Gynecologic Problems of Childhood

PART XXIII

Chapter 585

Gynecologic History and Physical Examination

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HISTORY

For the young patient, developmentally appropriate social questions directed to the patient can put them at ease and help to develop cooperation and rapport that will facilitate a subsequent examination. Specific patient, caregiver, or provider concerns about vaginal discharge or bleeding, pruritus, external genital lesions, or abnormalities should direct a problem-focused history. In a patient presenting with vaginal bleeding, questions should focus on recent growth and development, signs of pubertal progression, trauma, vaginal discharge, medication exposure, and any history of foreign objects in the vagina. For complaints of vulvovaginal irritation, pruritus, or discharge, questions should concentrate on perineal hygiene, the onset and duration of symptoms, the presence and quality of discharge, exposure to skin irritants, recent antibiotic use, travel, presence of medical comorbidities or infections in the patient and their family members, and other systemic symptoms of illness or skin conditions. Throughout the history, the patient should be encouraged to ask their own questions. Occasionally, the child is brought to the clinician because they or their parents have concerns about anatomic findings, developmental changes, or congenital anomalies. It helps to understand the family's concerns and if a specific reason, event, or family history raised the need for a gynecologic consultation.

GYNECOLOGIC EXAMINATION

The physical examination of the patient should be tailored to the child's age, complaint, and any other concerns elicited in the history. The date of onset of the last menstrual period should be included with an assessment of other vital signs as age appropriate.

Neonates

At the time of delivery, a brief examination of the external genitalia of female infants to visually confirm the patency of the vagina and assess the presence of any obvious genital anomalies should be performed. The newborn examination should note any abnormal findings, such as ambiguous genitalia, imperforate hymen, urogenital abnormalities, abdominal mass, or inguinal hernia, that might herald a gynecologic problem.

Placing the infant in the supine position with thighs flexed against the abdomen allows visualization of the neonate's external genitalia. Estrogenic effects commonly notable in neonates include prominence of the labia majora and a white vaginal discharge. The labia minora and hymen may protrude slightly from the vestibule. A small amount of neonatal vaginal bleeding from endometrial sloughing after maternal hormone withdrawal might occur. Bleeding that is excessive or persistent beyond the first month of life requires further evaluation. Breast buds may be palpable at the time of the neonatal examination but should regress in the first 3 months of life; occasionally, nipple discharge occurs.

The vaginal orifice may be difficult to see. Gentle lateral traction on the labia majora usually allows complete visualization of the hymen and vaginal orifice. The hymen should be evaluated for patency. Most hymenal variations—imperforate, microperforate, septate—do not require treatment during the neonatal period (Fig. 585.1). Variations should be noted and readdressed in subsequent visits. The hymen originates from the urogenital sinus. The uterus and upper vagina originate from the Müllerian ducts. The concomitant renal malformations seen with Müllerian anomalies are not associated with hymenal anomalies because of different embryologic origin of the two structures. Similarly, uterine anomalies are typically not observed with hymenal anomalies (see Chapter 591). Hymenal polyps seen in newborns typically regress in size as the maternal estrogen effects subside. Cervicovaginal mucus secretions can accumulate behind the blocked outflow tract of an imperforate hymen and manifest as a mucocolpos. *In this instance and if urinary obstruction occurs, correction of the imperforate hymen in the neonatal period is indicated.* In the absence of any concern for urinary obstruction, the imperforate hymen and associated mucocolpos can be observed for resolution, and the imperforate hymen is ideally repaired surgically after onset of puberty, specifically thelarche. This allows for improved healing of tissue in the presence of endogenous estrogen production.

The clitoris may appear large in proportion to the other genital structures, especially in premature infants. If the clitoris appears enlarged, the clitoral width and length should be measured; width values >6 mm or length values >6.5 mm in a newborn indicate a need for further evaluation. *If clitoromegaly and ambiguous genitalia are present, the provider should immediately obtain expert (endocrine) consultation for evaluation of the infant and to counsel the parents.* Congenital adrenal hyperplasia is the most common cause of ambiguous genitalia (accounting for >90% of cases), and the salt-wasting forms can lead to rapid dehydration with subsequent fluid and electrolyte imbalance (see Chapter 616). Delay in the diagnosis and treatment of congenital adrenal hyperplasia may be life-threatening.

In the neonate, the ovaries are <1 cm in diameter and average 1 cm^3 in volume. Antenatal or postnatal abdominopelvic ultrasound might reveal small simple ovarian cysts, which represent normal follicles. Because of the abdominal location of ovaries in the neonate, ovarian enlargement can manifest as a palpable abdominal mass. Large cysts (>4-5 cm) or those of a complex nature pose the risk of ovarian torsion, hemorrhage into the cyst, or, uncommonly, an ovarian tumor. A nonresolving or enlarging neonatal ovarian cyst warrants pediatric surgery or pediatric gynecology consultation. Percutaneous decompression has been described in cases where benign nature can be reliably ascertained. Cyst aspiration can provide temporary relief but is not recommended if cystectomy can safely be performed because the aspirated fluid may not be reliable for diagnosis and may reaccumulate. If a cystectomy is done for appropriate clinical indications, the cyst wall should be surgically excised to prevent reaccumulation of fluid and to provide a pathologic diagnosis, the remaining ovarian tissue should be left in situ, and the contralateral ovary should be inspected. Preservation of normal ovarian tissue is recommended for all benign lesions, and salpingo-oophorectomy should not be performed unless clinically indicated.

Infants and Prepubertal Girls

When the maternal estrogen effect subsides, the genitalia of the female infant change in appearance. The labia begin to flatten. The hymenal membrane loses its redundancy and becomes translucent. The hypoestrogenic prepubertal vaginal epithelium appears thin, red, and sensitive to the touch. The vaginal mucosa of young children can have longitudinal ridges running along the axis of the vagina at 3 o'clock, 6 o'clock, and 9 o'clock, which can cause small protrusions on the hymen at these locations. The cervix usually appears flat and flush with the vaginal vault. During infancy, the uterus regresses in size and does not return to its birth size until the child is 5-6 years old. The prepubertal cervix:fundus ratio is 2:1.

When puberty approaches, the child experiences increasing endocrine activity of the hypothalamus, pituitary gland, adrenal

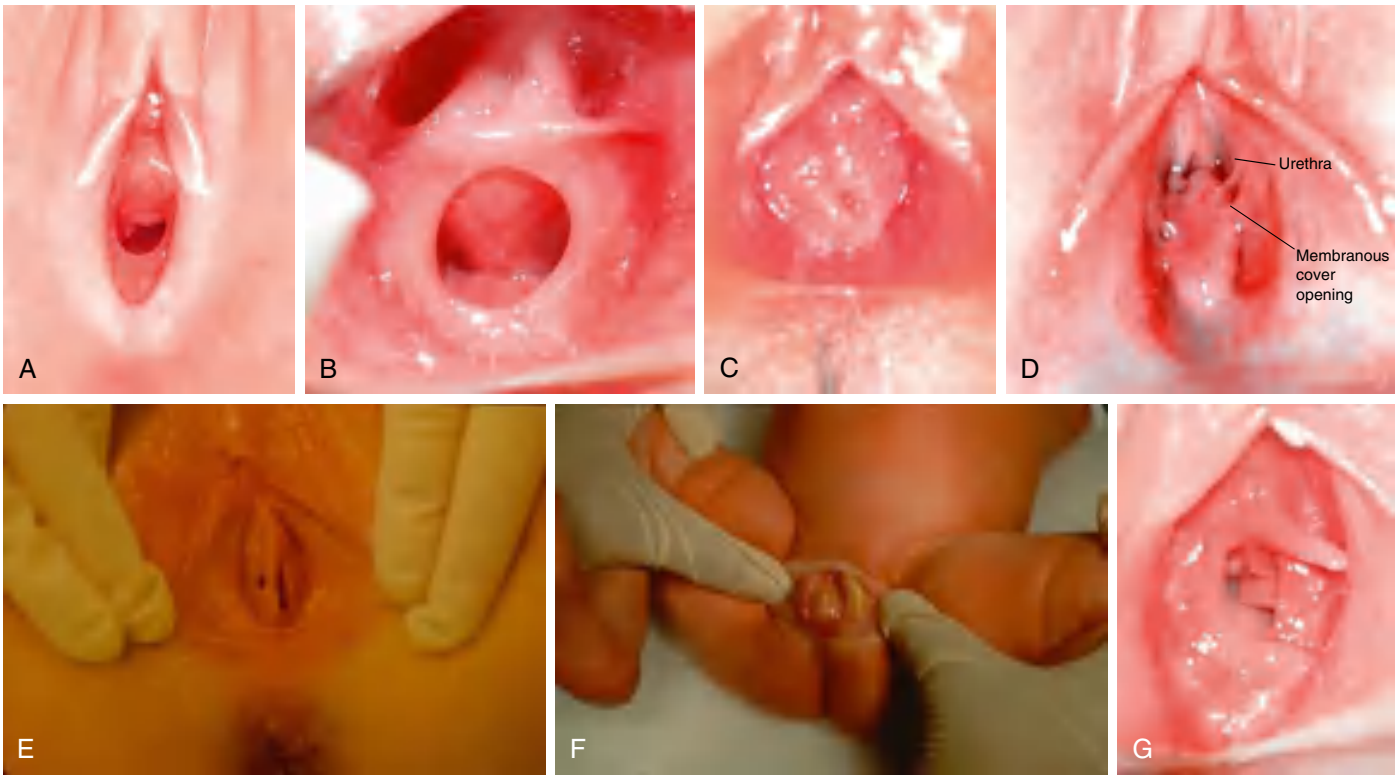

Fig. 585.1 Types of hymens. **A,** Crescentic. **B,** Annular. **C,** Redundant. **D,** Microperforate. **E,** Septated. **F,** Imperforate. **G,** Hymeneal tags. *(**A–F** from Perlman SE, Nakajima ST, Hertweck SP, eds: Clinical Protocols in Pediatric Adolescent Gynecology. Parthenon Publishing Group, 2004; G, from McCann JJ, Kerns DL [eds]: The Child Abuse Atlas. St Louis: Evidentia Learning, 2021, www.childabuseatlas.com.)*

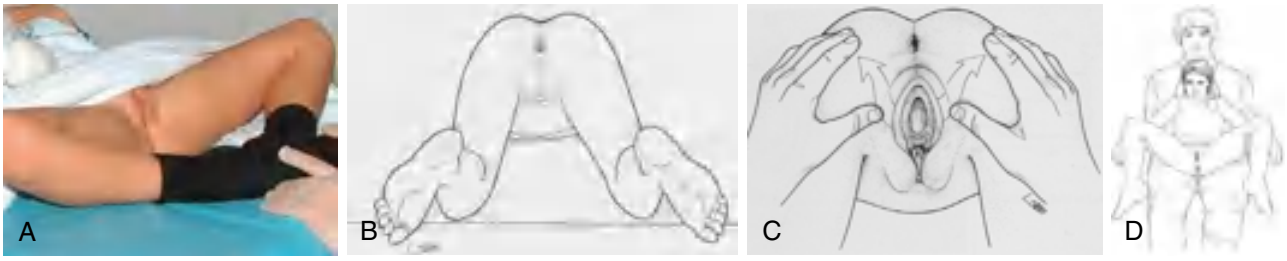

Fig. 585.2 Different exam positions for performing a gynecologic exam on a child. **A,** Frog-leg position. **B,** Knee-chest position. **C,** Prone position. **D,** Sitting on caregiver's lap. *(**A** from McCann JJ, Kerns DL, eds : The Child Abuse Atlas. St Louis: Evidentia Learning, 2021, www.childabuseatlas.com; **B–D** from Finkel MA, Giardino AP [eds]: Medical Examination of Child Sexual Abuse: A Practical Guide. Elk Grove Village, Illinois: American Academy of Pediatrics Publications, 2009;46–64.)*

gland, and ovaries (see Chapter 599). The labia majora begin to fill out, and the labia minora thicken and elongate as a result of increased estrogen levels. The hymen thickens and becomes more redundant. Clear or white physiologic secretions may be present. Breast buds begin to appear, either bilateral or initially unilateral with subsequent development of the contralateral breast. Pubic hair begins to appear.

Indications for Genital Examination

Genitourinary complaints or suspected genitourinary pathology warrants assessment of the external and internal genitalia of pediatric patients, specifically in cases of vaginal bleeding, vaginal discharge, vulvar trauma, presence of a foreign body, perineal or pelvic masses, vulvovaginal ulcerative or inflammatory lesions, congenital anomalies, or suspected sexual abuse.

Preparation

An examination of the external genitalia in prepubertal females requires a gentle, patient approach to maximize cooperation and minimize fear and embarrassment. A clear, simple explanation of what the examination involves can facilitate the child's comfort and cooperation. The presence of a parent or caregiver during the entire examination provides reassurance for most children. For the older prepubertal patient, the physician may discuss whether the patient wishes to have a family member present during the examination. Even in the presence of the caregiver, the examiner should speak directly to the child. Before initiating any part of the examination, the provider should explicitly verify with both the patient and their caregiver that the caregiver has given permission for the examination. This provides an opportunity to explain to the child the privacy of body parts and who may examine or touch those areas. It is useful to educate the patient and caregiver about the basic anatomy and hygiene of the external genital area. Before each step of the examination, the physician should explain what will occur. Allowing an older child the option of watching their examination with a handheld mirror may contribute to their comfort and understanding. Forcible restraint is never indicated; if optimal evaluation is not possible, the clinician must assess the acuity of the complaint and pathology and determine the potential need for multiple visits to complete the examination or an examination under anesthesia.

Positioning

A variety of techniques and positions can facilitate the genital examination in prepubertal patients. Children younger than 4 years of age can be placed on the parent or caregiver's lap with the child's legs straddling the caregiver's thighs (Fig. 585.2). If the child permits, they may be positioned on the table in the supine position with the hips fully abducted and the feet together in the frog-leg (diamond or butterfly) position. Older children may prefer to use the stirrups. The head of the examination table should be raised so that eye contact can be maintained with the patient throughout the examination. When the child is supine, grasping the labia majora along the inferior portion between the thumb and index finger and gently pulling outward and posteriorly (labial traction) allows visualization of the vaginal introitus. Alternatively, the child may be placed in the knee-chest position with elevation of the buttocks and hips (see Fig. 585.2). This position provides exposure of the inferior portion of the hymen, the lower vagina, and possibly the upper vagina and cervix but has the disadvantage of having the child face away from the examiner.

Some extremely cooperative children tolerate a vaginoscopic examination in an outpatient office setting for better intravaginal assessment. The endoscope (either a cystoscope or a hysteroscope) is placed in the vagina, and the labia are gently opposed, allowing the vagina to distend with water. This technique permits visualization of the vagina and cervix, allowing for the evaluation of an injury, lesion, and anatomic variant or for the presence of a foreign body. Application of 2% lidocaine gel at the introitus makes the insertion easier and less irritating for the patient. If a more complete examination is indicated or if the child is too young, frightened, or unable to cooperate, an examination under anesthesia is recommended.

Documentation

Clinicians should thoroughly and accurately document the genital examination findings in the medical record, reserving conclusions and diagnostic terms for the impression and plan portion of the documentation rather than in the description of exam findings. Each structure visualized should be noted (e.g., clitoris, labia majora, labia minora, urethra, vestibule, and rectum) with attention to describing normal appearance and any anatomic variations (e.g., the configuration of the hymen as annular, crescentic, and so forth). Describing any findings or lesions using a clock-face method provides a consistent reference point; a sketch or magnified photograph may also be helpful. Future examiners will rely on this documentation as a record with which they compare their findings and note any variances. Changes should be noted in any follow-up examinations.

Adolescents

Some teens prefer to initially meet and discuss the reason for their visit with the provider without their parent or guardian present, and this request should be honored (see Chapter 151). Obtaining a history from an adolescent usually begins with meeting the patient and parent or caregiver together to review their history and the reason for the visit and to explain the concepts of confidentiality and privacy. Care should be taken to ask the patient their preferred name and pronouns when addressing them. Familiarity with local laws governing limitations to confidential services should guide the protection of the adolescent and their parents' rights to information access and privacy. The Guttmacher Institute provides an up-to-date listing of state and federal laws in the United States affecting access to medical care (https://www.guttmacher.org/geography/united-states). Brief discussions of normal pubertal development and menstruation can reassure both patients and their parents or guardians and provide valuable education on appropriate menstrual flow, menstrual hygiene, and the duration and frequency of bleeding. Introducing the menstrual diary as an invaluable tool for the teen can help patients, parents, and clinicians identify abnormal bleeding patterns that might require further evaluation. Many applications are available for tracking menstrual periods on a smart phone or computer.

After the initial interview with the teen and their parent or caregiver, the confidential and sensitive portion of the history, particularly sexual history and alcohol, tobacco, and drug use, is taken with the teen alone. Such a request could be phrased as follows: "I would like to give your child an opportunity to ask any questions they might have privately, so would you mind stepping out of the room for a moment?" After obtaining the teen's assent for the confidential interview, questions regarding gender identity, sexual orientation, mental health, safety, and use of illicit substances should be asked. Any concerns regarding parent or caregiver access to personal electronic health records should be addressed. Concerns for the presence of vaginal discharge, the potential for sexually transmitted infections, pregnancy, or menstrual aberration should be explored. Teens and their parents should be informed of the proper use and accessibility of condoms, all contraceptive methods, and emergency contraception.

Resources for educating adolescents regarding their first pelvic examination and in-depth sexual history and psychosocial screening tools are available. These include the North American Society for Pediatric and Adolescent Gynecology (http://www.naspag.org), the American Academy of Pediatrics (http://www.aap.org), the Society for Adolescent Health and Medicine (http://www.adolescenthealth.org), and the American College of Obstetricians and Gynecologists (http://acog.org/Patients).

Individuals with Special Needs

Special care should be taken in the approach to individuals with both physical and cognitive disabilities (see Chapter 592). The assistance of Child Life services can be beneficial in decreasing patient anxiety.

Pelvic Examination

Table 585.1 presents the indications for the first pelvic examination in adolescents. If an adolescent does not meet one of the criteria listed in Table 585.1, the American College of Obstetricians and Gynecologists (ACOG) recommends that the first gynecologic encounter occur between the ages of 13-15 years (Table 585.2), with attention toward anticipatory guidance focusing on normal pubertal development and menstruation. All sexually active patients age

Table 585.1 Suggested Indications for Pelvic Examination in Adolescents

Age 21 yr of age for initial Papanicolaou test (Pap smear)
Unexplained menstrual irregularities, including pubertal aberrations (especially delayed puberty)
Severe dysmenorrhea
Unexplained abdominal or pelvic pain
Unexplained dysuria
Abnormal vaginal discharge
Concern for pelvic inflammatory disease
Placement of intrauterine device
Removal of foreign body
Inability to place tampons

Data from American College of Obstetricians and Gynecologists' Committee on Adolescent Health Care. The initial reproductive health visit: ACOG Committee Opinion, Number 811. *Obstet Gynecol*. 2020;136: e70–e80.

Table 585.2 Recommendations for First Gynecologic Evaluation

Occurs between 13 and 15yr of age
Focuses on patient education
Increases comfort with issues regarding adolescent sexuality
Ensures opportunity for adolescent to speak 1-on-1 with the provider
Makes the adolescent aware of limitations of confidentiality (including issues related to mandatory reporting, insurance billing, electronic health record notifications, and legal requirements)
Pelvic examination with Papanicolaou test (Pap smear) is generally not indicated until 21 yr of age, unless otherwise indicated by Table 585.1

Data from American College of Obstetricians and Gynecologists' Committee on Adolescent Health Care. The initial reproductive health visit: ACOG Committee Opinion, Number 811. *Obstet Gynecol*. 2020;136: e70–e80.

<25 years should undergo annual screening for sexually transmitted infections (STIs). This testing can also be obtained 3 months after treatment of a positive screening, with new symptoms, or with each new sexual partner. With the availability of urine and vaginal swab nucleic acid amplification testing for chlamydia, gonorrhea, and trichomoniasis, STI screening does not necessitate a speculum exam. Extragenital (rectal or pharyngeal) chlamydia and gonorrhea testing can be considered for patients based on self-reported sexual behaviors through shared clinical decision-making between the patient and the provider. Expedited partner treatment may be used according to the state law.

Before the initiation of a physical examination, all patients should be offered the choice of having a medical attendant, family member, or friend present during their examination. Presence of the chaperone is advised based on the laws of the state and the policies of the institution. At the initial gynecologic exam, the physician should explain the process in understandable terms. A thorough evaluation begins with an assessment of body mass index, blood pressure, menstruation status, thyroid, lymph nodes, breast development, abdominal exam, and skin. The external genitalia should be examined with the patient in the dorsal lithotomy position while communication is maintained between the physician and patient. Elevating the head of the examination table allows the teen and their examiner to maintain eye contact. The teen can hold a mirror to follow along with the examination, and they should be encouraged to ask questions. Inspection of the vulva is followed by inspection of the Bartholin, urethral, and Skene glands. The clitoris, normally 2-4 mm in width, is then assessed; a clitoris wider than 10 mm, especially in the presence of other signs of virilization, suggests a need for further evaluation. The hymenal anatomy should also be evaluated. Throughout the examination, the proper nomenclature for genital anatomy should be emphasized with the teen to empower them to use proper wordage with the avoidance of slang when referring to their body.

Because the initial Papanicolaou (Pap) test is deferred until 21 years of age except in certain immunocompromised patients and cultures for STIs can be obtained from urine or vaginal swabs, the need for a speculum exam is decreasing in this age group. If a speculum exam is indicated, use an appropriately sized speculum, such as the Huffman (½ in wide × 4 in long) or Pedersen (⅞ in wide × 4 in long) speculum. Shorter speculums will not allow visualization of the entire vaginal canal. The adolescent patient should be reassured that the exam may be uncomfortable but should not be painful and that their request to stop or wait will be honored. Encouraging the patient to watch with a handheld mirror facilitates patient education and can be empowering. They may be told before the insertion of the speculum that they will experience a pressure sensation. Before touching the introitus, it may be useful to touch the inner thigh with the speculum. Compression of the urethra anteriorly should be avoided. Gentle pressure with a finger for displacement of the fourchette posteriorly further facilitates proper speculum placement. After visualization of the vagina and cervix, specimens should be obtained as indicated. A bimanual examination, sometimes with a single digit, allows palpation of the vaginal walls and cervix and bimanual assessment of the uterus and adnexa. Reassurance of normal findings throughout the examination should be provided, and normal variants to anatomy should be pointed out to the teen as they are encountered (e.g., asymmetric labia minora).

After the examination, it is appropriate to review the exam findings with the teen (and parents or caregivers as appropriate) and initiate a collaborative discussion of the management plan. Encouraging the adolescent to participate in decision-making empowers them to undertake responsibility for their health, may strengthen compliance with the medical plan, and will acknowledge them as a unique individual.

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Chapter 586

Vulvovaginitis

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Vulvovaginitis is the most common gynecologic-based problem for prepubertal children, with a reported incidence of 17–50%. It is most typically caused by either inadequate or excessive hygiene or chemical irritants. The age of presentation peaks at 4-8 years of age. The condition is usually improved by hygiene measures and education of the caregivers and child.

ETIOLOGY

Vulvitis refers to external genital pruritus, burning, redness, or rash. **Vaginitis** denotes inflammation of the vagina, which can manifest as a discharge with or without an odor or bleeding. If these occur simultaneously, the term vulvovaginitis is used. When a child presents with vulvovaginitis, the history should include questions on hygiene (wiping from front to back) and information about possible exposure to chemical irritants (bath soaps, bubble bath, bath bombs, laundry detergents, swimming pools, or hot tubs). A detailed history of recent diarrhea, perianal itching, or nighttime itching is important. The possibility of foreign objects being placed into the vagina should also be asked, although the young child is unlikely to recall. Approximately 75% of cases of vulvovaginitis in children are nonspecific for a variety of reasons, including their lack of vaginal estrogenization and resulting atrophy and alkalinic pH, poor perianal hygiene, and the proximity of the anus to the vagina, which is without geographic barriers given the flattened labia and lack of pubic hair. Table 586.1 lists other vulvovaginal disorders commonly seen in children.

EPIDEMIOLOGY

Infectious vulvovaginitis, where a specific pathogen is isolated as the cause of symptoms, is commonly associated with fecal or respiratory pathogens, and cultures may reveal *Escherichia coli* (see Chapter 246), *Streptococcus pyogenes* (Chapter 229), *Staphylococcus aureus* (see Chapter 227), *Haemophilus influenzae* (see Chapter 240), *Enterobius vermicularis* (see Chapter 340), and, rarely, *Candida spp*. (see Chapter 280). These organisms may be transmitted by the child using improper toilet hygiene or manually from the nasopharynx to the vagina. Typical presentation includes perianal redness, introital inflammation, and often a yellow-green or mildly bloody discharge. Children may be observed to be grabbing their genital area or "digging" in their underwear, which is usually stained with yellow-brown discharge. Attempts to treat these bacterial etiologies with antifungal medication will fail, and often the antifungal product will lead to more irritation. Table 586.2 gives specific treatment recommendations based on the bacteria identified.

Neisseria gonorrhoeae or *Chlamydia trachomatis* are also causes of specific infectious vulvovaginitis (see Chapter 163). If acquired after the neonatal period, some diseases (e.g., gonorrhea, syphilis, and chlamydia) are virtually 100% indicative of sexual contact. Management of prepubertal children who have **sexually transmitted infections** requires close cooperation between clinicians and child-protection authorities. Official investigations for sexual abuse, when indicated, should be initiated promptly (see Chapter 17). For some diseases (e.g., human papillomavirus infection and herpes simplex virus), the association with sexual contact is not as clear. Presumptive treatment for prepubertal children who have been sexually assaulted or abused is not recommended, because (1) the incidence of most sexually transmitted infections in children is low after abuse/assault, (2) prepubertal females appear to be at lower risk for ascending infection than adolescent or adult women, and (3) regular follow-up of children usually can be ensured. Although *Trichomonas vaginalis* can be transmitted vertically

Table 586.1 Specific Vulvar Disorders in Children

CONDITION	PRESENTATION	DIAGNOSIS	TREATMENT
Molluscum contagiosum (Fig. 586.8)	1- to 5-mm discrete, skin-colored, dome-shaped, umbilicated lesions with a central cheesy plug	Diagnosis usually made by visual inspection	• Disease is generally self-limited and the lesions can resolve spontaneously. • Treatment choices in children may include cryosurgery, laser, application of topical anesthetic and curettage, podophyllotoxin, and topical silver nitrate. • Use of topical 5% imiquimod cream and 10% potassium hydroxide has been reported with similar effects.
Condyloma acuminata	Skin-colored papules, some with a shaggy, cauliflower-like appearance	• Diagnosis is usually made by visual inspection. • Biopsy should be reserved for when the diagnosis is in question. • Human papilloma-virus DNA testing is not helpful.	• Many lesions in children resolve spontaneously, with "wait and see" often used in children (60 days). • Topical treatment with imiquimod cream (3 times/wk at bedtime × 16 wk, wash 6-10 hr after application) and podophyllotoxin (bid × 3 days followed by 4 day break; typical treatment duration is 4 wk) is the most studied. • General anesthesia is usually required for surgical/ablative procedures (cryotherapy, laser therapy, electrocautery); reserve for symptomatic or large lesions. • Other treatments have been used in adults, including trichloroacetic acid, 5-fluorouracil, sine catechins, topical cidofovir, and cimetidine. • The efficacy and safety of these treatments in children has not been established.
Herpes simplex	Blisters that break, leaving tender ulcers	Visual inspection confirmed by culture from lesion	• *Infants*: Acyclovir 20 mg/kg body weight IV q8 hr × 21 days for disseminated and central nervous system disease or × 14 days for disease limited to the skin and mucous membranes. • *Genital/mucocutaneous disease:* • *Age 3 mo-2 yr:* 15 mg/kg/day IV divided q8h × 5-7 days. • *Age 2-12 yr (first episode):* Same as above or 40-80 mg/kg/day PO divided tid-qid × 7-10 days (max 1,000-1,200 mg/day). • *Age 2-12 yr (recurrence):* 1,000 mg/day PO in 5 divided doses × 5 days or 1,600 mg/day PO divided bid × 5 days or 2400 mg PO divided q8 × 2 days.
Labial adhesions (see Fig. 586.1)	May be asymptomatic or can cause vulvitis, urinary dribbling, urinary tract infection, or urethritis	Diagnosis made by visual inspection of the adherent labia, often with a central semitranslucent line.	• Does not require treatment if the patient is asymptomatic. • Symptomatic patients: Topical estrogen cream or betamethasone ointment applied alone or in combination daily for 6 wk directly to the line of adhesion, using a cotton swab while applying gentle labial traction. • Estrogen should be interrupted if breast budding occurs. • Mechanical or surgical separation of the adhesions is rarely indicated. • The adhesions usually resolve in 6-12 wk; unless good hygiene measures are followed, recurrence is common. • To decrease the risk of recurrence, an emollient (petroleum jelly, A and D ointment) should be applied to the inner labia for 1 mo or longer at bedtime.
Lichen sclerosus (see Fig. 586.4)	A sclerotic, atrophic, parchment-like plaque with an hourglass or keyhole appearance of vulvar, perianal, or perineal skin; subepithelial hemorrhages may be misinterpreted as sexual abuse or trauma. The patient can experience perineal itching, soreness, or dysuria.	Diagnosis usually is made by visual inspection. Biopsy should be reserved for when the diagnosis is in question.	• Ultrapotent topical corticosteroids are the first-line therapy (clobetasol propionate ointment 0.05%) once or twice a day for 4-8 wk. • Once symptoms are under control, the patient should be tapered off the drug unless therapy is required for a flare-up. • In many females, the condition resolves with puberty; however, this is not always the case and patients may require long-term follow-up. • Immunomodulators can be used: tacrolimus 1% (applied once daily) and pimecrolimus 1% (applied twice daily for 3 mo, then every other day).
Psoriasis	Children are more likely than adults to have vulvar psoriasis noted as pruritic, well-demarcated, nonscaly, brightly erythematous, symmetric plaques. The classic extragenital lesions are similar but with a silver scaly appearance.	Diagnosis may be confirmed by locating other affected areas on the scalp or in nasolabial folds or behind the ears.	Vulvar lesions may be treated with low- to medium-potency topical corticosteroids, increasing strength as necessary.
Atopic dermatitis	Chronic cases can result in crusty, weepy lesions that are accompanied by intense pruritus and erythema. Scratching often results in excoriation of the lesions and secondary bacterial or candidal infection.	May be seen in vulvar area but characteristically affects the face, neck, chest, and extremities	Children with this condition should avoid common irritants and use topical corticosteroids (such as 1% hydrocortisone) for flare-ups. If dry skin is present, lotion or bath oil can be used to seal in moisture after bathing.

