment of endometriosis-related pain. It is safe and well tolerated.
- Danazol

- Danazol acts by inhibiting the midcycle follicle-stimulating hormone (FSH) and luteinizing hormone (LH) surges and preventing steroidogenesis in the corpus luteum.
- Danazol is associated with a higher incidence of adverse effects including:

  Oily skin
  Acne
  Weight gain
  Deepening of the voice
  Facial hirsutism
  Emotional lability
  Hot flashes
  Vaginal dryness
  Reversible breast atrophy

- The recommended dose is 600–800 mg/day.
- Danazol is a synthetic steroid analogue with strong antigonadotropic activity (inhibits luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) and weak androgenic action.
- Aromatase inhibitors work by blocking the aromatase activity in extraovarian sites that suppress the conversion of androstenedione and testosterone to estrogen. This action may result in suppression of endometriosis at a local level.
- Letrozole is a competitive inhibitor of the aromatase enzyme system that leads to a reduction in plasma estrogen levels in postmenopausal women.
- Letrozole may decrease pain in patients whose conditions have previously failed other treatments.

15.8 Surgical Management

- The diagnosis of endometriosis is based on histologic diagnosis from a surgical biopsy.
- Surgical therapy is indicated for patients who are refractory to medical treatment.
- Endometriosis is a progressive disease and most adolescents will have mild disease to start with.
- The typical powder burn blue—black, chocolate or fibrotic lesions are commonly seen in adults.
- Adolescent girls on the other hand predominately have clear vesicular lesions, white implants, and/or small hemorrhagic or petechial spots of the pelvic peritoneum (white vesicles or red lesions).
- Laparoscopic excision is the treatment of choice.
  - This allows for histologic diagnosis
  - This allows for complete excision of endometriosis

- Fulguration of lesions is not reliable as this sometimes spares deeper endometriosis.
- The recurrence rate of pain after surgery, however, has been reported to range from 30 to 51%.
- Medical treatment following surgery is recommended to treat lesions that could not be completely removed surgically.
- The simultaneous use of a levonorgestrel IUD and an etonogestrel subdermal implant can be used to treat adolescent girls with debilitating endometriosis who had previously undergone unsuccessful surgical excision and other medical therapy.
- Surgical Intervention
  - The aim is to remove endometrial implants and correct anatomic distortions.
  - Resection of the implants and adjacent peritoneum is considered the treatment of choice.
  - A radical surgical approach involves total hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO).
- Conservative Surgery
  - The aim is to destroy visible endometriotic implants and lyse peritubal and periovarian adhesions that are a source of pain and may interfere with ovum transport.
  - The laparoscopic approach is the method of choice for treating endometriosis conservatively.
  - Ablation can be performed with laser or electrodiathermy.
  - Laparoscopic ablative surgery with bipolar diathermy or laser for endometriomas was shown to be effective for relieving pelvic pain in 87% of patients.
- Ovarian endometriomas can be treated by drainage or cystectomy.
  - Laparoscopic cystectomy was found to yield better pain relief and pregnancy rates than drainage.
  - Medical therapy with gonadotropin-releasing hormone (GnRH) agonists reduces the size of the cyst but does not influence pain relief.
- Semiconservative surgery
  - Semiconservative surgery involves hysterectomy and cytoreduction of pelvic endometriosis.
  - This is indicated for young females or females who have completed their childbearing.
  - Patients who undergo hysterectomy with ovarian conservation have a sixfold higher rate of recurrence compared to women who undergo oophorectomy.
  - Ovarian endometriosis can be removed surgically.
- Radical surgery
  - Radical surgery involves total hysterectomy with bilateral oophorectomy (TAH-BSO) and cytoreduction of visible endometriosis.

  - Adhesiolysis is performed to restore mobility and normal intrapelvic organ relationships.

- Presacral neurectomy
  - Presacral neurectomy is used to relieve severe dysmenorrhea.
  - The nerve bundles are transected at the level of the third sacral vertebra, and the distal ends are ligated.
  - Complications of presacral neurectomy include:

    Vascular injury to the middle sacral artery and vein.
    Constipation

  - To avoid vascular injury, prophylactic ligation is advocated.
- Laparoscopic uterine nerve ablation (LUNA) is performed to interrupt the pain fibers.
  - Complications of this procedure include uterine prolapse and pelvic denervation.
- Postoperative adjunctive hormone therapy
  - For patients with mild disease, postoperative adjunctive hormonal treatment has been shown to be effective in reducing pain related to endometriosis.
  - These medications include:

    GnRH analogues
    Danazol
    Medroxyprogesterone

- Ureteric obstruction may warrant surgical release or excision of a damaged segment.
- Bowel obstruction may require a resection anastomosis or a wedge resection if the obstruction is confined to the anterior rectosigmoid.
- Endometriosis may recur in 15% of women after extirpative surgery, irrespective of whether estrogen-replacement therapy (ERT) is given postoperatively.

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Chapter 16
Amenorrhea in Adolescents

Ahmed H. Al-Salem and Salah Radwan

16.1 Introduction

- The age of menarche usually occurs between the ages of 12 and 13 years.
- The length of the normal menstrual cycle is highly variable.
- Normal menstrual cycles are characterized by a cycle length of 28 days, duration of flow of 4.5 days, and a blood loss of less than 80 mL.
- Menstrual cycles are considered abnormal if they last longer than 8 days or if more than 80 mL of blood loss occurs.
- Abnormal or irregular menstrual patterns are common in the early adolescent period.
- The most common etiology of amenorrhea in adolescent is dysfunction of the hypothalamic-pituitary-ovarian axis.
- A careful history, a detailed examination and appropriate investigations are necessary to diagnose these abnormalities.
- Normally, menarche occurs during late stage of breast development and usually lags behind thelarche by 2–3 years.
- It takes about 5 years after menarche for the establishment of regular menstrual cycles.
- The interval between the first menstrual period and second can be quite long, but subsequent cycles usually vary from 21 to 45 days.
- In the years after menarche, the cycles are typically anovulatory accounting for the wide variation in the length of the cycle during this phase of development.
- Once the hypothalamo-pituitary-ovarian axis matures, the pattern of menstrual cycle normalises as the cycle becomes increasingly ovulatory.

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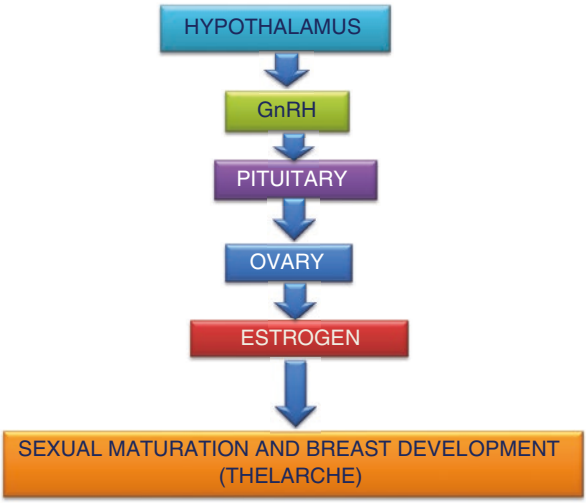
- Amenorrhea is defined as the absence or abnormal cessation of menstruation in women of reproductive age.
- In adolescents, menstrual disorders can be common amongst adolescents, particularly in the first few years after menarche but amenorrhea may warrant investigation, and pregnancy should always be ruled out.
- Amenorrhea is divided into primary and secondary.
- Amenorrhea can be a transient, intermittent, or permanent.
- Failure to attain menarche is primary amenorrhea.
- Evaluation is needed if menarche has not occurred by:
  - Age 15 years in females with normal secondary sexual development
  - Age 13 years in females lacking any secondary sexual characteristics
  - Within 5 years after thelarche
- Secondary amenorrhea is defined as menstrual cessation for at least 3 months in those with previously established regular menses, or lack of menses for over 6 months in patients who previously experienced irregular menses.
- Amenorrhea results from dysfunction of the hypothalamus, pituitary, ovaries, uterus, or vagina.
- Menstrual disorders such as amenorrhea are particularly common in adolescent girls.
- In adolescent girls, this is a source of anxiety for the patients and the parents.
- Menstrual irregularities are common during the early post menarche years, but complete absence or cessation of menses is abnormal and requires careful evaluation and management.
- Amenorrhea except that occurring before puberty, during pregnancy or early lactation, and after menopause should be considered pathologic and further evaluation is important.
- Amenorrhea may be caused by:
  - Anatomic abnormalities
  - Hypothalamic disorders
  - Pituitary, or other endocrine dysfunction
  - Ovarian failure
  - Genetic causes
- The most common causes of amenorrhea are:
  - Hypothalamic disorders
  - Polycystic ovarian syndrome
  - Hyperprolactinemia
  - Ovarian failure
- To diagnose amenorrhea it is important to obtain a detailed medical history and careful clinical examination which should identify the type of amenorrhoea, whether primary or secondary, together with presence or absence of secondary sexual characteristic.
- Laboratory investigation should include:
  - Gonadotropin release hormones

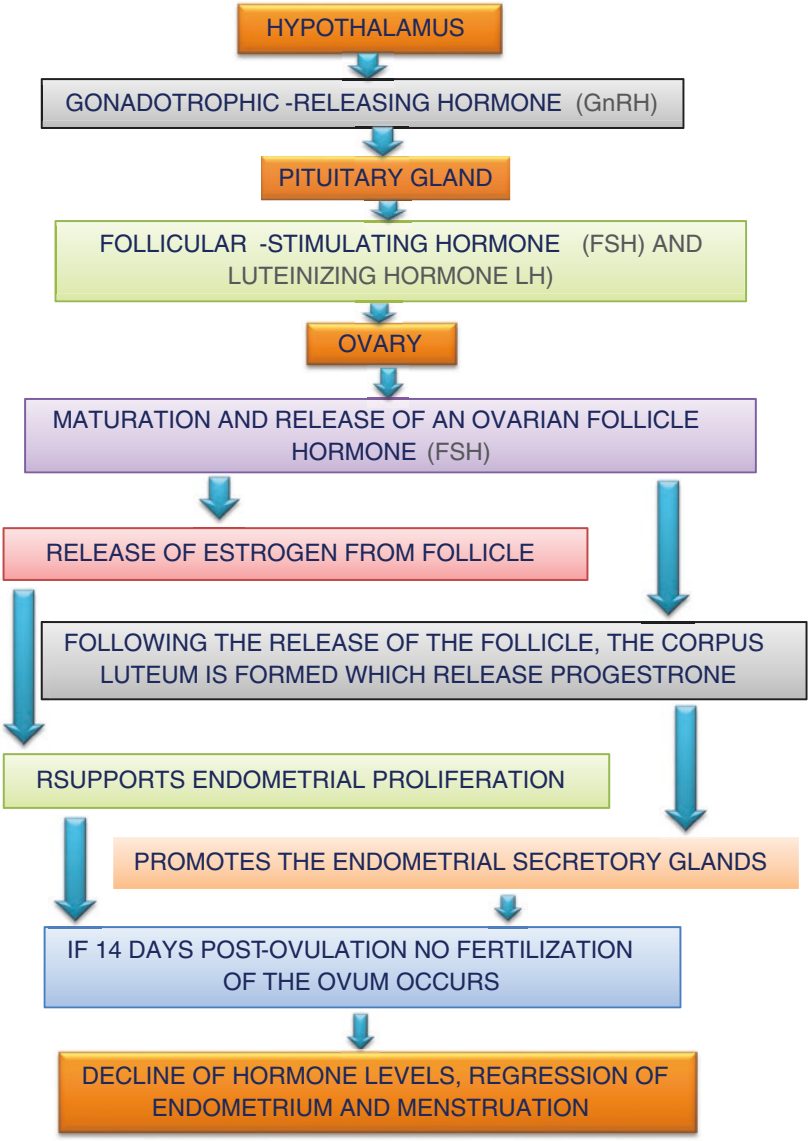
  - Prolactin level
  - Androgens in the presence of acne or hirsutism



- Amenorrhea is classified as either:
  - Primary: Absence of menarche by age 15 years or thereafter.
  - Secondary: Absence of menses for more than 3 months in girls or women who previously had regular menstrual cycles or 6 months in girls or women who had irregular menses.
- Oligomenorrhea is defined as fewer than nine menstrual cycles per year or cycle length greater than 35 days.
- Amenorrhea lasting 3 months or more and oligomenorrhea require investigation.
- A pregnancy test is recommended as a first step in evaluating any woman with secondary amenorrhea.
- Measurement of serum beta subunit of human chorionic gonadotropin (hCG) is the most sensitive test for pregnancy.
- Once pregnancy has been ruled out, a women with either primary or secondary amenorrhea should be evaluated based upon the levels of control of the menstrual cycle: hypothalamus, pituitary, ovary, and uterus.
- Determining the site of the defect in the control of the menstrual cycle is important because it determines the appropriate therapeutic approach.
- The most common causes of secondary amenorrhea are likely to be functional hypothalamic amenorrhea or polycystic ovary syndrome (PCOS) but disorders with an anatomic or pathologic cause must be ruled out.
- It is currently recommended to start the evaluation process for amenorrhea:
  - In an adolescent who is 15 years old if she is showing normal secondary sexual characteristics development.
  - In any girl who did not have her first menses 5 years after thelarche.

16.2 Pathophysiology

- Menarche is a normal occurring phenomenon in all pubertal girls with its usual timing occurring at least 2 years from thelarche.
- Several genetic and environmental factors affect the initiation and progression of menarche in otherwise healthy female adolescents.



- In the United States, the average age of menarche for Caucasian female adolescent is 12.6 years.
- The menstrual cycle is divided into the follicular (proliferative) and the luteal (secretory) phases.
- The hypothalamus, pituitary and ovaries form a functional endocrine axis, known as HPO axis.
- The hormonal regulations and feedback loops of this endocrine axis is important for normal Menarche and menstrual cycles.
- The menstrual cycle occur as a result of coordinated hormonal events in the female.
- These hormones stimulate the growth and release of an ovarian follicle and prepare a site for implantation if fertilization should occur.
- Failure of fertilization with its subsequent drop in hormones levels will lead to sloughing of the endometrium and flow of menses.
- Menarche and sustained menstrual cycles requires normal function of the endocrine axis comprising the hypothalamus, pituitary, and ovaries.
- Any disruption in this axis may result in amenorrhea.

16.3 Polycystic Ovary Syndrome (PCOS)

- PCOS is the most common endocrine disorder seen in females presenting with either primary or secondary amenorrhea
- PCOS affects 3.6–15% of reproductive age women.
- In PCOS, amenorrhea, primary or secondary, occurs due to the blunted effects of hyperandrogenism on GnRH secretion resulting in elevated LH secretion. There are other neurotransmitters involved in the pathogenesis of PCOS such as neurokinin B and dynorphins that also affect LH activity.
- The 2003 Rotterdam criteria are used for diagnosis of PCOS.

16.4 Causes of Amenorrhea in Adolescents

- The causes of amenorrhea in adolescents can be classified into:
  - Anatomic abnormalities of the outflow tract
  - Primary hypogonadism
  - Hypothalamic disorders
  - Pituitary causes
  - Other endocrine disorders
  - Ovarian causes
  - Genetic defects
  - Multifactorial causes

- Other causes of secondary amenorrhea:
  - Prolactinoma
  - Hyperthyroidism
  - Hypothyroidism
  - Polycystic ovarian syndrome
  - Late-onset congenital adrenal hyperplasia
  - Virilizing tumor
- Anatomic abnormalities of the outflow tract
  - The most commonly identified anatomic defects of the outflow tract include:

    Mullerian agenesis
    Intrauterine synechiae
    Imperforate hymen
    Transverse vaginal septum
    Cervical agenesis
    Cervical stenosis
    Vaginal agenesis
    Congenital endometrial hypoplasia or aplasia
  - These causes result in primary amenorrhea except for intrauterine synechiae and cervical stenosis which cause secondary amenorrhea. These two conditions are very rare in adolescents.
- Imperforate hymen is a common cause of primary amenorrhea that can be easily diagnosed and treated.
- Patients with a transverse vaginal septum will also present with primary amenorrhea.
- Ashermann syndrome or intrauterine synechiae cause secondary amenorrhea. This disorder is uncommon in adolescents and is usually a consequence of postpartum endometritis. Other causes include uterine tuberculosis, ceserian section and myomectomy.
- Patients with incomplete cervical agenesis "cervical dysgenesis" will present with primary amenorrhea.
- Genital tract abnormalities account for about 20% of all cases of primary amenorrhea.
- Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome
  - Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome is another cause of genital tract abnormality presenting as primary amenorrhoea.
  - It affects 1 of 4500 women and can be associated with renal, vertebral, auditory and cardiac defects.
  - In MRKH there is vaginal agenesis caused by agenesis or partial agenesis of the müllerian duct system.
  - It is characterized by congenital aplasia of the uterus and upper two thirds of the vagina in women with developed secondary sexual characteristics and a normal 46, XX karyotype.

- These patients are phenotypically and genetically females but they lack the development of a uterus and upper two thirds of the vagina
- The first sign is primary amenorrhea.

16.5 Primary Hypogonadism

- The most common causes of primary hypogonadism include:
  - Gonadal dysgenesis
  - Turner syndrome
  - Pure gonadal dysgenesis
  - Swyer syndrome
  - Gonadal agenesis
  - 17-hydroxylase deficiency
  - 17,20-Lyase deficiency
  - Aromatase deficiency
  - Idiopathic premature ovarian failure
  - Secondary ovarian failure due to chemotherapy or irradiation
  - FSH receptor gene mutations
  - LH resistance
  - Galactosemia
  - Glycoprotein syndrome type 1

16.6 Hypothalamic Causes of Amenorrhea

- The main cause of this condition is that the hypothalamus stops producing gonadotropin-releasing hormone (GnRH), the hormone that initiates the menstrual cycle in females.
- Hypothalamic amenorrhea which is the most prevalent cause of amenorrhea in the adolescent age group.
- It occurs as a result in decreased or inhibited GnRH secretion, which affects the pulsatile release of pituitary gonadotropins, LH and FSH, causing anovulation.

16.7 Functional Hypothalamic Amenorrhea

- Functional hypothalamic amenorrhea is a common cause of amenorrhea.
- It is characterized by abnormal hypothalamic GnRH secretion, decreased gonadotropin pulsations, low or normal LH concentrations, absent LH surges, abnormal follicular development, and low serum estradiol.

- It is important to note that the Serum FSH concentrations are usually in the normal range, with high FSH-to-LH ratio.
- Functional hypothalamic amenorrhea can be caused by eating disorders, exercise, or high levels of prolonged physical or mental stress.
- This can also include major psychiatric disorders such as depression.
- Hypothalamic causes of amenorrhea include:
  - Hypothalamic dysfunction due to stress, malnutrition and anorexia nervosa or excessive exercise.
  - Kallmann syndrome
  - Idiopathic hypogonadotropic hypogonadism
  - Tuberculosis
  - Syphilis
  - Sarcoidosis
  - Brain tumors
  - Chronic systemic illness
  - Isolated gonadotropin deficiency
  - Chronic systemic illness
- Idiopathic hypogonadotropic hypogonadism leads to low gonadotropin (FSH/LH) levels.
- When this occurs with anosmia, it is diagnosed as Kallmann syndrome, the signs of which include midline facial defects, renal agenesis, and neurologic deficiencies.

16.8 Kallman Syndrome

- Kallmann syndrome results from a failure of GnRH cells to migrate to the forebrain, a phenomenon associated with mutations in the genes KAL1, FGFR1, FGF8, PROKR2, and PROK2.
- This is a genetic disorder that is characterized by gonadotropin-releasing hormone deficiency plus anosmia.
- This condition usually causes primary amenorrhea.
- The syndrome includes:
  - Primary amnorrhea
  - Anosmia
  - Midline facial defects
  - Renal agenesis

16.9 Pituitary Causes of Amenorrhea

- A deficiency in gonadotropins may result from GnRH receptor gene mutations. These mutations however are very rare.

- Mutations in the FSH beta gene have also been described and are associated with amenorrhea. Patients with these mutations have low FSH and estradiol levels and high LH levels.
- Hyperprolactinemia is the most common cause of pituitary amenorrhea.
- Primary amenorrhea caused by hyperprolactinemia is a rare condition characterized by the onset of thelarche and pubarche at appropriate ages but arrest of pubertal development before menarche.
- Hyperprolactinemia may be associated with suppression of the GnRH from the hypothalamus and subsequent inhibition of LH and FSH, suppressed gonadal function and galactorrhea.
- Prolactinomas are more commonly noted in secondary amenorrhea.
- Pituitary tumors may suppress gonadotropin secretion, such as in Cushing disease or hypothalamic tumors, craniopharyngioma, or germinoma.
- Brain injury or cranial irradiation may also result in amenorrhea.
- Hyperprolactinemia can be secondary to antipsychotic therapy.
- The pituitary causes can all cause amenorrhea due to pituitary gland hormonal dysfunction and include:
  - Prolactinomas
  - Craniopharyngioma
  - Metastatic tumors to the pituitary gland
  - Empty Sella syndrome
  - Arterial aneurysms
  - Postpartum pituitary necrosis ‘Sheehan syndrome’
  - Panhypopituitarism
  - Sarcoidosis
  - Hemochromatosis
- It is important to rule out an occupying pituitary lesion in females with amenorrhea, headaches, and vision changes.
- Receptor and enzyme defects
  - Congenital adrenal hyperplasia as a result of 17 alpha-hydroxylase deficiency (CYP17) causes an excess of deoxycortisone to be produced and deficiency of cortisol and adrenal and gonadal sex steroids.
  - Patients with this disorder who experience primary amenorrhea can be either genotypic males (XY) or females (XX).
  - Complete androgen insensitivity syndrome is caused by a defective androgen receptor.
  - Although patients with this syndrome have a 46, XY karyotype and produce testicularly derived testosterone, the testosterone cannot activate cellular transcription; therefore, the patient has female external genitalia.
  - In most cases the disorder is X-linked.
  - The testes, located internally and sometimes in the labia or inguinal area, also produce müllerianinhibiting hormone, so all müllerian-derived structures (i.e., the fallopian tubes, uterus, upper third of the vagina) are absent.

- Gonadal dysgenesis is characterized by the congenital loss or underdevelopment of germ cells within the gonad during organogenesis.
- The gonads usually contain only fibrous tissue and are called streak gonads.
- In females, the most common form of gonadal dysgenesis is Turner syndrome (45, X), in which gonadotropin levels, especially the FSH levels, are high during early childhood and after age 9–10 years.
- Depletion of ovarian follicles causes amenorrhea.
- Premature ovarian failure should be investigated if suspected.
- The fragile X permutation accounts for approximately 6% of cases of overt POF.
- Autoimmune oophoritis occurs in 3–4% of POF cases.
- Amenorrhea is also seen in pure 46, XX gonadal dysgenesis and in 46, XY gonadal dysgenesis.
- These women have significantly elevated FSH levels due to the absence of ovarian follicles and reduction in negative feedback on FSH from estradiol and inhibin A and B.

16.10 Multifactorial Causes of Amenorrhea

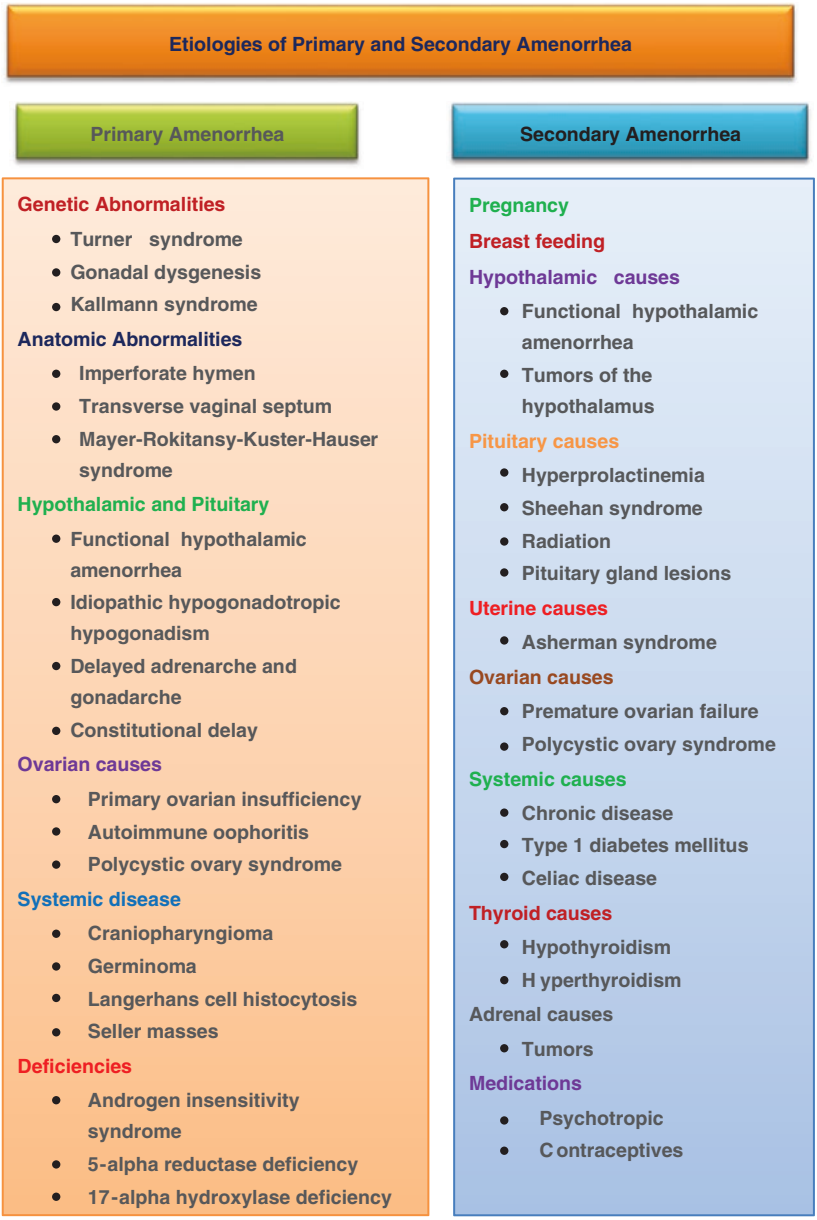
- Polycystic ovary syndrome
  - Polycystic ovary syndrome is characterized by:

    Secondary or primary amenorrhea
    Obesity
    Insulin resistance
    Hyperandrogenism
    Infertility

  - This usually presents as secondary amenorrhea, but in some cases may present as primary amenorrhea.
  - A critical body fat level must be present for the reproductive system to function normally.
  - In some female athletes, the synergistic effects of excessive exercise and disordered eating cause severe suppression of GnRH, leading to low estradiol levels.
  - Anorexia nervosa is a serious psychiatric disease with severe medical complications including primary amenorrhea, osteopenia, and osteoporosis.
  - Functional causes of amenorrhea include severe chronic disease, rapid weight loss, malnutrition, depression or other psychiatric disorders, recreational drug abuse, and psychotropic drug use.
  - Hypothyroidism, hyperthyroidism, sarcoidosis, galactosemia or any severe chronic medical condition may result in amenorrhea.
  - Evidence suggests a negative correlation between body fat levels and menstrual abnormalities.

16.11 Laboratory Investigation

- Measurement of serum levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH).
- When FSH and/or LH are elevated, then the cause of amenorrhea is most likely related to primary gonads' disease.



- Low or normal FSH and LH levels indicate delayed puberty, pituitary dysfunction, or hypothalamic disorders.
- Abdominal and pelvic ultrasound
  - This is to assess the ovaries and the uterus.
  - Karyotype should be done in the presence of abnormal ovaries such as streak ovaries.
  - The most common chromosomal disorders that can cause primary amenorrhea include:

    Turner Syndrome
    Androgen insensitivity syndrome
    Gonadal dysgenesis

- Pregnancy test:
  - An adolescent patient with secondary amenorrhea should have a pregnancy test to exclude pregnancy, the most common cause of secondary amenorrhea.
- The presence of acne, hirsutism, deepening of voice and clitoromegaly is suggestive of hyperandrogenism, another common cause of secondary amenorrhea.
- Patients with secondary amenorrhea should have:
  - FSH
  - LH
  - Testosterone
  - Dehydroepiandrosterone sulfate
- Moderate elevation of testosterone and an LH/FSH ratio that is above two suggests polycystic ovary syndrome.
- Dehydroepiandrosterone sulfate levels between 5 and 700 mg/dl suggests possible adrenal gland disorder and this will require further diagnostic evaluation.
- When the levels of dehydroepiandrosterone sulfate are above 700 mg/dl, the diagnosis of late-onset type congenital adrenal hyperplasia becomes very likely.
- Patients with secondary amenorrhea and no signs of hyperandrogenism should get their FSH, LH and thyroid stimulating hormone levels evaluated.
- Hyperprolactinemia due to a pituitary adenoma can also cause secondary amenorrhea in an adolescent.
- The diagnosis of PCOS is made if a female meets any of the two diagnostic criteria (clinical or biochemical) evidence of :
  - Hyperandrogenism

    Excess androgens is documented by testing total and free testosterone DHEAS, or androstenedione
    Because testosterone has high affinity to sex hormone binding globulin, the latter is found to be low in PCOS cases with elevated free testosterone levels.
    The anti-mullerian hormone (AMH) correlates with ovarian reserve and is found to be increased in females with PCOS.

  - Anovulation or oligomenorrhea
  - Ultrasound findings of polycystic ovarian appearance

- The typical presentation is presence of menstrual irregularities which can be amenorrhea or oligomenorrhea usually associated with worsening acne and hirsutism.
- In adolescents, the diagnosis of PCOS should not be taken lightly in the setting of anovulatory cycles typical in the early post-menarchal years and elevated androgen levels common in pubertal development.
- PCOS should however be considered in female adolescents who have attained full height and pubertal potential, but yet to have menarche.
- Hyperinsulinism is manifested with the presence of acanthosis nigricans.
- PCOS is known to be associated with comorbidities including:
  - Obesity
  - Type 2 diabetes mellitus
  - Obstructive sleep apnea
  - Mood disorders
  - Nonalcoholic fatty liver disease
- Amenorrhea and eating disorders
  - Eating disorders can be associated with low body weight, excessive exercise, stress, and caloric restrictions which can result in a negative energy balance that can predispose a woman to amenorrhea.
  - Menstrual disorders have been associated with early onset eating disorders in adolescents.
  - Amenorrhea is associated with eating disorders in 68% of cases.
  - Approximately one-third of adolescents with eating disorders suffered from menstrual disorders.
  - The exact pathogenesis of amenorrhea in these patients is not known but changes in the hypothalamic-pituitary axis (HPA) may be the underlying explanation.
  - Caloric restriction can cause suppression in the HPA resulting in changes in GnRH release, which reverts LH pulsatile release to pre-pubertal forms, culminating in cessation of pituitary production of LH and FSH. The lack of pulsatile secretions of LH and FSH leads to low levels of estrogen, and therefore ovulation does not occur.
  - Increased insulin levels can result in increases in testosterone thus leading to menstrual dysfunction via disruption of follicular maturation and ovulation.
  - Bulimia has also been associated with polycystic ovarian syndrome (PCOS) which also has menstrual dysfunction as a result of insulin resistance-mediated increases in testosterone.
  - Up to 25% of patients with anorexia nervosa experience amenorrhea before significant weight loss occur and resumption of menses does not occur immediately with appropriate weight gain.

  - While nutritional rehabilitation and weight restoration help solve amenorrhea, they do not ensure resumption of menses.
  - It is interesting to note that low weight as well as obesity can cause reproductive dysfunction due to hormonal changes.

16.12 Amenorrhea in Female Athletes

- The female athlete triad (FAT) is a medical condition seen in girls and women involved in physical activities.
- This is known to be associated with three interconnected dysfunctions:
  - Menstrual irregularities
  - Reduced bone mineral density
  - Decreased energy availability
- An athletic female may present with one or more of the components in the triad.
- Menstrual dysfunction results from lack of energy availability.
- The risk of developing menstrual irregularities and the FAT is increased in sports including skating, gymnastics, ballet, and long-distance running.
- Functional hypothalamic amenorrhea in the female adolescent athlete can arise due to a variety of factors, including:
  - Decreased nutritional intake
  - Decreased body weight and low relative body fat
  - Intensity of sports training
  - Stress
- The ultimate effect is diminishing the GnRH pulsatility, causing a decreased secretion of LH and FSH, which then disrupts ovarian hormonal production and leads to a decrease in estrogen and progesterone.
- Two other hormones that play a role in leading to the loss of GnRH pulsatility necessary for the maintenance of menstruation include leptin and ghrelin.
  - Leptin, a hormone released by adipose tissue, is critical in maintaining pubertal development, acting as an influencer of overall energy maintenance and a maintenance factor of the GnRH pulsatile release.
  - Leptin has been shown to be decreased in those with low body fat and hypothalamic amenorrhea.
  - Ghrelin is an orexigenic peptide hormone which plays an important role in energy balance.
  - Ghrelin has been shown to be elevated in those with functional amenorrhea seen in athletes.
- Adolescence is a crucial time in terms of bone growth and development of bone mass; however, with disruptions in the hypothalamic system comes disruptions

in bone mineral density, leading to increased incidences of stress fractures and scoliosis in adolescent athletes with amenorrhea or delayed puberty.
- Adolescents suffering from amenorrhea and the FAT are at increased risk of subsequent cardiac dysfunction including an increased risk for atherosclerosis with higher amounts of cholesterol and LDL.
- These adolescents are at an increase in musculoskeletal dysfunction with a lack of complete regeneration of the bone mineral density lost.
- Add to this the risk of psychological morbidities such as depression, anxiety, and detrimental changes in self-esteem.

16.13 Management

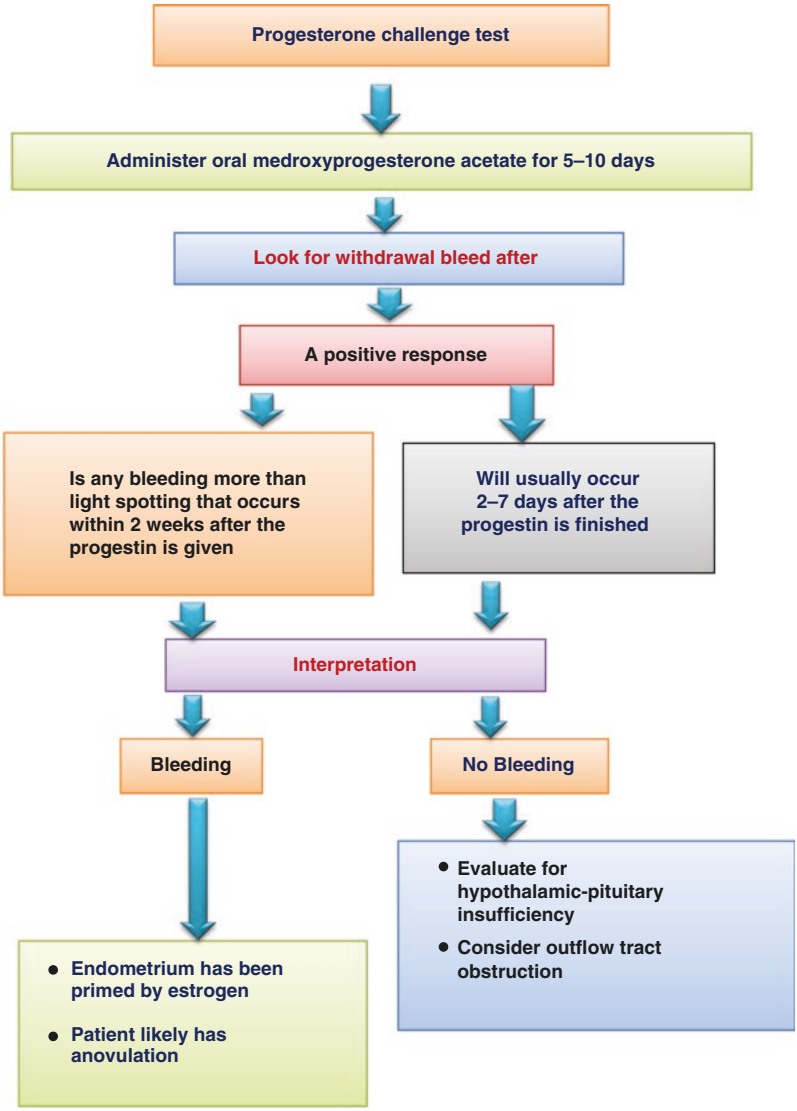
- A thorough systematic evaluation is important to diagnose and treat adolescents with amenorrhea.
- This includes a detailed medical history, a thorough physical examination, and laboratory assessment of selected serum hormone levels.
- Medical History:
  - History of childhood growth and development
  - Age at thelarche and menarche
  - Family history to determine age at menarche of the mother and female siblings.
  - Duration and flow of menses
  - Duration of cycle days
  - Date of last menstrual period
  - History of a chronic illness such as HIV, sickle cell disease, thalasaemia, diabetes mellitus, epilepsy, chronic kidney disease and malignancy.
  - History of trauma, surgery and psychosocial issues
  - Psychiatric illness, medications, physical activity and sports, and sexual behavior.
- Physical Examination:
  - Assess degree of sexual development, nutritional status and evidence for chronic disease, cachexia or obesity.
  - Look for sweaty palms, tachycardia, hypertension, and nervousness, warm and moist skin, which are suggestive of hyperthyroidism.
  - Look for short stature, webbed neck, low-set hairline and/or ears, pubertal delay, cubitus valgus, nail hypoplasia, short fourth metacarpal, high-arched palate, chronic otitis media and cardiac abnormalities, which are seen in Turner syndrome.
  - Look for hirsutism, hair loss, and acne which are evidence of androgen excess.
  - Look for thin, parchment-like skin, wide purplish striae, and evidence of easy bruising as seen in Cushing's syndrome.

- Look for presence of axillary and pubic hair which are evidence of adrenal and ovarian androgen secretion.
- Adolescents who have a combination of autoimmune premature ovarian failure and autoimmune primary adrenal insufficiency are also markedly androgen deficient and have scant axillary and pubic hair.
- Assess for the state of breast development.
- Underdeveloped breasts with sparse pubic hair are seen in cases of delayed puberty while undeveloped breasts with normal growth of pubic hair are seen in cases of gonadal dysgenesis (e.g. Turner syndrome).
- Also examine the breast for the presence of galactorrhea.
- A thorough examination of the external genitalia or pelvic examination is required as this may detect ambiguous genitalia, absence or abnormalities of cervix or uterus, presence of transverse vaginal septum, imperforate hymen, reddened or thin vaginal mucosa.
- Observe and measure the size and length of the clitoris. A clitoral index greater than 100 mm is evidence of virilization. The size of the glans clitoris can be quantitated by determining the clitoris index, which is the product of the sagittal and transverse diameters of the glans. The clitoral index is a useful bioassay for the clinical recognition of excess androgenic stimulation.
- During pelvic examination, ovarian enlargement may be found especially in cases of autoimmune oophoritis or 17-hydroxylase deficiency.
- Ovarian enlargement is also commonly associated with polycystic ovary syndrome.

- Laboratory Investigations:
  - These investigations are ordered depending on the findings from history and clinical examination.
  - The goal is to confirm a suspected diagnosis.
  - The basic investigations to confirm diagnosis in adolescent with amenorrhea include:

    Pregnancy test
    Complete blood count
    Erythrocyte Sedimentation rate (ESR)
    Thyroid function tests
    Prolactin
    Determination of serum gonadotropins (serum FSH and LH determination)
    Progesterone challenge test
    Karyotype testing
    Bone age film
    Free and total testosterone
    Dehydroepiandrosterone sulphate (DHEA-S)
    Fasting glucose and insulin
    Pelvic/abdominal ultrasound with or without CT Scan or MRI
    Magnetic resonance imaging (MRI) of head or Sella

- Treatment:
  - Amenorrhoea is treatable and this depends on the etiology.
  - The treatment should be directed at correcting the underlying pathology.
  - Physicians caring for these patients should be guided towards making diagnosis of the cause of amenorrhoea by identifying from the history the type of amenorrhoea, together with presence or absence of secondary sexual characteristic.
  - The most common causes of adolescent amenorrhoea are hypothalamic amenorrhea, polycystic ovarian disease, hyperprolactinemia, and ovarian failure.



- Treatment should be focused at restoration of ovulatory cycle and prevention of short and long-term consequences of estrogen deficiency.
- Surgery is indicated in those with outflow genital tract abnormalities.
- Polycystic Ovary Syndrome

  In polycystic ovary syndrome, the mainstay of treatment is oral contraceptives.
  These are effective in regulating menstrual cycles and lowering androgen levels.
  Weight reduction by healthy diet and exercise with or without pharmacologic intervention, such as metformin.

- Eating disorders

  Many young females with eating disorders may present to the obstetrician first due to menstrual abnormality.
  The treatment of this group of patients necessitates a team approach and it is not recommended to just treat the menstrual problem.
  According to the American Psychiatric Association, the goals of nutritional rehabilitation for seriously underweight patients are to restore weight, normalize eating patterns, achieve normal perceptions of hunger and satiety, and correct biological and psychological sequelae of malnutrition.
  Weight restoration is the mainstay of treatment. This eventually leads to restoration of periods.
  Calcium and vitamin D supplementation should be given.
  There is no well-established role of hormonal treatment in eating disorders patients who present with amenorrhea.
  There is no consensus about the precise target weight to be reached in adolescents with eating disorders.

- Athletic females:

  A multidisciplinary team approach is the mainstay of management of these patients.
  An increase in fat and protein nutrition.
  A relative decrease in exercise to restore energy balance and maintain good energy availability for the adolescent.
  Calcium and vitamin D supplements
  Oral contraception including the use of estrogen and cyclic progesterone (avoiding progesterone-only medications for possibility of increased bone loss) may return adolescents to a normal state of menstruation.

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Chapter 17
Ovarian Cysts and Tumors

Ahmed H. Al-Salem, Munther J. Haddad, and Moustafa Hamchou

17.1 Introduction

- Ovarian tumors are relatively rare, but they are the most common genital neoplasms occurring in childhood.
- Ovarian tumors occur in children and young girls and can be:
  - Symptomatic commonly presenting with abdominal pain
  - Asymptomatic presenting as an abdominal mass
  - Discovered incidentally during imaging studies for other reasons
- The size of an ovarian tumor is not indicative of its malignant potential.
- The probable pathological diagnosis of ovarian tumors varies according to the age of the patient.
- Ovarian tumors may represent:
  - Physiologic cysts (Functional) (24%)
  - Benign neoplasms (70%)
  - Malignant neoplasms (6%)
- A solid ovarian mass in childhood is always considered malignant until proven otherwise by histological examination.

