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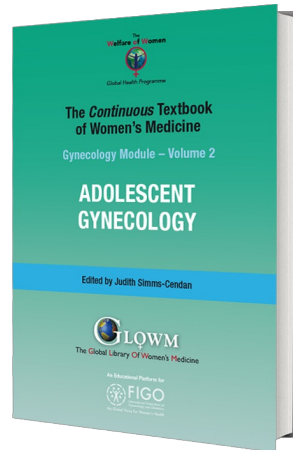
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Chapter

Prepubertal Genital Bleeding

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INTRODUCTION

Genital bleeding in prepubertal girls is multifactorial, with etiologies often differing from those seen in adult women. A careful history and thorough physical examination are required to adequately elucidate these cases.

PHYSICAL EXAMINATION OF THE PREPUBERTAL PATIENT

A complete physical examination, including assessment of the skin, tanner stage of breasts and pubic hair, is indicated when a child presents with vaginal bleeding. The vaginal length of a prepubescent girl is usually less than 5 cm. Therefore, the distal portion of the vagina can be visualized relatively easily, as long as the child is appropriately positioned and cooperative and adequate lighting is provided. The hymen walls should be pulled taut by the examiner by gentle traction on the labia majora, as shown in Figure 1. In some cases, examination under anesthesia with vaginoscopy is required to clarify clinical suspicion of lesions (vaginal neoplasms, foreign bodies, etc.), infections, or isolated premature menarche.



Figure 1 Proper examination technique: hymen and vagina. Gentle traction should be applied on the labia majora toward the examiner to pull the hymen taut and allow visualization of the distal vaginal walls. (Personal case, LDH.)

CLASSIFICATION OF VAGINAL BLEEDING IN PREPUBERTAL PATIENTS

For educational purposes, genital bleeding in children can be divided into two large groups by etiology: non-hormonal causes and hormonal causes, as shown in Box 1.

Non-hormonal causes are usually related to trauma (accidental falls, sexual abuse, scratching), inflammatory processes (purulent genital discharge, foreign body, vulvar lichen sclerosus et atrophicus, parasitic infestations, urethral prolapse), or neoplasms (vaginal or uterine tumor).

Hormonal causes usually co-occur with other signs of hyperestrogenism: breast development (breast buds), physiologic leukorrhea, areolar and/or labia minora pigmentation, and enlargement of the labia minora.

Rare cases of recurrent bleeding with normal clinical (including vaginoscopy) and laboratory evaluation are ascribed to early isolated menarche, probably due to the presence of endometrial estrogen receptors that are highly sensitive to normal variations in serum estrogen in children.

Box 1 Causes of genital bleeding in prepubertal children.

Non-Hormonal Causes:

- Vulvovaginitis
- Parasitosis
- Foreign body

- Lichen sclerosus et atrophicus
- Urethral prolapse
- Lower genital tract tumors
- Hemangioma

Hormonal Causes:

- Pseudomenstruation (false menses)
- Autonomous ovarian follicular cyst
- McCune–Albright syndrome
- Estrogen-producing tumors
- Exogenous estrogen administration
- True precocious puberty
- Isolated premature menarche

NON-HORMONAL CAUSES

Genital bleeding in children is a sign that requires prompt evaluation and etiological diagnosis. Most cases are non-hormonal. Vaginal tumors, whether benign or malignant, are rare.

Vulvovaginitis

Vulvovaginitis is the most common gynecological condition of childhood. It is usually due to irritation of the sensitive, non-estrogenized vaginal mucosa. The most common clinical picture in vulvovaginitis includes hyperemia, leukorrhea, itching, and burning. However, some cases present with bloody vaginal discharge or frank vaginal bleeding due to severe inflammation, as described below.²

In most cases, no specific pathogen is identified, and vaginal discharge cultures are either negative or grow bacteria from the normal flora of the skin, respiratory tract or gut. This is known as non-specific vulvovaginitis.

In the remaining approximately 25% of cases, a pathogen can be isolated and identified (specific vulvovaginitis). The most commonly identified pathogens in these cases are group A β -hemolytic *Streptococcus* (GAS; *Streptococcus pyogenes*), *Haemophilus influenzae*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Shigella*, and *Enterobius vermicularis* (pinworms). In children who have been abused, sexually transmitted pathogens such as *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Trichomonas vaginalis* may be identified.¹

GAS infection is usually caused by self-inoculation through the child's own contaminated hands, usually after a respiratory tract infection. Discharge may be purulent or bloody. Onset is abrupt, with marked vulvar erythema and, possibly, pruritus and pain. Treatment consists of penicillin-class antibiotics.

Most cases of vaginal *Shigella* infection are due to direct contact of the vulva with contaminated feces after a gastrointestinal infection (diarrhea with bloody mucus). The presence of profuse, bloody vaginal discharge is suggestive of *Shigella* vulvovaginitis; stool cultures confirm the diagnosis. Treatment consists of appropriate antibiotic therapy (sulfamethoxazole/trimethoprim).

Vaginal infection by *Neisseria gonorrhoeae* is rarely asymptomatic, usually presenting with greenish, frankly purulent, or blood-streaked purulent vaginal discharge. The diagnosis is established by culturing vaginal discharge or by PCR (polymerase chain reaction) of vaginal discharge or urine specimens. Gram staining can only suggest the diagnosis, never confirm it, as false-positive rates are high. In such cases, further investigation is required. Detection of gonococci by PCR or cultures of vaginal discharge samples is pathognomonic of sexual abuse, except in the first 2 to 3 years of life, as contamination through the birth canal can also be a route of transmission. If sexual abuse is confirmed or suspected, the proper authorities must be notified. Due to the significance of a diagnosis of gonococcal infection in this age group, the use of two different techniques (e.g., both PCR and cultures) is recommended to confirm the diagnosis, preventing a false-positive result and all the legal consequences that would entail.³

Pinworms, or threadworms (*Enterobius vermicularis*), are intestinal parasites. The main symptom of enterobiasis

(pinworm infection) is anal itching, especially at night. It affects school-aged children most frequently. In girls, it can cause vulvovaginitis with severe vaginal itching; this, in turn, may cause bleeding due to scratching. The diagnosis may be established through Graham's test, whereby clear adhesive tape is applied to the perianal skin so that any pinworm eggs will stick to the tape. These eggs are then placed on a slide and viewed under a microscope. Treatment consists of antiparasitic agents, such as albendazole and mebendazole, and may be done empirically in girls thought to have a higher likelihood of exposure. Proper hand hygiene is essential to preventing such infections, as is proper washing of bedding, towels, underwear, and pajamas.