Continued

Table 586.1 Specific Vulvar Disorders in Children—cont'd

CONDITION	PRESENTATION	DIAGNOSIS	TREATMENT
Contact dermatitis	Erythematous, edematous, or weepy vulvar vesicles or pustules can result, but more often the skin appears inflamed	Associated with exposure to an irritant, such as perfumed soaps, bubble bath, talcum powder, lotions, elastic bands of undergarments, or disposable diaper components	Avoidance of irritant; topical corticosteroids for flare-ups
Seborrheic dermatitis	Erythematous and greasy, yellowish scaling on vulva and labial crural folds associated with greasy dandruff-type rash of scalp, behind ears and face	Diagnosis usually made by visual inspection	Gentle cleaning, topical clotrimazole with 1% hydrocortisone added
Vitiligo (see Fig. 586.6)	Sharply demarcated hypopigmented patches, often symmetric in vaginal and anal regions; may be present in periphery at body orifices and extensor surfaces	Clinical. Test for associated illness if clinically warranted (thyroid disease, Addison disease, pernicious anemia, diabetes mellitus).	If desired, treat limited lesions with low-potency corticosteroids or tacrolimus. See dermatologist for extensive lesions.

Table 586.2 Antibiotic Recommendations for Specific Vulvovaginal Infections

ETIOLOGY	TREATMENT
Streptococcus pyogenes *Streptococcus pneumoniae*	• Penicillin V, 250 mg PO bid-tid for children < 27 kg, and 500 mg bid-tid for children > 27 kg × 10 days • Amoxicillin, 50 mg/kg/day (max: 500 mg/dose) PO divided tid × 10 days • Erythromycin ethyl succinate, 30-50 mg/kg/day (max: 400 mg/dose) PO divided qid • TMP-SMX, 6-10 mg/kg/day (TMP component) PO divided bid × 10 days • Clarithromycin, 7.5 mg/kg bid (max: 1 g/day) PO × 5-10 days • Recurrence most likely from asymptomatic pharyngeal carriage in child or family member; however, failure of penicillin regimens can occur • For penicillin resistance: Rifampin 10 mg/kg PO every 12 hr × 2 days
Staphylococcus aureus	• Topical mupirocin 2% tid to the affected skin area • If systemic therapy required: Amoxicillin-clavulanate, 45 mg/kg/day (amoxicillin) PO divided bid-tid × 7 days (first-line treatment because of high penicillin resistance) • Extensive resistance to common antibiotics noted; recommend susceptibility testing for further antibiotic use • MRSA: TMP-SMX double-strength 8-10 mg/kg/day; culture abscesses, incision and drainage
Haemophilus influenzae	• Amoxicillin, 40 mg/kg/day PO divided tid × 7 days • For cases of treatment failure or nonencapsulated *H. influenzae*, amoxicillin–clavulanate is recommended.
Yersinia	• TMP-SMX 6 mg/kg (TMP component) daily for 3 days
Shigella	• TMP-SMX 10/50 mg/kg/day (max: 160/600) PO divided bid × 5 days • Ampicillin 50-100 mg/kg/day PO divided qid (adult max: 4 g/day) × 5 days • Azithromycin 12 mg/kg (max: 500) PO × 1 day, then 6 mg/kg/day (max: 250 mg) × 4 days (in areas of high resistance to above regimens or when sensitivities are unknown) • For resistant organisms: Ceftriaxone 50-75 mg/kg/day IV or IM divided into 1 or 2 doses (max: 2 g/day) × 2-5 days

Chlamydia trachomatis	• Children weighing < 45 kg: Erythromycin base or ethylsuccinate 50 mg/kg/day PO divided qid × 14 days
	• Children weighing > 45 kg but age younger than 8 yr: Azithromycin 1 g PO in a single dose
	• Children age older than 8 yr: Azithromycin 1 g PO in a single dose or Doxycycline 100 mg PO bid × 7 days
	• Adolescents and Adults:
	  • *Preferred*: Doxycycline 100 mg PO bid × 7 days
	  • *Alternative*: Azithromycin 1 g PO in single dose or Levofloxacin 500 mg PO once daily × 7 days

Neisseria gonorrhoeae	• Children weighing < 45 kg: Ceftriaxone, 25-50 mg/kg body weight IV or IM in a single dose (max 250 mg IM) • Children weighing ≥ 45 kg: Treat with adult regimen of 500 mg IM in a single dose; add azithromycin 1 g PO in a single dose if chlamydia has not been excluded. In persons > 150 kg, provide 1 g ceftriaxone.
Trichomonas	• Metronidazole, 15-30 mg/kg/day PO bid (max: 500 mg/dose) × 7 days or Tinidazole 50 mg/kg (max 2 g) PO as a single dose for children older than 3 yr
Pinworms (*Enterobius vermicularis*)	• Mebendazole, 100 mg chewable tablet once, repeated in 2 wk or Albendazole, 200 mg PO for child younger than age 2 yr or 400 mg PO for older child once, repeated in 2 wk • Pyrantel pamoate 11 mg/kg PO once (max 1 g), repeated in 2 wk

MRSA, Methicillin-resistant *Staphylococcus aureus*; TMP-SMX, trimethoprim-sulfamethoxazole.

and can be seen in children up to 1 year of age, it is an uncommon cause of specific infectious vulvovaginitis in the unestrogenized prepubertal female.

Other causes of specific infectious vulvovaginitis include *Shigella* (see Chapter 245), which often manifests with a blood-tinged purulent discharge, and *Yersinia enterocolitica* (see Chapter 249). Candida infections (yeast) commonly cause diaper rash (diaper dermatitis), but they are unlikely to cause vaginitis in children because the alkaline pH of the prepubertal vagina does not support fungal infections. Diabetic or immunocompromised children and children taking prolonged antibiotics may be at increased risk for fungal vaginitis. Pinworms are the most common helminthic infestation in the United States, with the highest rates in school-age and preschool children. Perianal itching can lead to excoriation and, rarely, bleeding.

CLINICAL MANIFESTATIONS

Diaper Dermatitis

Diaper dermatitis is the most common dermatologic problem in infancy and occurs in half of all diaper-wearing infants and children. The moisture and contact with urine and feces irritates the skin, and colonization with *Candida spp*. increases the severity of the dermatitis. First-line treatment includes hygiene measures such as increasing the frequency of diaper changes, allowing the infant to be diaper free, frequent bathing, and application of water-repellant barriers such as zinc oxide. If diaper dermatitis persists after these conservative measures, or if the classic satellite lesions of *Candida* are present, treatment with a topical antifungal can decrease the inflammation.

Physiologic Leukorrhea

Neonates and peripubertal children can present with a white, clear, or mucus discharge, which is physiologic in nature and secondary to exposure to estrogen. Some patients may complain of the moisture and mucus. Hygiene measures, including plain warm water baths, may help decrease symptomatology, but education should also be provided to reassure the patient and their parents.

Labial Agglutination

Labial agglutination (**labial adhesions**) are described most frequently in infants and young children (Fig. 586.1). This phenomenon is thought to be secondary to an inflammatory response in the labia minora in combination with a hypoestrogenic state. Diagnosis is made on routine genital examination. Asymptomatic patients usually require no intervention. Most common symptoms include urinary frequency, vaginitis, and postvoidal dribbling; labial adhesions also increase a patient's susceptibility to urinary tract infections. First-line therapy in symptomatic patients includes topical estrogen (estradiol cream 0.01%) or a topical steroid (betamethasone dipropionate 0.05% ointment) applied twice daily to the midline raphe under gentle traction. Surgical correction is rarely necessary, but recurrence is common until the age of puberty. Liberal use of bland emollients for 6-12 months after resolution of adhesions can limit recurrences.

Genital Ulcers

Acute genital ulceration of the vulva (Fig. 586.2) is described in young adolescents who are not sexually active and can occur in association with oral aphthous ulcers. Although linked to infectious causes such as Epstein-Barr virus, cytomegalovirus, mycoplasma, mumps, and influenza A, these ulcers may also be idiopathic vulvar aphthoses. Other potential etiologies include Crohn disease, Behçet disease, pemphigoid, Stevens-Johnson syndrome, fixed drug eruption, or mouth and genital ulcers with inflamed cartilage (MAGIC) syndrome, which has combined features of relapsing polychondritis and Behçet disease.

These lesions usually appear on the mucosal surfaces of the introitus as painful red or white lesions that evolve into sharply demarcated, red-rimmed ulcers with a necrotic or eschar-like base. The time course is generally 10-14 days until remission occurs. The lesions are painful; dysuria and vulvar pain are common complaints as well. Patients with acute genital ulcers show a fairly consistent picture of flulike prodromal symptoms, including fever, nausea, and abdominal pain. One

Fig. 586.1 Labial adhesions. *(Photo courtesy Diane F. Merritt, MD.)*

Fig. 586.2 Aphthous ulcers. *(Photo courtesy Diane F. Merritt, MD.)*

third of patients present with a history of or develop oral ulcerations. Evaluation includes culture or polymerase chain reaction (PCR) test for herpes simplex virus to exclude this etiology. Special testing for systemic disease depends on the history. Biopsies are usually nondiagnostic because they yield acute and chronic inflammatory changes. Figure 586.3 outlines the suggested evaluation and management of initial and recurrent disease. Evaluation for Behçet disease (see Chapter 202) using the International Study Group diagnostic guidelines should be considered with recurrent or severe cases (see Table 586.1 for other common etiologies). Treatment of acute genital ulcers should include topical lidocaine 2% jelly, sitz baths, good hygiene, and acetaminophen. Nonsteroidal antiinflammatory drug *avoidance* is suggested because of a possible causative link. Hospitalization may be required for pain management not controlled with oral narcotics or urinary retention requiring Foley catheterization, or for whirlpool debridement should hygiene become difficult. Antibiotic treatment is not required, unless evidence of bacterial superinfection exists or the patient is immunocompromised. Insufficient evidence exists to recommend whether oral steroid treatment is effective, but this may be helpful in the setting of recurrent outbreaks and extensive disease. Ultrapotent topical steroids (clobetasol 0.05% ointment) are beneficial in oral aphthous ulcers and may prove helpful in acute genital ulcers as well.

Dermatoses

Dermatologic conditions often affect the vulvar area in children; it is important to determine if the child presenting with vulvar irritation has a skin condition elsewhere on the body. **Lichen sclerosus** is commonly seen in the anogenital region and has a characteristic appearance of thinning and whitened skin changes associated with areas of erosion, ulceration, and petechiae. This disease can cause severe discomfort and most commonly presents with vulvar or perianal pruritus, dysuria, and constipation. Patients may also present without any symptoms, which may lead to underrecognition and undertreatment. If untreated, lichen sclerosus can lead to destruction and scarring of

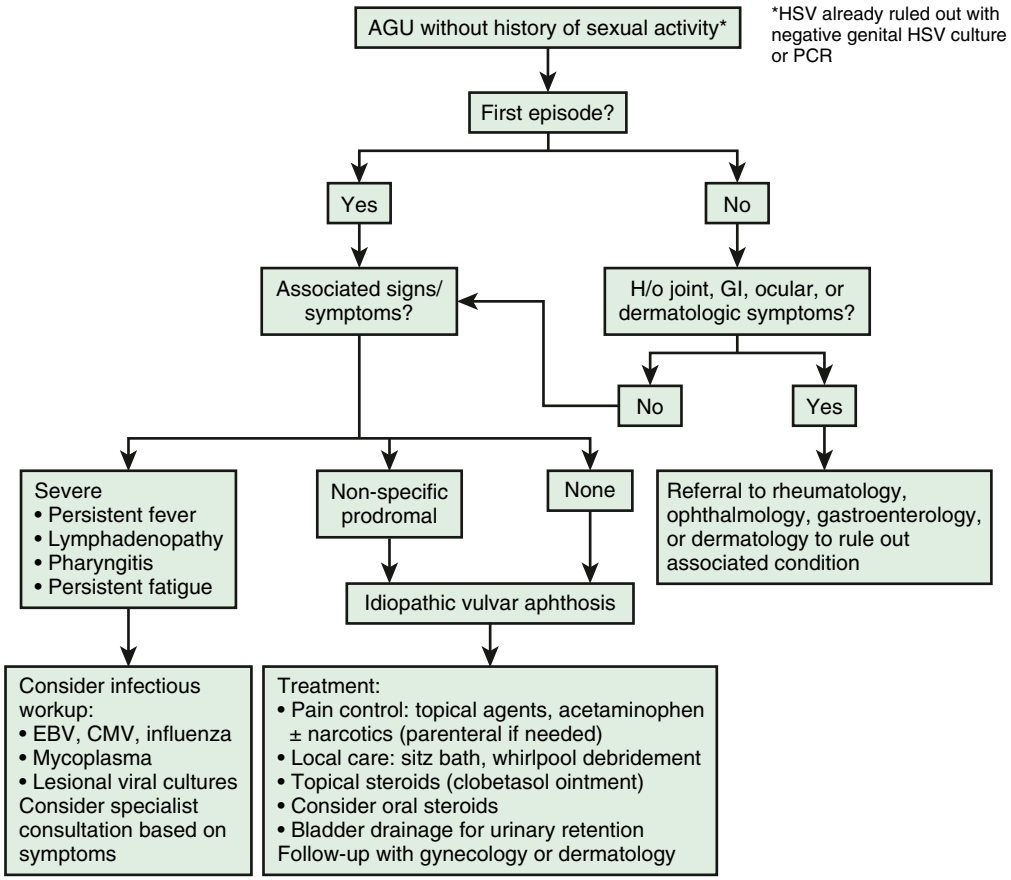

Fig. 586.3 Algorithm for evaluation and management of acute genital ulcers in non–sexually active young girls. AGU, Acute genital ulcer; CMV, cytomegalovirus; EBV, Epstein-Barr virus; GI, gastrointestinal; HSV, herpes simplex virus; PCR, polymerase chain reaction. *(From Rosman IS, Berk DR, Bayliss SJ, et al. Acute genital ulcers in nonsexually active young girls: Case series, review of the literature, and evaluation and management recommendations. Pediatr Dermatol. 2012;29[2];147-153.)*

Fig. 586.4 Lichen sclerosus. *(Photo courtesy Diane F. Merritt, MD.)*

normal genital architecture, including labial resorption, obliteration of the clitoris, narrowing of the introitus, and painful fissures that may become secondarily infected. Once thought to resolve with puberty, this theory is now controversial, and many postmenarchal adolescents still suffer from disease (Fig. 586.4). Lichen sclerosus may be treated with potent topical steroids, such as clobetasol propionate 0.05% applied once or twice daily until the symptoms resolve, and then tapered down through lower-dose topical steroids. Topical calcineurin inhibitors such as tacrolimus and pimecrolimus have been used in the treatment of lichen sclerosus. Patients should be followed every 6-12 months to evaluate for recurrence (Fig. 586.5).

Vitiligo is an acquired skin depigmentation resulting from an autoimmune process directed at epidermal melanocytes. Lesions appear as sharply demarcated patches of pigment loss, often symmetrically located around the vagina and anal area. Similar lesions of hypopigmentation can be found surrounding body orifices and extensor surfaces (Fig. 586.6). Although the diagnosis is clinical, there is an association with other autoimmune or endocrine disorders (hypothyroidism, Graves disease, Addison disease, pernicious anemia, insulin-dependent diabetes mellitus), and the workup should include evaluation for thyroid dysfunction. Mild topical corticosteroid cream or ointment may be prescribed for children. Dermatologists may offer immunomodulators (tacrolimus) and phototherapy.

Vulvar psoriasis presents as pruritic, well-demarcated, erythematous, symmetric plaques that involve the vulva, perineum, and/or gluteal folds. Lesions on the mons pubis may have the more characteristic scaly appearance. The classic signs of psoriasis may also be appreciated with pitting nailbeds, posterior auricular erythema, or a silvery scaling rash found elsewhere on the body. Many of the treatments used in adults may not be appropriate in children. Psoriasis may be treated with moisturizers, topical steroids, and light therapy. Teens may be treated with coal tar, retinoids, tacrolimus, and calcipotriene, which is a derivative of vitamin D_3.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Children with symptoms of vulvovaginitis often have had previous evaluations and treatment failures. Cultures with sensitivities to test for specific pathogens may be obtained with cotton swabs or urethral (Calgiswab) swabs moistened with nonbacteriostatic saline. Use of a swab can cause discomfort or, rarely, minimal bleeding. The

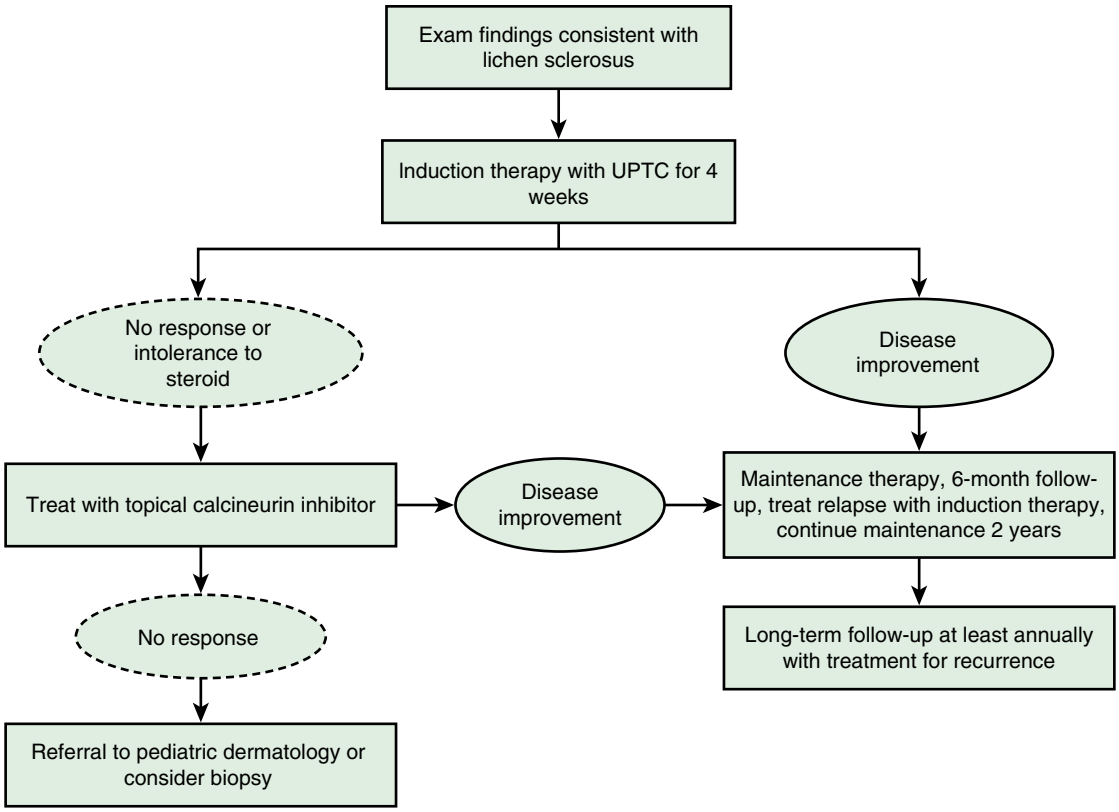

Fig. 586.5 Management algorithm for lichen sclerosus. UPTC, Ultrapotent topical corticosteroids. *(From Simms-Cendan J, Hoover K, Marathe K, Tyler K. NASPAG clinical opinion: Diagnosis and management of lichen sclerosis in pediatric and adolescent patients. J Pediatr Adolesc Gynecol. 2022;35[2]:112-120; Fig. 6.)*

Fig. 586.6 Vitiligo. *(Photo courtesy Diane F. Merritt, MD.)*

premoistened swab can be placed vertically between the labia minora to collect secretions, as it is not necessary to place the swab into the vagina. Testing for gonorrhea and chlamydia may be done by culture or by nucleic acid amplification testing, depending on institutional or state and Centers for Disease Control and Prevention guidelines. Tests for *Shigella* and *H. influenzae* might require special media and collection procedures.

If pinworms (see Chapter 340) are suspected, transparent adhesive tape or an anal swab should be applied to the anal region in the morning before defecation or bathing and then placed on a slide. Eggs seen on microscopic examination confirm the diagnosis, and sometimes the pinworms can be seen at the anal verge. Clinical history is often more indicative of disease than physical examination, and a negative tape test does not rule out this pathogen as a cause.

If the vaginal discharge is serosanguineous, if a foul odor is present, or if the discharge fails to respond to hygiene measures, presence of a vaginal foreign body (Fig. 586.7) should be considered. If inspection suggests the presence of a foreign body, the vagina can be irrigated, or an examination under anesthesia may reveal the foreign body. Vaginal irrigation may occasionally lead to expulsion of the foreign body; in cases where this does not occur, vaginoscopy is an excellent diagnostic tool and can be performed in an unsedated cooperative patient in an outpatient setting, or under general anesthesia if necessary. Using a cystoscope with saline or water irrigation to gravity, insert the endoscopic device into the vagina and gently oppose the labia; the vagina will distend, and the entire vaginal cavity and cervix may be easily assessed.

TREATMENT AND PREVENTION

The treatment of specific vulvovaginitis should be directed at the disorder or organism causing the symptoms (see Tables 586.1 and 586.2). Treatment of nonspecific vulvovaginitis includes sitz baths

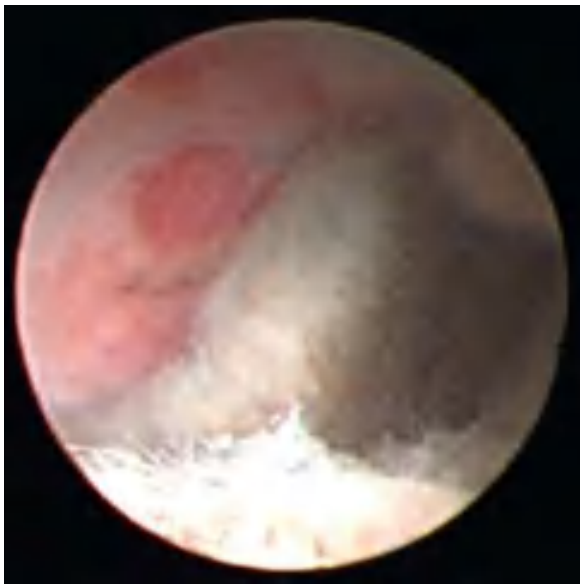

Fig. 586.7 Vaginal foreign body as seen through vaginoscope. *(Photo courtesy Diane F. Merritt, MD.)*

Fig. 586.8 Molluscum contagiosum. *(Photo courtesy Diane F. Merritt, MD.)*

and avoidance of irritating or harsh soaps and chemicals and tight clothing that abrades the perineum. External application of bland emollient barriers such as nonprescription diaper rash medications and petroleum jelly may be helpful. Proper perineal hygiene is critical for long-term improvement. Younger children need supervised perineal hygiene, and caregivers should be advised to wipe the genital area from front to back. Use of a warm moistened washcloth or diaper wipe is helpful after initially wiping with toilet tissue. Children should wear cotton underwear and limit time spent in tights, leotards, leggings, tight jeans, and wet swimsuits. Soaking in warm clean bathwater for 15-minute intervals (no shampoo or bubble bath) is soothing and helps with cleaning the area. Parents should be counseled to avoid all scented, antiseptic, and deodorant-based soaps, and to eliminate the use of fabric softeners or dryer sheets when laundering undergarments.

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Chapter 587

Vaginal Bleeding in the Prepubertal Child

Kathryn C. Stambough and Christina Davis-Kankanamge

Newborn females may experience physiologic bleeding (**neonatal withdrawal bleeding**) in the first week of life secondary to diminished circulating maternal estrogen and stimulation of endometrial sloughing; this bleeding resolves in 3-4 days. Vaginal bleeding in infants lasting longer than a few days and all other vaginal bleeding in prepubescent children should be promptly evaluated because there are many pathologic etiologies that require expeditious workup. Common causes include vulvovaginitis, dermatologic conditions, vaginal foreign bodies, and urethral prolapse; less common are the effects of endogenous or exogenous estrogen; and the least common but most worrisome sources include neoplasms and trauma.

Although many cases of pediatric vaginal bleeding are idiopathic, many can be attributed to **vulvovaginitis** (see Chapter 586) stemming from transmission of respiratory, oral, fecal, or sexually communicated pathogens. Vulvovaginitis may present with serosanguineous vaginal drainage (e.g., *Streptococcus, Shigella*) or vulvar irritation. Age-appropriate anatomic and physiologic factors put prepubertal females at higher risk of developing vulvovaginitis. The protective barrier of fully developed labia is absent, leaving the vaginal introitus exposed to the external environment. The hypo-estrogenized vagina is marked by an alkaline milieu prone to infection because of lack of the protective acidic pH afforded by the lactobacilli colonization that occurs with puberty. Routine handwashing, improved perineal hygiene (e.g., wiping from front to back, use of wet wipes after bowel movements, proper cleansing of genitalia during baths), and avoidance of topical irritants, chemicals, and perfumed or deodorant soaps and bubble baths reduces nonspecific vulvovaginitis. Topical application of bland emollient barriers (e.g., over-the-counter diaper rash ointments, petroleum jelly) may be protective against and mitigate symptoms of external irritation. Antibiotics should be employed in the event of recurrent or persistent infections where a specific pathogen has been identified (see Table 586.2).

Vulvar dermatoses may initially present with bleeding. **Lichen sclerosus** (see Table 586.1 and Fig. 586.4) is characterized by chronic inflammation, intense pruritus, loss of normal architecture, and thinning and whitening of vulvar and perianal skin, often in a butterfly or keyhole distribution. Petechiae or blood blisters can complicate the classic clinical picture, leading to a mistaken assumption of sexual trauma. A tissue biopsy can provide a definitive diagnosis but is not usually necessary in prepubertal children and, if needed, is most appropriately performed under anesthesia. The first-line treatment is ultrapotent topical steroids (e.g., clobetasol propionate 0.05%). Appropriate timing and duration of application is practitioner dependent, but guidelines suggest treating children similarly to adults by starting with once or twice daily application for 4 weeks. Tapering of topical corticosteroid use can then occur with symptom control and include a decrease in the frequency of corticosteroid application, potency of the corticosteroid used, or both. Follow-up evaluations for response should start at 1 month after initiation of treatment. In the event of flare-ups, long-term maintenance therapy with a lower potency steroid may be initiated with appropriate counseling because side effects are rare.

Vaginal foreign bodies are a common finding in children presenting with blood-tinged and foul-smelling discharge. Quick identification and removal of the foreign body avoids potential complications, including recurrent urinary tract infections, dermatologic

abnormalities, vaginal perforation, or fistula formation. The most common object found in the prepubertal vagina is retained toilet paper. If physical exam in knee-chest or frog-leg position reveals the object, an attempt at removal in the office can be made using warm water flushes through a small feeding tube. If the object is not visible, irrigation is unlikely to remove it, and examination under anesthesia and vaginoscopy are often required. Direct visualization via vaginoscopy facilitates extraction of an object, as well as evaluation for potential sites of injury or unrelated sources of bleeding. In-office vaginoscopy may also be a possibility in the appropriate patient (see Chapter 585).

Several urologic conditions may have a mixed clinical picture suspicious for vaginal bleeding, including **gross hematuria** (see Chapter 558) and **urethral prolapse** (see Chapter 581) (Fig. 587.1). Prolapse involves protrusion of urethral mucosa through the external meatus, resulting in a friable hemorrhagic mass that often obscures the adjacent vaginal introitus. Predisposing factors include hypoestrogenic state, neuromuscular diseases, urethral anomalies, fascial defects, trauma, and chronic increases in intraabdominal pressure (e.g., recurrent Valsalva related to constipation or forceful coughing). Treatment of prolapse is conservative, involving twice-daily sitz baths followed by topical application of estrogen cream (e.g., Estradiol 0.01%) at the affected area for 2 weeks. If on reevaluation the prolapse remains, application should be continued until complete resolution is achieved. Surgical excision is rarely necessary and reserved primarily for management of necrotic tissue.

Vaginal bleeding may be a presenting sign of **precocious puberty** (see Chapter 600), defined as premature pubertal development occurring 2.0-2.5 standard deviations earlier than the average age in the general population. A formal evaluation should be conducted if pubic hair or breast development occurs rapidly or initiates before age 8 years in a female child. The most common source of premature development is **gonadotropin-dependent** or **central precocious puberty** (see Chapter 600.1), resulting in early enhancement of pulsatile release of hypothalamic gonadotropic-releasing hormone (GnRH) that stimulates ovarian follicular growth and subsequent estrogen production. **Gonadotropin-independent** or **peripheral precocious puberty** occurs less commonly and in the absence of hypothalamic influence, with estrogen being a product of ovarian or adrenal tumors, or McCune-Albright syndrome (see Chapter 600.6). In both instances, elevated estrogen levels lead to a thickened endometrium capable of shedding as in menses.

Fig. 587.1 Prepubertal urethral prolapse with high crescent-shaped hymen. *(From Lara-Torre E, Valea FA. Pediatric and adolescent gynecology: Gynecologic examination, infections, trauma, pelvic mass, precocious puberty. In Lobo RA, Gershenson DM, Lentz GM, Valea FA [eds]: Comprehensive Gynecology. Elsevier, 2022: 227; Fig. 12.6.)*

Evaluation of precocious puberty starts by examining for secondary sex characteristics and documenting the Tanner stage of breast and pubic hair development using the **Sexual Maturation Index** (see Chapter 150). Plotting height and weight on a growth chart may assist in identifying accelerated growth velocity. Supportive laboratory findings include elevated serum luteinizing hormone levels, but the gold standard remains measurement of gonadotropin levels after stimulation with GnRH or a GnRH receptor agonist. Estradiol levels greater than 100 pg/mL can indicate either the presence of premature ovarian follicles or a peripheral tumor (e.g., ovarian germ cell tumor). A pelvic ultrasound should be used to evaluate for ovarian or adrenal pathology, as well as uterine maturation in response to estrogen. However, premature ovarian follicles typically produce estrogen for a very short period, in quantities just sufficient to stimulate growth and shedding of the endometrium. Follicular involution and return of estrogen to prepubertal levels may occur before an ultrasound can be obtained. An x-ray for bone maturity is simple and noninvasive. Other supportive radiologic findings include a brain MRI demonstrating a mass in the context of central precocious puberty. If indicated, central precocious puberty can be suppressed with GnRH agonist therapy. Peripheral tumors (i.e., ovarian germ cell tumors) are treated by surgical excision with staging and chemotherapy as indicated by oncologic protocols.