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- In the past, all ovarian masses discovered in infants, children, and adolescents were removed surgically.
- Currently, every attempt should be made to preserve the ovary (ovarian preservation) except in cases of ovarian cancer.
- Simple ovarian cysts less than 2 cm in diameter are considered physiological cysts.
- Follicular ovarian cysts in fetuses are relatively common and based on the ultrasonographic size and appearance they are classified into two types:
  - Physiological cysts
  - Pathological cysts
- Spontaneous regression of simple ovarian cysts often occurs either antenatally or by 6 months of age and so the management of these cysts is usually expectant.
- The management of patients with simple ovarian cysts consists of:
  - Serial ultrasound examinations at birth and every 4–6 weeks.
  - This should be continued:

    Until the cyst resolves
    Or if the cyst enlarges
    Or if the cyst persists for 4–6 months
    Or if the cyst becomes symptomatic

  - Intervention is recommended as follows:

    Aspiration of simple cysts ≥4–5 cm
    Surgical intervention for:

    - Complex cysts
    - Cysts that are increasing in size
    - Symptomatic cysts
    - Cysts persisting for more than 4–6 months

OVARIAN TUMORS

- PHYSIOLOGICAL CYSTS (FUNCTIONAL) 24%
- BENIGN NEOPLASMS (70%)
- MALIGNANT NEOPLASM (6%)

- Ovarian cysts in infants and children often:
  - Present as an asymptomatic abdominal mass or cause:

    Increasing abdominal girth
    Abdominal pain
    Abdominal fullness or distension
    Urinary frequency or retention

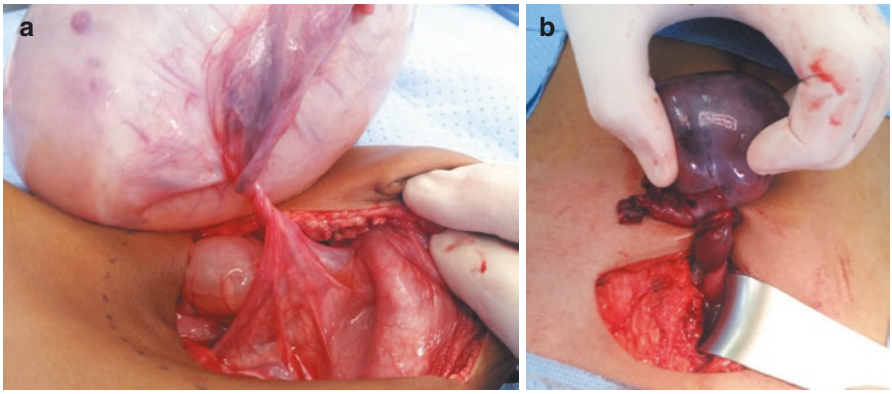


Fig. 17.1 (**a**, **b**) Intraoperative photographs showing torsion of ovarian tumors. Note the gangrenous ovarian tumor in the second photograph

- In adolescents between menarche and 18 years of age, both simple and complex ovarian cysts are common.
- The cysts may be asymptomatic or cause:
  - Menstrual irregularities
  - Abdominal and pelvic pain
  - Urinary frequency
  - Constipation
- Ovarian torsion is a serious and potential complication of ovarian tumors (Fig. 17.1a, b).
- It is important for the clinician to establish an early diagnosis to reduce the risk of ovarian torsion with possible loss of adnexa and to improve the prognosis for those lesions that are malignant.
- Fortunately, the vast majority of ovarian cysts are benign.
- Most ovarian cysts, however, occur during infancy and adolescence.
- Simple ovarian cysts usually do not require treatment and they disappear spontaneously.
- Ovarian cysts larger than 4 cm in diameter have been shown to have a torsion rate of approximately 15%.
- Classically, ovarian torsion occurs unilaterally and approximately 60% of cases of torsion occur on the right side.
- Ovarian torsion is more common on the right side owing to the sigmoid colon restricting the mobility of the left ovary.
- Malignancy may be seen in up to 2% of cases of ovarian torsion.
- The most common ovarian mass associated with torsion is a dermoid cyst.
- Treatment options of ovarian cysts that have undergone torsion include:
  - Laparoscopic detorsion and adnexal preservation
  - Laparotomy and detorsion
  - Salpingo-oophorectomy if the ovary is non-viable

- Most childhood ovarian masses are benign.
- The World Health Organization classifies ovarian neoplasms based upon histologic cell type and benign versus malignant.
- The majority of ovarian tumors in girls and adolescents are of germ cell origin.
- By comparison, epithelial tumors account for the largest proportion of ovarian neoplasms in adults.
- The incidence of clinically significant ovarian cysts is about 1 in 2500.
- Follicular ovarian cysts in fetuses and neonates are common and increase in frequency with:
  - Advancing gestational age
  - Maternal complications, such as:

    Diabetes mellitus
    Preeclampsia
    Rhesus isoimmunization

- The diagnosis of ovarian cysts has increased as a result of the widespread regular physical examinations and ultrasound evaluation.
- Benign epithelial neoplastic cysts (60% of benign ovarian tumors)
  - Serous cystadenoma:

    These develop papillary growths which rapidly proliferate to the extent that the cyst appears solid.
    They are most common in women aged between 40 and 50 years.
    About 15–25% are bilateral.
    About 20–25% are malignant.

  - Mucinous cystadenoma:

    These are the most common large ovarian tumors
    Their size may become enormous
    They may be multilocular
    They are filled with mucinous material
    Their rupture may cause pseudomyxoma peritonei
    They are most common in the 20–40 age groups.
    About 5–10% are bilateral.
    About 5% will be malignant.

- Benign neoplastic cystic tumors of germ cell origin
  - Benign cystic teratoma

    They arise from primitive germ cells
    A benign mature teratoma (dermoid cyst) may contain well-differentiated tissue (hair, and teeth).
    They are rarely malignant (Poorly differentiated, malignant teratomas)

About 20% are bilateral
They are most common in young women

- Benign neoplastic solid tumors
  - Fibroma

    These are usually small, solid benign tumors
    Less than 1% are malignant
    They are associated with Meigs' syndrome and ascites

  - Thecoma

    Less than 1% are malignant

  - Adenofibroma
  - Brenner's tumor:

    These are rare ovarian tumors
    They can be benign, borderline or proliferative, and malignant
    Over 95% are benign
    More than 90% are unilateral
    They may be associated with mucinous cystadenoma and cystic teratoma

- Benign ovarian tumors occur in 30% of females with regular menses and 50% of females with irregular menses.
- They occur predominantly in premenopausal women
- They may also occur perinatally.
- Benign ovarian tumors are uncommon in premenarchal and postmenopausal women.
- The likelihood of malignancy in women of childbearing age is low and a large proportion of cysts are of functional origin, tending to resolve over time.
- Benign neoplastic cystic tumors of germ cell origin are most common in young women.
- They account for 15–20% of all ovarian neoplasms.
- Risk factors for ovarian tumors include:
  - Obesity
  - Tamoxifen therapy has been associated with an increased risk for persistent ovarian cysts.
  - Early menarche
  - Infertility
  - Genetic as dermoid cysts have been shown to run in families
- Ovarian malignancies in children are rare.
- They represent only 0.2% of all ovarian neoplasms.

- Tumors of germ cell origin constitute approximately 70% of ovarian tumors in children and include:
  - Mature teratoma
  - Malignant teratoma
  - Endodermal sinus tumor (yolk sac tumor)
  - Embryonal carcinoma
  - Dysgerminoma
  - Primary choriocarcinoma
- All these tumors with the exception of the mature teratoma are malignant.
- The dysgerminoma in its pure form is considered a low-grade malignancy.
- Surface epithelial stromal tumors (common epithelial tumors) are rare in children and represent the same morbidity and mortality in children as in adults.
- Granulosa-stromal cell tumors are the most common of the sex-cord stromal cell tumors, vary greatly in their clinical course, and are rare in children.

17.2 Incidence

- Ovarian tumors are rare in children with a reported incidence about 1.7:100,000 per year.
- Germ cell tumors account for approximately 70% of ovarian neoplasms in children and adolescents.
- 17% of ovarian tumors are seen in children between birth and 4 years of age.
- In infants, germ cell tumors constitute 5% of ovarian tumors.
- In infants, sex-cord stromal tumors constitute 10% of ovarian tumors.
- In the 10–14-year-old group, sex-cord stromal tumors constitute 5–10% and surface epithelial-stromal tumors constitute approximately 12–25% of ovarian tumors.
- Approximately, 20–30% of ovarian tumors are malignant and 70–80% are benign.

17.3 Classification

- The majority of ovarian tumors in girls and adolescents are of germ cell origin.
- By comparison, epithelial tumors account for the largest proportion of ovarian neoplasms in adults.
- Most childhood ovarian tumors are benign.

- It is important to establish an early diagnosis to reduce the risk of ovarian torsion with possible loss of adnexa and to improve the prognosis for those lesions that are malignant.

Ovarian tumors are also classified based on their sonographic appearance as follows:

- Cystic tumors:
  - Simple cysts:
  - Follicular cyst
  - Serous cystadenoma
- Complex tumors:
  - Follicular cyst
  - Corpus luteum cyst
  - Serous cystadenoma
  - Brenner's tumor
  - Mature teratoma
  - Immature teratoma
- Solid tumors:
  - Immature teratoma
  - Granulosa cell tumor
  - Endodermal cell tumor
  - Dysgerminoma
  - Embryonal carcinoma

- The World Health Organization Histological Classification for ovarian tumors separates ovarian neoplasms according to the most probable tissue of origin:
  - Surface epithelial tumors (65%)
  - Germ cell tumors (15%)
  - Sex cord-stromal tumors (10%)
  - Metastases (5%)
  - Miscellaneous

Ovarian cysts are classified according to the age at diagnosis as follows:

- Ovarian tumors in the fetus
- Ovarian tumors in the neonates
- Ovarian tumors in infants and prepubertal girls
- Ovarian cysts in adolescents

Classification of Ovarian tumors

- **Non neoplastic tumors:**
  - **Simple cyst**
  - **Follicular cyst**
  - **Corpus luteum cyst**
- **Neoplastic tumors:**
  - **Epithelial tumors:**
    - **Serous cystadenoma**
    - **Brenner's tumor**
  - **Sex cord-stromal tumors:**
    - **Granulosa cell tmor**
  - **Germ cell tumors:**
    - **Teratoma:**
      - **mature**
      - **immature**
    - **Dysgerminoma**
    - **Endodermal sinus tumor**
    - **Embryonal carcinoma**

- Most malignant tumors are surface epithelial tumors (90%).
- It has been estimated that gynecologic malignant conditions account for approximately 2% of all types of cancer in children and 60–70% of these lesions arise in the ovary.
- Ovarian cysts are classified according to the age at diagnosis.

17.4 Ovarian Cysts in the Fetus

- Follicular ovarian cysts are common in fetuses and neonates.
- They increase in frequency with:

  - Advancing gestational age
  - Maternal complications such as:

    Diabetes mellitus
    Preeclampsia
    Rhesus isoimmunization

- The estimated incidence of clinically significant ovarian cysts is about 1 in 2500 live female newborns.
- Etiology of fetal cysts:
  - In the fetal and neonatal period, the fetal ovaries are exposed to excessive stimulation by human chorionic gonadotropin.
  - Other maternal hormone levels are also high, which can lead to disordered folliculogenesis in the fetal ovaries.
  - In addition, the fetal pituitary gland is also producing follicle-stimulating hormone (FSH), which increases the size and number of fetal ovarian follicles.
- Often diagnosed in the third trimester during routine ultrasound surveillance.
- These lesions are typically cystic (99%) and can be either simple or complex.
- The contralateral ovary also may be cystic. The contralateral ovary must be evaluated both preoperatively and intraoperatively.
- Of all fetal cysts, 97% are functional, and the average size is approximately 3.4 cm.
- Half of these cysts spontaneously resolve, and of the remainder, 25–40% undergoes torsion.

17.5 Diagnosis

- The diagnosis is made by antenatal ultrasound and it is based upon the presence of four criteria:
  - Female sex
  - A non-midline regular cystic structure
  - Normal-appearing urinary tract
  - Normal-appearing gastrointestinal tract

Surface epithelial-stromal tumors

- Serous tumors:
  - Benign (cystadenoma)
  - Borderline tumors (serous borderline tumor)
  - Malignant (serous adenocarcinoma)
- Mucinous tumors,endocervical-like and intestinal type:
  - Benign (cystadenoma)
  - Borderline tumors (mucinous borderline tumor)
  - Malignant (mucinous adenocarcinoma)
- Endometrioid tumors:
  - Benign (cystadenoma)
  - Borderline tumors (endometrioid borderline tumor)
  - Malignant (endometrioid adenocarcinoma)
- Clear cell tumors:
  - Benign
  - Borderline tumors
  - Malignant (clear cell adenocarcinoma)
- Transitional cell tumors:
  - Brenner tumor
  - Brenner tumor of borderline malignancy
  - Malignant Brenner tumor
  - Transitional cell carcinoma (non-Brenner type)
- Epithelial-stromal:
  - Adenosarcoma
  - Carcinosarcoma (formerly mixed Muellerian tumors)
- Monodermal (e.g., struma ovarii, carcinoid)
- Dysgerminoma
- Yolk sac tumor (endodermal sinus tumor)
- Mixed germ cell tumors

(A) Sex cord-stromal tumors

- Granulosa tumors:
  - Fibromas
  - Fibrothecomas
  - Thecomas
- Sertoli cell tumors
- Leydig cell tumors
- Sex cord tumor with annular tubules
- Gynandroblastoma
- Steroid (lipid) cell tumors

(B) Germ cell tumors

- Teratoma:
  - Immature
  - Mature
  - Solid
  - Cystic (dermoid cyst)
- Monodermal (e.g., struma ovarii, carcinoid)
- Dysgerminoma
- Yolk sac tumor (endodermal sinus tumor)
- Mixed germ cell tumors

(D) Malignant, not otherwise specified

- Metastatic cancer from nonovarian primary:
  a. Colonic, appendiceal
  b. Gastric
  c. Breast

- The size and ultrasound appearance are used to characterize these cysts as:
  - Physiological cysts
  - Pathological cyst
- Simple cysts less than 2 cm in diameter are considered physiological.
- Larger and complex cysts are more likely to be non-physiological.
- Associated anomalies are rare since the cysts usually result from hormonal stimulation.
- The etiology of these cysts is unclear, but they most likely arise from ovarian stimulation by maternal and fetal gonadotropin.
- The majority of fetal ovarian cysts are unilateral, although both ovaries may be involved.

17.6 Management and Outcome

- Spontaneous regression of both simple and complex cysts often occurs either antenatally or postpartum by 6 months of age (Fig. 17.2a–c).
  - 50% resolve by 1 month of age
  - 75% resolve by 2 months
  - 90% resolve by 3 months

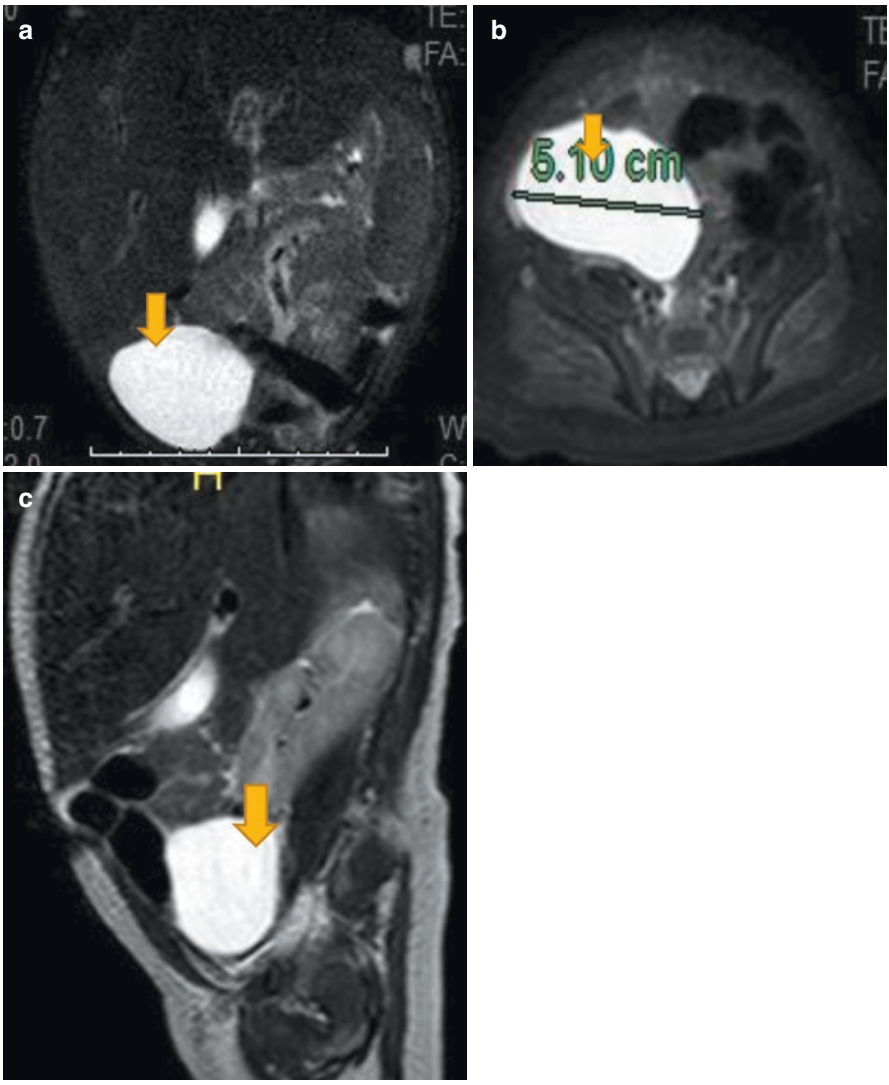


Fig. 17.2 (**a–c**) Abdominal CT-scan showing a right ovarian cyst in a newborn. This was diagnosed intra-uterine and followed up. Subsequently, the cyst disappeared completely

- The rate of malignancy is so low that it need not be considered in making therapeutic decisions.
- Complications that can occur include:
  - Intra-cystic hemorrhage
  - Rupture with possible intraabdominal hemorrhage
  - Gastrointestinal or urinary tract obstruction
  - Ovarian torsion and necrosis
  - Respiratory distress at birth from a mass effect on the diaphragm.
  - If in-utero torsion occurs, the ovary may undergo necrosis and develop into a calcified mass, a sessile mass, or disappear entirely.
- Prenatally detected ovarian cysts should be closely monitored, particularly if the cyst appears complex on postnatal sonography, due to the increased risk of torsion and subsequent ovarian loss.
- Antenatal aspiration of large cysts (greater than 4–6 cm) under ultrasound guidance has been advocated to reduce the risk of complications.
- Advantages of aspiration include:
  - Elimination of the cyst and the risk of cyst-related complications.
  - Eliminating the need for neonatal surgery.
- Disadvantages of aspiration include:
  - Risk of spillage
  - Complex cysts cannot be aspirated

17.7 Ovarian Cysts in Neonates

- A pelvic mass in a newborn is most likely a physiologic ovarian cyst resulting from maternal hormonal stimulation in-utero.
- This can be confirmed by ultrasound examination which may show:
  - A simple (clear, fluid-filled) cyst (Figs. 17.3, 17.4, and 17.5a, b)
  - A complex (fluid, debris, septa, solid components, echogenic wall) cyst.
- Torsion can occur with a cyst of any size, particularly when long pedicles are present ad when this happens, every attempt should always be made to salvage the ovary by:
  - Untwisting the vascular pedicle.
  - A bivalve technique (opening of the ovarian cortex with a linear incision).
  - This technique decreases the intraovarian pressure caused by venous occlusion and permits arterial flow into the ovary.
  - In rare instances, oophorectomy is necessary when there is severe necrosis, or nonviable appearance.

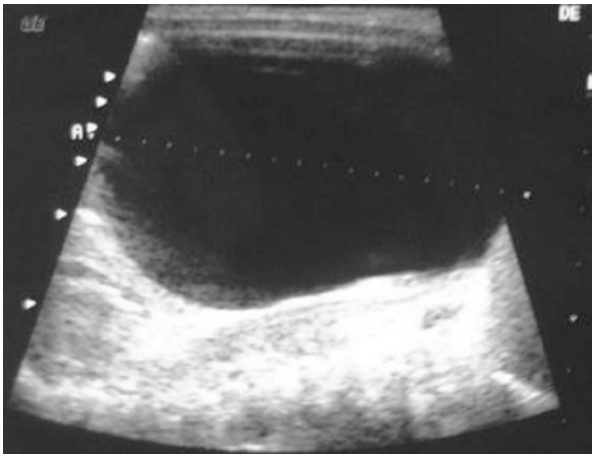


Fig. 17.3 An abdominal ultrasound showing a large ovarian cyst in a neonate

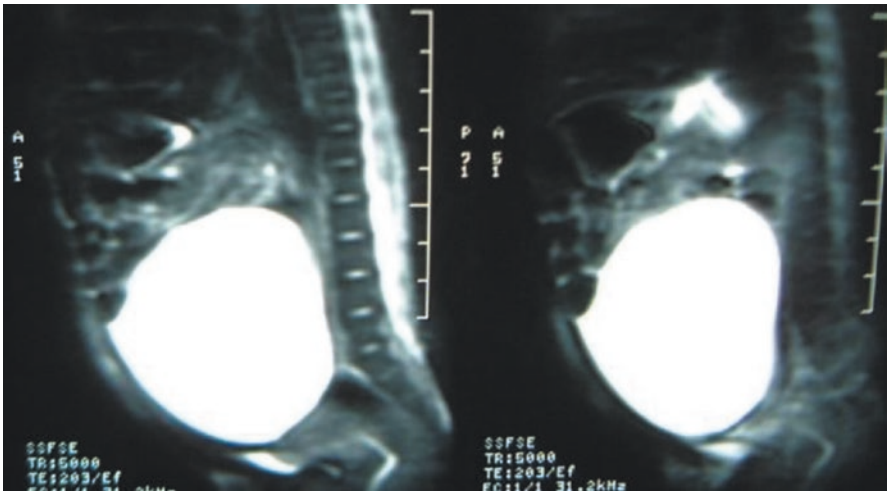


Fig. 17.4 Abdominal and pelvic CT-scan showing a very large ovarian cyst in a neonate

17.8 Management

- The management is conservative.
- Spontaneous regression usually occurs by 4–6 months of age.
  - Approximately 50% resolve in the first 3 months of life.
  - 30–40% undergo torsion or another complication.
- The management of neonatal cysts consists of:
  - Serial ultrasound examinations:

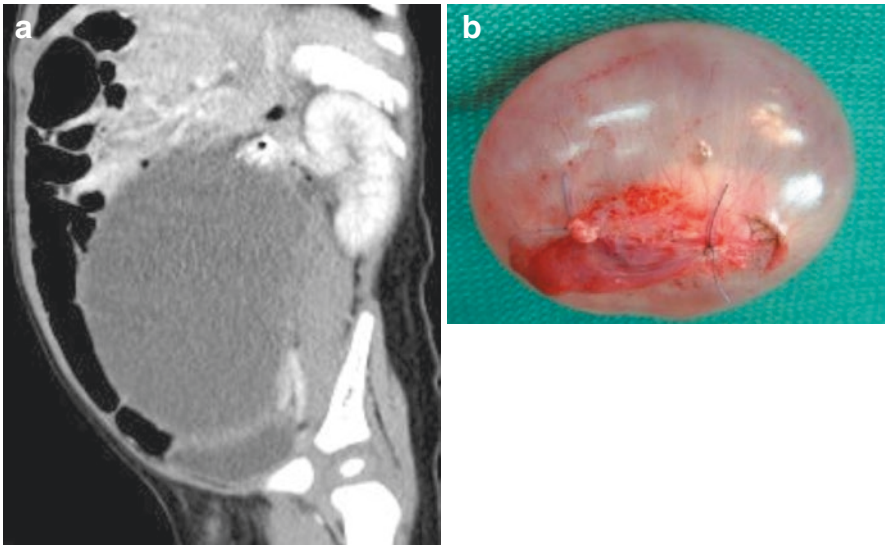


Fig. 17.5 (**a**, **b**) Abdominal CT-scan and a clinical photograph showing large ovarian cyst that was completely excised

These should be done at birth and every 4–6 weeks thereafter until the cyst resolves, enlarges, has persisted for 4–6 months, or becomes symptomatic.

- Aspiration of simple cysts if they are ≥4–5 cm. This should be done following a period of observation as there is still a possibility of spontaneous regression.
- Surgical intervention is indicated for (Fig. 17.5a, b):

  Complex cysts
  Cysts that are increasing in size
  Symptomatic cysts
  Cysts that persists for more than 4–6 months

- Laparoscopic surgery is feasible and safe in neonates with ovarian cysts.

17.9 Ovarian Cysts in Infants and Prepubertal Girls

- Physiologic cysts are uncommon between the neonatal period and puberty because gonadotropin stimulation of the ovary decreases in infancy and early childhood and then increases as puberty is approached.
- Most simple ovarian cysts in children are physiologic and result from enlargement of a cystic follicle.
- Some ovarian cysts are hormonally active and result in precocious pseudopuberty with premature vaginal bleeding (McCune-Albright syndrome).

- In girls with hormonally active cysts, the ovarian enlargement may be mistaken for an ovarian tumor, leading to unnecessary oophorectomy.
- Other ovarian cysts occur in response to gonadotropin stimulation in patients with idiopathic central precocious puberty; these should resolve after administration of gonadotropin-releasing hormone analog therapy.
- Clinical manifestations:
  - An ovarian cyst in a young girl is often asymptomatic discovered incidentally.
  - May present as an abdominal mass or abdominal distension (Fig. 17.6).
  - Chronic abdominal pain, either periumbilical or localized to a lower abdominal quadrant.
  - Urinary frequency or retention.
  - Acute severe pain simulating appendicitis or peritonitis may result from torsion, perforation, infarction, or hemorrhage.
  - Intermittent abdominal pain, presumably because of partial or intermittent torsion, which may resolve without therapy or act as a warning sign of impending torsion requiring emergency surgery.
  - Torsion also causes nausea, vomiting, pallor, and leukocytosis.

17.10 Investigations

- Abdominal and pelvic ultrasonography is the main investigation (Fig. 17.7a, b). This is important to evaluate the size, site and nature of the cyst.
- Abdominal CT-scan and MRI (Fig. 17.8a, b).
- Children with recurrent, large, or multicystic ovarian masses and signs of early sexual development should be evaluated for precocious puberty.

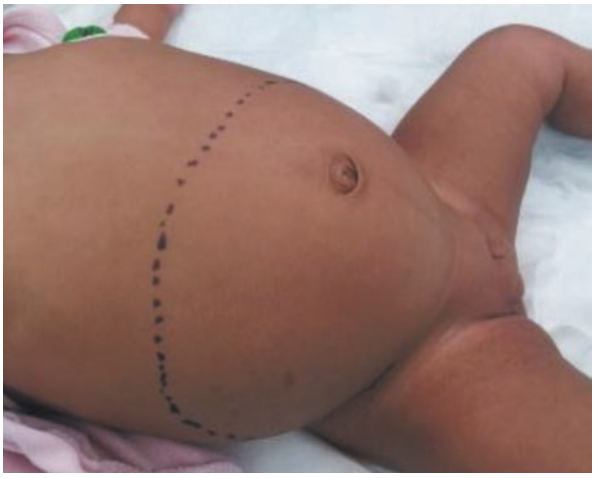


Fig. 17.6 A clinical photograph showing a large abdominal cyst which proved to be an ovarian cyst

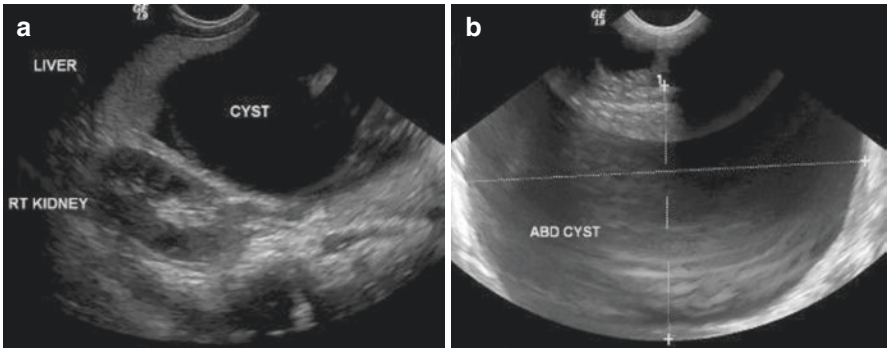


Fig. 17.7 (**a**, **b**) Abdominal and pelvic ultrasound showing a large ovarian cyst

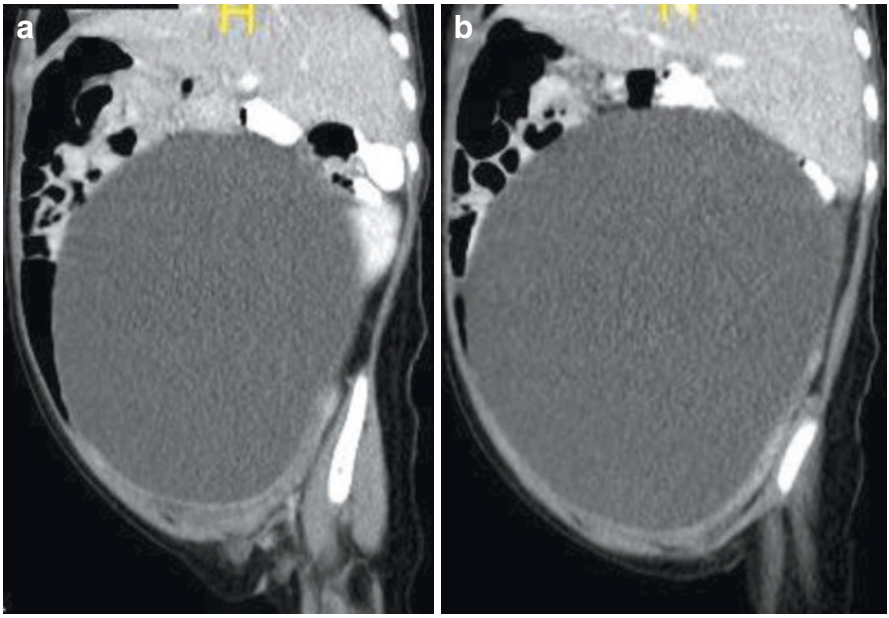


Fig. 17.8 (**a**, **b**) Abdominal CT-scan showing a very large ovarian cyst filling the whole abdomen. Note also the consistency of the cyst

17.11 Management and Outcome (Fig. 17.9a–c):

- The management of an ovarian cyst in the prepubertal age group depends upon the appearance of the cyst on ultrasonography and the clinical manifestations.
- An ovarian mass that is purely cystic is almost certainly benign and can be managed conservatively.

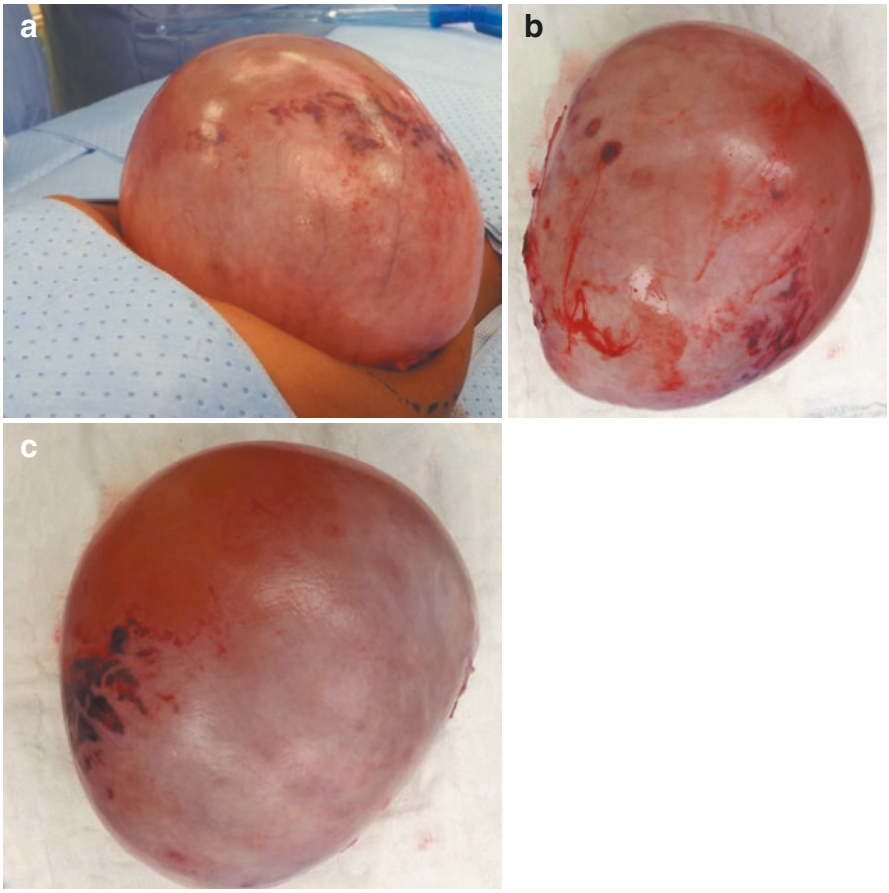


Fig. 17.9 (**a**–**c**) Clinical intraoperative photographs showing a very large ovarian cyst that was completely excised

- A follow-up ultrasound examination in 4–8 weeks should be performed.
  - If the cyst has not resolved and the ultrasonic characteristics are still the same and it is asymptomatic, conservative management should be continued.
  - If acute rupture with hemorrhage occurs, the child should be stabilized and then treated either through the open technique or laparoscopically.
  - Surgery is indicated if there is ovarian torsion (Figs. 17.10 and 17.11).

17.12 Ovarian Cysts in Adolescents

- Simple and complex ovarian cysts are common in young women between menarche and 18 years of age.

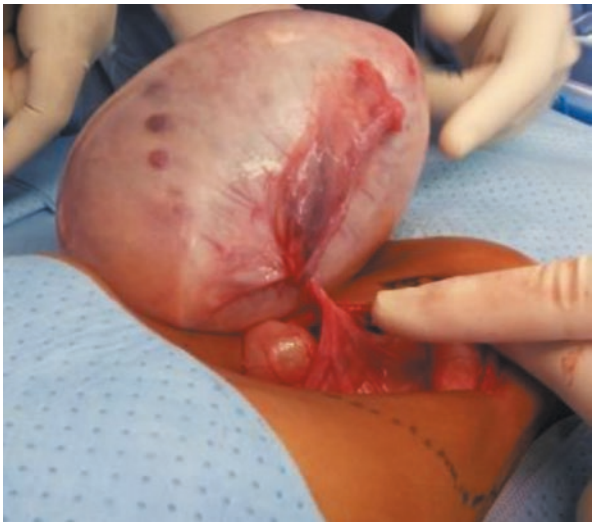


Fig. 17.10 A clinical intra-operative photograph showing a large ovarian cyst that was complicated by torsion

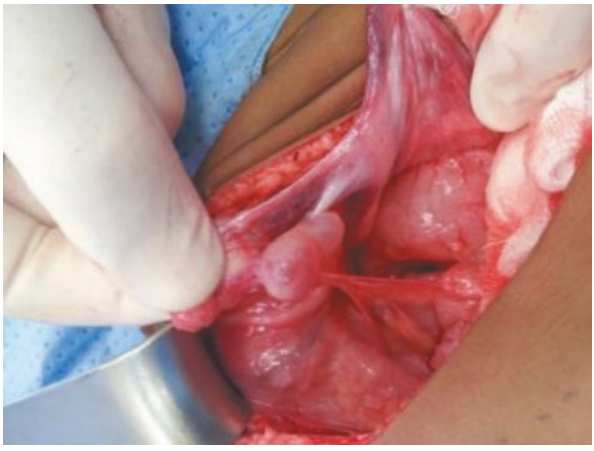


Fig. 17.11 A clinical intra-operative photograph showing inspection of the contralateral ovary in a patient with large ovarian cyst

- Most simple ovarian cysts result from failure of the maturing follicle to ovulate and involute.
- Ovarian cysts in the postmenarcheal adolescent may:
  - Be asymptomatic found incidentally (Fig. 17.12).
  - May cause menstrual irregularities, pelvic pain, urinary frequency or urgency, constipation, or pelvic heaviness.
- Rupture leads to intraabdominal pain and bleeding.
- Torsion also causes acute pain, as well as nausea, vomiting, pallor, and leukocytosis (Fig. 17.13a, b).
- These cysts can be simple or complicated by intracystic hemorrhage, rupture or torsion (Figs. 17.14a–d and 17.15)

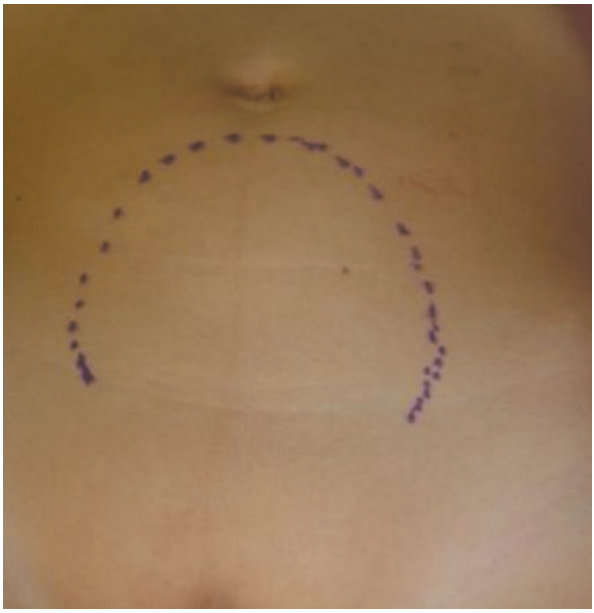


Fig. 17.12 A clinical photograph showing a large ovarian cyst

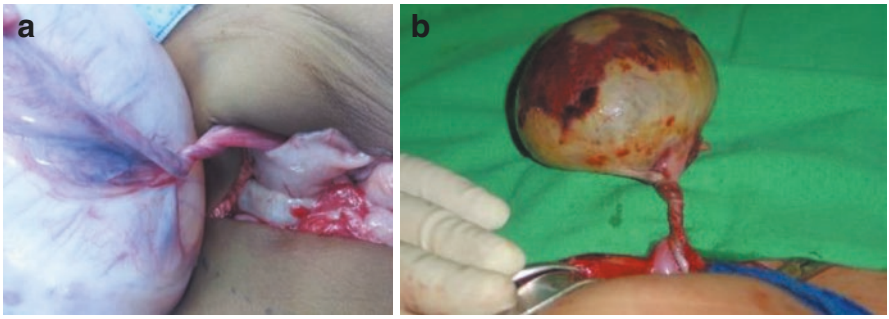


Fig. 17.13 (**a**, **b**) Clinical intra-operative photographs showing torsion of ovarian cysts

17.13 Management and Outcome

Follicular Cysts

- Follicular cysts of the ovary are the most common cystic ovarian lesions.
- These cysts arise from temporary pathologic variations of a normal physiologic process and are not neoplastic.
- The tumors result from either failure of a dominant mature follicle to rupture or failure of an immature follicle to undergo the normal process of atresia.
- Many follicular cysts lose the ability to produce estrogen; in other instances, the granulosa cells remain productive, with prolonged secretion of estrogen.

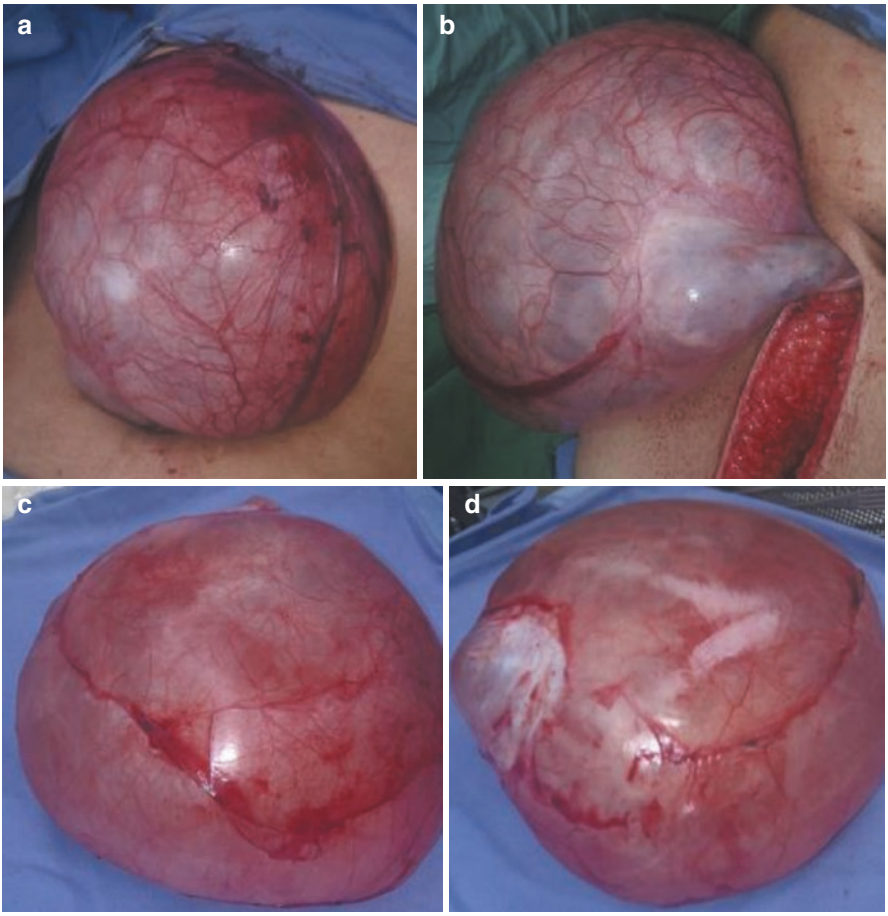


Fig. 17.14 (**a**–**d**) Clinical photographs showing very large ovarian cyst that was completely excised

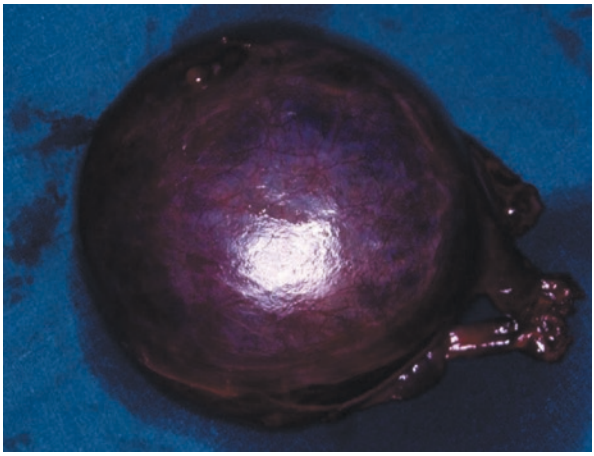


Fig. 17.15 A clinical photograph showing a large ovarian cyst that was complicated by intracystic bleeding

- Solitary follicular cysts are common and occur during all stages of life, from the fetal stage to the postmenopausal period.
- Folliclular cysts are lined with an inner layer of granulosa cells and an outer layer of theca interna cells.
- The cysts are thin-walled and unilocular, usually ranging from several millimeters to 8 cm in diameter (average, 2 cm).
- Usually, cysts with dimensions less than 2.5 cm are classified as follicles and therefore are not of clinical significance.
- Most follicular cysts found on routine examination in adolescents resolve spontaneously in 1–2 months.
- Asymptomatic simple cysts <6 cm on ultrasound examination can be observed with or without administration of oral contraceptive pills.
- Some advocate the administration of oral contraceptives to suppress the ovarian-hypothalamic axis so new cysts will not form. This is controversial and low-dose oral contraceptive pills appear to have minimal effect in preventing development of functional cysts.
- The patient should be evaluated monthly by ultrasound examination.
- Open surgical or laparoscopic ovarian cystectomy is indicated if:
  - The cyst increases in size
  - The cyst is greater than 6 cm
  - The cyst is symptomatic
- It is possible that cysts larger than 6 cm will regress spontaneously, and thus, observation is an alternative.
- If a cystectomy is performed, the cyst wall should be sent for pathologic examination.
- Ovarian cystectomy is preferred to cyst aspiration due to the high rate of recurrence after aspiration.

