Good Practice in Pediatric and Adolescent Gynecology

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Editor
Anna Maria Fulghesu
Department of Obstetrics and Gynecology
University of Cagliari
Cagliari
Italy

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Preface

This book is a very useful text to consult when a specific gynecological problem affects a child or a young girl who needs your help.

This text is focused on a special time of women's lives when the prevention of sexual and reproductive problems is very important, and it is aimed at clinical pediatricians and gynecologists. Each author is an expert scientist in the field, a member of the Italian Society of Gynecology of Childhood and Adolescence (SIGIA), and every chapter reports the most up-to-date knowledge. The text has a strong practical relevance, and represents the guidelines of this scientific society.

The order of the chapters follows the age of girls from infancy, with genital malformations, vulvovaginitis, to puberty, studying delayed puberty and postpubertal gonadal failure.

Menstruation disorders, such as dysmenorrhea, heavy menstrual bleeding, menstrual irregularities, eating disorders and polycystic ovary syndrome, are studied in depth in individual chapters.

The prescription of contraceptives and the diagnosis and treatment of ovarian cysts are specifically tailored to the adolescent age.

Sexual mutilation and abuse are also dealt with, and how to prevent, diagnose, and treat the most frequent sexually transmitted diseases.

Finally, pregnancy in adolescence, which represents a difficult clinical responsibility for gynecologists because of the high frequency of pregnancy-related disorders, is described.

Happy reading!

Cagliari, Italy — Anna Maria Fulghesu

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About the Author

Anna Maria Fulghesu is a medical doctor specializing in obstetrics and gynecology. As researcher of Obstetrics and Gynecology, from 1988 until 2000, she worked in the Department of Obstetrics and Gynecology at the Sacred Heart of Rome (Policlinico Gemelli), and since 2000 in Cagliari as Associate Professor at the Università degli Studi. She is founder and is responsible for the Outpatient Service of Pediatric and Adolescent Gynecology (PAG) in Calgliari. At the same hospital, she has been involved in the Sexual Abuse Service in Childhood and Adolescence. As an invited speaker, she has taken part in several national and international events. As a teacher, she has given her services on many courses for medical doctors and health caregivers. She has herself organized several courses on PAG, including six national day courses. Author of more than 100 published scientific papers, she is also a referee for several national and international scientific journals and she is a member of the following scientific societies:

- International Federation of Infantile and Juvenile Gynecology (FIGJI)
- Società Italiana di Ginecologia dell'Infanzia e dell'Adolescenza (SIGIA, Italian Society of Gynecology of Childhood and Adolescence): executive board member since 2013.

Vulvovaginitis in Childhood

1

Cristina Vezzani, Gilda Di Paolo, Terryann Spagnuolo, and Gabriele Tridenti

1.1 Introduction

Vulvovaginal complaints account for 80–90% of outpatient pediatric gynecologic visits [40]. Most cases may be attributed to vulvovaginitis but other less common conditions, such as vulvar diseases or vulvar manifestations of systemic disease, should be taken into account. Rare causes of vulvovaginitis have to be considered especially when symptoms are recurrent or not responsive to standard treatment. In this chapter, the causes, manifestations, and management options of vulvovaginitis in childhood will be reviewed. Furthermore, common vulvar diseases affecting children were outlined, since their knowledge is essential for differential diagnosis. The prepubertal child is particularly susceptible to vulvovaginitis for anatomic, physiologic, and behavioral factors: absence of hair and minimal labial development; close proximity of the vagina to the anus; physiological hypoestrogenism which causes atrophic genital mucosa; neutral pH and unbalanced vaginal flora; absence of cervical mucus; and lack of antibodies [1]; furthermore, children's tendency to have poor local hygiene and to explore their bodies increases the risk of developing this conditions. Germs may easily reach the genital area as a result of contiguity from the rectum, urethra, or the surrounding skin. Diffusion of bacteria from the upper

C. Vezzani, M.D. • G. Tridenti, M.D.
Department of Obstetrics and Gynaecology, Santa Maria Nuova Hospital-IRCCS, Reggio Emilia, Italy
e-mail: cristina.vezzani@ausl.re.it; gtride@tin.it

G. Di Paolo, M.D. (✉)
Pediatric and Adolescent Gynecology Service, Department of Gynaecology and Obstetrics, Santo Spirito Hospital, Pescara, Italy
e-mail: gildipa55@gmail.com

T. Spagnuolo, M.D.
Studio Madreperla, Pescara, Italy
e-mail: terryannspagnuolo@gmail.com

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airways is also possible through autoinoculation and occasionally hematic spread [2]. Obesity, diabetes, anatomic anomalies, and use of antibiotics may play a role in facilitating vulvovaginitis.

1.2 Etiology

Vulvovaginitis are easily classified into two groups on the basis of etiology [3]

- Nonspecific
- Specific

Nonspecific vulvovaginitis refers to vulvovaginal irritation without an identifiable pathogen, accounting up to 25–75% of all cases of vulvovaginitis in children [4]. Symptoms may often be caused by irritative-allergic reaction to topical or food agents, nickel, or by poor perineal hygiene. Vaginal cultures are usually negative or positive for skin flora/anaerobes/enteric organism [5]. However, in many cases etiology cannot be found.

Specific vulvovaginitis are caused by specific pathogens. It has been reported that infective vulvo vaginitis were found in one-third of young girls presenting with vulvovaginitis [6]. Infectious may be caused by bacterial agents, pinworms, viruses, and sexually associated pathogens.

Knowledge of the **normal vaginal microflora** in prepubertal age is an essential prerequisite for definition of the pathogens of the lower genital tract and will limit the overtreatment of non-pathogens (lactobacilli, diphtheroids, alpha-hemolytic streptococci) [7].

It has been reported that some microorganisms, other than those traditionally considered part of normal flora, can be isolated from vaginal culture of girls without symptoms (*Escherichia coli*, *Candida*, *Staphylococci*, *enterococci*, *Streptococcus viridans*, *Streptococcus agalactiae*, *Corynebacterium*, *Proteus Mirabilis*, *Pseudomonas aeruginosa*). As these organisms are present in healthy prepubertal girls, their growth in culture is not diagnostic [8]. Many of those bacteria may spread from skin or bowel and may act as **opportunistic pathogens** and cause infection only when the child has a temporary immune system depression. *Escherichia coli* and *Candida* may be present in vaginal flora, respectively, in 8 and 4% of asymptomatic patient populations [7]. Clinician should consider that *Candida* infection is unlikely unless the girl has predisposing factors: recent antibiotic use, diabetes mellitus, immunodeficiency syndromes, poor perineal aeration, inflammatory skin conditions such as diaper dermatitis, seborrheic dermatitis, and atopic dermatitis [9]. *Escherichia coli* and other enteric opportunistic microorganisms typically spread from intestinal tract after pinworm infestation or poor hygiene or dysfunctional intestinal disorders. *Staphylococcus aureus* may cause opportunistic skin infections which may appear as impetiginous, bullous, or suppurative.

The non-sexually transmitted pathogens responsible for vulvovaginitis are represented by **respiratory pathogens** such as group A beta-hemolytic *Streptococcus*

(*Streptococcus pyogenes*), *Haemophilus influenzae, Streptococcus* and *Staphylococcus pneumonia*, *Staphylococcus aureus*, *Branhamella catarrhalis*, *Neisseria meningitidis* and **enteric pathogens** such as *Shigella*, and *Yersinia* [7].

Streptococcus pyogenes and *Haemophilus influenzae*, transferred from the upper respiratory tract, are the two most common causative agents, in both primary care settings and referral populations [10, 11]. Shigella and Yersinia typically cause diarrhea, therefore in some cases vulvovaginitis may be associated.

Another frequent cause of vulvovaginitis is **pinworm** (*Enterobius vermicularis*) infestations. Pinworms are helminths that commonly cause vulvar and perianal pruritus. Female pinworms lay eggs at night around the anus and vulva. The mature worms may carry colonic bacteria to the perineum, causing recurrent vulvovaginitis. *E. coli* is common with spread of the pinworms from the anus to the vagina [12].

The most common genital viral infections in childhood are **Molluscum contagiosum**, **Papilloma virus**, and **Herpes simplex**.

Vulvovaginal complaint may be attributed, other than vulvovaginitis, to: foreign body, polyps and tumor of cervix/vagina, systemic illness (measles, chickenpox, scarlet fever, mononucleosis, Crohn disease, Kawasaki disease, histiocytosis), anatomic anomalies (double vagina, fistula, pelvis abscess, ectopic ureter, prolapsed urethra), vulvar skin disease, and psychosomatic complaints [7].

1.3 History

The first step to diagnosis is to spend time obtaining the history. As vulvovaginitis could be associated to a large number of conditions, a detailed anamnesis is very important in narrowing the etiology and directing treatment. Information can be obtained from parents and, when age allows, from the child. Questions should focus on the onset, duration, characteristic and localization of symptoms, history of skin disease or systemic disease, allergic diathesis (atopic dermatitis, asthma, rhinitis), allergies to medications, autoimmune disease, urogenital and anorectal malformation, recent illness and treatment (antibiotics, corticosteroids, immunomodulators drugs). A list of possible acute or chronic irritant exposures such as bubble baths, cleaning agents, lotions, powders, fabric softeners, and hair products should be investigated. Family history of chronic illness, allergies, and contact sensitivities are also important.

Information on perineal hygiene habits, urinary or intestinal dysfunctions, incorrect behavior when urinate and defecate, practice of cycling or horsing, sexual activity, and masturbatory activity should be elicited. Social contest, psychological distress, and the possibility of sexual abuse also must be considered.

1.4 Physical Examination and Diagnostic Testing

The examination of the child presenting with gynecologic complaints should include systemic physical assessment and genital inspection. It is important to invest time in communication, explaining parents and patients, when age is

appropriate, the examination techniques and that the procedure will be painless. Interpersonal and communication skills, time, and adequate setting are required to achieve good relationship with parents and girls. General examination should be focused on observing signs of dermatological conditions such as allergic reactions or dermatitis. Genital examination can be performed in most cases without sedation or anesthesia. The ideal position for good visualization of external genitalia is supine with legs in the "frog leg position." The genupectoral position may be useful in some cases. In order to assess the introitus and the lower third of the vagina, finger may be used to gently grasp labia laterally and downward or anteriorly. The magnification of either an otoscope or a colposcope or a hand lens facilitates the examination. The appearance of female genitalia varies through ages, whereas hormonal changes induced by maternal estrogenization or puberty may have remarkable influences on the skin. Practitioners have to deal with various genital features in newborn infant, prepubertal and peripubertal girls. Specific knowledge of anatomy and physiology of genital system and experience in pediatric gynecology are required to recognize normal genital anatomy since normal findings are poorly described in the evidence-based literature and wide variability in appearance of genitalia among individuals may be confounding factor.

The clinician should describe Tanner stage of breast and pubic hair, size and configuration of clitoris, configuration of hymen, labia, urethra meatus, sign of estrogenization, perineal hygiene, anatomic anomalies (dislocation of urethral or anal openings, signs of suspected vescicovaginal or enterovaginal fistulae), vulvar and perianal skin conditions, and genital mutilations. Inguinal areas should be palpated for hernia, gonad, and lymphadenopathy. When anomalies of external genitalia are detected, either gynecologic conditions, dermatologic disease or systemic disease have to be taken into account.

Clinically it is possible to discern two conditions:

- Vulvitis: it is the inflammation of the vulva characterized by hyperemia and other skin alterations limited to the vulvar region. In most cases, vulvitis are caused by allergies or simply a reaction to an irritant (33%) [13].
- Vulvovaginitis: it is vulvar inflammation accompanied by vaginal involvement. Vaginal abnormal discharge is present. Usually it is caused by proliferation of pathogenic or opportunistic agents [14].