Differential diagnoses of vaginal bleeding attributed to premature estrogenization must also include exposure to **exogenous estrogens,** including hormonal contraceptives, certain foods (soy), beauty products (lavender, tea tree oil), and plastics with endocrine disruptors. Ingesting large quantities of Bisphenol A (BPA), a product that may leach into the contents of plastic cups and bottles, is known to convey an estrogenic effect, although the impact remains unknown. Treatment involves elimination of any problematic sources of estrogen from the patient's daily use.

Juvenile hypothyroidism (see Chapter 603) commonly causes pubertal delay, but severe cases may present with premature breast development, vaginal bleeding, and abdominal distention secondary to ovarian enlargement and ascites. The mechanism for this condition is unclear, but it has been proposed that elevated levels of thyroid-stimulating hormone cross-react with follicle-stimulating hormone receptors, resulting in follicle maturation and estradiol production. Treatment with thyroid hormone replacement (e.g., levothyroxine) results in improvement and ultimately reversal of symptoms.

Neoplasms of the vulva and vagina (see Chapter 590) are rare causes of bleeding in the pediatric patient. **Infantile hemangiomas** are the most common benign vascular neoplasm of infancy, affecting up to 5% of all infants. Most lesions initially proliferate before resolving spontaneously and seldom require intervention. However, on identifying a perineal hemangioma, a neurologic assessment should be performed due to an association with spinal dysraphism. If a persistent lesion is superficial, application of topical β blockers (e.g., Timolol 0.5%) 2-3 times daily for 6-12 months has demonstrated good response rates. Oral β blocker use and intralesional corticosteroids may be used as well. If conservative therapies fail, laser therapy and surgical excision may be beneficial. Vaginal polyps may result in bleeding, and vaginoscopy for evaluation of any upper vaginal or cervical etiologies for bleeding with expedient excision and pathologic evaluation is recommended.

Malignant gynecologic neoplasms (see Chapter 590) are a source of pediatric genital bleeding that requires scrupulous evaluation and timely management. **Rhabdomyosarcoma** is the most common soft tissue sarcoma of childhood; 3% arise from the uterus or vagina. The embryonal variant is responsible for uterine sarcomas, whereas the embryonal subvariant sarcoma botryoides is found in the vagina. Primary **endodermal sinus** (i.e., yolk sac) **tumors** of the vagina are exceedingly rare, but early diagnosis is imperative given the malignancy's aggressive nature and poor prognosis. Both sarcomatous and endodermal sinus tumors arise primarily in the first 3 years of life, presenting on examination with a cystic or polypoid mass, bloody discharge, and occasionally urinary retention. Treatment consists of a multimodal approach, including surgery, radiation, and chemotherapy per oncologic guidelines.

Vulvovaginal trauma is an especially concerning cause of pediatric genital bleeding. Most traumatic injuries are accidental, but physical and sexual abuse must be ruled out (see Chapter 17.1). **Straddle injuries** are commonly seen after falls at home, particularly after slipping on a wet surface in the bathroom; they may result in bruising, hematomas, or lacerations (Fig. 587.2). Accidental trauma usually spares the hymen and vagina, instead affecting the external impact-absorbing tissue of the mons and labia. *However, a physical finding consistent with external injuries does not exclude the need to rule out involvement of internal genital structures. If there are no eyewitnesses to the injury, if the history does not clarify or support the clinical findings, and especially if there is a hymenal laceration, abuse must be considered in the differential diagnosis and a forensic interview of the patient and family conducted.* If after initial inspection a penetrative injury is suspected, further examination and imaging are necessary to assess for potential damage to the urethra, bladder, anus, or intraabdominal structures. An examination under anesthesia may be needed to fully assess and repair extensive injuries, while minor lacerations in a cooperative child may potentially be repaired using local anesthesia and/or conscious sedation. If the patient can void spontaneously, nonexpanding hematomas can be observed and treated with ice, pressure, and pain medications. Large expanding hematomas may require drainage, ligation of bleeding vessels, and placement of a closed suction drain if the overlying skin is showing signs of necrosis. A Foley catheter should be placed in all children who are having difficulty with voiding secondary to the injury.

Vaginal bleeding in the infant or prepubertal female is distressing to the patient and their family and can result from a wide spectrum of pathologic conditions or traumatic incidents. A detailed history and thorough physical examination must be done to identify the source of bleeding and for a management plan to be established efficiently. Presentations suspicious for trauma or abuse should involve the appropriate healthcare staff and authorities from an early stage, with findings meticulously documented. If an intervention is indicated to manage bleeding, regardless of its source, the risks and benefits of any therapy should be reviewed carefully with the family before initiation.

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Fig. 587.2 Vulvar hematoma in an adolescent female as a result of a straddle injury. *(From Mok-Lin EY, Laufer MR. Management of vulvar hematomas: Use of a Word catheter. J Pediatr Adolesc Gynecol. 2009; 22:e156-e158.)*

Chapter 588

Breast Health

Marcene R. McVay-Gillam and Amy D. DiVasta

Breast complaints in pediatric patients typically include concerns about breast appearance or development, pain, nipple discharge, or a lump/mass. Although the development of breast cancer is very rare during childhood and adolescence, this patient population should be evaluated by practitioners who have experience with the immature and developing breast to avoid overtreatment with unnecessary diagnostic or invasive procedures.

BREAST DEVELOPMENT

Prenatal breast development begins around the fifth week of gestation, when the ectoderm on the anterior body wall thickens into two **mammary ridges.** These ridges extend from the axilla to the region of the inguinal canal (Fig. 588.1). The ridge above and below the area of the pectoralis muscle recedes in utero, leaving the **mammary primordium**, which is the origin of the lactiferous ducts. The lactiferous ducts form between weeks 10 and 20 and become interspersed through the developing mesenchyme, which develops into the fibrous and fatty portions of the breast. The **breast bud**, under the stimulation of maternal estrogen, becomes palpable at week 34 of gestation. This breast bud regresses within the first month of life once estrogen stimulation is no longer present. The **areola** appears at 5 months of gestation, and the nipple is seen shortly after birth. It is initially depressed or inverted, and later becomes elevated.

Thelarche, the onset of pubertal breast development, is hormonally mediated. It occurs when the hypothalamus releases gonadotropin-releasing hormone (GnRH), which stimulates the pituitary gland to produce follicle-stimulating hormone (FSH) and luteinizing hormone (LH) (see Chapter 599). FSH and LH then stimulate the ovaries to produce estradiol, which leads to breast development. Thelarche typically occurs between ages 8 and 13 years. Age at thelarche is affected by familial predisposition and varies by ethnicity.

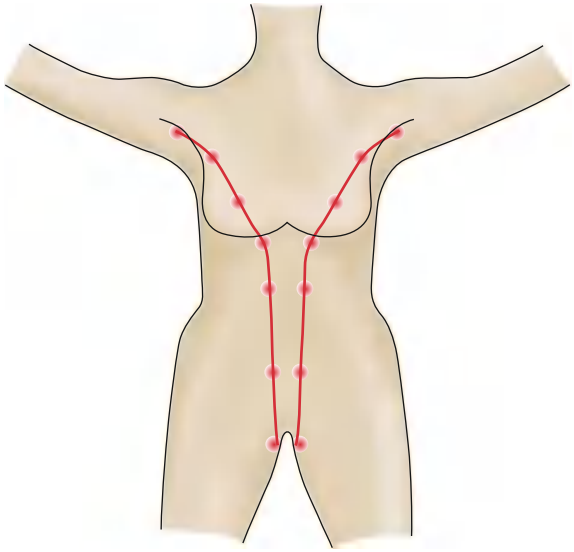

Fig. 588.1 Milk lines or mammary ridges. *(From Gao Y, Saksena MA, Brachtel EF, terMeulen DC, Rafferty EA. How to approach breast lesions in children and adolescents. Eur J Radiol. 2015;84:1350-1364; Fig. 1.)*

Breast development continues over a 2-4 year period after thelarche and is classified by the **Sexual Maturity Rating (SMR) system** (also known as **Tanner staging**) into five stages (see Chapter 150). Lack of breast development (**amastia**) by age 13 years is considered delayed and warrants evaluation. **Menarche** (onset of menses) usually occurs 2-3 years after thelarche.

BREAST EXAMINATION

Breast examination should be included in the routine healthcare maintenance examinations of all children and adolescents. Assessment of the newborn includes breast size, nipple position, presence of accessory nipples, and nipple discharge. Assessment of the prepubertal female includes inspection and palpation of the chest wall for masses, pain, nipple discharge, and signs of **premature thelarche.** Examination of the adolescent is performed with the patient in the supine position; the arm ipsilateral to the breast that is being examined should be placed next to the patient's head. The breast tissue is examined with the flat pads of the middle fingers, and the examiner should palpate all of the breast tissue in a uniform manner. The SMR should be noted and the axillary, supraclavicular, and infraclavicular nodes evaluated for lymphadenopathy. The areola should be gently compressed to assess for nipple discharge.

BREAST SELF-AWARENESS

Controversy exists as to the utility of breast self-examination in the adolescent population. Experts believe that it might be ill-advised to encourage breast self-examination in the adolescent because of a potential for unnecessary anxiety and possible unwarranted treatment in a population that is at low risk for malignant disease. The American College of Obstetricians and Gynecologists (ACOG) endorses breast self-awareness, which is defined as a female's awareness of the normal appearance and feel of their breasts. Breast self-awareness may increase an adolescent's understanding of their body, increase their comfort with exams, and provide opportunities for questions or discussion. Instruction in self-exam techniques should be considered for high-risk patients, such as those with a family history of conditions that may increase breast cancer risk or those at risk of secondary tumors. Adolescents should be educated to report any changes in their breasts or concerns to their healthcare providers.

Neonatal Breast Hypertrophy

Breast bud enlargement is a common condition in term newborns of either gender. It occurs as a result of elevated circulating maternal steroid hormones in late gestation. As maternal estrogen levels fall, prolactin levels can increase, and the breasts may produce a clear or cloudy (milk like) nipple discharge ("witch's milk") in male and female infants. Repeated manipulation of the breast can exacerbate the condition and should be discouraged.

ABNORMAL DEVELOPMENT

Premature Thelarche

Premature thelarche is defined as isolated unilateral or bilateral breast development in a female child under age 8 years without other signs of puberty; this is commonly seen in children under 3 years of age. Patient assessment includes a careful review of medications (including creams, ointments), home exposures to potential estrogens, review of growth charts, and x-ray for determination of bone age. Treatment consists of reassurance and follow-up to confirm that thelarche remains benign. Serial examinations, with particular emphasis on growth velocity, secondary sex characteristics such as pubic hair, pigmentation of the labia or areola, or vaginal bleeding, are imperative. Occasionally, patients with premature thelarche eventually develop true **central precocious puberty** (see Chapter 600.1). If puberty progresses, further workup should be performed to exclude central nervous system disorders or possible adrenal or gonadal neoplasm.

Amastia and Athelia

Complete absence of the breast, or **amastia,** is rare and is thought to occur from lack of formation of or obliteration of the mammary ridge. Amastia is usually unilateral and can be congenital or associated with systemic disorders (e.g., ectodermal dysplasia), endocrine disorders (e.g., congenital adrenal hyperplasia, gonadal dysgenesis, hypogonadotropic hypogonadism), or novel pathogenic gene variants. It can be associated with anomalies of the underlying mesoderm, such as the absence or hypoplasia of the pectoralis muscles seen in **Poland syndrome** (aplasia of the pectoralis muscles, rib deformities, webbed fingers, and radial nerve aplasia) (Fig. 588.2). Amastia or hypomastia can also be iatrogenic, resulting from injuries sustained during thoracotomy, chest tube placement, radiotherapy, severe burns, or incisional/excisional procedures on the breast bud. Surgical correction is individualized to the patient and the etiology. **Athelia**, the absence of a nipple either unilaterally or bilaterally, is rare and can be familial. It is also associated with exposure to endogenous androgens during pregnancy.

Fig. 588.2 Preoperative frontal view of a patient with left breast hypoplasia secondary to Poland syndrome. *(From Laberge LC, Bortoluzzi PA. Correction of breast asymmetry in teenagers. In: Hall-Findlay EJ, Evans GRD, eds. Aesthetic and Reconstructive Surgery of the Breast. London: Elsevier, 2010. Fig 39.14.)*

Fig. 588.3 Accessory nipple located inferior to the right breast. *(From Swartz MH. Textbook of Physical Diagnosis. Philadelphia: Elsevier, 2014; Fig 13-5.)*

Polymastia and Polythelia

Accessory breast tissue **(polymastia)** or accessory nipples **(polythelia)** occur in approximately 1–6% of the population (Fig. 588.3). The abnormally placed tissue can be seen anywhere along the mammary ridges ("milk lines") as a result of incomplete involution but is usually noted on the chest, axilla, or just inferior to the normally positioned breast. Polythelia has been reported in association with congenital malformations, particularly renal anomalies; it is therefore reasonable to perform a genitourinary ultrasound in an infant with supernumerary nipples. Surgical excision of the accessory breast or nipple is usually performed for pain (mastodynia), nipple discharge, or cosmesis.

Breast Hypoplasia and Asymmetry

Breast hypoplasia varies in degree from a near-total absence of breast tissue to well-formed breasts that are considered by the patient to be too small. Poor or absent breast development may simply be a delay in the development of normal secondary sex characteristics; the breasts develop slowly but are normal in all other respects. Family history may reveal other family members with a similar pattern. Other causes include ovarian dysfunction, hypothyroidism, eating disorders, chest wall irradiation, or surgery. Hypoplastic breast tissue can also be associated with a **tuberous breast** anomaly. Tuberous breasts are characterized by hypoplasia, a narrow breast base, and the appearance of herniation of the glandular tissue through enlarged areolae (Fig. 588.4).

More commonly, patients complain of *breast asymmetry*. Some degree of breast asymmetry is normal; it may be more pronounced during puberty while the breasts are developing. In asymmetry, the goals of evaluation are twofold. First, it is essential to exclude a neoplasm as the cause of the larger breast. Other etiologies may include a solitary large fibroadenoma, multiple fibroadenomas, or a parenchymal abscess. Alternatively, the possibility of tuberous breast development or Poland syndrome should be considered when evaluating the smaller side. Treatment depends on the underlying cause. Patients with mild asymmetry and no other associated pathology should be reassured. If a child has marked breast asymmetry, they may be initially offered cosmetic options, such as use of bra inserts or prostheses for the underdeveloped breast. Surgical correction may be pursued after breast development is complete. The American Society of Plastic Surgeons generally recommends that uncommon chest deformities or congenital breast asymmetry are the only cases in which a board-certified plastic surgeon should deem breast augmentation appropriate for a teenager. It is important that patients undergoing surgery have a realistic understanding of the potential results as well as the possible need for additional surgery. Saline-filled implants are the only type of implant approved by the U.S. Food and Drug Administration for females <22 years; saline-filled implants typically have a life span of about 10 years.

Macromastia

Adolescents may develop very large breasts **(macromastia)**, leading to both physical and psychologic symptoms. Common complaints include back pain, postural kyphosis, breast pain, intertrigo, limitation of physical activities, unwanted negative attention, diminished self-esteem, and eating disordered behaviors. Strong emotional support should be provided because macromastia can affect an adolescent's self-esteem at a vulnerable time in their psychologic development. The differential diagnosis for macromastia includes obesity, pregnancy, fibrocystic disease, end organ hormonal hypersensitivity, or lesions described in the previous paragraphs. Options for treatment of simple macromastia include surgical and nonsurgical interventions. Bras that provide maximal support can help correct symptoms. Alternatively, breast reduction mammoplasty may be desired. When adolescents are seeking breast surgery, ACOG first recommends education and reassurance regarding normal variations in anatomy, growth, and development for the patient and her family. Nonsurgical alternatives for comfort and appearance should be emphasized, and knowledge regarding indications and timing of surgical intervention and referral should be provided. Assessment of the adolescent's physical and emotional maturity level must be performed, as well as screening for **body dysmorphic disorder.**

Juvenile hypertrophy, or spontaneous massive growth of one or both breasts, is rare and should be distinguished from simple adolescent macromastia. This rapid growth of breast tissue may occur any time after thelarche but more commonly occurs abruptly over a several month period, after a preceding sustained period of normal breast development. Circulating estradiol levels are normal. Juvenile hypertrophy can cause extreme mastalgia, skin hyperemia or necrosis, and even damage to normal breast parenchyma due to compromised vascular supply. It can be unilateral or bilateral (Fig. 588.5). The etiology has not been elucidated; therefore treatment options include both pharmacologic and surgical interventions. The key to management is prompt recognition and intervention before the development of complications. Reduction mammoplasty is often the treatment of choice, with pharmacologic treatment (e.g., tamoxifen) or even mastectomy reserved for recurrence following surgery.

Infections

Mastitis is the most common infection of the breast and can occur any time from the neonatal period through adolescence and into adulthood. **Neonatal mastitis** is an infection that usually occurs in the first 2 months after delivery in term or near-term infants. Breast infections in adolescents occur most commonly with lactation. Adolescents can also develop **nonlactational mastitis** or a **breast abscess** as a result of irritation of the skin (e.g., acne lesions of the chest, shaving, or nipple stimulation), trauma, a foreign body (e.g., piercing), or ductal abnormality (such as ductal ectasia). *Staphylococcus aureus* is the cause of nearly all breast infections, but anaerobic bacilli *(Bacteroides)* may also be involved in the adolescent population. Methicillin-resistant *S. aureus* (MRSA) coverage should be considered in communities where the prevalence is high,

Fig. 588.5 Juvenile hypertrophy in a 12-year-old female. *(From Al-Saif AA, Al-Yahya GM, Al-Qattan MM. Juvenile mammary hypertrophy: is reduction mammaplasty always feasible? J Plast Reconstr Aesthet Surg. 2009;62:1470-1472; Fig. 1.)*

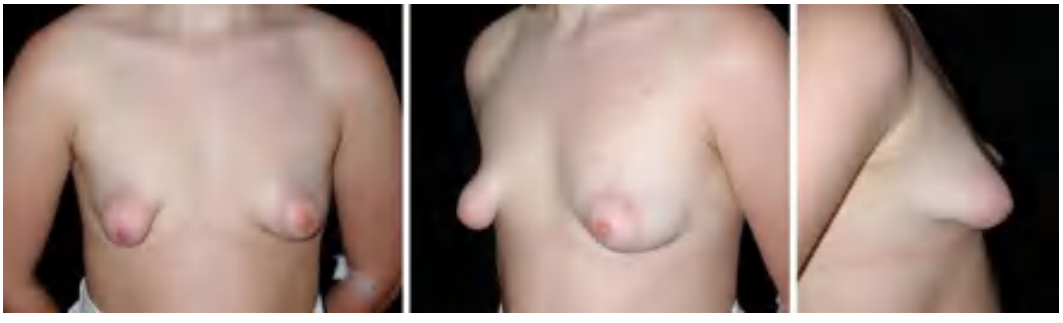

Fig. 588.4 Bilateral tuberous breast anomaly. *(Adapted from Pacifico MD, Kang NV. The tuberous breast revisited. J Plast Reconstr Aesthet Surg. 2007;60:455-464; Fig. 5.)*

especially for infants. Mastitis may be initially treated with warm compresses, analgesics, and oral antibiotics for 7-10 days. Antibiotic options include dicloxacillin, clindamycin, trimethoprim-sulfamethoxazole, or amoxicillin-clavulanic acid. If symptoms fail to resolve after a course of antibiotics, ultrasonography may reveal an abscess and can be used to guide needle aspiration. Incision and drainage should be reserved for failure of aspiration, and a periareolar incision is most cosmetic. Follow-up ultrasonography should be considered in adolescents to ensure that there is no remaining parenchymal lesion (e.g., cyst).

Trauma and Inflammation

Breast trauma is common in adolescent girls participating in contact sports. The trauma usually takes the form of contusion or **hematoma** and can resolve spontaneously or may be associated with late cystic changes in the breast, **fat necrosis** with calcium deposition over time, or fibrosis with retraction of the skin or the nipple over the injured area. When diagnosed with a hematoma, or when a palpable mass is present at the area of injury, serial follow-up by ultrasound is recommended until complete resolution. Persistent calcifications lasting more than 18 months after injury may require additional investigation by advanced imaging or biopsy.

Nipple Discharge

Nipple discharge must be carefully evaluated and characterized. Discharge may be milky and white **(galactorrhea)**, bloody, purulent, or serous (Table 588.1). A careful history and physical examination will help the practitioner determine the etiology. Examination of the discharge assists in diagnosis. Infection is usually associated with a purulent discharge; **ductal ectasia** (dilated subareolar ducts and periductal inflammation) may present with sticky, green or brown, or serosanguineous discharge. Discharge from the ducts of Montgomery (coming from the areola itself rather than through the nipple) may appear clear or brownish.

Galactorrhea is a specific type of nipple discharge that appears milky and is usually bilateral. Causes of galactorrhea are listed in Table 588.2. Cytologic evaluation of milky nipple discharge is not recommended. Laboratory evaluation should include a pregnancy test, prolactin, estradiol, and thyroid-stimulating hormone (TSH); these measures are obtained to rule out pregnancy, a pituitary prolactinoma, and/or the presence of a thyroid abnormality. If the prolactin level is elevated, visual field studies and a brain MRI might reveal the presence of a pituitary adenoma (see Chapter 598). Treatment is directed by results of the history, physical exam, and lab and imaging studies. Patients should be instructed to avoid nipple stimulation and stop any offending drugs, if appropriate to do so. Hypothyroidism should be treated and prolactin-releasing tumors managed with appropriate medical or surgical care. Medical treatment of galactorrhea consists primarily of dopamine agonists such as bromocriptine or cabergoline. Surgical intervention, usually transsphenoidal hypophysectomy, is rarely required.

Bloody discharge may be due to chronic nipple irritation (such as from **jogger's nipple**), ductal ectasia, phyllodes tumor, or intraductal papilloma (a rare, benign proliferative tumor). Unless the etiology of the bloody discharge is superficial (i.e., from obvious skin breakdown related to jogger's nipple), cytologic assessment of bloody discharge should be performed. Breast ultrasound may also be obtained to determine whether a mass or cyst is present.

Table 588.1 Common Causes of Nipple Discharge

DISCHARGE CHARACTERISTICS	POTENTIAL ETIOLOGY
Milky (galactorrhea)	Pregnancy or postpartum Medication use/drug use Herbal supplements Hypothyroidism Prolactinoma Chest wall trauma
Serous, serosanguineous	Ductal ectasia Intraductal papilloma
Sticky	Ductal ectasia Fibrocystic changes
Purulent	Mastitis Abscess
Bloody	Intraductal papilloma Phyllodes tumor Ductal ectasia Trauma ("jogger's nipple")
Episodic, clear to brown	Montgomery tubercles

Mastalgia

Mastalgia, or breast tenderness, is common in reproductive-age females. Mastalgia may be due to exercise, medications, early pregnancy, or benign breast changes **(fibrocystic changes)**. Physiologic swelling and tenderness can occur on a cyclic basis, most commonly during the premenstrual phase, and are secondary to hormonal stimulation and resulting proliferative changes. Hormonal imbalance can cause exaggerated responses in the breast tissue, especially in the upper and outer quadrants. Evaluation should include a pregnancy test and a breast examination. Nodularity,

Table 588.2 Etiologies of Hyperprolactinemia

PITUITARY DISEASE
Prolactinomas
Acromegaly
Empty sella syndrome
Lymphocytic hypophysitis
Cushing disease
HYPOTHALAMIC DISEASE
Craniopharyngiomas
Meningiomas
Dysgerminomas
Nonsecreting pituitary adenomas
Other tumors/metastatic disease
Sarcoidosis
Eosinophilic granuloma
Chiari-Frommel syndrome
Encephalitis
Pituitary stalk section or compression
MEDICATIONS
Anesthetics, including cocaine
Opiates
Selective serotonin reuptake inhibitors
Phenothiazines
Benzodiazepines
Protease inhibitors
Prostaglandins
Tricyclic antidepressants
Atypical antipsychotics
α-Methyldopa
Reserpine
Metoclopramide
Marijuana
Herbal supplements (fennel, anise, fenugreek)
NEUROGENIC DISORDERS
Chest wall lesions/surgery
Spinal cord lesions
Breast stimulation
OTHER CAUSES
Pregnancy, postpartum, and postabortion
Hypothyroidism
ROHHAD
Chronic renal failure
Cirrhosis
Stress
Idiopathic disorders

ROHHAD, rapid-onset obesity, hypothalamic dysregulation, hypoventilation, and autonomic dysregulation.
Modified from Chanson P, Maiter D. Prolactinoma. In Melmed S (ed). *The Pituitary*. 4th ed. Philadelphia: Elsevier, 2017; 467-514.

poorly localized tenderness, and soreness radiating to the axilla and arm are usual accompanying findings. Treatments for mastalgia include utilization of a firm, supportive sports-type bra, heat, and analgesics (oral or topical). Low-dose combined estrogen/progestin oral contraceptives often improve the breast pain. A course of NSAIDs is also typically effective. The effect of caffeine and chocolate on mastalgia is controversial, but if pain is worsened with increased intake, they should be avoided. Evening primrose oil, vitamin E, and chamomile extract are popular but unproven treatments.

BREAST MASSES

Peripubertal Masses

Initial breast development at the onset of thelarche can be unilateral and asymmetric, with the developing breast bud being mistaken for a "mass." Such asynchronous thelarche should be recognized to avoid unnecessary biopsy and potential injury to the maturing breast. If there is any question as to the etiology of the lump, ultrasound can be used to evaluate for a mass.

Adolescent Breast Masses

The differential diagnosis for breast masses in the adolescent patient is broad (Table 588.3). The patient should be questioned about variations associated with the menstrual cycle, associated symptoms such as nipple discharge, recent trauma to the breast, family history of breast masses or cancer, and personal history of chest radiation or malignancy. Physical examination should characterize the mass location, size, and firmness and determine whether tenderness, skin changes, nipple discharge, or lymphadenopathy is present. Because breast cancer in the adolescent is extremely rare (3.2 cases per million person-years for women <25 years), masses in this population can often be expectantly managed for extended periods of time.

Fibroadenomas are the most common solid mass found in the adolescent breast. Fibroadenomas are slow-growing, hormonal dependent masses most often located in the upper, outer quadrant of the breast. The average size at diagnosis is 2-3 cm; 10–25% of patients have multiple lesions. On examination, these lesions are well circumscribed, rubbery, mobile, and not tender. Given the slow-growing nature and lack of malignant potential, conservative management is recommended for most patients. If expectant management is chosen, serial exams and/or ultrasounds every 6-12 months may be done to prove lack of progression or rapid growth. Fibroadenomas have defined sonographic characteristics; biopsy is not required to make the diagnosis. A subset of fibroadenomas behave differently and can be distinguished from their routine counterparts by rapidity of growth and excisional biopsy alone. **Juvenile fibroadenomas** (or **giant fibroadenomas**) grow rapidly over 3-6 months to >5 cm and can replace the breast tissue or cause skin necrosis. The distinction between these and **phyllodes tumor** on core needle biopsy is difficult, so excisional biopsy is the recommended intervention. The only true histologic difference between juvenile and routine fibroadenomas is hypercellularity. Surgical excision of fibroadenomas is recommended when a mass has complex ultrasonographic signs, is >5 cm or rapidly growing, or causes anxiety to the patient or their family. The presence of five or more fibroadenomas in an adolescent should prompt a genetic evaluation for *PTEN* pathogenic variant.

Breast cysts are common, often arising from ductal ectasia, glands of Montgomery, or lymphatic malformations. Ultrasound is used for diagnosis and surveillance. Simple cysts are usually self-limited. If a simple cyst persists, it may be aspirated with a needle. Aspirated fluid that is clear may be discarded. Bloody fluid and other aspirated material should be sent for cytologic examination. Cysts that resolve with aspiration should be reevaluated in 3 months by ultrasound. If they recur, biopsy or excision should be considered.

Table 588.3 Breast Masses in the Adolescent Female

Developmental	Unilateral thelarche Macromastia, simple Juvenile hypertrophy or gigantomastia Intramammary lymph node
Infectious	Mastitis Abscess
Traumatic	Fat necrosis Hematoma
Cystic	Fibrocystic change Vascular malformation (hemangioma, lymphatic malformation) Galactocele
Benign tumors	Fibroadenoma (simple or juvenile/giant) Lipoma Hamartoma Intraductal papilloma Juvenile papillomatosis
Malignant tumors	Cystosarcoma phyllodes Breast carcinoma (secretory or ductal) Metastatic disease (lymphoma, neuroblastoma, sarcoma, rhabdomyosarcoma, acute leukemia)

Malignant Masses

Phyllodes tumors are classified as sarcomas and are the most common nonepithelial tumor of the breast. They are classified as benign, borderline, or malignant based on histopathology and are characterized by asymmetric breast enlargement in association with a firm, mobile, circumscribed mass. The tumor often grows rapidly and can become quite large, mimicking a giant or juvenile fibroadenoma. The majority of these tumors have a favorable prognosis, but malignant phyllodes can recur locally or with metastases. Excision with 1 cm margins is the preferred initial therapy in adolescent patients, regardless of the histologic classification of the lesion. Survival at 10 years approaches 90% after complete excision.

Juvenile papillomatosis is a rare proliferative tumor that often presents as a discrete mass. It is a marker for increased breast cancer risk in family members, and in patients with this condition, up to 15% may have a juvenile secretory carcinoma. Treatment of juvenile papillomatosis is total resection of the lesion with preservation of the breast. Family members of these patients should be screened.

Primary breast carcinoma is extremely rare in adolescents. Surveillance Epidemiology and End Results (SEER) data from 2015–2019 established an age-specific rate for female invasive breast cancer of 0.1/100,000 for ages <20 years. Although malignancy is rare, suspicion may be raised if a lesion is enlarging, hard, immobile, and poorly circumscribed. Biopsy of lesions with suspicious imaging findings (e.g., irregular shape or microlobulated/spiculated margins) or progressive growth is imperative. Contrary to adults with primary ductal carcinoma, 10-year survival is only slightly better than 50% in adolescents.