Corpus Luteum Cysts

- Corpus luteum cysts are less prevalent than follicular cysts.
- They result from the normal formation of a corpus luteum after ovulation or from intracystic hemorrhage and can reach 5–12 cm in diameter.
- They may be seen in the second half of the menstrual cycle.
- They are hormonally inactive but may tend to rupture with intraperitoneal bleeding, especially in patients on anticoagulant therapy.
- The ultrasound appearance of these cysts is characterized by increased internal echoes.
- Bleeding into the cyst or rupture with intraperitoneal hemorrhage may occur.
- In the absence of pain or intraperitoneal bleeding, the management is conservative. The cyst will usually resolve spontaneously, and the free intraperitoneal blood will be reabsorbed. Surgery is rarely needed.
- Some clinicians advocate therapy with oral contraceptive pills to prevent the development of new cysts.

- Most corpus luteal cysts will involute during the 2-week to 3-month observation period.
- Corpus luteum cysts are at increased risk of torsion due to increased ovarian size and weight.
- Persistent/noninvoluting ovarian cysts should be managed surgically. An ovarian cystectomy and conservation of the stretched-out normal ovarian cortex with preservation of normal ovarian tissue is the treatment of choice.

17.14 Ovarian Tumors

17.15 Introduction

- Ovarian neoplasms account for approximately 1% of all tumors in children and adolescents.
- Ovarian enlargement, whether cystic or solid, it must be evaluated to exclude malignancy because approximately 10–20% of all ovarian masses occurring during childhood and adolescence are malignant.
- There are three major types of ovarian neoplasms:
  - Epithelial cell tumors (>70%) comprising the largest group of tumors.
  - Germ cell tumors occur less frequently (20%)
  - Sex cord–stromal tumors make up the smallest proportion, accounting for approximately 8% of all ovarian neoplasms.
- Histologically, benign ovarian tumors include:
  - Fibroma
  - Thecoma
  - Cystadenoma
  - Granulosa cell tumor
- Granulosa-theca cell tumors:
  - This is more commonly known as granulosa cell tumors.
  - It accounts for about 2% of ovarian tumors.
  - It is considered part of the sex cord–stromal tumors.
  - Granulosa cell tumors are divided into two types based on histologic findings:

    Adult type (95%)
    Juvenile type (5%) based on histologic findings.

  - The adult type usually occurs in postmenopausal women and has late recurrences.

  - Most juvenile granulosa cell tumors occur in individuals younger than 30 years and often recur within the first 3 years.
  - Histologically, it is made up of granulosa cells, theca cells, and fibroblasts in varying degrees and combinations.
  - Both subtypes commonly produce estrogen.
  - Theca cell tumors almost always are benign and carry an excellent prognosis.

- Meigs syndrome:
  - This is defined as the triad of:

    Benign ovarian tumor
    Ascites
    Pleural effusion that resolves after resection of the tumor

  - Ovarian fibromas constitute the majority of the benign tumors seen in Meigs syndrome.
  - Meigs syndrome in prepubertal girls with benign teratomas and cystadenomas has been reported.
  - Meigs syndrome, however, is a diagnosis of exclusion, only after ovarian carcinoma is ruled out.

MEIGS' SYNDROME

- BENIGN OVARIAN TUMOR
  - OVARIAN FIBROMA
  - BENIGN TERATOMA
  - CYSTADENOMA
- ASCITES
- PLEURAL EFFUSION THAT RESOLVES AFTER RESECTION OF THE TUMO

- Ovarian tumors can be asymptomatic discovered on routine physical examination or during ultrasound evaluation for some other condition.
- Ovarian tumors can be symptomatic causing:
  - Dull aching abdominal pain
  - The pain is usually in the lower abdomen
  - Low back pain
  - Ovarian tumors can undergo torsion, infarction, hemorrhage or rupture and present with severe abdominal pain and fever.
  - Torsion may be intermittent, presenting with intermittent episodes of severe pain.
  - Rupture of a large cyst may cause peritonitis and shock.

  - Rupture of mucinous cystadenomas may disseminate cells which continue to secrete mucin and cause pseudomyxoma peritonei.
  - Dyspareunia
  - Abdominal distension, with palpable mass arising out of the pelvis
  - This can be confused with a distended urinary bladder but the swelling does not disappear if the bladder is emptied.
  - Urinary frequency
  - Varicose veins and leg edema due to pressure effect of the tumor.
  - The presence of ascites suggests malignancy or Meigs' syndrome.
  - Hormone-secreting tumors may cause virilization, menstrual irregularities or postmenopausal bleeding.

- Most patients with ovarian cysts are asymptomatic, with the cysts being discovered incidentally during ultrasonography or routine abdominal and pelvic examination.
- Some cysts, however are symptomatic and may be associated with a range of symptoms including:

  - Pain or discomfort in the lower abdomen
  - Severe pain indicate torsion or rupture
  - Cyst rupture is characterized by sudden, sharp, unilateral pelvic pain
  - Cyst rupture can lead to peritoneal signs, abdominal distention, and bleeding
  - Changes in bowel movements such as constipation
  - Pelvic pressure causing tenesmus or urinary frequency
  - Precocious puberty and early menarche in young children
  - Abdominal fullness and bloating
  - Indigestion, heartburn, or early satiety
  - Tachycardia and hypotension may result from hemorrhage caused by cyst rupture
  - Hyperpyrexia may result from torsion of an ovarian cyst
  - Underlying malignancy may be associated with:

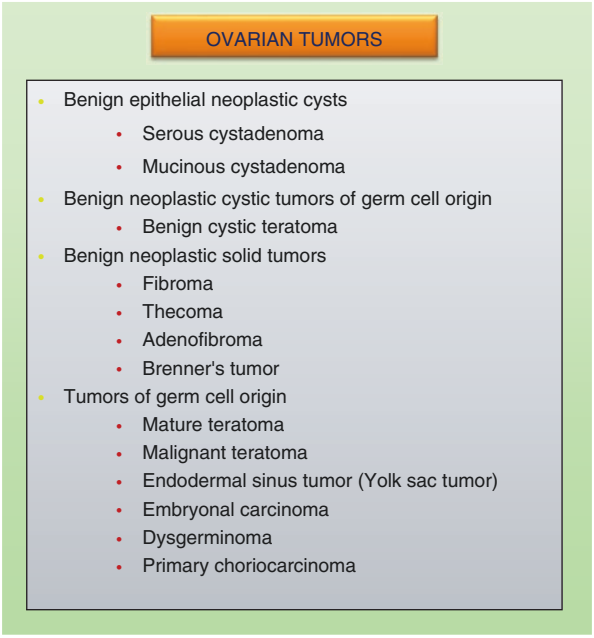
    Early satiety
    Weight loss
    Cachexia
    Lymphadenopathy
    Shortness of breath related to ascites or pleural effusion

  - A large cyst may be palpable on abdominal examination
  - The cyst may be tender to palpation

- The most common presenting symptom is abdominal pain, which is present in more than 50% of patients.

  - The pain is classically periumbilical.
  - Pelvic pain can result from:

Peritoneal stretching
Pressure on adjacent organs
Rupture of the cyst
Hemorrhage into a cyst
Torsion of the cyst



- The incidence of torsion range from 14 to 71%.
- 30% of mature teratomas present with torsion and they manifest as:
  - Acute onset of abdominal pain
  - The pain can radiate to the groin, lower extremity, or costovertebral areas
  - Nausea and vomiting.
- Isosexual precocious puberty is associated with ovarian tumors in 5% of patients
  - Approximately 16% of children with ovarian tumors present with premature secondary sexual development.
  - Tumor-related precocious puberty is seen in the following ovarian tumors:

    Granulosa cell tumor (28%)
    Granulosa-theca cell tumor (14%)
    Immature teratoma (14%)
    Adenocarcinoma (7%)

Sertoli cell tumor (5%)
Non-neoplastic cysts of follicular origin (25%).

– The malignancy rate for endocrinologically functioning ovarian tumors is 50–60%.

17.16 Fibromas

- These are the most common benign ovarian neoplasms (Fig. 17.16a, b).
- Fibromas are connective-tissue tumors that arise from the ovarian cortical stroma.
- They occur most commonly in women of postmenopausal age.
- They are unilateral and often at least 3 cm in size.
- If the stroma is estrogenic or luteinized, the tumors are actually thecomas.

17.17 Thecoma

- Thecomas or theca cell tumors are benign ovarian neoplasms composed only of theca cells.
- Histogenetically they are classified as sex cord-stromal tumors.
- They are typically estrogen-producing and they commonly occur in older women (mean age 59).
- 84% of thecomas occur after menopause.
- 60% of patients present with abnormal uterine bleeding.
- 20% have endometrial carcinoma.
- Microscopically, the tumor cells have abundant lipid-filled cytoplasm.

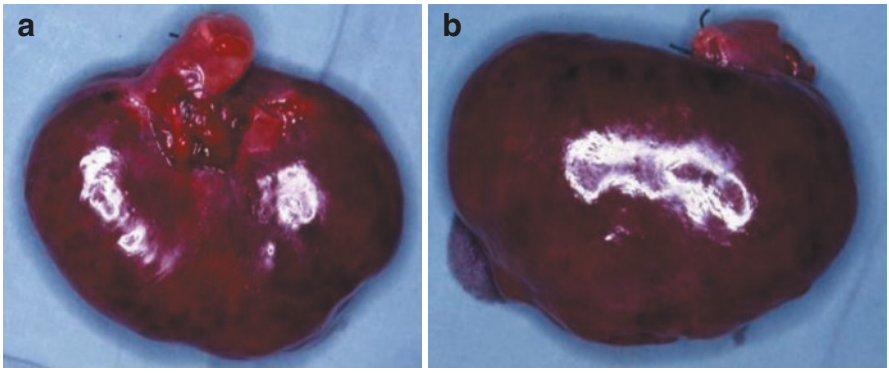


Fig. 17.16 (**a**, **b**) Clinical photographs showing ovarian fibroma thar was completely excised

17.18 Ovarian Cystadenoma

- An ovarian cystadenoma is a benign ovarian neoplasm.
- There are two types of cystadenomas:
  - Serous cystadenoma
  - Mucinous cystadenoma
- Serous cystadenoma:
  - Serous cystadenomas are filled with a thin, watery liquid.
  - They usually grow up to between two and six inches in diameter.
  - Mucinous cystadenomas:

    These tumors are characterized by cystic masses separated by septa with thin walls and filled with a sticky thick liquid.
    They make up 15–20% of all ovarian tumors.
    They have peak occurrence in people of 40–70 years of age.
    If left untreated, they grow to a large size between 6 and 12 inches in diameter.
    If the tumor ruptures, the contents will be spilled in to the abdomen causing Psedomyxoma peritonei.
    Mucinous ovarian cystadenoma is divided in to three types according to the histology.

    - Benign
    - Malignant
    - Borderline

    Of all mucinous ovarian tumors, benign mucinous cystadenoma accounts for 80 %, borderline mucinous cystadenoma make 10% and malignant mucinous cystadenoma account for the remaining 10%.
    15–30% of the malignant mucinous cystadenoma are bilateral.
  - The treatment for an ovarian cystadenoma is surgical excision which can be done through the open technique or more commonly laparoscopically.

17.19 Germ Cell Tumors

- In the pediatric age group, germ cell tumors are considered the most common ovarian neoplasms appearing in the first two decades of life.
- This is in contrast to adults where germ cell tumors constitute only 10–15% of ovarian tumors.

- Mature teratomas are the most prevalent tumors occurring in the second decade of life.
- These tumors are the most common type in children.
- Among these, teratoma is the most common type.
- These tumors include:
  - Teratomas
  - Dysgerminomas
  - Yolk sac tumors
  - Choriocarcinomas
- Approximately 35–45% of ovarian cancers in children are germ cell tumors.
- Germ cell tumors make up 50–75% of ovarian neoplasms in girls up to 18 years of age compared with 20% of ovarian tumors in adult women.
- In girls less than 9 years of age, approximately 80% of ovarian neoplasms are malignant.
- Epithelial neoplasms are rare in the prepubertal age group.
- The incidence of ovarian germ cell tumors increases with age and peaks around age 15–19 years.
  - <10% of tumors occurs in girls younger than 5 years of age.
  - 20% of tumors occur in girls aged 5–9 years.
  - >70% of tumors occur in girls aged 10–14 years.
- The majority of ovarian tumors in children are benign and teratoma is the commonest.
- 70% of malignant ovarian tumors in childhood are germ cell tumors, one quarter is epithelial, and the remainder is stromal tumors.
- Among malignant germ cell tumors in children, yolk sac tumors are the commonest.

17.20 Ovarian Teratoma

- Mature cystic teratomas account for 10–20% of all ovarian neoplasms.
- They are the most common ovarian germ cell tumor and also the most common ovarian neoplasm in patients younger than 20 years.
- Mature cystic teratomas are bilateral in 8–14% of cases (Fig. 17.17a, b).
- For those with mature teratoma, it is important to sample the entire tumor to ensure that no immature neural elements or occult foci of malignancy are present.
- Ovarian teratomas have a potential for malignancy and this is found more commonly in solid teratomas. Solid teratomas however are less common than the cystic variety.

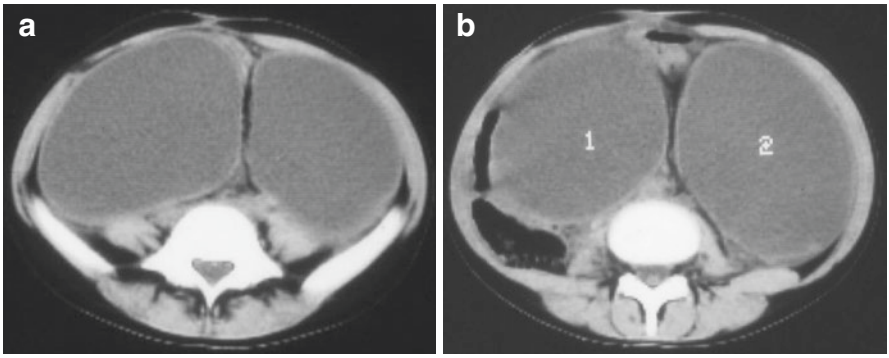


Fig. 17.17 (**a**, **b**) Abdominal and pelvic CT-scans showing large bilateral ovarian teratomas

- Teratomas commonly present in adolescent females and usually grow to a large size, large enough to twist and produce abdominal pain.
- Teratomas are usually benign tumors. They have a characteristic appearance and teeth, bone, and hair are found inside the tumor.
- They are subdivided into:
  - Mature teratomas, which are benign (Figs. 17.18, 17.19a, b, 17.20a, b)
  - Immature teratomas which may be either malignant or benign (Figs. 17.21, 17.22a, b, 17.23, 17.24a, b, 17.25, and 17.26a, b).
- Most benign teratomas are composed of mature cells, but 20–30% also contain immature elements, most often neuroepithelium.
- The tumors may be picked up on plain film due to the presence of calcification in two thirds of teratomas.
- Malignant germ cell tumors: These tumors include:
  - Yolk sac tumors
  - Choriocarcinoma
  - Immature tearatomas
- Benign Cystic Teratomas (Dermoid cysts):
  - This is the most common benign ovarian tumor in childhood and is composed of mature, well-differentiated tissue.
- Approximately 10% are bilateral
- About 50% will have a calcification visible on x-ray (Figs. 17.27 and 17.28).
- The average age of patients with benign ovarian teratomas is 12 years (Fig. 17.29a–c).
- These teratomas tend to undergo torsion.
- Dermoid cysts are normally treated with oophorectomy.

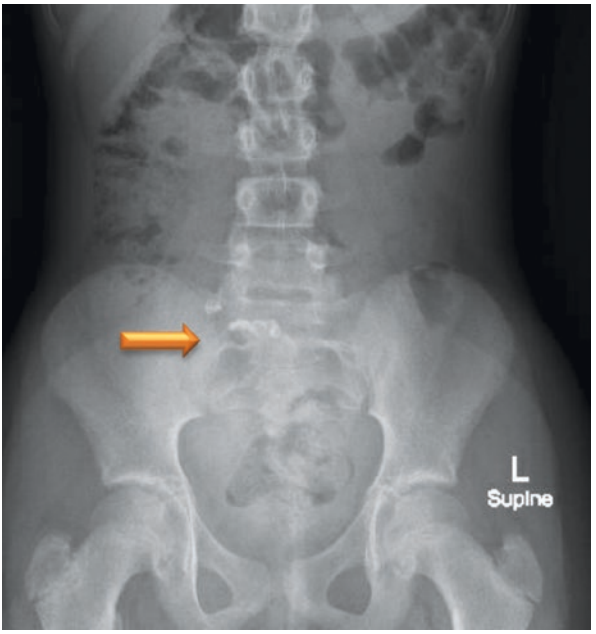


Fig. 17.18 Abdominal x-ray of a young girl with an abdominal mass. Note the calcification in the mass

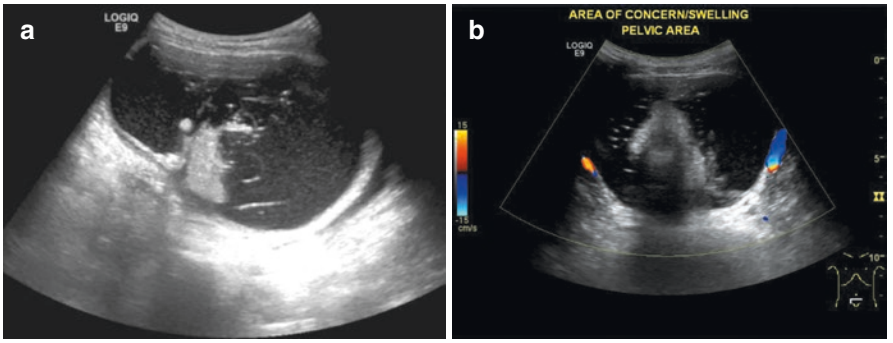


Fig. 17.19 (**a**, **b**) Abdominal and pelvic ultrasound of a young girl with an abdominal mass. Note the different consistencies of the contents of the swelling

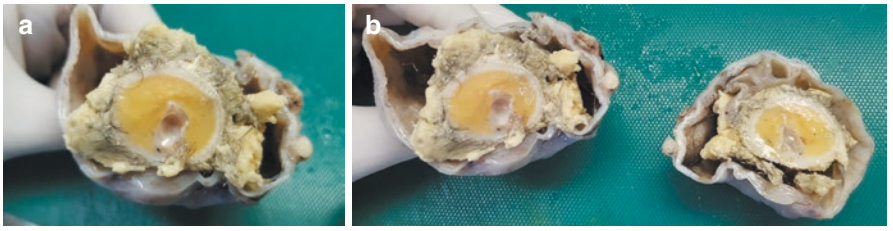


Fig. 17.20 (**a**, **b**) Clinical photographs of the already excised mass which was found to be a mature teratoma. Note the different contents of the ovarian mass

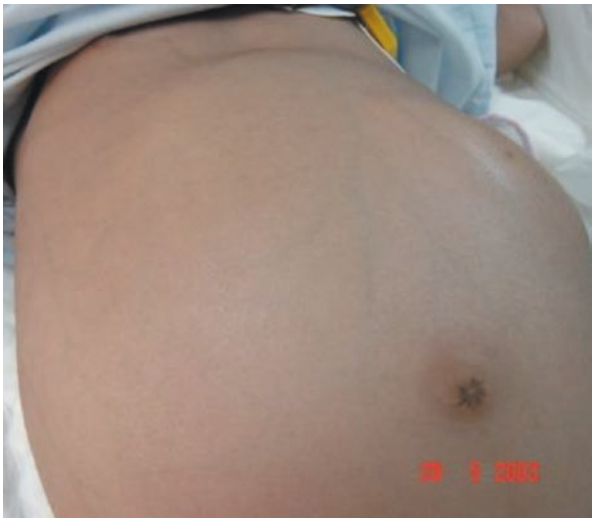


Fig. 17.21 A clinical photograph showing a large ovarian teratoma

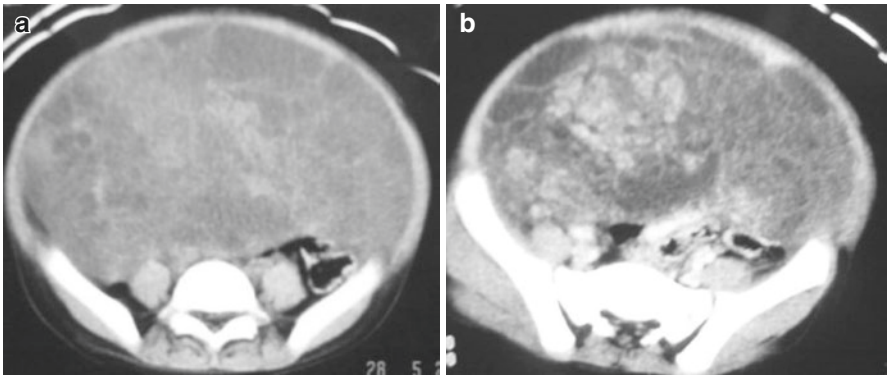


Fig. 17.22 (**a**, **b**) CT-scan showing a very large ovarian tertoma

17.21 Immature Teratoma

- Immature teratomas constitute 28% of germ cell tumors.
- Immature teratomas constitute 19.7% of ovarian malignancies in children.
- The median age at diagnosis is 11 years.
- Immature teratoma is also referred to as:
  - Embryonal teratoma
  - Teratocarcinoma
  - Solid teratoma
  - Malignant dermoid

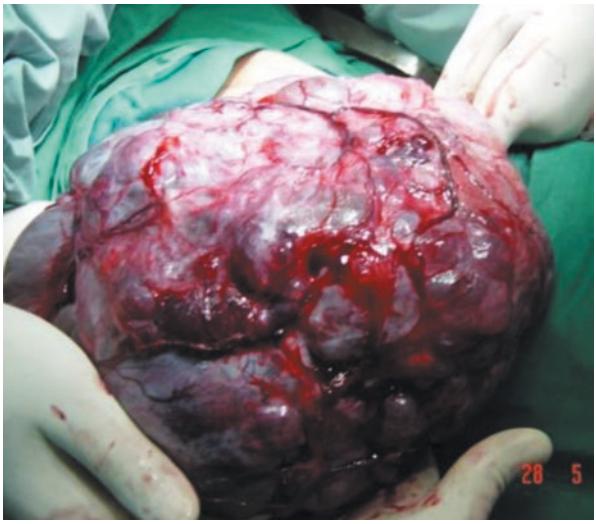


Fig. 17.23 A clinical operative photograph showing a very large ovarian immature teratoma that was excised completely

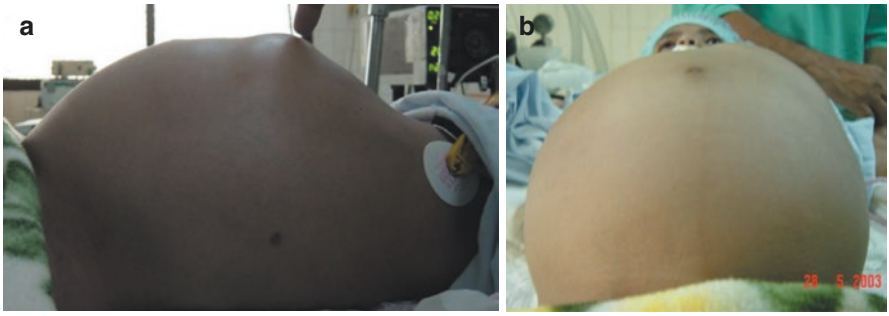


Fig 17.24 (**a**, **b**) Clinical photographs of a female child with a very large abdominal mass that was found to be immature teratoma

  - Embryoma
  - Teratoblastoma

- Pathology of immature teratomas:
- Grossly immature teratoma is similar to its benign counterpart, the mature teratoma.

  - They range in size from 7 to 28 cm
  - They are encapsulated, bosselated, and usually solid with cystic areas
  - Bilateral involvement is seen in approximately 10% of cases.
  - Histologically the immature teratoma exhibits:

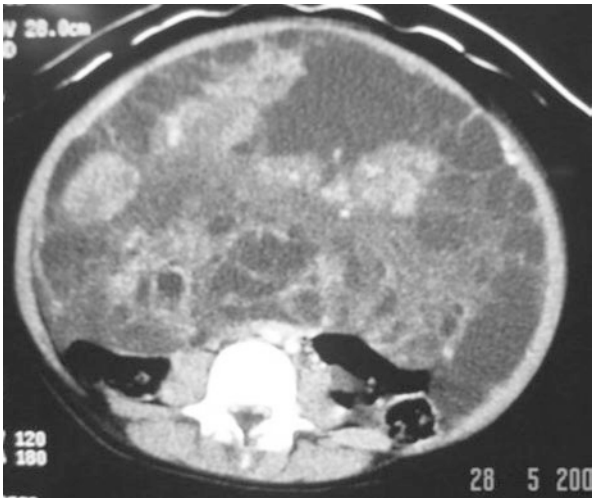


Fig. 17.25 Abdominal CT-scan showing a very large abdominal tumor which was found to be a large immature teratoma

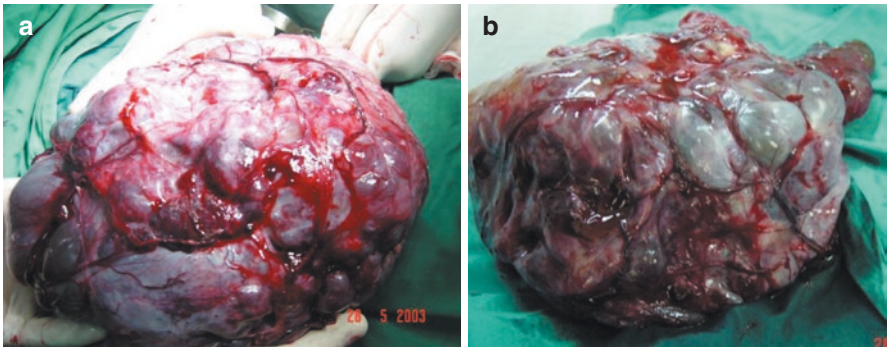


Fig. 17.26 (**a**, **b**) Clinical intraoperative photographs showing a completely resected large ovarian tumor that was found to be immature teratoma

A mixture of mature and immature tissues of mesenchymal and epithelial origin.
The most common pattern is undifferentiated cellular stroma with structures suggesting immature neural epithelium.
Fetal glands and squamous epithelium are seen with mesenchymal derivatives, such as cartilage, bone, smooth muscle, neuroglia, and ganglion cells.

– Immature teratomas are graded on the basis of the amount of cellular immaturity.

The grading scheme ranges from grade 0 (a solid teratoma with all tissue mature) to grade 3 (markedly atypical immature embryonal tissue with a high degree of mitotic activity).

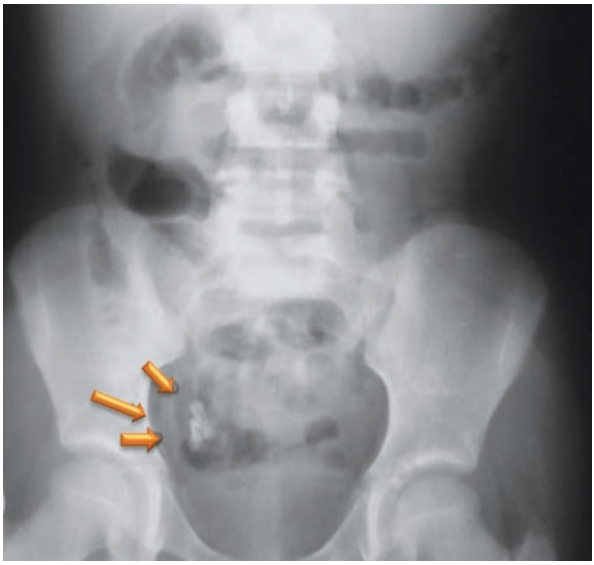


Fig. 17.27 Abdominal x-ray showing calcification in an ovarian teratoma

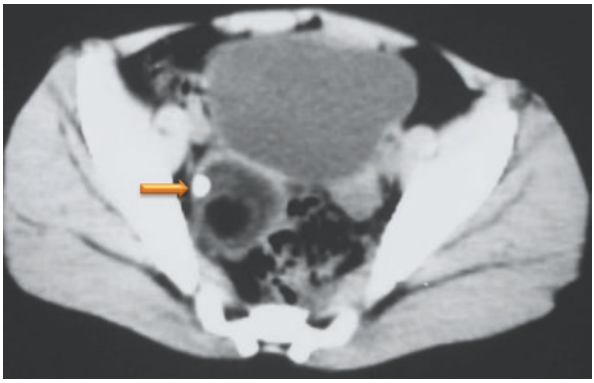


Fig. 17.28 Abdominal and pelvic CT-scan showing calcification in an ovarian teratoma

Metastasis and spread of immature teratoma depends on the histology and stage of the tumor
The histologic grade of metastatic immature teratoma is the major factor in predicting prognosis.

- Treatment
  - The surgical treatment of choice is a unilateral salpingo-oophorectomy.
  - Removal of the uterus, including uterine tubes and ovaries, and the omentum is recommended if there is local extension, metastasis, or contralateral involvement.
  - Radiotherapy offers no benefit.
  - Stage I: Treatment is oophorectomy

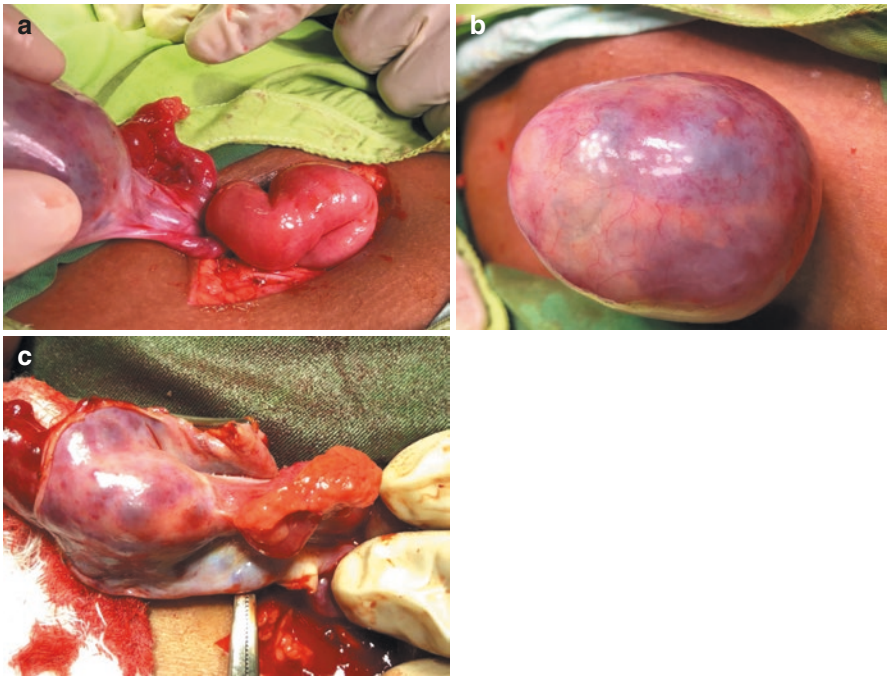


Fig. 17.29 (**a–c**) Clinical intraoperative photographs showing a young girl with a large ovarian tumor that was excised completely. Histological evaluation showed benign teratoma. Note the preserved ovarian tissue after complete excision

Grade I: Oophorectomy and follow up

- Biopsy and grading must be done for all peritoneal metastases.
- All other patients should receive adjuvant triple chemotherapy if they have:

  Evidence of extra ovarian spread
  A tumor that is grade 2 or 3
  Implants or recurrences which are graded 1, 2, or 3,

- PVB (cisplatin, vinblastine, and bleomycin) has been used successfully to treat patients who have had VAC failures.
- BEP (Bleomycin, etoposide and platinum) chemotherapy, in 5-day regimens, is currently the treatment of choice because of the decreased toxicity of etoposide compared with vinblastine (i.e., in PVB treatment, which apparently is superior to VAC (vincristine, Dactinomycin and cyclophosphamide) chemotherapy).
- It has been suggested that a predominance of malignant neural tissue or thyroid tissue (struma ovarii) indicates a more optimistic prognosis than the finding of chorioepitheliomatous or vitelline elements.

17.22 Yolk Sac (Endodermal Sinus) Tumors

- Yolk sac tumors constitute 6% of pediatric ovarian tumors.
- Yolk sac tumors constitute 7.2% of ovarian malignancies in children.
- The average age of patients at diagnosis is 13–14 years.
- Yolk sac tumors are also called:
  - Endodermal sinus tumor
  - Embryonal carcinoma
  - Mesonephroma ovarii of Schiller
  - Teilum tumor
  - Extraembryonic mesoblastoma
  - Yolk sac carcinoma
  - Mesometanephric rest tumor
  - Elevated serum AFP levels in these tumor cells show their close relationship with the yolk sac, which is the source of AFP in the human fetus.
- Pathology
  - The gross appearance of the yolk sac tumor is classically yellow-red-gray
  - It is soft and friable
  - It has a thin, smooth capsule
  - It is composed of Cystic spaces and contains areas of hemorrhage and necrosis
  - Microscopically the yolk sac tumor is composed of a loose network of pleomorphic, poorly differentiated cells.
  - These cells have an epithelial appearance in some areas, with papillary clusters thrusting into cystic spaces.
  - Extracellular and intracellular round or oval hyaline globules (Schiller-Duval bodies) are a frequent finding.
- Treatment
  - Yolk sac tumors are highly malignant and grow and metastasize rapidly.
  - The treatment includes extensive surgery with chemotherapy.
  - Radiotherapy is ineffectual.
  - The general consensus is that all patients, regardless of stage, should receive chemotherapy with VAC, BEP or PVB.
  - With this combined treatment (surgery and chemotherapy), disease-free intervals range from 2 to 8 years.
  - Now, with aggressive chemotherapy, an 80% overall survival is achievable.

17.23 Primary Choriocarcinoma

- Primary choriocarcinomas of the ovary are extremely rare.
- They constitute about 0.6% of germ cell tumors.

- They constitute about 0.9% of ovarian malignancies in children.
- A true primary choriocarcinoma is believed to arise from the primordial germ cell.
- This tumor also may form in a teratoma of the ovary or may metastasize to the ovary from an extragonadal teratoma.
- Primary Choriocarcinoma produces β-hCG, which can be detected in blood and urine.
- Pathology
  - Primary choriocarcinomas are hemorrhagic and friable.
  - They consist of cells resembling syncytiotrophoblasts and cytotrophoblasts, with extensive areas of hemorrhage and necrosis.
- Treatment
  - Primary choriocarcinoma in children is rapidly fatal.
  - N0 patient has been reported to survive more than 8 months after diagnosis.
  - It is characterized by rapid hematogenous metastasis and local extension.
  - The tumor is radio resistant and historically rarely responds to chemotherapeutic agents.
  - Occasionally, success has been reported with a triple regimen including actinomycin D, methotrexate, and chlorambucil.

17.24 Mixed Germ Cell Tumors

- Neoplasms containing two or more germ cell derivatives account for 4% of ovarian tumors and 8.6% of ovarian malignancies in children or adolescents.
- The yolk sac tumor is seen in 88% of mixed germ cell tumors.
- Choriocarcinoma is the second most frequent germ cell element seen in 25% of mixed germ cell tumors.
- Treatment
  - The biologic behavior of mixed germ cell tumors follows that of its most malignant component.
  - The prognosis is generally poor because of the preponderance of a yolk sac or choriocarcinomatous component.
  - Most of these tumors result in death in less than 1 year, despite treatment with VAC chemotherapy.
  - BEP chemotherapy may be recommended as the treatment of choice.

17.25 Sex-Cord Stromal Cell Tumors

- Sex-cord stromal cell tumors are less common than germ cell neoplasms in the first two decades of life.

- These tumors are generally of low-grade malignancy.
- They constitute 12.6% of all pediatric ovarian neoplasms
- They constitute 17% of ovarian malignancies in children.
- The primary sex-cord stromal cell tumors are the granulosa-stromal cell tumors and the Sertoli-stromal cell tumors (the gynandroblastoma and the pure Leydig cell tumor have not been reported in pediatric patients).
- The primary significance of neoplasms of mesenchymal origin is their capacity to be endocrinologically active.
  - The granulosa-stromal cell tumors, which represent half of the potentially malignant sex-cord stromal tumors, are the most common neoplasms causing gonadal isosexual precocious puberty.
  - Most cases of isosexual precocity are idiopathic
  - Less than 5% are associated with granulosa-stromal cell tumors.
  - The postpubertal child may present with hypermenorrhea (75%) or amenorrhea (25%) as a result of the estrogen secretion from the granulosa-stromal cell tumor.
  - Heterosexual precocious puberty may be stimulated by the most common masculinizing tumor of the ovary, androblastoma (arrhenoblastoma or Sertoli-Leydig cell tumor).
  - If the Sertoli cells predominate, the effects of excess estrogen may be seen.
  - If the Leydig cells predominate, the androgenic effect prevails.
- Juvenile granulosa cell tumors
  - These tumors have a characteristic appearance of cellular nodules within a myxoid spindle cell stroma.
  - They are made up of larger cells in a predominantly diffuse or solid pattern.
  - Two thirds of children with Juvenile granulosa cell tumors present with endocrine abnormalities.

    Precocious pseudopuberty
    Virilization
    Menstrual irregularities

  - The juvenile granulosa cell tumors are usually unilateral, present as stage IA, and seldom recur.
- The prognosis for the sex-cord stromal tumors is generally excellent.
- Histologically, it is difficult to differentiate between benign and malignant lesions.
- The diagnosis of malignant tumors is confirmed by:
  - Recurrence
  - Local extension
  - Metastasis.
- Between 5 and 30% of granulosa-stromal cell tumors and fewer than 15% of androblastomas are malignant.

- The granulosa-stromal cell tumors have a propensity for late recurrence.
- The androblastomas show a lesser malignant potential, with an 85–95% survival rate.
- Treatment
  - Unilateral salpingo-oophorectomy is the treatment of choice for sex-cord stromal tumors
  - Radiotherapy is useful for metastatic disease or tumor recurrence, particularly in granulosa cell tumors.
  - PVB and more recently BEP chemotherapy has been advocated.

17.26 Epithelial Ovarian Tumors

- Epithelial cystic tumors account for about 60% of all true ovarian neoplasms.
- One third of all ovarian tumors are serous, and two thirds of these serous tumors are benign.
- By definition, serous tumors are characterized by a proliferation of epithelium resembling that lining the fallopian tubes.
- They are virtually all cystic, are most commonly seen in women in their 40s and 50s, and are bilateral in 15–20% of cases.
- Benign lesions (e.g., mucinous cystadenoma) may be unilocular or multilocular; have a smooth lining surface; and contain thin, clear, yellow fluid.
- Mucinous epithelial tumors account for approximately 10–15% of all epithelial ovarian neoplasms.
- Of these tumors, 75% are benign and are found in women aged 30–50 years.
- Mucinous cysts are usually smooth-walled; compared with the serous variety; they rarely are associated with true papillae.
- The tumors are generally multilocular, and the mucus-containing loculi appear blue through the tense capsules.
- These tumors can grow quite large, measuring up to 30 cm; patients often present with ovarian torsion.
- Mucinous tumors are most common in the third to fifth decades of life and are only rarely bilateral. The larger varieties are associated with an increased risk of rupture, with resultant pseudomyxoma peritonei.
- Solid epithelial ovarian tumors are almost invariably malignant.
  - Approximately 80% of epithelial tumors are of the serous type.
  - 10% are mucinous
  - 10% are endometrioid, with rarer varieties including clear cell tumors, Brenner tumors, and undifferentiated ovarian carcinomas.
- Brenner tumors:
  - These are usually found incidentally at pathologic evaluation.
  - They are often in conjunction with a mucinous cystadenoma or dermoid cyst.

  - They are relatively rare tumors and are most common in the fifth to sixth decades of life.
  - Brenner tumors may be benign, intermediate, or malignant transitional cell tumors.
  - These tumors are usually small, firm, and solid, and when confined to the ovary.
  - They carry a good prognosis, depending on the malignancy status.

- Intersex anomalies have also been associated with development of germ cell tumors.
  - Children with intersex anomalies particularly those with testicular feminizing syndrome and 5-alpha reductase deficiency are at increased risk of development of germ cell tumors.
  - These patients with testicular feminization are sometimes discovered incidentally during a hernia repair.
  - The timing of gonadectomy is still controversial in these patients.
  - There are those who advocate early gonadectomy to avoid early development of malignant change as gonadoblastoma has been observed in patients as young as 2 months and also to avoid losing the patients for follow-ups.
  - Others advocate waiting a gonadal estrogen production may benefit the patient in terms of growth and development and do the gonadectomy just prior to menarche.
  - Gonadoblastoma is seen in about one third of patients with intersex anomalies.
  - Gonadoblastoma is considered a carcinoma in situ but frequently it can develop into:

    Dysgerminoma
    Yolk sac tumors
    Immature teratomas
    Choriocarcinomas

  - Turner syndrome is also a risk factor for gonadoblastoma.

- Gonadoblastoma is an uncommon tumor occurring almost exclusively in patients with DSD, who have either molecular evidence of a Y chromosome or a Y chromosome on karyotype analysis.
- The karyotype of these individuals is most often 46, XY; 45, X/46, XY; or 45, XO.
- Phenotypically, 80% of patients with gonadoblastoma are females and 20% are males.
- The exact prevalence of gonadoblastoma is not known.
- Patients with mixed gonadal dysgenesis (45, X/46, XY) have a 55% incidence, whereas the incidence of developing gonadoblastoma in individuals with androgen insensitivity and male pseudohermaphrodism (46, XY) has been reported to be 30-66%.
- A normal or partially deleted Y chromosome or marker chromosome derived from Y has been found in 6–9% of patients with Turner syndrome (TS). The

molecular presence of a Y chromosome in individuals with Turner Syndrome results in as high as a 43% incidence of developing gonadoblastoma. Additionally, the rate of contralateral disease for all patients is substantial at 36%.