Vulvitis and vulvovaginitis may exhibit different clinical feature:

- Symptoms (with or without signs)
- Vulvar signs (nonspecific or characteristic lesions)
- Vaginal discharge

Symptoms and nonspecific vulvar skin findings such as itching, dysuria, pain, burning, scratching lesions, mild redness, and edema are signs of irritations and may be present in vulvovaginitis whether or not caused by infective agents. Nevertheless, if girl presents with those clinical features, given that only 1/3 of vulvovaginitis can be attributed to infections and after reviewing the clinical history, clinicians should consider that "nonspecific vulvovaginitis" is likely. Bacterial infection, which in any

case has to be taken into account, is often indistinguishable by genital examination and may require further testing to be diagnosed if suspected; vulvovaginal candidiasis is rare unless predisposing factors are present.

Itching in childhood may have multiple origins [15, 16]. Vulvar irritation is often erroneously attributed to "yeast" infection by clinicians even though candida infection is sporadic in prepubertal child. It has been calculated that up to 75% of vulvar itching is associated with negative culture and absence of vulvar disease [17]. In some cases, itching's characteristic may give a clue to diagnosis. In presence of vulvar and perianal **hitch, especially at night**, it is necessary to consider the diagnosis of pinworms. Most often pinworms associate with no vulvar findings or low grade of vulvovaginitis; however, vaginal discharge can be present, especially if superinfection occurs. Touching transparent adhesive tape to the perianal area for microscopic examination of the eggs is actually the diagnostic technique, but often is difficult to obtain. Nocturnal pruritus may also be caused by Sarcoptes scabiei hominis. Spread is by personal contact. In this case, the inspection of the skin will detect vesicles or pustules in linear distributions, often in interdigital folds, flexor, and extensor surface of extremities and genital areas. Classic lesions appear as grey or white lines but most become excoriated with scratching. Diagnosis is done with microscopic examination of scarped burrows.

Vaginal discharge is the most common reason for referral of a prepubertal girl to a gynecologist [5]. It has been reported that, among prepubertal girls presenting with **vaginal discharge**, vulvovaginitis is responsible for the majority of cases (82%), whereas suspected sexual abuse, foreign body, labial adhesions, malformations, and other causes are less common [18]. Whitish mucoid vaginal discharge due to estrogen effect is normal in infant, and in girls is associated with pubertal onset and frequently precedes menarche [7, 19]. Abnormal vaginal discharge can be clear, yellow, green, bloodstained, and may be offensive smelling [5]. If abnormal vaginal discharge is present, it may be indicated testing the child for bacterial organisms associated with vulvovaginitis. Specimens for **standard culture** may be obtained by introducing into the lower tract of the vagina an urethral swab moistened in saline water. If the hymeneal opening is narrow, it is possible to insert a small urethral catheter attached to a syringe and obtain vaginal secretions or vaginal wash sample. Recently, it has been recommended to reserve culture for severe or recurrent vulvovaginitis [20]. The predominant growth of a pathogen in an appropriate culture is considered the primary diagnostic tool [2]; in contrast, the presence of normal flora or opportunistic agents does not necessarily imply that it is the cause of infection [21].

The most common infective agent causing vulvovaginitis in prepubertal girls is *Streptococcus pyogenes*. This infection is thought to be transmitted from the throat to the vulva (up to 92% of throat culture are positive) and it is characterized by sudden onset of seropurulent–hematic vaginal discharge often associated with distinctive "beefy red" erythema of vulvar and perianal areas (Fig. 1.1); aspecific signs and symptoms of vulvovaginitis, pharyngitis, scarlet fever, and guttate psoriasis may be associated [7].

Staphylococcus aureus may cause opportunistic skin infections which may appear as impetiginous, bullous, or suppurative.

In case of suspected sexually transmitted disease, evaluation for *Neisseria Gonorrhoeae* and *Chlamydia Trachomatis* can be obtained sending a **urine or vaginal sampling for NAAT** (nucleic acid amplification testing). Trichomonas

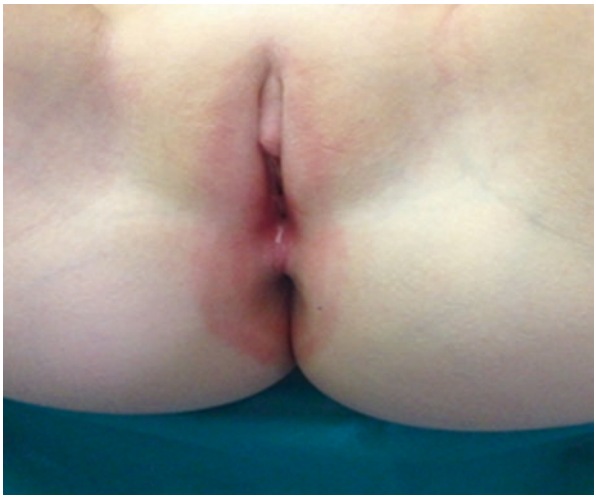

Fig. 1.1 Streptococcus pyogenes vulvovaginitis

vaginalis can be identified in vaginal secretions by **wet mount examination, culture or NAAT**. When sexually transmitted diseases are detected and mother to child transmission can be excluded, sexual abuse should be considered.

Physical examination is usually sufficient to diagnose viral genital infection, since they show characteristic lesions.

Feces and urine culture may be useful respectively in cases of diarrheal illness and dysuria.

1.4.1 Vulvar Lesions

As symptoms of vulvovaginitis, vulvar dermatosis, and systemic disease with vulvar manifestations may often overlap, recovery of specific vulvar lesions may give a clue to diagnosis. Hence, awareness of vulvar lesion is essential for differential diagnosis. It has been calculated that, in a series of 130 children presenting with vulvar symptoms to a dermatologic clinic, 33% had atopic or irritant dermatitis, 18% had lichen sclerosus, 17% psoriasis, 15% hemangiomas, less than 20% had infection, and 10% had streptococcal infection; vulvar manifestations of systemic disease were rare [13]. Systemic diseases with vulvar manifestations include: measles, chickenpox, varicella, scarlet fever, mononucleosis, Stevens-Jonhnson syndrome, Kawasaki disease, Langherans cell histiocytosis, Crohn disease, Behçet's syndrome, Staphylococcal scaled skinsyndrome, Henoch-Schönlein purpura, zinc deficiency [7, 13].

Skin lesions may be differentiated in primary and secondary types (Table 1.1) [22, 23].

For clinical purpose, it may be helpful to adopt the 2011 ISSVD (International Society for the Study of Vulvovaginal Disease) Terminology and Classification of Vulvar Dermatological Disorders as suggested by Lynch [23]. Vulvar diseases may be clustered into groups with similar clinical presentations. As some skin disease

Table 1.1 Primary and secondary skin lesions

Primary lesions	Definitions
Macule	Small area (<1.5 cm) of color change; no elevation and no substance on palpation
Patch	Large area (>1.5 cm) of color change; no elevation and no substance on palpation
Papule	Small (<1.5 cm) elevated and palpable lesion
Plaque	Large (> 1.5 cm elevated, palpable, and flat topped lesion
Nodule	Large (>1.5 cm) papule; often hemispherical or poorly marginated; may be located on the surface, within, or below the skin; nodules may be cystic or solid
Vesicle	Small (<0.5 cm) fluid filler blister; the fluid is clear (blister: a compartmentalized, fluid filled elevation of the skin or mucosa)
Bullae	A large (>0.5 cm) fluid filled blister; the fluid is clear
Pustula	Pus-filled blister; the fluid is white or yellow
Secondary lesions	**Definitions**
Eczema	A group of inflammatory diseases that are clinically characterized by the presence of itchy, poorly marginated red plaques with minor evidence of microvesiculation and seven or more frequent surface disruption
Lichenification	Thickening of the tissue and increase prominence of skin markings. Scale may or may not be detectable in vulvar lichenification. Lichenification may be bright-red, dusky-red, white, or skin colored in appearance
Excoriation	Surface disruption (notably excoriation) occurring as a result of the "itch-scratch" cycle
Erosion	A shallow defect in the skin surface; absence of some, or all, of the epidermis down to the basement membrane; the dermis is intact
Fissure	A thin, linear erosion of the skin surface
Ulcer	Deeper defect; absence of the epidermis and some, or all, of the dermis

are polymorphic they may be listed in more than one group. For each group, a list of diseases which may occur in childhood is reported below (adapted from [23]):

1.4.1.1 Skin Colored Lesions

Papules and nodules may be caused by Human Papilloma Virus, Molluscum contagiosum, skin tag, epidermal and mucinous cyst, scar, and nevus. If the lesion is single and appears on the median rafe of perineum the differential diagnosis include the **infantile perianal pyramidal protrusion**, which is a peduncolated congenital protrusion typically located anterior to the anus [7]. Plaques are present in lichen simplex chronicus and other lichenified disease.

The hallmark of **Human Papilloma Virus** (HPV) infection is condyloma acuminata which may appear as papule or nodule, solitary or multiple. Lesion may be skin colored, red, white, or dark colored. Acquisition of the virus may occur by mother during gestation or delivery. Postnatal infection may be acquired through inoculation from nongenital mucocutaneous lesion or fomite transmission [24, 25].

Umbilicated and caseous-plug containing papules are typically caused by **Molluscum contagiosum**. Lesions may be single or, more often, multiple; skin

colored, white, red, dark colored. Size of lesions ranges from 1 to 5 mm (giant lesions up to 1.5 cm are rare, may be present in HIV infection) [26]. Transmission may occur by casual contact, fomite spread, autoinoculation, and sexual contact. Treatment options include: watchful waiting (spontaneous resolution may take month or years), off-label application of imiquimod or tretinoin, curettage, and diatermocoagulation [7].

1.4.1.2 Red Patches and Plaques

Clinicians should consider allergic/irritant/atopic dermatitis, eczematous changes superimposed on other vulvar disorders, candidiasis, psoriasis, lichen simplex chronicus, lichen planus, hemangioma of infancy, cellulitis, pityriasis rosea, zinc deficiency, Langherans cell histiocytosis.

Psoriasis is a chronic immune-mediated inflammatory disease which may involve skin and/or joints [27]. Lesions are red-pink, symmetric, well-demarcated plaques. Scales are seen at the periphery. Skin lesions affecting the scalp and extensor surfaces of the limbs (elbows and knees) are typical of adulthood, whereas vulvar and anogenital localization are the most frequent in childhood [26].

Atopic dermatitis is a skin chronic disease with complex pathogenesis (genetic, immunologic, and environmental factors are involved). Lesions are erythematous scaly plaques with undefined margins. Lichenifications may compare with time and scratching. The disease may be indistinguishable from contact dermatitis (Fig. 1.2).

Contact dermatitis (irritant and allergic) may present as acute or subacute/chronic disease. Acute manifestations may be erythema, edema, and vesicle which evolve into painful erosions and ulcerations. Subacute and chronic dermatitis may appear with erythema, lichenification, red plaques, excoriations, and fissures [7].

A particular condition frequently found in pediatric age is **irritant diaper dermatitis**. It commonly affects infants with a peak incidence between 9 and 12 months. It appears as perineal erythema, restricted to the area covered by diapers but

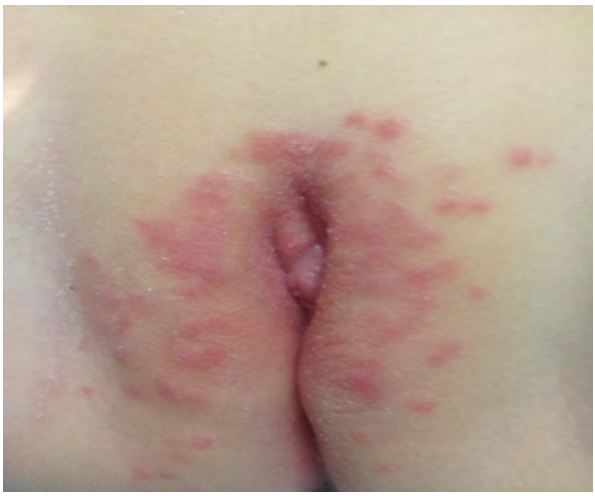

Fig. 1.2 Atopic dermatitis

usually spares inguinal areas [28, 29]. Macerations, erosions, and ulcerations may be associated. It is caused by overhydration of the skin, maceration, prolonged contact with urine and faces, retained diaper soap and is a prototypical example of irritant contact dermatitis [30]. Moreover, the onset of secondary infection caused by *Candida albicans* or bacteria such as Bacillus faecalis, Proteus, *Pseudomonas*, *Staphylococcus*, and *Streptococcus* is frequent. **Candidal diaper dermatitis** is a superficial infection of skin, involving perineal skin, buttock, lower abdomen, inguinal areas, characterized by beefy red erythema often associated to maceration, erosions, and ulcerations [7].