Rather than primary breast cancer, **secondary** cancers or **metastatic** tumors are more prevalent. Adolescents with previous *therapeutic radiation* to the chest or with malignancies with the potential to metastasize to the breast should be monitored more closely for breast masses. Rhabdomyosarcoma is the most common to metastasize to the breast. Other malignancies with risk of breast metastases include neuroblastoma, melanoma, renal cell carcinoma, and Ewing sarcoma. Breast tumors also may be the first manifestation of relapse (extramedullary) in acute lymphoblastic leukemia. Those with previous radiation therapy have increased risk of developing breast cancer at a young age and require careful ongoing surveillance.

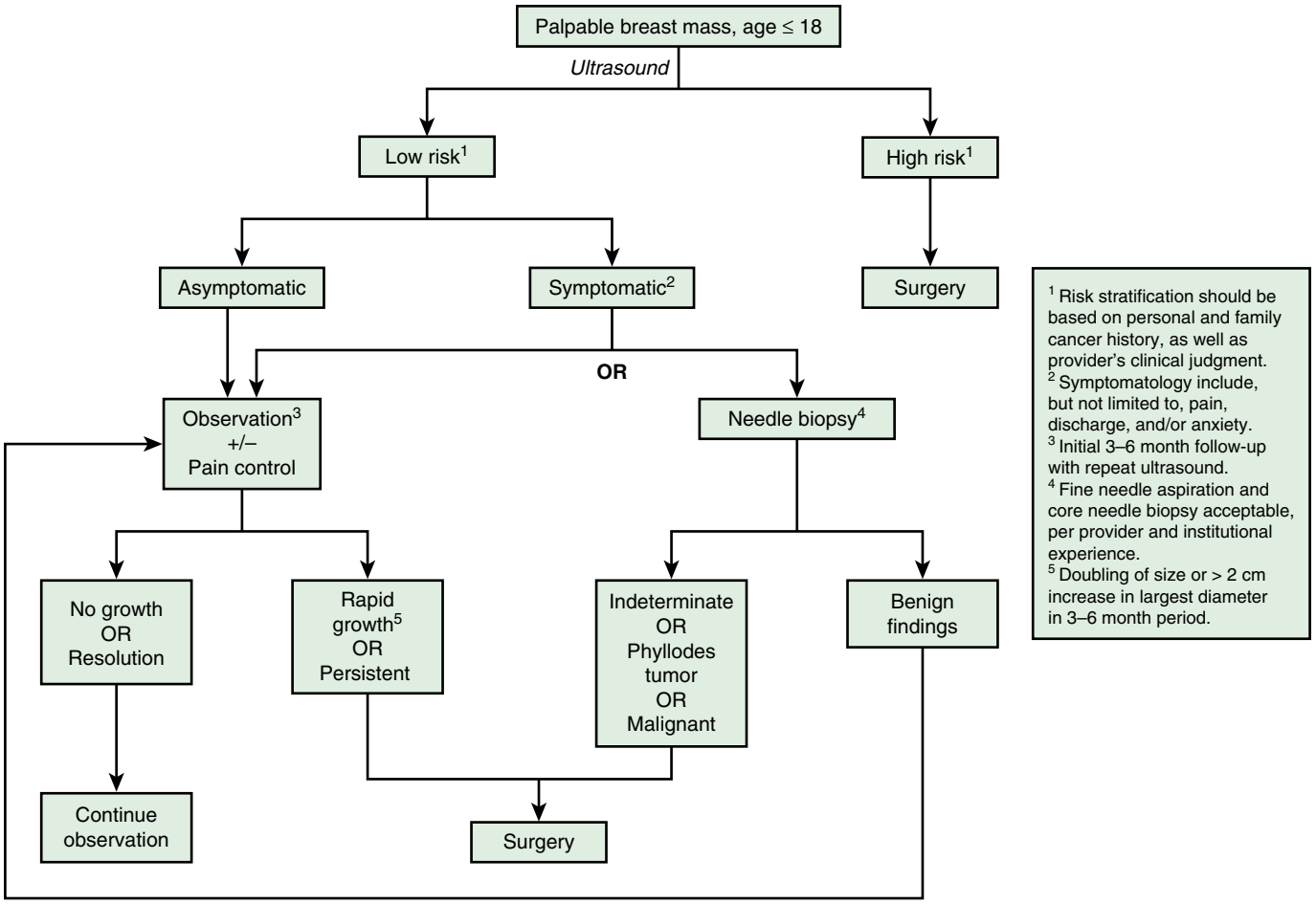

Fig. 588.6 Suggested clinical care algorithm for children presenting with a palpable breast mass. *(From McLaughlin CM, Gonzalez-Hernandez J, Bennett M, Piper HG. Pediatric breast masses: An argument for observation. J Surg Res. 2018;228:247-252; Fig 3.)*

Imaging of Breast Masses

Ultrasonography is the imaging modality of choice for palpable abnormalities in the pediatric and adolescent breast, given the diagnostic specificity and lack of ionizing radiation. MRI may be useful in select disease processes, but its use should be guided by a surgeon or oncologist. Because of the dense breast tissue in this patient population, there is no role for mammography.

MANAGEMENT OF BREAST MASSES

Figure 588.6 represents management algorithms for pediatric patients undergoing imaging for an identified breast mass. Core needle biopsy as a diagnostic tool is very sensitive but lacks specificity in distinguishing the hypercellular stroma of a juvenile fibroadenoma from a phyllodes tumor. Core needle biopsy should be recommended only for indeterminate masses, and based on co-decision-making between the patient, family, and clinician. Generally, observation and ultrasound surveillance should be the initial management for masses under 4 cm in size and excisional biopsy considered for those >4-5 cm.

Recommendations for Daughters of Women with Breast Cancer

Risk Reduction

There are a limited number of things that young people can do to lower their risk of breast cancer. The American Cancer Society recommends regular physical activity, limiting alcohol, eliminating cigarette smoking, and maintaining a healthy weight. Some studies have shown that breastfeeding for at least 1 year may slightly lower the breast cancer risk.

Screening Procedures

Screening mammography and/or ultrasound are not currently recommended in adolescents, regardless of family history. Routine testing of children and adolescents for the *BRCA1* and *BRCA2* pathogenic variants in families with a known history is also not typically recommended, because there are no guidelines for additional screening or treatment at this age, and *children* are very unlikely to develop a cancer related to an inherited *BRCA* variant.

Even in high-risk families, development of breast cancer below the age of 18 years is extremely rare. The American Cancer Society recommends a breast-screening regimen including mammography and MRI beginning at age 30 years for females with a known *BRCA* pathogenic variant or history of chest radiation between the ages of 10 and 30 years. Patients with an identified familial predisposition for malignancy should be referred for genetic evaluation to determine whether and/or when screening tests should occur. Any adolescent patient with a known primary breast malignancy should also be referred to a geneticist to be screened for pathogenic variants such as Li-Fraumeni (p53) or Cowden syndrome (*PTEN*).

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Chapter 589

Polycystic Ovary Syndrome and Hirsutism

Heather G. Huddleston, Molly M. Quinn, and Mark Gibson

POLYCYSTIC OVARY SYNDROME

Etiology and Definition

Polycystic ovary syndrome (PCOS) is a common disorder of reproductive hormone function. The most widely accepted approach to the diagnosis of PCOS in adult females is the Rotterdam criteria, which require two out of three of the following features: **oligomenorrhea**, clinical or biochemical **hyperandrogenism**, and ovaries with a **polycystic morphology** on ultrasound examination (≥20 follicles in one ovary and/or ovarian volume >10 mm^3). Increased levels of antimüllarian hormone may be a marker of ovarian dysfunction and antral follicle count. Alternative criteria, such as the Androgen Excess Society and National Institutes of Health, place a greater emphasis on requiring hyperandrogenism be present (Table 589.1). The disorder, affecting 5–10% of females of reproductive age, depending on the diagnostic criteria used, typically emerges in adolescence when a normal menstrual pattern is not established and there is clinical evidence of androgen excess. Although not part of the *diagnostic* schemes, PCOS is often accompanied by cardiovascular disease risk factors, including insulin resistance, obesity, and dyslipidemia. Depression and anxiety have also been found to be more prevalent in females with PCOS.

Pathology, Pathogenesis, and Genetics

PCOS has a high concordance rate in twins, and in some studies either epigenetic or dominant inheritance patterns are observed. Nonetheless, a consistent hereditary pattern has not been identified.

Gonadotropic dysregulation with increased luteinizing hormone (LH) pulsatility and abnormally high ratios of circulating LH to follicle-stimulating hormone (FSH) are found in many patients with PCOS. Increased *ovarian* production of androgen in response to LH and impaired folliculogenesis owing to lower FSH are attributed to this gonadotropic pattern (Fig. 589.1). An increased ratio of circulating levels of LH:FSH is *not* a diagnostic criterion for PCOS.

Alterations in activities of steroidogenic enzymes that would explain *ovarian androgenic* hyperfunction are seen in PCOS subjects, but they are not consistently present in all patients, and it is unclear whether these alterations are a cause of PCOS or are a consequence of ovarian dysregulation. The size of ovarian stromal cells responsible for androgen production is increased; surgery that reduces this ovarian component (ovarian wedge resection or laparoscopic ablative procedures) reduces circulating androgen levels and often restores ovarian cyclicity. Patients with hyperandrogenic congenital or adult-onset adrenal hyperplasia exhibit PCOS-like ovarian dysfunction that can be reversed by reducing the *adrenal-derived* androgens with glucocorticoid therapy. A primary role for androgen excess in the pathophysiology of all instances of PCOS seems unlikely; many patients have minimal hyperandrogenism, and elimination of androgen excess (with gonadotropin-releasing hormone agonists) does not affect associated insulin resistance.

Measures of **insulin resistance** are greater and more prevalent among females with PCOS than controls even when accounting for body mass index (BMI). Insulin enhances ovarian androgen production directly and contributes to elevation of free testosterone levels through its suppression of hepatic production of sex steroid–binding globulin. Treatment with insulin sensitivity–enhancing agents that can reduce insulin levels is associated with modest reductions in measures of androgen excess and, in some patients, restoration of regular ovulation. The association of insulin resistance with weight might explain the appearance of features of PCOS among some females who gain weight, as well as the resolution of PCOS among affected females who lose weight.

Clinical Manifestations

PCOS, a lifelong disorder, commonly manifests as puberty progresses, but its onset can occur later, in young adulthood. Clinical hallmarks are menstrual abnormalities and manifestations of hyperandrogenism, but the severity of the disorder is variable (Table 589.2). Ovulation is typically irregular or absent, and menses are consequently irregular or absent. When menstrual bleeding does occur, it may be *anovulatory* bleeding, which is often heavy and/or protracted, resulting from an extended period of unopposed endometrial growth. Alternatively, bleeding can be relatively normal in character as a consequence of a preceding ovulation. Protracted spells of anovulation, with accompanying unopposed estrogen, are a risk factor for endometrial hyperplasia, and more severe premalignant and frankly malignant changes may eventuate. Hyperandrogenism is most commonly manifest as **hirsutism**, which is graded by the extent and locations of excessive male pattern hair growth (Fig. 589.2).

Obesity is common among individuals with PCOS. In some patients, the expression of features of PCOS is conditional on elevation of BMI and is reversible with weight loss. However, there is a subset of patients who present with a lean PCOS phenotype, and thus normal or low weight should not preclude consideration of the PCOS diagnosis. PCOS is associated with an increased prevalence of insulin resistance and type 2 diabetes independent of the tendency for many affected patients to have an elevated BMI. Additionally, PCOS confers a substantial and specific increase in risk for **metabolic syndrome** (hyperlipidemia, insulin resistance, type 2 diabetes) in adults as well as adolescent females after accounting for BMI.

Laboratory Findings, Diagnosis, and Differential Diagnosis

The diagnosis of PCOS requires exclusion of disorders that would otherwise account for hyperandrogenism and anovulation. Serum 17-hydroxyprogesterone should be measured when there is clear androgen excess to screen for adult-onset 21-hydroxylase deficiency (see Chapter 616). In the adolescent with amenorrhea but minimal hyperandrogenic findings, consideration should be given to functional hypothalamic suppression as a result of excessive exercise and/or dieting, and a careful history taken to rule out such behavioral patterns. All patients should be clinically evaluated for Cushing syndrome, and biochemical evaluation is indicated when clinical findings, including

Table 589.1 Diagnostic Criteria for Polycystic Ovary Syndrome in Adult Females*

NATIONAL INSTITUTES OF HEALTH CRITERIA	ROTTERDAM CRITERIA**	ANDROGEN EXCESS SOCIETY
Oligoovulation or anovulation *and* Clinical or biochemical hyperandrogenism	Two of three of the following: • Oligoovulation or anovulation • Polycystic ovaries on ultrasonography (20 or more follicles in a single ovary or ovarian volume of > 10 mm^3 in one ovary) • Clinical and/or biochemical hyperandrogenism	Clinical or biochemical hyperandrogenism and at least one of the following: • Polycystic ovaries *or* • Oligoovulation or anovulation

**In adolescents, diagnosis should be made when both hyperandrogenism and oligomenorrhea are present, with ultrasound criteria not required/recommended.

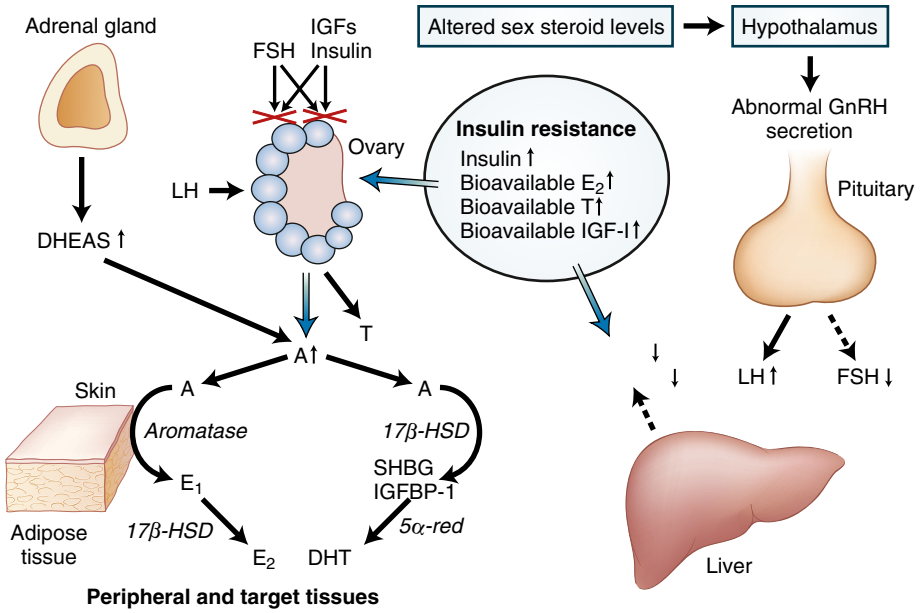

Fig. 589.1 Pathologic mechanisms in polycystic ovary syndrome (PCOS). A deficient in vivo response of the ovarian follicle to physiologic quantities of follicle-stimulating hormone (FSH), possibly because of an impaired interaction between signaling pathways associated with FSH and insulin-like growth factors (IGFs) or insulin, may be an important defect responsible for anovulation in PCOS. Insulin resistance associated with increased circulating and tissue levels of insulin and bioavailable estradiol (E_2), testosterone (T), and IGF-I gives rise to abnormal hormone production in a number of tissues. Oversecretion of luteinizing hormone (LH) and decreased output of FSH by the pituitary, decreased production of sex hormone–binding globulin (SHBG) and IGF-binding protein 1 (IGFBP-1) in the liver, increased adrenal secretion of dehydroepiandrosterone sulfate (DHEAS), and increased ovarian secretion of androstenedione (A) all contribute to the feed-forward cycle that maintains anovulation and androgen excess in PCOS. Excessive amounts of E_2 and T arise primarily from the conversion of A in peripheral and target tissues. T is converted to the potent steroids estradiol or DHT (dihydrotestosterone). Reductive 17β-hydroxysteroid dehydrogenase (17β-HSD) enzyme activity may be conferred by protein products of several genes with overlapping functions; 5α-reductase (5α-red) is encoded by at least two genes, and aromatase is encoded by a single gene. GnRH, Gonadotropin-releasing hormone. *(From Bulun SE. Physiology and pathology of the female reproductive axis. In Melmed S, Auchus RJ, Goldfine AB, eds. Williams Textbook of Endocrinology, 14th ed. Philadelphia: Elsevier, 2020. Fig 17-30.)*

Table 589.2 Phenotypes for Polycystic Ovary Syndrome Based on 2003 Rotterdam Criteria

SIGNS, RISKS, AND PREVALENCE	SEVERE PCOS	HYPERANDROGENISM AND CHRONIC ANOVULATION	OVULATORY PCOS	MILD PCOS
Periods	Irregular	Irregular	Normal	Irregular
Ovaries on ultrasonography	Polycystic	Normal	Polycystic	Polycystic
Androgen concentrations	High	High	High	Mildly raised
Insulin concentrations	Increased	Increased	Increased	Normal
Risks	Potential long term	Potential long term	Unknown	Unknown
Prevalence in affected females	61%	7%	16%	16%

PCOS, Polycystic ovary syndrome.
From Norman RJ, Dewailly D, Legro RS, Hickey TE. Polycystic ovary syndrome. *Lancet.* 2007;370(9588):685-697.

hypertension and/or characteristic exam features, are suggestive (see Chapter 619). The two disorders have in common a tendency for overweight and varying degrees of insulin resistance and androgen excess, but they differ in that Cushing syndrome demonstrates muscle wasting as a result of catabolism.

Evidence for androgen excess that is *rapid in onset and/or severe,* especially if masculinizing, warrants measurement of androgens (total testosterone, dehydroepiandrosterone [DHEAS]) to exclude the possibility of an androgen-secreting adrenal or ovarian tumor. The laboratory evaluation is completed with the exclusion of hyperprolactinemia, premature ovarian failure, and thyroid disease as causes of anovulation by measurement of prolactin, FSH, and thyroid-stimulating hormone, respectively.

The diagnosis of PCOS in reproductively mature females (at 8 years post menarche) is confirmed by the constellation of oligoovulation or anovulation, androgen excess (clinically or with biochemical confirmation), and typical ovarian morphology on ultrasound. Various experts weigh these three features differently and do not, as a rule, require the presence of all (see Table 589.1). Antimüllarian hormone levels are elevated in PCOS and may be a marker for ovarian dysfunction and cyst formation. Other recommendations have clarified that ultrasound features need not be assessed in adolescents, because normative values for ovarian anatomy have not been established. Indeed, young females often exhibit the multifollicular ovaries without any evidence of hyperandrogenism or oligomenorrhea, and not all patients with PCOS by the criteria of hyperandrogenism and ovulatory disruption exhibit ovarian changes typical of PCOS. *Therefore in the adolescent, diagnosis should only be made when both oligomenorrhea and hyperandrogenism are present and other causes of these symptoms have been ruled out.* Findings of anovulatory cycles and hyperandrogenism, particularly acne, may accompany the normal pubertal transition.

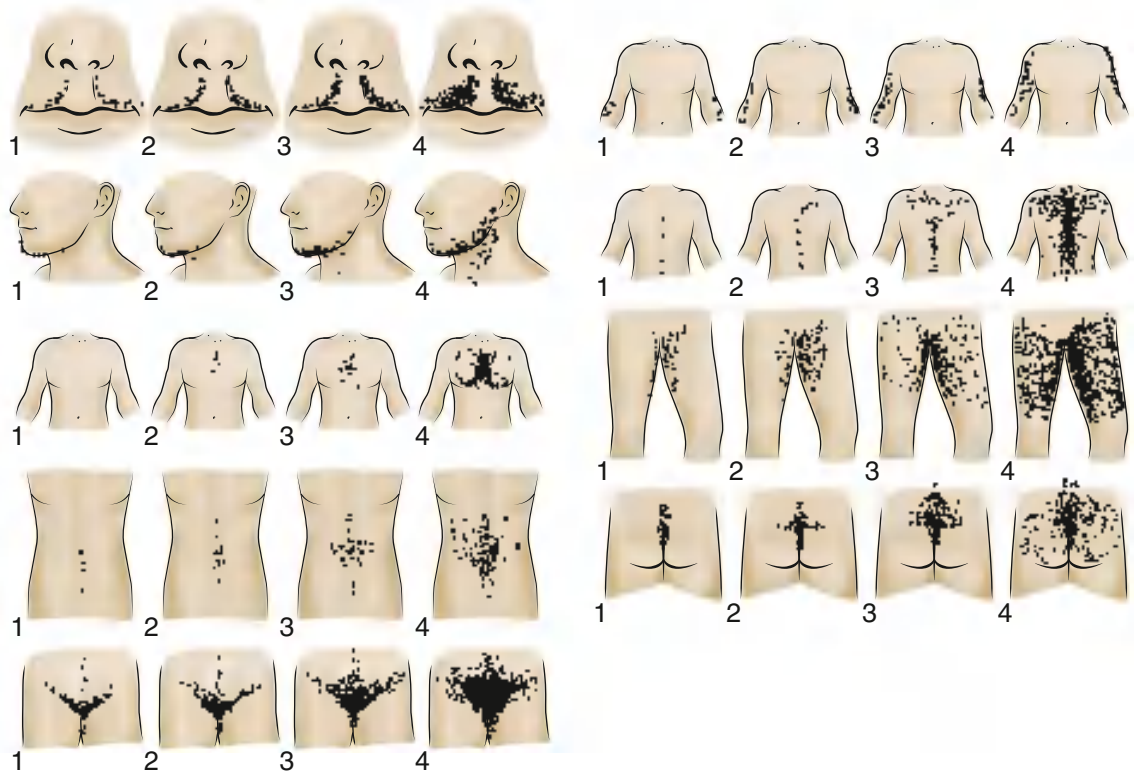

Fig. 589.2 Gender-neutral modified Ferriman-Gallwey (mFG) diagram. *(From Grimstad F, Moyer Q, Williams CR, Kremen J. A body-neutral and gender-neutral modified Ferriman-Gallwey diagram. J Pediatr Adolesc Gynecol. 2021;S1083-318800334-X. Fig 2.)*

For this reason, it is recommended that a formal PCOS diagnosis not be considered until at least 2 years post menarche. Adolescents with features of PCOS before this time can be considered "at risk" for PCOS, and a plan can be made for reevaluation in the future.

Insulin resistance is common among females with PCOS, and although not requisite for diagnosis, it should be considered when PCOS is identified. Adults, as well as adolescents, with hyperandrogenemia and anovulation should be evaluated for diabetes or impaired glucose tolerance with a 2-hour (75-g glucose load) glucose tolerance test.

Complications and Long-Term Outlook

Management of the features of hyperandrogenism, assistance with fertility, prevention of endometrial cancer, and reduction in the likelihood and severity of the common accompanying risk for the metabolic syndromes are long-term tasks for the PCOS patient and their healthcare providers (Table 589.3). Although there is a tendency for symptoms to ameliorate as menopause approaches, PCOS usually requires management throughout the reproductive years. Young patients should be counseled that modern fertility management allows most affected females to have children without great difficulty, and they should also know that the disorder does not confer reliable protection from unintended pregnancy. Endometrial cancer can develop as early as the third decade in females with PCOS who are not managed with progestins or ovulation induction; thus patients should understand the importance of long-term strategies for endometrial protection. Impaired glucose tolerance, type 2 diabetes, and metabolic syndrome are more common in females with PCOS compared to weight-matched controls. Metabolic disturbance can manifest as early as adolescence, and the prevalence increases over time. Weight control through diet and lifestyle measures, detection and management of impaired glucose tolerance and diabetes, and management of abnormal lipids are targets for long-term management.

Table 589.3 Lifelong Health Complications of Polycystic Ovary Syndrome

PRENATAL OR CHILDHOOD	ADOLESCENCE, REPRODUCTIVE YEARS	POST-MENOPAUSAL
REPRODUCTIVE		
Premature adrenarche Early menarche	Menstrual irregularity Hirsutism Acne Infertility Endometrial cancer Miscarriage Pregnancy complications	Delayed menopause
METABOLIC		
Abnormal fetal growth	Obesity Impaired glucose tolerance Insulin resistance Dyslipidemia Type 2 diabetes	Obesity Impaired glucose tolerance Insulin resistance Dyslipidemia Type 2 diabetes
OTHER		
	Sleep apnea Fatty liver Depression	Cardiovascular disease risk factors

From Norman RJ, Dewailly D, Legro RS, Hickey TE. Polycystic ovary syndrome. *Lancet.* 2007;370(9588):685-697.

Treatment

The management of PCOS is multifaceted and depends on the specific complaints of the patient. Primary goals include management of menstrual abnormalities, treatment of symptoms of androgen excess, and optimization of metabolic health. Weight loss through lifestyle

change, use of hormonal contraceptive agents for menstrual regulation as well as androgen suppression, antiandrogens as adjuncts for hirsutism treatment, and insulin-sensitizing agents are common components of treatment.

Lifestyle Changes

Comprehensive lifestyle programs for overweight and obese adults with PCOS aimed at fitness and weight loss can yield restoration of normal menstrual function in some patients. Lifestyle changes also lead to a reduction in the free androgen index, reduction in measures of insulin resistance, and improvement in serum lipids. Limited data show similar benefits from such interventions for obese adolescents with PCOS. Successful weight loss programs for adolescents with PCOS using both psychologic and nutritional counseling may result in improved menstrual function.

Hormonal Contraceptives

Combined (estrogen and progestin) hormonal contraceptive medications are considered first-line therapy for patients not desiring fertility (see Chapter 160). Avoidance of hyperplastic endometrial states resulting from unopposed estrogen and management of abnormal uterine bleeding in anovulatory episodes can be accomplished with the use of combined hormonal contraceptives. The progestational component inhibits endometrial proliferation, and the schedule of pill administration predictably regulates menstrual bleeding. The estrogenic component of the combined oral contraceptive elevates circulating sex hormone–binding globulin (SHBG), which reduces free and bioavailable testosterone levels. Both of the hormonal elements in oral contraceptives combine to suppress gonadotropic (particularly LH) stimulation of ovarian androgen production. DHEAS levels, often contributory to hyperandrogenemia in PCOS, are usually decreased by combined contraceptive use. Products with less androgenic progestational components (drospirenone, desogestrel) may provide better relief from androgenic symptoms.

Using hormonal contraception that is well tolerated in long-term use is more important than using a product with a particular progestational component. Products with reduced frequency and duration of pill-free intervals can provide superior androgen suppression and a welcome decrease in the frequency of bleeding episodes. Depot medroxyprogesterone acetate for contraception, endometrial protection, and androgen suppression may be a suitable alternative to combined hormonal contraceptives; it provides even more profound suppression of ovarian androgen production, but it does not elevate SHBG. Low-dose progestin-only regimens (oral minipills, implantable progestational contraceptives, and progestin-releasing intrauterine devices) also provide effective endometrial protection but would be expected to provide only partial and/or inconsistent androgen suppression and would not elevate SHBG.

Patients without the need for management of hyperandrogenic symptoms or contraception are often treated with periodic use of oral progestins to induce predictable menstrual bleeding and prevent endometrial hyperplasia and malignancy. Twelve-day courses of medroxyprogesterone acetate 10 mg daily or norethindrone acetate 5 mg daily are effective and safe for this purpose when taken every 1-2 months.

Oral contraceptives also provide the added benefit of contraception. Given the relative infrequency of ovulation, fertility in females with PCOS would be expected to be reduced relative to that of their peers, but they are still at risk for pregnancy and should be counseled accordingly.

Metformin

Metformin is a biguanide medication used to treat type 2 diabetes, which is its only FDA-approved indication. It has been used in a variety of settings and with differing objectives for patients with PCOS. Metformin exerts its principal effect by reducing hepatic production of glucose and limiting intestinal absorption of glucose. A subset of females with PCOS resume regular ovulation and menses when treated with metformin, obviating the need for progestational therapy to protect endometrial health or medications to induce ovulation. For some patients, the resulting normal reproductive function is appealing regardless of interest in fertility.

Metformin reduces insulin resistance and the levels of androgens. Its extended use can reduce the likelihood of development of impaired glucose tolerance or the progression of impaired glucose tolerance to type 2 diabetes; these effects are not yet proven for patients with PCOS. It should not be used in the presence of renal or hepatic impairment. Typical dosing is 1,500-2,000 mg/day, achieved through gradual increments because gastrointestinal intolerance is common. Long-acting preparations are helpful when gastrointestinal intolerance is a problem. The use of metformin in the treatment of PCOS depends on the patient's goals and preference. For the treatment of hyperandrogenic symptoms, metformin effects may be modest compared with other available agents. There are no empirical data supporting the theoretical benefits of long-term use of metformin in adolescents with PCOS and obesity compared with the outcomes achieved with weight loss and oral contraceptive medications. Use of metformin as a first-line agent is favored by some experts, in part for improvement in serum measures of intermediate outcomes, and in part because of evidence in other populations of reduced progression of insulin resistance. There is no evidence for a long-term benefit for clinical outcomes of adding metformin to treatment for patients managed primarily with oral contraceptives. For adolescents receiving metformin as a first-line medication, some element of progestational management (combined contraceptives or periodic progestins) will still be necessary for those not resuming ovulatory function, and oral contraceptives may still be an important adjunct for management of clinical hyperandrogenism and/or contraception. Metformin side effects include nausea, emesis, and diarrhea; more serious effects include lactic acidosis and vitamin B12 deficiency. Glucagon-like peptide receptor agonists are being studied as a possible add on therapy to metformin or as a single agent to treat PCOS.

Antiandrogens

Antiandrogenic medications may be added to other therapies or used alone for the treatment of hirsutism. These agents are usually used adjunctively with ovarian hormonal suppression, in part because of better reduction in hirsutism when antiandrogens are combined with ovarian suppression but also to reduce the risk of unintended embryonic or fetal exposure. The highly active androgen antagonist and progestin, cyproterone, is available in Europe and in Canada as a single agent for treatment of hirsutism or in combination with ethinyl estradiol as an oral contraceptive with enhanced antiandrogenic profile. In the United States, spironolactone is the most commonly used antiandrogen. Spironolactone antagonizes androgens at their receptor and also impairs androgen synthesis. Doses of 100-200 mg daily are commonly used. Other agents that have been studied are finasteride, a 5α-reductase inhibitor, and flutamide, a nonsteroidal and highly specific androgen receptor antagonist. These are rarely used because of lack of evidence of superior effectiveness, cost, and, in the case of flutamide, the potential for hepatotoxicity.