- Approximately 80% of patients with gonadoblastoma are phenotypic females, and 20% are males.
- Nearly all of the patients who develop gonadoblastoma have a chromosomal anomaly consistent with an intersex syndrome, and the genotypic sex is frequently inconsistent with the phenotypic appearance. The karyotype analyses demonstrate the most common genotypes to be 45, X/46, XY and 46, XY in patients at risk of developing gonadoblastoma.
- The surface epithelial-stromal tumor, representing 80–90% of adult ovarian neoplasms, account for only 7% of malignancies in children.
- These include endometrial and clear cell carcinomas and mucinous and serous cystadenocarcinomas.
- Endometrial and clear cell carcinomas are not found in the first two decades of life.
- The mucinous and serous cystadenocarcinomas are rare before puberty and have not been reported in children younger than 4 years old.
- These tumors are bilateral in 10% of cases.
- Treatment
  - The malignant potential of surface epithelial-stromal tumors in children is 7.1–13.5% of cystadenomas.
  - Serous lesions have the poorest prognosis.
  - Tumors of low malignant potential behave in a generally benign fashion.
  - Stage IA is treated with salpingo-oophorectomy only.
  - The treatment of malignant surface epithelial-stromal tumors other than stage IA include:

    Total abdominal hysterectomy
    Bilateral salpingo-oophorectomy
    Omentectomy
    Pelvic/para-aortic lymph node sampling
    Appendectomy
    Adjuvant chemotherapy regimens of cis-platinum or carboplatin with an alkylating agent (e.g., cyclophosphamide [Cytoxan] or PVB).
    Radiotherapy may be beneficial.

17.27 Dysgerminoma

- A dysgerminoma is a tumor of the ovary that is composed of primitive, undifferentiated germ cells.
- Germ cell tumors arise from primordial germ cells of the ovary.

- Of the ovarian lesions, 97% are benign proliferations (i.e., mature teratomas); the remaining 3% are malignant.
- Dysgerminomas are the most common malignant germ cell tumor occurring in the ovary.
- Dysgerminomas occur most commonly in adolescents and young adults.
- Approximately 60% of cases are diagnosed in patients younger than 20 years.
- Unlike other germ cell tumors, dysgerminomas occur bilaterally (approximately 10–20% of cases).
- Common signs and symptoms of ovarian dysgerminomas include:
  - Abdominal/pelvic pain (55–85%)
  - Abdominal mass (35%)
  - Fever (10–25%)
  - Vaginal bleeding (10%)
  - Occasionally ascites
- Dysgerminomas are the most common ovarian malignancies in children.
- They constituting 9.5–11% of childhood ovarian tumors and 24.5% of pediatric ovarian malignancies.
- There is an increased frequency of dysgerminomas among patients with genetically abnormal gonads.
- The average age at diagnosis of dysgerminomas is 22 years.
  - 7% of dysgerminomas are found in patients younger than 10 years.
  - 34% of dysgerminomas are found in patients 10–19-year-old.
- A pure dysgerminoma is endocrinologically inactive.
  - Signs of pronounced hormonal activity indicate the presence of a functioning dysgerminomas.
- Pathology of dysgerminomas:
  - They are rubbery, gray, smooth, or bosselated
  - They are surrounded by a dense capsule
  - Their size range from several centimeters to as large as 50 cm in diameter.
  - The cut surface is soft and homogeneous and has a brain like consistency
  - In 5–20% of patients, the tumor is bilateral.
  - Histologically, dysgerminomas are made up of well-defined clusters of cells that are separated by fibrous tissue septa with lymphocytic infiltration and an occasional Langhans' giant cell.
  - The presence of marked cellular atypia and frequent mitosis are associated with a poorer prognosis.
  - The presence of a marked inflammatory response suggests a good immunologic reaction in the tumor.
- The incidence of recurrence of dysgerminoma is high (33–50%).

- Predisposing factors for recurrence of dysgerminomas include:
  - No adjunctive treatment
  - Peritoneal spillage
  - Capsule extension
  - Bilaterally
  - A mixture of other malignant germ cell tumors
- Treatment
  - Salpingo-oophorectomy to treat pediatric unilateral dysgerminomas.
  - For stage IA no postoperative therapy is indicated.

    Negative peritoneal washings
    Negative lymph nodes
    Negative omental biopsies
    No capsular penetration
    No ascites
    No detectable metastases

  - The treatment of bilateral dysgerminoma:

    Bilateral salpingo-oophorectomy
    Full staging operation

  - The presence of metastatic disease demands complete cytoreductive surgery.
  - Recurrence can be resected surgically and subsequently treated with chemotherapy or radiotherapy.
  - All patients with advanced dysgerminoma are treated with platinum-based chemotherapy.
  - The current recommendation for adjuvant chemotherapy in the treatment of metastatic germ cell tumors is BEP.

17.28 Clinical Manifestations of Ovarian Tumors

- Patients with an ovarian tumor may present with:
  - Abdominal pain
  - Increasing abdominal girth
  - Nausea, and vomiting
  - Abdominal mass
  - Asymptomatic abdominal mass discovered during routine examination.
  - Severe abdominal pain with tenderness suggests torsion or hemorrhage (Fig. 17.30a–d).

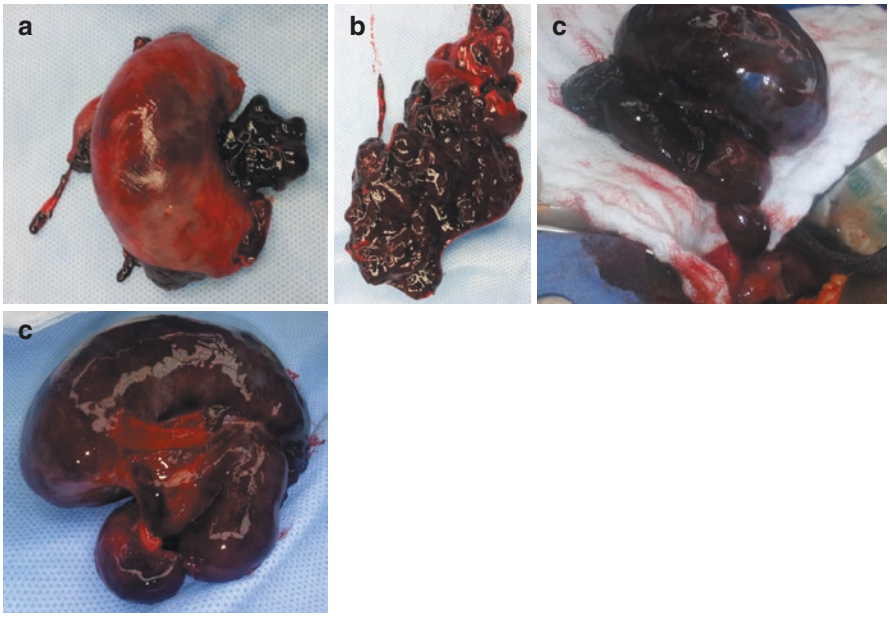


Fig. 17.30 (**a**–**d**) Clinical intraoperative photographs showing ovarian tumors that were complicated by hemorrhage in one and torsion in the other

17.29 Investigations

- CBC and differential
- Liver function tests (bilirubin, alkaline phosphatase, alanine aminotransferase (SGPT), total protein, and albumin levels)
- Renal function tests (BUN, creatinine)
- Urine analysis and culture
- Uric acid level
- Electrolytes, calcium, and magnesium
- Abdominal x-ray may reveal:
  - Soft tissue densities suggestive of ascites or a mass
  - Intestinal obstruction
  - Tumor calcification
- A chest radiograph may show:
  - A pleural effusion consistent with Demons-Meigs syndrome
  - Pulmonary metastasis
- Intravenous urography and barium enema are indicated in those with suspected urinary or gastrointestinal tract pathology.
- Abdominal and pelvic ultrasound (Fig. 17.31a–c):

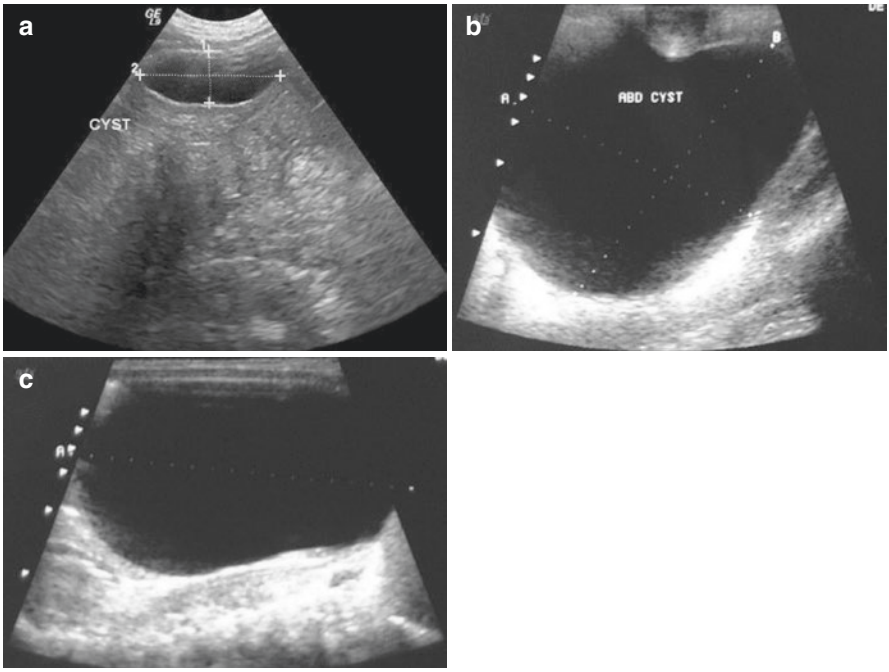


Fig. 17.31 (**a–c**) Abdominal and pelvic ultrasounds showing a small ovarian cyst in the upper one and a large ovarian cyst in the lower one

- Ultrasonography is the main investigation
- It is a simple noninvasive investigation
- This is used to determine the overall size of the mass
- To identify whether it is simple, complex, solid, bilateral, or associated with free fluid.
- Abdominal and pelvic ultrasonography may aid in the detection of ovarian tumor spread and in monitoring certain masses without the risk of ionizing radiation.
- A solid ovarian mass in childhood is always considered malignant until proven otherwise by histological examination.
- Transvaginal ultrasonography is preferable due to its increased sensitivity over transabdominal ultrasound.

• CT scanning and magnetic resonance imaging of the abdomen and pelvis:

- These are more valuable
- They provide more accurate information regarding the site, size and consistency of the tumor.
- They provide more accurate information regarding the presence or absence of lymphadenopathy and retroperitoneal involvement
- It is essential for the staging of abdominal and pelvic tumors at presentation.

  - CT scanning is needed at relapse to determine the extent and location of the disease.

- Chest CT scanning is necessary to evaluate the presence and extent of metastatic disease that originates in the abdomen or pelvis.
- Bone scanning is used to detect metastatic disease.
- CT scanning or MRI of the brain should be performed whenever brain metastases are suspected (Fig. 17.32).
- Positron emission tomography (PET) scanning is useful to detect relapse. The presence of elevated tumor marker levels, without the depiction of new disease on CT scans or MRIs, is an indication for PET scanning.
- Germ cell tumors may be associated with chromosomal abnormalities and genetic screening is advisable in these cases.
- Tumor markers:
  - Some ovarian neoplasms secrete tumor markers
  - These tumor markers are helpful in making a diagnosis and also during follow-up to monitor the clinical response to treatment.
  - Alpha-fetoprotein (AFP) is an oncofetal antigen that is a glycoprotein. It is produced by:

    Endodermal sinus tumors
    Mixed germ cell tumors
    Immature teratomas
    Embryonic carcinoma

  - Lactate dehydrogenase (LDH): This is elevated in those with the histologic features of an endodermal sinus tumor.

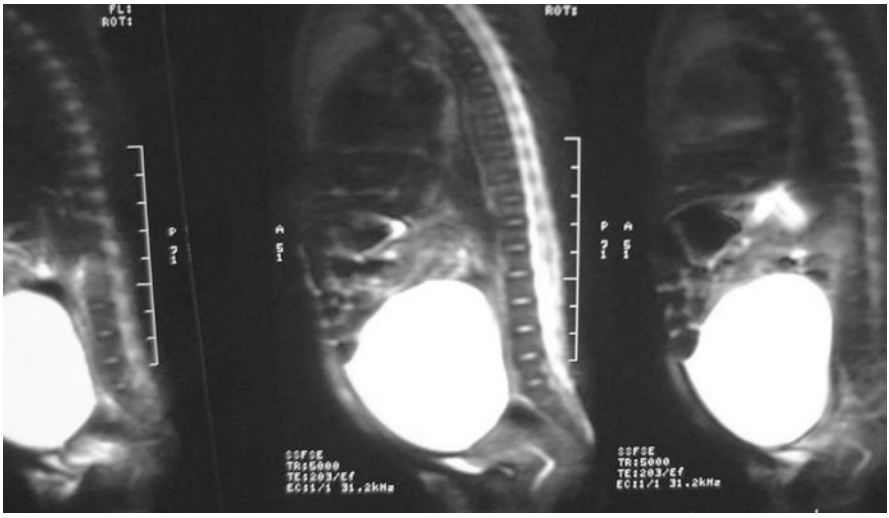


Fig. 17.32 Abdominal MRI showing a large ovarian cyst in a newborn

- Tumor markers:
  - Alpha-fetoprotein (AFP) levels can be elevated in:

    Embryonal carcinomas
    Yolk sac tumors
    Teratoid tumors with a significant yolk sac tumor component

  - β-Human chorionic gonadotropin (β-hCG) is elevated in:

    Nongestational choriocarcinomas
    Dysgerminoma variant with syncytiotrophoblast cells

  - AFP and β-hCG levels are elevated in embryonal carcinomas.
  - CA-125:

    CA 125 is unreliable in differentiating benign from malignant ovarian masses in premenopausal women because of the increased rate of false positives and reduced specificity.
    An elevated CA 125 levels can be seen with other benign and malignant conditions.
    CA 125 is primarily a marker for epithelial ovarian carcinoma and is only raised in 50% of early-stage disease.
    Repeated estimations showing rapidly rising levels of CA 125 are more likely to be associated with malignancy than high levels which remain static.
    The main use of CA 125 is in assessing response over time to treatment for malignancy.
    This is a marker for epithelial ovarian cancer that is highly sensitive, but not very specific.
    It is also elevated with other conditions (endometriosis, pelvic inflammatory disease, pregnancy, Crohn's disease).
    It is important in determining the response to treatment
    It important to detect recurrences of surface epithelial stromal tumors

  - Inhibin

    May be elevated in mucinous and granulosa cell tumors.

  - Carcinoembryonic antigen

    May be elevated in ovarian malignancies.

  - Human chorionic gonadotropin (hCG):

    This is produced by trophoblastic cells and thus will be elevated with pregnancy, hydatidiform moles, placental site tumors, nongestational choriocarcinoma, teratoma and embryonal ovarian carcinomas.

  - Carcinoembryonic antigen (CEA): This can be produced by epithelial or germ cell tumors.

  - Inhibin and mullerian inhibiting substance (MIS): These are elevated in children with granulosa-theca cell tumors.

- Thrombocytosis: This has been associated with ovarian malignancies in girls and adolescents.
- Diagnostic laparoscopy may be performed in some cases.
- Fine-needle aspiration and cytology may be used to confirm the impression that a cyst is benign.
- Lactate dehydrogenase (LDH), alpha-fetoprotein (AFP) and human chorionic gonadotrophin (hCG) should be measured in all women under the age of 40 with a complex ovarian mass because of the possibility of germ cell tumors.
- Risk of Malignancy Index (RMI)

  - There are different risks of malignancy scores which can be used to assess an ovarian mass.
  - The RMI I is the most effective for women with suspected ovarian cancer.
  - This is also recommended by the National Institute for Health and Care Excellence (NICE) guideline on ovarian cancer.
  - It should not be used for premenopausal women though.
  - RMI I combines three pre-surgical features:

    Serum CA 125 (CA 125)
    Menopausal status (M)
    Ultrasound score (U)

  - The RMI is a product of the ultrasound scan score, the menopausal status and the serum CA 125 level (IU/mL) as follows:

    $RMI = U \times M \times CA\ 125.$

- The ultrasound result is scored 1 point for each of the following characteristics:

  - Multilocular cysts
  - Solid areas
  - Metastases
  - Ascites
  - Bilateral lesions
  - U = 0 (for an ultrasound score of 0), U = 1 (for an ultrasound score of 1), U = 3 (for an ultrasound score of 2–5).

- The menopausal status is scored as 1 = premenopausal and 3 = postmenopausal.
- Serum CA 125 is measured in IU/ml.
- Recommendations are that those women suspected of having ovarian cancer who have an RIM score greater than 200 should have a CT of the abdomen and pelvis performed.

17.30 Staging

- There are two staging systems for ovarian tumors.
- The International Federation of Gynecology and Obstetrics/American Joint Committee on Cancer (FIGO/AJCC) staging system was initially developed for use in adults, and it is most relevant for epithelial malignancies.
- The Children's Oncology Group (COG) system is germ-cell tumor specific; it was developed specifically for pediatric tumors.
- FIGO/AJCC staging for ovarian tumors
  - Stage I: The tumor is limited to the ovaries.

    IA: The tumor is limited to one ovary, no tumor on the external surface, capsule intact.
    IB: The tumor is limited to both ovaries, no tumor on the external surface, capsule intact.
    IC: Stage IA or IB with ascites or peritoneal washings that contain malignant cells, tumor on the surface, or ruptured capsule.
  - Stage II: The tumor involves one or both ovaries, with pelvic extension.
  - Stage III: The tumor involves one or both ovaries, with peritoneal implants outside the pelvis or positive retroperitoneal or inguinal nodes. Superficial liver metastasis indicates stage III disease. Tumor is limited to the true pelvis, but histologically proven malignant extension to small bowel or omentum is present.
  - Stage IV: The tumor involves one or both ovaries, with distant metastases. If pleural effusion is present, cytological findings must be positive to indicate stage IV disease. Parenchymal liver metastasis indicates stage IV disease.
- COG staging for ovarian tumors:
  - Stage I: The tumor is limited to one or both ovaries. Peritoneal fluid and washings are negative for tumor. No clinical, radiographic, or histologic evidence of disease is present beyond the ovaries. Tumor marker levels return to the reference range after an appropriate postsurgical half-life decline. The presence of gliomatosis peritonei does not worsen the stage.
  - Stage II: Microscopic residual or positive lymph nodes (<2 cm as measured by pathologist) are present. Peritoneal fluid or washings are negative for malignant cells. Tumor markers are positive or negative.
  - Stage III: Lymph node or nodes with malignant metastatic nodule (>2 cm as measured by a pathologist) are present. Gross residual or biopsy only. Contiguous visceral involvement (omentum, intestine, or bladder) is observed. Peritoneal washings are positive for malignant cells. Tumor markers are positive or negative.
  - Stage IV: Distant metastases, including liver metastases, are present.

17.31 Treatment

- General principles
  - Gonadal tumors in children carry an overall malignancy rate of 35%.
  - It is important to maintain the child's reproductive and developmental potential.
  - This calls for initial conservatism in the surgical treatment of pediatric ovarian tumors.
  - A definitive histologic diagnosis and a thorough understanding of the behavior of each of these tumors are necessary for appropriate therapy.
  - Peritoneal washings and diaphragmatic scrapings for cytology with a radio isotopic and radiographic oncology survey dictate whether further therapy is necessary.
  - A second surgical procedure may be required, depending on the tumor type and histologic grade.
  - Because of the low incidence of bilateralism and lymphatic metastasis in most pediatric ovarian tumors, a wedge biopsy of the contralateral ovary and pelvic/para-aortic lymphadenectomy are rarely indicated.
  - In stage IA lesions, dysgerminomas (with their characteristic bosselated appearance and increased frequency of bilaterality and lymphatic metastasis) may be the one exception.
  - Unilateral salpingo-oophorectomy provides adequate surgical treatment for tumors of low-grade malignancy which include:

    Dysgerminomas
    Granulosa-stromal cell tumors
    Androblastomas
    Cystadenocarcinomas of low malignant potential

  - Unilateral salpingo-oophorectomy is also sufficient for tumors of a greater malignant nature, if staged as IA. This category include:

    Immature teratomas
    Yolk-sac tumors
    Embryonal carcinomas
    Nongestational choriocarcinomas, in which adjunctive therapy is mandatory.

  - Total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and appendectomy are indicated in germ cell and sex-cord stromal cell tumors staged beyond IA.
  - Stage IA Dedifferentiated serous and mucinous cystadenocarcinomas, even when stage IA, should be treated aggressively.
  - The treatment of Stage IA mucinous and serous cystadenocarcinomas with a low malignant potential is unilateral salpingo-oophorectomy.

- Surgical intervention is directed toward preservation of the reproductive and sexual function.
- Unless a malignancy is diagnosed definitively on frozen section at the time of exploration, conservative surgery should be undertaken with excision of the lesion and ovarian preservation. A second exploration after the final pathology confirmation can be performed.
- If tumor markers are abnormal and malignancy is suspected, then a unilateral salpingo-oophorectomy and appropriate staging is performed.
- If malignancy is suspected or confirmed, adequate staging includes:
  - Abdominal and pelvic exploration
  - Peritoneal washings for cytology
  - Biopsies of suspicious areas
  - Periaortic and pelvic lymph node sampling
- Surgical treatment:
  - Open surgical resection of ovarian tumors is the preferred treatment (Fig. 17.33).
  - Ipsilateral oophorectomy or salpingo-oophorectomy should be performed.
  - Uninvolved fallopian tubes should be preserved if possible.
  - Some authors advocate ovary-sparing resection of mature teratomas but this may not be possible.
  - Bilateral malignant tumors require bilateral oophorectomy, but hysterectomy is unnecessary for germ cell tumors.
  - The peritoneal cavity should be inspected and suspicious implants should be sampled or resected.

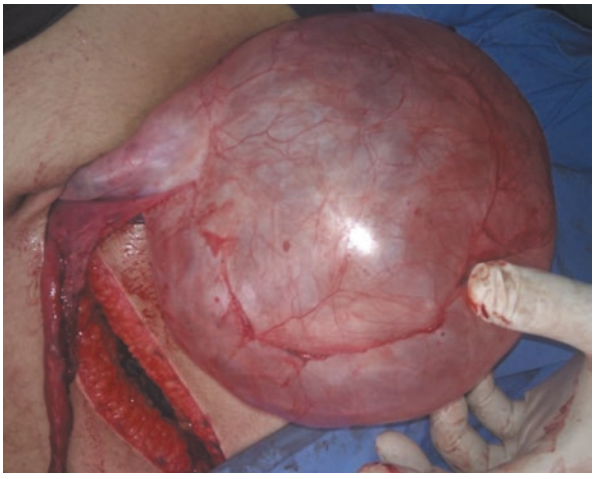


Fig. 17.33 Intraoperative clinical photograph showing a very large ovarian tumor in a child

  - Ascites or peritoneal washings should be sent for cytologic analysis.
  - The omentum should be inspected and affected areas should be resected at this time.
  - Samples of suspicious and involved lymph nodes should be obtained.
  - Gliomatosis peritonei does not worsen the stage of a tumor, but all implants must have mature glial tissue. Immature tissue suggests metastatic disease and requires more intensive therapy.

- In the past, the 10-year survival rate for malignant germ cell tumors ranged from 25% for embryonal carcinoma to 75% for dysgerminoma.
- Today, the overall survival rates are >90%.
- Many patients with simple ovarian cysts based on ultrasound findings do not require treatment.
- Expectant management:
  - Women with small (less than 50 mm in diameter) simple ovarian cysts generally do not require follow-up, as these cysts are very likely to be physiological and almost always resolve within three menstrual cycles.
  - Women with simple ovarian cysts of 50–70 mm in diameter should have yearly ultrasound follow-up and those with larger simple cysts should be considered for either further imaging (MRI) or surgical intervention.
  - For those that are persistent, unchanged, less than 10 cm, and with normal CA 125 values, the likelihood of an invasive cancer is sufficiently low that observation should usually be offered.
  - However, ovarian cysts that persist or increase in size are unlikely to be functional and may need surgical management.

- Surgery
  - If conservative measures fail or criteria for surgery are met, surgical therapy for benign ovarian tumors is generally very effective and provides a cure with minimal effect on reproductive capacity.
  - Persistent simple ovarian cysts larger than 5–10 cm, especially if symptomatic and complex ovarian cysts should be considered for surgical removal.
  - In children and younger women, cystectomy may be preferable to oophorectomy.
  - Laparoscopic surgery for benign ovarian tumors is usually preferable to open surgery.
  - Ovarian torsion (Fig. 17.34a, b):

    This can be treated initially by laparoscopy with untwisting of the affected ovary and possible oophoropexy.
    Salpingo-oophorectomy is indicated if there is severe vascular compromise, peritonitis or tissue necrosis.
    Immediate surgical intervention is indicated for a haemorrhagic cyst.
    Pseudomyxoma peritonei is treated by surgical debulking.

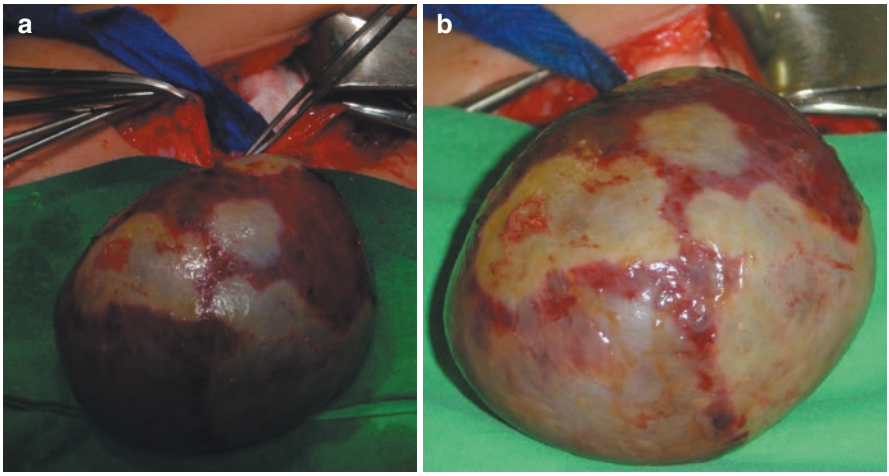


Fig. 17.34 (**a**, **b**) Clinical intraoperative photographs showing ovarian tumor complicated by torsion. Note the change in the colour of the capsule

17.32 Prognosis

- This is variable and depends on:
  - The type of tumor
  - The size of tumor
  - The presence of associated complications
  - The patient's age
  - The histology of tumor
- Most small ovarian cysts in premenopausal women will resolve spontaneously.
- Ovarian torsion:
  - If operated within 6 h of onset of symptoms, tissue will usually remain viable.
- Persistent simple ovarian cysts larger than 10 cm (especially if symptomatic) and complex ovarian cysts should be considered for surgical removal.
- The surgical approaches include an open technique (laparotomy) or a minimally invasive technique (laparoscopy).
- A fertility sparing surgery should be attempted in younger women.

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Chapter 18
Rhabdomyosarcoma of Female Children Genital Tract

Ahmed H. Al-Salem

18.1 Introduction

- Rhabdomyosarcoma is the most common soft tissue sarcoma in children.
- Rhabdomyosarcoma is derived from the Greek words *rhabdo,* which means rod shape, and *myo,* which means muscle.
- Weber was the first to describe rhabdomyosarcoma in 1854.
- Stout in 1946 was the first to give a clear histologic definition of rhabdomyosarcoma.
- He recognized the distinct morphology of rhabdomyoblasts and described rhabdomyoblasts as appearing in round, strap, racquet, and spider forms.
- Rhabdomyoblasts are usually positive for intermediate filaments and other proteins typical of differentiated muscle cells, such as desmin, vimentin, myoglobin, actin, and transcription factor myoD.
- Rhabdomyosarcoma is believed to arise from primitive muscle cells.
- It can occur anywhere in the body except bones where a primary bone rhabdomyosarcoma has not been reported.
- It accounts for 4.5% of all cases of childhood cancer.
- It is the third most common extracranial solid tumor of childhood.
- Rhabdomyosarcoma is a malignant tumor of mesenchymal origin that is included in the group of small round blue cell tumors of childhood.
- Small round blue cell tumors of childhood include:
  - Neuroblastoma
  - Lymphoma

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  - Primitive neuroectodermal tumors
  - Rhabdomyosarcoma

- The most common sites for rhabdomyosarcoma are:
  - The head and neck (28–38%)
  - Extremities (18–24%)
  - Genitourinary tract (18–21%)
  - The trunk (7–11%)
  - Orbit (7%)
  - Retroperitoneum (6–7%)
  - Other sites (<3%)

SMALL ROUND BLUE CELL TUMORS OF CHILDHOOD

- Neuroblastoma
- Lymphoma
- Primitive neuroectodermal tumors
- Rhabdomyosarcoma
- Ewings sarcoma

- The botryoid variant of ERMS arises in mucosal cavities, such as the:
  - Urinary bladder
  - Vagina
  - Nasopharynx
  - Middle ear

SITES OF RHABDOMYOSARCOMAS

• Head and neck	28%-38%
• Genito-urinary tract	18%-21%
• Extremities	18%-24%
• Trunk	7%-11%
• Retroperitoneum	6%-7%
• Orbit	5%-7%
• Other sites	3%-9%

- Lesions in the extremities are most likely to have an alveolar type of histology.
- Rhabdomyosarcoma metastasizes to the:
  - Lungs
  - Bone marrow
  - Bones

  - Lymph nodes
  - Breasts
  - Brain
- The cause of rhabdomyosarcoma is unknown.

SITES OF THE BOTRYOID EMBRYONAL RHABDOMYOSARCOMA

- Urinary bladder
- Vagina
- Nasopharynx
- Middle ear

- Four major histologic subtypes of rhabdomyosarcoma are identified:
  - Embryonal
  - Alveolar
  - Botryoid
  - Pleomorphic/undifferentiated
- The alveolar variant is so named because of the thin criss-crossing fibrous bands that appear as spaces between cellular regions of the tumor (reminiscent of lung alveoli).

HISTOLOGICAL SUBTYPES OF RHABDOMYOSARCOMA

- Embryonal (The commonest type) (60%)
  - Botryoid rhabdomyosarcoma variant (6%)
  - Spindle cell rhabdomyosarcoma variant (3%)
- Alveolar (30%)
- Pleomorphic (Undifferentiated) (2%)

- This variant is usually associated with 1 of 2 chromosomal translocations, namely, t(2;13) or t(1;13).
- These result in the fusion of the DNA-binding domain of the neuromuscular developmental transcription factors, encoded by *PAX3* on chromosome 2 or *PAX7* on chromosome 1, to the transcriptional activation domain of a relatively ubiquitous transcription factor, FKHR (or FOXO1a), which is encoded on chromosome 13.
- Less common translocations involving the *PAX* genes have been found in some rare cases.
- The resulting hybrid molecule is a potent transcription activator. It is believed to contribute to the cancerous phenotype by abnormally activating or repressing other genes.

- The embryonal subtype usually has a loss of heterozygosity at band 11p15.5; this observation suggests the presence of a tumor suppressor gene.
- Other molecular aberrations that may provide clues to the origin of the tumor and that may be useful for future treatment strategies include *TP53* mutations (which occur in approximately one half of patients), an elevated N-myc level (in 10% of patients with alveolar rhabdomyosarcoma), and point mutations in N-*ras* and K-*ras* oncogenes (usually embryonal).
- In addition, levels of insulinlike growth factor-2 may be elevated, suggesting pathways involving autocrine and paracrine growth factors.
- Rhabdomyosarcoma may be associated with certain genetic disorders including:
  - Beckwith-Wiedemann syndrome
  - Costello syndrome
  - Neurofibromatosis type 1
  - Li-Fraumeni syndrome
  - Noonan syndrome
- Sarcoma botryoides is a malignancy that arises from embryonal rhabdomyoblasts.
- It is also called embryonal rhabdomyosarcoma.
- The word botryoid in Greek means a bunch of grapes which characteristically describes the clinical appearance of the tumor.
- It is the most common soft tissue sarcoma in childhood and young adulthood, and account for 4–6% of all malignancies in this age group.
- The botryoid embryonal rhabdomyosarcoma:
  - This is a rare variant.
  - It arises in mucosal cavities, such as:

    The vagina
    Bladder
    Nasopharynx
    Middle ear
- Sarcoma botryoides is usually reported as a vaginal tumor in female reproductive tract of infants.
- However, it also occurs rarely in the cervix or uterine fundus.
- Unlike its counterpart in the vagina, which has poor prognosis, sarcoma botryoides of the cervix in young women has a favorable outlook.
- The survival rate of vaginal and cervical lesions has been reported to be 60–96%, respectively.
- Vaginal bleeding is the most common presenting feature even though non-specific.
- It may also present as a polypoid or fleshy mass in the vagina, or more classically projecting from the introitus.
- Other forms of presentations include urinary symptoms especially when the tumor is anteriorly situated or tenesmus where there is posterior extension.

- There are different approaches in the management of this tumor, from simple excision to extensive radical mutilating procedures.
- These procedures may be combined with radiotherapy.
- However radiotherapy has been abandoned as it is now generally agreed that these tumors are not radiosensitive.
- New multidrug chemotherapy regimens with or without radiotherapy are also used in combination with less radical surgery with good results, although outcome data are not yet available.
- Radical surgery takes the center stage in treatment as the disease is uniformly fatal with a 5-year survival rate of between 10 and 35%.
- Sarcoma botryoides has marked tendency for recurrence locally after excision and to invade adjacent organs.

18.2 Histology

- Rhabdomyosarcoma is a fast-growing, primitive, high-grade, malignant mesenchymal tumor.
- Embryonal rhabdomyosarcoma is the commonest malignant tumor arising in the pediatric female genitourinary tract.
- It makes up 60–70% of all Rhabdomyosarcomas.
- Sarcoma botryoides is the most common variant.
- The tumor cells of rhabdomyosarcoma are characterized by histological features that more or less can be found in the cells of skeletal muscles (Fig. 18.1a, b).
- The cells show a close resemblance to various stages in the embryogenesis of normal skeletal muscle.
- These features are essential for the diagnosis and depend on their degree of differentiation. These features include:
  - The presence of myofibrils and cross striations (on light and electron microscopy).
  - The tumor cells are positive immunohistochemical staining for markers of muscle differentiation such as desmin and myoD1.

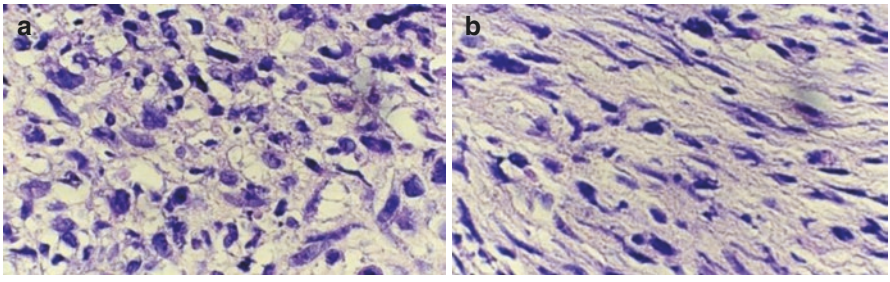


Fig. 18.1 (**a**, **b**) Histological slides showing cells separated by fibrous septa. Note the large nuclei

- Based on morphology, RMS is traditionally subdivided into three types:
  - Embryonal
  - Alveolar
  - Pleomorphic
  - Botryoid rhabdomyosarcoma and spindle-cell rhabdomyosarcoma are considered subtypes of embryonal rhabdomyosarcoma.
- When embryonal rhabdomyosarcoma arise in the submucosa, they may present as a fast-growing exophytic, polypoidal mass.
  - This macroscopic variant is called botryoid embryonal rhabdomyosarcoma.
  - This botryoid embryonal rhabdomyosarcoma is a primary exophytic and not invasive tumor and because of this it has a better prognosis.
- Rhabdomyosarcoma is one of the small, round blue-cell tumors of childhood which include:
  - Neuroblastoma
  - Rhabdomyosarcoma
  - Ewings sarcoma
  - Non-Hodgkin lymphoma
  - Primitive neuroectodermal tumors
- Occasionally, these types of tumors can be difficult to differentiate histologically.
- Rhabdomyosarcoma is divided into 5 major histologic types (Figs. 18.2, 18.3 and 18.4):
  - Embryonal
  - Alveolar
  - Botryoid embryonal
  - Spindle cell embryonal
  - Anaplastic

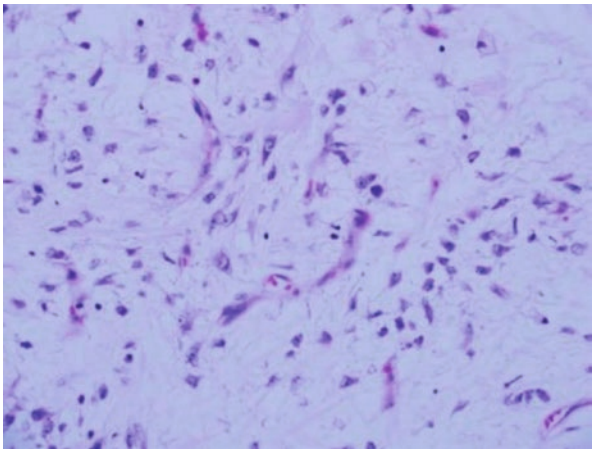


Fig. 18.2 Histological slide showing rhabdomyoblasts with myxoid background

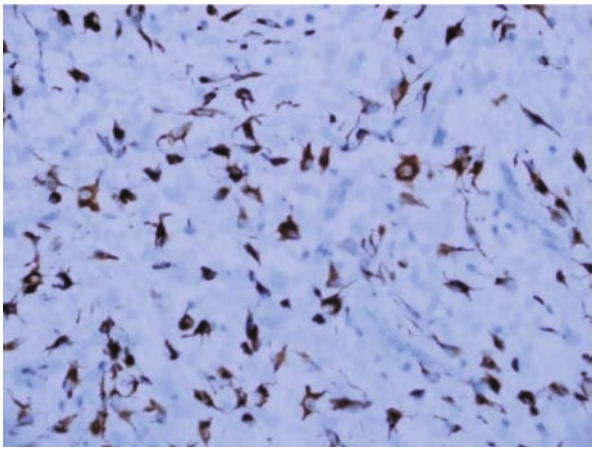


Fig. 18.3 A histological slide showing rhabdomyoblasts positive for vimentin and desmin

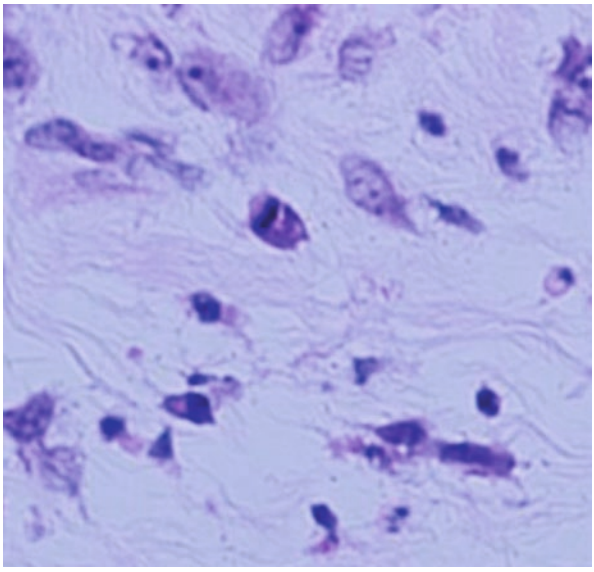


Fig. 18.4 A histological slide showing mitoses in a rhabdomyosarcoma

- This histological classification is important for treatment and prognosis.
- Embryonal rhabdomyosarcoma:
  - Embryonal rhabdomyosarcoma is the most common subtype observed in children.
  - It account for approximately 60% of all cases in this age group.
  - The tumors can occur at any site, but they are most commonly observed in the genitourinary region or the head and neck region.
  - They have high cytological variability.

- They may range from highly differentiated neoplasms containing rhabdomyoblasts with large amounts of eosinophilic cytoplasm and cross striations similar to that of poorly differentiated tumor cells.
- These are desmin and actin positive.
- Embryonal rhabdomyosarcoma consists of:

  Small, round cells with hyperchromatic nuclei.
  Large, polygonal-shaped cells with abundant eosinophilic cytoplasm.
  Often contains diagnostic cross striations.

- Embryonal rhabdomyosarcoma cells show a loss of specific genome material from the short arm of chromosome 11 (11p15 region).
- Another molecular feature is its lack of gene amplification.
- The cellular DNA content of embryonal rhabdomyosarcoma is hyperdiploid (1.1–1.8 X normal DNA).

• Alveolar rhabdomyosarcoma:

- The alveolar subtype makes up about 31% of all cases of rhabdomyosarcoma.
- It is most frequently observed in adolescents and in patients whose primary sites involve the extremities, the trunk, and the perianal and/or perirectal region.
- On microscopy, alveolar rhabdomyosarcoma:

  Have the appearance of club-shaped tumor cells arranged in clumps and outlined by fibrous septa.
  In the center, the clusters are arranged loosely, and therefore, they appear in an alveolar pattern.
  Cells stain intensely with eosinophilic stain.
  Cross-striated malignant rhabdomyoblasts are observed in 25% of cases.

- Alveolar rhabdomyosarcoma consists of:

  Uniform cells with a high nuclear-to-cytoplasmic ratio.
  The cells are arranged in variably sized nests separated by fibrous tissue septa.
  In places, the cells appear loosely dispersed, mimicking a pulmonary alveolar pattern.

- Alveolar rhabdomyosarcoma has a unique translocation which occurs between the *FKHR* gene on chromosome 13 and either the *PAX3* gene on chromosome 2 (70%) or the *PAX7* gene on chromosome 1 (30%).
- Alveolar rhabdomyosarcoma commonly demonstrates gene amplification, and its DNA content is typically tetraploidy.

• Botryoid rhabdomyosarcoma:

- This is a subset of embryonal rhabdomyosarcoma.
- It accounts for 6% of all cases of rhabdomyosarcoma.

  - This subtype characteristically arises under the mucosal surfaces of body orifices such as the:

    Vagina
    Bladder
    Nares

  - It is distinguished by the formation of polypoid and grapelike tumors.
  - On histology, it shows malignant cells in an abundant myxoid stroma.

- Spindle cell rhabdomyosarcoma:

  - This is a subtype of embryonal rhabdomyosarcoma.
  - It accounts for 3% of all cases.
  - It is characterized by:

    A fascicular, spindled, and leiomyomatous pattern.
    Rhabdomyoblastic differentiation.
    Marked collagen deposition.
    A nested, storiform growth pattern.

  - This subtype occurs predominantly in the paratesticular region and is rare in the head and neck.

- Anaplastic rhabdomyosarcoma:

  - This is previously called pleomorphic rhabdomyosarcoma.
  - It is the least common of all subtypes of rhabdomyosarcomas.
  - It occurs most commonly in patients aged 30–50 years and rarely seen in children.
  - Anaplastic rhabdomyosarcoma is characterized by large, lobate hyperchromatic nuclei and multipolar mitotic figures.