Foreign body

Recurrent vaginal discharge is a common presentation of retained foreign bodies in the vagina in children. The clinical presentation usually involves fetid vaginal discharge and recurrent vaginal bleeding, even after initial treatment. Although rare, complications have been described in the literature, such as vaginal stenosis, vesicovaginal fistula, abscess formation, and urethral obstruction. The most common retained foreign body is toilet paper; however, many types of small objects can be found, such as toys.⁴

Imaging (including pelvic X-ray and pelvic ultrasound) is of little value, since, in most cases, the objects are small and radiolucent. A thorough physical examination and clinical history are of greater diagnostic utility. Figure 2 illustrates the presence of a foreign bodies in the vagina (2a, a bath sponge; 2b, toilet paper fragments in the distal third of the vagina).

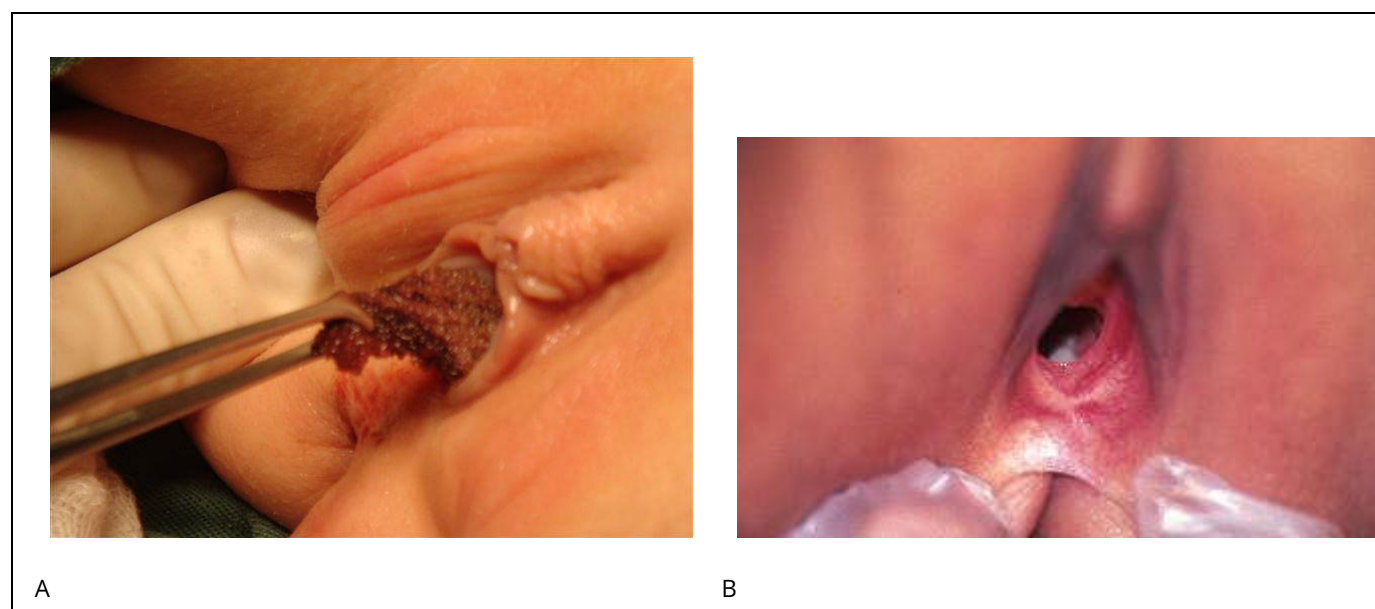


Figure 2 (A) Removal of a bath sponge during vaginoscopy; (B) toilet paper fragments in the distal third of the vagina, removed in office. (Personal case, LDH.)

In some cases, the foreign body may be visualized directly upon traction of the labia majora. When a foreign body is identified in the office setting, vaginal washout and instillation of saline solution can be performed in an attempt to remove the retained object. When children introduce a foreign body into their vaginas, they rarely do so deeply, so most foreign bodies are located in the lower third of the vagina and can be visualized and removed in the office if the patient is cooperative.

When necessary, vaginoscopy with a hysteroscope is the gold standard for diagnosis. This procedure allows visualization and examination of the vaginal walls, identification of the foreign body, and subsequent removal, which generally suffices as treatment.

Lichen sclerosus et atrophicus

Lichen sclerosus is a chronic skin disease of poorly defined etiology. Certain factors are believed to trigger immune-system changes in predisposed patients, causing a chronic inflammatory skin reaction. There is an established relationship between lichen sclerosus and autoimmune diseases, such as thyroiditis and vitiligo.

The clinical picture is characterized by severe vulvar itching, fissures (which may lead to bleeding), burning, and dysuria. On physical examination, hypopigmented areas are visible in the perineal region; these can coalesce and take on the characteristic figure-of-eight configuration, surrounding the vaginal introitus and perianal skin. In the absence of adequate diagnosis and treatment, lichen sclerosus leads to epithelial thinning, atrophy of the labia minora, clitoral fusing, and bruising and abrasions as a result of scratching (Figure 3).