HIRSUTISM

Hirsutism is defined as abnormally increased terminal (mature, heavy, dark) hair growth in areas of the body where hair growth is normally androgen dependent (see Chapter 703). Its presence is a result of the combination of the extent of androgenic stimulation and familial regional follicle sensitivity to androgens, which varies considerably among ethnic groups. Patients' cosmetic concerns generally determine whether findings of hirsutism are a matter for clinical investigation and treatment. Hirsutism as an isolated finding is to be distinguished from **masculinization.** The latter includes alteration in muscle mass, clitoral enlargement, and voice change, generally manifesting as a rapid

Table 589.4 Treatment of Hirsutism

SYSTEMIC THERAPIES
Suppression of androgen production
Combined oral contraceptives (ethinyl estradiol + progestin with low androgenic activity)
Androgen blockers
Spironolactone
Finasteride
Flutamide
Cyproterone acetate (not available in the United States)
COSMETIC STRATEGIES
Temporary measures
Shaving, bleaching, chemical depilation
Permanent measures
Electrolysis
Laser therapy

evolution (over months). *Masculinization mandates a search for a neoplastic source of androgen.* Elevations of testosterone or DHEAS commonly indicate an ovarian or adrenal androgen source, respectively; specific imaging and occasionally selective catheterization studies are indicated (see Chapters 590 and 617).

Hirsutism without masculinization is common. The potential causes to consider are PCOS (when there is hyperandrogenism and anovulation), benign functional androgen excess (measurable hyperandrogenism without anovulation), idiopathic hirsutism (increased hair in androgen-dependent areas without measurable androgen excess), and adult-onset adrenal hyperplasia. Patients can be primarily distinguished by evidence of an ovulatory disorder by menstrual history, and for those with absent or irregular menses, a diagnosis of PCOS can be made. The remainder, for whom adult-onset adrenal hyperplasia and PCOS have been excluded, either have normal androgen levels with enhanced end-organ sensitivity owing to familial or ethnic predisposition or have a functional and benign overproduction of ovarian androgens. Measures of androgens (testosterone, DHEAS) may be normal or mildly elevated in the latter group. Testosterone suppresses circulating sex-steroid binding globulin, so states of testosterone overproduction might not be accompanied by elevated measures of total testosterone, although estimates of "free" or "bioavailable" testosterone reveal hyperandrogenism. Measures of unbound testosterone distinguish idiopathic hirsutism from mild benign hyperandrogenic states; making this distinction contributes little to patient management and adds cost. Idiopathic hirsutism (without evidence of androgen excess) usually responds to antiandrogen or androgen suppression therapy similarly to hirsutism associated with elevated androgens and anovulation (PCOS) and benign hyperandrogenism not associated with PCOS.

If hirsutism is present, and clinical evaluation excludes neoplasm, adult-onset adrenal hyperplasia, and Cushing syndrome, then management for symptoms of hyperandrogenism (regardless of whether measures of circulating androgens are elevated or not) can proceed as for patients with PCOS (Table 589.4). Estrogen and progestin suppression of ovarian function, with or without added antiandrogen treatment, is the mainstay of therapy for these patients. Androgen suppression and/or antagonism results in gradual regression of the size and productivity of follicles in androgen-sensitive areas of the face and body, and these changes will evolve over successive and months-long generations of hair growth and shedding. Patients should therefore be advised that the effects of medical therapy accrue slowly, over many months.

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Chapter 590

Gynecologic Neoplasms and Prevention Methods for Human Papillomavirus Infections in Adolescents

Joan R. Tymon-Rosario, Levent Mutlu, and Alla Vash-Margita

OVERVIEW OF GYNECOLOGIC MALIGNANCIES IN CHILDREN AND ADOLESCENTS

Cancer is the second most common cause of death in children and adolescents, surpassed only by childhood injuries. The highest death rate is in the 5- to 14-year-old age group. Although rare, gynecologic malignancies can result in long-term sequelae such as infertility, depression, and a poor self-image, which may cause significant morbidity.

In children and adolescents younger than 18 years, ovarian cancer accounts for 87.5% of gynecologic malignancies, vaginal cancer for 4.5%, cervical cancer for 3.9%, uterine cancer for 2.5%, and vulvar cancer comprises 1.6% of all gynecologic cancers.

Ovarian cancers usually manifest as an abdominal or pelvic mass with acute or chronic lower abdominal pain and/or menstrual irregularities. The diagnostic workup includes a physical exam and laboratory tests such as a urine pregnancy test, hormone levels, and tumor markers. The preferred initial method of imaging is transabdominal pelvic ultrasonography. The differential diagnosis includes gynecologic tumors, other abdominal and pelvic organ-based tumors, and functional, physiologic, inflammatory/infectious, or pregnancy-related ovarian pathology. Although the majority of ovarian neoplasms are benign, approximately 9–33% of all pediatric or adolescent ovarian neoplasms are malignant. Ovarian neoplasms constitute 1.3% of all childhood malignancies but account for 60–70% of all gynecologic malignancies in this age group. Germ cell tumors are the most common type of neoplasm. Less often, the vagina or cervix is a site of malignant lesions in children, with a few specific tumors having their greatest incidence in this population. Vulvar and endometrial malignancies in children and adolescents are exceedingly rare.

IMPACT OF CANCER THERAPY ON FERTILITY

The treatment of gynecologic cancer, depending on the type and extent of disease, may include fertility-sparing cytoreductive surgery with adjuvant chemotherapy, definitive surgery including bilateral salpingo-oophorectomy, and comprehensive surgical staging, radiation, and/or secondary salvage surgery. Fertility-sparing surgery is defined as unilateral salpingo-oophorectomy, lymph node sampling, and omentectomy, whereas maximal cytoreduction includes hysterectomy and contralateral salpingo-oophorectomy. For malignant ovarian germ cell tumors, the most common adolescent gynecologic malignancy, the use of fertility-sparing surgery, is seen as the gold standard. This approach achieves a good prognosis, and the majority of patients achieve normal hormonal function and future pregnancies. Importantly, it does not seem to be associated with lower progression-free survival, overall survival, or mortality rates compared with radical surgery.

Platinum-based chemotherapeutic regimens are most often used for malignant ovarian tumors. The need for chemotherapy and radiation therapy is associated with acute ovarian failure, premature menopause, and infertility (Table 590.1). Risk factors include older age, abdominal or spinal radiation, and certain chemotherapeutic drugs, such as

Table 590.1 Effect of Cancer Treatment on the Development of Amenorrhea

TREATMENT	AGENT/MODALITY	IMPACT	TREATMENT FOR
Protocols containing nonalkylating agents or lower levels of alkylating agents	ABVD, CHOP, COP, multiagent therapies for leukemia	LOWER RISK <20% of women develop amenorrhea posttreatment	Non-Hodgkin lymphoma Leukemia
Protocols containing	Multiagent therapies using vincristine	VERY LOW/NO RISK No effect on menses	Leukemia Lymphomas
Protocols containing	Procarbazine MOPP and BEACOPP 3 cycles >6 cycles	HIGH RISK More than 80% develop amenorrhea posttreatment	Hodgkin lymphoma
Protocols containing	Temozolomide or BCNU + cranial radiation	HIGH RISK More than 80% develop amenorrhea posttreatment	Brain tumor
Abdominal or pelvic radiation	10-15 Gy in prepubertal females 5-10 Gy in postpubertal females	INTERMEDIATE RISK 30–70% of women develop amenorrhea posttreatment	Acute lymphoblastic leukemia Brain tumor Neuroblastoma Non-Hodgkin lymphoma Hodgkin lymphoma Spinal tumor Wilms tumor
Whole abdominal or pelvic radiation	>15 Gy in prepubertal females >10 Gy in postpubertal females >6 Gy in adult women	HIGH RISK More than 80% develop amenorrhea posttreatment	
Total cyclophosphamide	5 g/m^2 in women >30 yr 7.5 g/m^2 in women and females <20 yr	HIGH RISK More than 80% develop amenorrhea posttreatment	Non-Hodgkin lymphoma
Any alkylating agent + pelvic radiation	Busulfan, carmustine, cyclophosphamide, ifosfamide, lomustine, melphalan, procarbazine	HIGH RISK More than 80% develop amenorrhea posttreatment	Ovarian cancer Sarcoma
Any alkylating agent + total body irradiation	Busulfan, carmustine, cyclophosphamide, ifosfamide, lomustine, melphalan, procarbazine	HIGH RISK More than 80% develop amenorrhea posttreatment	Lymphomas Myelomas Choriocarcinoma Ewing sarcoma, neuroblastoma
Any cancer requiring bone marrow transplant/stem cell transplant		HIGH RISK More than 80% develop amenorrhea posttreatment	Hodgkin lymphoma Non-Hodgkin lymphoma Acute myeloid leukemia Chronic myeloid leukemia Myeloma Acute lymphoid lymphoma Chronic lymphoid lymphoma Some solid tumors (e.g., breast, ovarian, kidney, brain)

ABVD, Doxorubicin, bleomycin, vinblastine, dacarbazine; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; COP, cyclophosphamide, vincristine, prednisone; MOPP, mechlorethamine, vincristine, prednisone, procarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; BCNU, carmustine; Gy, gray.

Adapted from Female Fertility Preservation LIVESTRONG, a registered trademark of the LIVESTRONG Foundation. https://www.livestrong.org/we-can-help/just-diagnosed/female-fertility-preservation.

alkylating and platinum-based agents (cisplatin, cyclophosphamide, busulfan). Uterine irradiation is associated with infertility, spontaneous pregnancy loss, and intrauterine growth restriction. The vagina, bladder, ureters, urethra, and rectum can also be injured by radiation. Vaginal shortening, vaginal stenosis, urinary tract fistulas, and diarrhea are potential side effects of pelvic irradiation.

Advancements in oncologic treatments of gynecologic and systemic tumors have led to improvements in childhood cancer survival rates. Unfortunately, with these advances come an increase in short- and long-term adverse effects, which include gonadotoxicity and infertility. Approximately 15% of *all* childhood cancer survivors experience infertility, and pregnancy outcomes appear to be influenced by prior chemotherapy and radiation treatment (see Chapter 543). Cancer survivors have an increased rate of spontaneous abortion, premature delivery, and low birthweight infants compared with their healthy siblings. No data support an increased incidence of congenital malformations in offspring. Individualized risk of infertility should be discussed before gonadotoxic therapies and options for fertility preservation should be made available to all patients, with referrals to reproductive specialists and mental health professionals as appropriate. Multiple recommendations specifically address the pediatric population, stating that parents/guardians should be allowed to act for and consent in the interest of their minor children.

Mature oocyte and embryo cryopreservation are both standard of care preservation options available to postpubertal females with ample time before treatment to allow for ovarian stimulation (2-6 weeks). Ovarian tissue cryopreservation (OTC) is the only available option for prepubertal females. OTC is also an option for fertility preservation for postpubertal females with time-limiting treatment plans. The safety and feasibility of OTC and transplantation after nonsterilizing chemotherapy and in select leukemia survivors have been favorable, and there have been over 130 live births reported after orthotopic transplantation

of previously cryopreserved and thawed ovarian tissue as of 2017. Laparoscopic ovarian transposition can be used before radiation therapy where a high risk of ovarian radiation exposure in its anatomic position is expected. Hormone suppression with gonadotropin-releasing hormone (GnRH) analogs has been investigated as a means of fertility preservation, but evidence is lacking as to its efficacy.

Gonadotoxicity can also lead to primary ovarian insufficiency, which is associated with an increased risk for cardiovascular complications, osteoporosis, and difficulties with sexual function. Risks and benefits of hormone replacement therapy should be addressed as appropriate.

NEONATAL AND PEDIATRIC OVARIAN CYSTS

Normal follicles or physiologic ovarian cysts can be seen by ultrasound examination of the ovaries in healthy neonates, infants, and prepubertal females. The true incidence of neonatal cysts is unknown, but most are physiologic. Ovarian cysts are often detected during prenatal imaging and should be differentiated from masses originating from the urinary or gastrointestinal (GI) tract. Ovarian cysts that are less than 2 cm, sonolucent, and have a simple appearance on ultrasound are most likely physiologic. Simple neonatal ovarian cysts will resolve spontaneously and should be followed with observation. Larger cysts may be seen; in these cases, the interval to complete resolution is usually longer. Because of the risk of **ovarian torsion** and resultant autoamputation of the ovary, treatment modalities have been developed to prevent ovarian torsion, including ultrasound-guided aspiration, laparoscopic cystectomy, and detorsion, with the goal of ovarian preservation. Oophorectomy should be avoided. Treatment is usually reserved for the postnatal period unless the cyst is large enough to prevent embryonic development. Similarly, intervention might be necessary if the cyst is large enough to complicate delivery or if there is concern for compromise of the other organs because of the mass effect. If a conservative approach is chosen, serial ultrasonographic evaluation is reasonable until resolution in the prenatal and neonatal period. In the neonatal period, aspiration is an option for cysts that are larger than 6 cm and persistent over 4 months. Surgical exploration is generally reserved for complex, symptomatic, or enlarging cysts, with a great deal of effort exerted to preserve the surrounding normal ovary.

In **prepubertal** children, ovarian cysts are rare and, if present, usually asymptomatic and hormonally inactive. However, a careful exam is indicated because prepubertal ovarian cysts may be associated with peripheral precocious puberty. If symptomatic, cysts might present as an abdomino-pelvic mass resulting in pain, constipation, or urinary frequency. In **adolescents**, ovarian cysts are common and usually represent normal follicular development.

Cysts that are simple appearing, without septations or internal echogenicity, and less than 10 cm on transabdominal ultrasound are almost always benign, and observation is preferred (Fig. 590.1). Careful counseling and patient education should be provided for early recognition of complications related to ovarian cysts, such as cyst rupture and ovarian torsion. Unless associated with intractable symptoms or intraabdominal bleeding because of cyst rupture, cysts can be managed conservatively. Large ovarian cysts pose a risk of ovarian torsion. *Ovarian torsion* is a surgical emergency and can happen with ovarian cysts of any size, although the risk increases in adnexal masses larger than 5 cm. Rarely, torsion of the adnexa can occur without presence of an ovarian cyst, which is more common in prepubertal patients.

Functional Cysts

Over the course of several menstrual cycles, a **dominant follicle** forms and increases in size. After ovulation, the dominant follicle becomes a corpus luteum that, if it bleeds, is termed a **hemorrhagic corpus luteum**. These can become symptomatic owing to size or peritoneal irritation, and they have a characteristic complex appearance on ultrasound. Expectant and symptomatic management for a presumed functional or hemorrhagic cyst is appropriate. Physiologic cysts are usually ≤5 cm and resolve over the course of 6-8 weeks or several menstrual cycles without the need for any intervention. Monophasic oral contraceptives can be used to suppress future follicular development and prevent formation of additional cysts. When a cyst is found on ultrasound, a pregnancy test should be obtained because an adnexal mass on imaging could represent either a corpus luteum cyst that physiologically supports a normal pregnancy or an abnormal pregnancy state such as an ectopic pregnancy in the adnexa.

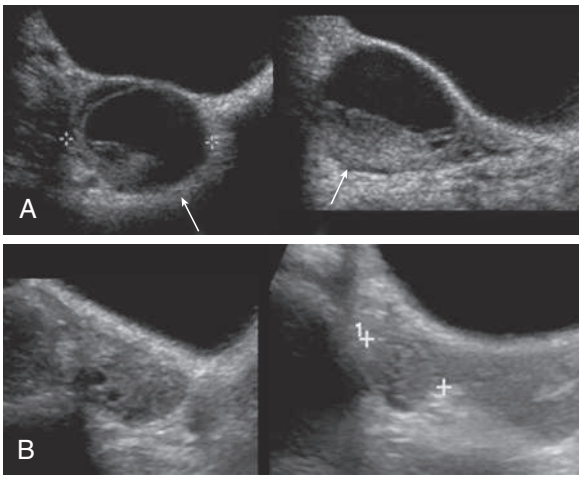

Fig. 590.1 Ovarian cyst. 14-yr-old female with pelvic pain. **A,** Transverse and sagittal images from a transabdominal pelvic ultrasound demonstrate a well-circumscribed cystic lesion in the right adnexa with a fluid–debris level *(arrows).* **B,** Follow-up imaging 6 weeks later demonstrates complete resolution of the cyst. *(From Walters MM, Robertson RL. Pediatric Radiology: The Requisites, 4th ed. Philadelphia: Elsevier, 2017:186; Fig. 6.70.)*

OVARIAN NEOPLASMS

Teratomas

Ovarian teratomas are the most common pediatric ovarian neoplasm and account for 25% of all pediatric teratomas. Aberrant migration and differentiation of primordial germ cells from the yolk sac to the gonadal ridge during embryogenesis is considered to be the embryologic origin of teratomas. Ovarian teratomas are usually asymptomatic but may become quite large and present with abdomino-pelvic pain and a palpable mass; ovarian torsion may be the initial presenting symptom. Ovarian teratomas are usually unilateral, but about 10% of cases are bilateral. **Mature cystic teratomas** (**dermoid cysts**) account for more than 95% of all teratomas. Depending on the germ layers, teratomas can be polydermal or monodermal and may contain mature tissue of ectodermal (skin, hair, sebaceous glands, neuroectodermal tissue), mesodermal (muscle, bone, cartilage, fat, teeth), and/or endodermal (thyroid, salivary, respiratory, GI) origin (Fig. 590.2). Mature teratomas are usually benign; malignant transformation is reported in less than 2% of the cases. Although any of the components of the mature teratoma can undergo malignant transformation, the most common secondary neoplasm arising from mature teratoma is squamous cell carcinoma. Teratomas have a characteristic sonographic appearance that includes findings such as fluid-fluid levels, Rokitansky nodules (a solid protuberance projecting from an ovarian cyst), echogenic sebaceous material, calcification, and hyperechoic regions. On abdominal radiograph, calcification is often a hallmark for teratomas. Ultrasound has a high sensitivity and specificity for diagnosing dermoid cysts with excellent diagnostic accuracy. Monodermal teratomas are rare and contain elements originating from a single germ cell layer. **Struma ovarii** is a monodermal teratoma that is composed of mature thyroid tissue that may result in clinically overt hyperthyroidism. **Ovarian carcinoid tumors** are another example of a monodermal teratoma. These rare tumors are generally associated with a mature teratoma but can be encountered in a pure form as a monodermal teratoma in a minority of cases. Approximately 30% of the time, clinical signs of carcinoid syndrome such as diarrhea, flushing, abdominal pain, and wheezing

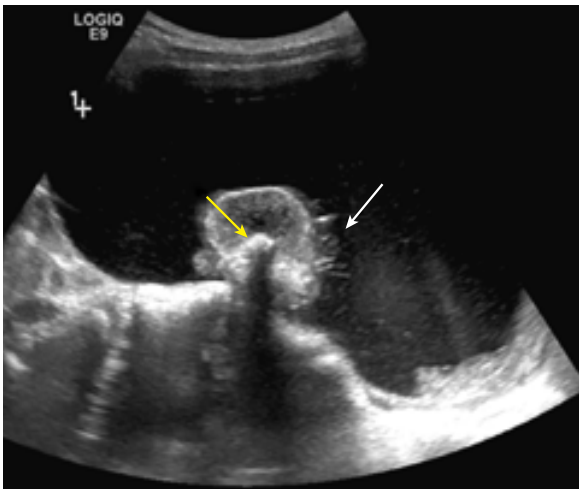

Fig. 590.2 Mature teratoma. 12-yr-old female with increasing abdominal girth. Transabdominal pelvic ultrasound image demonstrates a large pelvic mass with cystic and solid components. There is a rounded echogenic area in the center of the large, hypoechoic cystic portion. A central dense echogenic focus *(yellow arrow)* demonstrates posterior acoustic shadowing, consistent with calcification. Tiny linear echogenic foci *(white arrow)* are also associated with the central echogenic mass, representing hair. This constellation of findings is seen with a mature teratoma or dermoid cyst. *(From Walters MM, Robertson RL. Pediatric Radiology: The Requisites, 4th ed. Philadelphia: Elsevier, 2017: 187; Fig. 6.71.)*

may be present because of vasoactive amines secreted by the carcinoid tumors.

Benign teratomas can be observed if they are asymptomatic and small (<5 cm). However, when they are large or symptomatic, they should be surgically resected to prevent torsion or rupture, with preservation of the surrounding healthy ovarian parenchyma. Cystectomy is the treatment of choice, and minimally invasive techniques are increasingly used. Rupture of the cyst should be avoided as much as possible because of concerns for chemical peritonitis secondary to fatty acids of a teratoma and the rare risk of inadvertent upstaging of an occult carcinoma. During surgery, both ovaries should be evaluated for lesions. Intraoperative concern for a malignant lesion should prompt an evaluation of both the gross specimen and frozen section by pathology because malignant transformation of mature teratomas can occasionally occur.

An **immature teratoma (IT)** of the ovary is an uncommon tumor, accounting for <1% of ovarian teratomas. In contrast to the mature cystic teratoma, which is encountered most often during the reproductive years but occurs at all ages, IT has a specific age incidence, occurring most commonly in the first 2 decades of life. IT contain cells originating from three germ cell layers, but in contrast to mature teratomas, these elements have varying degrees of maturation. IT are histologically separated into three categories based on the proportion of the immature neural elements. Grade 3 IT have the highest percentage of immature neural elements, which correlates with the greatest risk of extraovarian spread. The presence of a yolk sac component also confers a higher risk of extraovarian spread. Clinically, IT present similarly to mature teratomas with pelvic pain or a mass. There is an association of dermoid tumors with neural elements and *anti–N-methyl-D-aspartase receptor (anti-NMDAR) encephalitis*. Patients may present with flu-like symptoms and progress to psychiatric and cognitive symptoms, autonomic instability, and seizure activity (see Chapter 638). The sonographic appearance of IT is nonspecific but is typically a heterogenous, partially solid mass with coarse calcifications.

Although the data are scant in the pediatric population, the stage and grade of the IT ultimately determines the treatment approach. Surgical staging for germ cell tumors in the pediatric population may differ from the adult population, and surgical staging in pediatric patients include collection of ascites and pelvic washings, examination of peritoneal surfaces with biopsy and excision of any nodules, examination of lymph nodes with sampling of any firm/enlarged lymph nodes, inspection/palpation of omentum with biopsy of any abnormal areas, and unilateral oophorectomy with preservation of the fallopian tube if uninvolved. It should be emphasized that grossly normal lymph nodes on palpation and normal appearing omentum may not need to be routinely removed. Stage I and grade 1 ITs can be managed with serial monitoring of associated tumor markers and pelvic imaging after initial fertility-sparing surgery. Grade 2-3 or stage II-IV IT are typically treated with systemic treatment in the form of the BEP chemotherapy regimen (bleomycin, etoposide, cisplatin).

Cystadenomas

Serous, mucinous, and mixed serous/endometrioid or mucinous/endometrioid cystadenomas are the second most common benign ovarian tumor in adolescents, representing 10–28% of adolescent tumors (Fig. 590.3). These tumors are usually thin walled, cystic, and may be associated with mild elevation of tumor markers such as carcinoembryonic antigen (CEA), CA-125, and CA 19-9, but high levels of these markers should raise suspicion for malignancy. These cystic lesions can become very large, yet, with care, these tumors can be resected, preserving normal ovarian tissue for future reproductive potential. Recurrence rates may be as high as 9%, and thus patients and providers may choose to continue surveillance postoperatively with pelvic ultrasound.

Endometriomas

Endometriosis is a syndrome defined by the presence of ectopic endometrial tissue usually located within the pelvis and abdomen but outside of the uterus. The principal clinical symptoms in adolescents consist of severe menstrual pain and pelvic pain but may also include abnormal uterine bleeding and GI, genitourinary, or constitutional symptoms. Diagnosis is often delayed, and a high clinical suspicion should be maintained. Although endometriosis has a variable presentation, it is associated with endometriomas in approximately 17–44% of adolescent cases; they may be unilateral or bilateral. **Endometriomas (chocolate cysts)** form when collections of old blood and hemosiderin deposit within an endometrium-lined cyst within or on the ovary. They have a typical homogeneous "ground glass" echogenic appearance on ultrasound and are more common in adults than in adolescents. Conservative management (suppressive therapy with ovulation suppression, nonsteroidal antiinflammatory drugs, combined oral contraceptives, or progestin therapy) is recommended for adolescents. An ovarian-sparing cystectomy should be performed if conservative care fails to control the symptoms or the size of the endometrioma is concerning for torsion. Recurrence of endometriosis occurs more commonly in adolescents than adults, and future fertility is associated with stage of disease. Early diagnosis and initiation of menstrual suppression with estrogen-progesterone, progesterone-only formulations, GnRH agonist, or GnRH antagonist may prevent progression of the disease.

Pelvic Inflammatory Disease and Tuboovarian Abscess

Pelvic inflammatory disease (PID) complicated by a tuboovarian abscess (TOA) should be considered in a sexually active adolescent with an adnexal mass and pain on examination (see Chapter 163). PID is a spectrum of upper genital tract inflammation and includes some combination of endometritis, salpingitis, and TOA. Rarely, TOA can occur in nonsexually active adolescents, particularly in association with obstructive Müllerian anomalies, ruptured appendicitis, obesity, and severe constipation. Patients with PID and TOA typically exhibit fever with leukocytosis, cervical motion, uterine or adnexal tenderness, vaginal discharge, nausea, peritoneal signs, and abnormal vaginal bleeding. TOAs are usually demonstrated on transvaginal ultrasound, but pelvic CT imaging may be used for uncertain cases. Treatment of PID with TOA consists of inpatient administration of intravenous (IV) antibiotics. After 48-72 hours of treatment with antibiotics

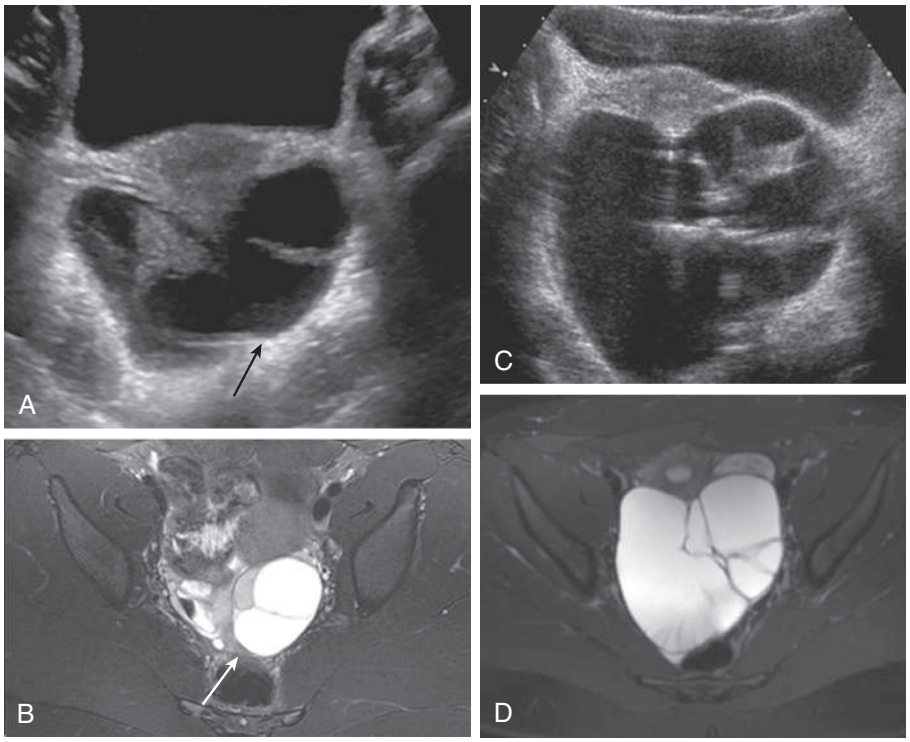

Fig. 590.3 Serous cystadenoma and mucinous cystadenoma. **A** and **B**, 20-yr-old female with pelvic pain. **A**, Transverse ultrasound and (**B**) axial T2 fat-saturated magnetic resonance images (MRIs) demonstrate a complex cystic mass with septations in the left adnexa *(arrows)*. This was removed and found to be a serous cystadenoma. **C** and **D**, 15-yr-old female with pelvic pain. **C**, Transverse ultrasound and (**D**) axial T2 fat-saturated MRIs demonstrate a cystic, septated mass posterior to the uterus. After surgical resection, pathology confirmed a mucinous cystadenoma. Note that the imaging appearances of serous and mucinous cystadenoma are similar. A specific diagnosis is difficult to discern based on imaging alone. *(From Walters MM, Robertson RL. Pediatric Radiology: The Requisites, 4th ed. Philadelphia: Elsevier, 2017; 188: Fig. 6.72.)*

alone, patients with TOAs who do not respond or who worsen should undergo imaging-guided abscess drainage. Conservative management with IV and then oral antibiotics and/or image-guided drainage is recommended as long as the patient continues to improve. TOAs that are large (>7-8 cm in the largest diameter) are associated with the need for surgical intervention and/or radiologically guided drainage. Clinical deterioration is an indication for surgical exploration, and a familiarity with bowel surgery is important with any attempt at resection of a pelvic abscess because of the challenges of encountering anatomic distortion, other organ involvement, and friable tissue planes.

Adnexal Torsion

Adnexal torsion of the ovary and/or fallopian tube is the fifth most common gynecologic emergency and occurs more often in children and adolescents than in adults. If ovarian torsion is suspected, timely surgical intervention is necessary to preserve ovarian function and future fertility. About 60% of ovarian torsions are on the right side; this is possibly because the right utero-ovarian ligament is longer than the left and/or due to the protective effect of the descending colon to the left adnexa. The most common presentation is *sudden*-onset abdominal pain, which is typically intermittent and nonradiating, with associated nausea and vomiting. Abdominal tenderness is common on physical exam and may be accompanied by peritoneal signs. Ultrasound with Doppler is the imaging modality of choice (Fig. 590.4). In adnexal torsion, ovarian venous flow is obstructed, and the fallopian tube and/or ovary become enlarged. Pelvic ultrasound findings include an edematous appearance of the ovary with subsequent hyperechogenicity, increase in size, "whirlpool" sign (twisted vascular pedicle of the ovary), and peripherally displaced follicles. Doppler studies in the evaluation of torsion are limited because of low sensitivity, and the presence of arterial flow does not rule out torsion. Therefore Doppler flow alone should not guide clinical decision-making. Prompt surgical intervention (i.e., diagnostic laparoscopy and laparoscopic ovarian detorsion) is essential to preserve ovarian function. Appearance of the ovary during surgery is not a reliable indicator for ovarian viability as even devascularized-appearing ovaries during laparoscopy have been reported to regain normal perfusion and function in several days. The goal of surgery should be to preserve the ovary regardless of the color and time from onset of symptoms to intervention. A torsed ovary should not be removed in adolescents unless it is severely necrotic and is disintegrating.