18.3 Botryoid Embryonal Rhabdomyosarcoma

18.4 Introduction

- This is also called Sarcoma botryoides.
- It is also called:

  - Embryonal Rabdomyosarcoma of Vagina
  - Vaginal Embryonal Rhabdomyosarcoma

- The word botryoid in Greek means a "bunch of grapes" and this characteristically describes the clinical appearance of the tumor as it protrudes from the introitus.
- Botryoid morphology is characteristic, but not specific for rhabdomyosarcoma within the vagina because yolk sac tumor may have a similar appearance.
- Sarcoma botryoides is a vaginal tumor arising in female reproductive tract of infants.
- It is the most common malignancy arising in the genitourinary tract of female children prior to the age of 15.
- Rhabdomyosarcoma of Vagina is a very uncommon, high-grade malignant tumor of the vagina.
- It is a rare and invasive tumor affecting very young girls, less than 5 years old.
- It typically affects very young girls (mostly below age 2 years).
- Over 90% of Embryonal Rhabdomyosarcoma of Vagina is seen in children below the age of 5 years.
- The average age is around 1.8 years.
- There are 3 types of rhabdomyosarcomas:
  - Embryonal
  - Alveolar
  - Pleomorphic (anaplastic)
- Embryonal Rhabdomyosarcoma of Vagina is the most common histological subtype of vaginal rhabdomyosarcoma and the most common soft tissue tumor in childhood.
- The vast majority of cases occur sporadically with no recognized predisposing risk factors, although in a small proportion of the cases there may be a genetic link between cervical rhabdomyosarcoma and other primary tumors; most notably Sertoli–Leydig tumor.
- Typically, grape-like structure arises under the mucosal surface of the organs and the vagina is the most common site.
- They present with vaginal bleeding and a vaginal mass.
- Some patients may present with additional symptoms included leukorrhea, bleeding and malodorous discharge.
- The three criteria essential for the diagnosis of botryoid variety of rhabdomyosarcoma are:
  - A polypoid appearance of the lesion
  - An origin below a mucous membrane covered surface
  - The presence of a cambium layer
- The role of histopathology in the diagnosis of rhabdomyosarcoma cannot be underestimated and it is the gold standard test in the diagnosis.

- Although three varieties of RMS have been described (Embryonal, Alveolar and Undifferentiated), the embryonal type is the most common and has a favorable prognosis, whereas the alveolar type is rare with a poor prognosis.
- Embryonal rhabdomyosarcoma of the cervix must be distinguished pathologically from adenosarcomas, malignant mixed Müllerian tumors and low-grade stromal sarcomas as the optimal management strategies and clinical outcomes differ for each.
- There are many reports of neoadjuvant chemotherapy being used to shrink large tumors before the surgery.
- The optimal number of adjuvant chemotherapy cycles needed varies; it depends upon the clinical and radiological response.
- The VAC protocol is the most widely used chemotherapy regimen in rhabdomyosarcoma.
- 10 cycles of VAC protocol (vincristine, d-actinomycin and cyclophosphamide) may be given.
- Surgery should aim to preserve the ovarian function knowing that she may receive radiation therapy too.
- Limited surgery with adjuvant chemotherapy and/or irradiation showed improved survival.

18.5 Clinical Features

- This is commonly seen in infants or children less than 2 years old.
- Their most common presentation is vaginal bleeding.
- They may also present as a polypoid or fleshy (grape-like) mass of polyps in the vagina.
- They may present as an infiltrative mass in the vagina.
- More commonly, they present as a fleshy polypoid mass projecting from the introitus.
- The tumor may appear fluid-filled (edematous).
- In some cases, the skin overlying the mass may ulcerate and result in bleeding.
- Other presentations include:
  - Urinary symptoms, especially when the tumor is anteriorly situated.
  - Leukorrhea and malodorous discharge.
  - Frequent urination due to compression and pressure of the tumor.
  - The tumor may obstruct the bladder and lead to retention of urine
  - Tenesmus when the tumor has a posterior extension.
  - Pain in the pelvic or abdominal region.
  - Lower back pain

- The survival rate of vaginal and cervical lesions has been reported to be 60–96%, respectively.
- Invasion of adjacent structures by the primary tumor may make the precise origin of genitourinary rhabdomyosacoma difficult to determine on cross-sectional images.
- Recent refinements in multidisciplinary imaging modalities have dramatically improved the diagnosis of genitourinary RMS.
- Diagnostic imaging also plays an important role in monitoring response to therapy.

18.6 Investigations and Diagnosis

- History and a thorough physical examination
- Ultrasonography:
  - Rhabdomyosarcoma presents as a well-defined, slightly hypoechoic inhomogeneous mass that can show significantly increased blood flow.
  - Ultrasonography can also demonstrate pelvic retroperitoneal lymphadenopathy.
  - Via ultrasonography, an image-guided biopsy of the tumor can be obtained.
  - A 3-D ultrasonography can be used to demonstrate the relation of vaginal rhabdomyosarcoma mass to the fornices and the cervical lip which may suggest local invasion.
  - A transvaginal ultrasound of the uterus if feasible can provide an image of the vagina and surrounding pelvic organs.
- Plain chest x-ray can provide evidence if the tumor has spread to the lungs.
- CT scans are rarely used to diagnose vaginal cancer, but can be used to determine if metastasis to other sites especially the lungs has occurred
- MRI:
  - MRI is the primary imaging modality to investigate rhabdomyosarcoma.
  - It is superior to ultrasound ad CT-scan.
  - Axial T1-weighted and T2-weighted images are important for anatomic detail and assessment of neurovascular structures.
  - Other images include coronal T1-weighted images, and imaging after gadolinium administration.
  - It is important that at least two series should be identical, one before and one after contrast agent administration.
  - Contrast-enhanced series are mandatory and ideally be performed with fat saturation.
  - Rhabdomyosarcoma show low to intermediate signal intensity on T1-weighted images and on T2-weighted images they tend to be of intermediate-to-high signal intensity.

  - The high T2 signal due to abundant myxoid stroma within these tumors may give it a multiseptated cystic appearance and suggest the botryoid variant.
  - On post contrast imaging rhabdomyosarcoma demonstrate strong enhancement.
  - In very rare instances, the tumor may show a predominantly cystic appearance.
- Positron emission tomography-Computed tomography (PET-CT) and CT studies are valuable when investigating for metastasis.
- A vaginal biopsy may be necessary to establish the diagnosis and type of rhabdomyosarcoma.

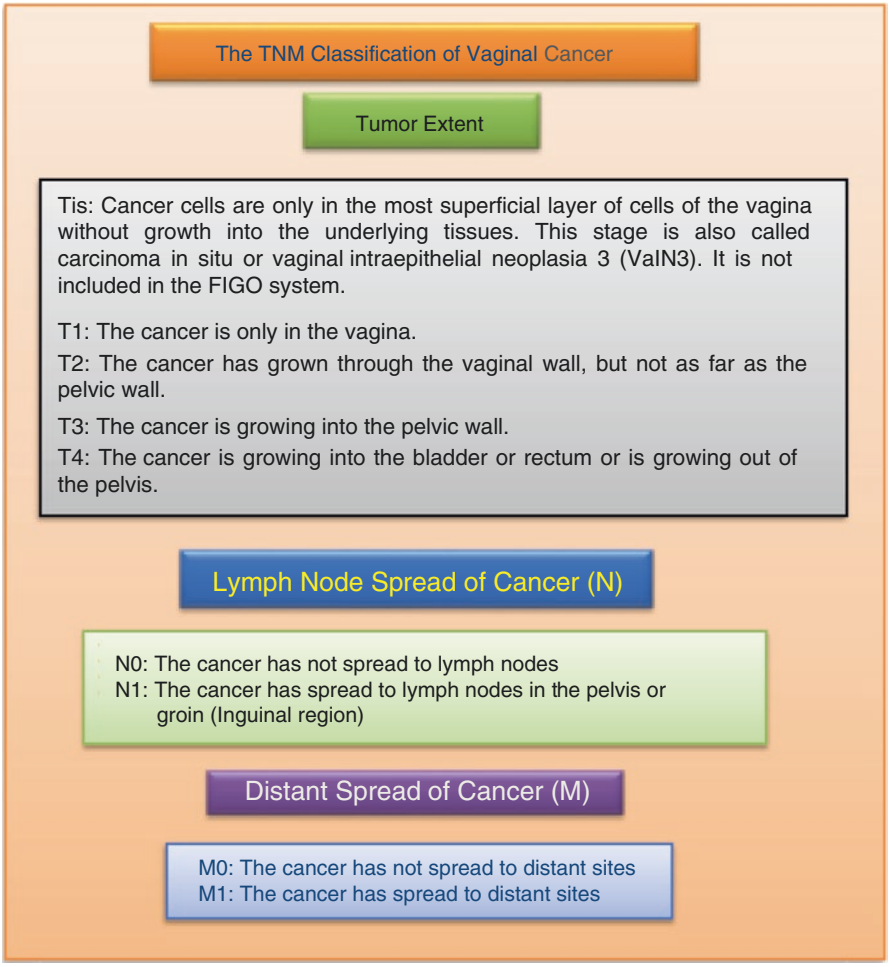
18.7 Staging

- Once a diagnosis of vaginal cancer has been made, it is important to assess spread and establish a stage of the tumor.
- The staging for vaginal cancer is based upon the FIGO (International Federation of Gynecology and Obstetrics) and the AJCC (American Joint Committee on Cancer) TNM staging systems.
- The TNM classification for vaginal cancer:
  - Tumor extent (T):

    Tis: Cancer cells are only in the most superficial layer of cells of the vagina without growth into the underlying tissues. This stage is also called carcinoma in situ (CIS) or vaginal intraepithelial neoplasia 3 (VaIN 3). It is not included in the FIGO system
    T1: The cancer is only in the vagina
    T2: The cancer has grown through the vaginal wall, but not as far as the pelvic wall
    T3: The cancer is growing into the pelvic wall
    T4: The cancer is growing into the bladder or rectum or is growing out of the pelvis
  - Lymph node spread of cancer (N):

    N0: The cancer has not spread to lymph nodes
    N1: The cancer has spread to lymph nodes in the pelvis or groin (inguinal region)
  - Distant spread of cancer (M)

    M0: The cancer has not spread to distant sites
    M1: The cancer has spread to distant sites



- Stage grouping: Once the T, N, and M categories have been assigned, an overall stage is assigned as follows:
  - Stage 0 (Tis, N0, M0):

    In this stage, cancer cells are only in the top layer of cells lining the vagina (the epithelium) and have not grown into the deeper layers of the vagina
    Cancers of this stage cannot spread to other parts of the body
    Stage 0 vaginal cancer is also called carcinoma in situ (CIS) or vaginal intraepithelial neoplasia 3 (VaIN 3)
    This stage is not included in the FIGO system

– Stage I (T1, N0, M0):

  The cancer has grown through the top layer of cells but it has not grown out of the vagina and into nearby structures (T1)
  It has not spread to nearby lymph nodes (N0) or to distant sites (M0)

– Stage II (T2, N0, M0):

  The cancer has spread to the connective tissues next to the vagina but has not spread to the wall of the pelvis or to other organs nearby (T2)
  The pelvis is the internal cavity that contains the internal female reproductive organs, rectum, bladder, and parts of the large intestine
  It has not spread to nearby lymph nodes (N0) or to distant sites (M0)

– Stage III - either of the following:

  T3, any N, M0:

  • The cancer has spread to the wall of the pelvis (T3)
  • It may (or may not) have spread to nearby lymph nodes (any N), but it has not spread to distant sites (M0)
    OR

  T1 or T2, N1, M0:

  • The cancer is in the vagina (T1) and it may have grown into the connective tissue nearby (T2)
  • It has spread to lymph nodes nearby (N1), but has not spread to distant sites (M0)

– Stage IVA (T4, Any N, M0):

  The cancer has grown out of the vagina to organs nearby (such as the bladder or rectum) (T4)
  It may or may not have spread to lymph nodes (any N)
  It has not spread to distant sites (M0)

– Stage IVB (Any T, Any N, M1):

  Cancer has spread to distant organs such as the lungs (M1)

Stage 0 (Tis, N0, M0)

- In this stage, cancer cells are only in the top layer of cells lining the vagina (the epithelium) and have not grown into the deeper layers of the vagina.
- Cancers of this stage cannot spread to other parts of the body.
- Stage 0 vaginal cancer is also called carcinoma in situ or vaginal intraepithelial neoplasia 3 (VaIN3).
- This stage is not included in the FIGO system.

Stage I (T1, N0, M0)

- The cancer has grown through the top layer of cells but it has not grown out of the vagina into nearby structures (T1).
- It has not spread to nearby lymph nodes (N0) or to distant sites (M0)

Stage II (T2, N0, M0)

- The cancer has spread to the connective tissues next to the vagina but has not spread to the wall of the pelvis or to other organs nearby (T2)
- The pelvis is the internal cavity that contains the internal female reproductive organs, rectum, bladder, and parts of the large intestine.
- It has not spread to nearby lymph nodes (N0) or to distant sites (M0)

Stage III

T3, any N, M0

- The cancer has spread to the wall of the pelvis (T3)
- It may (or may not) have spread to nearby lymph nodes (any N), but it has not spread to distant sites (M0)

OR

T1 or T2, N1, M0

- The cancer is in the vagina (T1) and it may have grown into the connective tissue nearby (T2)
- It has spread to lymph nodes nearby (N1), but has not spread to distant sites (M0)

Stage IVA (T4, Any N, M0)

- The cancer has grown out of the vagina to organs nearby (such as the bladder or rectum) (T4)
- It may or may not have spread to lymph nodes (any N)
- It has not spread to distant sites (M0)

Stage IVB (Any T, any N, M1)

- Cancer has spread to distant organs such as the lungs (M1)

18.8 Treatment and Outcome

- Rhabdomyosarcoma of vagina is treated using several methods depending on the stage of the cancer.
- The treatment options may include the following measures:
  - If the tumor can be surgically removed with minimal damage and mutilation of the genitalia, then a conservative surgery is the first option.
  - Otherwise, a combination of radiation and chemotherapy may be administered to shrink and confine the tumor, before invasive procedures are undertaken.
- Following a surgical excision and tumor removal, chemotherapy and/or radiation therapy may be administered.
- Radiation therapy and chemotherapy may be necessary for metastatic cancer.
- Advanced stage tumors with metastasis may be treated symptomatically with radiation and/or chemotherapy.
- A combination of stem cell transplant with chemotherapy may be necessary to treat the more aggressive tumors.
- Surgery:
  - Surgery is the most common treatment option for Embryonal Rhabdomyosarcoma.
  - Vaginectomy:

    Partial vaginectomy: The removal of a part of the vagina.
    Total vaginectomy: The removal of the entire vagina.
    Radical vaginectomy: The removal of the vagina and its surrounding affected structures/tissues.

  - Radical trachelectomy:

    This involves the removal of the cervix, upper part of the vagina, and nearby lymph nodes, while preserving the ability to have children in the future.
  - Pelvic exenteration:

    This involves the removal of the entire vagina, the surrounding tissues, and the pelvic lymph nodes.
    In addition, depending on the extent of tumor spread, parts affected around the region (such as the cervix, uterus, rectum, colon, etc.) may be removed.

  - Arterial embolization may be used to provide temporary relief from the symptoms, and reduce blood loss during surgical excision.
- Chemotherapy:
  - Chemotherapy may be used in addition to radiation and/or surgery.
  - Chemotherapy is used to treat cancers that have spread or recurred.

- When chemotherapy and radiation therapy are used together, it is called concurrent chemoradiation.
- The VAC protocol is the most widely used chemotherapy regimen in rhabdomyosarcoma.
- 10 cycles of VAC protocol (vincristine, d-actinomycin and cyclophosphamide) may be given.
- Side effects of chemotherapy may include:

  Nausea and vomiting
  Hair loss
  Loss of appetite
  Diarrhea
  Fatigue
  Increased risk of infection
  Mouth sores
  Easy bruising

- Radiotherapy:
  - Possible side effects may include:

    Fatigue, nausea, vomiting, and diarrhea
    Bladder irritation, leading to cystitis
    Ovaries may be affected resulting in menstrual changes, or premature menopause.
    The vulva and vagina may be affected, causing soreness, or even scar tissue formation

- The prognosis of Embryonal Rhabdomyosarcoma of Vagina depends on a combination of factors that include:
  - The size of the tumor and the extent of its invasion
  - Stage of cancer
  - Cell growth rate of the cancer
  - Overall health of the patient
  - Involvement of the regional lymph nodes
  - Involvement of vital organs
  - The surgical respectability of the tumor
  - Whether the tumor is occurring for the first time, or is a recurrent tumor.
  - Response to treatment
  - Progression of the condition

- As a result of medical advancements and comprehensive treatment, the prognosis of Embryonal Vaginal Rhabdomyosarcoma has shown great improvement.
- The overall cure rates range from between 90 and 95%.
- The 10 year survival rate is around 90%.
- Prognosis based on risk groups:

- The overall survival rate at 5 years for low risk group is more than 90%.
- The overall survival rate at 5 years for intermediate risk group is 55–70%.
- The overall survival rate at 5 year for high risk group is approximately 30%.

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Chapter 19
Disorders of Sexual Development

Ahmed H. Al-Salem

19.1 Introduction

- In the past several names such as intersex or ambiguous genitalia were used to describe disorders of sexual development but they were not accurately descriptive.
- The term hermaphroditism, after the Greek god of sexuality Hermes and the goddess of love and sexuality, Aphrodite was also used to describe disorders of sexual development.
- All these were replaced by the term Disorders of Sexual Development (DSD).
- This was coined by International Consensus Conference on Intersex organized by the Lawson Wilkins Pediatric Endocrine Society and the European Society for Pediatric Endocrinology in 2006.
- DSD is currently used to describe various disorders of sexual development and it replaces the earlier terms Intersex and ambiguous genitalia which were controversial and associated with a lot of confusion and social stigma.
- Although there are still some potential criticisms to this nomenclature, DSD terminology has been generally accepted and is now popularly used in the literature.
- Disorders of sexual development include:
  - A variety of conditions in which the reproductive system or the external genitalia are not normal for a female or male.
- There are three general descriptive terms used to describe the sex of a person:
  - Genotypic sex: This depends on the presence of 46, XX or 46, XY chromosomes.

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  - Anatomical sex: This depends on the presence of a uterus, ovaries and tubes for females and testes, epididymis, seminal vesicles, ejaculatory ducts and prostate for males.
  - Phenotypic sex: This results from the differentiation of the external genitalia under the influence of sex-determining genes and hormones.

- Abnormalities in any of these result in a range of conditions that lead to abnormal development of the sex organs and genitalia (Disorders of sex development) (Figs. 19.1a, b, 19.2, 19.3, 19.4, 19.5a, b, 19.6a, b).
- Children with DSD often have both male and female characteristics internally as well as externally.
- When a child is born with DSD, the gender may not be obvious.
- The development of sex organs and external genitalia is a very complex process that starts at around 7–8 weeks of pregnancy in the developing fetus and is complete by 12 weeks.
- DSD occurs in 1 in 4500 live births.
- The most common DSD is Congenital Adrenal Hyperplasia (CAH).
- This results in a female (XX chromosomes) having genitals that look somewhat masculine.
- In mild cases, CAH results in a slightly enlarged clitoris.
- In more severe cases it can be difficult to decide whether a baby is male or female.
- Most children with CAH think of themselves as girls (Fig. 19.4).
- CAH when it occurs in males (XY), the result is over-masculinization and premature puberty.
- Another common DSD is Androgen Insensitivity Syndrome (AIS).

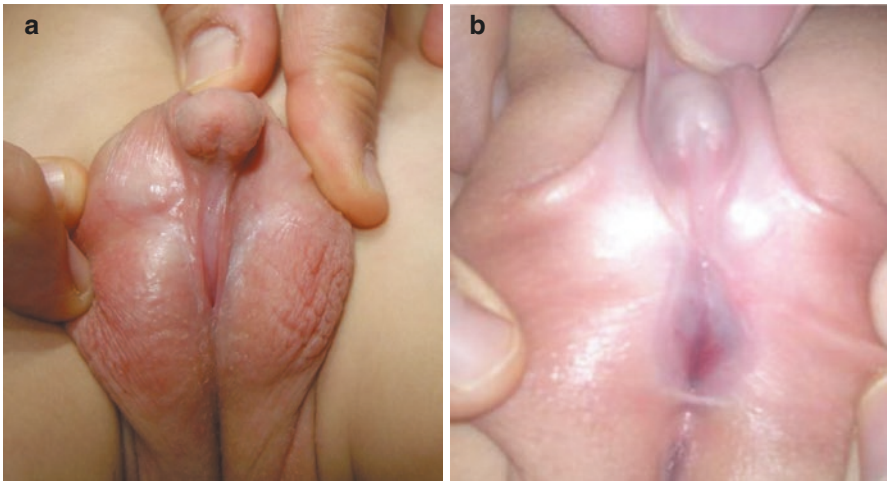


Fig. 19.1 (**a**, **b**) Clinical photographs of patients with severe hypospadias (Perineal hypospadias). These patients should be investigated to roll out DSD

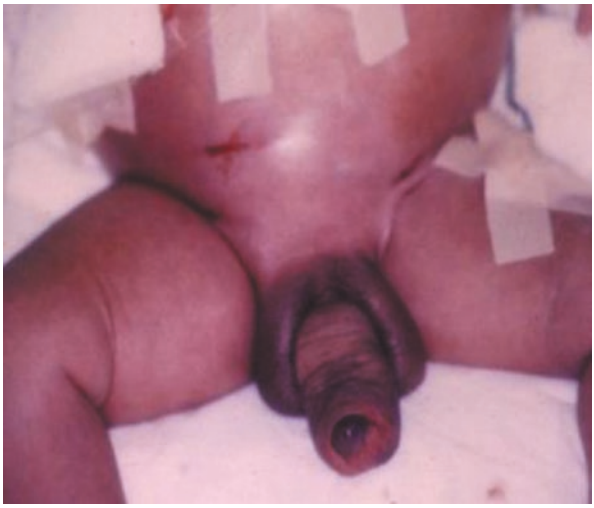


Fig. 19.2 A clinical photograph of a patient with DSD. It is difficult to decide whether this is a true male or not. This patient was investigated and found to have severe virilization secondary to congenital adrenal hyperplasia leading to enlargement of the clitoris resembling a male penis

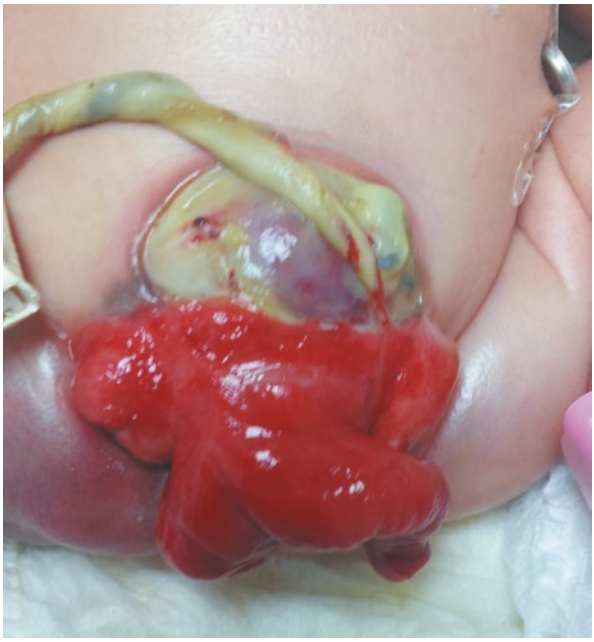


Fig. 19.3 A clinical photograph of a newborn with cloacal extrophy. In this patient, there are no clear external genitalia and this patient needs further evaluation prior to sex assignment

- This occurs in males (XY chromosomes) who do not respond to testosterone normally.
- This results in a feminine appearance.
- There are two types, complete and partial.

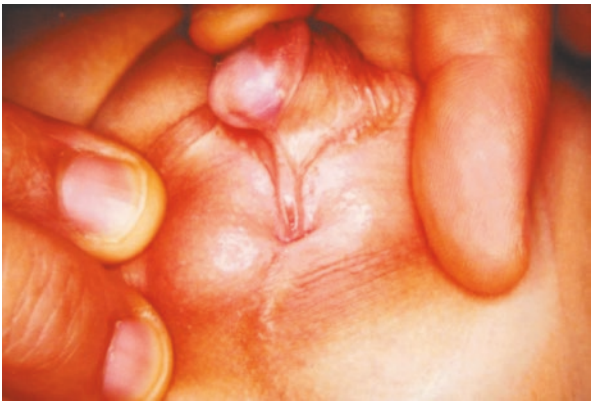


Fig. 19.4 A clinical photograph showing a newborn with congenital adrenal hyperplasia. Note the enlarged clitoris and the abnormally looking external genitalia

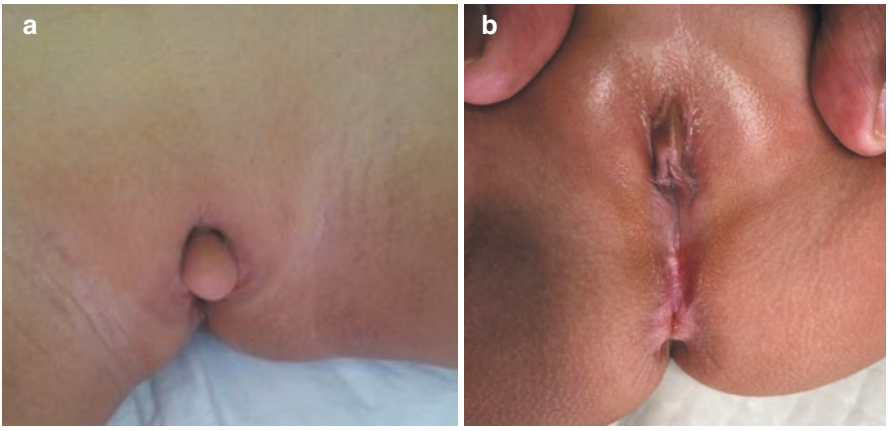


Fig. 19.5 (**a**, **b**) Clinical photographs showing abnormal external genitals. This female patient was found to have a dermoid cyst overring the clitoris causing abnormalities of the external genitalia. The other patient has fused labia

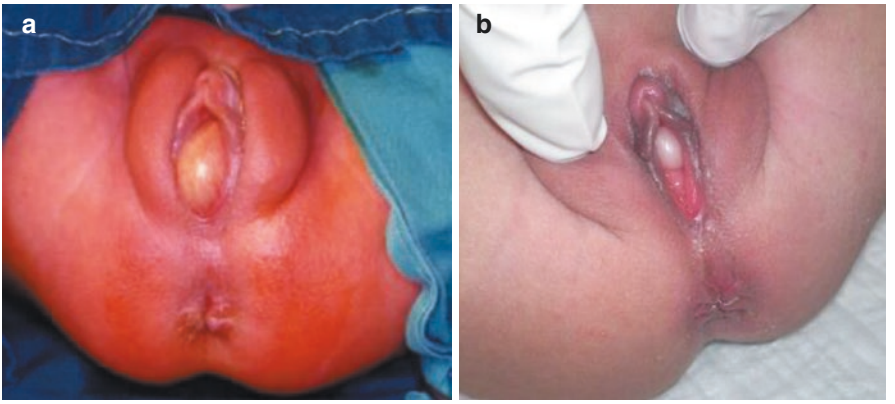


Fig. 19.6 (**a**, **b**) Clinical photographs of two newborns with imperforated hymen with hydrocolpos causing abnormalities of external genitalia and a paraurethral cyst

  - In Complete Androgen Insensitivity Syndrome (CAIS) the result is a totally feminine appearance, including typical female breast development.
  - In the Partial Androgen Insensitivity Syndrome (PAIS), the genitals can vary from mostly female to almost completely male.

- One of the more unusual DSDs is 5-Alpha Reductase Deficiency (5ARD), popularly known as "Penis at 12."
- It is caused by a deficiency of the enzyme 5-Alpha Reductase which converts testosterone to dihydrotestosterone.
- Dihydrotestosterone is responsible for the development of the male external genitalia.
- The management of patients with DSD has also changed over the years.
- In the past, corrective surgeries were often performed in infancy, but in recent years the tendency has been to postpone surgery until the child has expressed a clear gender preference and is old enough to participate actively in decisions about his/her medical and surgical treatment.

19.2 Embryology and Physiology of Sex Development

- Normal sexual differentiation depends on the genetic sex (XX or XY), which is established at the time of conception.
- Until about 7 weeks of gestation, the fetus is sexually indifferent with:
  - Two different bipotential gonads which can develop into testes or ovaries.
  - And two internally developing Wolffian and Mullerian ducts.
- Embryologically, there are two undifferentiated bipotential gonads in every embryo.
- These bipotential gonads develop from the urogenital ridge and ultimately develop into either a testis or an ovary.
- In addition to these bipotential gonads, fetuses of both sexes have two sets of internal ducts which develop by 6–7 weeks of intra-uterine life:
  - The Müllerian ducts
  - The Wolffian ducts
- Expression of sex-determining genes on the early bipotential gonad promotes development of the gonad into a testis or ovary.
- Various genes expressed by the Y chromosome at very specific times during development are responsible for the differentiation of the testes.
- A 35-kilobase (kb) gene determinant located on the distal short arm of the Y chromosome, known as the SRY (sex determining region of the Y chromosome)

is responsible for initiating testes formation (the development of the bipotential gonad into testes).

- SRY codes for a transcription factor that acts in the somatic cells of the genital ridge.
- Expression of this gene triggers a cascade of events that ultimately leads to the development of testicular Sertoli and Leydig cells.
- SRY expression directs testicular morphogenesis, leading to the production of MIS (Müllerian-Inhibiting Substance), and, later, testosterone.
- The external genitalia at 6–7 weeks gestation appear female and include a genital tubercle, the genital folds, urethral folds and a urogenital opening.
- Male Differentiation:
  - The male sexual differentiation depends on two important steps:

    The development of the bipotential gonad into a testis.
    Internal and external genitalia differentiation.

  - The development of the bipotetial gonad into a testis occurs at about the sixth week of gestation.
  - The SRY gene that is located on the short arm of the Y-chromosome (Yp11.3) is responsible for this as it initiates sex differentiation by downstream regulation of sex-determining factors.
  - Expression of several genes including WT1, CBX2 (M33), SF1, GATA4/FOG2 is critical to SRY activation.
  - The SOX9 gene, located on 7q24.3–25.1, is essential for early testis development.
  - The second step in male sex differentiation involves internal and external genitalia differentiation.
  - There are two types of cells in the developing gonad.
  - These cells are:

    The Leydig cells
    The Sertoli cells

  - The Sertoli cells produce the anti-Müllerian hormone (AMH).
  - The Leydig cells produce androgens.
  - The AMH acts on its receptor in the Müllerian ducts and causes their regression.
  - Androgens act in a critical concentration-dependent and time-dependent manner to induce male sexual differentiation.

  - Testosterone acts on the androgen receptor in the Wolffian ducts to induce the formation of:

    Epidydimis
    Ejaculatory ducts
    Seminal vesicles

  - The Leydig cells also produce insulin-like factor 3 (INSL3, relaxin-like factor).
  - Insulin-like factor 3 plays a role in the descent of testes to the scrotum.
  - Testosterone is also converted to dihydrotestosterone (DHT) under the influence of 5-alpha reductase enzyme.
  - Dihydrotestosterone acts on the androgen receptor of the prostate and external genitalia to cause its masculinization.
  - Binding of Testosterone and Dihydrotestosterone (DHT) to androgen receptors is necessary for androgen effect.

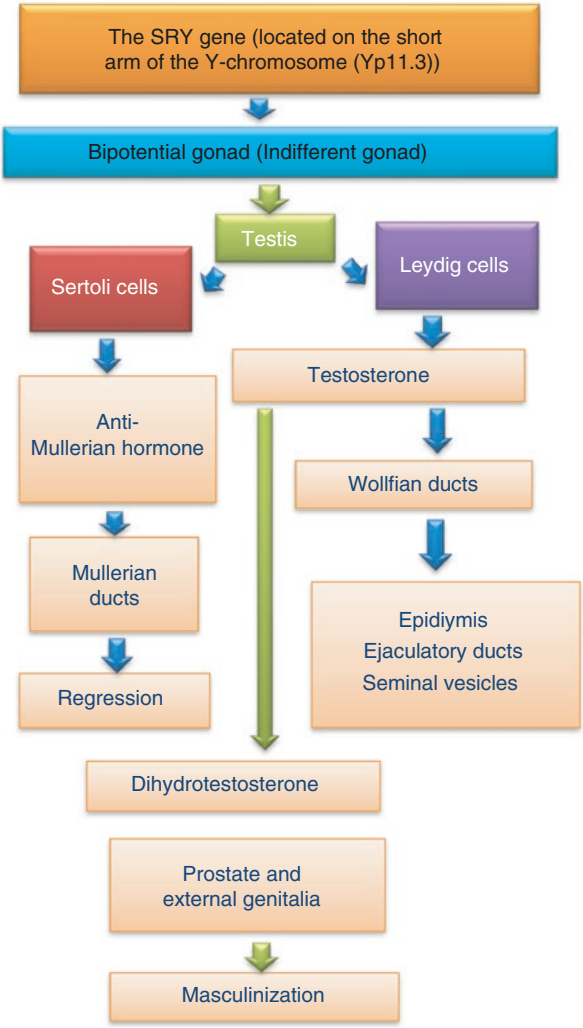
- Female Differentiation:

  - In the absence of SRY gene, the bipotential gonad develops into an ovary.
  - DAX1 gene is necessary for both testicular and ovarian development.
  - WNT4-signaling pathway plays a major role in ovarian development, Müllerian ducts development and ovarian steroidogenesis.
  - The second step in female sex differentiation involves internal and external genitalia differentiation
  - Absence of the anti-mullerian hormone which is secreted by the testes leads to development of the Mullerian ducts.
  - The Müllerian ducts give rise to:

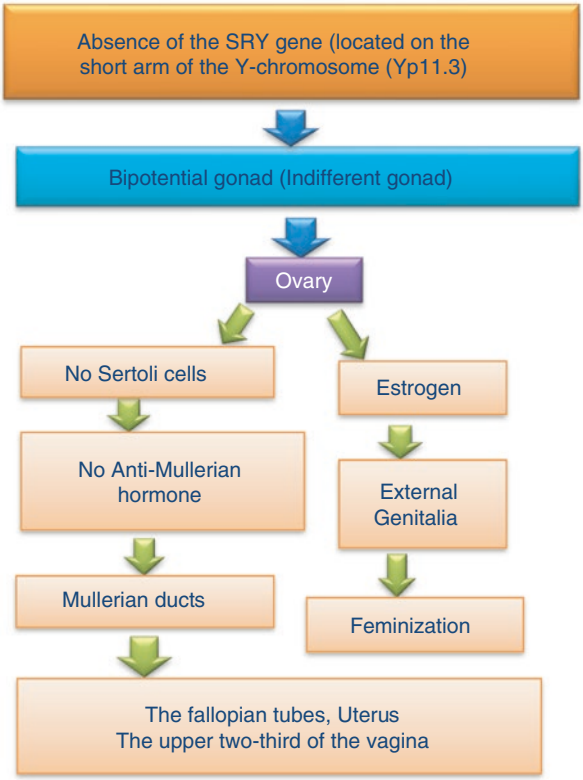
    The fallopian tubes
    The uterus
    The upper two-third of the vagina

  - Absence of testosterone leads to regression of the Wollfian ducts.
  - Estrogen secreted by the developing ovary leads to the development of the external genitalia of the female.
  - In the female:

    The genital tubercle becomes the clitoris.
    The labio-scrotal folds become the labia majora.
    The urethral folds become the labia minora.



- The management of patients with DSD involves a team approach.
- This team involves:
  - Neonatologists
  - Geneticists/ genetic counselor
  - Pediatric endocrinologists
  - Pediatric surgeons
  - Social worker
  - Obstetrician/ Pediatric urologist
  - Psychologist



19.3 Classification

- In the past, several names were used to describe disorders of sexual development.
- These include:
  - Intersex
  - Ambiguous genitalia
  - Hermaphroditism
  - Sex reversal
- Currently, all these are grouped under one common name, disorders of sexual development, "DSD".
- This term is broad and includes other common entities such as Turner syndrome and Klinefelter syndrome as well as rare disorders such as cloacal exstrophy and aphallia.

- There are several classifications for DSD.
- In the past, intersex disorders were subdivided into three main groups:
  - Those associated with gonadal dysgenesis
  - Those associated with undervirilization of 46, XY individuals
  - Those associated with prenatal virilization of 46, XX individuals
- Another commonly used classification divides intersex disorders into four main groups:
  - Female pseudohermaphroditism
  - Male pseudohermaphroditism
  - True hermaphroditism
  - Mixed gonadal dysgenesis
- The new classification of DSD was proposed by The Lawson Wilkins Pediatric Endocrine Society (LWPES) and the European Society for Paediatric Endocrinology (ESPE) group as follows:
  - Sex chromosome DSDs
  - 46, XY DSDs
  - 46, XX DSDs

Old	Proposed
Intersex	DSD
Male pseudohermaphrodite, undervirilization of an Y male, and undermasculinization of an XY male	46, XY DSD
Female pseudohermaphrodite, overvirilization of an XX female, and masculinization of an XX female	46, XX DSD
True hermaphrodite	Ovotesticular DSD
XX male or XX sex reversal	46, XX testicular DSD
XY sex reversal	46, XY complete gonadal dysgenesis

19.4 Sex Chromosome DSDs

- This occurs when the number or structure of the sex chromosomes (X, Y chromosomes) is abnormal.
- The abnormalities include:
  - XX male (46XX)
  - 46 XX/45X
  - 46XY/45X Mixed gonadal dysgenesis
  - 45, XO Turner (Gonadal dysgensis) and variants

  - 47, XXY Klinefelter and variants
  - 45X/46XY mixed gonadal disgenesis (MGD)

- Chromosomal ovotesticular (True hermaphroditism) DSD "46XX/46XY chimeric type or mosaic type"), (The DSD nomenclature has recently divided "ovotesticular DSD" (formerly true hermaphroditism) into 46, XY ovotesticular DSD, 46, XX ovotesticular DSD, and chromosomal ovotesticular DSD (46, XX/46, XY "chimerism or 45, X/46, XY" mosaic type).
- Sex chromosome DSD was formerly termed as gonadal dysgenesis.
- If a testis is poorly formed, it is called a dysgenetic testis, and if an ovary is poorly formed, it is called a streak gonad.
- A patient with a Y chromosome is at high risk of developing a tumor in a streak ovary or dysgenetic gonad.
- Klinefelter and Turner syndromes are the most frequently encountered sex chromosomal abnormalities.
- The most common genotype of Klinefelter syndrome is XXY.
- More than half of girls with Turner syndrome have chromosomal mosaicism.
- The clinical manifestations of patients with 45X/46XY MGD, are highly variable, ranging from partial virilization and ambiguous genitalia at birth to a completely normal male or female phenotype.
- The most common feature of MGD is asymmetric development of the testes, often with a dysgenetic testis on one side and a streak gonad on the other. Asymmetrical external and internal genitalia may also be present.

SEX CHROMOSOMES DISORDERS

- XX male (46XX)
- 46 XX/45X
- 46XY/45X
- 45,XO Turner (Gonadal dysgenesis) and variants
- 47,XXY Klinefelter and variants
- 45X/46XY mixed gonadal dysgenesis (MGD)
- Chromosomal ovotesticular :
  - 46,XY ovotesticular DSD
  - 46,XX ovotesticular DSD
- Chromosomal ovotesticular DSD:
  - 46,XX/46,XY chimerism
  - 45,X/46,XY mosaic type

- Chromosomal ovotesticular DSD (chimeric type or mosaic type) is associated with ovarian and testicular tissues found in either the same or opposite gonad just as in 46, XX and 46, XY ovotesticular DSD. The genital duct develops according to the ipsilateral gonad.
- 46, XY disorders of sex development (46, XY DSD):
  - Here, the chromosomes are male but the external genitals are either ambiguous or those of a female.
  - The testes may be absent, malformed or normal.
  - In the past, the term "male pseudohermaphrodite" was used to describe patients with 46, XY chromosomes and incompletely masculinized external genitalia.
  - These patients are characterized by ambiguous or female external genitalia, caused by incomplete intrauterine masculinization.
  - Infants with this condition tend to have penoscrotal hypospadias, abnormal development of the testes, and reduced to no sperm production.
  - Some individuals with 46, XY DSD have fully to underdeveloped female reproductive organs (e.g., uterus and fallopian tubes), while others do not.
  - Patients with 46, XY DSD may be raised as males or females.
  - Patients with 46, XY DSD are at an increased risk for gonadal tumors and benefit from regular surveillance or surgery to remove abnormally developed gonads.
  - The two main causes of 46, XY DSDs are:

    Disorders of testicular development (Fig. 19.7)
    Disorders of androgen synthesis/androgen action

  - The spectrum of 46, XY DSDs include:

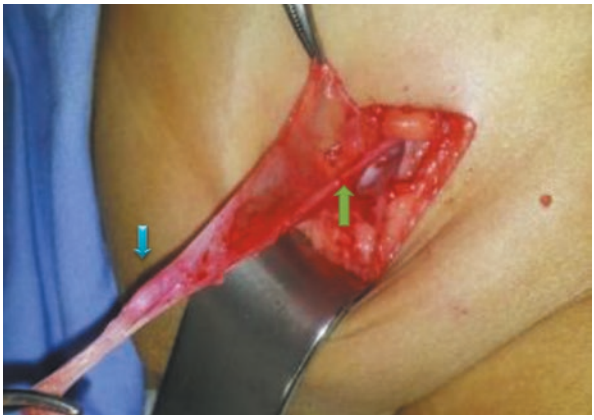


Fig. 19.7 A clinical intraoperative photograph showing a very small atrophic testis. Note also the vas

Complete or partial forms of gonadal dysgenesis with or without syndromic phenotype
Ovotesticular DSD
Testicular regression syndrome
Androgen synthesis defects
Disorders of androgen action

- 46, XY partial gonadal dysgenesis is characterized by partial testicular differentiation and ambiguous genitalia.
- 46, XY complete gonadal dysgenesis (Swyer syndrome) is characterized by:

  A female phenotype with full development of unambiguous female genitalia.
  Normally developed Müllerian structures
  Streak gonads
  These streak gonads should be removed due to their association with gonadoblastoma.
  These patients usually present because of delayed puberty.

- Patients with agonadism (vanishing testicular syndrome, testicular regression syndrome) are boys with normal male genitalia (Fig. 19.8).
- This indicates that these patients must have had testicular function in the fetal period followed by bilateral anorchia.