Piritiasis rosea is a papulosquamous eruption usually presenting on the trunk along the skin tension lines. In children lesions may involve the pubic, inguinal and axillary areas. Viral etiology is suspected [7, 14].

Hemangioma of infancy is a benign vascular neoplasm, the most common tumor of infancy. Usually not evident at birth, it grows rapidly during the first year of life, appearing as a flat or raised lesion, red or blue colored. Sometimes ulcerate and lead to infection. It may be associated with urogenital an anorectal malformations.

Zinc deficiency is a rare inherited (acrodermatitis enteropathica) or aquired disorder characterized by the inability of absorb sufficient zinc from diet. Skin findings include red, erosive plaques that may contain vesicles and pustules, simmetrically distributed in the perioral, acral, and perineal areas [7, 31].

1.4.1.3 Red Papules and Nodules

Red papules and nodules may be caused by folliculitis, HPV, Molluscum contagiosum, hidradenitis suppurativa, urethral prolapse, hemangioma of infancy, pityriasis rosea.

1.4.1.4 White Lesions

The most frequent white lesion in childhood is caused by lichen sclerosus. Other diseases are vitiligo, Molluscum contagiosum, and HPV.

Lichen sclerosus is a chronic autoimmune skin disease, in adulthood often associated with other autoimmune disease. Genetic and hormonal factors are involved also [12]. It affects all areas of the body in both sexes and all ages, but in children extragenital lesions are rare and average age of onset is 5 years [14, 31]. The key feature of lichen is a well-demarcated white plaque in a figure of eight distribution surrounding the vulva and perineal areas. Petechiae and ecchymoses may be present (Fig. 1.3). Skin is usually wrinkled (Fig. 1.4). The vulvar rash is extremely pruritic, and irritation, pain, dysuria, bleeding, constipation, and dyschezia may associate. In contrast, many cases are asymptomatic. Generally the diagnosis is made by clinical examination, therefore biopsy is not necessary. Symptoms usually improve at menarche. Many patients have relapses and remits over time. It has been reported that lichen sclerosus may increase the risk of vulvar squamous cell carcinoma. Treatment of choice, whose objective is to relief symptoms and avoid scars, is topical corticosteroids (clobetasol propionate 0.05% or betamethasone valerate 0.05%). Off-label treatment with topic tacrolimus or pimecrolimus may be an option as second-line treatment [20].

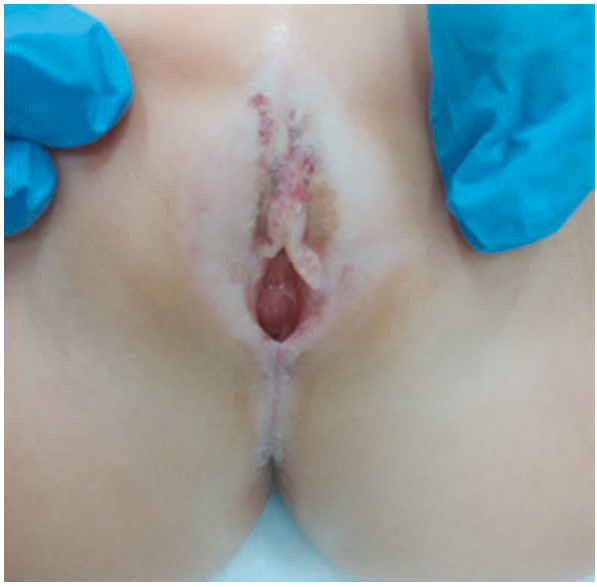

Fig. 1.3 Lichen sclerosus

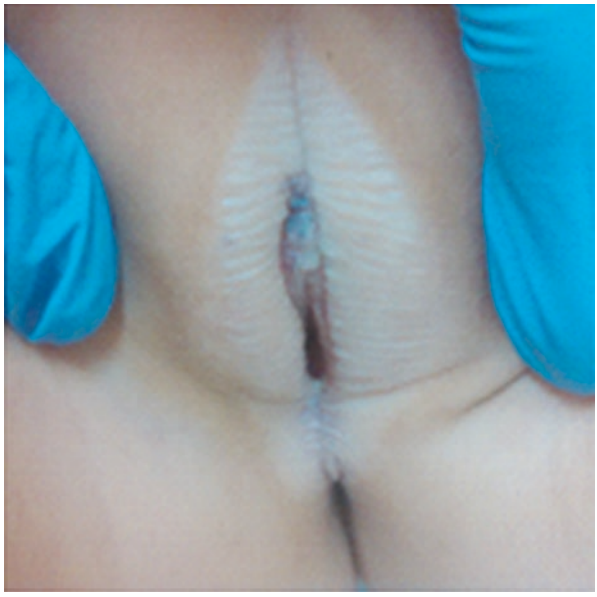

Fig. 1.4 Lichen sclerosus

Lichen simplex chronicus may be present in all ages and may be distinguished in primary (arising from normal appearing skin) or secondary (superimposed on some other underlying dermatological disorders). It is characterized by the presence of itch-scratch cycle and clinically by a palpable thickening of the tissue and

increased prominence of skin markings. Color of lesions may vary from white to skin colored or red [23].

Vitiligo is an aquired, autoimmune disorder due to an absence of epidermal melanocytes. Lesions are asymptomatic, sharply demarcated patches with complete loss of pigment, often involving periorificial areas in a symmetric manner [7].

1.4.1.5 Dark-Colored Lesions

Acanthosis nigricans, nevi, lentigines, HPV, and seborrheic keratosis may appear as dark-colored lesions.

Acanthosis nigricans is characterized by thickening and hyperpigmentation of the skin. Symptoms are absent. It usually involves the skin of axillae, posterior neck, groins, bell line, dorsal surface of fingers, mouth and around areolas. It is considered as markers of insulin resistance.

1.4.1.6 Blisters

If blister lesions (vesicles and bullae) are present, clinician should consider HSV, varicella, eczema but also **autoimmune disease** such as childhood vulvar pemphigoid and chronic bullous disease of childhood should be kept in mind.

1.4.1.7 Erosions and Ulcers

Genital erosions and ulcers may be caused by infections, inflammatory diseases, malignancy medications, and trauma.

Infectious agents typically associated with ulcers are **Herpes simplex viruses** (Fig. 1.5), Haemophilus ducreyi (chancroid), Treponema pallidum (syphilis),

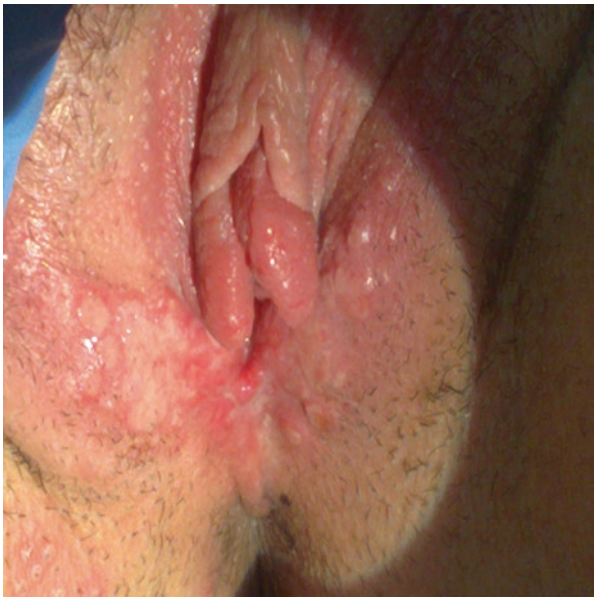

Fig. 1.5 Herpes Simplex Virus

Epstein Barr virus (mononucleosis), Cytomegalovirus, Influenzae viruses, and streptococci [32, 33].

Ulcers may be caused by inflammatory disease such as Behçet's syndrome and Crohn disease, childhood vulvar pemphigoid, hidradenitis suppurativa, Jacquet erosive dermatitis, pyoderma gangrenosus, and Reiter syndrome.

Behçet's syndrome is a chronic, relapsing systemic vasculitis of unknown etiology. It is rare in childhood but may be considered when child presents with recurrent, painful oral and/or genital ulcers that may be single or multiple, shallow or deep, round to oval in shape, and have a yellowish necrotic base [34, 35]. Diagnosis includes presence of oral aphthous ulcers recurring at least three times a year, plus at least two of the following: recurrent genital ulcers, uveitis or retinal vasculitis, skin involvement such as erythema nodosum, or a positive pathergy test.

Crohn disease is a chronic inflammatory bowel disease characterized by transmural skip lesions that can occur anywhere in the gastrointestinal tract from the mouth to the anus. In addition to gastrointestinal tract lesions several reports have described cutaneous and genital manifestations, defined as "metastatic Chron." Vulvar Crohn disease may be the first clinical sign of the disease. Lesions typically begin with painful vulvar asymmetric edema or mass, erythema and progressive ulceration. A biopsy of the lesion is necessary to a definitive diagnosis [36].

Lipschutz ulcers or vulvar aphthosis refers to acute genital ulcers associated with viral or unknown etiology. Usually it is preceded by febrile illness and it may be associated to mouth ulcers. Diagnosis is made on the basis of clinical history and exclusion of other diseases (Herpes viruses and Behçet's syndrome) [7].

Depending on the level of suspicion, consultation with a specialist (dermatology, gastroenterology, ophthalmology, or rheumatology) may be necessary to exclude a specific diagnosis. The biopsy is necessary in some cases and serology may be helpful. If sexually transmitted disease is diagnosed, sexual abuse should be excluded in absence of evidence of different transmission.

1.4.1.8 Edema

Mild edema may occur with any inflammatory disease. Diffuse genital edema may be present in Crohn disease or post staphylococcal and streptococcal cellulitis.

1.4.2 Labial Adhesions

Although not included in the classification described above, agglutination of labia minora represents a vulvar condition affecting up to 2–5% of young girl, usually among 6 months and 7 years age [14]. Initial small posterior adhesions may progress to near-total fusion. Possible explanation for adhesions is hypoestrogenism combined with tissue hyper-reactivity and vulvar flogosis. Symptoms, when present, include postvoid leakage of urine, urinary infections, and nonspecific vulvovaginal complaints. The diagnosis is made by visual inspection of the vulva (Fig. 1.6). Treatment is not always necessary, especially when symptoms are absent, since spontaneous resolution occurs in up to 80% of cases. Topical medication

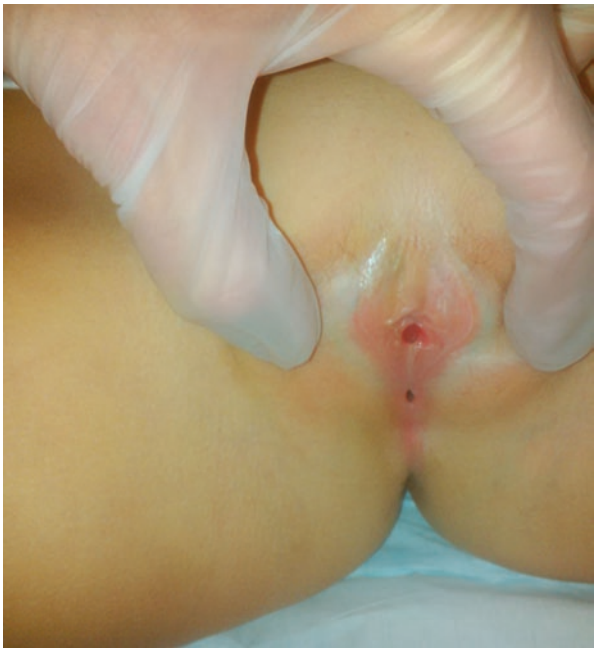

Fig. 1.6 Labial adhesions

consists in estrogen containing cream twice daily for 3 weeks and then once a day for 2–4 weeks [37]; in alternative, betamethasone cream 0.05% can be applied twice daily for 4–6 weeks [38]. In cases of symptomatic adhesions or urinary obstruction, application of topical anesthetic followed by manual separation can be performed: Q-tip is inserted behind the labia minora and slides gently along the adhesions [38]. Risk or recurrence is elevated (40%) but can be reduced by improving perineal hygiene and with use of ointment [20].