Although adnexal torsion may occur in individuals with normal ovaries, torsion occurs more commonly in adnexa enlarged by cystic changes or ovarian neoplasms. The rate of malignancy among premenarchal adolescents with ovarian torsion ranges from 0.4–5%. If an ovarian cyst is easily identified at the time of detorsion, it is reasonable to proceed with concomitant cystectomy; however, it should be noted that the concomitant cystectomy could be challenging because of the friable edematous ovary, which can result in ovarian damage and bleeding leading to oophorectomy. Given that most cysts are benign, drainage of the cyst's fluid is reasonable, and repeat ultrasound in 6-12 weeks usually demonstrates resolution of the cyst. Another approach may include detorsion and second-stage surgery at delayed interval for cystectomy. Oophoropexy is controversial, and the two most compelling reasons are the absence of a contralateral ovary and a history of recurrent ovarian torsion. Initiation of ovarian suppression is reasonable to prevent recurrent ovarian cysts.

OVARIAN MALIGNANCIES

Ovarian cancer is very uncommon in children; only 1.3% of all ovarian cancers are diagnosed in patients < 20 years old. Surveillance, Epidemiology, and End Results (SEER) age-adjusted incidence rates for 2016–2020 are 1.35/100,000 for females 15–19 years; mortality rates for this age group are 0.05/100,000.

Germ Cell Tumors

Germ cell tumors are the most common ovarian malignancy and originate from primordial germ cells that develop into a number of heterogeneous tumor types. **Dysgerminomas** are the most common malignant germ cell tumor of the ovary and have the best prognosis (Table 590.2). They may contain syncytiotrophoblastic cells that produce alpha-fetoprotein (AFP) and lactate dehydrogenase (LDH), making these serum proteins useful tumor markers for monitoring disease activity during surveillance (Table 590.3). Because of rapid growth and expansion, dysgerminomas may present as large abdomino-pelvic masses, and hemoperitoneum may result due to capsular rupture. Dysgerminomas are the most common bilateral ovarian germ cell tumor, occurring bilaterally in 10–15% of patients. **Yolk sac tumors**, also

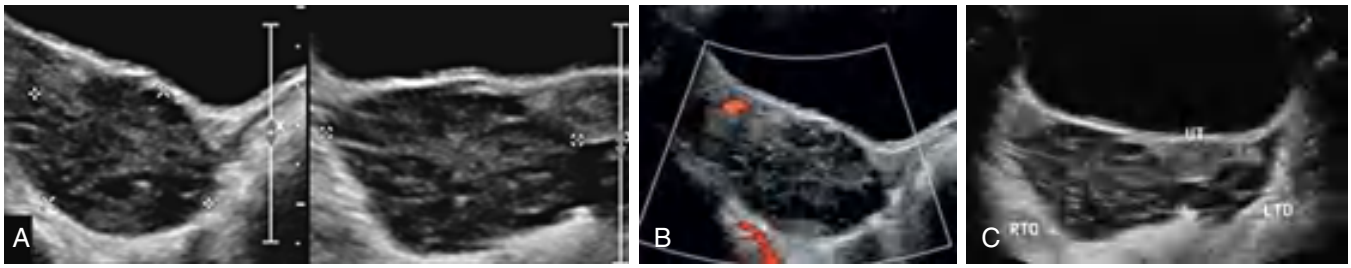

Fig. 590.4 Ovarian torsion. 15-yr-old female with acute-onset pelvic pain. **A,** Sagittal and transverse transabdominal pelvic ultrasound images demonstrate a rounded appearance of the right ovary, which is displaced medially and positioned posterior to the uterus. There is peripheralization of the ovarian follicles. **B,** Power Doppler imaging shows no demonstrable flow within the ovarian parenchyma. **C,** Transverse image of the pelvis shows marked asymmetric enlargement of the right ovary (RTO) in comparison with the normal left ovary (LTO). This patient went to surgery, and right ovarian torsion was confirmed. UT, Uterus. *(From Walters MM, Robertson RL. Pediatric Radiology: The Requisites, 4th ed. Philadelphia: Elsevier, 2017; 189: Fig. 6.74.)*

Table 590.2 Malignant Ovarian Tumors in Children and Adolescents

TUMOR	OVERALL 5-YR SURVIVAL	CLINICAL FEATURES
GERM CELL TUMORS		
Dysgerminoma	85%	10–20% bilateral Most common ovarian malignancy Gonadal dysgenesis/androgen insensitivity Sensitive to chemotherapy/radiation
Immature teratoma	97–100%	All three germ layers present
Endodermal sinus tumor	80%	Almost always large (>15cm) Schiller-Duval bodies
Choriocarcinoma	30%	Rare Can mimic ectopic pregnancy
Embryonal carcinoma	25%	Endocrinologic symptoms (precocious puberty) Highly malignant
Gonadoblastoma	100%	Primary amenorrhea Virilization 45,X or 45,X/46,XY mosaicism
SEX CORD STROMAL TUMORS		
Juvenile granulosa stroma cell tumor	92%	Produce estrogen Menstrual irregularities Isosexual precious pseudopuberty Call-Exner bodies rare
Sertoli-Leydig cell tumor	70–90%	Virilization in 40% Produce testosterone
Lipoid cell tumors	~80%	Rare heterogeneous group with lipid-filled parenchyma
Gynandroblastoma	90% or greater	Rare low-grade mixed tumors that produce either estrogen or androgen

referred to as **endodermal sinus tumors**, clinically present similarly to dysgerminomas with a rapidly enlarging pelvic mass and associated abdominal pain. Schiller Duval bodies are pathognomonic on pathology and contain a central blood vessel surrounded by cuboidal tumor cells. AFP is a useful marker for monitoring response to treatment and for surveillance. Immature teratomas and yolk sac tumors are more aggressive malignancies than dysgerminomas. Embryonal carcinomas are a relatively undifferentiated product of the primordial germ cells and are one of the most malignant germ cell tumors of the ovary. They may secrete β-hCG and AFP. **Gonadoblastomas** are almost always associated with chromosomal abnormalities; therefore chromosomal analysis is essential. Polyembryoma is a very aggressive ovarian malignancy and contains embryoid bodies. The treatment for stage Ia dysgerminomas and stage I immature teratomas is resection. For stage Ic and higher, treatment is surgical excision followed by postoperative chemotherapy. Radiotherapy may be administered for disease recurrence in dysgerminomas, but it is not included in routine treatment. For unresectable tumors or for patients who cannot undergo surgery, neoadjuvant chemotherapy is an option. Recurrences are treated with chemotherapy. Germ cell tumors may recur in up to 10% of cases, and thus yearly follow-up ultrasound is recommended.

Sex-Cord Stromal Tumors

Sex-cord stromal tumors (SCSTs) originate from the stromal component of the gonads and include benign **thecomas** and **fibromas,** as well as malignant **Sertoli-Leydig cell tumors** and **juvenile granulosa cell tumors**. Individuals with Peutz-Jeghers syndrome are at increased risk for developing SCSTs. SCSTs clinically present as an abdomino-pelvic mass, pain, and symptoms of excess sex steroid hormone production, such as hirsutism, virilization, and heterosexual or isosexual precocious puberty. When an SCST is suspected, serum levels of inhibin B, AFP, estradiol and testosterone should be obtained. SCSTs usually present as a unilateral solid mass on imaging, but some degree of necrosis could lead to a heterogenous appearance (Figs 590.5 and 590.6).

Most **juvenile granulosa** cell tumors have an intact capsule and therefore are associated with a good prognosis; however, in the case of capsular rupture or invasion, they potentially have an aggressive course. Juvenile granulosa cell tumors are usually associated with excess estrogen and precocious puberty in prepubertal females. Approximately 20% of the SCSTs in the pediatric population are **Sertoli-Leydig cell tumors,** which may be associated with clinical signs and symptoms of androgen excess. The *DICER1* pathogenic variant is associated with Sertoli-Leydig cell tumors, and the presence of the variant increases the risk of metachronous tumor in the contralateral ovary. Karyotype and referral to genetics is recommended for patients with SCSTs.

Epithelial Ovarian Cancers

Epithelial ovarian cancers are less common than germ cell tumors in the pediatric and adolescent population, comprising only 12.4% of ovarian malignancies in this group. Borderline ovarian tumors are similarly exceedingly rare in adolescents. Individuals with *BRCA1* and *BRCA2* pathogenic variants are at higher risk of developing epithelial ovarian cancer at younger ages compared with females without *BRCA* variants. Similarly, low-grade epithelial ovarian carcinomas tend to occur at younger ages compared with high-grade ovarian carcinomas. Common presenting symptoms include dysmenorrhea, abdominal pain, abdominal distention, nausea and vomiting, and vaginal

Table 590.3 Serum Tumor Markers

TUMOR	CA-125	AFP	β-HCG	LDH	E2	T	INHIBIN	MIS	VEGF	DHEA
Epithelial tumor	+									
Immature teratoma	+	+			+					+
Dysgerminoma			+	+	+					
Endodermal sinus tumor		+								
Embryonal carcinoma		+	+		+					
Choriocarcinoma			+							
Mixed germ cell		+	+	+						
Granulosa cell tumor	+				+		+	+		
Sertoli-Leydig						+	+			
Gonadoblastoma					+	+	+			+
Theca-fibroma									+	

AFP, α-Fetoprotein; CA-125, cancer antigen 125; DHEA, dehydroepiandrostenedione; E2, estradiol; β-hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; T, testosterone; MIS, Müllerian-inhibiting substance; VEGF, vascular endothelial growth factor.

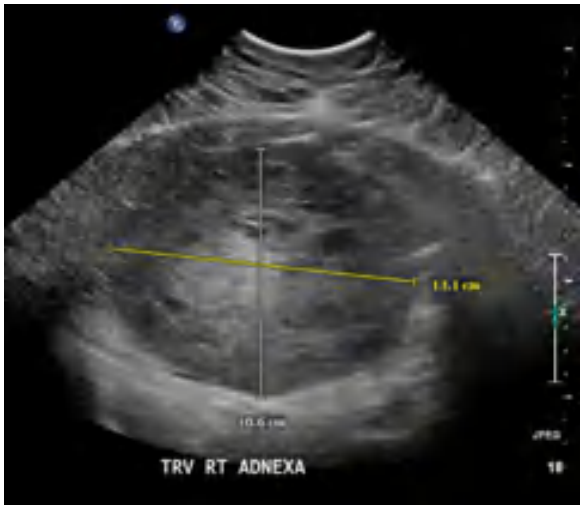

Fig. 590.5 Complex 13.1 × 8.1 × 10.6 cm solid mass with smaller cystic foci, arising from the right ovary. Final pathology demonstrated juvenile granulosa cell tumor. *(Image courtesy Alla Vash-Margita, MD.)*

discharge; CA-125 is almost always elevated. Treatment involves surgical salpingo-oophorectomy, pelvic washings, and biopsies of suspicious omental, peritoneal, and lymph node lesions, with adjuvant chemotherapy for patients with Federation of Gynecology and Obstetrics (FIGO) stage II-IV disease. Given the young age of this population, although this is not the standard of care for adult patients, fertility-sparing surgery is recommended for stage I cancer to conserve the contralateral ovary and uterus if they appear normal. Data suggest that in patients with early-stage disease, such an approach with appropriate surgical staging results in optimal outcomes but is not recommended for stage II-IV disease due to the high rate of recurrence. The number of term pregnancies and use of oral combined hormonal contraceptive pills decrease the risk of invasive epithelial ovarian cancer. Young females with a family history of ovarian cancer should consider the use of long-term oral combined hormonal contraceptive pills for the preventive benefits when pregnancy is not being sought.

UTERINE MALIGNANCIES

Uterine malignancies account for 2.5% of all gynecologic malignancies of children and adolescents less than 18 years of age. The most common types are sarcomas (34%), followed by adenocarcinomas (34%) and squamous cell carcinomas (10%). **Rhabdomyosarcomas** are the most common type of soft tissue sarcoma occurring in patients <20 years of age (see Chapter 549). They can develop in any organ or tissue in the body except bone, and roughly 3% originate from the uterus or vagina. Of the various histologic subtypes, embryonal rhabdomyosarcomas in the female patient most often occur in the genital tract of infants or young children. They are rapidly growing entities that can cause the tumor to be expelled through the cervix, with subsequent complications such as uterine inversion or large cervical polyps. Irregular vaginal bleeding may be another presenting clinical symptom. They are defined histologically by the presence of mesenchymal cells of skeletal muscle in various stages of differentiation intermixed with myxoid stroma. A genetic link has been found between Li-Fraumeni cancer susceptibility syndrome, Beckwith-Wiedemann syndrome, pleuropulmonary blastoma, Costello syndrome, Noonan syndrome, and neurofibromatosis type I. Treatment recommendations are based on protocols coordinated by the Intergroup Rhabdomyosarcoma Study Group and consist of a multimodal approach including radiation therapy and chemotherapy. Vincristine, Adriamycin-D, and cyclophosphamide (VAC) with or without radiation therapy make up the first line of treatment. Intensity-modulated radiation therapy and proton beam radiotherapy are used to reduce the therapy burden and long-term toxicity. Resection rates are very low because of the risk of losing the form and function of local tissue; chemotherapy with restrictive surgery and adjunctive irradiation has enabled many patients to retain the uterus while achieving excellent long-term survival rates.

Leiomyosarcomas and **leiomyomas** are extremely rare, occurring in <2 in 10 million individuals in the pediatric and adolescent age-groups, although their numbers are increasing among pediatric patients with AIDS. They usually involve the spleen, lung, or GI tract, but they could also originate from uterine smooth muscle. Epstein-Barr virus pathogenesis has been shown in AIDS and solid-organ transplant patient populations (see Chapter 301). Despite treatment that demands complete surgical resection (and chemotherapy for the sarcomas), they tend to recur frequently.

Endometrial stromal sarcoma and **endometrial adenocarcinoma** of the uterine corpus are extremely rare in children and adolescents. A comprehensive review described 19 cases of endometrial cancer (EC) among adolescent females younger than 21 years in which five subjects (26.3%) had a genetic condition (Cowden syndrome and Turner syndrome). This emphasizes the consideration of genetic evaluation in very young patients with EC. In most cases, patients presented with abnormal uterine bleeding and had associated comorbidities such as obesity and polycystic ovary syndrome. Standard of care for treatment of EC consists of hysterectomy, removal of both ovaries and fallopian tubes and surgical staging, followed by adjunctive radiotherapy and/

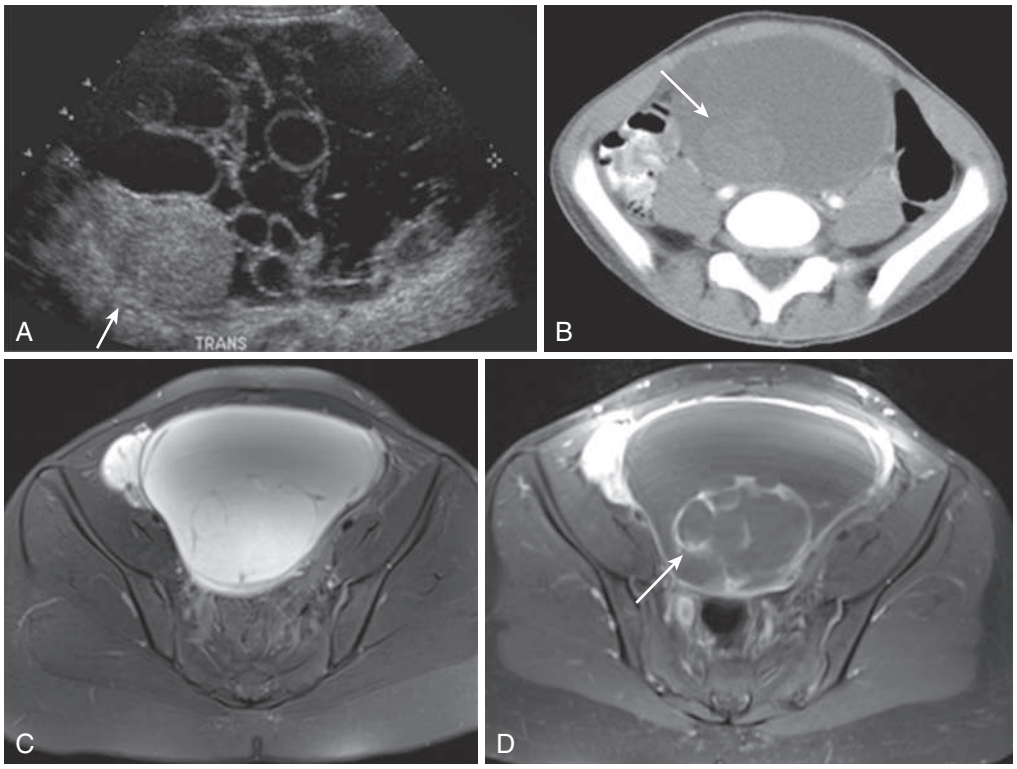

Fig. 590.6 Sertoli-Leydig cell tumor. 2-yr-old female with a palpable pelvic mass and secondary sex characteristics. **A**, Transabdominal pelvic ultrasound demonstrates a complex cystic, septated mass, with a solid component posteriorly *(arrow)*. **B**, Contrast-enhanced computed tomography shows a predominantly cystic mass, with an enhancing mural nodule along the posterior margin *(arrow)*. **C**, T2-weighted and **D**, contrast-enhanced magnetic resonance images in a different patient demonstrate a T2 hyperintense lesion in the pelvis, with enhancing internal solid components noted after contrast administration *(arrow)*. *(From Walters MM, Robertson RL. Pediatric Radiology: The Requisites, 4th ed. Philadelphia: Elsevier, 2017; 188: Fig. 6.73.)*

or chemotherapy as indicated by final pathology and stage. In young patients who desire childbearing, fertility-sparing approaches with preservation of the uterus have been increasingly utilized. Per National Comprehensive Cancer Network (NCCN) guidelines, candidates for this approach are patients with grade 1 endometrioid adenocarcinoma on dilation and curettage, patients with disease confined to endometrium by MRI (preferred imaging modality) or ultrasound, absence of metastatic disease on imaging, and no contraindications to medical therapy or pregnancy. Patients should undergo counseling that fertility-sparing options are not standard of care for the treatment of endometrial carcinoma. Existing data on hormonal therapy come from observational studies and have variable rates of outcomes. Although there is no standard follow-up protocol, patients with EC treated with hormonal therapies should be reexamined with endometrial sampling every 3-6 months.

VAGINAL MALIGNANCIES

Vaginal tumors are rare with a variable clinical presentation that may include abdomino-pelvic pain, an abdominal mass, bloody vaginal discharge, genital ulceration, or tissue protruding from the vagina. **Embryonal rhabdomyosarcoma (RMS)** is the most common vaginal malignancy followed by germ cell tumor (GCT) and clear cell adenocarcinoma (CCA). The management of pediatric vaginal tumors consists of neoadjuvant chemotherapy followed by local control with surgery or radiotherapy.

Embryonal rhabdomyosarcoma (RMS) or **sarcoma botryoides** typically arises in the anterior wall of the vagina or within the wall of the bladder and presents as an edematous grapelike mass protruding from the vagina. Overall, RMS arising in the female genital tract accounts for less than 4% of all pediatric RMS. Approximately 90% of these sarcomas present before age 5 years. Embryonal RMS of the vagina is managed with multimodality treatment. A series of Intergroup Rhabdomyosarcoma Study Group (IRSG) reports demonstrated survival rates in excess of 85% employing the use of combination chemotherapy treatment with vincristine, actinomycin-D, and cyclophosphamide (VAC) and wide excision with or without adjuvant radiation treatment. This approach spares most patients from exenterative surgery. Because of the high rates of local recurrences in patients who did not receive radiation, the Soft Tissue Sarcoma committee of the Children's Oncology Group recommends local radiation treatment unless potential toxicity is considered unacceptable.

Endodermal sinus tumors or **yolk sac tumors** are the most common subtype of pediatric germ cell tumor of the vagina but are still quite rare. These tumors present almost exclusively in children under the age of 3 years with vaginal bleeding. Typically, patients have a markedly elevated serum AFP, which can be used to monitor treatment effect and disease recurrence. Management involves combination of surgery and chemotherapy (either carboplatin/etoposide/bleomycin, BEP regimen, or VAC regimen). Unfortunately, survival rates are low despite treatment.

There is an increased incidence of **clear cell adenocarcinoma** (CCA) of the vagina in young females related to in utero exposure to diethylstilbestrol (DES) during the first 16 weeks of pregnancy. The suggested mechanism of carcinogenesis involves the retention of nests of abnormal cells of Müllerian duct origin that, after stimulation by endogenous hormones during puberty, are promoted into adenocarcinomas. Most cases involve the anterior upper third of the vaginal wall. Treatment of CCA of the vagina includes a surgery and/or radiation treatment depending on the extent of disease. Fortunately, the incidence of CCA of the vagina has decreased since the practice of prescribing DES during pregnancy has been eliminated.

VULVAR MALIGNANCIES

Pediatric vulvar malignancies are rare. Patients typically present with an ulcerated or raised lesion and/or a mass. It is imperative that any concerning vulvar lesion be biopsied and submitted for pathologic evaluation. Vulvar malignancies that have been described in the literature include invasive squamous cell carcinomas, yolk sac tumors, Ewing sarcoma/primitive neuroectodermal tumors (ES/PNET), and melanomas. Each of these entities make up approximately 10% of reported cases. Cases of pediatric vulvar squamous cell carcinoma include those lesions that are **human papillomavirus (HPV)**-mediated and HPV-independent. Possible risk factors include HPV infection, immunosuppression, Fanconi anemia, and lichen sclerosis. Extragonadal germ cell tumors involving the vulva are very uncommon, and the leading hypothesis behind their pathogenesis is possible aberrant germ cell migration along the gubernaculum. These are aggressive tumors, and treatment options include various combinations of excisional

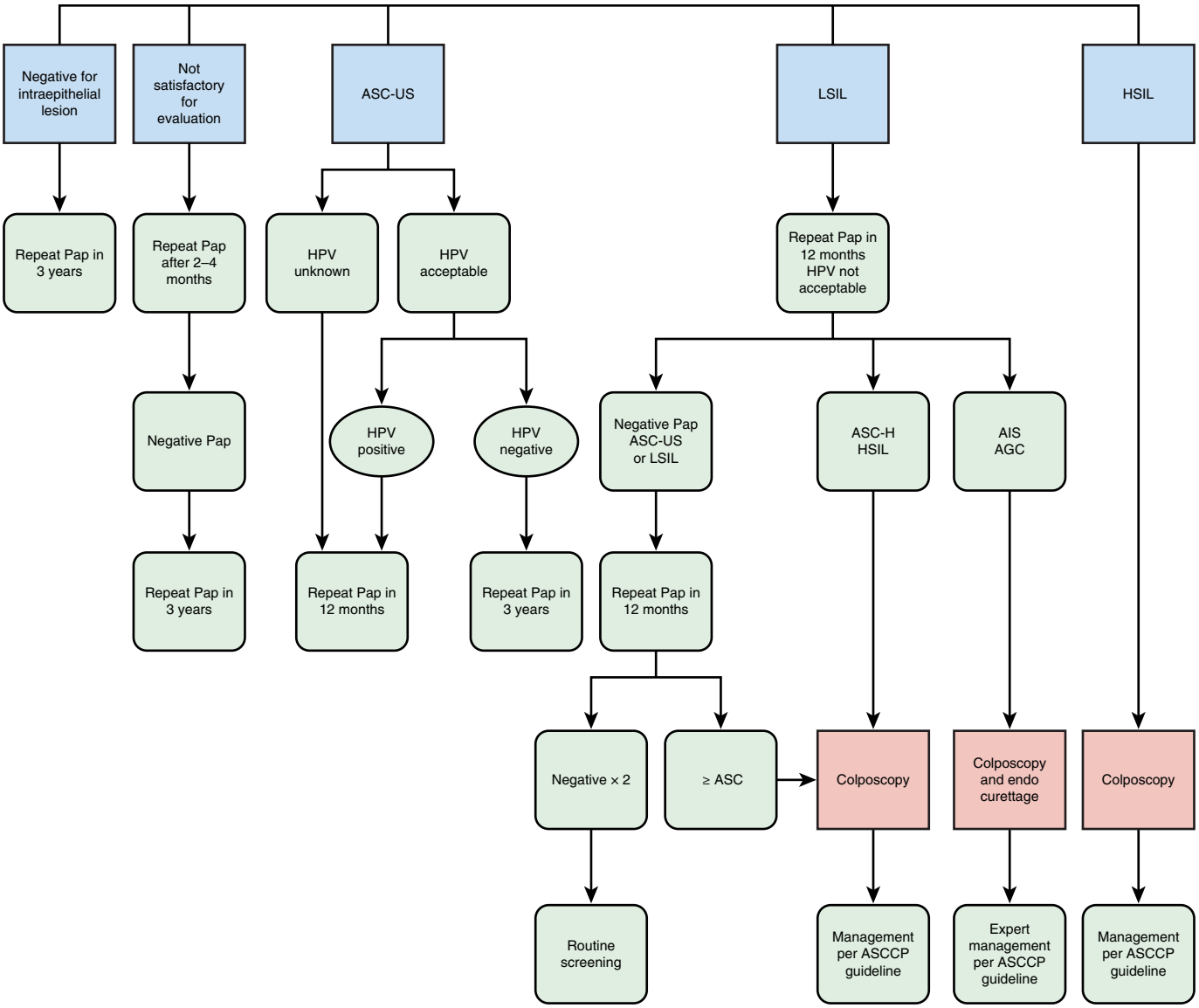

Fig. 590.7 Algorithm for the management of Pap smear results in women between age 21-24. AIS, adenocarcinoma in situ; AGC, atypical glandular cells; ASC, atypical squamous cells; ASCCP, American Society for Colposcopy and Cervical Pathology; ASC-H, atypical squamous cells that cannot exclude HSIL; ASC-US, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; HPV, human papilloma virus; HSIL, high-grade squamous intraepithelial lesion *(From Trotman GE, Vash-Margita A, Kahn JA, et al. Human papillomavirus infection and cervical cancer screening and prevention in adolescents. In: Emans SJ, Laufer MR, Di Vasta DP, eds. Pediatric and Adolescent Gynecology. Philadelphia: Lippincott Williams & Wilkins, 2020; 330–348: Fig 20.9.)*

procedures and neoadjuvant or adjuvant chemotherapy. **Malignant melanoma** of the vulva represents 2.4–10% of all vulvar malignancies, second to invasive squamous cell carcinomas in frequency. Early-stage melanoma treatment involves surgical excision followed by possible radiation treatment. Treatment of advanced stage melanoma involves systemic chemotherapy and/or targeted treatment agents such as checkpoint inhibitor immunotherapy. **Rhabdomyosarcomas** are the most common vulvar sarcomas reported in pediatric patients. The second most common sarcoma of the vulva in pediatric patients is ES/PNET. Management of both vulvar sarcomas includes surgical excision, multi-agent chemotherapy, and radiation treatment. ES/PNET cases often present in the advanced stage and have a poor prognosis.

Condyloma acuminata are common, raised, verrucous lesions of the vulva that result from squamous cell proliferation associated with HPV infection (most common genotypes HPV 6 and 11). Prevention of HPV infection and subsequent formation of condyloma acuminata has been achieved through HPV vaccination. *In young children with condyloma acuminata, sexual abuse must be ruled out.* These lesions are benign and can spontaneously regress. If lesions are bothersome, treatment modalities consist of topical podophyllin resin, imiquimod, trichloroacetic acid, local cryotherapy, electrocautery, excision, and laser ablation. Imiquimod is approved by the U.S. Food and Drug Administration (FDA) for individuals 12 years of age and above.

CERVICAL MALIGNANCIES AND THEIR PREVENTION

In 2020, cervical cancer accounted for an estimated 604,000 new cancer cases and 342,000 deaths worldwide, making it the fourth most common cancer in females of all ages. From 2016 to 2020, the United States age-adjusted incidence of cervical cancer in females under age 20 was <0.1 per 100,000. The adolescent population is at greatest risk of HPV infection, which predisposes them to development of cervical cancer because about half of HPV infections occur before the age of 24. Thus prevention of initial infection in the adolescent population is critical to decreasing cervical cancer rates.

Primary prevention of HPV infection includes vaccination before the onset of sexual activity with the HPV vaccine. The HPV vaccine is approved for males and females ages 9-26. The Centers for Disease Control and Prevention (CDC) recommends two doses of the HPV 9-valent vaccine for patients before age 15 years (typically between ages 11-12) given 6-12 months apart (see Chapter 215). For those initiating the vaccine series at 15 years of age or older, three doses of the HPV vaccine should be given at 0, 1-2, and 6 months. Three doses are also recommended for patients who are immunocompromised (i.e., solid organ transplant recipient, HIV infection). Children with a history of sexual abuse should start immunization at age 9. In 2018, the FDA approved the use of the HPV 9-valent vaccine to include adults age 27-45 years; while the vaccine is not routinely recommended in this group, it may be given after shared clinical decision-making between a patient and their healthcare provider. The HPV vaccine can be administered despite prior infection with HPV. Cervical cancer screening via Papanicolaou (Pap) testing and HPV co-testing are important secondary prevention strategies. ACOG recommends cervical cancer screening for females starting at age 21 years in immunocompetent females regardless of onset of penetrative vaginal intercourse or primary prevention with HPV vaccination. Separate guidelines describe cervical cancer screening recommendations for immunocompromised individuals. Briefly, sexually active immunocompromised adolescents (such as solid organ or hematopoietic stem cell transplant recipients, patients with inflammatory bowel disease on immunosuppressive therapy, and patients with systemic lupus erythematosus) should start screening 1 year after of onset of sexual activity and thereafter annually for 3 years. If consecutive screening is negative, patients may follow the guidelines for immunocompetent females. HIV positive patients should start screening at age 21 regardless of sexual activity. Additionally, condom use, limiting the number of sexual partners, and smoking cessation are recommended to lower the risk for cervical cancer.