Figure 3 Hypopigmented plaques and areas of hemorrhagic rash due to lichen sclerosus et atrophicus in a child. (Personal case, LDH.)

Proper diagnosis is often delayed and occurs only after numerous courses of inadequate treatment, often for candidiasis. The diagnosis is clinical and confirmation by biopsy is rarely necessary. High-potency topical corticosteroids, such as clobetasol propionate and betamethasone valerate, are the most commonly used treatment. They can be administered up to twice a day in highly symptomatic periods and continued at low doses for maintenance. There is evidence to support the use of topical immunosuppressants such as tacrolimus in persistent cases.⁵

Urethral prolapse

Urethral prolapse is due to the circular protrusion of the distal urethral mucosa through the external urethral meatus. Congestion and tissue ischemia gradually occur due to the intrinsic muscle tone of the urethral meatus. This leads to edema, further congestion, and, very rarely, tissue necrosis.

The pathophysiology is poorly understood, but weakness of the smooth muscles of the urethra, compounded by tissue fragility due to a lack of estrogen stimulation and recurrent increases in intra-abdominal pressure, have been implicated. It can be asymptomatic in some cases, or present as blood on underwear or diapers in others. Less commonly, it can cause urinary retention, dysuria, and perineal discomfort.

The diagnosis is again clinical, confirmed through a thorough history and physical examination. The presence of circumferential edematous tissue around the urethral meatus (as shown in Figure 4) is diagnostic. Urethral prolapse can be graded from first-degree to fourth-degree according to the severity of impairment identified on physical examination, ranging from mild (minimal edema only) to severe (hemorrhage, necrosis, and ulceration).

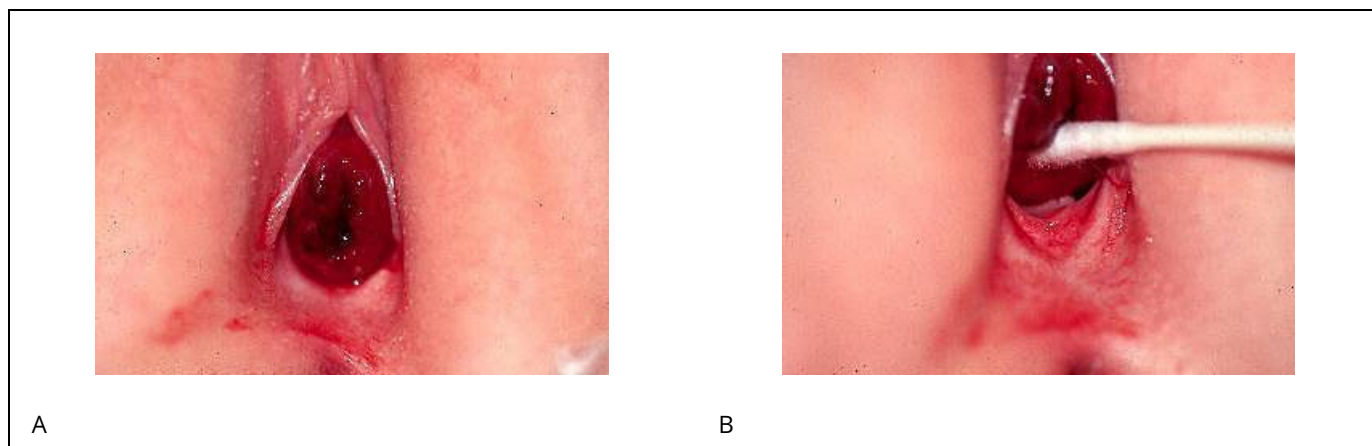


Figure 4 (A) Genital bleeding with a urethral annular mass due to urethral prolapse in a child; (B) cotton swab pushing back the annular mass, allowing visualization of an intact hymen and normal vaginal cavity. (Personal case, LDH.)

There is still no consensus on the optimal course of treatment, which depends on the severity of the physical examination findings. General hygiene, sitz baths with warm water, and local application of topical estrogens are usually sufficient to resolve the condition. In the case of severe pain, hemorrhage, and necrosis, surgical excision of the prolapsed mass is indicated.⁶

Hymenal polyp

Hymenal polyps or tags can affect children, but occur most frequently in neonates (due to stimulation by maternal hormones) or in pubescent girls.

On physical examination, a firm, smooth tissue growth the same color as the hymen is seen (Figure 5). In most cases, hymenal polyps are asymptomatic, but they can occasionally cause vaginal bleeding.



Figure 5 Hymenal polyp in a pubescent girl. (Personal case, LDH.)

In asymptomatic cases, no treatment is necessary. In cases of bleeding or a particularly large polyp, surgical resection is an option.⁷

Vaginal hemangioma

A hemangioma is a vascular anomaly that is characterized by the abnormal growth of blood vessels in a disordered, convoluted manner, which leads to the formation of a tumor.

In children, hemangiomas are usually present at birth, grow rapidly in the child's first year of life and may show involution thereafter. Hemangiomas of the female genital tract are rare, but may affect the vulva, vagina, cervix, or urethra. Some may cause bleeding, as shown in Figure 6.