1.5 Management of Vulvovaginitis

Most cases of nonspecific vulvovaginitis resolve by following hygiene education and lifestyle recommendations:

- Wiping front to back after using the toilet
- Void with legs open
- Use plain white toilet paper
- Wash hands frequently
- Use and frequent changes of cotton underpants
- Avoidance of tight induments
- Avoidance of harsh soap and bubble baths
- Vulva and perianal area should be washed with water or mild unscented soap

Table 1.2 Treatment of specific vulvovaginal infections

Etiology	Drugs	Dosage
Pinworm	Mebendazole	Oral, 100 mg or 5 mL suspension once, repeated in 2 weeks
	Pyrantel pamoate	Oral, 11 mg/kg once, repeated in 2 weeks
	Albendazole	Oral, 400 mg once, repeated in 2 weeks
Sarcoptes scabiei	Permethrin	5% cream applied from head to toe, at least 8 h overnight, repeated 7 days later
Streptococcus pyogenes	Amoxicillin	Oral, 20 mg/kg every 12 h, for 5–10 days (21 days for perianal infection)
Haemophilus influenzae	Amoxicillin	Oral, 20 mg/kg every 12 h, for 5–10 days
Candida albicans	Clotrimazole	Topical, 6 days
	Miconazole	
Candida glabrata	Isoconazolo	Topical, 10 days
	Sertaconazole	
	Boric acid	
Yersinia and Shigella	Trimethoprim-sulfamethoxazole	Oral 5 mg/kg every 12 h for 5–10 days

Dei and Bruni [14], Zuckerman and Romano [40] and Emans and Laufer [7]

– Vulva and perianal area should be let dried avoiding rubbing

If symptoms are mild, using an emollient cream or ointment may be useful. In severely symptomatic patient, a 1–2.5% hydrocortisone cream can be used once or twice a day for 2 weeks [39].

The need for pharmacologic treatment in cases of positive culture for normal flora/opportunistic pathogens is questionable, as the presence of a microorganism does not necessarily imply that it is the cause of infection [21]. Furthermore, the extensive use of antibiotics is associated to emergence of multidrug resistant bacteria. The first step of treatment should be the use of oral probiotics, sitz bath, and local application of antiseptic ointment or solution (benzydamine/clorexidine). Empirical administration of topic antimicrobials (gentamicin/fusidic acid/metronidazole + nifuratel/netilmicin + chloride benzalkonium/cyclopiroxilamine) may be acceptable when aspecific superinfection is suspected. Severity of symptoms and patient's state of health may indicate need for specific systemic treatment [2, 40].

Patients with specific infection should be treated as follows (Table 1.2):

Pinworm should be treated in cases of suspected or confirmed infection. Family members should be treated if symptomatic. Washing of underwear and bedding is recommended.

Treatment for Sarcoptes scabiei should be applied by patients and closed contacts [31].

Impetiginous lesions of buttocks or vulvar skins, caused by *Staphylococcus aureus*, can be treated with topical mupirocin 2% applied three times daily. If systemic antibiotic is necessary, susceptibility test should be performed.

1.6 Recurrent Vulvovaginitis

If vulvovaginitis persist despite lifestyle changes and first-line treatment, it is important to overview the diagnosis, evaluate urinary and intestinal function and consider the possibility of multidrug resistant bacteria.

Foreign body (rolled toilet paper is the most frequent) is responsible for up to 20% of recurrent vulvovaginal discharge and may be associated to hematic discharge. Urinary dysfunctions (especially hyperactive bladder, dysfunctional urination, urinary vaginal reflux) and chronic constipation also may play a role in favoring recurrences of infections [14]. Relapses of vulvovaginitis caused by *Streptococcus pyogenes*, which occur in up to a third of treated individuals, may be associated with pharyngeal carriage [5].

Moreover, other causes have to be excluded: polyps, tumor, sexual abuse, psychosomatic vaginal complaints, draining pelvic abscess, prolapsed urethra, allergy to pollen, ectopic ureter in vagina, vaginal malformation with stagnation of mucus and pus in obstructed hemivagina, rectovaginal fistulae due to genital mutilation or Crohn disease. If inspection of upper vaginal canal or cervix is needed, vaginoscopy under general anesthetic should be performed. Allergologic consultation may be useful in patients with allergic diathesis or familiarity for allergies [14].

Single course of estrogen containing cream applied for 1–2 weeks can be used in selected cases to thicken the epithelium and facilitate healing (Emans and Laufer 2012; [14, 39]). Even in absence of specific studies many clinicians have found that 10–14 days of empirical treatment with topical gentamicin/mupirocin/metronidazole/cyclopiroxilamine or systemic (amoxicillin/clavulonate or cephalosporin) antibiotics for 10–14 days [7] may lead to resolution of recurrences. In cases of recurrent candida infections, secondary to prolonged antibiotic treatment or immune deficiency, oral fluconazole 3 mg/kg once daily is recommended [14].

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Delayed Puberty

2

Metella Dei and Francesca Pampaloni

Abbreviations

AMH	Anti-Mullerian hormone
CD	Coeliac disease
CDGP	Constitutional delay of growth and puberty
CSF	Cerebrospinal fluid
DP	Delayed puberty
FHH	Functional hypogonadotropic hypogonadism
FSH	Follicle stimulating hormone
GD	Growth hormone deficiency
Gh	Growth hormone
GhRH	Growth hormone releasing hormone
GnRH	Gonadotropin hormone releasing hormone
HH	Hypogonadotropic hypogonadism
IGD	Isolated Gh deficiency
IGF-1	Insulin growth factor-1
KS	Kallmann syndrome
LH	Luteotropic hormone
PRL	Prolactin
SSRI	Selective serotonin reuptake inhibitors
TIDA	Tuberoinfundibular dopamineagonists

M. Dei, M.D. (✉)
Italian Society of Pediatric and Adolescent Gynecology, Florence, Italy
e-mail: meteldei@alice.it

F. Pampaloni, M.D.
Pediatric and Adolescent Gynecology Unit, Careggi Hospital, Florence, Italy
e-mail: pampa@virgilio.it

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2.1 Definition and Pathogenesis

We define a delayed puberty (DP), warranting a diagnostic evaluation, as:

1. Lack of breast development by age 13
2. Lack of menarche by age 15 in the presence of secondary sexual characteristics
3. Lack of menarche 4 years after the beginning of breast development (thelarche)

These criteria, based on two standard deviations from normal range of pubertal timing of European Caucasian girls, can be, in the clinical practice, extended also to African girls (whose pubertal development starts earlier) and to Asian girls. The presence of clues of specific conditions (malnutrition, poor growth, reduced sense of smell, cyclic pelvic pain, androgen excess) can suggest the need of an earlier evaluation.

As the first menstrual bleeding is the endpoint of the maturation of genital organs and of various endocrine systems, the failure to undergo menarche could be secondary to:

– Genital malformations as genital tract outflow obstructions or Mullerian Agenesis (or Rokitansky, Kuster, Hauser, Mayer syndrome) described in Chap. 3
– Primary gonadal failure, present in more than 25% of girls with lack of physiological sexual development (see Chap. 4)
– Secondary gonadal failure due to antineoplastic therapy or, rarely, to autoimmune processes
– Deficiency of gonadotropin production, the specific topic of this chapter

Impaired gonadotropin release is linked to a wide variety of underlying conditions leading to delayed or absent puberty (Table 2.1). Recent genetic studies have demonstrated a significant overlap between CDGP and GD and among different forms of HH, so our classification will probably change in the next years.

Considering the relative frequencies of the various etiologies, we estimate that more than 30% of female subjects with DP have a constitutional delay; functional hypogonadisms now account for almost 40% (for the increasing incidence of eating disorders in very young girls). The remaining subjects are affected by other causes.

2.1.1 Hypogonadotropic Hypogonadism

HH includes various congenital deficiencies of GnRH production, not involving other pituitary tropins. In Table 2.2, the well-defined syndromes in female subjects are summarized.

The Kallmann syndrome (KS) is the association of isolated hypogonadotropic hypogonadism (HH) and reduced or absent smell sense: the association provides evidence that the dysfunction of GnRH neurons activity is related to their impaired migration during intrauterine life from olfactory area to hypothalamus. The prevalence of Kallmann syndrome is rare (1:50,000 in females) and related to mutations

Table 2.1 Pathogenesis of hypogonadism

Hypogonadotropic hypogonadism (HH)	Kallmann syndrome
	Isolated gonadotropin deficiency
	Charge syndrome
	Leptin deficiency
Organic CNS pathologies	Congenital hypopituitarism (complete or partial)
	Congenital hypogonadotropic hypogonadism
	Midline cerebral and cranial malformations
	Empty sella syndrome
	Iron overload secondary to hemoglobinopathies, aplastic anemias, juvenile hereditary hemochromatosis
	Sarcoidosis, granulomatous infections (tuberculosis), Langerhans cell histiocytosis
	Autoimmune hypophysitis
	Rathke's pouch cysts
	Arachnoid, dermoid, or epidermoid cysts
	Obstructive hydrocephalus
	CNS tumors
	Repercussions of trauma, surgery, vasculopathies
	Long-term effects of antineoplastic treatments
Hyperprolactinemia	Prolactinoma or other pituitary adenomas
	Pituitary stalk lesions
	Drugs affecting prolactin secretion
Gh deficiency (GD)	Isolated
	Syndromic (Noonan syndrome, Prader–Willi syndrome)
Constitutional delay of growth and puberty (CDGP)	
Functional hypogonadotropic hypogonadisms (FHH)	Eating disorders
	Strenuous physical activity
	Coeliac disease (CD)
	Chronic diseases
	Endocrinopathies (Cushing syndrome, 21α hydroxylase deficiency, hypothyroidism)
	Long-term corticosteroid treatment
	Endocrine disrupters

Table 2.2 Hypogonadotropic hypogonadism

	Associated defects	Known involved genes
Kallmann syndrome	Hypo-anosmia; infrequently cleft palate, synkinesis, unilateral kidney agenesis, hearing defects	ANOS1, FGFR1, FGF8, PROK2, PROKR2, WDR11, CHD7, NELF, HS6ST1, SOX10, SEMA3A, FEZf1
Isolated hypogonadism		GnRHR, GnRH1, FSHb, FGFR1, GPR54/KISS1R, KISS1, TAC3/TACR3, NR5A1, PIN1, NNKB, NKR3 (FGFR1, FGF8, PROKR2, CHD7, WDR11)
Charge syndrome	Coloboma, cardiac malformations, atresia choanae, external genital hypoplasia, ear anomalies, growth anomalies	CHD7
Leptin deficiency	Obesity, immunological deficiency	LEP, LEPR

of different genes; it is mainly sporadic; sometimes familiar transmissions X linked or autosomic recessive or autosomic dominant have been documented. Consequently, the phenotype is also variable concerning olfactory ability, secondary sex characteristics development and associated defects. The possibility of a late recovery of hypogonadism has been described in few cases [1].