• Androgen synthesis defect can be secondary to:

- Leydig cell aplasia/hypoplasia, due to abnormalities in hCG/LH receptor
- Testosterone biosynthesis defects:

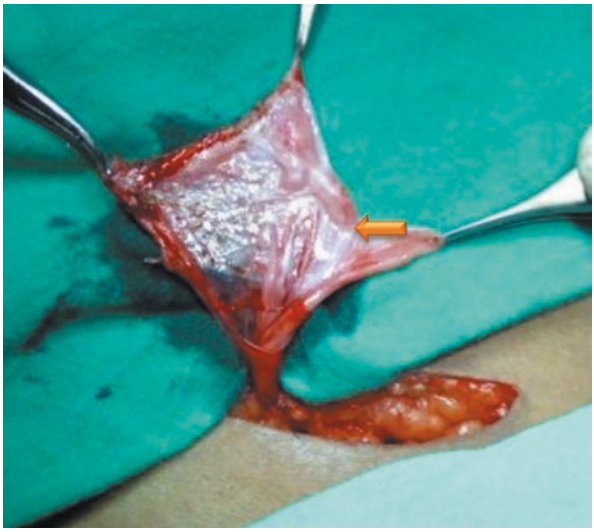


Fig. 19.8 A clinical photograph showing a very small atrophic testis in a male child. Note the normal vas

STAR deficiency
P450scc deficiency
3-b hydroxysteroid dehydrogenase type II deficiency
17a-hydroxylase and 17,20-lyase deficiency
Isolated 17,20-lyase deficiency
P450 oxidoreductase "POR gene" defect
17b-hydroxysteroid dehydrogenase III deficiency

- Disorders of Anti-Mullerian Hormone (AMH) and Anti-Mullerian Hormone receptors result in persistent Müllerian duct syndrome (PMDS).
  - PMDS is inherited as a sex-limited autosomal recessive type.
  - It is caused by a mutation in the AMH or AMH-receptor genes.
  - These patients are males and usually present with undescended testis or a hernia.
  - They also have a uterus, Fallopian tube and rudimentary vagina.
- Disorders of androgen action:
  - 5a-reductase type 2 deficiency
- Complete/partial forms of androgen insensitivity syndromes.
- 46, XX disorders of sex development (46, XX DSD):
  - In this condition, the chromosomes (46, XX) and ovaries are of a female but the external genitals appear to be male (masculinized external genitalia).
  - In the past, this was called female pseudohermaphroditism.
  - 46, XX DSDs can result either from:

    Disorders of ovarian development.
    Excess exposure to fetal androgen.

- SRY positivity; WNT4, RSPO1, b-catenin gene defects; and duplication of SOX9 gene lead to testis-like formation within the ovary (streak gonad, dysgenetic testis or ovotestis) in the 46, XX patients.
- In ovotesticular DSDs, the most common karyotype is 46, XX followed by 46, XX/46, XY chimerism or mosaicism, and 46, XY.
- Most 46, XX ovotesticular DSDs are SRY-negative, and the genes responsible have not yet been identified.
- The main cause of a virilized female with two ovaries, XX karyotype and ambiguous genitalia is excess exposure to testosterone before birth.
- The excess testesterone exposure is usually of fetal origin

- Rarely this excess is of maternal origin.
- The majority of virilized 46, XX infants will have congenital adrenal hyperplasia (CAH) secondary to enzyme deficiency:
  - 21a-hydroxylase deficiency (most common)
  - 11b- hydroxylase deficiency
  - 3b-hydroxysteroid dehydrogenase deficiency (rare)
  - A combined P450c17 and P450c21 deficiency is a very rare variant of CAH.
- Cytochrome POR is a protein that transfers electrons from NADPH to all microsomal cytochrome P450 enzymes and three steroidogenic enzymes, namely:
  - P450c17 (17a-hydroxylase/17,20 lyase)
  - P450c21 (21-hydroxylase)
  - P450aro (aromatase)
  - Mutations of POR gene cause disordered steroidogenesis with prenatal virilization.
- Causes of fetal androgen excess in XX infants are rare and include:
  - Maternal androgen ingestion
  - Maternal virilizing disease
  - fetoplacental aromatase deficiency
  - Virilizing luteoma of pregnancy
  - Glucocorticoid receptor mutation
- Aromatase deficiency:
  - This is rare type of enzyme deficiency.
  - Aromatase is the enzyme that catalyzes conversion of androgens into estrogens.
  - As a result of this enzyme deficiency, DHEA produced by the fetal adrenal glands cannot be converted to estrogen by the placenta, and is converted to testesterone peripherally.
  - This results in virilization of both fetus and mother.
  - These patients can present during childhood and adolescence with cystic ovaries and delayed bone maturation.
  - They may also present at puberty with primary amenorrhea, failure of breast development, virilization, and hypergonadotrophic hypogonadism.

CAUSES OF 46, XY DISORDERS OF SEXUAL DEVELOPMENT(DSD) (DSD)

- Defects in testicular development
- Defects in testesterone biosynthesis
- Defects in testesterone action
- Defects in anti-mullerian hormone

DEFECTS IN TESTICULAR DEVELOPMENT

- 46,XY complete gonadal dysgenesis (Swyer syndrome)
- 46,XY partial gonadal dysgenesis (Denys-Drash syndrome, Frasier syndrome)
- Ovotesticular DSD
- Testicular regression syndrome (vanishing testes syndrome)
- Leydig cell aplasia/hypoplasia

DEFECTS IN TESTESTERONE BIOSYNTHESIS

- STAR deficiency
- P450scc
- 3-b hydroxysteroid dehydrogenase deficiency
- 17a-hydoxlase and 17,20-lyase deficiency
- Isolated 17,20-lyase deficiency
- P450 oxidoreductase “POR” gene defect
- 17b-hydroxysteroid dehydrogenase III deficiency
- POR gene abnormality (defective 17,20-lyase activity of P450c17)

DEFECTS IN ANTI-MULLERIAN HORMONE

- Persistant mullerian duct syndrome

DEFECTS IN TESTESTERONE ACTION

- 5a-reductase type 2 deficiency
- Complete androgen insensitivity syndromes
- Partial androgen insensitivity syndromes

19.5 Classification of Disorders of Sexual Development (Fig. 19.9)

- Another way of classifying disorders of sexual development is as follows:
  - Disorders of sex chromosomes
  - Disorders of gonads
  - Disorders of phenotype
- Disorders of sex chromosomes (Chromosomal sex):
  - These result from abnormalities in the chromosomes.
  - This occurs when the number or structure of the sex chromosomes (X, Y chromosomes) is abnormal.
  - The abnormalities include:

    Klinefelter syndrome 47 XXY
    XX male (46XX)
    Turner syndrome (gonadal dysgenesis) 45 XO
    46 XX/45X
    Mixed gonadal dysgenesis 46XY/45X
    True hermaphroditism 46 XX, 46XY or mosaics
- Disorders of gonads (Gonadal sex):
  - Disorders of gonadal sex result when chromosomal sex is normal but differentiation of the gonads is abnormal.
  - The abnormalities include:

    Pure gonadal dysgenesis
    Dysgenetic testes
    Absent testes

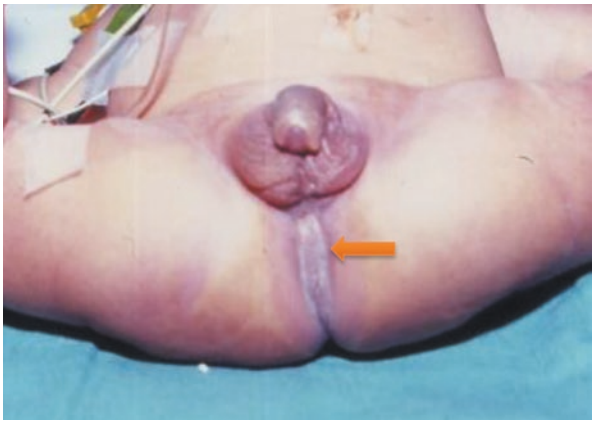


Fig. 19.9 A clinical photograph of a newborn with DSD. Note also the associated anorectal agenesis

- Disorders of phenotype (Phenotypic sex):
  - In these disorders the gonads and sex chromosomes are normal but with abnormal urogenital tract.
  - The abnormalities include:

    Female pseudo-hermaphrodite
    Congenital adrenal hyperplasia
    Nonadrenal female pseudo-hermaphroditism

- Developmental disorders of mullerian duct
  - Male pseudo-hermaphrodite
  - Abnormalities in androgen synthesis
  - Abnormalities in androgen action
  - Persistent mullerian duct syndrome
  - Developmental defects of male genitalia

46, XX DISORDERS OF SEXUAL DEVELOPMENT (DSD)

- Disorders of ovarian development
- Excess exposure to fetal androgen
- Disorders of ovarian development:
  - Ovotesticular DSD
- Excess exposure to fetal androgen
  - Congenital adrenal hyperplasia
    - 21a-hydroxylase deficiency (most common)
    - 11b-hydroxylase deficiency
    - 3b-hydroxysteroid dehydrogenase deficiency (rare)
    - P450c17 (17a-hydroxylase/17,20 lyase) deficiency
    - P450c21 (21-hydroxylase) deficiency
    - P450aro (aromatase) deficiency
  - Maternal excess of and androgens:
    - Maternal androgen ingestion during pregnancy
    - Fetoplacental aromatase deficiency
    - Virilizing luteoma of pregnancy

19.6 Evaluation of a Newborn with DSD

- The evaluation and diagnostic approach to a newborn with ambiguous genitalia involves a multidisciplinary team approach.
- This includes:

- A pediatric endocrinologist
- Geneticist
- A pediatric surgeon
- A pediatric urologist
- A neonatologist

19.7 Sex Assignment

- It is important not to assign a sex immediately and delay it till after full evaluation.
- During the evaluation stage, the newborn is referred to as "baby," not boy or girl.
- The family should be encouraged to delay naming the baby until the sex has been assigned.
- There are other factors that must be taken in consideration during this process including:
  - The social and cultural background
  - Expectations of the parents
  - Religious factors
- The parents are also involved, educated and should participate in the process and should understand that a child with a DSD can live normal live and function well in society.
- Although different DSDs may present with similar findings on physical examination, there are certain clinical and laboratory aspects that are important and will help define the type of DSD.
- It is important to rule out a malformation syndrome that may present as ambiguous genitalia.
- Clinical evaluation of the gonads and external genitalia is very important.
- It is important to note the size and degree of differentiation of the phallus.
- Note the phallus length:
  - A normal-term male penis is 3.5 ± 0.7 cm.
  - A length <2.0 cm is considered abnormal.
  - A normal-term female clitoris is less than 1.0 cm.
  - Micropenis is thus defined as a stretch penile length of less than 2.0 cm in a term male infant.
  - Clitoromegaly as a clitoris greater than 1.0 cm in a term female.
  - In preterm infant males, the penile length is shorter.

- Note the position of the urethral meatus:
  - Hypospadias associated with bifid scrotum or undescended testis suggests a DSD (Fig. 19.10a, b).
  - If the urethral opening is at the base of the phallus, it could be a urogenital sinus in a virilized female.

CLASSIFICATION OF DSD

- **SEX CHROMOSOMES DSD:**
  - 45X Turner and variants
  - 47 XXY Klinefelter and variants
  - 45X/46XY mixed gonadal disgenesis (MGD)
  - Chromosomal ovotesticular DSD
- **46, XY DSD:**
  - Disorders of testicular development
  - Complete gonadal dysgenesis
  - Partial gonadal dysgenesis
  - Gonadal regression
  - Ovotesticular DSD
  - Disorders of Androgen synthesis/ action
  - Androgen synthesis defects
  - LH-receptor defect
  - Androgen insensitivity
  - 5-alpha reductase deficiency
  - Disorders of Anti-Mullerian hormone
  - Leydig cell aplasia/hypoplasia
  - Cloacal extrophy
- **46, XX DSD:**
  - Disorders of ovarian development
  - Ovotesticular DSD
  - Gonadal dysgenesis
  - Testicular DSD
  - Fetal androgen excess
  - Congenital adrenal hyperplasia (21-Hydroxylase and 11-hydroxylase deficiency)
  - Aromtase deficiency
  - Maternal androgen ingestion
  - Virilizing luteoma of pregnancy

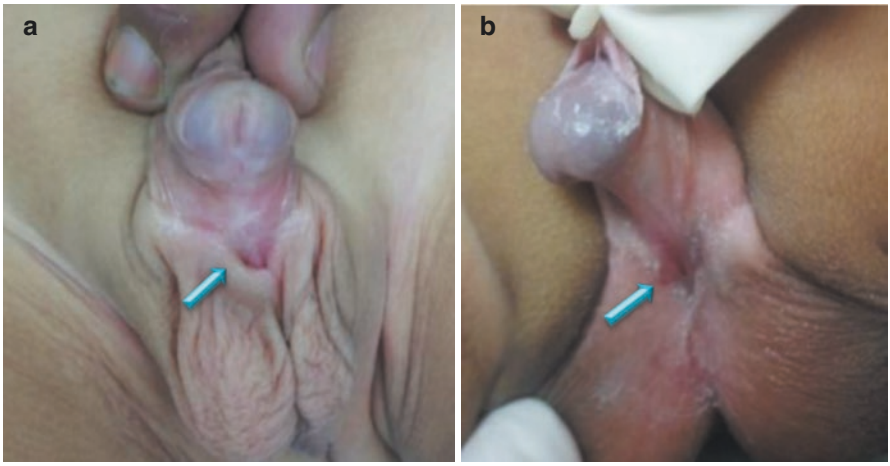


Fig. 19.10 (**a**, **b**) Clinical photographs of two patients with penoscrotal hypospadias. These patients need to be evaluated to exclude DSD

- Labioscrotal folds may be separated or be fused at the midline, giving an appearance of a scrotum.
- Newborns with 46XX DSD due to CAH may have hyperpigmented labioscrotal folds.
- The anogenital ratio:
  - This is the distance between the anus and posterior fourchette divided by the distance between the anus and base of the clitoris/phallus.
  - A ratio greater than 0.5 suggests virilization.
  - In a fully virilized male the ratio is 1.0.
- Documentation of palpable gonads is important:
  - Although ovotestes have been reported to descend completely into the bottom of labioscrotal folds, in most patients, only testicular components descend fully.
  - If clinical evaluation reveals palpable gonads in the inguinal area, the diagnoses of pure gonadal dysgenesis can be eliminated.
  - Impalpable gonads, even in an apparently fully virilized infant, should raise the possibility of a severely virilized 46XX DSD patient with CAH.
  - The presence of two palpable gonads strongly favors the diagnosis of a 46XY DSD.
  - The presence of only one palpable gonad suggests mixed gonadal dysgenesis, although it does not rule out a 46 XX ovotesticular DSD.

19.8 Diagnosis and Investigations

- The optimal care of patients with DSD requires a multidisciplinary team and begins in the newborn period.
- Some cases of DSD are obvious at birth while others are diagnosed during childhood or remain undiagnosed until a child reaches puberty.
- The investigations depend on the suspected type of DSD.
- The diagnostic evaluation of DSD includes:
  - A complete CBC and electrolytes
  - Hormone measurements
  - Hormone stimulation tests
  - Diagnostic radiological evaluations
  - Ultrasonography shows:

    The presence or absence of Müllerian/Wolfian structures and can locate the gonads and their echo texture.
    Ultrasonography also can identify associated malformations such as renal abnormalities.

  - Cytogenetic and molecular studies
  - Endoscopy, laparoscopy and gonadal biopsy
  - The genetic evaluation includes:

    Chromosomal analysis (Karyotype)
    FISH
    Specific molecular studies to screen the presence of mutations or gene dosage imbalance (AR, SRY, SF1, WT1, CYP21, SOX9, DAX-1, 17b hydroxysteroid dehydrogenase, 5a-reductase-2, and others). These are not readily avaliable.
    Current molecular diagnosis is limited by cost, accessibility, and quality control.

- Common findings suggesting DSD are:
  - A male appearance with associated abnormalities of genitalia including:

    Severe hypospadias with bifid scrotum
    Undescended testis/testes with hypospadias
    Bilateral non-palpable testes
    Micropenis with chordee

  - A female appearance with associated abnormalities of genitalia including:

    Enlarged clitoris
    Posterior labial fusion
    An inguinal/labial mass
    The location of the gonads and presence or absence of a uterus will provide a provisional clinical diagnosis.

- If no gonads are palpable:

  46, XX DSD (with two ovaries) is the most commonly seen.
  MGD
  The presence of a uterus and absence of palpable gonads in a virilized female primarily suggest a clinical diagnosis of 21-hydroxylase deficiency. MGD, ovotesticular, and 46, XY DSD remain as diagnostic possibilities.

- If two gonads are palpable:

  46, XY DSD and ovotesticular DSD are the most likely diagnoses.
  Symmetrical external genitalia, with or without palpable gonads, and an absent uterus suggest an undervirilized XY male.
  The presence of a uterus and asymmetric external genitalia and palpable gonad(s) suggest gonadal dysgenesis with Y and ovotesticular DSD.

- A gonadal biopsy is required to classify the type of gonadal dysgenesis and ovotesticular DSD, to assess gonadal chromosomal mosaicism and to detect the presence of a gonadal tumor.
- Hormone measurements should include hCG and ACTH stimulation tests to assess testicular and adrenal steroid biosynthesis.
- The endocrine evaluation of patients with 46, XY DSDs and sex chromosome DSDs include assessment of testicular function by basal measurement of LH, FSH, inhibin B, Testosterone, Dihydrotestosterone (DHT), Anti-Mullerian hormone (AMH), and DHEAS.
- In patients with Testosterone synthesis defects, neonatal and post pubertal diagnosis is made based on basal steroid levels.

• Testosterone stimulation test:

- The stimulation of Testosterone production by HCG is used to determine abnormalities in Testosterone biosynthesis and also to document the presence of functioning testicular tissue.
- Testosterone and DHT should be measured at baseline and 72 h after HCG stimulation.
- The increase in the level of Testosterone should be at least threefold.
- A failure to respond to HCG in combination with elevated LH/FSH levels and low/undetectable value of AMH is consistent with anorchia or gonadal dysgenesis.
- Androgen insensitivity should be considered in individuals with a 46, XY karyotype and with normal Testosterone biosynthesis.
- Patients with 5a-reductase deficiency have normal Testosterone levels, low or normal DHT levels and a high Testosterone/DHT ratio after HCG stimulation test.
- The diagnosis of 17bHydroxysteroid dehydrogenase deficiency is made when a 10–15-fold elevation is observed in the ratio of A/T.
- Inhibin B and AMH are useful markers for the presence of Sertoli cells and their assessment could help in diagnosing testis determination disorders.

- Serum AMH level:
  - This is indicative of the presence of testicular tissue.
  - In boys with bilateral cryptorchidism, serum AMH correlates with the presence of testicular tissue.
  - Undetectable values are highly suggestive of absence of testicular tissue.
  - In XY patients, AMH is low in those with DSD secondary to abnormal testicular determination (including complete and partial gonadal dysgenesis).
  - AMH will be normal or elevated in patients with impaired Testosterone secretion.
  - AMH level will be elevated during the first year of life and at puberty in those with androgen insensitivity.
  - In 46, XX patients with DSDs, a high serum AMH level is indicative of the presence of testicular tissue.
  - The diagnosis of 21-hydroxylase deficiency in 46, XX DSDs with two ovaries depends on:
  - The detection of elevated 17-OHP levels either as a basal measurement or after a short ACTH stimulation test.
  - High concentration of 11-deoxycortisol and deoxycortisol (DOC) with low levels of plasma renin activity (PRA).
  - This will help differentiate 11-hydroxylase from 21-hydroxylase deficiency.
- Study of androgen target cells:
  - Defects in peripheral sensitivity to androgens may be responsible for genital ambiguity in male individuals with partial androgen insensitivity.
  - Androgen receptor activity can be determined in fibroblasts grown from a genital skin biopsy sample.
  - 5-alpha reductase activity can be determined by this method.
  - Chromosomal characteristics, gonadal histology and presence or absence uterus are taken into consideration in the classification of DSDs.

19.9 Management of Patients with DSD

- The management of patients with DSD depends on the underlying cause.
- Supplemental hormone therapy may be given if gonadal function is compromised.
- In a virilized female, the surgical management is feminizing genitoplasty and this includes vaginoplasty and clitoroplasty.
- Undervirilized males typically have hypospadias and this is corrected with urethroplasty.
- Gender reassignment may be considered in patients with 46XY males and inadequate external genitalia.
- Sex assignment and therapy:

- There are several factors which must be considered during sex assignment.
- These include:

  The phenotype
  The appearance of the genitals
  The surgical options
  The need for future hormonal replacement therapy
  The potential for future fertility
  The culture and preferences of the family
  The effect of high levels of testosterone exposure on the brain development
  Sex assignment also depends on the type of DSD (46XX DSD, 46XY DSD or chromosomal DSD)

- 46 XX chromosomes:

  Congenital adrenal hyperplasia:

  - These patients are usually assigned a female sex.
  - Their fertility is preserved.
  - These patients are given hydrocortisone to replace cortisol, and, if there is associated salt wasting, fludrocortisone are given to replace aldosterone.
  - Surgical treatment is required to correct the external genitalia. This should be done early and includes:

    - Clitoroplasty
    - Vaginoplasty

- 46 XY chromosomes:

  Testosterone biosynthesis defects

  - These patients are assigned a male sex.
  - Fertility is preserved.
  - Some of these patients have deficiencies of glucocorticoids and/or mineralocorticoids and these are treated with glucocorticoids and/or mineralocorticoids.
  - Patients with hypospadias require urethroplasty.
  - Testosterone replacement may be required at puberty, particularly if testosterone levels remain low.

  5-alpha-reductase deficiency

  - These patients are assigned a male sex.
  - Fertility is preserved.
  - Patients with hypospadias require urethroplasty.
  - These patients do not typically require hormonal replacement and the rise in testosterone levels at the onset of puberty is sufficient to induce development of secondary sexual characteristics.

Partial androgen resistance

- Most of these patients are raised as males and fertility is preserved.
- Some patients with severe partial androgen resistance may be raised as females, as adequate virilization at puberty may not be possible.
- If the patient is raised as a male, early surgical correction of hypospadias is recommended.
- Testosterone replacement may be required at puberty, particularly if testosterone levels remain low.
- If the patient is raised as a female:
  - Early vaginoplasty is recommended.
  - Clitoroplasty in those with severe virilization.
  - Gonadectomy before puberty to prevent virilization at puberty and also malignant transformation.
  - Estrogen supplements are required at puberty to allow development of secondary sexual development.

– Gonadal dysgenesis

The sex assignment in these patients depends on several factors including:

- The likelihood of fertility
- The genital appearance
- The size of the phallus
- The presumed testicular function in puberty which is based on hormonal tests and gonadal development.

If the patient is raised as a female:

- Early vaginoplasy is recommended.
- Clitoroplasty in those with severe virilization.
- Gonadectomy before puberty to prevent virilization at puberty and possible malignant transformation.
- Estrogen supplements at puberty to allow development of secondary sexual development.

If the patient is raised as a male:

- Early surgical correction of hypospadias is recommended.
- Testosterone replacement may be required at puberty, particularly if testosterone levels remain low.

– 45 X/ 46 XY mixed gonadal digenesis

Sex assignment is more complex in these patients.
If fertility is likely to be maintained, then sex assignment is best chosen to be consistent with fertility.
Other factors that must be taken in consideration including:

- The genital appearance
- The size of the phallus
- The presumed testicular function in puberty based on hormonal tests and gonadal development.
- The risk of gonadal malignancy is highest in mixed gonadal dysgenesis in which there is a Y chromosomal and in those with an intra-abdominal testis.
- In children assigned a male sex, hypospadias is corrected with urethroplasty.
- A streak ovary, if present, should be removed.
- Testosterone replacement may be required at puberty, particularly if testosterone levels remain low.
- In children assigned a female sex, the following corrective procedures are required:
  - Early vaginoplasty
  - Clitoroplasty in those with severe virilization
  - Gonadectomy should be performed early to prevent malignancy and avoid any risk of virilization.
  - Estrogen supplements at puberty to allow development of secondary sexual development.
  - Some of these patients have Mullerian structures (uterus) and need treatment with cyclic progesterone once breakthrough bleeding occurs.

Further Reading

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Chapter 20
Congenital Adrenal Hyperplasia (CAH)

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20.1 Introduction

- CAH is the most frequent cause of DSD in the newborn.
- The term congenital adrenal hyperplasia (CAH) encompasses a group of autosomal recessive disorders, each of which involves a deficiency of an enzyme involved in the synthesis of cortisol, aldosterone, or both.
- Deficiency of 21-hydroxylase, resulting from mutations or deletions of *CYP21A*, is the most common form of CAH, accounting for more than 90% of cases.
- In the past, patients with CAH are called female pseudohermaphrodites.
- It results from excessive androgens production leading to a virilized phenotype.
- CAH is caused by an enzyme deficiency (commonly 21-hydroxylase deficiency) that leads to insufficient cortisol production and biofeedback via the pituitary gland causes accumulation of the precursor above the enzymatic block.
- CAH presents a spectrum of abnormalities, including:
  - The degree of phallic enlargement
  - The extent of urethral fold fusion
  - The size and level of entry of the vagina into the urogenital sinus (Figs. 20.1a, b, 20.2, and 20.3).
- The level of entry of the vaginal opening into the urogenital sinus is divided into two types:
  - Below the urethral sphincter
  - Above the urethral sphincter

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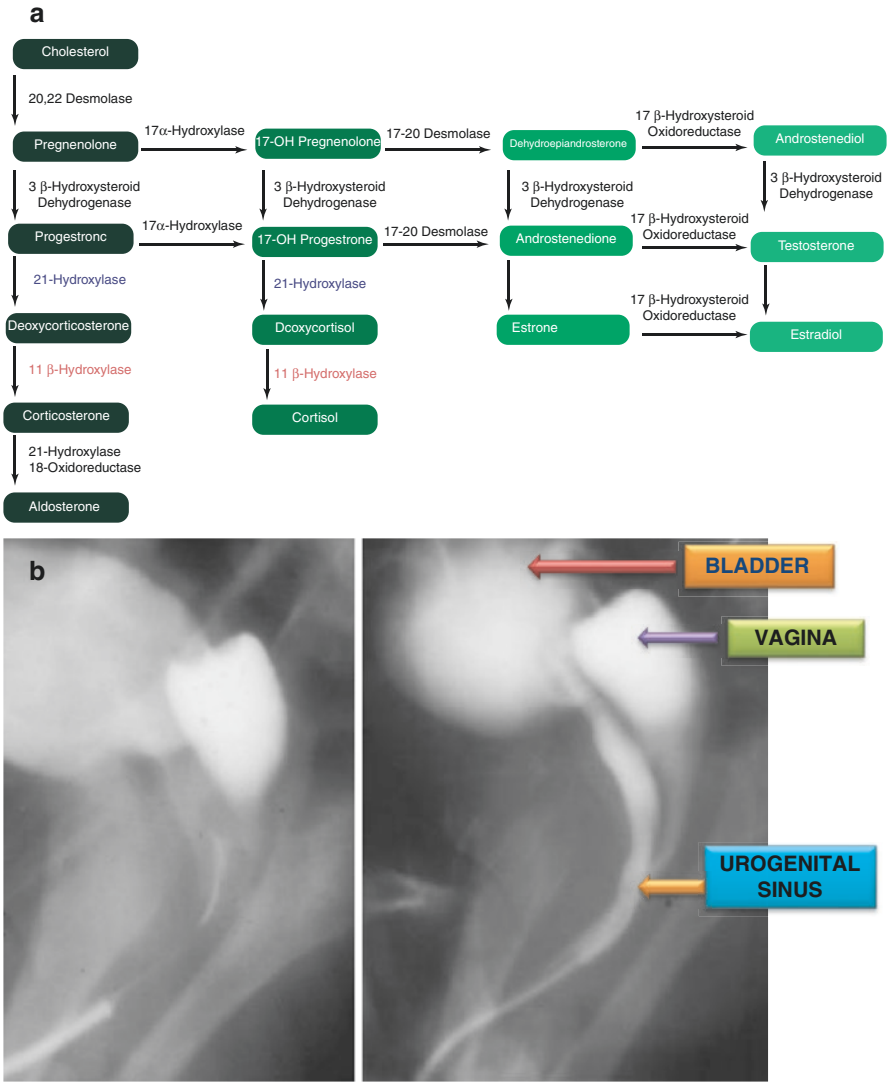

Fig. 20.1 (**a**, **b**) Genitograms showing the level of entry of the vaginal opening into the urogenital sinus. This shows a low level of insertion where the vagina enters the urogenital sinus below the level of the urinary sphincter. This is important for surgical repair

- The internal Müllerian structures are well developed in these patients and females with this condition are usually fertile with the ability to become pregnant and give birth.
- There is a salt-losing variety of CAH and this is fatal in infants if left untreated.
- Causes of CAH:

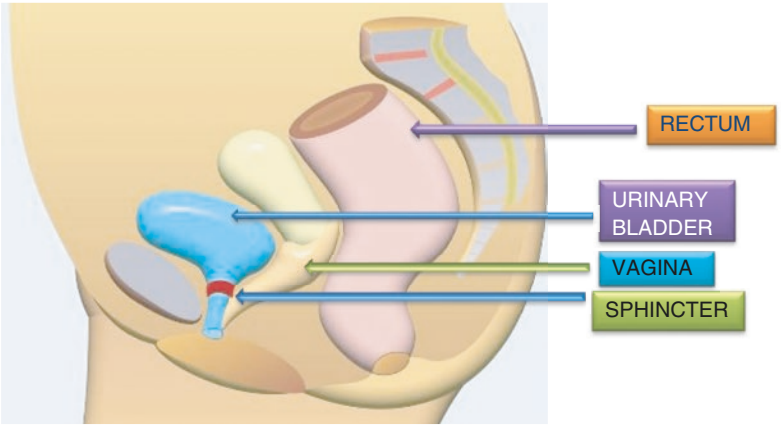

Fig. 20.2 Diagrammatic representation of urogenital sinus showing low insertion of the vaginal opening into the urogenital sinus. Note the point of entry below the sphincter

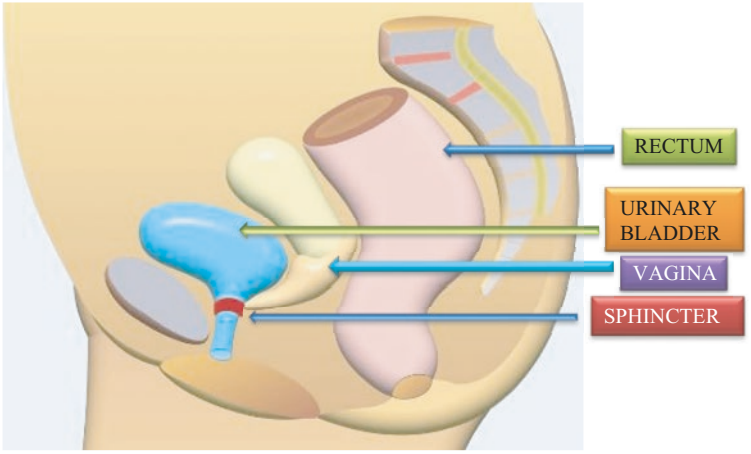

Fig. 20.3 Diagrammatic representation of urogenital sinus showing high insertion of the vaginal opening into the urogenital sinus. Note the point of entry above the sphincter

- CAH is commonly caused by enzyme deficiencies in the sex hormones pathway as follows:

  21-Hydroxylase deficiency
  11-Hydroxylase deficiency
  3-Beta-hydroxysteroid dehydrogenase deficiency

- Rarely, CAH is cause by maternal androgens
- The clinical presentation of CAH depends on the nature and severity of the enzyme deficiency.

- The presentation of CAH also varies according to chromosomal sex of the newborn.
- The sex of a neonate with CAH is often initially unclear because of genital ambiguity.
- Females with severe CAH due to deficiencies of 21-hydroxylase, 11-beta-hydroxylase, or 3-beta-hydroxysteroid dehydrogenase have ambiguous genitalia at birth.
- Their genital anomalies range from complete fusion of the labioscrotal folds and a phallic urethra to clitoromegaly, partial fusion of the labioscrotal folds, or both.
- Females with mild 21-hydroxylase deficiency are not diagnosed early and identified later in childhood because of precocious pubic hair, clitoromegaly, or both, often accompanied by accelerated growth and skeletal maturation.
- Some of these females with mild degree of CAH may present in adolescence or adulthood with oligomenorrhea, hirsutism, and/or infertility.
- Females with 17-hydroxylase deficiency appear phenotypically female at birth but do not develop breasts or menstruate in adolescence; they may present with hypertension.
- This is in contrast to males with 21-hydroxylase deficiency who normally have normal genitalia.
- Males with severe CAH may result in in salt wasting congenital adrenal hyperplasia. These male neonates present with:

  Failure to thrive
  Recurrent vomiting
  Dehydration
  Hypotension
  Hyponatremia
  Hyperkalemia, and shock

- Males with less severe deficiencies of 21-hydroxylase present later in childhood with:

  Early development of pubic hair
  Phallic enlargement, or both
  Accelerated linear growth
  Advancement of skeletal maturation

- Males with steroidogenic acute regulatory (StAR) deficiency, classic 3-beta-hydroxysteroid dehydrogenase deficiency, or 17-hydroxylase deficiency generally have ambiguous genitalia or female genitalia.

  They may be raised as girls and seek medical attention later in life because of hypertension or a lack of breast development.

- Males or females with 11-hydroxylase deficiency may present:

  In the second or third week of life with a salt-losing crisis.
  They may present later in life with hypertension, hypokalemic alkalosis, or both.

– 21-Hydroxylase deficiency:

This is the commonest cause seen in 90% of patients with congenital adrenal hyperplasia.
This leads to a mineralocorticosteroid deficiency.
As a result of this, there is accumulation of androgenic byproducts, which causes masculinization of female external genitalia (Figs. 20.4a, b, 20.5a, b, and 20.6a, b). The degree of masculinization is variable.
The end result is a female infant with varying degrees of virilization.
A large number of these patients (75% of patients) have also salt-wasting. This is a serious condition which must be recognized and treated to avoid vascular collapse.
The 21-hydroxylase deficiency is hereditary inherited as an autosomal recessive trait.
The transmitted trait may have two varieties, which explains the clinical heterogenicity seen in patients with salt-wasting nephropathy.

- This classification is important surgically and must be determined prior to any surgical intervention.

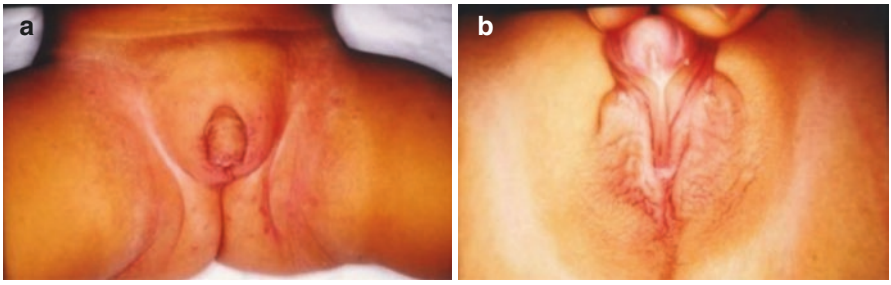

Fig. 20.4 (**a**, **b**) Clinical photographs showing a patient with congenital adrenal hyperplasia. Note the degree of masculinization of the female external genitalia

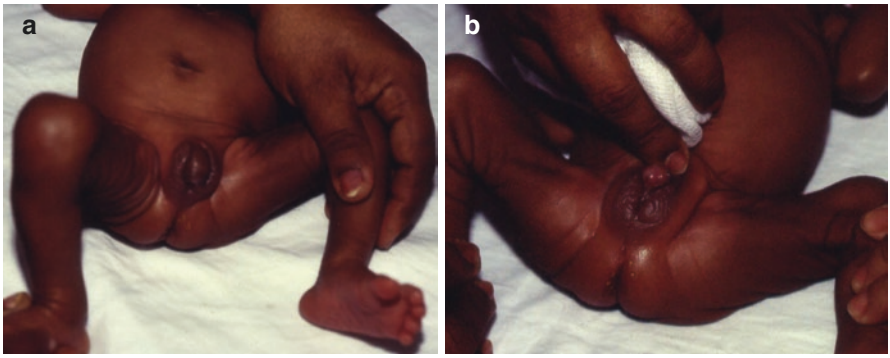

Fig. 20.5 (**a**, **b**) Clinical photographs of a newborn with congenital adrenal hyperplasia with 46XX karyotype. Note masculinization of external genitalia

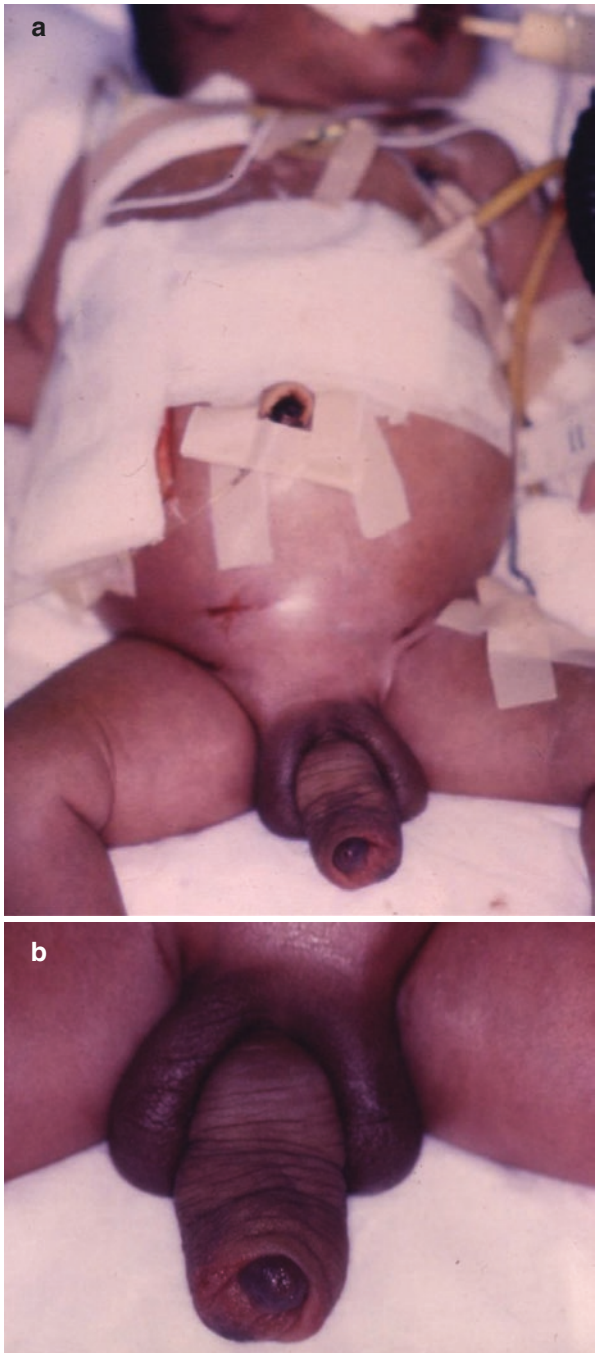

Fig. 20.6 (**a**, **b**) Clinical photographs of a newborn with a salt losing congenital adrenal hyperplasia. Note the marked degree of masculinization of external genitalia. This condition is fatal if not recognized and treated early

- CAH can be diagnosed prenatally by an elevated amniotic fluid level of 17-hydroxyprogesterone (17-OHP) during the second trimester or by HLA typing of amniotic cells.
- CAH is commonly diagnosed in newborns during evaluation of a 46XX newborn with ambiguous genitalia and the diagnosis is confirmed by demonstrating an elevated serum level of 17-hydroxyprogesterone.
- 17-Hydroxyprogesterone levels may be elevated also in the 11-hydroxylase deficiency form of CAH, as well as in the rare type seen in those with the 3-beta-hydroxysteroid dehydrogenase deficiency.
- 11-Hydroxylase deficiency:
  - CAH secondary to 11-hydroxylase deficiency leads to accumulation deoxycorticosterone (DOC) and 11-deoxycortisol.
  - This leads to salt retention and hypertension because deoxycorticosterone is a strong mineralocorticoid.
  - CAH secondary to 11-hydroxylase deficiency should be suspected in a 46XX child with ambiguous genitalia in whom:
  - The 17-Hydroxyprogesterone level is mildly elevated.
  - There is accumulation of deoxycorticosterone and 11-deoxycortisol.
- 3-Beta-hydroxysteroid dehydrogenase deficiency:
  - CAH secondary to 3-beta-hydroxysteroid dehydrogenase deficiency is rare.
  - This causes less severe virilization of a female infant than the virilization caused by 21-hydroxylase or 11-hydroxylase deficiency.
  - This enzyme deficiency leads to buildup of pregneninolone, which is converted in the liver to testosterone leading to virilization.
  - These patients can present with a salt-losing crisis caused by deficient mineralocorticoid production, similar to that seen in patients with 21-hydroxylase deficiency.
  - The diagnosis of 3-Beta-hydroxysteroid dehydrogenase deficiency can be confirmed by demonstrating an elevated serum level of dehydroepiandrosterone or its sulfate metabolite.
  - 3-beta-hydroxysteroid dehydrogenase deficiency is the only common form of CAH that can also cause ambiguous genitalia in the genetic male.
  - These ambiguous genitalia occur because this enzyme defect is present in both the adrenal glands and the testes, leading to inadequate production of testosterone in utero.
- Maternal androgens:
  - Rarely, female pseudohermaphroditism may be drug induced.
  - These drugs were used to treat females with habitual abortions.
  - Virilization of a female fetus may occur if these progestational agents or androgens are used during the first trimester of pregnancy.

- After the first trimester, these drugs cause only phallic enlargement without labioscrotal fusion.
- Extremely rare, various functional ovarian tumors have caused virilization of a female fetus.
- These tumors include:

  Arrhenoblastomas
  Krukenberg tumors
  Luteomas
  Lipoid tumors of the ovary
  Stromal cell tumors of the ovary

20.2 Diagnosis

- The diagnosis of CAH depends on finding inadequate production of cortisol, aldosterone, or both and of accumulation of excess concentrations of precursor hormones.
- 21-hydroxylase deficiency:
  - There will be high serum concentration of 17-hydroxyprogesterone (usually >1000 ng/dL).
  - There will be high urinary pregnanetriol (metabolite of 17-hydroxyprogesterone).
  - Elevated 24-h urinary 17-ketosteroid levels.
- 11-beta-hydroxylase deficiency:
  - There will be excess serum concentrations of 11-deoxycortisol and deoxycorticosterone.
  - There will be an elevation in the ratio of 24-h urinary tetrahydrocompound S (metabolite of 11-deoxycortisol) to tetrahydrocompound F (metabolite of cortisol).
  - Elevated 24-h urinary 17-ketosteroid levels.
- 3-beta-hydroxysteroid dehydrogenase deficiency:
  - There will be an abnormal ratio of 17-hydroxypregnenolone to 17-hydroxyprogesterone and of dehydroepiandrosterone to androstenedione
- Salt-wasting congenital adrenal hyperplasia:
  - Low serum aldosterone concentrations
  - Hyponatremia
  - Hyperkalemia
  - Elevated plasma renin activity (PRA), indicating hypovolemia
- Hypertensive forms of adrenal hyperplasia (i.e., 11-beta-hydroxylase deficiency and 17-alpha-hydroxylase deficiency) are associated with suppressed PRA and, often, hypokalemia.

- In mild forms of congenital adrenal hyperplasia secondary to 21-hydroxylase deficiency and 3-beta-hydroxysteroid dehydrogenase deficiency:
  - Synthetic corticotropin stimulation testing demonstrates the abnormal accumulation of precursor steroids.
- Abdominal CT scan can help exclude bilateral adrenal hemorrhage in patients with signs of acute adrenal failure without ambiguous genitalia.
- Pelvic ultrasond may be performed in an infant with ambiguous genitalia to demonstrate a uterus or associated renal anomalies, which are sometimes found in other conditions that may result in ambiguous genitalia (e.g., mixed gonadal dysgenesis, Denys-Drash syndrome)
- Genitogram:
  - This is often helpful in defining the anatomy of the internal genitalia.
  - It is also helpful in defining the level of entry of the vaginal opening into the urogenital sinus.
- A bone-age study is useful to evaluate for advanced skeletal maturation in a child who develops precocious pubic hair, clitoromegaly, or accelerated linear growth
- A karyotype is essential in an infant with ambiguous genitalia, to establish the chromosomal sex.
- Genetic testing is essential for genetic counseling and prenatal diagnosis of congenital adrenal hyperplasia.
- Newborn screening programs for 21-hydroxylase deficiency may be lifesaving in an affected male infant who would otherwise be undetected until presentation with a salt-wasting crisis.