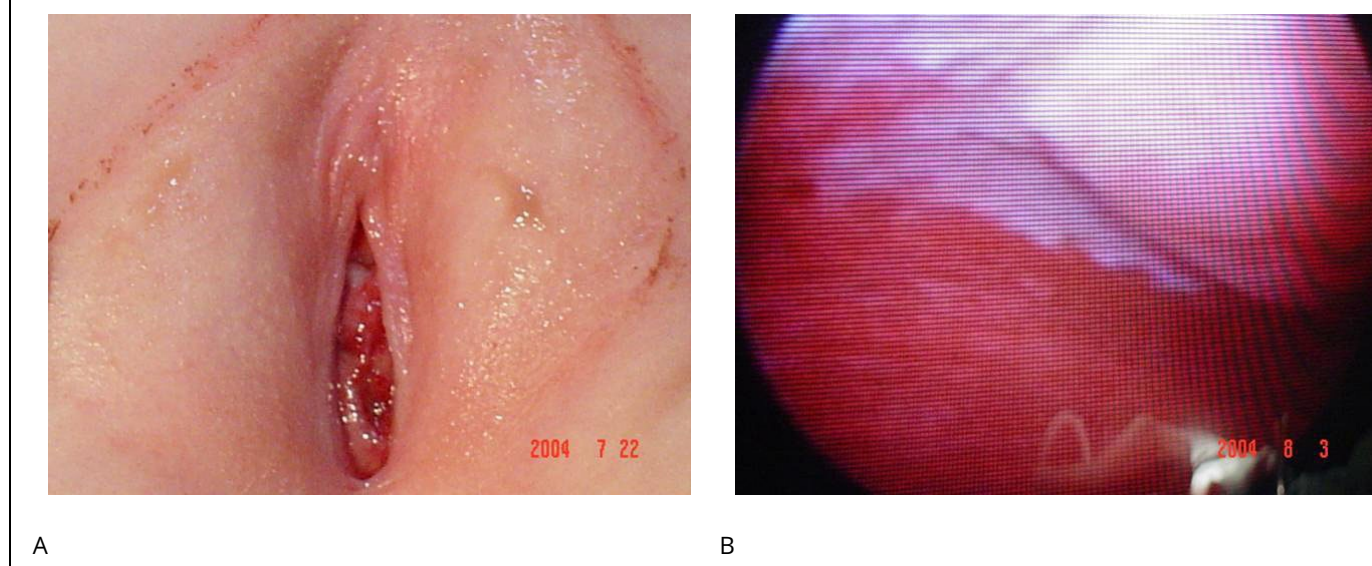


Figure 6 (A) Child with non-estrogenized vulva showing active genital bleeding; (B) a vaginal hemangioma in the same child, visualized through vaginoscopy. (Personal case, LDH.)

In vaginal cases, the diagnosis is established through vaginoscopy with a hysteroscope and infusion of saline solution. Treatment depends on symptom severity. Deep hemangiomas can be treated with oral or intralesional corticosteroids.⁸ In persistent cases, the potential for benefit (or need) of surgical removal can be assessed.

Malignant neoplasms of the lower genital tract

Benign or malignant genital tract tumors are unusual causes of bleeding in prepubescent girls.

Among malignant vaginal neoplasms, the most common is embryonal rhabdomyosarcoma, followed by endodermal sinus tumor. These tumors usually present with irregular vaginal bleeding and, occasionally, extrusion of the tumor through the vagina. Some malignancies, such as endodermal sinus tumor, may be accompanied by a significant rise in alpha-fetoprotein levels, which can also be used to assess the response to treatment and to detect disease recurrence. Vaginoscopy under anesthesia has a diagnostic sensitivity of 100%; therefore, it should always be recommended in the investigation of children with vaginal bleeding when tumors of the genital tract are suspected.⁹

Sarcoma botryoides

This is an aggressive subtype of embryonal rhabdomyosarcoma that usually manifests in the first two decades of life, especially in infants. It is the most common soft-tissue tumor of early childhood, corresponding to 4 to 6% of all malignant neoplasms in the pediatric age group. It is particularly common in children under 6 years of age. It appears to occur sporadically and no risk factors are known to date. The term botryoides comes from the Greek *bótrys*, which describes the tumor's similarity to "a bunch of grapes".¹⁰

The typical presentation of the tumor is a nodular mass resembling a bunch of grapes (as the name implies), which projects out of the vagina (Figure 7) and usually causes genital bleeding. Early diagnosis is essential to allow multidisciplinary treatment, which consists of a variety of surgical procedures, radiation therapy, and systemic chemotherapy, seeking to reduce mortality and attempt to preserve fertility.