For the diagnostic workup, it should be kept in mind that the self-evaluation of smell is generally unreliable except in subjects who admit anosmia; so it should be investigated with a selection of essential oils or scented papers or with specific standard kits. In KS the growth is linear, without spurts, exceeding the average for chronological age and inappropriate for bone age, with a prevalent increase of arms and legs, because the physiological pubertal shift between legs and trunk increase doesn't take place.

Isolated hypogonadism includes various diseases with different stages of pubertal delay without other functional (even if small impairment in olfactory ability is sometimes present) or somatic defects and with normal brain imaging. The underlying genetic mutations are various and overlapping with alterations in genes involved also in KS [2].

The CHARGE syndrome (Coloboma, Heart defects, Choanal atresia, Retarded growth and development, Genital abnormalities, Ear anomalies) is a rare association, mainly sporadic of several anomalies related in more than 60% of cases to CHD7 gene mutation. The hypogonadism may result from the same migration defects of KD and is associated with growth, coloboma of iris and sometimes of retina, choanal atresia, internal and external ear abnormalities, and heart malformations. Cranial nerve defects with problems with breathing and feeding, orofacial clefts, defective sense of smell, vestibular abnormalities, hearing loss, and genital hypoplasia are also common.

The association between hypogonadotropic hypogonadism and leptin deficiency or leptin receptor anomalies entails, in typical forms, obesity and a higher prevalence of infections for an associated T cell functional anomaly; actually leptin mutations have been described even in subjects mildly overweight or normal and with normal immunologic defenses.

2.1.2 Organic CNS Pathologies

Gonadotropin deficiency can be present in congenital diseases involving the production of other pituitary hormones, linked to mutations of genes encoding transcription factors involved in the ontogenesis of pituitary gland or of hypothalamus-pituitary axis. The diagnosis is usually made during infancy and a definite cytogenetic testing is very important in order to plan the follow-up needed to prevent clinical outcomes related to late onset deficiencies [3]. Rare congenital midline cerebral and cranial malformations, i.e., septo-optic dysplasia or absence of septum pellucidum with optic hypoplasia, are associated with endocrine pituitary dysfunction. More frequent is the empty sella syndrome, characterized by cerebrospinal fluid filling the sella; as a result, the pituitary gland is often compressed and

flattened. Empty sella may occur as a primary disorder because of an herniation of the arachnoid through a defect in the diaphragma sellae or as a secondary disorder due to damage to the pituitary itself, for instance as long-term consequence of surgery, radiation therapy, or of autoimmune hypophysitis. In most cases empty sella is asymptomatic; in adolescents could be associated with endocrine abnormalities: Gh and gonadotropin deficiency or hyperprolactinemia.

The pituitary gland is characterized by a very high blood flow (0.8 mL/g/min) and therefore is very exposed to overload phenomena especially iron overload. A pituitary injury may arise, in spite of the progress of chelation therapy, as a consequence of iron deposition in reticuloendothelial cells in subjects with hemoglobinopathies (thalassemia, hemolytic or aplastic anemias), who need transfusion therapy (transfusional hemosiderosis). The iron overload increases gradually reducing the pituitary volume and function; chronic hypoxia and ineffective erythropoiesis contribute to the endocrine impairment often involving also the growth hormone production. A significant iron overload in pubertal age is rare in subjects affected by hereditary idiopathic hemochromatosis [4]: in this disease, the deposition is mainly at parenchymal level but very slow and endocrine repercussions appear in older age. The history of relatives affected by the disease, the tiredness, the elevation of liver enzymes and ferritin, and the transferrin saturation of more than 45% address to a more detailed study including genotype.

Neurosarcoidosis and Langerhans cell histiocytosis are uncommon in adolescence; pituitary tuberculous infiltration has been described in adolescents living in other countries. Autoimmune hypophysitis is an inflammation of the pituitary gland due to the attack of T lymphocytes against secreting pituitary cells, sometimes secondary to systemic diseases, infections, or immunomodulating treatments. It occurs more commonly during and shortly after pregnancy, but it is described also in adolescence. Autoimmune damage of the pituitary gland results in the deficiency of various tropins and often diabetes insipidus. Autoantibodies against pituitary (APA), sometimes against hypothalamus (AHA) and thyroid gland, can be detectable. Specific mutation of CTLA-4 gene can predispose to this disease.

The Rathke's pouch is embryologically an ectodermic evagination at the roof of the developing mouth that gives rise to the anterior pituitary; its posterior wall remains as intermediate lobe of the gland. Fluid-filled cysts can arise from the expansion of remnants of this formation. They are generally asymptomatic, but sometimes exert compression on adjacent pituitary tissue and distortion of the pituitary stalk. Arachnoid cysts are probably derived by congenital splitting of the arachnoid layer with accumulation of CSF within this potential space and usually located in the middle cranial fossa. The majority of arachnoid cysts are asymptomatic, but sometimes their gradual enlargement produces a mass effect resulting in either direct neurological or endocrine dysfunction or distortion of normal CSF pathways.

A chronic obstructive hydrocephalus may be derived from a congenital stenosis at or below the level of the aqueduct of Sylvius, connecting the third to fourth ventricle (often on genetic basis), or from compression gradually exerted by a colloid or an arachnoid cyst on the third ventricle located on the diencephalon of the

forebrain between the right and left thalamus. It may cause a distension of the periventricular or medial basal hypothalamus disrupting the physiological release of GnRH; sometimes hypothyroidism and anomalies of Gh secretion are associated. In congenital aqueduct stenosis, the presence of symptoms of increased intracranial pressure (headache, nausea, vomiting, papilledema) is very rare and the situation is mainly asymptomatic.

Considering the tumors affecting the hypothalamic-pituitary region, craniopharyngioma is a dysontogenic lesion arising, near the pituitary stalk, from the epithelial nests of craniopharyngeal duct or of Rathke's pouch. The prevalence is about 1:50,000 subjects. It is a capsulated tumor, with slow evolution but with a tendency to invade surrounding structures and to recur after resection. At the beginning of its growth symptoms are uncommon, so the diagnosis is often delayed when the pressure on the optic tract or on the pituitary gland causes impaired vision, growth and pubertal delay, obesity, insipid diabetes or when an intracranial hypertension has been established. Vomiting in the morning and pathological rate of growth are generally the early manifestations of the disease [5]. Pituicytoma arising from pituitary parenchyma or germinoma and teratoma growing from germ cells inclusions can also involve the sella region as well as neoplastic lesions coming from adjacent structures.

Traumatic brain injuries can lead to acute endocrine changes but also both temporary and permanent alterations of pituitary function in the long term: the most common are Gh deficiency and alterations of puberty. We estimate that 3 months after the trauma about 35% of children and adolescents display pituitary secretion abnormalities and 30% after 12 months. A spontaneous recovery is possible, but permanent deficiencies have been documented [6]. A deficiency in gonadotropin secretion can be the long-term effect of treatments (mainly radiation) of leukemia and brain tumors even if therapeutic procedures with less impact on endocrine function are increasingly under study.

2.1.3 Hyperprolactinemia

An hyperprolactinemia is infrequently a cause of delayed puberty. A prolactin excess can be related to a PRL secreting (or Gh secreting) adenoma or to other intracranial pathologies (chordoma or other neoplasia) causing a pituitary stalk interruption or dislocation (pseudo-prolactinoma). The compression on the stalk may impair the function of TIDA (TuberoInfundibular DopAmine) neurons that physiologically inhibit the secretory activity of PRL cells. An hyperprolactinemia can also be associated to hormone deficiencies secondary to pathologies damaging the hypothalamus-pituitary region, as already mentioned. A prolactin excess related to primary hypothyroidism, linked to TSH secreting cells hyperplasia, has also been described. Increased prolactin concentrations as a consequence of drug intake, especially psychiatric drugs (Table 2.3), are more frequent; so a pharmacological anamnesis is always mandatory.

Table 2.3 Hyperprolactinemic drugs

Antipsychotic	Haloperidol, Chlorpromazine, Thioridazine, Thiothixene	
	Risperidone, Paliperidone, Sulpiride, Amisulpride, Molindone, Zotepine (Olanzapine, Clozapine)	
Antidepressants	Tricyclic	Amitriptylin, Desipramine, Clomipramine, Amoxapine
	SSRI	Sertraline, Fluoxetine, Paroxetine
Prokinetics		Metoclopramide, Domperidone
Opiates		Morphine
H_2 antagonists		Cimetidine, Ranitidine
Others		Physostigmine, antineoplastic drugs

In subjects with prolactinoma, the history and the symptomatology can be insignificant: the linear growth is generally normal, neurological symptoms mostly absent, and galactorrhea is rare in this age group.

2.1.4 Gh Deficiency

Isolated Gh deficiency (IGD) can be acquired (as result of trauma, infection, radiation therapy, or tumor growth), or congenital on genetic basis: the genes coding for Gh (Gh1), its receptor (GhRHR) and Ghrelin receptor (GhSR) are the most commonly involved; less often mutations of transcription factors active in pituitary development are involved. However, known mutations explain only a small percentage of clinical cases (several GD are diagnosed as idiopathic); moreover, genotype–phenotype correlation is not univocal and is variable over time. Subjects with GD may present with insufficient growth velocity and delayed growth spurt, considering their chronological age. Slow tooth eruption and poor nail growth can be present in the history. In subjects with previous diagnosis of IGD and under treatment the pubertal timing is generally normal.

Noonan syndrome is a heterogeneous genetic disorder, typically evident at birth, characterized by a wide spectrum of physical features: abnormalities of head and face, skeletal and vascular malformations, heart defects, delay of growth and puberty. The incidence is 1:1500 subjects. The Prader–Willi syndrome is a genetic disorder affecting 1:30,000 births due to the missed expression of genes imprinted on the chromosome 15. The girls affected display growth and sexual development delay and obesity secondary to hyperphagia. The hypogonadism can be related to a central defect with late menarche (about 20 years); a primary gonadal defect can also be present.

2.1.5 Constitutional Delay of Growth and Puberty

In more than 60% of cases a familiarity can be demonstrated, with an autosomic dominant transmission. Genetic studies highlighted mutations of GnRH Receptor, GhSR, an endogenous Ghrelin ligand, of genes involved also in IGD, and of genes significant in the pathogenesis of HH. Subjects affected by CDGP have an overall delay in the appearance of sex characteristics, the growth spurt, and the development of internal genitalia of, on average, 2 years and a half, with normal nutritional status. The time span between the thelarche and the beginning of growth spurt is generally reduced; but height velocity is lower than in normal subjects. The current height is in agreement with bone age more than with chronological age.

2.1.6 Functional or Secondary Hypogonadotropic Hypogonadism

Eating disorders are becoming more frequent in preadolescent, considering the trend to a precocious onset of these unhealthy behaviors. Restrictive food intake or selective eating can induce an energy deficiency impairing the normal timing of GnRH neurons activation. Dissatisfaction with their own look and concern about weight can be evident or not. Sometimes, a history of eating disturbances in infancy or of precocious traumatic events is present. Psychopathological traits (anxiety or depression) in the relatives are frequent. A reduced nutritional intake induces a decrease of linear growth and a slowing of pubertal maturation, evident at breast level. Considering body composition a reduced fat deposition and a slow bone mass apposition occur, with a slight increment in fracture risk. The symptoms are related to the mechanisms of adjustment to reduced energy intake (see Chap. 8) and are directly related to the seriousness of the clinical situation. The young athletes undertaking strenuous training programs in peripubertal age may undergo to a period of reduced energy availability for the needs of anabolic processes related to pubertal development, with resulting repercussion on hypothalamus-pituitary-ovarian axis activation. This effect is particularly evident if restrictive eating is associated, sometimes following the esthetic appeal required for certain physical activities, as in gymnasts, dancers, skaters, and wrestlers. From a clinical point of view the prepubertal phase is prolonged, as well as the first stages of puberty development, the growth potential is attenuated, and the relative proportions of lean and fat body mass are modified.