Because of the high prevalence of HPV infection in the adolescent population and because HPV-associated lesions typically regress, HPV screening should be not done before age 21 years in immunocompetent patients. If an inadvertent HPV test is done in adolescents, the results should not be acted on. Guidelines on management of the abnormal results of cervical cancer screening (Pap smear) for females age 21-24 are shown in Figure 590.7. Overall, data shows that prevention strategies such as widespread implementation of HPV vaccine translates into reduced incidence of cervical cancer in the future. Pediatric providers should educate patients and caregivers about benefits of the HPV vaccine and offer it at the recommended age.

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Chapter 591

Vulvovaginal and Müllerian Anomalies

Laura L. Hollenbach, Emanuele Pelosi, Miranda Margetts, and Alla Vash-Margita

EMBRYOLOGY

The formation of a normal reproductive system occurs in the developing embryo and early fetus and is regulated by several processes, including cellular differentiation, duct elongation, fusion, resorption, canalization, and programmed cell death. Numerous Müllerian and/or vulvovaginal anomalies can result from interruption of the intricate sequence or functions of any one of these processes during formation of the reproductive system (Table 591.1). Genetic, epigenetic, and environmental factors all have been described as playing some role in these processes (Table 591.2).

Table 591.1 Congenital Müllerian Anomalies

MÜLLERIAN ANOMALY	DESCRIPTION
Agenesis	Absence of uterus, cervix, and upper portion of vagina
Hypoplasia	Incomplete development of uterus, cervix, and upper portion of vagina
Unicornuate uterus	One cervix and one uterine horn, the result of failure of one Müllerian duct to descend
Septate uterus	Septum dividing the uterus, partially or completely
Didelphic uterus	Two cervices, each associated with one uterine horn
Bicornuate uterus	One cervix associated with two uterine horns
OHVIRA (obstructed hemivagina and ipsilateral renal anomaly)	Double uterus with unilateral obstructed hemivagina and ipsilateral renal agenesis
CONDITIONS ASSOCIATED WITH MÜLLERIAN ANOMALIES	**DESCRIPTION**
Hydrocolpos	Accumulation of mucus or nonsanguineous fluid in the vagina
Hematocolpos	Accumulation of blood in the vagina
Hematometra	Accumulation of blood in the uterus
Hydrosalpinx	Accumulation of serious fluid in the fallopian tube, often a result of pyosalpinx

Table 591.2 Genetic Conditions Associated with Müllerian Anomalies

MODE OF INHERITANCE	SYNDROME	ASSOCIATED MÜLLERIAN DEFECT
Autosomal dominant	Camptobrachydactyly	Longitudinal vaginal septum
	Hand-foot-genital	Incomplete Müllerian fusion
	Denys-Drash	Persistent Müllerian duct derivatives
Autosomal recessive	McKusick-Kaufman	Vaginal atresia, transverse vaginal septum
	Johanson-Blizzard	Longitudinal vaginal septum
	Renal-genital-middle ear anomalies	Vaginal atresia
	Fraser	Incomplete Müllerian fusion
	Persistent Müllerian duct	Persistent Müllerian duct derivatives
	Urioste syndrome	Persistent Müllerian duct derivatives
Polygenic/ multifactorial	Mayer-Rokitansky-Küster-Hauser	Müllerian aplasia
X-linked	Persistent Müllerian duct	Persistent Müllerian duct derivatives

Phenotypic sexual differentiation, especially during formation of the vulvovaginal and Müllerian systems, is determined from genetic, gonadal, and hormonal influences (see Chapter 622). Gonadal development determines the hormonal production regulating progression or regression of the genital ducts and subsequently the external genitalia.

In 46,XY embryos, the *SRY* (sex-determining region of Y-chromosome) gene is one of the first regulators driving the formation of a testis from a primitive gonad and triggering the expression of a cascade of additional factors responsible for testis development as well as spermatogenesis. The testis begins to develop between 6-7 weeks of gestation, first with Sertoli cells, which produce anti-Müllerian hormone (AMH), followed by Leydig cells, which produce testosterone starting at approximately 8 weeks of gestation. The genital tract in both male and female embryos initially includes both the Wolffian and the Müllerian (or paramesonephric) ducts and begins to differentiate later than the gonads. The differentiation of the Wolffian ducts, the primordia of the male reproductive tract, is regulated by testosterone, and the local action of testosterone activates development of the epididymis, vas deferens, and seminal vesicle. Concomitantly, the anti-Müllerian hormone (or Müllerian-inhibiting substance) will cause regression of the Müllerian ducts. Further male genital duct and external genital structures depend on the conversion of testosterone to dihydrotestosterone. Failure of Müllerian duct regression results in retention of Müllerian derivatives in males. One example is **persistent Müllerian duct syndrome (PMDS)**, which is characterized by the presence of Müllerian structures usually associated with undescended testes. The majority of PMDS cases are due to pathogenic variants in the *AMH* gene or its receptor *AMHR2*. Other conditions featuring the presence of Müllerian derivatives in males are **Denys-Drash syndrome** (characterized by gonadal dysgenesis), nephropathy, and Wilms tumor, each caused by pathogenic variants in the *WT1* gene, and Müllerian derivatives-lymphangiectasia-polydactyly syndrome **(Urioste syndrome)**, a condition of unknown etiology.

In a 46,XX embryo, female sexual differentiation occurs about 2 weeks later than gonadal differentiation in the male. The regression of the Wolffian ducts results from the lack of local gonadal testosterone production, and the persistence of the Müllerian ducts results from the absence of anti-Müllerian hormone production. The Müllerian ducts continue to differentiate into the fallopian tubes, uterus, and upper one-third of the vagina without interference from anti-Müllerian hormone. Because the ovaries develop separately from the Müllerian ducts, females with Müllerian ductal anomalies usually have normal ovaries and steroid hormone production. There are complex interactions among the Wolffian, Müllerian, and metanephric ducts (the latter giving rise to the urinary tract) early in embryonic development, and normal development of the Müllerian system depends on such interaction. If this process is interrupted, coexisting Müllerian and renal anomalies are often discovered in the female patient at the time of evaluation. Although most Müllerian defects seem sporadic, familial recurrence or clustering has been observed, which strongly supports the influence of genetic factors. The molecular processes underlying the developmental program of the female reproductive tract are extremely intricate and are regulated by numerous gene products, including *WNT4*, *WNT5*, *WNT7A*, *WNT9B*, *LIM1*, *HNF1B*, *EMX2*, *PAX8*, and *HOX*. The WNT family plays crucial roles in both the formation and differentiation of the Müllerian ducts, providing inductive signals for the correct patterning of the developing tract. Homeobox genes *LIM1* and *HNF1B* are expressed in duct epithelial cells and are necessary for the development of the entire urogenital tract. Similarly, *EMX2* and *PAX8* play fundamental roles in the initial steps of urogenital development by regulating the formation of the Wolffian and Müllerian ducts. The family of *HOXA* genes is one of the most well described and comprises regulatory molecules that encode highly conserved transcription factors regulating the developmental axis of the female reproductive tract. These genes display a characteristic expression pattern along the developing reproductive tract (Fig. 591.1). A role for environmental factors in Müllerian anomalies has also been proposed. During gestation, the Müllerian ducts develop in an estrogen-free environment because of the presence of α-fetoprotein

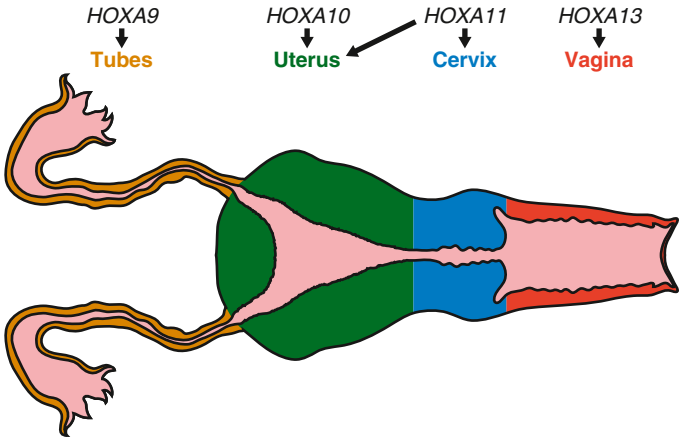


Fig. 591.1 Expression of *HOXA* genes in the developing Müllerian system. *(Adapted from Taylor HS. The role of HOX genes in the development and function of the female reproductive tract. Semin Reprod Med. 2000;18:81-89.)*

peptides that sequester estrogen molecules. Therefore attention has been turned to **endocrine-disrupting chemicals (EDCs)**, especially compounds with estrogenic activity, for their potential teratogenic role in Müllerian anomalies. A striking example is provided by diethylstilbestrol (DES), an estrogen agonist once given to pregnant patients to prevent pregnancy-related complications, including miscarriage. However, DES was found to induce epigenetic modifications and cause reproductive malformations, including a T-shaped uterus ultimately associated with higher spontaneous abortion rates.

By 10 weeks of gestation, the caudal portions of the Müllerian ducts fuse together in the midline to form the uterus, cervix, and upper vagina, in a Y-shaped structure, with the open upper arms of the Y forming the primordial fallopian tubes. Initially, the Müllerian ducts are solid cords that gradually canalize as they grow along and cross the mesonephric ducts ventrally and fuse in the midline. The Müllerian ducts caudally open into the **urogenital sinus,** where proliferation of the cells at the point of contact form the Müllerian tubercle. Cells between the Müllerian tubercle and the urogenital sinus continue to proliferate, forming the vaginal plate. At the same time of the midline fusion of the Müllerian ducts, the medial walls—forming the septum—begin to degenerate, forming the central cavity of the uterovaginal canal. Uterine septal resorption is thought to occur in a caudal to rostral direction and to be complete at approximately 20 weeks of gestation. This theory has been scrutinized because some anomalies do not fit the standard classification system; it is possible that septal resorption starts at some point in the middle and proceeds in both directions. At approximately 16 weeks of gestation, the central cells of the vaginal plate desquamate, and resorption occurs, forming the vaginal lumen. The lumen of the vagina is initially separated from the urogenital sinus by a thin hymenal membrane. The hymenal membrane undergoes apoptosis and central resorption and is usually perforate before birth.

EPIDEMIOLOGY

Müllerian anomalies can include abnormalities in portions or all of the fallopian tubes, uterus, cervix, and vagina (Fig. 591.2). True estimates of prevalence are difficult because of the varied presentations and asymptomatic nature of some of the anomalies, use of different diagnostic procedures, subjectivity of the diagnostic criteria, and the inconsistent interpretation of the classification of Müllerian anomalies.

It is estimated that Müllerian anomalies are present in 6.7% of the general female population. The prevalence of Müllerian anomalies increases in females with a history of adverse pregnancy outcomes or infertility: 8% of females who are infertile, 15% of females with primary amenorrhea, 16.7% of females with recurrent pregnancy loss, and 24.5% of females with both miscarriage and infertility have Müllerian defects.

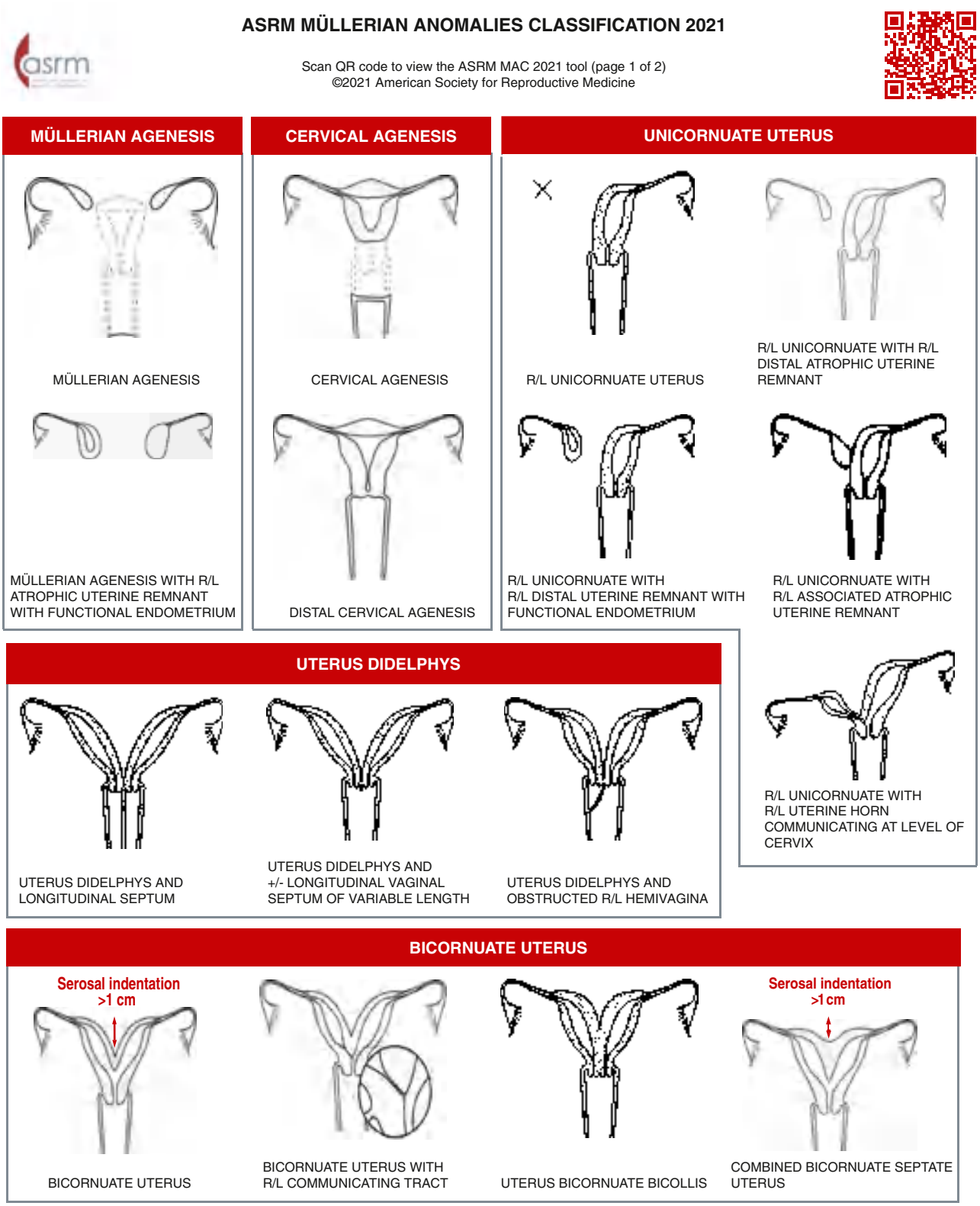
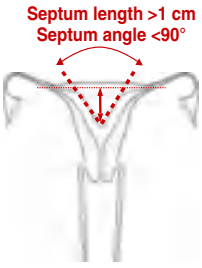
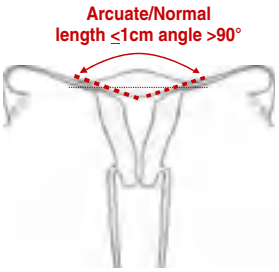


Fig. 591.2 Classification system of Müllerian duct anomalies developed by the American Society of Reproductive Medicine. *(From Pfeifer SM, Attaran M, Goldstein J, et al. ASRM Müllerian anomalies classification 2021. Fertil Steril. 2021;116:1238-1252; Fig 1.)*

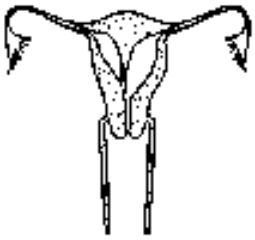
SEPTATE UTERUS



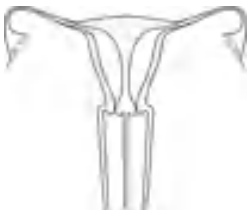
PARTIAL SEPTATE UTERUS



NORMAL/ARCUATE UTERUS



ROBERT'S UTERUS



COMPLETE SEPTATE UTERUS WITH DUPLICATED CERVICES AND LONGITUDINAL VAGINAL SEPTUM

COMPLETE SEPTATE UTERUS WITH SEPTATE CERVIX AND LONGITUDINAL VAGINAL SEPTUM

COMPLETE SEPTATE UTERUS, DUPLICATED CERVICES, AND OBSTRUCTED R/L HEMIVAGINA

TRANSVERSE VAGINAL SEPTUM

MID VAGINAL SEPTUM

DISTAL VAGINAL AGENESIS

LONGITUDINAL VAGINAL SEPTUM

LONGITUDINAL VAGINAL SEPTUM OF VARIABLE LENGTH

LONGITUDINAL VAGINAL SEPTUM OF VARIABLE LENGTH AND UTERUS DIDELPHYS

OBSTRUCTED R/L HEMIVAGINA AND UTERUS DIDELPHYS

LONGITUDINAL VAGINAL SEPTUM OF VARIABLE LENGTH AND COMPLETE SEPTATE UTERUS WITH DUPLICATED CERVIX

OBSTRUCTED R/L HEMIVAGINA AND COMPLETE SEPTATE UTERUS WITH DUPLICATED CERVICES

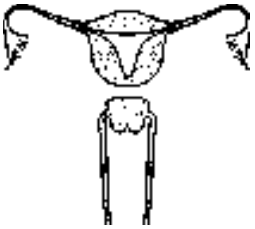
COMPLEX ANOMALIES

BICORNUATE UTERUS WITH BILATERAL OBSTRUCTED ENDOMETRIAL CAVITIES

UTERUS DIDELPHYS WITH COMMUNICATING HEMIUTERI AND UNILATERAL R/L CERVICO-VAGINAL ATRESIA

OBSTRUCTED R/L HEMIVAGINA, HEMIUTERUS AND SINGLE CERVIX WITH SEPARATE CONTRALATERAL R/L PATENT HEMIUTERUS, CERVIX AND VAGINA

BICORNUATE UTERUS WITH R/L COMMUNICATING TRACT AND TRANSVERSE VAGINAL SEPTUM



UTERUS ISTHMUS AGENESIS

Scan QR code to view the ASRM MAC 2021 tool (page 2 of 2)

Fig. 591.2 cont'd

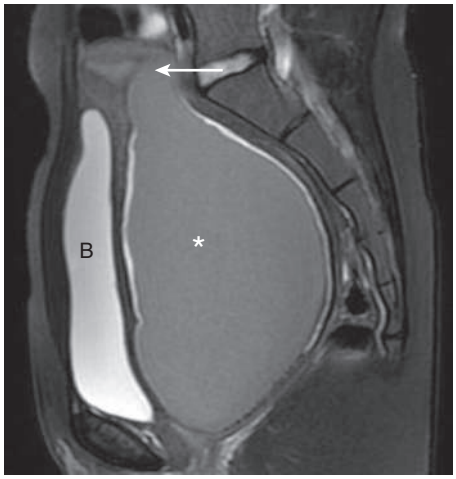


Fig. 591.3 Sagittal MRI of pelvis showing large volume hematocolpos (*asterisk*). *B,* Bladder; *arrow*, hematometra.

Combinations of congenital anomalies in other organ systems are prevalent in females with Müllerian anomalies. Renal and musculoskeletal abnormalities are the most common. An estimated 29% of females with a renal anomaly will have an associated Müllerian abnormality. Concomitant congenital malformations are also prevalent in approximately 54.4% of females with **Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome**.

CLINICAL MANIFESTATIONS

Vulvovaginal and Müllerian anomalies can manifest at a variety of chronological time points during a female's life: from infancy, through childhood and adolescence, and during adulthood (see Table 591.1). The majority of external genitalia malformations manifest at birth, and often even subtle deviations from normal in either a male or female newborn warrant evaluation. Structural reproductive tract abnormalities can be seen at birth or can cluster at menarche or any time during a patient's reproductive life. Some Müllerian anomalies such as arcuate uterus are asymptomatic and have no implications clinically, whereas others can cause gynecologic, obstetric, or fertility issues.

Clinical manifestations and treatments depend on the specific type of Müllerian anomaly and are varied. There may be a pelvic mass, which may or may not be associated with symptoms. A mass bulging at the introitus or within the vagina indicates complete or partial **outflow tract obstruction.** A newborn can present with no evidence of a vaginal opening. An adolescent can present with cyclic pelvic pain either in association with **primary amenorrhea** or several months after the onset of menarche. Patients also may be asymptomatic until they present with miscarriage, pregnancy loss, or preterm delivery. When presentation is acutely symptomatic, emergency management may be required. Obstruction can result from a number of distinct anomalies, including an **imperforate hymen,** a **transverse vaginal septum,** a distal **vaginal agenesis,** or a **noncommunicating rudimentary horn.** As menstrual fluid accumulates proximal to the obstruction, the resulting **hematocolpos** (Fig. 591.3) and **hematometra** cause cyclic pain, pelvic mass and, occasionally, urinary dysfunction.

Prenatal or neonatal presentation of hydrometrocolpos from distal vaginal obstruction produces fluid accumulation in the vagina and uterus and presents as a lower abdominal mass with or without associated acute urinary tract obstruction. Hydrometrocolpos with polydactyly may be a result of two autosomal recessive disorders: **McKusick-Kaufman syndrome** (with associated congenital heart disease) and **Bardet-Biedl syndrome** (with associated obesity, learning disabilities, retinitis pigmentosa, and renal anomalies).

Adolescent patients can present with acute obstruction of the outflow tract because of a Müllerian anomaly, which requires emergency evaluation and surgical treatment. A small percentage of females can present with concomitant urinary retention caused by an altered urethral angle or pressure on the sacral plexus. Urinary hesitancy and incomplete emptying symptoms may be present before abdominopelvic pain increases from the obstruction in a patient of any age. Some menstruating adolescents may present with increasing cyclic abdominopelvic pain with their menses due to an obstructed hemivagina with uterine didelphys and ipsilateral renal agenesis (OHVIRA).

LABORATORY AND RADIOGRAPHIC FINDINGS

Laboratory evaluation in the setting of primary amenorrhea would include hormonal evaluation with assessment of the beta chorionic gonadotropin (beta-hCG) to rule out pregnancy, follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, and thyroid-stimulating hormone (TSH). Androgen evaluation may be done if virilization is seen on physical examination. The patient's karyotype may be obtained based on clinical presentation. Other hormonal testing might be indicated in specific cases. Several radiographic studies have been used, often in combination, to aid in diagnosis including ultrasound, hysterosalpingogram, sonohysterography (saline-infusion sonography), and MRI. The least invasive initial study for a young adolescent with cyclic pain, a pelvic mass, or amenorrhea is a transabdominal pelvic ultrasound; transvaginal pelvic ultrasound can be used in sexually active teens. MRI is considered the gold standard of care and best suited for complex anomalies because of its noninvasive, high-quality capabilities. MRI is the most sensitive and specific imaging technique used for evaluating Müllerian anomalies because it can image nearly all reproductive structures, blood flow, external contours, junctional zone resolution on T2-weighted images, and associated renal and other anomalies. MRI also has a high correlation with surgical findings because of its multiplanar capabilities and high spatial resolution. Three-dimensional ultrasound is another useful diagnostic tool and may be superior to traditional pelvic ultrasound and hysterosalpingogram but may not be easily accessible. Evaluation of the external contour of the uterus is important for differentiating types of uterine anomalies. This often requires a combination of radiologic modalities for the uterine cavity, external contour, and possible tubal patency. Diagnostic laparoscopy or hysteroscopy may be necessary depending on the presentation, but it is less common with advancement of MRI and other imaging modalities.

Diagnosis of Müllerian anomalies should include a complete history, including family history, with special attention to history of infertility for female relatives and renal and skeletal abnormalities. A complete physical exam including skeletal inspections for associated anomalies should be performed in addition to the radiology studies discussed above. Renal anomalies are noted in 30–40% and skeletal anomalies are associated in 10–15% of patients with Müllerian anomalies. Unilateral renal agenesis occurs in 15% of patients. The most common skeletal anomaly is scoliosis. Patients usually have a normal female karyotype (46, XX), and most malformations are sporadic, with a polygenic mechanism and multifactorial etiology (Table 591.2).

UTERINE ANOMALIES

Anomalous development of the uterus may be symmetric or asymmetric and/or obstructed or nonobstructed. Patients can present with primary amenorrhea or have either irregular or regular menstrual cycles. There may be an asymptomatic pelvic mass or dysmenorrhea. In adolescents and adults, pregnancy loss can cause the first suspicion of a uterine anomaly. Treatment is tailored to the specific anomaly.

Septate Uterus

Uterine septum (also known as a septate uterus) is the most common Müllerian anomaly, accounting for just over half of all abnormalities, and it is the most common structural uterine anomaly. After the two Müllerian ducts fuse in the midline, resorption must occur to unify the endometrial cavities; failure of this process results in some degree of uterine septum. It can vary in length from just below the fundus to beyond the cervix, depending on the amount of caudal resorption, but is generally defined as >1 cm. A septate uterus has a normal external uterine contour, which is what distinguishes it from a bicornuate or

didelphic uterus. An MRI can help delineate between a predominantly fibrous septum and a muscular or myometrial septum. There is insufficient evidence between an association of the uterine septum and infertility. Controversy still exists regarding whether a female should have such surgical removal of the septum as part of infertility treatment. A previous recommendation for surgical septum resection has been challenged by recent research, which demonstrated that septum resection did not improve live birth rates compared with expectant management. Limited data exist on the influence of the thickness and the length of the septum on the choice of treatment and reproductive outcomes. Differentiating precisely between bicornuate and septate uteri is extremely important to determine effective and safe treatment plans.

Bicornuate Uterus

Both Müllerian ducts develop and elongate in this anomaly, but they do not completely fuse in the midline. The vagina and external cervix are normal, but the extent of division of the two endometrial cavities can vary, depending on the extent of failed fusion between the cervix and the fundus. Bicornuate uteri are also associated with increased preterm labor and delivery, malpresentation, and miscarriage. This anomaly accounts for approximately 10–20% of Müllerian anomalies. Presently there is no pregnancy outcome data to provide evidence to support unification of a uterine duplication, and expectant management should be encouraged.

Unicornuate Uterus and Rudimentary Horns

A unicornuate uterus results from the normal creation of a fallopian tube, functional uterus, cervix, and vagina from one Müllerian duct. The other side fails to develop, resulting in either absence of the contralateral Müllerian duct or a rudimentary horn. There is a 30–40% association of renal anomalies. If a rudimentary horn is identified, it is important to determine whether functional endometrium is present (usually with T2-weighted MRI images). About two-thirds of rudimentary horns are noncommunicating, some with a fibrous band connecting the two structures. Rudimentary horns can also communicate with the contralateral uterus. A fertilized ovum can implant and develop within a rudimentary horn. Pregnancies within a rudimentary horn are incompatible with expectant management, and rupture of the horn could be life-threatening. Rupture tends to occur at a later gestation than with an ectopic pregnancy, and hemorrhage is severe. Patients with rudimentary horns with functioning endometrium can also present with pain caused by accumulating menses. Because the contralateral uterine horn has a normal outflow pathway, these patients present with cyclic pain and/or a mass, not primary amenorrhea. Pregnancies that arise in a unicornuate uterus are associated with increased preterm labor and delivery, malpresentation, and miscarriage. The patient should be counseled regarding these increased obstetric risks and be offered a preconception consult with a high-risk obstetric physician to best manage pregnancy.

Uterus Didelphys

A uterus didelphys is the result of a complete failure of fusion and represents 5% of Müllerian anomalies. There are two fallopian tubes, two separate uterine cavities, two cervices, and often two vaginal canals or two partial canals because of an associated longitudinal vaginal septum (75% of the time). At times, the longitudinal septum attaches to one sidewall and obstructs one side of the vagina (or hemivagina) (Fig. 591.4). Evaluation for renal anomalies should be pursued because they are common as well. The combination of uterine didelphys, obstructed hemivagina, and ipsilateral renal agenesis is a variant of the broad spectrum of Müllerian anomalies that is referred to as **obstructed hemivagina and ipsilateral renal anomaly (OHVIRA) syndrome** or **Herlyn-Werner-Wunderlich syndrome.** Adolescents with this disorder usually present with abdominal pain shortly after menarche. Although there still may be a risk of adverse pregnancy outcomes with a uterine didelphys (preterm labor, malpresentation), overall pregnancy outcomes are good and are associated with less risk than in other uterine anomalies, but preconception counseling and a consult with a high-risk obstetric physician should be offered.

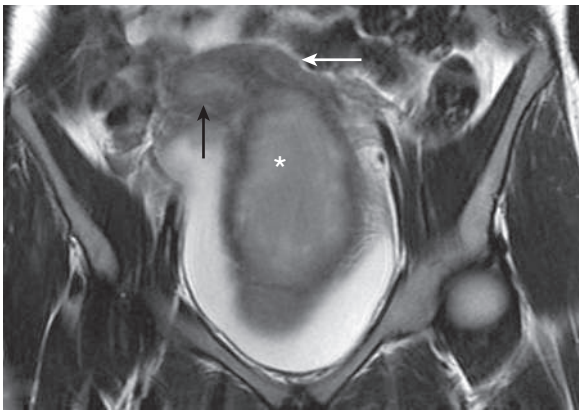


Fig. 591.4 Coronal MRI demonstrating large volume hematocolpos (*asterisk*) in a case of uterine didelphys with longitudinal vaginal septum. *Black arrow,* obstructed right uterus resulting in hematometra; white arrow, unobstructed left uterus.

Arcuate Uterus

An arcuate uterus is a uterine cavity that has a small midline septum from lack of a small amount of resorption (<1 cm), and sometimes a slight indentation of the uterine fundus. An arcuate uterus might represent a variant of normal rather than a Müllerian anomaly. Untoward pregnancy outcomes are rare, and *surgical correction is not warranted.*

Treatment

Treatment depends on the specific diagnosis and should be determined by a clinician with expertise in management of Müllerian anomalies. Most treatments focus on relief of obstruction and consider a patient's reproductive goals and history. Hysteroscopic surgical resection of the uterine septa was widely employed in the past, but a Cochrane systematic review shows no evidence to support surgical excision of the septum. Each individual case should be discussed with the patient, and a shared decision approach should be exercised based on the evidence of the benefit of such surgery.