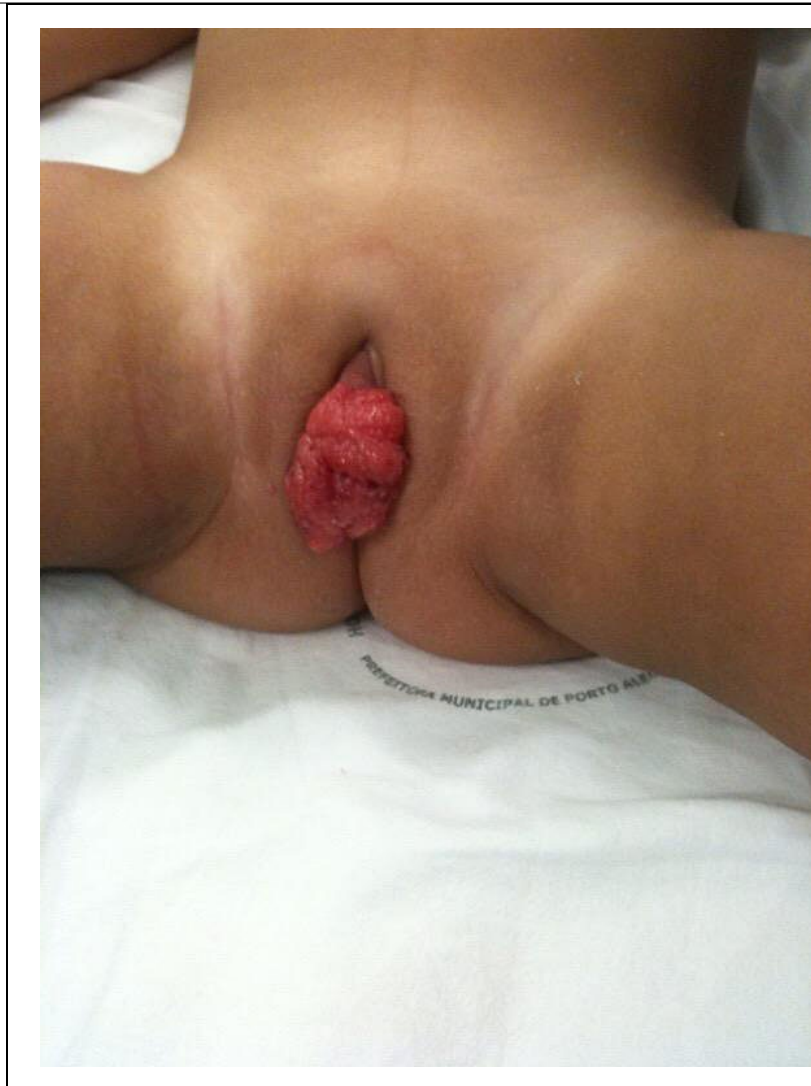


Figure 7 Nodular mass projecting out of the vagina 15 days after first vaginal bleeding. (Courtesy of Dr Soraia Schmidt.)

Magnetic resonance imaging is the gold standard for determining tumor origin (whether endometrial, myometrial, or cervical), as well as spread and involvement of neighboring structures.

The prognosis for sarcoma botryoides depends on the extent and initial stage of the disease at the time of diagnosis, and is generally favorable (with a 5-year survival rate of 95%), despite a high risk of recurrence at all stages in the first 2 years after initiation of treatment (mean survival of 64% in recurrent cases). Lesions originating from the cervix seem to have a better prognosis than those originating from elsewhere in the genital tract.

Endodermal sinus tumor

Malignant germ cell tumors account for 3% of all childhood malignant tumors. Thus, primary vaginal yolk sac tumors are exceedingly rare and have previously been reported to occur in young girls, typically less than 3 years of age, with a presentation of painless vaginal bleeding. There are variable reports of serum tumor markers in the literature; however, serum alpha-fetoprotein levels can be elevated. As treatment has changed over time to favor chemotherapy over radical surgical resection, diagnosis has come to rely more heavily on biopsy specimens.¹¹

Figure 8 shows an illustrative example of an 11-month-old girl with vaginal bleeding since 5 months of age. Vaginoscopy with biopsy identified an endodermal sinus tumor.



Figure 8 11-month-old girl with intermittent genital bleeding since age 5 months. MRI shows a mass occupying the entire vaginal cavity (endodermal sinus tumor). The alpha-fetoprotein level was 28,053 ng/ml. (Personal case, NTF.)

Trauma

Genital trauma can be accidental or non-accidental. Accidental trauma, which accounts for the majority of cases, includes straddle injuries, falls, motor vehicle accidents, animal bites, burns, pelvic fractures, penetrating injuries, in-line skating, and hair tourniquet. Non-accidental trauma includes childbirth, sexual abuse, and female genital cutting (female circumcision).¹²

Some genital trauma presents with a normal physical examination or erythema alone. However, other cases also present with genital bleeding, lacerations, or bruising.

Unintentional hymenal injuries are rare; when they do occur, they are usually associated with injury to adjacent tissues.

When sexual trauma occurs, it is noted most often in the posterior fourchette.¹² The most common finding in the setting of sexual abuse or history of sexual assault, however is a normal perineum, and the evidence should be based on the patient's history.

As the clinician never knows whether genital bleeding is accidental, it is important to obtain a detailed history from the patient and/or witnesses, to verify its consistency, and to register the exact words said by the child in the medical record.

During the physical examination, it is important to verify vital signs, airway, breathing, and circulation. The importance of the genital examination notwithstanding, one must also examine the perianal region and the entire body, looking for other injuries. An estimated 10 to 16% of sexually abused children have extragenital injuries.¹² In severe genital injuries, or when a child will not allow examination and there is substantial bleeding, exam under sedation is strongly recommended to evaluate the extent of the injury and allow for adequate repair. A speculum examination is only indicated in cases of active, significant bleeding from within the vaginal canal, in the setting of trauma, and should be done under sedation.

Vulvar hematomas

These are generally caused by accidental straddle-type trauma and can range in size from small to giant (Figure 9). Blunt straddle injury – usually involving impact onto a bicycle bar, fences, ladders, edges of pools, etc. – can cause bruising (ecchymoses) or hematomas.



Figure 9 10-year-old girl with a straddle injury (fall onto bed rail).
(Personal case, LDH.)

In cases of superficial trauma, local application of ice is enough to reduce swelling.

If major hematomas are present, however, it is essential to ascertain whether the patient is able to void. If urinary retention occurs, bladder catheterization is mandatory until the swelling is reduced. There is usually no single large vessel or bleeder to clamp and routine surgical evacuation of the hematoma is not indicated; only rest, analgesics, and ice. However, it is important to observe the patient for a few hours to check vital signs and rule out pressure of overlying tissue or dissection along fascial planes. In these cases, the hematoma should be evacuated. Before discharging the patient home, it is important to again check whether voiding is normal. Sitz baths or phenazopyridine can help if dysuria is present.

Vulvar laceration

Vulvar laceration can be due to accidental or non-accidental injury. Abused children in general have an intact hymen, but can also present with a sexually transmitted infection or typical emotional symptoms. Condyloma, genital herpes, purulent vaginal discharge, etc. must be ruled out. Vaginal intercourse with hymen laceration is more common in adolescent girls.

When the laceration is superficial, small, and no longer actively bleeding, and does not involve the edge of the labia majora or minora, sutures are not required. Labia minora lacerations in prepubertal girls should be repaired to avoid development of elongated appendages with pubertal development. Minor lacerations can sometimes be repaired under local anesthesia alone. Deeper lacerations should be examined and repaired under general anesthesia.



Figure 10 8-year-old girl with a straddle injury (fall onto edge of pool).
(Personal case, LDH.)