Undiagnosed or untreated coeliac disease (CD) is often associated with pubertal maturation delay and sometimes with growth impairment considering the genetic target. The pathogenesis is multifactorial: in addition to nutrients deficiency and body composition alterations, the involvement of autoimmune processes is now under study. The estimated prevalence of this condition is 1% of population. The hallmark of CD is an immune-mediated enteropathy elicited by gluten in genetic susceptible individuals, but gastrointestinal symptoms can be absent; sideropenic

Table 2.4 Chronic diseases associated with pubertal delay

Chronic liver diseases, alpha1-antitrypsin deficiency, congenital biliary tract atresia
Congenital heart malformations
Chronic inflammatory bowel diseases
Cystic fibrosis
Epilepsy, cerebral palsy
Hemoglobinopathies (thalassemia, sickle cell disease), Fanconi anemia
HIV infection
Insulin-dependent diabetes
Nephrotic syndrome, renal insufficiency
Juvenile idiopathic arthritis
Juvenile LES
Severe chronic asthma

anemia, raised liver enzymes, and autoimmune thyroiditis may be found. The research and the identification of CD in adolescents with faltering growth and delayed puberty are supported by evidence criteria [7].

We estimate that a chronic disease (Table 2.4) affects more than 10% of young people: in a majority of cases the energy deficiency, the metabolic impairment, the changes in body composition, the chronic hypoxia, the opportunistic infections, sometimes the treatments impact on pubertal development slowing it down and delaying menarche. The level of involvement depends on the type of disease, the age of onset, its duration and severity, and on the individual response to therapy [8]. Considering 25% begins under 18 years of age: Crohn disease especially is associated with growth and puberty delay. In adolescents suffering from insulin-dependent diabetes and following intensive insulin therapy in agreement with current guidelines, the improved glycemic entails minimal impact on timing of menarche.

Undiagnosed or untreated endocrine diseases can condition pubertal maturation:

- Hypothyroidism implicates reduced linear growth with higher trunk development related to legs and delay in facial bones modifications.
- Cushing syndrome is very rare in prepuberty and can induce growth delay, trend to overweight, skin signs of hypercortisolism (striae, acne, hair growth excess); an episodic cortisol hypersecretion has been described, more difficult to identify.
- The glucocorticoid treatment of congenital adrenal hyperplasia can have an impact on growth and pubertal maturation.

Similar effects can be evident in subjects under extended treatment with glucocorticoids for juvenile LES, idiopathic arthritis, and asthma.

Finally, a mention of the possibility of exposure to endocrine disrupters: lead, dioxins, and polychlorinated dibenzodioxins have been pointed out as possible causes of pubertal delay [9].

2.2 Diagnostic Workup

The diagnostic evaluation of a patient with pubertal delay is easier if history taking, physical examination, and laboratory tests are performed bearing in mind the possible pathogenic spectrum, in order to orient the tests required. So the diagnostic workup here proposed is illustrative and does not include an in-depth analysis of all the diseases underlying a secondary functional hypogonadism. Moreover, few differential diagnoses usually require a follow-up. In Table 2.5, the first-level diagnostic approach is synthetized.

Sitting height reflects the proportion of girl's height that is attributed to the head and the trunk, in relation to legs and is a useful measurement to detect conditions that affect growth in a disproportional manner. In HH, legs growth is typically reduced (and SH/TH ratio is less than 50%) while in growth hormone or thyroid hormones deficiencies it is reduced and SH/TH ratio results increased.

Pelvic ultrasonography, in addition to excluding uterovaginal malformations, offers a first evaluation of ovarian echostructure and biological appraisal of estrogenization. The study of uterine length and/or volume and the ratio of anteroposterior diameters of corpus and cervix are well-known criteria of staging of pubertal maturation. In many cases of functional hypogonadism, pelvic US shows a uterus of normal morphology but reduced volume and ovaries with microfollicles similar to physiological prepubertal period. Pelvic US is also an easy method of follow-up if a CDGP or secondary hypogonadism is suspected.

The bone age, evaluated on a single X-ray of left hand and wrist, is a measure related to pubertal maturation more than to chronological age; for this reason in the majority of conditions linked to pubertal delay it results also delayed [10]. In subjects with CDGP and GD bone age is usually coherent with the mean age corresponding to current height; this coherence is not present in girls suffering from HH who display delayed bone age and increased linear growth considering chronological age. In chronic diseases, bone age is delayed but in agreement with Tanner stage and internal genitalia US development. In functional hypogonadotropic hypogonadism, secondary to energy deficiency, the deviation between bone and chronological age is probably the most significant.

Table 2.5 First-level diagnostic approach

Clinical history	Familiar: pubertal delay, shortness, autoimmune diseases
	Personal: onset of pubertal signs, physical activity, eating habits, headache, visual impairment, gastrointestinal problems, pelvic pain known pathologies, previous or current drugs used, surgery, head trauma
Physical exam	BMI, Tanner stages, eventual dysmorphisms, smelling ability, external genitalia inspection, neurological signs, eventually fundus examination
Auxology	Weight (W), height (H), sitting height (SH) and SH/TH ratio, growth chart, target height (TH)
Imaging	Pelvic US scan, bone age
Laboratory	FSH, LH, PRL, TSH, FT_4, IGF-1 if growth impairment or suspected low energy availability
	Blood tests suggested by history and physical exam

Concerning endocrine evaluation, the increase in FSH level is diagnostic of gonadal failure (see Chap. 4); in central deficiency gonadotropin concentrations, especially of LH, are in the lower range, but current assays are not so accurate in the lower detection limits. So a basal plasma determination is generally unable to differentiate between organic deficiency, constitutional delay, and functional impairment. PRL sampling should be performed in the morning but not just after the awakening, in order to avoid misleading increases related to the circadian rhythm of the hormone [11]. It is advised to repeat the assay in case of high levels, together with thyroid hormones and IGF-1 to exclude the involvement of other tropins. If it is available, Polyethylene Glycol (PEG) precipitation should be tested in order to screen the presence of macroprolactinemia, large molecular masses of PRL together with IgG and anti-PRL autoantibodies, with poor biological activity. This phenomenon is however rare in young ages. The 17β estradiol dosage is generally not so significant because it is usually performed with methodology with poor sensitivity in the lower range: the use of integrated measurement (i.e., early morning urinary determination) and of different methodology (liquid chromatography and gas spectrometry) could add more information. The usefulness of follicular activity markers (AMH, Inhibin B) is under study: interesting preliminary data about basal inhibin level with a cutoff 20 pg/mL have been published [12].

Serum levels of Insulin growth factor-1 (IGF-1) in adolescent girls are physiologically related to pubertal stage more than to age, with a peak in late puberty [13]. Very low concentrations (less than two SD for age range) are a marker of congenital or acquired Gh deficiency (as in thalassemia major); in constitutional delay of growth and puberty (CDGP), IGF-1 levels are in agreement with growth and Tanner stage, more than with chronological age. In situation of energy deficiency, such as restrictive eating, an acquired growth hormone resistance with low IGF-1 levels is present. As already mentioned, in subjects with hyperprolactinemia, not related to pharmacological treatment, IGF-1 levels should be investigated in order to identify mixed Gh and PRL secreting adenoma.

Blood tests should include serum creatinine to exclude kidney disease before programming a brain RMI with gadolinium-containing contrast medium and the anti-tissue transglutaminase (tTg) together with the dosage of IgA (to exclude misleading results related to IgA deficiency). IgA endomysial antibodies (EMA) should be required if IgA tTG is weakly positive and the use of IgG EMA, IgG deamidated gliadin peptide (DGP), or IgG tTG should be considered if IgA are deficient.

In a second-level diagnostic workup, we include further tests:

1. To confirm the hypothesis of functional hypogonadism:

   Body impedance analysis (BIA) or total body Dual X Ray absorptiometry (DXA) to assess body composition: a significant reduction in fat mass as a percentage of body weight puts in evidence subject with BMI not so far from the normal range, but with energy deficiency. This evaluation is also useful to estimate the metabolic homeostasis in subjects with chronic diseases. It is mandatory to remind that we do not have standard references values for BIA in peri-pubertal years, even if it has been demonstrated that fat mass increases in

the 6 months before menarche, reaching a plateau after around 1 year [14]. We estimate as 18% of weight the fat mass necessary for the onset of menstrual function, considering that BIA underestimate fat measurement, in comparison to DXA. The use of total body DXA is accurate, but expensive and minimally radiant, so it find an indication when also an evaluation of bone mass deficiency is necessary.

Hormonal markers of reduced energy availability as FT3, insulin, cortisol and leptin (see Chap. 8)

Nutritional tests: folate, zinc, albumin, pre-albumin, transferrin, retinol-binding globulin;

2. To study the possibility of hypothalamus-pituitary organic disease:

   Magnetic Resonance Imaging (MRI) of brain and head with contrast medium (gadolinium) should be performed if headache or neurological sings are present, Kallmann or Charge syndrome are suspected, hyperprolactinemia has been found, a Gh or other tropins deficiency are supposed, the clinical history orients to iron overload and when hypogonadotropic hypogonadism without known etiology is present. The exam can put in evidence the olfactory tract and bulbs hypoplasia (Kallmann and Charge syndrome, septo-optic dysplasia), the presence of obstructive hydrocephalus, pituitary adenoma, empty sella, tumors compressing the stalk or the hypothalamic region, pituitary infiltrates or autoimmune hypophysitis (even if the differential diagnosis with pituitary adenoma is not easy from a radiological point of view);
3. To evaluate the hypothesis of Gh deficiency:

   Gh provocation tests (Insulin tolerance test of GhRH + arginine test);
4. To confirm the option of autoimmune hypophysitis:

   APA, AHA, TPO Ab, TSHR Ab should be tested;
5. To differentiate HH with normal MRI from CDGP

   GnRH test is largely used but the response in the two conditions show great overlap. The choice of GnRH analogue test seems to be diagnostic, but the published data are poor and the cut-off not univocal (LH/FSH ratio increase of 0.7, after 2 or 3 h has been proposed as a confirmation of the possible activation of hypothalamus-pituitary axis). It is useful also to evaluate estradiol production 24 h after the release injection [15]. The response to exogenous kisspeptin as diagnostic test is under study;
6. Genetic testing is useful in hypogonadotropic hypogonadisms, in syndromic diseases or in presence of additional phenotypic features, for diagnosis, prognosis and genetic counselling to siblings.

2.3 Therapeutic Approaches

When a diagnosis of hypogonadotropic hypogonadism has been defined, a puberty induction should start, to promote secondary sex characteristics, internal genitalia growth and function. Current guidelines [16] advise the use of preferably transdermal estradiol starting with low-dose formulations, in order to mimic physiological

puberty [17]. If the diagnosis is evident at about 10 years of age it is possible to start with 0.05–0.07 μg/kg nocturnally, obtained cutting 25 μg/kg patches and advising the use of occlusive dressing if the patch tends to detach. If the girl is older, as usual, the starting dose can be 0.08–0.12 μg/kg (at the beginning only during the night and then with normal change of the patch twice a week) to promote breast development. The dose is slowly increased every 9–12 months. As an alternative percutaneous or oral estradiol can be chosen, using prepared pharmaceutical formulations with equivalent dosages. The progesterone (100 mg per os) or dihydrogesterone, a progestin similar to progesterone from a metabolic point of view, (10 mg per os) should be added for 12 days after at least 2 years of estrogen treatment, when spotting is present or US endometrial thickness well documented (usually with an estradiol dosage of 25 μg/kg/day). In girls with panhypopituitarism deydroepiandrosterone, starting with 15 mg/day, should be added to promote pubarche. After the first menstrual bleeding, the treatment must convert to a hormone replacement therapy, increasing the transdermic estradiol dosage to at least 75 μg and redoubling the dose of progesterone or progestin. Oral therapy with 2 mg of estradiol or with combined natural estrogens and progestin is another option. A serum estradiol assay could be used to check if hormonal concentrations are in the normal range for age. It is also important to remind that in the future fertility will be possible using gonadotropins or GnRH therapy.