A noncommunicating horn with functional endometrium should be resected to improve the quality of life or prevent future complications. Opinions vary as to whether resection of a communicating horn or one with no functional endometrium is warranted. Any surgical resection of a rudimentary horn requires careful surgical technique to protect the ipsilateral ovarian blood supply and the myometrium of the remaining unicornuate uterus.

Although metroplasty (also known as the Strassman unification method) had been employed with didelphic and bicornuate uteri in the past, currently most clinicians feel there is not enough evidence to support such a complicated procedure. Any obstruction to the outflow tract must be relieved; this can necessitate creation of a vaginal window or excision of the vaginal septum.

VAGINAL ANOMALIES

Abnormalities of the Hymen

An imperforate hymen is the most common obstructive anomaly, and familial occurrences have been reported (see Fig. 591.1). Its incidence is approximately 1 in 1,000. In the newborn period and early infancy, it may be diagnosed by a bulging membrane caused by a **mucocolpos** from maternal estrogen stimulation of the vaginal mucosa. This can eventually reabsorb if it is not too large or symptomatic. More often, it is diagnosed at the time of menarche when menstrual fluid accumulates **(hematocolpos)**. The clinical manifestations often are a bulging blue-black membrane, pain, and/or primary amenorrhea in a setting of normal secondary sex

characteristics. A mucocolpos or hematocolpos may obstruct urinary outflow. Depending on the circumstance, patients might have cyclic abdominal pain or a pelvic mass. Other hymenal variations can occur such as annular (most common) or crescentic configurations. In some cases, the hymenal membrane does not undergo complete resorption or perforation, resulting in a microperforate, cribriform, or septate-shaped hymen. Age of recognition varies, but hymenal variations are often discovered after menarche when it is difficult for an adolescent to place or remove a tampon.

Congenital Absence of the Vagina and Mayer-Rokitansky-Küster-Hauser Syndrome

Vaginal agenesis or atresia results when the vaginal plate fails to canalize. On physical exam, it appears as an extremely foreshortened vagina, sometimes referred to as a *vaginal dimple.* Isolated (partial) vaginal agenesis involves an area of aplasia between the distal vaginal portion and a normal upper vagina, cervix, and uterus. These patients present with cryptomenorrhea and eventually have cyclic pain caused by obstructed outflow. Each subsequent menses distends the upper vagina with menstrual blood. On initial presentation it may be confused with a low transverse septum or imperforate hymen, and therefore clear delineation of the anomaly with appropriate imaging is critical before attempting surgical repair. Surgical repair and reconstruction are complicated and best performed with consultation of specialists with expertise in managing these anomalies.

Uterine and **vaginal agenesis/aplasia** often occur together because of their close association during development, when Müllerian ductal development fails early in the process. The most common cause of uterovaginal agenesis/aplasia is **Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome,** with an incidence reported at 1 in 5,000 female births. The etiology is believed to be multigenetic and multifactorial. This condition is present at birth but often not diagnosed until mid-adolescence. Females with MRKH syndrome have normal ovarian function and undergo normal secondary sexual development at puberty but do not have a menstrual cycle (primary amenorrhea). The range and severity of MRKH syndrome can vary greatly and the disorder may be type I (isolated uterovaginal anomaly) or type II, involving additional organ systems, including the renal, skeletal, auditory, or cardiac systems. Absence of the vagina and uterus has significant anatomic, physiologic, and psychologic implications for the patient and family, and counseling is recommended. Although most patients with Müllerian agenesis have small rudimentary Müllerian bulbs, approximately 2–7% of patients can have active endometrium within these uterine structures. These patients will often present with cyclic pelvic pain. MRI may be necessary to determine if any small uterine remnant is present (often located on the pelvic sidewall or near the ovaries) and to clearly delineate the anomaly. Laparoscopy is not necessary to diagnose Müllerian agenesis but may be useful in the treatment of rudimentary uterine horns, particularly when removal of obstructed uterine structures or associated endometriosis is indicated for pelvic pain. Any diagnosis of Müllerian agenesis must be differentiated from **androgen insensitivity**; karyotype, serum testosterone levels, and pubic hair distribution help distinguish between the two because testosterone levels and adrenarche will be normal in females with MRKH syndrome.

Abnormalities involving other organ systems occur in association with MRKH type II, or Müllerian duct aplasia, renal dysplasia, and cervical somite anomalies (MURCS) association. The most common are urinary tract anomalies (15–40%) primarily involving unilateral absence of a kidney; a horseshoe or pelvic kidney; and skeletal anomalies (5–10%), which primarily involve vertebral development but can also include cardiac anomalies and hearing impairment, and these should be evaluated at the time of diagnosis.

Longitudinal Vaginal Septum

Longitudinal vaginal septa represent failure of complete canalization of the vagina. These often occur in the presence of uterine anomalies. These septa can vary in length from the cervix or cervices caudally and at times extend fully to the introitus. Patients may report menstruation that overflows their tampon because they only have a single side of the vagina occluded.

Transverse Vaginal Septum (Vertical Fusion Defects)

Vertical fusion defects can result in a transverse septum, which may be imperforate and associated with hematocolpos or hematometra in adolescents or with mucocolpos in infants. These are uncommon anomalies, reportedly found in 1 in 80,000 females. Patients commonly present with primary amenorrhea and cyclical abdominal pain around the time of menarche. However, patients who have a small opening in the transverse septa might present with prolonged vaginal drainage and mucopurulent or sanguineous discharge. Transverse vaginal septa can vary in location (15–20% occur in the lower third, but the majority are in the middle or upper third of the vagina) and thickness (but are generally ≤1 cm). High locations, thicker septa (>1 cm), and narrow vaginal orifices present challenging surgical cases.

Transverse vaginal septa may be associated with other congenital anomalies, although this occurs less often than with Müllerian agenesis. These patients have a functional normal uterus, unlike females with MRKH syndrome. In the majority of cases with outflow obstruction, there is also an increased incidence of endometriosis secondary to retrograde menstruation.

Evaluation of transverse vaginal septa includes careful pelvic examination and pelvic imaging, usually with MRI and ultrasound, to delineate the anatomic abnormalities. MRI is especially helpful to determine the thickness of the septum and verify the presence of a cervix for surgical planning. Diagnosis and treatment plans should be made as soon as possible after menarche because significant accumulation of hematometra and/or hematosalpinx could affect future reproductive success by negatively affecting uterine and/or tubal function. Alternately, menstrual suppression is another option to provide adolescent patients time to mature psychologically and participate in the treatment phase of the resection of the transverse septum.

Treatment

An imperforate hymen requires resection to prevent or relieve the outflow tract obstruction. Many approach it with a horizontal, lunate, or cruciate incision; excision of excess tissue; and approximation of the mucosal edges. Repair should be done at time of diagnosis if the patient is symptomatic, although the lesion may be repaired any time during infancy, childhood, or adolescence. Elective surgery with general anesthesia is discouraged in the very young. Elective hymenal excision in the prepubertal child may have improved healing if topical estrogen is placed at the site postoperatively. Elective excision of an imperforate hymen can be performed after onset of thelarche but ideally before menses. Variants in the hymen with microperforations or hymenal septa may interfere with tampon use, and resection of this tissue is usually electively performed using local anesthesia or sedation according to patient preference.

Treatment of congenital absence of the vagina is usually delayed until the patient is mature enough to discuss and participate in the treatment. The nonsurgical approach using vaginal dilation is the most common first-line therapy because it is safer, patient-controlled, more cost effective than surgery, and successful in 90–96% of patients. If done correctly, it is possible to achieve a functional vaginal length (6-8 cm), width, and physiologic angle for intercourse in about 6-8 months of therapy. When the ultimate size that accommodates coitus is reached, the patient must use the dilator or have coitus with a frequency that maintains adequate length.

Surgical approaches require expertise and often some postoperative vaginal dilation to ensure a functional result. Controversy exists as to when creation of a neovagina should occur. Surgery is indicated at any age if there is a medical indication such as mucocolpos that causes urinary obstruction or any other surgical emergency.

However, literature reports better outcomes with delaying creation of the neovagina to when the patient is interested in sexual activity and can participate in the decision to have surgery and in their own postoperative recovery. There is no consensus as to the best surgical option. Surgery should be reserved for the rare patient for whom primary dilator therapy was unsuccessful or for those who request surgery after a thorough informed consent. Referral to centers with expertise should be offered.

Future options for having children should be addressed, including adoption and gestational surrogacy. Assisted reproductive techniques using ovum retrieval, fertilization, and implantation of embryos into gestational carriers (surrogates) have been successful. Female offspring usually have normal reproductive tracts. Uterine transplantation has resulted in live births, but this procedure remains rare. Opportunities for family building enable patients and their families to appreciate the potential for becoming parents and help cope with the diagnosis and its implications.

Surgical resection of transverse vaginal septa should be undertaken only by surgeons with expertise. Some surgeons advocate waiting for one or more menstrual cycles or using preoperative dilators from below to increase the depth and circumference of the distal vagina and to allow menstrual blood to accumulate and dilate the upper portion of the vagina. Complete resection of the septum, with primary anastomosis of the upper and lower mucosal segments, should be attempted. A vaginal stent is sometimes placed postoperatively in the vagina to maintain patency and allow squamous epithelialization of the upper vagina and cervix. Follow-up dilation may be necessary after the stent is removed. Careful preoperative assessment is important because surgeons who begin a case believing they are operating on an imperforate hymen can find themselves in entirely different and more complex surgical planes. Regardless of the approach, vaginoplasty is often best deferred until the patient is mature and physically and psychologically prepared to participate in the healing process and postoperative dilator treatments. It can be challenging to differentiate a low transverse septum from distal vaginal agenesis. If the distal vagina cannot be palpated close to the anal sphincter by rectal examination, the patient should be allowed to continue to menstruate to distend the upper vagina to within 3 cm of the anal sphincter. This enables the surgeon to dissect up to the lower vagina and perform a pull-through procedure, anastomosing the upper vagina to the introitus. Proper timing and surgical execution yield excellent outcomes.

Longitudinal vaginal septa themselves do not lead to adverse reproductive outcomes but may be symptomatic in a patient, causing dyspareunia, traumatic bleeding with intercourse, difficulties with tampon insertion, or impedance during vaginal birth. Such complaints can warrant a resection of the vaginal septa. A carefully planned incision and resection of the oblique septum to maintain patency of the upper tract is performed in cases of OHVIRA (Herlyn-Werner-Wunderlich syndrome).

CERVICAL ANOMALIES

Congenital atresia or complete agenesis of the uterine cervix is extremely rare and often manifests at puberty with amenorrhea and pelvic pain. It is associated with significant renal anomalies in 5–10% of patients. A pelvic MRI is often warranted to completely define the abnormality. Usually, pain and obstruction are significant, and a hysterectomy is necessary. Attempts to reconnect the uterus to the vagina are rarely successful and are associated with significant morbidity and reoperation rates. The ovaries usually have normal function, and future reproduction can still occur using in vitro fertilization and a gestational carrier.

VULVAR AND OTHER ANOMALIES

Complete Vulvar Duplication

Duplication of the vulva is a rare congenital anomaly that is seen in infancy and consists of two vulvas, two vaginas, and two bladders, a didelphic uterus, a single rectum and anus, and two renal systems. Treatment is individualized and requires a multidisciplinary approach with gynecology, urology, and plastic surgery.

Labial Asymmetry and Hypertrophy

With the onset of puberty, the labia minora enlarge and grow to an adult size. A female's labia can vary in size and shape. Asymmetry of the labia, where the right and left labia are different in size and appearance, is a normal variant. Some patients are uncomfortable with what they perceive to be their asymmetric or enlarged labia minora and complain about self-consciousness and discomfort while wearing tight clothing, exercising, or having sex. The mature labia minora can protrude beyond the labia majora, and this normal variant can be functionally or psychologically bothersome. Local irritation, problems of personal hygiene with bowel movements or menses, or interference with sexual intercourse or while sitting or exercising have resulted in requests for labial reduction. Patients may find online procedures advertised to reduce uneven or enlarged labia minora. Education and reassurance are very important for adolescents who have concerns about the appearance of their labia. Surgery is not recommended unless there is significant congenital malformation or persistent symptoms directly related to the labia. Surgical alteration of the labia that is not necessary to the health of the adolescent less than age 18 is considered a violation of federal law in the United States. Complications of labial surgery include loss of sensation, keloid formation, and dyspareunia.

Clitoral Abnormalities

Agenesis of the clitoris is rare. Clitoral duplication has been reported, often associated with cloacal and bladder exstrophy. Exposure to male hormones will result in clitoral enlargement and is often a sign of a difference of sex development, a testosterone-producing tumor, or use of exogenous steroids.

Cloacal Anomalies

Cloacal anomalies are rare lesions representing a common urogenital sinus into which the gastrointestinal, urinary, and vaginal canals all exit. Usually there is an abnormality in all or some of the processes of fusion of the Müllerian ducts, development of the sinovaginal bulbs, or development of the vaginal plate. The single opening (cloaca) requires surgical correction, which is often done very early in life, preferably by a multidisciplinary pediatric surgical team.

Ductal Remnants

Even though the opposite duct regresses in both sexes, there can sometimes be a small portion of either the Müllerian or Wolffian duct that remains in either the male or female, respectively. Such remnants can form cysts, which are what make them clinically visible during surgery, examination, or imaging. Most do not cause pain, although torsion of some has been reported, and small asymptomatic ones usually do not require resection. The most commonly reported are hydatid of Morgagni cysts (remnant of a Wolffian duct arising from the fallopian tube), cysts of the broad ligament, and Gartner's duct cysts, which can form an ectopic ureter or be found along the cervix or vaginal walls.

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Chapter 592

Gynecologic Care for Adolescents with Special Needs

Elisabeth H. Quint and Melina L. Dendrinos

Adolescence presents challenges for all children and their families but particularly for teens with special needs and their families. The start of menstrual periods, the mood changes associated with puberty, the concerns about sexual activity with possible unplanned pregnancies, and worries about safety and abuse present teens with disabilities and their families with additional issues.

SEXUALITY AND SEXUAL EDUCATION

Adolescents with special needs can have physical and/or developmental disabilities. These young people are often seen as asexual by their families, care providers, and society and, therefore, sexual education might not have been provided or considered necessary, even though physically disabled teens report being sexually active. The care provider needs to assess the teen's knowledge of anatomy and sexuality, gender identity, social knowledge of relationships, ability to consent to sexual and intimate activities, and sexual orientation, as well as any previous sexual activity. Education regarding HIV and other sexually transmitted infections, disease prevention, and contraception, including emergency contraception, should be offered at a developmentally appropriate level.

ABUSE

The risk for sexual abuse in teens with disabilities is difficult to estimate. Teens with disabilities may be more at risk for isolation and depression during adolescence, leading to vulnerability.

Teens with disabilities are just as sexually active or even more so than their nondisabled counterparts, but more of their activity is nonvoluntary. Patients with cognitive impairment are often taught to be cooperative, which may make them more vulnerable to coercion. Abuse prevention education can include the No! Go! Tell! model. For teens with limited verbal capacity or developmental delay, abuse may be very hard to detect; thus screening for abuse is extremely important. The care provider needs to be vigilant in looking for signs on physical exam, such as unexplained bruises or scratches, or changes in behavior, such as regression, which may be indications of sexual abuse (see Chapters 17.1 and 162).

PELVIC EXAMINATION

An internal pelvic exam is rarely indicated in teens, as Papanicolaou smears are not recommended to start until age 21. An external genital exam can be performed if there are vulvovaginal issues such as discharge, irregular bleeding, suspicion for abuse, or foreign body. The frog-leg position is usually favored over the use of stirrups. If the vagina or cervix needs to be clearly visualized for a medical indication, an exam under anesthesia by a gynecologist can be considered. Testing for sexually transmitted infections can be accomplished by urine testing or vaginal swabs (see Chapter 163).

MENSTRUATION

Irregular menstruation is common in teenagers, especially during the first 5 years after menarche, because of immaturity of the hypothalamic-pituitary-ovarian axis and subsequent anovulation (see Chapter 159). Several conditions in teens with disabilities are associated with an even higher risk of irregular cycles. Thyroid disease is more common in teens with Down syndrome. There is a higher incidence of reproductive issues, including polycystic ovarian syndrome, in teens with epilepsy or those taking certain antiepileptic drugs. Antipsychotic medication can lead to hyperprolactinemia, which can affect menstruation.

For teens with disabilities, the main issue with menstrual cycles, whether they are regular, irregular, or heavy, is the impact of menstruation on the patient's life, health, and ability to perform their normal activities. The history should focus on this aspect, and menstrual calendars may be helpful to document the cycles, behavior, and impact of treatments. Most adolescents who self-toilet can learn to use menstrual hygiene products appropriately. Menstrual underwear have been very helpful for many teens. Premenarchal anticipatory guidance is recommended, but hormonal treatment before menarche should be avoided.

The medical evaluation for abnormal bleeding is the same as for all teens (see Chapter 159.2). Areas requiring particular attention for the teen with special needs are the consideration of menstrual suppression for hygiene or cyclical behavioral issues, like crying, tantrums, or withdrawal.

Treatment of Menstruation

If the impact of cycles, whether regular, irregular, or heavy, on the patient's well-being is significant (often documented through menstrual or behavioral charting for several months), the care provider, patient, and family may decide on menstrual intervention. Menstrual regulation or suppression is not much different from that in the nondisabled teenager in general, although there are some special considerations. Goals for treatment can be to decrease the heaviness of flow, regulate cycles to predictable bleeding, relieve pain or cyclical behavior symptoms, provide contraception, and/or obtain amenorrhea. Menstrual suppression leading to complete amenorrhea is usually difficult to obtain and infrequent scheduled bleeds may be easier to manage than unpredictable spotting, a common side effect of any suppressive treatment, for certain patients. After treatment has started, providers should continue to monitor outcomes, ideally with continued menstrual or behavioral calendars to assess efficacy and need for changes.

Nonhormonal Methods

If menorrhagia or dysmenorrhea (occasionally leading to cyclical behavior changes in nonverbal teens) is the main concern, the patient can be started on scheduled nonsteroidal anti-inflammatory drugs. These can decrease the flow by up to 20% in adequate doses and can be used alone or in combination with other treatments. Use of tranexamic acid during the first 5 days of menses can also be used to decrease heavy bleeding.

Estrogen-Containing Methods

All estrogen-containing medication can be used in a cyclical fashion with scheduled medication breaks to allow for monthly menses; in a more extended fashion, where the active hormonal method is used for 3 months with a scheduled break; or a more flexible schedule, where the hormones are used until bleeding starts, and a break for withdrawal bleeding can be done at that time.

Oral Contraceptives

Cyclical oral contraceptives usually lead to regular, lighter cycles with less cramping. Continuous daily use of active oral contraceptives can suppress cycles, with amenorrhea rates improving with time. Some unpredictable spotting is usually unavoidable, and often teens with special needs prefer to have predictable cycles several times a year. Chewable oral contraceptives are available for those with swallowing issues.

Contraceptive Ring
The contraceptive ring can be used in a pattern of 3 weeks in and 1 week out, but it can also be used (off-label) in a continuous 4-week pattern, which leads to less bleeding. However, the contraceptive ring may be difficult to use for a teen with dexterity problems, and help with placement has obvious privacy issues.

Contraceptive Patch
The weekly patch can also be used in a cyclic or extended fashion. Some teens with developmental disabilities and sensory issues may remove their patch erratically, and placement out of reach (e.g., on buttocks or shoulder) is advised.

Estrogen Use, Venous Thromboembolism, and Mobility Issues
Whether immobility and wheelchair use can lead to an increased risk of venous-thromboembolic events (VTEs) in association with estrogen-containing contraceptives remains controversial. The risk of thrombosis in young females is very low overall, but the use of combined hormonal contraceptives by adolescents who are immobile or who have limited mobility has not been studied. Immobility per se is not a contraindication to estrogen-containing contraceptives; however, it may increase the risk of VTE. There are limited data to support the concern that higher-dose oral estrogen and the third- and fourth-generation progestin preparations may have a higher risk for VTE. It is important to assess for other VTE risk factors in the patient's history before initiating estrogen therapy. Careful use of lower-dose (30 or 20 μg) ethinyl estradiol preparations after appropriate counseling may be advisable, and third-generation progestin combinations should only be used if second-generation medications have failed.

Progestin-Only Methods
Intramuscular Medroxyprogesterone Acetate
Intramuscular depot medroxyprogesterone acetate (DMPA) has long been used for menstrual suppression. Two issues are particularly relevant to teens with disabilities. Studies documenting a decrease in bone density associated with longer-term use of DMPA and a black box warning by the FDA have raised concerns about use of these products in young females, although research indicates that the bone density improves after the medication is stopped. For teens with mobility issues or those with very low body weight who are already at risk for low bone density, decreased bone density is a real concern, although the risk of fractures is unclear. Adequate calcium and vitamin D is recommended. The second issue for teens with mobility issues is weight gain associated with DMPA, especially among obese teens, which can lead to transfer and mobility issues. The potential health risks associated with the effects of DMPA on bone density and weight must be balanced against the need for menstrual suppression and the likelihood of unintended pregnancy. Weight should be monitored closely. Routine bone density scanning (DEXA) is not recommended in adolescents.

Oral Progestins
Continuous oral progestins can also be very effective in obtaining amenorrhea. The contraceptive progestin-only pill (norethindrone 0.35 mg) can cause significant irregular spotting, so if full suppression is the goal, then other progestins can be used daily, such as drospirenone 4 mg, norethindrone 2.5 or 5 mg, or micronized progesterone 200 mg.

Progesterone Intrauterine Device
The 8-year levonorgestrel-intrauterine device is used for many teenagers for contraception, as well as heavy menses and dysmenorrhea (off-label use). Teens with special needs might require anesthesia for insertion if the exam is difficult because of discomfort, contractures, or a narrow vagina. Checking for strings in a clinic setting may be challenging; however, the intrauterine device location can be confirmed by sonography. There may be a significant amount of irregular bleeding and spotting in the first several months, but there is 20% rate of amenorrhea after insertion and up to 50% rate of amenorrhea after 1 year of use. The bleeding profile of the smaller and lower dose 3-5 year levonorgestrel-intrauterine devices may not be as helpful for menstrual suppression; the amenorrhea rates from the initial studies by the manufacturer are 8–12% at 1 year, but more studies are needed.

Implants
Progestin subdermal implants have relatively low amenorrhea rates and higher rates of unscheduled bleeding; therefore they are often less desirable for menstrual suppression for teens with special needs. They also require significant patient cooperation for insertion.

Hormones and Antiepileptic Drugs
Certain enzyme-inducing seizure medications can interfere with estrogen-containing contraceptives, change their contraceptive effectiveness, and/or lead to intermittent bleeding. Higher estrogen dose or shorter injection intervals for DMPA may be considered. The only antiepileptic medication that is affected by combined oral contraceptives is lamotrigine; consequently, the dose of that medication may need to be adjusted if used in conjunction with hormones, so discussion with other providers is needed.

Surgical Methods
Surgical procedures, such as endometrial ablation, a procedure where the lining of the uterus is surgically removed, and hysterectomy, are available for treatment of abnormal and heavy bleeding in adults, but they should only rarely be used in extreme situations for teenagers where all other methods have failed, and the patient's health is severely compromised by their cycles. Endometrial ablation only leads to amenorrhea approximately 30% of the time, has a higher failure rate in females younger than 40 years of age, and is not recommended in the adolescent population. Ethical considerations around these methods leading to infertility and consent issues are complicated, and state law varies on this topic.

CONTRACEPTION
See also Chapter 160.

The menstrual management methods discussed above can also be used for contraception. A request for birth control, especially coming from a caregiver and not the teen, requires an evaluation of the teen's ability to consent to sexual activity and the safety of their environment. The method chosen should be the safest method for their situation with the highest protection rate. Therefore a long-acting reversible contraceptive method may be advisable. Sexually transmitted infections and condom use should be addressed with the teen and specific guidelines on how to obtain condoms and negotiate their use may be needed. A discussion about emergency contraception is recommended, as well as ways to help the teen obtain this if indicated.

Chapter 593

Female Genital Mutilation

Deborah Hodes and Sarah M. Creighton

Female genital mutilation (FGM) is a worldwide human rights issue that constitutes violence against women and children. It is defined by the World Health Organization (WHO) as procedures that involve partial or total removal of the external female genitalia, or other injury to the female genital organs for nonmedical reasons. In September 2015 the United Nations adopted the Sustainable Development Goals (SDGs), which includes the elimination of FGM by 2030. UNICEF (United Nations International Children's Emergency Fund) estimates that at least 200 million women and young females in 30 countries have undergone FGM. There has been a decline in the prevalence of FGM, but current trends suggest that actual numbers will rise because of population growth. FGM is commonly performed in Africa, the Middle East, and Asia, with data suggesting an estimated 40 million young females in Indonesia have undergone FGM. According to the UNICEF report 2020, the COVID-19 pandemic has caused disruption to the protection of young females from FGM leading to an estimated 2 million additional cases than would otherwise have occurred.

The migration of FGM-practicing communities means that FGM is a global problem, although there are scant data on the practice in high-income countries. Despite estimates, a British pediatric surveillance unit study found low numbers presenting to pediatricians; there were very few illegal cases and only one successful prosecution in the UK by 2021. FGM is almost always carried out on children, and pediatricians must be familiar with the identification of FGM, the impact on health, and ways to protect young females from this widespread form of child abuse.

FGM has no health benefits and can cause lifelong damage to physical and psychologic health. The WHO has classified FGM into four types, depending on the extent and type of genital tissue removed (Table 593.1). The traditional practitioner performs FGM without anesthetic or sterile conditions, and in some countries, it is done as part of a wider ritual related to early child marriage. The child is restrained whilst the external genitalia are removed or damaged using a knife, scalpel, or other sharp instrument. An increasing number of procedures are performed at a younger age, and the United Nations Population Fund (UNFPA) estimates that around one in five young females subjected to FGM were cut by a trained healthcare provider. Table 593.2 lists potential risks and protective factors for FGM.

COMPLICATIONS

Immediate complications of FGM include hemorrhage and infection. Deaths have been reported, although numbers are unknown. Infections include immediate wound infection, tetanus, and gangrene. FGM has been implicated in the transmission of blood-borne infections because of the use of shared and unsterile tools. Although procedure-related blood-borne infection is probable, there are no good studies to confirm this; infections such as hepatitis B and HIV are endemic in areas where FGM is prevalent. FGM leads to obstetric, gynecologic, and psychologic consequences in adult women. Gynecologic symptoms include painful and unsightly scarring, clitoral cysts, and recurrent urinary infections. Menstrual difficulties and infertility are reported, although the underlying mechanisms of these are unclear apart from type 3 FGM, where the vagina is narrowed. FGM damages sexual function by removing sensitive sexual tissue and narrowing the vagina. Mental health problems such as anxiety and depression have been linked to FGM. FGM also has a detrimental impact on obstetric outcomes for both the mother and baby, leading to increased risks of postpartum hemorrhage, perineal trauma, and perinatal death.

Table 593.1 Summary of WHO Classification of FGM

Type 1: Clitoridectomy: Partial or total removal of the clitoris (a small sensitive and erectile part of the female genitals) and, in rare cases, only the prepuce (the fold of skin surrounding the clitoris).
Type 2: Excision: Partial or total removal of the clitoris and labia minora with or without removal of the labia majora (the labia are the "lips" that surround the vagina).
Type 3: Infibulation: Narrowing of the vaginal opening through the creation of a covering seal. The seal is formed by cutting and repositioning the labia minora or majora with or without removal of the clitoris.
Type 4: Other: All other harmful procedures to the genitalia for nonmedical reasons (e.g., pricking, piercing, incision, scraping, and cauterizing the genital area).

From the World Health Organization Female Genital Mutilation Fact Sheet. https://www.who.int/news-room/fact-sheets/detail/female-genital-mutilation

CLINICAL MANAGEMENT OF FGM

Most pediatricians will not see a child who is acutely unwell due to FGM. Management of FGM in the acute situation should include assessment for blood loss, sepsis, and urinary retention and treatment with antibiotics, analgesia, tetanus toxoid, and urinary catheterization. Pediatricians are more likely to see a child in whom FGM has been found during the investigation of other often vague symptoms as well as recurrent urinary tract infections and vulvovaginitis. FGM may also be alleged by the child or family member, or concerns may be raised by other health and social care professionals, particularly if the mother herself has undergone FGM and has little support from the husband (see Table 593.2). Pediatricians may be asked to confirm FGM on genital examination; it should be performed using a colposcope for magnification and video documentation, which can be used for peer review and in a court of law. The examination must be done in a sensitive and gentle manner by an appropriately trained clinician and in an age-appropriate setting. It is often assumed that FGM will be obvious. However, whilst type 3 FGM, in which the vagina is sealed, is usually easy to detect, other types of FGM can be more difficult to diagnose. This is particularly true for type 4 FGM, which may involve a prick or small scratch on or adjacent to the clitoris and may heal without a trace. General assessment of the child's health should include screening for blood-borne viruses.

If the child has type 3 FGM, then a deinfibulation procedure will be required at some point. Deinfibulation is a minor surgical procedure to divide any scar tissue that obscures the vaginal introitus. If the child is asymptomatic, this can be deferred until adolescence or before sexual activity. Deinfibulation procedures are usually performed under a local anesthetic in adult women, but in children a brief general anesthetic is more appropriate. The psychologic impact of FGM on a child may be severe, and flashbacks and nightmares have been reported. Input from a child psychologist or psychotherapist with experience in working with children with FGM and their families should be available. If a child is confirmed to have FGM, then other children in the family may be at risk, and local safeguarding pathways should be activated. Pediatricians must be advocates against FGM and contribute to training

Table 593.2 Factors That Influence Whether or Not a Child May Have FGM

RISK FACTORS
Mother or sister cut
Isolated mother
Grandmother influential
Little information and discussion about FGM
PROTECTIVE FACTORS
Discussing with husband or friend
Knowing the law has been implemented
TV, global debate, media
Men's attitude and knowledge
Knowing an uncut person

healthcare workers who may treat patients. In developed countries, there are concerns that the emphasis on prosecution has stigmatized and alienated communities in the diaspora who have abandoned the practice; because of this, experts emphasize the need for a more community-centric approach to current and future FGM prevention efforts.

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