HORMONAL CAUSES

The hormonal causes of prepubertal genital bleeding are varied and are listed below. See the Pubertal Disorders chapter for full evaluation of precocious puberty.

Uterine bleeding in the neonatal period (mini-puberty or pseudomenstruation)

Fetal exposure to maternal and placental estrogen during intrauterine life can stimulate proliferation of the fetal endometrium, leading to estrogenization of the fetal breasts and vulva as well (Figure 11). After birth, the abrupt drop in hormone levels caused by delivery of the placenta leads to endometrial shedding and bleeding. This usually occurs in the first 8 days of life, but can present during the first 30 days after birth. The estimated prevalence of grossly visible bleeding is 3.1%; microscopic bleeding may be much more common. The average duration of bleeding is 3 to 4 days. Uterine bleeding in the neonatal period is self-limiting and does not require any intervention. It has been postulated by some authors that this neonatal uterine bleeding might cause retrograde menstrual flow and increase the odds of early implantation of endometriotic foci, which could become symptomatic in adolescence or even in the prepubertal period.¹³



Figure 11 Estrogenized vulva and gross vaginal bleeding caused by neonatal uterine bleeding (pseudomenstruation or false menses). (Personal case, LDH.)

Hormonal stimulation of the breasts can cause development up to Tanner stage 2 or 3. Neonatal galactorrhea, popularly known as “witch’s milk” and first described in the medical literature in 1686, may occur. The duration of neonatal galactorrhea is no more than 3 weeks and treatment is not required.¹⁴

Central precocious puberty

Genital bleeding in girls may also represent menarche. Puberty is considered precocious, or early, in girls when it starts before 8 years of age or menarche occurs before 9 years of age. This may be due to a central cause (central precocious puberty), resulting from premature reactivation of the hypothalamic–pituitary–gonadal (HHG) axis with GnRH release; it may be peripheral (peripheral precocious puberty), i.e., when there is an increase in sex steroids without an increase in GnRH; or it may occur in isolation due to a minor, transient increase in sex steroids and/or increase in sensitivity of estrogen receptors in target organs, triggering thelarche, pubarche, or isolated menarche.¹⁵

Differential diagnosis between these forms is based on a thorough history and physical examination, with additional testing as necessary such as hand and wrist radiography (bone age study), pelvic ultrasound, and measurement of serum hormone levels.

The physical examination should look for signs of estrogenization, such as breast development, pigmentation of the areola and labia minora or majora, and physiologic leukorrhea (Figure 12). In precocious puberty, timing and order of pubertal development is preserved due to estrogen exposure, so that breasts should be Tanner 3 development prior to onset of bleeding. In central precocious puberty growth velocity is increased (>6 cm per year) and stature exceeds the genetic potential or target height. Hand and wrist radiography demonstrates an increase in bone age of more than

1 year or two standard deviations, while pelvic ultrasound shows a uterus and ovaries of pubertal size. Laboratory tests should rule out thyroid disease, and baseline or stimulated LH at pubertal levels confirms the diagnosis. Treatment, if indicated, consists of HHG axis blockade with GnRH analogs.¹⁶

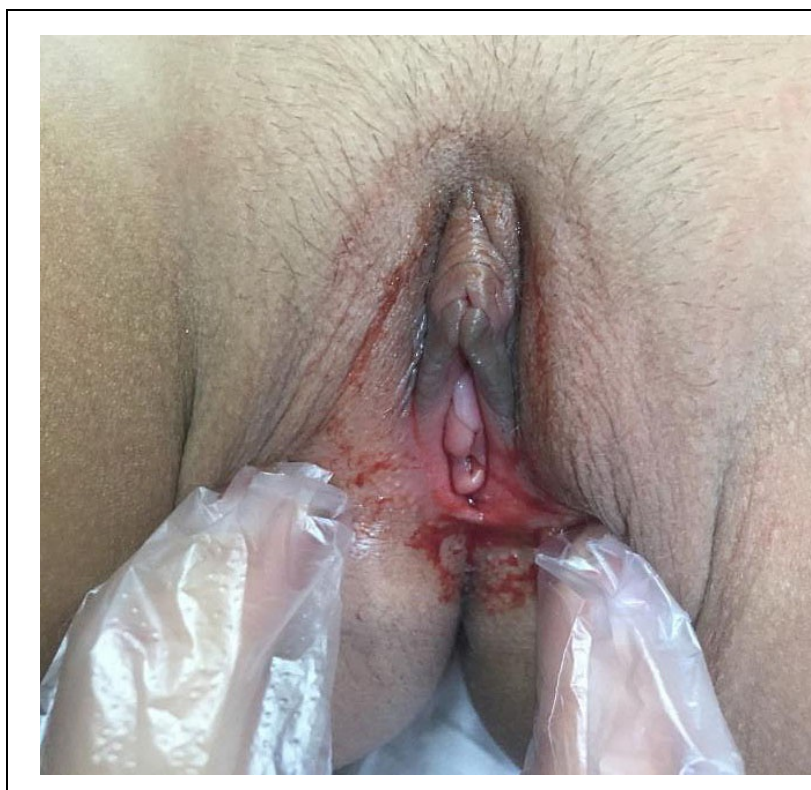


Figure 12 Girl with CPP at 3 years of age. There is enlargement of the clitoral hood, darkening of the labia minora, some elongated pubic hairs, and presence of menstrual bleeding. (Personal case, LDH.)