20.3 Management

- It is important that newborns with ambiguous genitalia should be closely observed for symptoms and signs of salt wasting while being investigated and a diagnosis is being established.
- Abnormal weight loss or lack of expected weight gain should give a clue in these patients.
- Electrolyte abnormalities generally take from a few days to 3 weeks to appear.
- In mild forms of salt-wasting congenital adrenal hyperplasia, salt wasting may not become apparent until an illness stresses the child.
- Patients with dehydration, hyponatremia, or hyperkalemia and a possible salt-wasting form of CAH should receive an IV bolus of isotonic sodium chloride solution (20 mL/kg or 450 mL/m^2) over the first hour, as needed, to restore intravascular volume and blood pressure.
- This may be repeated if the blood pressure remains low.
- Dextrose must be administered if the patient is hypoglycemic and must be included in the rehydration fluid after the bolus dose to prevent hypoglycemia
- Blood samples should be taken to measure:

  - Serum Electrolyte
  - Blood sugar
  - Cortisol, aldosterone, and 17-hydroxyprogesterone concentrations

- These patients should be treated with glucocorticoids after confirmatory results are obtained.
- After the patient's condition is stabilized, treat all patients who have adrenal hyperplasia with long-term glucocorticoid or aldosterone replacement (or both), depending on which enzyme is involved and on whether cortisol and/or aldosterone synthesis is affected
- Patients who are sick and have signs of adrenal insufficiency should receive stress dosages of hydrocortisone (50–100 mg/m^2 or 1–2 mg/kg IV administered as an initial dose), followed by 50–100 mg/m ^{2}/day IV divided every 6 h
- The Endocrine Society's 2010 clinical practice guidelines note the following :

  - Prenatal treatment for CAH should be regarded as experimental
  - Glucocorticoid therapy should be carefully titrated to avoid Cushing syndrome
  - Mineralocorticoid replacement is encouraged; in infants, mineralocorticoid replacement and sodium supplementation are encouraged
  - Use of agents to delay puberty and promote growth are experimental
  - Psychiatric support should be encouraged for patients with adjustment problems
  - Medication should be used judiciously during pregnancy and in symptomatic patients with non-classical CAH

- Infants with ambiguous genitalia require surgical evaluation and, if needed, plans for corrective surgery, as follows:

  - Female patients with ambiguous genitalia due to congenital adrenal hyperplasia undergo clitoral recession early in life followed by vaginoplasty after puberty.
  - Others advocate one stage approach (clitoral recession and vagioplasty).
  - This approach by challenged and opposed by the Intersex Society of North America.
  - Some female infants with adrenal hyperplasia have only mild virilization and may not require corrective surgery if they receive adequate medical therapy to prevent further virilization

- The Endocrine Society's 2010 clinical practice guidelines note the following :

  - Adrenalectomy should be avoided
  - Surgical reconstruction may not be necessary during the newborn period in mildly virilized girls but may be appropriate in severely virilized girls.
  - Surgical reconstruction should be a single stage genital repair, performed by experienced surgeons.

- Patients with congenital adrenal hyperplasia should be treated early.
- Hormone replacement with corticosteroids.

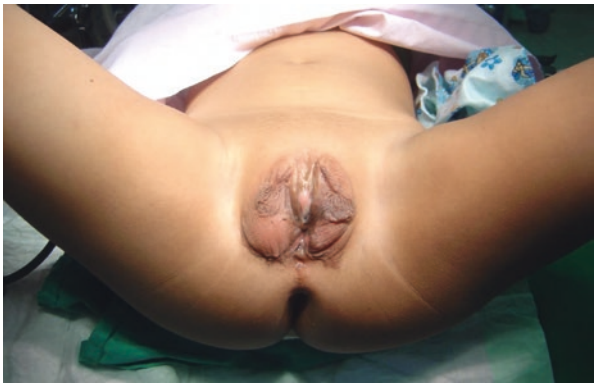

Fig. 20.7 A clinical photograph of a female with congenital adrenal hyperplasia. Note the bad cosmetic and functional results following surgical correction

- Those with salt-losing CAH must be recognized and treated with replacement therapy including corticosteroids and mineralocorticoids.
- The surgical management is variable depending on the extent of virilization and include:
  - Clitroplasty
  - Vaginoplasty depending on the level of entry of the vaginal opening into the urogenital sinus.
  - Labioplasty
- The surgical treatment is important for these patients and must be done by experienced surgeons to achieve excellent cosmetic and functional results and avoid complications (Fig. 20.7).

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Chapter 21
Androgen Insensitivity Syndrome (Testicular Feminization Syndrome)

Ahmed H. Al-Salem

21.1 Introduction

- Androgen insensitivity syndrome affects males.
- There are two types of androgen insensitivity syndrome:
  - Complete androgen insensitivity syndrome
  - Partial androgen insensitivity syndrome
- Partial androgen insensitivity syndrome results in ambiguous genitalia and there is no consensus whether to raise a child with this syndrome as a male or female.
- Complete androgen insensitivity syndrome causes a genetically male to have an incompletely developed and often blind ended vagina, clitoris and breasts.
- Patients with complete androgen insensitivity syndrome are raised as females.
- Patients with complete androgen insensitivity syndrome do not have a uterus or ovaries
- Patients with complete androgen insensitivity are infertile.
- Complete androgen insensitivity syndrome:
  - This is seen in a 46XY male.
  - It results from failure of the end organ (external genitalia and prostate) to respond appropriately to dihydrotestosterone (DHT).
  - This can be diagnosed based on assays of genital skin fibroblasts.
  - There are two subtypes of complete androgen insensitivity syndrome:

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Receptor-negative type:

- These patients are receptor negative and the main problem is that their cytosol receptors cannot bind DHT.

Receptor-positive type:

- These patients are receptor positive but in spite of DHT binding to its receptors it does not lead to normal differentiation of the external genitalia toward the male phenotype.

– Complete androgen insensitivity syndrome is inherited as X-linked.
– A large number of patients with complete androgen insensitivity syndrome present with inguinal hernias and sometimes the diagnosis is made during inguinal herniorrhaphy when a gonad is present in the hernia sac (Figs. 21.1a, b and 21.2a, b).

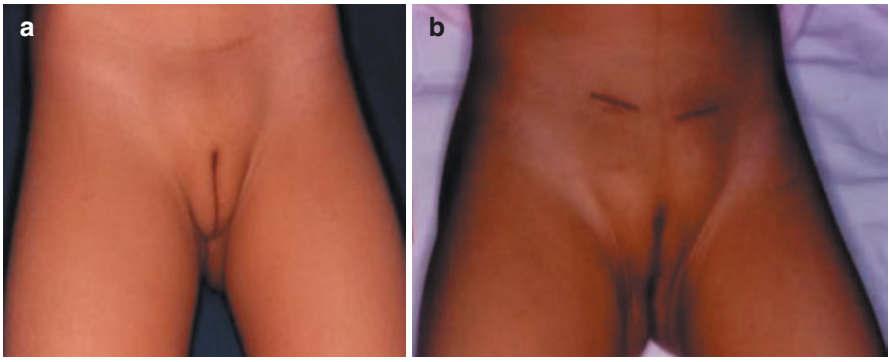


Fig. 21.1 (**a**, **b**) Clinical photographs showing two female patients who had unilateral and bilateral inguinal herniotomy and found to have complete androgen insensitivity syndrome. Note the female phenotype of external genitalia in both girls

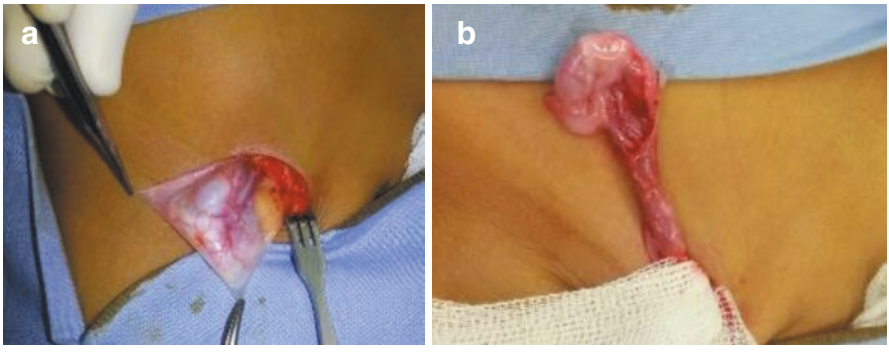


Fig. 21.2 (**a**, **b**) Clinical photographs showing two female patients who were found to have complete androgen insensitivity syndrome at the time of herniotomy. Note the normal looking testis in the hernial sac

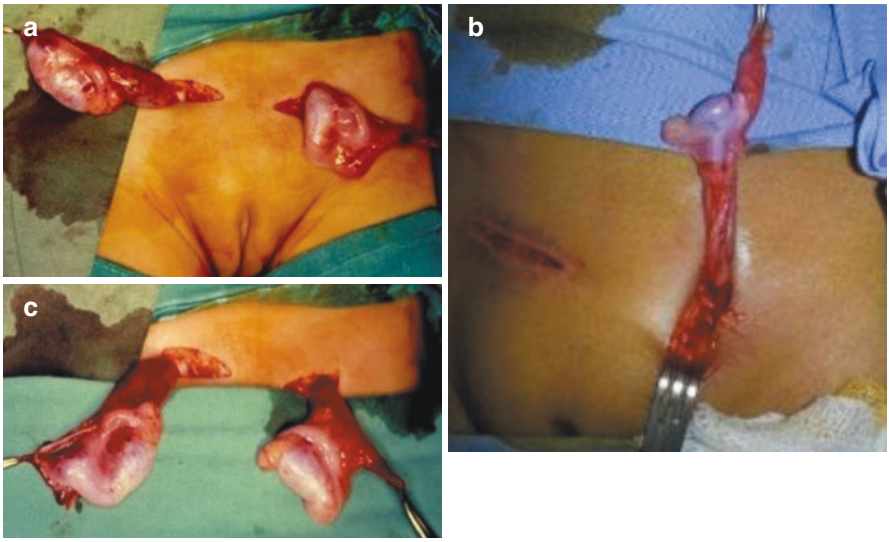
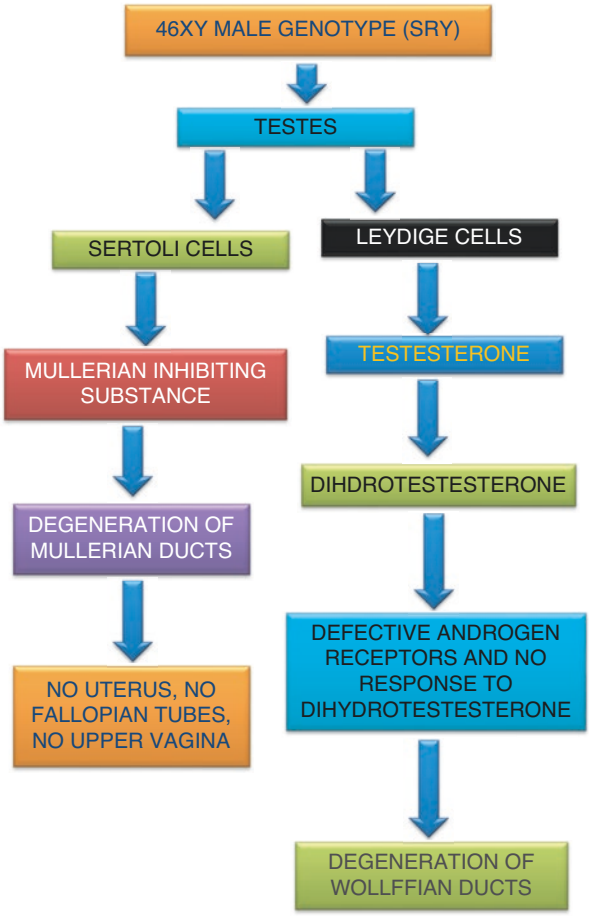


Fig. 21.3 (**a–c**) Clinical photographs showing complete androgen insensitivity syndrome with normal testes discovered at the time of herniotomy. The timing for gonadectomy is still controversial

- Failure to identify an internal Müllerian structure in a phenotypic female with an inguinal hernia should always raise the possibility of testicular feminization syndrome (Fig. 21.3a–c).
- The other presentation of complete androgen insensitivity syndrome is at puberty, when the patient presents with amenorrhea.
- Despite a 46XY karyotype and gonads with the typical appearance of testes, these patients are raised as females because of the completely feminine phenotype.
- It is important to establish the diagnosis in these patients because of the associated risk of gonadal malignancies.
- The overall frequency of gonadal malignancies in these patients is approximately 6%.
- The incidence of gonadal malignancy increases to more than 30% by age 50 years.
- Gonadoblastomas are the commonest malignant tumors in these patients.
- Other tumors include:
  - Sertoli cell and Leydig cell tumors
  - Tubular cell adenomas

21.2 Etiology

- The androgen insensitivity syndrome results from a defect in the androgen receptor gene.
- This androgen receptor gene has been localized to the long arm of the X chromosome (i.e., Xq11–13).
- More than 1000 mutations in the androgen receptor gene have been described, including:
  - Complete and partial gene deletions
  - Point mutations
  - Small insertions/deletions
- These mutations can cause a variety of functional defects, ranging from a complete loss of receptors on the cell surface because of incomplete protein synthesis to alterations in substrate binding affinity.
- Altered substrate binding affinity causes a signal transmission loss, despite normal cell surface receptor numbers.
- While the genotypes causing complete androgen insensitivity syndrome are fairly consistent in phenotypic presentation, the genotype/phenotype relationships for the mutations causing partial androgen insensitivity syndrome remain unclear.
- As a result of loss of androgen receptor gene, the post-receptor events that mediate the effects of testosterone on tissues do not occur. This is despite normal levels of androgen synthesis.
- This results in the phenotype of prenatal undervirilization of external genitalia, absence of pubic and axillary hair, lack of acne, and absence of voice changes at puberty.
- The exact incidence of androgen insensitivity syndrome is not known but an incidence of approximately 1 case per 20,400 live born males has been reported.
- Most cases of androgen insensitivity syndrome (AIS) are diagnosed in phenotypically females who present with inguinal hernias, which are identified to contain testes during surgery.
- Some patients with androgen insensitivity syndrome are first seen in the teenage years for evaluation of primary amenorrhea.



- Adults with partial androgen insensitivity syndrome often have gynecomastia and impaired phallic growth in association with elevated circulating concentrations of testosterone, estradiol, and luteinizing hormone in puberty, while follicle-stimulating hormone levels are normal.

21.3 Clinical Features

- Androgen insensitivity syndrome (AIS), formerly known as testicular feminization, is an X-linked recessive condition.
- It is seen in normally genetic males and results in a failure of normal masculinization of the external genitalia.

- This failure of virilization can lead to either complete androgen insensitivity syndrome (CAIS) or partial androgen insensitivity syndrome (PAIS), depending on the amount of residual receptor function.
- Both individuals with partial androgen insensitivity syndrome and individuals with complete androgen insensitivity syndrome have 46, XY karyotypes.
- Individuals with complete androgen insensitivity syndrome have female external genitalia with normal labia, clitoris, and vaginal introitus. Their external genitalias are phenotypically females.
- The phenotype of individuals with partial androgen insensitivity syndrome may range from:
  - Mildly virilized female external genitalia (clitoromegaly without other external anomalies)
  - Mildly undervirilized male external genitalia (hypospadias and/or diminished penile size)
- In both forms, affected individuals have normal testes with normal production of testosterone and normal conversion of testosterone to dihydrotestosterone (DHT).
- The testes in these patients are located intra-abdominally and commonly discovered during inguinal herniotomy.
- The testes in these patients produce normal amounts of müllerian-inhibiting factor (MIF), also known as müllerian-inhibiting substance (MIS) or anti-müllerian hormone/factor (AMH/AMF), and so affected individuals do not have fallopian tubes, a uterus, or a proximal (upper) vagina.
- A karyotype is essential to differentiate an under masculinized male from a masculinized female.
- The presence of a Y chromosome can also be confirmed by fluorescent in situ hybridization (FISH) probes for either the *SRY* region of the Y chromosome or a sub-telomeric Y chromosome probe.
- Mutation analysis of the androgen receptor gene is now commercially available. It detects up to 95% of the mutations for complete androgen insensitivity syndrome and partial androgen insensitivity syndrome.

21.4 Treatment

- The management of patients with androgen insensitivity syndrome is based on the followings:
  - Hormone replacement therapy
  - Surgical treatment
  - Psychological support

- Hormone replacement therapy
  - Adolescent and adult patients with androgen insensitivity syndrome require hormone replacement.
  - For patients with complete androgen insensitivity syndrome, hormone therapy consists of estrogen replacement.
  - These women do not require progesterone because they have no uterus.
  - Some evidence suggests that progesterone therapy combined with estrogen replacement may lessen the long-term risk of breast cancer, although this type of therapy is debatable.
  - For patients with partial androgen insensitivity syndrome, the treatment is similar to those with complete androgen insensitivity syndrome.
  - Patients with partial androgen insensitivity syndrome, who have a male gender identity, may be treated with testosterone and/or dihydrotestosterone (DHT). The advantage of DHT is that it cannot be aromatized to estrogen.
- Psychological support
  - Psychological support is probably the most important aspect of medical care for these patients.
  - Parents need genetic counseling to understand the nature of the condition and the risk of recurrence (25% for each subsequent pregnancy), as well as to identify other potential carriers.
  - They need a pediatric psychologist or child and adolescent psychiatrist to help adjust to their child's condition, including support on how to inform the child, over time and in an age-appropriate manner, about the condition.
  - The patient needs to establish a long-term relationship with the therapist to discuss new issues that arise as the child matures as well as emotional and psychological support.
  - Carefully communication and coordination among primary care physicians, genetic specialist, endocrinologist, and surgeons is important to avoid trauma to the child and family.
- Surgical management
  - The surgical treatment for patients with androgen insensitivity syndrome is an orchidectomy to prevent possible malignant degeneration of the testes (Fig. 21.4a, b).
  - The timing of orchidectomy is still controversial.
  - There are those who advocate late orchidectomy because the majority of tumors occur in the post pubertal age group.
  - Add to this the fact that delayed orchidectomy allows pubertal development to occur spontaneously with the production of estrogen from the aromatization of the high levels of testosterone normally produced.

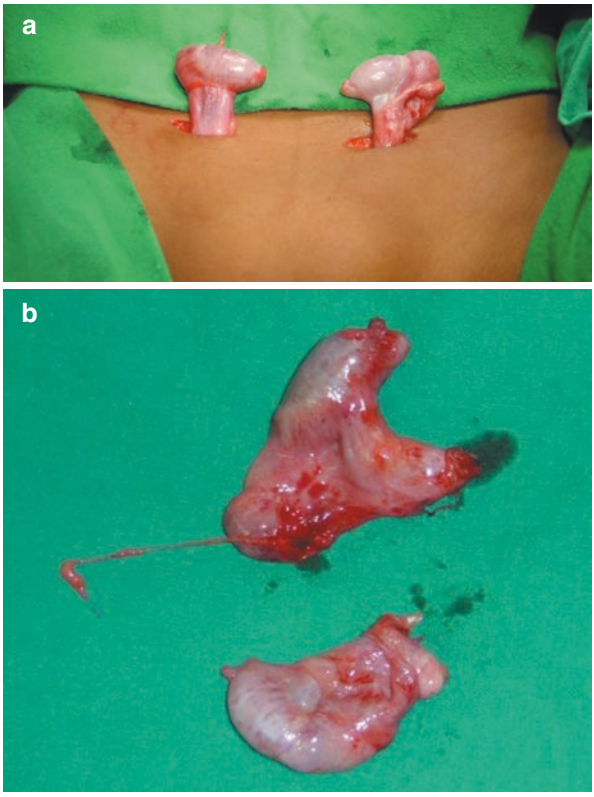


Fig. 21.4 (**a**, **b**) Intraoperative photographs of a patient with complete androgen insensitivity syndrome. Note the bilateral testes

- In addition, many women with androgen insensitivity syndrome require vaginal lengthening procedures.

  Orchidectomy and vaginal lengthening may be performed concurrently if surgery is postponed until the patient matures.
  Many support delaying these procedures until the patient is sufficiently mature to participate actively in treatment decisions.
  Some of these patients have an adequate vagina, requiring no vaginoplasty or possibly only vaginal dilation.

- Others advocate early orchidectomy because of associated inguinal hernia and to avoid subsequent psychological trauma.
- Similarly, in female gender patients with partial androgen insensitivity syndrome who have some degree of masculinization of the genitalia at birth, cosmetic reconstructive surgery traditionally has been performed in infancy.
- Patient advocates, including medical ethicists and intersex advocates, now endorse delaying this reconstructive surgery until children are old enough to decide for themselves.

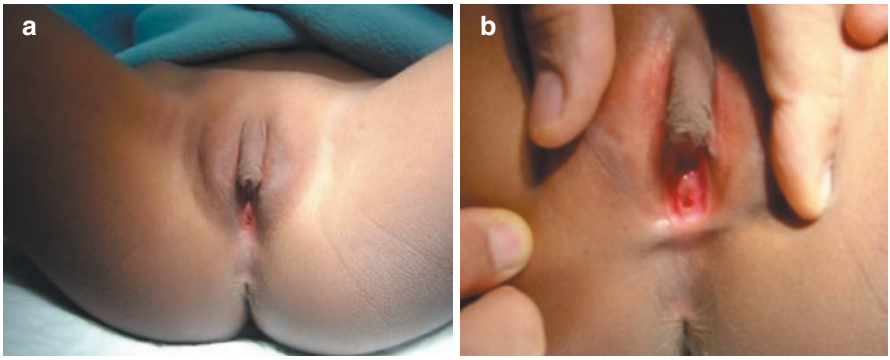


Fig. 21.5 (**a**, **b**) Clinical photographs of a patient with incomplete androgen insensitivity syndrome. Note the slightly enlarged clitoris and also the normal looking vagina

- Partial (incomplete) androgen insensitivity syndrome:
  - An incomplete form of androgen insensitivity also occurs.
  - This is not as severe as complete androgen insensitivity syndrome.
  - These patients have a spectrum of external genitalia ranging from:

    A very feminine female (Lubs syndrome)
    An increasingly masculine male (Gilbert-Dreyfus syndrome) (Fig. 21.5a, b).
    The most masculine male (Reifenstein syndrome).

  - They may present only with micropenis or cliteromegaly and causes a problem with gender assignment.
  - The diagnosis of incomplete androgen insensitivity syndrome is suggested by:

    Elevated LH levels
    Normal levels of plasma DHT
    Normal 5-alpha-reductase activity in genital skin fibroblasts

  - These patients are managed with:

    Early gonadectomy (Fig. 21.6a, b).
    Clitroplasty (Fig. 21.7a, b)
    Feminizing genitoplasty
    Hormonal replacement at puberty to induce female secondary sexual characteristics.
    Patients who are assigned as males will require hormonal treatment to virilize their body.

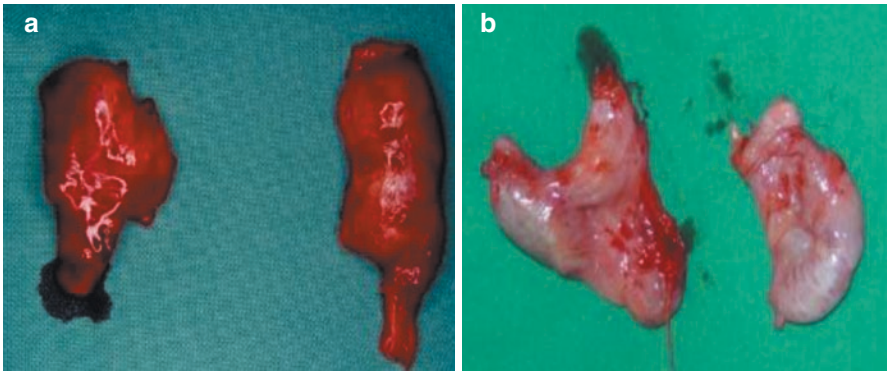


Fig. 21.6 (**a**, **b**) Clinical photographs of patients with androgen insensitivity syndrome who had bilateral gonadectomy. Note the two normally looking testes

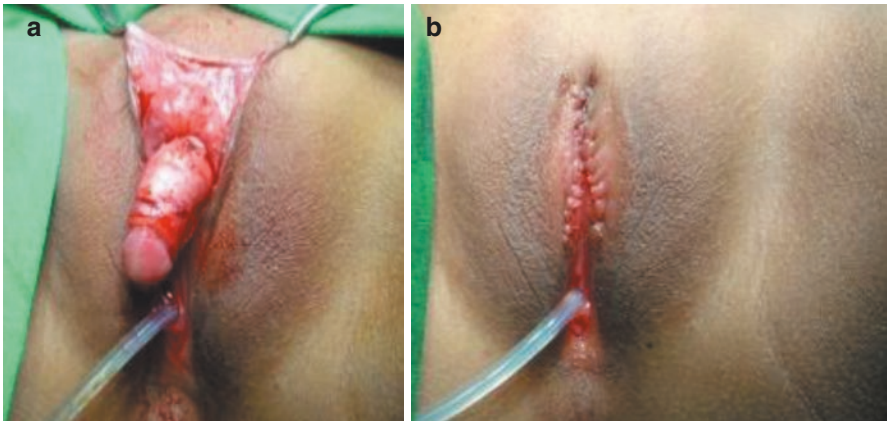


Fig. 21.7 (**a**, **b**) Clinical intraoperative photographs showing clitroplasty in a patient with incomplete androgen insensitivity syndrome

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Chapter 22
Deficient Testosterone Biosynthesis

Ahmed H. Al-Salem

22.1 Introduction

- In normal development, sex development is governed by two consecutive processes:
  - Sex determination
  - Sex differentiation
- Sex determination:
  - This is the formation of a testis or ovary from a bipotential gonad and is driven by the sequential expression of a number of genes.
- Sex differentiation: This is the development of internal and external physical characteristics brought about by gonadal hormone action on target tissues.
- Testosterone is the primary male sex hormone and also an anabolic steroid.
- In males, testosterone has several important functions:
  - It plays a key role in the development of male reproductive organs such as seminal vesicles, vas and prostate.
  - It promotes the development of secondary sexual characteristics such as increased muscle and bone mass, and the growth of body hair.
  - Testosterone is involved in health and well-being, and the prevention of osteoporosis.
  - Testosterone promotes protein synthesis and thus growth of tissues with androgen receptors.

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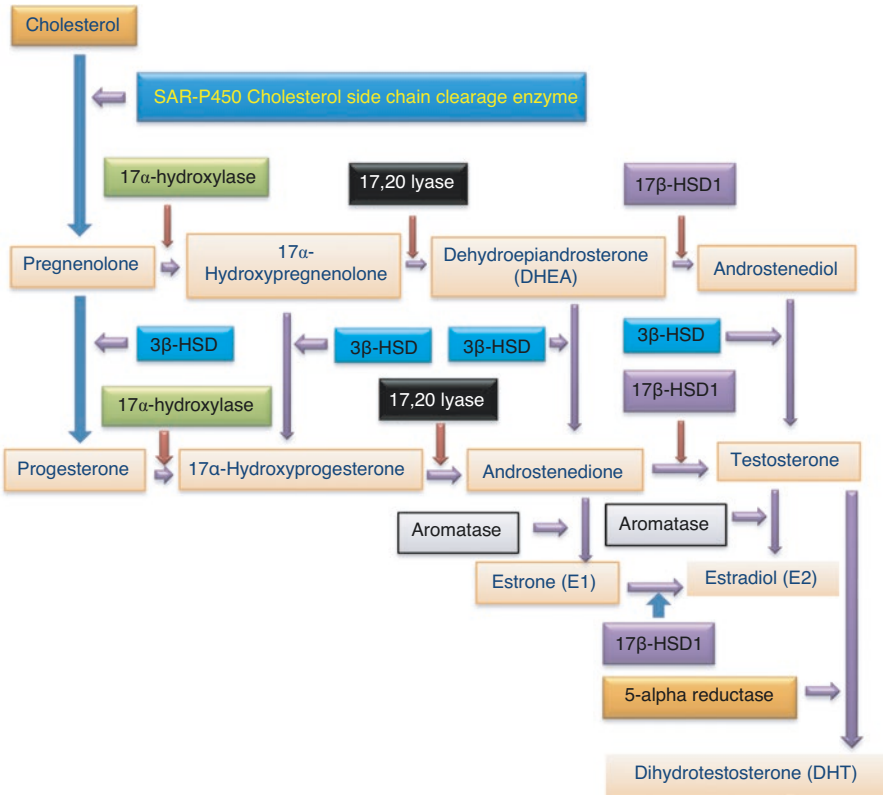
- Testosterone has virilizing and anabolic effects.
  - Anabolic effects include:

    Growth of muscle mass and strength
    Increased bone density and strength
    Stimulation of linear growth and bone maturation

  - Androgenic virilizing effects include:

    Maturation of the sex organs, particularly the penis and the formation of the scrotum in the fetus.
    Development of male secondary sex characteristics (Deepening of the voice, growth of facial hair (such as the beard) and axillary hair at puberty.

- Testosterone is biosynthesized in several steps from cholesterol and is converted in the liver to inactive metabolites.
- Only 1–3% of total testosterone is unbound in plasma (free testosterone). The rest is bound to the sex hormone-binding globulin (SHBG) and to other proteins as albumin. Albumin-bound testosterone can also display biological activity. Therefor bioavailable testosterone is testosterone not bound to the SHBG (free testosterone + albumin-bound testosterone).
- Testosterone exerts its action through binding to and activation of the androgen receptor.
- Testosterone is produced from cholesterol and this process involves five enzymatic steps.
- Enzyme defects have been identified at each of these five steps.
- Three of these five enzymes are shared with the adrenal gland, and their deficiency leads to ambiguous genitalia and symptoms of congenital adrenal hyperplasia.
- These three enzymes are:
  - 20–22, desmolase
  - 3-beta-hydroxysteroid dehydrogenase
  - 17-alpha hydroxylase
- The other two enzymes occur only as part of the normal testosterone biosynthesis and their defects leads to ambiguous genitalia without the symptoms of congenital adrenal hyperplasia.
- These two enzymes are:
  - 17, 20 desmolase
  - 17-beta hydroxysteroid dehydrogenase
- The diagnosis of these enzyme deficiencies is possible by measuring the levels of precursor products.
- This however is available in specialized centers only.
- Testosterone Biosynthetic Defects affect 46, XY individuals and can be complete or partial, which leads to newborns who appear either completely female or ambiguous, respectively.



- In the past, these patients were grouped as male pseudohermaphrodite without Mullerian structures.
- The term male pseudohermaphroditism (MPH) describes an individual with ambiguity of the internal or external genitalia whose karyotype is 46, XY and who has testes.
- Currently, they are grouped under 46, XY disorders of sexual development (DSD).
- Disorders of androgen biosynthesis include mutations in genes involved in the pathway of testosterone synthesis that either are common to the adrenal gland and the testes, and thus may also cause deficiencies of glucocorticoids and/or mineralocorticoids (with some forms of congenital adrenal hyperplasia [CAH]), or are just found in the testes and thus only lead to defects in testosterone biosynthesis.
- In 46, XY DSD presenting as ambiguous genitalia, the degree of virilization depends on:
  - The amount of residual functioning testes
  - The amount of testosterone synthesized
  - The degree of androgen insensitivity

- The infant with male pseudohermaphroditism without mullerian structures always has a normal male (46XY) karyotype and normally functioning testes.
- Genital ambiguity is the result of:
  - An abnormal testosterone level
  - A decreased tissue response to testosterone leading to decreased masculinization of the external genitalia.
- The etiology of male pseudohermaphroditism can be categorized into three groups:
  - Defects in the biosynthesis of testosterone
  - Inability to convert testosterone to dihydrotestosterone (DHT)
  - Androgen receptor defects
- Defects in the biosynthesis of testosterone are related to a deficiency in one of the five enzymes required for the biosynthesis of testosterone from cholesterol.
- These enzymes include:
  - 17, 20-desmolase
  - 20, 22-desmolase
  - 17 alpha-hydroxylase
  - 3 beta-hydroxysteroid dehydrogenase
  - 17 beta-hydroxysteroid dehydrogenase
- This deficiency leads to a diminished testosterone level and genital ambiguity.
- Three of these enzymes also are necessary for the synthesis of cortisol, with a deficiency resulting in adrenal hypertrophy and potential salt wasting.
- Diagnosis can be ascertained by determining there are decreased serum testosterone levels with an increased level of steroid precursors before the enzyme blockage.
- Dihydrotestosterone, a more potent masculine hormone than testosterone, is responsible for virilization of the external genitalia and development of male secondary sex characteristics at puberty.
- This hormone is converted from testosterone by the enzyme 5 alpha-reductase.
- A deficiency of 5 alpha-reductase will lead to inadequate virilization of the male external genitalia.
- Infants with this condition (5 alpha-reductase deficiency) have:
  - Normal levels of testosterone
  - Normal Mullerian-inhibiting substance
  - Normal male internal genitalia (are masculinized)
  - The external genitalia appear to be predominantly female
- Diagnosis is made by determining that there is an increased level of testosterone compared with that of Dihydrotestosterone.
- Both testosterone and DHT must bind to receptor sites located in the cytoplasm of peripheral tissue.

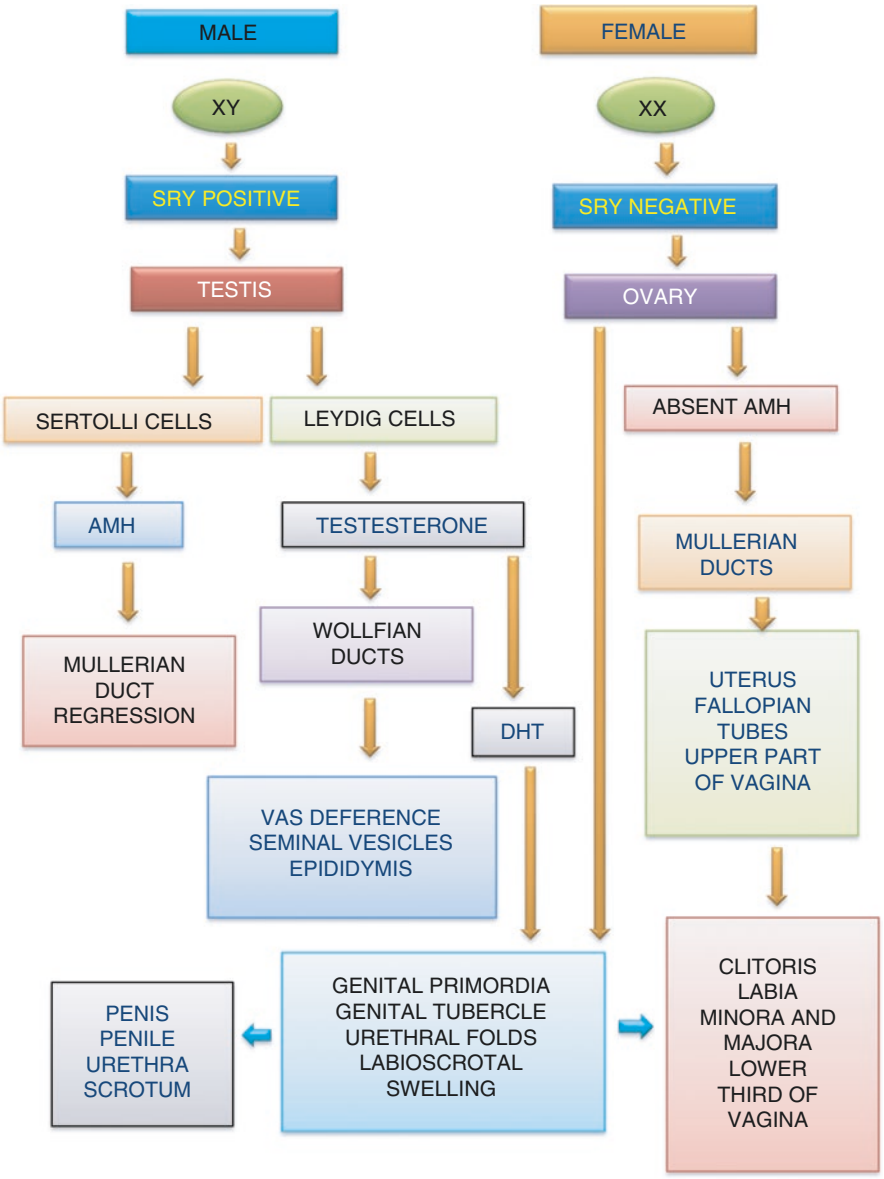
  - If an androgen receptor defect is present, hormonal effects are not produced, and feminization of both the internal duct system and the external genitalia occurs.
  - Diagnosis is made by examination, finding increased serum levels of testosterone and abnormal binding of DHT to androgen receptors in fibroblasts obtained from genital skin.

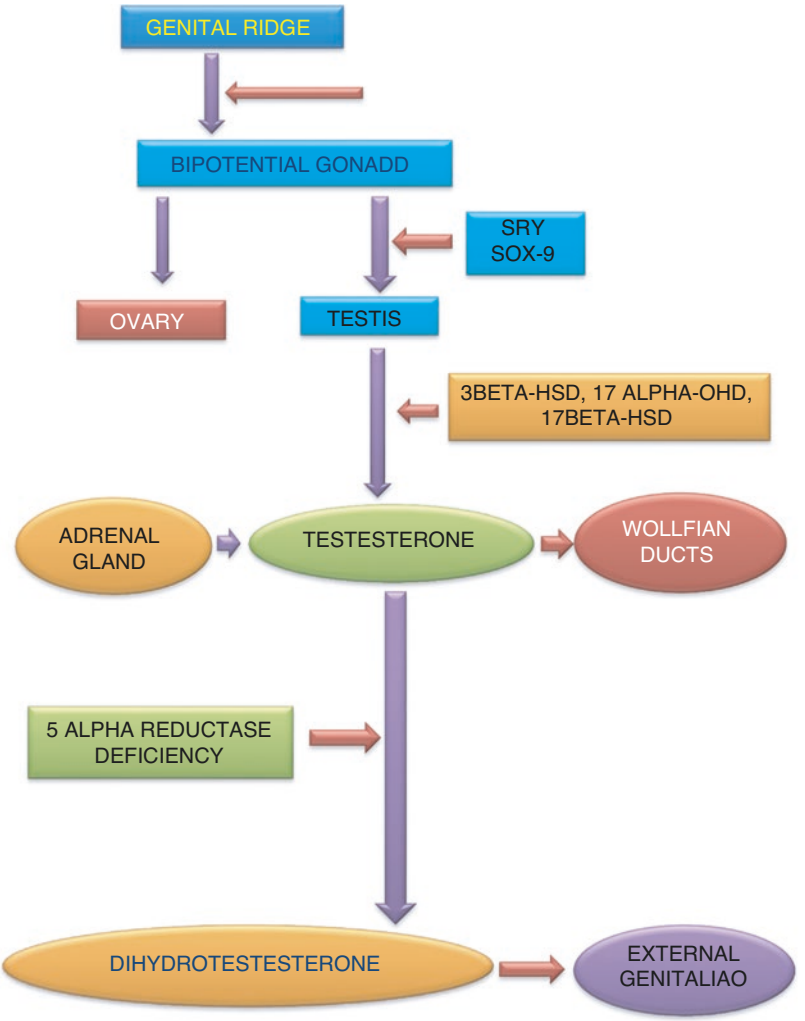
- The male pseudohermaphrodite may present with varying degrees of genital feminization ranging in appearance from normal female with a blind vagina to normal male with a hypospadias.
- In infants with normally appearing female genitalia, the condition may not be suspected until puberty and the development of male secondary sex characteristics or lack of breast development and presence of amenorrhea.
- Other rare causes of testosterone production deficiencies include:
  - Leydig cell agenesis
  - Leydig cell hypoplasia
  - Abnormal Leydig cell gonadotropin receptors
  - Delayed receptor maturation

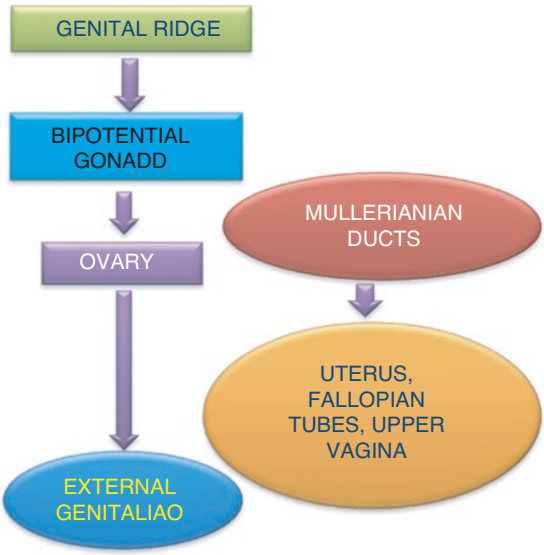
22.2 Pathophysiology

- Complete differentiation of male external and internal genitalia requires the secretion of three hormones:
  - Anti-Mulllerian hormone
  - Testosterone
  - Dihydrotestosterone
- Anti-Mulllerian hormone and testosterone are secreted by the fetal testis.
- Anti-Mullerian hormone causes regression of the Mulllerian ducts, the anlage of the uterus, Fallopian tubes and upper vagina.
- Testosterone stabilizes the Wolffian ducts and permits the development of the Wolffian ducts into vasa differentia, epididymis, and seminal vesicles.
- Testosterone is converted peripherally to dihydrotestosterone via the enzyme 5-alpha reductase.
- Dihydrotestosterone:
  - This is required for the development of the prostate from the urogenital sinus.
  - And in the development of the male external genitalia from the genital tubercle, genital folds and genital swelling.
- Testosterone is produced from cholesterol.