In the rare cases of leptin deficiency a treatment with human recombinant leptin may be proposed, starting with low dosages (0.04 mg/kg/day) given by subcutaneous injection at 6 p.m., adjusting the dose in order to achieve circulating level of the hormone in the normal range for age and BMI.

In organic pathology of CNS the definition of the clinical situation and of the best strategy of therapy require a strict cooperation with the neuroradiologist and the neurosurgeon. An operation, to be performed in specialized units, is usually indicated in cases of obstructive hydrocephalus, compressive pathologies, expansive tumors. The use of intraoperative MRI can be a support. Considering the craniopharyngioma, if the neoplasia does not invade the hypothalamus, the treatment of choice is the complete excision of the tumor; if hypothalamic involvement is present, the treatment consists in subtotal resection associated with postoperative radiotherapy. The overall 5 years survival rate is 80%, even if it is associated with marked morbidity (hypothalamic dysfunction, modifications of the neuropsychological profile). The treatment of autoimmune hypophysitis is medical and mostly using corticosteroids, sometimes in association with azathioprin. In all the situations of persistent gonadotropin damage an endocrine therapy of pubertal induction and replacement is indicate, eventually associated with substitution of other inadequate tropins.

In subjects with hyperprolactinemia related to microadenoma or stalk anomalies not secondary to expansive pathology, a treatment with dopamine agonist (cabergoline, bromocriptine) can be started, in order to consent a normal pubertal development, the attainment of bone mass peak and, frequently the reduction in the dimensions of the tumor. To reduce possible side effects (nausea, orthostatic hypotension) the bromocriptine should be started with a dose not more than 1.25 mg

daily and eventually increased; and the cabergoline with initial dose of 0.25 mg once a week, then twice a week, checking prolactin levels. Only in prolonged treatments with high dosages, it is advisable to program an echocardiographic control for the rare possibility of cardiac valve alterations. Only in selected situations or when the response to dopamine agonists is lacking a neurosurgical intervention can be indicated. Concerning psychotropic drug-induced hyperprolactinemia, it is useful to discuss with the psychiatrist taking care of the girl the possible options. The choice is among the use of an alternative drug less active on dopamine receptor (as aripiprazole as substitution or added at low doses) [18], the addition of dopamine agonist to the treatment (not always effective and sometimes with the risk of worsening the psychotic symptoms) or the possibility of starting a hormone therapy to induce puberty and maintain menstrual function.

Gh deficiency requires a specific replacement treatment, able to promote growth and pubertal progression.

The management of constitutional delay of growth and puberty is essentially a follow-up supported by explanation and reassurance about its spontaneous evolution. In selected situations, the use of a short cycle of estrogen therapy has been proposed, using a dosage related to the degree of development of secondary sex characteristics (for instance 12.5–25 μg transdermal estradiol daily). This option, above all justified by the psychological repercussions in the comparison with peers, induces an acceleration in breast and genitals development and in linear growth, combined with the spontaneous pubertal progression. The treatment does not influence final height, which results anyway slightly reduced in these subjects with regard to their genetic target [19].

In functional hypogonadisms the therapeutic goal is usually to improve the general health, suggesting for girls with eating disorders a psychological counselling and an adequate nutritional support, for athletes a nutritional counselling and sometimes the reduction of intensity of training.

In coeliac disease, a gluten free diet is generally sufficient to promote a spontaneous pubertal development. In several chronic diseases, the pathogenesis of pubertal delay is multifactorial: so it is important an in-depth evaluation of energetic and metabolic homeostasis and, sometimes, of the therapeutic regimen. The treatment plan should be evaluated also in adolescents with pubertal delay suffering from endocrine dysfunctions; particularly in subjects with 21-hydroxylase deficiency under treatment with hydroxycortisone, because pubertal endocrine milieu modifies the metabolic clearance of cortisol but from the other side the linear growth is extremely sensitive to a glucocorticoid excess. A reduction of dosages could sometimes be required to allow an adequate growth and sexual development [20].

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Diagnosis and Treatment of Genital Malformations in Infancy and Adolescence

3

Tiziano Motta and Chiara Dallagiovanna

Abbreviations

AFS	American Fertility Society
AMH	Antimüllerian hormone
ASRM	American Society for Reproductive Medicine
DES	Diethylstilbestrol
ESHRE/ESGE	European Society of Human Reproduction and Embryology/ European Society of Gynaecological Endoscopy
GnRH analogues	Gonadotropin-releasing hormone analogues
IVF	In vitro fertilization
MIF	Müllerian inhibitory factor
MRI	Magnetic resonance imaging
MRKHS	Mayer–Rokitansky–Küster–Hauser syndrome
MURCS	Müllerian renal cervical somite
OHVIRA	Obstructed hemivagina and ipsilateral renal anomaly
PID	Pelvic inflammatory disease
TVS	Transverse vaginal septum
US	Ultrasonography
2D-US	Two-dimensional ultrasonography
3D-US	Three-dimensional ultrasonography
VCUAM	Vagina, cervix, uterus, and adnexa-associated malformation

T. Motta (✉) • C. Dallagiovanna
Department of Obstetrics and Gynecology, University of Milan, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Via Commenda, 12, 20122 Milan, Italy
e-mail: teamotta@alice.it; c.dallagiovanna@gmail.com

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3.1 Embryology Development

The development of the female genital tract represents a complex process beginning at 3–4 weeks of gestation and continuing into the second trimester of pregnancy. Until 8 weeks of gestation, the human fetus is sexually undifferentiated and contains both male (Wolffian) and female (Müllerian) genital ducts. Wolffian structures differentiate into the vas deferens, epididymis, and seminal vesicles. Müllerian or paramesonephric ducts develop into the fallopian tubes (the unfused cranial portions), uterus, cervix and, according to recent views, upper one-third of the vagina [1]. In fact, there is general agreement that the vagina is a composite formed partly by the most caudal portion of the Müllerian ducts (sinovaginal bulbs) and partly by the posterior wall of the urogenital sinus (vaginal plate): the point of contact between the two is the Müllerian tubercle [2] (Fig. 3.1). This dual origin theory best explains the various levels of vaginal obstruction that are seen clinically. Otherwise most experts suggest that the vagina develops under the influence of the estrogenic stimulation and the Müllerian ducts development [3]. In the female fetus, without the influence of the müllerian inhibitory factor (MIF), otherwise known as antimüllerian hormone (AMH), from week 8 to week 16 the Müllerian ducts undergo a process of elongation, fusion, canalization, and septal resorption that will ultimately give rise to the abovementioned female reproductive structures [4]. During this time, the Wolffian ducts regress; however, they are suggested to act as a guide in the downward growth of the Müllerian ducts to form part of the vagina [5]. The cranial parts of the Wolffian ducts can persist as the epoöphoron of the ovarian hilum; the caudal parts can persist as Gartner's ducts. The urogenital sinus also gives rise to the sinovaginal bulbs which proliferate to form the hymenal tissue. The hymen is formed by expansion of the caudal aspect of the vagina with the subsequent invagination of the posterior wall of the urogenital sinus. It serves to separate the vaginal lumen from the urogenital sinus cavity until late in fetal development. Normally it becomes

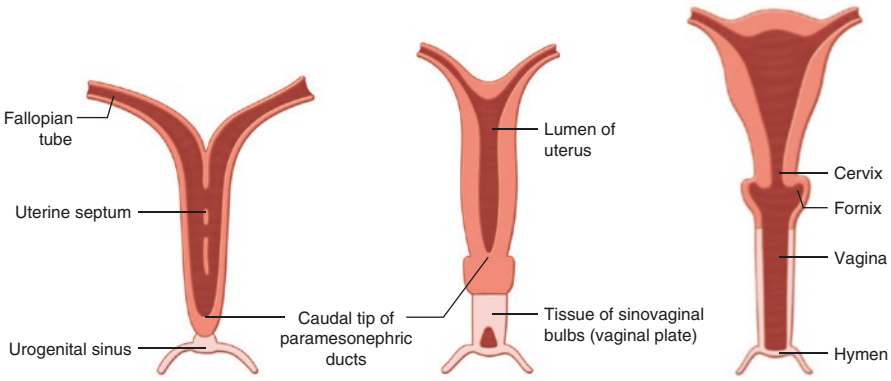

Fig. 3.1 Embryonic formation of female reproductive system

perforate before birth. The external genitalia of female and male are similar at the indifferent stage of development between weeks 4 and 7. Distinguishing sexual characteristics begins to appear at week 9, although full differentiation is not achieved until week 12. Mesenchyme at the cranial aspect of the cloacal membrane proliferates, forming the genital tubercle. In the absence of testosterone and dihydrotestosterone, the genital tubercle develops into the clitoris, and the labioscrotal folds do not fuse, leaving labia minora and majora. Because of the close association of mesonephric and paramesonephric ducts, urinary tract anomalies are frequently associated with female genital anomalies. Failure of development of a Müllerian duct is likewise associated with failure of development of a ureteric bud from the caudal end of the Wolffian duct. Thus, the kidney can be absent on the side ipsilateral to the agenesis of the Müllerian duct. Therefore it is extremely important that thorough urologic studies be performed on all patients with Müllerian anomalies.

3.2 Etiology of Genital Malformations

The etiologies for the majority of congenital anomalies of the female reproductive tract are largely unknown. Most structural anomalies of the internal reproductive tract are a consequence of arrest at specific embryologic developmental stages. Although the definitive etiology is often elusive, some genetic, intrauterine, and extrauterine factors, as well as teratogens, such as diethylstilbestrol (DES) and thalidomide, have been implicated [6]. The genetics of various congenital anomalies of the reproductive tract are quite complex and go beyond the scope of this chapter. Briefly, most cases occur sporadically. In familial cases, many anomalies appear to be multifactorial. Associations with other modes of inheritance also exist and include autosomal dominant and autosomal recessive patterns of inheritance as well as X-linked disorders. Recently, HOX and WNT4 genes have been shown to play a crucial role in sexual differentiation and female genital tract development, in particular during genital tract development. In fact, expression or function defects of one or several HOX and WNT clusters may affect differentiation of Müllerian structures of the female reproductive tract [7, 8]. Müllerian anomalies can also represent a component of a multiple malformation syndrome. Müllerian defects are associated with a higher incidence of other congenital anomalies, most notably those of the urinary tract (20–25%), gastrointestinal tract (12%), musculoskeletal system (10–12%), and heart, eye, and ear (6%).

3.3 Epidemiology

The true incidence of Müllerian duct anomalies is uncertain. Different authors have described a wide range of prevalence rates depending on whether a general population is evaluated at the time of obstetric delivery or has a history of infertility or habitual miscarriage [9, 10]. March reported uterine anomalies in 0.1–2% of all

women, in 4% of infertile patients and up to 15% in women with recurrent abortions [11]. The discrepancy in these prevalence rates presumably relates to the application of different diagnostic methods, with variable test performance, and the use of different classification systems to define the abnormalities. More recently, Chan et al. evaluated the prevalence of congenital uterine anomalies in unselected populations and in women with infertility, including those undergoing IVF treatment, women with a history of miscarriage, women with infertility and recurrent miscarriage combined, and women with a history of preterm delivery [12]. The prevalence of uterine anomalies diagnosed by optimal tests—i.e., three-dimensional ultrasonography (3D-US), laparoscopy, or laparotomy performed in conjunction with hysteroscopy or hysterosalpingography, MRI, and saline sonohysterography—was 5.5% in the unselected population, 8.0% in infertile women, 13.3% in those with a history of miscarriage, and 24.5% in those with miscarriage and infertility. The most common uterine anomaly diagnosed in these unselected population is the arcuate uterus (3.9%), followed by the canalization defects (2.3%) and then the bicornuate uterus (0.4%). This is not consistent with the findings from other studies or reviews, which have generally found canalization defects to be the most common [9, 13, 14]. This discrepancy is again likely to reflect the lack of a uniform system of classification and possibly the misclassification of some arcuate uteri as normal or small subseptate uteri.