Autonomous ovarian follicular cyst

Autonomous estrogen-producing follicular cysts are the most common cause of peripheral precocious puberty (PPP). They usually exhibit spontaneous involution and do not require treatment. However, they should be closely monitored due to the risk of permanence, recurrence, or association with the McCune–Albright syndrome. When recurrent, due to prolonged or repeated exposure to estrogen, they may sensitize the hypothalamus and secondarily trigger CPP. The laboratory workup shows elevated estradiol levels and low or suppressed gonadotropins (FSH, LH). Due to the acute nature of the event, there is usually no impact on radiographic bone age. The pelvic ultrasound reveals a simple, unilocular, anechoic, thin-walled cyst (Figure 13). Surgical intervention is indicated only in those rare cases of adnexal torsion or permanence of the same functional cyst. In these cases, cystectomy with preservation of normal ovarian tissue is indicated.¹⁷



Figure 13 A 5-year-old girl presented with sudden onset of thelarche, physiologic leukorrhea, and vaginal bleeding. Pelvic ultrasound showed a uterus measuring ≥ 10 cm, right ovary measuring ≥ 3.7 cm, and left ovary measuring ≥ 11 cm, the latter containing an anechoic cyst 2.6 cm in diameter. Estradiol: 600 pg/ml; LH: 1.1 mIU/ml (RIA); FSH: 0.8 mIU/ml (RIA). The clinical manifestations were transient and self-limiting, consistent with an autonomous follicular cyst. Menarche occurred normally at 12 years of age. (Personal case, LDH.)

McCune–Albright syndrome

The McCune–Albright syndrome was originally described in 1936 as the triad of café au lait spots, fibrous dysplasia, and peripheral precocious puberty. It is due to a somatic mutation that activates the gene encoding the alpha subunit of the heterotrimeric G protein, which leads to hyperfunctioning endocrinopathies.¹⁸

Patients develop one or multiple estrogen-producing functional cysts, leading to rapid pubertal progression and frequent uterine bleeding, even before full breast development. Because this is a peripheral and not central precocious puberty, estradiol levels are usually elevated, gonadotropins are suppressed, and pelvic ultrasound typically demonstrates a pubertal uterus and functional cysts (Figure 14). Cyst resolution is associated with an abrupt drop in estradiol levels, which triggers vaginal withdrawal bleeding. Autonomous ovarian activity persists into adulthood and is commonly associated with abnormal uterine bleeding and effects on fertility.¹⁸

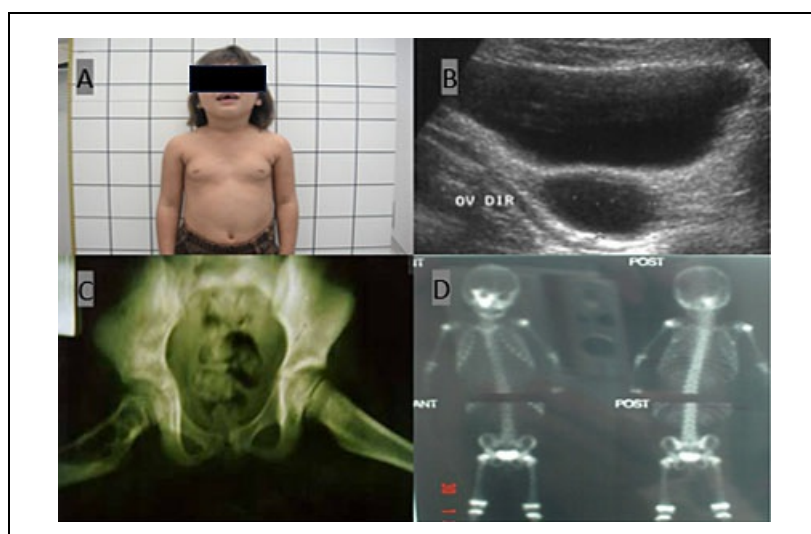


Figure 14 (A) Breast development; (B) simple follicular cyst on pelvic ultrasound; (C) plain radiograph of the pelvis demonstrating an area of bone rarefaction in the right femur; (D) bone scintigraphy

demonstrating increased uptake in the skull. (Personal case, LDH.)

Letrozole is the first-line therapy of choice; tamoxifen or fulvestrant may be used as second-line or adjuvant treatments. The goal is to reduce bleeding episodes and inhibit progression of bone age.¹⁹

This mutation can also lead to other endocrinopathies of hyperfunction, such as thyrotoxicosis, excess growth hormone (gigantism or acromegaly), Cushing's syndrome, renal phosphate wasting (hypophosphatemic rickets), and various combinations thereof. Mutations can be found in other non-endocrine organs, such as the liver and heart, resulting in cholestasis and/or hepatitis and cardiac arrhythmias, respectively.¹⁹

Granulosa cell tumor

Granulosa cell tumors correspond to 4% of all ovarian tumors in children. As they produce sex steroids (estradiol, testosterone, progesterone, and 17-hydroxyprogesterone) autonomously, they most commonly manifest as rapidly progressive isosexual precocious pseudopuberty (PPP), as shown in Figure 15.²⁰