- A critical step in steroid hormone biosynthesis is delivery of the cholesterol substrate to the inner mitochondrial membrane sites, where cholesterol side-chain cleavage P450scc is located, and the enzyme that catalyzes the conversion of cholesterol to pregnenolone takes place.
- StAR is a hormone-induced mitochondria-targeted protein that has been shown to initiate cholesterol transfer into mitochondria.
- StAR is synthesized as a short-lived cytoplasmic 37-kDa protein with a mitochondrial targeting peptide that is cleaved upon mitochondrial import to yield the long-lived intramitochondrial 30-kDa form.
- StAR functions as a sterol transfer protein, binds cholesterol, mediates the acute steroidogenic response by moving cholesterol outer mitochondrial membrane to inner mitochondrial membrane, acts on the outer mitochondrial membrane, and requires structural change previously described as a pH-dependent molten globule.
- Mutations in the StAR gene cause a fatal condition in newborns, the congenital lipoid adrenal hyperplasia (lipoid CAH), characterized by severe impairment of steroiodogenesis, hypertrophied adrenals containing high levels of cholesterol esters and free cholesterol and increased amounts of neutral lipids in the testicular Leydig cells.
- In accordance with its role in the acute regulation of steroidogenesis, StAR is expressed mainly in the adrenal cortex, steroid producing cells of the ovary and testicular Leydig cells.
- Testosterone is produced from cholesterol and this involves five enzymatic steps.
- Each enzyme deficiency shows considerable phenotypic heterogeneity. Different mutational events altering either structural or regulatory genes may explain the phenotypic spectrum of these patients.
- The first three enzymatic deficiencies result in cortisol as well as testosterone deficiency and present as forms of congenital adrenal hyperplasia.
- The inheritance is autosomal recessive in 17-hydroxylase and 3-beta-hydroxysteroid dehydrogenase deficiency.
- In the other three defects, the inheritance is unclear.
- Heterozygous subjects are phenotypically normal.
- Inhibition of the Mullerian ducts is usually complete in these patients and the uterus or Fallopian tubes are not present.
- Masculinization of the external genitalia is incomplete.
- Inhibition of the Mullerian ducts is usually complete in these patients and the uterus or Fallopian tubes are not present.
- Masculinization of the external genitalia is incomplete.
- Androgen action is normal in these patients in contrast to patients with androgen resistance (e.g. testicular feminization).
- Disorders of androgen biosynthesis are a relatively rare cause of disorders of sexual development in 46, XY genetic males.


MALE
XY
SRY POSITIVE
TESTIS
SERTOLLI CELLS
LEYDIG CELLS
AMH
TESTESTERONE
MULLERIAN DUCT REGRESSION
WOLLFIAN DUCTS
DHT
VAS DEFERENCE SEMINAL VESICLES EPIDIDYMIS
PENIS PENILE URETHRA SCROTUM
GENITAL PRIMORDIA GENITAL TUBERCLE URETHRAL FOLDS LABIOSCROTAL SWELLING
FEMALE
XX
SRY NEGATIVE
OVARY
ABSENT AMH
MULLERIAN DUCTS
UTERUS FALLOPIAN TUBES UPPER PART OF VAGINA
CLITORIS LABIA MINORA AND MAJORA LOWER THIRD OF VAGINA


GENITAL RIDGE
BIPOTENTIAL GONADD
SRY
SOX-9
OVARY
TESTIS
3BETA-HSD, 17 ALPHA-OHD,
17BETA-HSD
ADRENAL
GLAND
TESTESTERONE
WOLLFIAN
DUCTS
5 ALPHA REDUCTASE
DEFICIENCY
DIHYDROTESTESTERONE
EXTERNAL
GENITALIAO



TESTESTERONE BIOSYNTHETIC DEFECTS

1. STEROIDOGENIC ACUTE REGULATORY PROTEIN (StAR) DEFECIENCY
2. CYTOCHROME P450scc
3. CYTOCHROME P450c17
4. SIDE-CHAIN CLEAVAGE (CYP11A) DEFICIENCY
5. 3 B-HYDROXYSTEROID DEHYDROGENASE DEFICIENCY II
6. 17 B-HYDROXYSTEROID DEHYDROGENASE DEFICIENCY III
7. CYTOCHROME P450 (P450 OXIDOREDUCTASE (POR) DEFECT)
8. CYP17 DEFICIENCY
9. 17-KETOSTEROID REDUCTASE DEFICIENCY
10. CYTOCHROME b5 (CYB5) DEFECT
11. 17 B-HYDROXYLASE/17,20-LYASE DEFICENCY
12. DEFECTS IN LUTEINIZING HORMONE ACTION (LHCGR DEFECT)

- The biosynthesis of androgens requires several enzymes including:
  - The steroidogenic acute regulatory protein (StAR)
  - P450scc
  - P450c17
  - 3betaHSDII
  - 17betaHSDIII
  - 5alpha-reductase
- Deficiencies can occur at any step of these enzymes leading to male pseudohermaphroditism.
- Deficiencies of steroidogenic enzymes include a group of genetic conditions involving adrenocorticcoid and gonadosteroid biosynthesis.
- The first three enzymes involved with androgen production are involved with the production of both cortisol and testosterone and their deficiencies are typically associated with varying degrees of adrenal insufficiency and sexual ambiguity:
  - Cholesterol-desmolase complex
  - 3-beta hydroxysteroid dehydrogenase
  - 17-alpha hydroxylase
- The other two enzymes are used in the production of androgens only and individuals with these deficiencies present with sexual ambiguity only:
  - 17-alpha hydroxylase
  - 17, 20 lyase
- Congenital adrenal lipoid hyperplasia:
  - This is characterized by severe adrenal insufficiency and massive amounts of cholesterol deposited in the adrenal gland cortex and gonads.
  - It results from deficiency of cholesterol-side chain cleavage system ($P\text{-}450_{SCC}$).
  - This is involved in converting cholesterol to pregnenolone.
  - This is very rare and usually fatal.
  - This will result in inability to metabolize cholesterol in the adrenal gland and leads to large, yellow, foamy adrenal gland.
  - It is characterized by low levels of cortisol, aldosterone and androgens.
  - Hyperpigmentation and respiratory distress occur in 25% of affected patients.
  - These patients present with:

    Failure to thrive
    Vomiting
    Diarrhea
    Hypernatremia
    Hypokalemia
    Hypertension

- Affected males present with ambiguous genitalia or female external genitalia.
- Affected females have normal female external genitalia.
- Treatment:

  Affected patients are assigned a female gender
  Glucocorticoids and mineralocorticoid replacement therapy
  Affected males should have bilateral orchidectomy
  Estrogen replacement therapy at puberty

• 3-beta-hydroxysteroid dehydrogenase deficiency

- Two forms of 3-beta-hydroxysteroid dehydrogenase deficiency have been described

  The classic type is associated with complete block of 3-beta-hydroxysteroid dehydrogenase deficiency
  The non-classic type is associated with partial block of 3-beta-hydroxysteroid dehydrogenase deficiency

- Those with the classic type present in infancy with severe sodium wasting ad the outcome is fatal if not recognized and treated early.

  There is deficient production of glucocorticoids, mineralocorticoids and sex steroids.
  Cortisol deficiency results in ACTH stimulation and congenital adrenal hyperplasia.
  There is incomplete virilization in males and partial virilization of females.
  This is secondary to Dehydroepiandrosterone (DHEA) as the major androgen produced.
  Diagnosis:

  • Elevated pregnenolone, DHEA
  • In males there are palpable testes with hypospadias or pseudovagina hypospadias
  • Females may have clitoral enlargement and partial or complete labial fusion

- The non-classic type of 3-beta-hydroxysteroid dehydrogenase deficiency is much more common and patients present with less severe clinical features.

  Affected females present with a picture similar to polycystic ovarian syndrome with hirsutism, menstrual irregularities and infertility
  In affected males, there is premature pubarche or pubertal hyperandrogenism
  ACTH stimulation leads to elevation of 17-pregnrnelone, DHEA, 17-pregnenelone: 17-hydroxyprogesterone ratio and 17-pregnenelone: cortisol ratio.
  Treatment is with glucocorticoids

22.3 Clinical Features

- During the newborn period, these patients present as 46/XY males with poor virilization and ambiguous genitalia.
- The genitalia in these patients respond to exogenously testosterone.
- This helps differentiate them from 5-alpha reductase deficiency which do not respond to testosterone but will respond to dihydrotestosterone.
- It is also important to treat those who present with CAH manifestations with replacement therapy including steroids and mineralocorticoid replacement.
- Genetic counseling is also important in these patients as 17-alpha hydroxylase and 3-beta-hydroxysteroid dehydrogenase deficiencies are transmitted as autosomal recessive traits.
- Defects in the chain of steroidogenic enzymes involved in the testosterone biosynthesis pathway result in insufficient androgen concentrations during fetal development. This will lead to four main clinical syndromes depending on the affected enzyme.
  - Congenital Lipoid Adrenal Hyperplasia (CLAH)
  - 3 beta-HDD deficiency
  - 17 alpha-hydroxylase/17, 20 lyase deficiency
  - 17 beta-hydroxysteroid dehydrogenase deficiency (17 beta-HSD).
- Congenital Lipoid Adrenal Hyperplasia (CLAH)
  - CLAH is caused by a defect in the steroidogenic acute regulatory (StAR) protein.
  - This is responsible for transporting cholesterol to the inner membrane of the mitochondria.
  - Insufficient testosterone in affected males leads to underdeveloped Wolffian duct structures and external male genitalia.
  - Mullerian structures are absent because there is normal testicular MIF production.
  - Male infants with CLAH present at birth with severe complete adrenal insufficiency:

    Vomiting
    Diarrhea
    Weight loss
    Hyponatremia
    Hypokalemia
    Hypotension
- Genital appearance is primarily female.
  - The congenital lipoid adrenal hyperplasia can be caused by mutations of two different genes.

Mutations of the gene coding steroidogenesis which is an active regulatory protein that serves as the intermediary of a fast input of cholesterol in a mitochondrion.
More rare mutations of a gene of CPY11A coding enzyme of splitting of a side chain of cholesterol 20, 22 desmolase.
These patients have decreased levels of glucocorticoids, mineralocorticoid, testosterone and DGT along with reduction of sodium and potassium.
Most of these children perish as neonates.
Survivors must be treated with constant replacement therapy which includes glucocorticoids and mineralocorticoids.

- 17-β-HSD3 deficiency
  - 17-β-HSD3 deficiency is a rare autosomal recessive disorder resulting from a defect in testosterone biosynthesis.
  - 17-β-HSD3 enzyme is involved in the conversion of androstenedione into testosterone.
  - 17-β-HSD3 deficiency results in normal male Wolffian duct structures but with female external genitalia at birth.
  - 46, XY patients with 17-β-HSD3 deficiency are characterized by the absence or presence of hypoplastic internal male genitalia (prostate and testes).
  - The diagnosis may be delayed until adolescence in phenotypic females and they present with:

    Inguinal hernia
    Mild clitoromegaly
    Urogenital sinus when presented with virilization
    Primary amenorrhea

  - 17-β-HSD3 deficiency is a genetic steroid disorder of testicular androgen synthesis.

    Male newborns with 17-β-HSD3 deficiency usually have external genitalia with feminizing features together with undescended testes usually in the inguinal region or in a bifid scrotum.
    The presence of Wolffian duct structures such as epididymis, seminal vesicles, vas deferens, and ejaculatory ducts may be explained by the low testosterone concentration, which appears to be sufficient for their development in utero.
    In addition, testosterone production through an alternative pathway catalyzed by other 17-β-HSD isoenzymes may contribute to the androgenization of these structures.

  - The laboratory diagnosis of 17-β-HSD3 deficiency is usually made based on finding a characteristic biochemical pattern with predominance in 17-ketosteroids (namely androstenedione, DHEA, and estrone) compared with 17-hydroxylsteroids (namely testosterone, androstendiol, and estradiol) with consequent increase in androstenedione: testosterone and estrone: estradiol ratios in basal state or postHCG stimulation.
  - The decision for sex rearing in patients with 17-β-HSD3 deficiency is difficult especially that the majority of cases are diagnosed late in childhood or at puberty.
  - Males the time of puberty when they develop marked virilization with penis enlargement, male pattern body hair, and muscle development may be raised as males with or without surgical correction, otherwise they require bilateral orchiectomy if the female social sex is chosen.
  - 39–64% of cases are raised as females.
  - Infants with 3 beta-HDD deficiency can present with varying degrees of genital ambiguity and evidence of salt-losing crisis.

- Insufficiency of a 17a-hydroxylase:

  - Insufficiency of a 17a-hydroxylase is characterized by decreased levels or total absence of the sex hormones synthesized both by gonads, and adrenal glands.
  - Simultaneous increase of synthesis of mineralocorticoid precursors.
  - Male newborns genital organs are developed on intermediate type while newborn girls have an underdevelopment of their genital organs.
  - For girls insufficiency of a 17a-hydroxylase is diagnosed often at early teenage age because of a delay of sexual development, lack of secondary sexual characteristics or primary amenorrhea though in certain cases diagnosis is possible at the birth.

- Mutations of a gene of CYP17 can clinically be shown in the form of insufficiency of a 17a-hydroxylase, 17, 20 lyase or their combinations. At insufficiency of a 17a-hydroxylase decrease in maintenance of cortisol stimulates corticotropin synthesis, and though products of steroids rise, it is all the same blocked at a 17a-hydroxylase stage. Kompensatorno 17-dezoksisteroida, including pregnenolon, progesterone, cortexone and corticosterone collect.
- Infants with 17 alpha-hydroxylase/17, 20 lyase deficiency have genital ambiguity.
- Patients with primary 17 alpha-hydroxylase deficiency also have hypertension.
- Male infants with 17 beta-HSD deficiency present with what appear to be external female genitalia that may include mild clitoral enlargement.
- An inguinal hernia may be present, possibly the only finding that will bring the infant to medical attention.

22.4 Diagnosis

- General laboratory investigations in suspected testosterone biosynthetic defects include:
  - Chromosomes analysis
  - Baseline levels of testosterone
  - Androgen precursors and DHT
  - Levels of steroids and steroid precursors.
  - An hCG stimulation test can be performed to measure the ratio of androstenedione to testosterone; an elevated ratio suggests 17 beta-HSD deficiency.
  - In CLAH, ultrasound, CT or MRI may show enlarged, lipid-laden adrenal glands.

22.5 Management

- Acute management of these disorders requires full steroid replacement with both glucocorticoids and mineralocorticoids.
- In CLAH and 3 beta-HDD, general supportive measures may be necessary, as severe adrenal insufficiency can cause rapid metabolic decompensation if the disorder is not recognized at birth.
- Genetic XY infants with CLAH are raised in the female gender.
- Children with 17 beta-HSD often virilize significantly at puberty owing to increased peripheral conversion of androstenedione to testosterone by 17 beta-HSD isoenzymes, making gender assignment of those diagnosed as neonates a less straightforward decision.

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Chapter 23
Gonadal Dysgenesis

Ahmed H. Al-Salem

23.1 Introduction

- Gonadal dysgenesis is characterized by incomplete or defective development of the gonads (ovary or testis).
- This results in dysgenetic gonads which are characterized by variable degrees of immaturity or dysfunction, which can manifest in a wide range of genital ambiguity.
- Gonadal dysgenesis is a unique form of disorders of sexual development (DSD) that encompasses a wide spectrum of phenotypes ranging from normally virilized males to slightly undervirilized males, ambiguous phenotype, and normal looking phenotypic females.
- In gonadal dysgenesis, there is an absence of both antimullerian hormone and testosterone.
  - The absence of testosterone will result in regression of the Wolffian ducts. The normal male internal reproductive tracts will not develop.
  - The absence of AMH will allow the Müllerian ducts to differentiate into the fallopian ducts, uterus and upper vagina.
  - As a result, these patients will:

    Have female-like internal and external reproductive characteristics
    Lack secondary sex characteristics, i.e. underdeveloped sex organs and ambiguous genitalia (sexual organs that aren't well formed or aren't clearly male or female).

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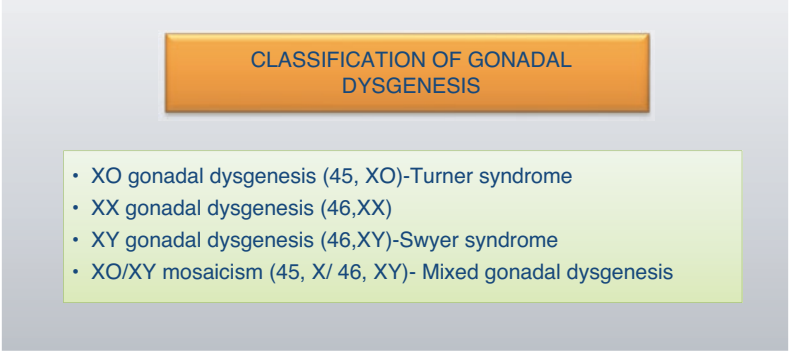
- Depending on the number and appearance of chromosomes, gonadal dysgenesis is classified into:
  - XO gonadal dysgenesis (45, XO)—Turner syndrome
  - XX gonadal dysgenesis (46, XX)
  - XY gonadal dysgenesis (46, XY)—Swyer syndrome
  - XO/XY mosaicism (45, X/46, XY)—Mixed gonadal dysgenesis



- The presence of a Y chromosome in patients with gonadal dysgenesis makes them at increased risk for developing gonadal malignancy such as gonadoblastoma or carcinoma in situ (CIS), with the potential for malignant transformation to dysgerminoma or seminoma, respectively.
  - Gonadoblastoma which was first introduced by Scully in 1953 is the most common germ cell tumor seen in patients with XY gonadal dysgenesis.
  - Gonadoblastoma usually presents in the second decade, but cases occurring in early infancy have been reported.
  - In 50–60% of cases, gonadoblastomas are associated with malignant germ cell tumors, most commonly dysgerminomas.
  - The prognosis is favorable when the gonadoblastoma is associated with dysgerminoma, but unfavorable when associated with other germ cell tumors including yolk sac tumors, seminomas, immature teratomas, embryonal carcinomas, or choriocarcinomas.
  - Gonadal dysgenesis is a known risk factor for carcinoma in-situ.
  - Carcinoma in-situ, otherwise known as intratubular germ cell neoplasia unclassified, is the common precursor for testicular germ cell tumors including seminomas, embyronal carcinomas, teratomas, and yolk cell tumors.
  - The natural history of untreated carcinoma in-situ is as follows:

    A 40% estimated risk of progression to invasive cancer within 3 years.
    A 50% estimated risk of progression to invasive cancer within 5 years.
    To prevent the development of malignancy in patients with XY gonadal dysgenesis, gonadectomy is recommended.
    The timing of gonadectomy and for which patient is still controversial.

- Gonadal dysgenesis can be classified as either complete gonadal dysgenesis or partial gonadal dysgenesis depending on the gonadal morphology.
- In complete gonadal dysgenesis (i.e., 46, XY Swyer syndrome), no gonadal development occurs, and, as a consequence, these patients have a completely female phenotype due to the lack of any gonadal steroid production.
- In partial gonadal dysgenesis in which a Y chromosome is present, there is incomplete testicular development and the external phenotype depends on the degree of testicular function.
  - The most common karyotype seen in partial gonadal dysgenesis is 45, X/46, XY, but 46, XY and other forms of mosaicism involving the Y chromosome also can be seen.

23.2 Partial Gonadal Dysgenesis

- Partial gonadal dysgenesis represents a spectrum of DSD in which the gonads are abnormally developed.
- Typically, at least one gonad is either dysgenetic testis or a streak ovary.
- Partial gonadal dysgenesis can be classified as:
  - 46, XY DSD
  - Sex chromosome DSD if there is mosaicism (45, X/46, XY).

    These represent a spectrum of disorders in which the gonads are abnormally developed.
    Typically, at least one gonad is either dysgenetic or a streak.
    In mixed gonadal dysgenesis (MGD), a streak gonad is usually present on one side and a testis (usually dysgenetic) on the opposite side.

23.3 A Dysgenetic Testis

- This histologically demonstrates immature and hypoplastic testicular tubules in a stroma of ovarian tissue that lack oocytes.
- This stroma has the appearance of that seen in streak gonads.
- There is a spectrum of faulty testicular differentiation, with streak gonad at one end of the spectrum, and dysgenetic testis lying between streak gonad and a normal testis.
- The degree of virilization is variable but all patients have a vagina and a uterus, and most have a fallopian tube, at least on the side of the streak gonad.
- There is a risk of gonadal malignancy in these patients especially when a Y chromosome is present in the karyotype.
- These malignant tumors include:

  - Gonadoblastomas
  - Seminomas
  - Embryonal cell carcinomas

- Patients with mixed gonadal dysgenesis (MGD) have a streak gonad on one side with a contralateral testis.
  - Although the degree of virilization varies, all patients have a vagina and a uterus, and most have a fallopian tube, at least on the side of the streak gonad.
  - Most patients with MGD have a mosaic karyotype, 45, X/46, XY.
  - A characteristic of patients with a 45, X karyotype is short stature.
  - Patients who have no internal müllerian remnants usually have no 45, X component.
- Gonadal malignancy is a risk when a Y chromosome is present in the karyotype.
  - In MGD, 25% of gonads, including streak gonads, can be expected to undergo malignant change, most often to gonadoblastoma.
  - In addition to gonadoblastomas, seminomas and embryonal cell carcinomas may develop.
  - To avoid this, early gonadectomy is recommended.
- Dysgenetic male pseudohermaphroditism (DMP):
  - This term is used to describe patients with bilaterally dysgenetic testes and incomplete virilization of the internal sex ducts and external genitalia.
- Gender assignment for patients with Dysgenetic male pseudohermaphroditism (DMP) and Mixed gonadal dysgenesis (MGD) remains under debate.
  - There are those who advocate assigning male gender to patients who are sufficiently virilized.
  - Others advocate an elective feminine gender assignment for patients with MGD because a uterus and vagina always are present and one half of patients are markedly short and have a high incidence of inadequate external virilization.
  - Hormonal estrogen replacement is recommended for patients who are raised as females.
  - Unopposed estrogen and in the presence of a uterus can increase the incidence of endometrial carcinoma and these patients must be cycled with a combination of estrogen and a progestational hormonal treatment.

23.4 Pure Gonadal Dysgenesis

- Pure gonadal dysgenesis is characterized by the followings:
  - It is seen in phenotypically female.

  - The chromosomal makeup is classically 46, XX.
  - Pure gonadal dysgenesis is inherited as an autosomal recessive trait, so genetic counseling is warranted.
  - They have bilateral streak gonads appearing as ovarian stroma without oocytes.
  - The external phenotype and internal duct structures are female.
  - These patients generally are seen at puberty with primary amenorrhea.
  - The gonads in those with 46, XX chromosomes do not carry risk of malignant degeneration.

- They have either a 46, XX or 46, XY karyotype.
- The 46, XX defect may be inherited as an autosomal recessive and may be associated with nerve deafness in 10%.
- The 46, XY defect may be inherited as an X-linked recessive.
  - They have clitoromegaly occurring in 10–15%.
  - They have gonadal tumors developing in 25% if the gonads are not removed.
- Other conditions are also closely related to bilateral streak gonads.
  - The chromosomal makeup is quite variable and can be 46, XY (XY sex reversal, Swyer's syndrome, or male Turner's syndrome)
  - 45, XO
  - Mosaic
  - Variants with a Y chromosome differ in that they carry a high rate of malignancy in the retained streak gonad and because of this risk, some of these patients may be first seen in infancy with gonadoblastomas or dysgerminomas, or with germ cell tumors that become more common in adolescence.
- Diagnosis
  - The finding of a female external phenotype and an internal duct structure with bilateral streak gonads confirms the diagnosis.
  - Follicle-stimulating hormone and LH levels are generally elevated, and estrogen and testosterone levels are decreased.
  - The diagnosis may be suggested by the physical stigmata of Turner's syndrome on physical examination (e.g., webbed neck, shield chest).
- Treatment
  - With the presence of a Y chromosome, gonadectomy should be performed, given the high incidence of malignancy.
  - In classic 46, XX pure gonadal dysgenesis, the gonads can be left in situ because there is no malignant potential.
  - In either case, hormonal replacement at puberty is required because the streak gonads provide no endocrine function.
  - Treatment of those with pure gonadal dysgenesis is primarily limited to appropriate estrogen and progesterone replacement therapy.

- Girls with Turner syndrome (45, XO) may be detected earlier by the characteristic associated anomalies:
  - Short stature
  - Webbing of the neck
  - Wide-spaced nipples
- Swyer Syndrome (Also known as Pure Gonadal Dysgenesis or XY gonadal dysgenesis):
  - This is a type of hypogonadism in a person whose karyotype is 46, XY.
  - The person is externally female with streak gonads, and if left untreated, will not experience puberty.
  - Such gonads are typically surgically removed as they have a significant risk of developing tumors.
- Neither Turner syndrome (45XO) nor the 46XX type of pure gonadal dysgenesis appears to be associated with increased risk of gonadal malignancy.
- Patients with 46XY pure gonadal dysgenesis on the other hand carry a significant risk for malignancy.
  - Nearly one third of patients develop a dysgerminoma or gonadoblastoma.
  - To avoid this, gonadectomy should be done as soon as the diagnosis is established.

23.5 Mixed Gonadal Dysgenesis (MGD)

- Mixed gonadal dysgenesis (*MGD*) refers to an asymmetric gonadal dysgenesis with ambiguous genitalia and a mosaic karyotype.
- A number of chromosomal karyotypes have been reported but most patients with MGD have a mosaic karyotype, 45XO/46XY.
- It occurs in approximately 1 in 20,000 births.
- Mixed gonadal dysgenesis is a frequent cause of ambiguous genitalia.
- It is characterized by a wide spectrum of phenotypes, ranging from a female with clitoral enlargement to a male with hypospadias, often penoscrotal hypospadias.
- There is an asymmetric external and internal genital development.
  - An incompletely formed uterus is found in almost all patients.
  - The Fallopian tubes are always found on the side of the streak gonad and often on the side with the dysgenetic gonad.
  - Wolffian structures may be developed on the side with the dysgenetic gonad.
- A genitourethrogram will demonstrate internal müllerian structures that can be confirmed by laparoscopy.
- The diagnosis will be confirmed by finding abnormal gonadal tissue on histopathologic examination.

- Gonadal pathologic features can vary and typically these patients have a testis on one side and a fibrous streak on the other.
- Some authors advocate female sex assignment in mixed gonadal dysgenesis for the following reasons:
  - The surgical repair of the vagina is usually easy.
  - A uterus or hemiuterus is present.
  - The dysgenetic gonad is at risk for development of a tumor and should be removed, particularly if the gonad cannot be brought down into the scrotum.
- Others feel that sex assignment is likely to be guided by the degree of virilization, with the more virilized cases being assigned as males.
- In all cases, the streak gonads should be removed because of the risk for malignancy.
- In MGD, 25% of gonads, including streak gonads, can be expected to undergo malignant change, most commonly to gonadoblastoma.

23.6 Management

- The management includes:
  - Early gonadectomy is recommended in these patients.
  - The gender assignment for patients with DMP and MGD remains controversial.
  - There are those who recommend a male gender assignment for those patients who are sufficiently virilized.
  - Others recommend a female gender assignment for patients with MGD because a uterus and vagina are present always and half of these patients have inadequate external virilization.
  - Patients who are raised as females require estrogen supplements.
  - If the uterus remains in place, the unopposed estrogen can increase the incidence of endometrial carcinoma and these patients should receive a combination of estrogen and a progestational agent.

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Chapter 24
Ovotestis Disorders of Sexual Development

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24.1 Introduction

- This is a rare condition in which the histology of a gonad contains both ovarian and testicular tissues.
- This was formerly known as true hermaphroditism.
- A diagnosis of Ovotestis-DSD is based solely on the presence of ovarian and testicular tissue in the gonad and not on the characteristics of the internal and external genitalia.
- The peripheral karyotype is also variable in these patients and include:
  - 46, XX ovotesticular DSD.

    This is the most common karyotype, seen in 60–80% of patients.
  - 46, XY ovotesticular DSD. This karyotype is found in about 10–15% of patients.
  - 46, XX/46, XY peripheral karyotype
  - 45, X/46, XY peripheral karyotype

24.2 Etiology

- Normal sexual differentiation depends primarily on the genetic sex (XX or XY) of the individual.
- This is established at the time of conception.

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- Until 7 weeks of gestation, the fetus is sexually indifferent with both Wolffian and Mullerian ducts.
- Expression of sex-determining genes on the early bipotential gonad promotes development of the testis or ovary.
- Various genes expressed by the Y chromosome at very specific times during development are responsible for the differentiation of the indifferent gonads into testes.
- It is the presence of the Y chromosome that governs the development of the indifferent or bipotential gonad into a testis.
- A 35-kilobase (kb) gene determinant located on the distal short arm of the Y chromosome, known as the *SRY* (sex determining region of the Y chromosome) is responsible for initiating differentiation of the indifferent gonads into testes.
- *SRY* triggers a cascade of events that leads to the development of testicular Sertoli and Leydig cells in the testes.
- Sertoli cells produce MIS (müllerian-inhibiting substance), and, later Leydig cells produce testosterone.
- In 46, XY males, the Sertoli cells of the testes are responsible for the production of mullerian-inhibiting substance, which causes regression of the mullerian ducts.
- The Leydig cells then produce testosterone, which promotes the development of the epididymis, vas deferens, and seminal vesicles.
- A complete 46, XX chromosomes are necessary for normal ovarian differentiation.
  - The absence of the Y chromosomes leads to the development of the indifferent gonads into ovaries.
  - Autosomal genes also appear to be involved in ovarian maintenance.
  - The X-linked gene *DAX1* (Dose sensitive sex reversal locus on X chromosome, gene 1) is important in ovarian determination.
  - The *DAX1* gene may actually be an anti-testes factor and may be antagonistic to the action of *SRY.*
  - An additional signaling molecule, Wnt4, is found in mullerian ducts and contributes to the development of female internal genitalia.
- Internal genitalia of the female fetus develop if there is no exposure to the *SRY* gene. As a result, the wolffian ducts regress and the mullerian ducts then mature into the oviduct, uterus, cervix, and upper vagina.
- The peripheral karyotypes of patients with ovotestes-DSD show marked variation.
  - Approximately 60% are 46, XX
  - 15% are 46, XY
  - 25% show various forms of mosaicism
  - Less than 1% show 46, XX/46, XY chimerism or the existence of two or more cell lines, each of which has a different genetic origin.
- Ovotesticular disorder of sexual development is a genetically heterogeneous condition.

- Phenotypic, gonadal, and molecular studies have led to several causation theories:
  - Genetic chimerism:

    Less than 1% of patients with Ovotesticular disorder of sexual development have 46, XX/46, XY chimerism or the existence of two or more cell lines, each of which has a different genetic origin.
    Chimerism can result from several events.
    Dispermic chimerism (double fertilization) which can arise from:

    - Fertilization of the secondary oocyte and first polar body
    - Fertilization of the ovum and the first polar body
    - Fertilization of the ovum and the second polar body.

    Chimerism can also arise as an exchange of cells between dizygous twins of different sex (i.e., fusion of two embryos).

  - Nondisjunction:

    Postzygotic mitotic errors arising from anaphase lag may occur in 45, X/46, XY or 45, X/46, XY/47, XYY mosaicism.
    Most 45, X/46, XY individuals have mixed gonadal dysgenesis as opposed to true hermaphroditism.

  - X-Y translocation:

    Paternal meiotic exchange between the pseudoautosomal regions of chromosomes X and Y could provide a mechanism for the translocation Y-chromosomal sequences, including *SRY* onto an X chromosome in some forms of 46, XX testicular differentiation.

  - Mutation:

    A mutation of a gene on the X chromosome or alternatively on an autosome that allows testis determination without the *SRY* gene could explain some forms of 46,XX testicular differentiation.
    Some 46, XX with Ovotesticular disorder of sexual development have been observed to have a translocation of *SRY* onto the X chromosome.
    However, most individuals with ovotesticular disorder of sexual development with 46, XX are *SRY* negative.

  - Occult mosaicism:

    Although most people with Ovotesticular disorder of sexual development have a 46, XX peripheral karyotype, occult mosaicism in the gonads of some of these individuals through molecular techniques was documented.
    Polymerase chain reaction (PCR) has identified *SRY*-positive tissue in gonads from several, but not all, people with 46, XX ovotesticular disorder of sexual development.

- Mutation of downstream autosomal genes involved with testicular differentiation and mutation/duplication or deletion of an X-linked locus may explain *SRY*-negative ovotesticular disorder of sexual development.

24.3 Pathophysiology

- The gonads in patients with Ovotesticular disorder of sexual development is variable and may be as follows:
  - Ovotestis on both sides.
  - A combination of an ovary on one side and a testis or ovotestis on the other side.
  - Ovotestes on both sides are the most frequent gonad present (60%), followed by the ovary and then the testis (9%).
- The anatomical location of these gonads is also variable.
  - The ovotestis tends to be anatomically located in the following anatomical positions:

    A normal ovarian position
    In the labioscrotal fold
    In the inguinal canal
    At the internal inguinal ring
  - Ovaries, when found, can occupy the normal abdominal position.
  - Ovaries may occasionally be found at the internal inguinal ring.
  - Interestingly, ovaries occur more commonly on the left side than the right.
  - The testes are usually found in the scrotum, although they can be found at any level along the path of descent from abdomen to scrotum, frequently presenting as inguinal hernias.
- Many patients with ovotesticular disorder of sexual development have a uterus.
- Internal duct development usually corresponds to the adjacent gonad so that (Fig. 24.1):

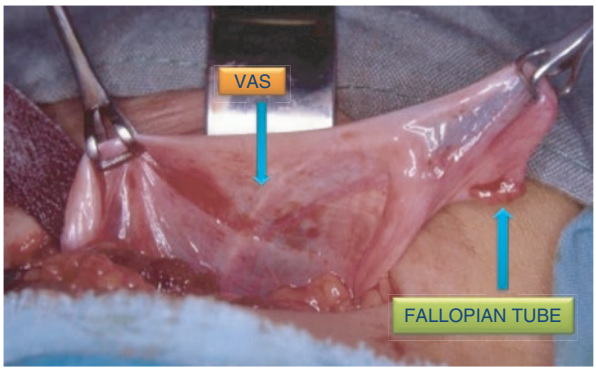

Fig. 24.1 A clinical intraoperative photograph of a patient with ovotesticular DSD. Note the presence of a fallopian tube and a vas

  - Müllerian duct structures are usually seen on the gonad side(s) not containing testicular tissue.
  - Wolffian duct structures are usually seen on the gonad side(s) containing functioning testicular tissue.

- Ovotestes are usually made up of ovarian part and testicular part with connective tissue between then. This is important surgically when separating the ovarian components from the testicular components. However, on rare occasions, it is difficult to separate the two.
- Ovaries and ovarian portions of ovotestes appear normal and demonstrate follicular growth with estradiol production.
- Approximately 50% of ovotestes show evidence of ovulation.
- The presence of estradiol in developing ovarian follicles usually inhibits spermatogonia development in adjacent or contralateral seminiferous tubules.
- Degeneration and hyalinization of the seminiferous tubules with poor germ cell development is frequently observed.
- In all documented biopsied cases, there is a significant decline in germ cell development and an increase in tubular sclerosis by puberty.
- Leydig cell hyperplasia may also occur with aging.
- Spermatogenesis in testis and ovotestis is very rare.
- Most patients with ovotestes DSD are reared as males due to the size of the phallus but male reproductive potential in these individuals is rare.
- This is not the case in those who are assigned a female gender with 46, XX chromosomes who have fertility potential.
- They also have varying degrees of labioscrotal fusion and/or hypospadias which needs correction.
- Most cases of ovotesticular DSDs are diagnosed during the adolescent period and because of functioning normal ovarian tissue, most of them experience breast development at puberty, and approximately two-thirds of those with a 46, XX peripheral karyotype menstruate.
- Patients with ovotestes DSD are at risk of gonadal tumors which occur in 2.6% of the cases.
- The testis or testicular part of an ovotestis is likely to be dysgenetic with a risk of developing:
  - Dysgerminomas
  - Seminomas
  - Gonadoblastomas
  - Yolk sac carcinomas
- The risk is more in those with 46, XY karyotype.
- Benign tumors, including mucinous cystadenomas, benign teratomas, and Brenner tumors, have also been reported in these patients.

24.4 Clinical Features

- In the neonatal period, these patients usually presents with ambiguous genitalia.
- Most affected individuals are reared as males due to the size of the phallus.
- Most of these patients have varying degrees of labioscrotal fusion and/or hypospadias.
- Inguinal hernia and cryptorchism are common in these patients.
- Although some cases of ovotestis DSD are diagnosed in the newborn period, only 20% are diagnosed prior to age 5 years.
- Most cases of ovotestis DSD are diagnosed in the pubertal period when the young male begins to experience feminization.
- However, because of functioning normal ovarian tissue, most people experience breast development at puberty, and approximately two-thirds of those with a 46, XX peripheral karyotype menstruate.

24.5 Investigations

- Chromosomal analysis
- Hormonal evaluation
- Serum 17-hydroxyprogesterone:
  - Patients with ovotesticular DSD have normal levels of this hormone which differentiate them from those with congenital adrenal hyperplasia.
- Basal and stimulated serum androgens:
  - The presence of functional testicular tissue can be determined with the use of a human chorionic gonadotropin (HCG) stimulation test.
  - In this test, basal levels of testosterone, dehydroepiandrosterone sulfate, androstenedione, and dihydrotestosterone (DHT) are measured.
  - HCG (3000–5000 IU/m^2/d IM) is then administered for 5 days.
  - On the day 6, the serum hormone levels tests are repeated.
  - A rise in serum testosterone demonstrates the presence of functioning Leydig cells.
  - Elevated testosterone precursors may suggest a specific defect of testosterone synthesis.
  - Failure of testosterone to reduce to DHT may suggest a 5-alpha reductase deficiency.
- Basal and stimulated estrogen levels:
  - The presence of functional ovarian tissue can be determined with the use of gonadotropin or clomiphene citrate administration.
  - An estradiol response to gonadotropin stimulation is a reliable test to differentiate ovotesticular disorder of sexual development from other disorders.

- Radiological evaluation:
  - A scrotal ultrasonography is used to detect occult gonads.
  - A genitogram is used to evaluate the structure of the urethra and to confirm the presence of a vagina and uterus (Fig. 24.2a, b).

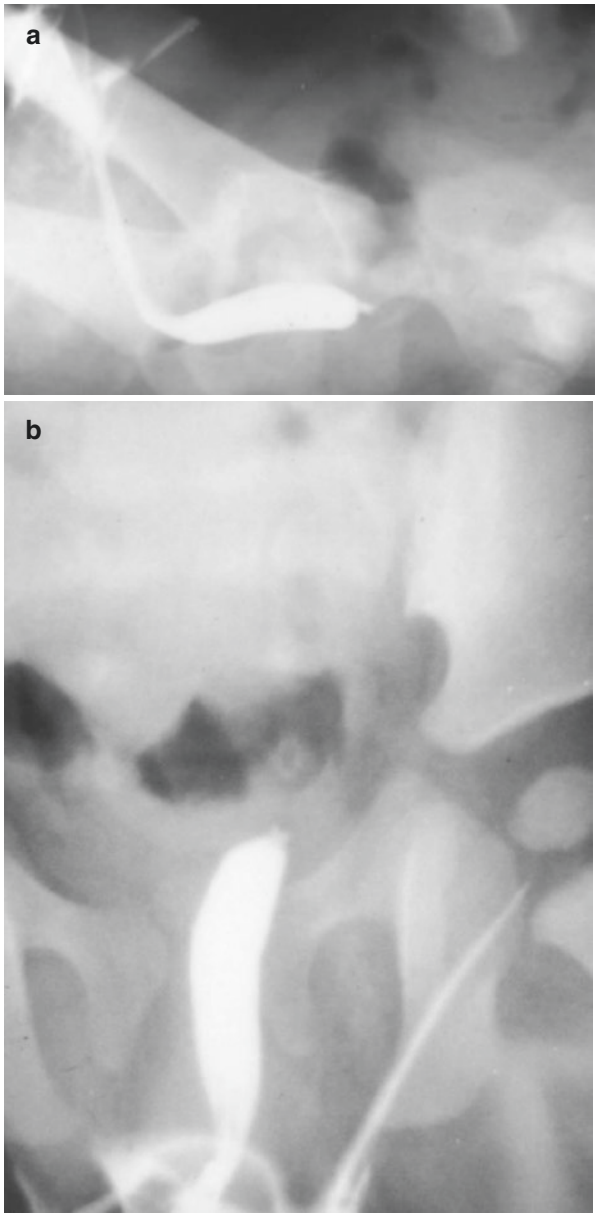

Fig. 24.2 (**a**, **b**) Ggenitograms showing a normal looking vagina in patients with ovotesticular DSD

- An intravenous pyelogram is important to rule out any associated urinary tract anomalies.
- Abdominal and pelvic ultrasonography, CT scan, or MRI is useful in delineating the gonads and duct structures.

24.6 Management

- The main point in the management of these patients is gender assignment.
- This must take in consideration two main points:
  - The potential for normal sexual function.
  - The potential for future reproductive function.
- It is important to establish histological confirmation with a gonadal biopsy which can be done via a laparotomy or laparoscopically.
- Surgery in these patients should be planned with the previous two goals in mind and conservative gonadal surgery is the procedure of choice.
- Ovotestes frequently can be separated into ovarian and testicular components and partial resection of ovotestes is feasible in a large number of these patients which should be guided by intraoperative histologic confirmation (Fig. 24.3a, b).
- It allows preservation of gonadal tissue concordant with sex of rearing, and removal of all discordant tissue.
- The ovarian tissue can be preserved in people who are given a female sex assignment. Frequently, these patients demonstrate normal ovarian function and potential for reproduction.
- The aim is to preserve the gonadal tissue that is concordant with sex of rearing, and excision of all other tissue.

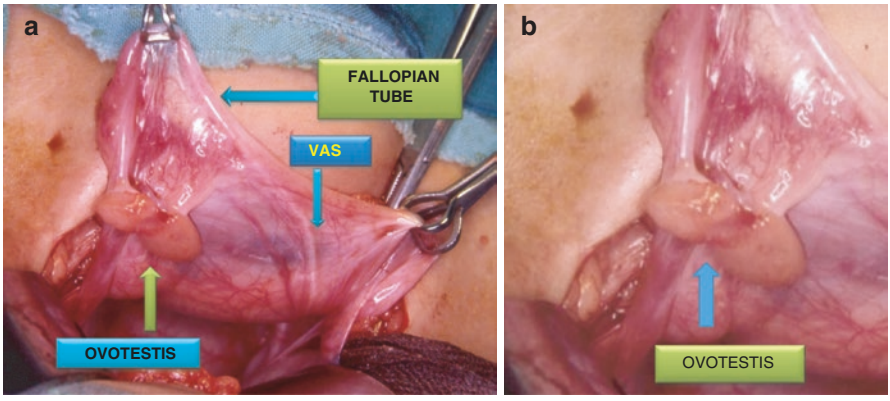

Fig. 24.3 (**a**, **b**) Clinical intraoperative photographs of a patient with ovotesticular DSD. Note the presence of an ovotestis on this side. Note also the vas and Fallopian tubes

- Cystoscopy is important and may be used to determine the position of entry of the vagina into the urethra or urogenital sinus.
- Prophylactic gonadectomy should be considered in those who manifest signs of virilization or are at an increased risk of developing gonadal malignancy. Previous
- Hormone replacement might be required for those with pubertal delay.
- The following operative procedures are indicated in patients with ovotestes DSD.
- These operative procedures depend on the sex of rearing and include:
  - Excision of intra-abdominal testis or streak gonads in those with Y chromosome-DNA because of increased risk of malignant transformation.
  - Excision of wolffian structures and testicular tissue if the patient has been given a female gender assignment.
  - Excision of Müllerian structures and ovarian tissue if the patient has been given a male gender assignment.
  - Orchidopexy to treat an undescended testis in a patient with male gender assignment.
  - For ovotesticular DSD who are given a female sex assignment, the following procedures are necessary:

    Clitoral recession
    Vaginoplasty
    Labioscrotal reduction

- These feminizing procedures should be performed as early as possible and preferably as a 1-stage procedure.
- Correction of penile deviation and hypospadias should be done in those given a male gender assignment.

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