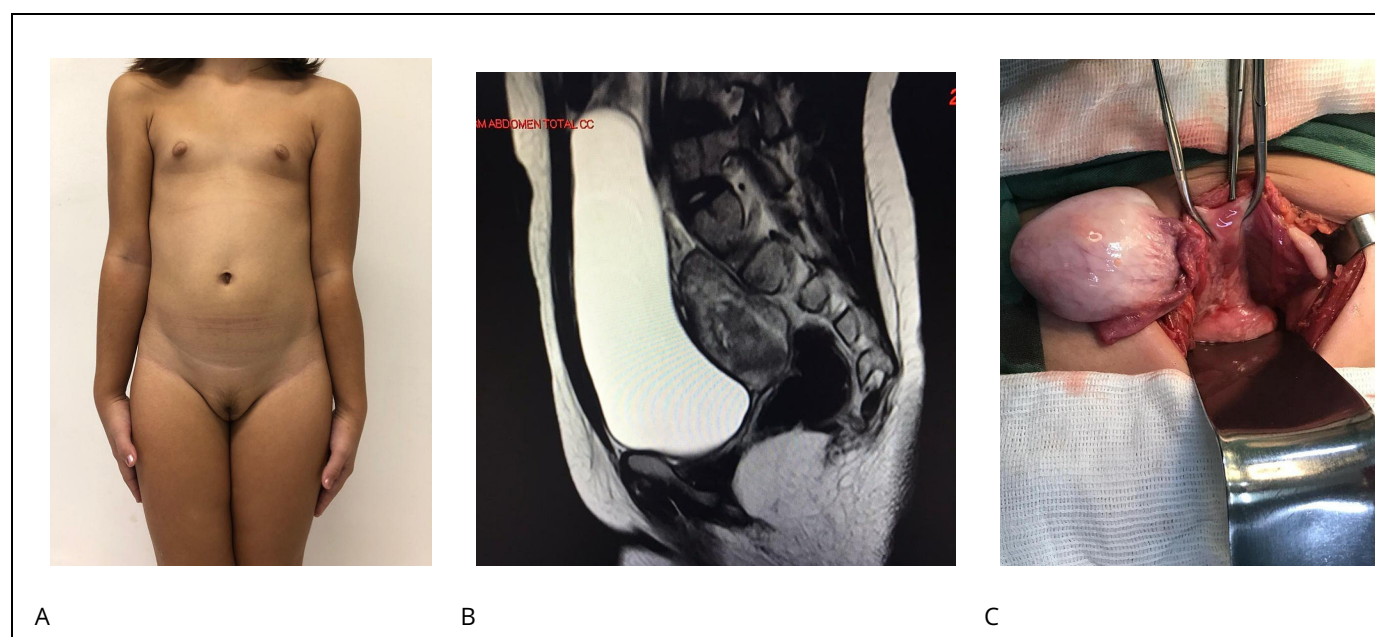


Figure 15 (A) 6-year-old girl with abrupt puberty due to PPP (M3P3 and genital bleeding); (B) MRI showing a large ($5.8 \times 4.2 \times 3.4$ cm, volume 43 cm^3), solid, heterogeneous mass in the area of the right ovary, extending into the posterior fornix and compressing the mid-rectum and body of the uterus. The mass was well-delimited, encapsulated and there was no evidence of invasion of adjacent organs. The endometrium was identifiable and its thickness measured at 2 mm. The uterine volume was 3.5 cm^3 ; (C) intraoperative view of right ovarian tumor. Histopathological examination was consistent with a granulosa cell tumor. (Personal case, NTF.)

They usually affect patients ranging from 6 months to 20 years of age, are much more frequent before the age of 10 and, unlike granulosa cell tumors in adult women, usually have favorable outcomes.

Some girls may experience acute abdominal pain and swelling as a result of the rapidly growing tumor. They may also occasionally present with adnexal torsion, tumor rupture, and ascites. These cases may have an unfavorable outcome.²¹ Because granulosa cell tumors cause a rapidly progressive isosexual PPP, plasma estradiol concentrations are usually high while gonadotropins are suppressed (to prepubertal levels), indicating the absence of stimulation of the gonadal axis.

Imaging modalities such as pelvic ultrasound and computed tomography are useful insofar as they will demonstrate a solid adnexal mass. Treatment consists of surgical resection with adjuvant chemotherapy; the prognosis after unilateral adnexectomy is excellent if the disease is restricted to the ovary.²⁰

Prognostic factors impacting survival include tumor stage and size, degree of mitotic activity, and the presence of

nuclear atypia.

Isolated menarche

Isolated premature menarche is a diagnosis of exclusion. There are no other signs of puberty or of any organic dysfunction. It also does not affect final height. Vaginoscopy may be required to rule out foreign bodies, tumors, or hemangiomas. Bleeding may be isolated or recurrent. It is generally a transient condition, but some patients may continue to experience bleeding into adulthood. It is most probably due to increased endometrial sensitivity to minute physiological fluctuations in endogenous estrogen levels.²² Figure 16 illustrates genital bleeding in a 3-year-old girl with no signs of puberty.



Figure 16 (A) Vaginal bleeding (underwear spotting) in a 3-year-old girl; (B) prepubertal-sized uterus containing a small intrauterine clot. (Personal case, LDH.)

PRACTICE RECOMMENDATIONS

- **Genital bleeding in children can be divided for educational purposes into hormonal and non-hormonal causes.**
- **In hormonal etiologies, physical examination will demonstrate signs of estrogen stimulation, such as breast development, pigmentation of the areola and labia minora, and physiologic leukorrhea.**
- **Inspection of the vulva aims not only to observe hormone status, but also to rule out abnormal findings such as lacerations, perineal, urethral, or vaginal lesions, retained foreign body in the vagina, etc.**
- **In cases with overt estrogenic stimulation, further investigation should include measurement of estradiol, LH, and FSH; pelvic ultrasound; and radiographs of the hands and wrists for bone age assessment. Pubertal LH and estradiol levels with bone age advancement greater than two standard deviations or 12 months, a pyriform uterus >3 ml in volume and ovarian volume >2 ml suggest central precocious puberty. On the other hand, high estradiol with suppressed FSH and LH levels suggest peripheral precocious puberty.**

- **Most cases of vaginal foreign bodies present with a foul-smelling, bloody purulent discharge. A thorough physical examination will usually identify the foreign body, as most are present in the distal third of the vagina.**
- **In the presence of traumatic injury, sexual abuse must be ruled out.**
- **If there is purulent leukorrhea, bacteriological examination of vaginal discharge should be ordered, with a focus on gonococci, chlamydia, group B streptococcus, and *Shigella*.**
- **In cases of unexplained genital bleeding, vaginoscopy is mandatory to rule out vaginal or cervical lesions.**

CONFLICTS OF INTEREST

The author(s) of this chapter declare that they have no interests that conflict with the contents of the chapter.

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