3.4 Classification Systems of Genital Malformations

Various classification systems have been proposed to describe genital malformations. The first classification system was introduced by Strassmann in 1907 [15]. Actually, the most widely accepted is the ASRM (American Society for Reproductive Medicine) classification system, formerly known as the AFS (American Fertility Society) classification system. The classification, initially proposed by Buttram and Gibbons in 1979 [16], revised and modified first in 1983 and then in 1988 by a subcommittee of ASRM, is based on the degree of failure of Müllerian development and fusion [17] (Fig. 3.2). The classification system is organized into seven basic groups according to the major developmental failure and separates the defects into groups having similar clinical manifestations, management requirements, and prognosis. It also includes a class characterizing uterine abnormalities related to in utero DES exposure. Additional findings referring to the vagina, cervix, fallopian tubes, ovaries, and urinary system must be separately addressed. Despite being widely accepted, the classification system has several drawbacks. It is unable to accurately classify uteri, which demonstrate multiple anomalies that encompass several categories. In the setting of multiple dissimilar anomalies, it is imperative to describe each anomaly as a component part, rather than attempt to classify it according to the most dominant anatomic feature. Furthermore combined/complex malformations (i.e., rudimentary uterus, cervical atresia, unilateral cervicovaginal atresia in a didelphys uterus, and utero-cervical and/or vaginal septation) are not considered and they are often incorrectly identified, inappropriately treated and sometimes

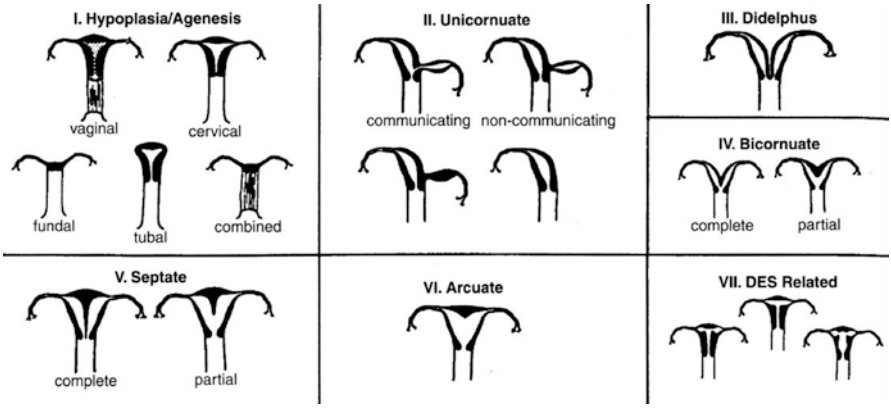

Fig. 3.2 American Society for Reproductive Medicine (ASRM) classification scheme for Müllerian anomalies. Reproduced with permission from [17]

inaccurately reported. Other classification schemes have been developed. Toaff et al. categorized the communicating uteri, rare uterine malformations characterized by separate utero-cervical cavities connected through a communication [18]. Otherwise, Troiano and McCarthy suggested that the AFS classification should function as a framework to describe anomalies, and that clinicians who are facing complex/combined anomalies should describe them according to their component parts rather than categorizing them into the class that most approximates the dominant feature [19]. This approach, adopted by Acièn et al., could lead to a better understanding of complex malformations before deciding on the best therapeutic approach [20]. A newer classification system has been proposed to more accurately characterize the genital malformations. It is an attempt to describe the genital anomalies based on their anatomic appearance, known as the "Vagina, Cervix, Uterus, and Adnexa-associated Malformation" (VCUAM) [21]. The most recent ESHRE/ESGE classification system "UCV" for female genital tract anomalies [22] incorporates concepts of the VCUAM classification and includes: (A) uterine anomalies (U) with six main classes and (B) cervical (C)/vaginal (V) anomalies as coexistent classes. Other anomalies are included as unclassified malformations (U6) and must be described as associated anomalies of non-Müllerian origin. Although the classification system may be useful for scholarly research purposes, it is likely too complex for widespread acceptance. In fact, this classification is yet to be widely accepted among clinicians.

3.5 Diagnosis of Genital Malformations

In the pediatric population, most examinations of the external genitalia require little in the way of instruments or supplies (a good light source, hand lens, or an otoscope). The normal external genital structures are usually easily visible with gentle, downward and lateral traction. In most of prepubertal girls, an otoscope

provides the magnification and light necessary to enable visualization of the lower vagina but vaginoscopy is the ideal method to achieve an adequate complete vaginal examination [23]; however, this is not routinely performed in the office. In adolescence and young adulthood, office examination should entail a detailed history, including menstrual features, and a confidential exam. Otherwise, pelvic and/or rectal exam is the first step of evaluation for a vaginal or cervical anomaly. Likewise, physical examination in an adolescent with primary amenorrhea and/or cyclic pain is essential, and evaluation of the external genitalia can be facilitated through the use of traction on the buttocks to separate the labia minora and visualize the vaginal introitus and hymen. A moistened q-tip can be also used to probe the vagina. A speculum exam can be currently avoided in adolescents and a Huffman speculum is appropriate for virginal adolescents aged more than 10 years. In the past, in pediatric and adolescent patients, suspected genital malformations were diagnosed primarily by laparotomy or laparoscopy. Nowadays, some authors consider laparoscopy performed concurrently with hysteroscopy to be the gold standard in the diagnosis of congenital uterine anomalies [14]. Despite being highly specific and accurate, laparoscopy (and hysteroscopy) is an invasive procedure with potential morbidity, making it hard to justify its use solely for diagnostic purposes in pediatric and adolescent population. More recently, the development and refinement of ultrasonography (US) and magnetic resonance imaging (MRI) have provided nonsurgical means of obtaining an accurate diagnosis in most cases. US has proven to be of considerable importance in defining the nature and complexity of obstructive defects of the reproductive tract in pediatric and adolescents patients [24–26]. In addition to the vertical-fusion defects, US has been shown to be quite effective in identifying lateral-fusion anomalies of the Müllerian duct system. In experienced hands, a sensitivity of 92% and a specificity of 100% have been reported in the assessment of bicornuate uteri [26]. Finally, the main point to keep in mind is that ultrasound imaging of the uterus is most accurate in the luteal phase when a thickened endometrial stripe will delineate the uterine cavity. The relatively recent advent of 3D-US has allowed an increasingly accurate evaluation of congenital uterine anomalies, which are best evaluated during the secretory phase of the menstrual cycle, when the endometrial echo complex is optimally visualized [27]. Transvaginal 3D-US appears to be extremely accurate for the diagnosis and classification of some congenital uterine anomalies, more than office hysteroscopy [28] and likewise MRI [29]. It may conveniently become the only mandatory step in the assessment of the uterine cavity in patients with a suspected septate or bicornuate uterus. Moreover, it has been recently demonstrated that 3D-US, if complemented by careful clinical examination, is comparable to MRI in identifying anomalies of the cervix [30].

In conclusion, although US should be the initial examination of choice in patients with suspected genital tract anomalies, MRI should be used to outline anatomy in complicated cases. Actually, MRI has emerged as the universally accepted standard in the imaging evaluation of genital malformations and has been considered the gold standard imaging technique [31].

3.6 Symptomatic Genital Malformations

3.6.1 Imperforate Hymen

Imperforate hymen is the most frequent anomaly of the female reproductive tract, occurring in 1/2000 girls [32] and it represents a persistent portion of the urogenital membrane. Familial inheritance has been reported; however, no common genetic trait has been recognized. Some reports suggest a dominant transmission [33], while others suggest a recessive trait [34] or a multifactorial transmission. Antenatal diagnosis of imperforate hymen and hydrocolpos has been reported as early as the second trimester [35]. In this case, drainage of the fluid should be the immediate intervention in the neonatal period, postponing the final surgical procedure. Occasionally, prepubertal girls can be referred with no obvious hymenal opening or with a poorly visible microperforation (Fig. 3.3). In the absence of a collection, definitive surgery should be deferred until the child is peripubertal. The imperforate hymen is usually seen in girls in their early teens. On the clinical examination, the hymen may be visualized as a bluish bulge at the perineum. Transabdominal or translabial US may be used to confirm the diagnosis [36]. Depending on the circumstance, an imperforate hymen may not be detected until an adolescent girl has recurrent bouts of lower abdominal crampy pain but does not menstruate. The problem may persist through several cycles until a pelvic mass becomes evident. This finding is diagnostic and no further investigation is needed. A simple cruciate incision of the hymen will release the menstrual flow and allow further normal menstruations. Some authors prefer a U-shaped incision at the base of the hymenal membrane as it maintains a normal hymenal remnant and avoids incision into the vaginal walls, which can cause bleeding [37].

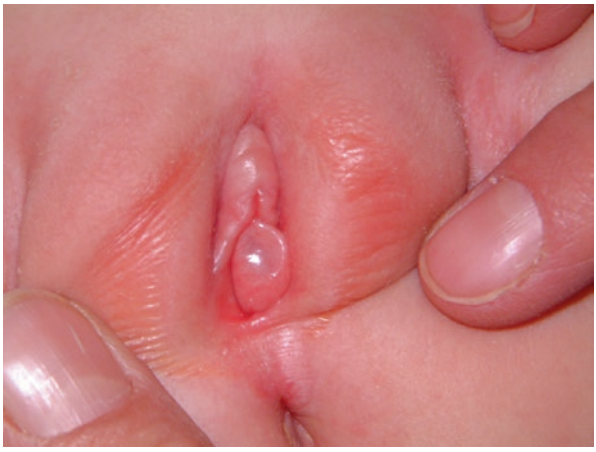

Fig. 3.3 Mucocolpos in a newborn with an imperforate hymen

3.6.2 Vaginal Atresia (Class I-a ASRM)

Vaginal atresia is a rare congenital defect resulting in uterovaginal outflow tract obstruction. It occurs when the caudal portion of the vagina, contributed by the urogenital sinus, fails to form. The caudal portion of the vagina is replaced with fibrous tissue. Although not Müllerian in origin, vaginal atresia can clinically mimic vaginal agenesis and imperforate hymen. Vaginal atresia, secondary adrenogenital syndrome, and cloacal anomalies are beyond the aim of this chapter. Fifteen percent of young patients with vaginal agenesis have segmental vaginal atresia [38] which is usually referred to as complete or partial vaginal atresia (lower vaginal atresia) (Fig. 3.4). Complete vaginal atresia is frequently associated with uterine agenesis, known as the Mayer–Rokitansky–Küster–Hauser syndrome (MRKHS). The fallopian tubes are normal, and the ovaries demonstrate normal endocrine function. Partial vaginal agenesis is rarer and is characterized by normal uterus, normal cervix, and small vaginal pouch distal to the cervix. Each examination of a newborn should include an inspection of the genitalia, as absence of the vagina or complete atresia could be detected during this simple evaluation. Complete vaginal atresia or agenesis is usually diagnosed at puberty when young adolescents present with primary amenorrhea. In infancy, partial vaginal agenesis can present as hydrocolpos or hydrometrocolpos; however, more commonly it occurs after menarche as a result of trapped menstrual secretions and, similarly to imperforate hymen, the adolescent girls are often in severe pain after only a few months of obstructed flow. Such pain may be either cyclic or noncyclic, and is located in the pelvis or in the vagina,

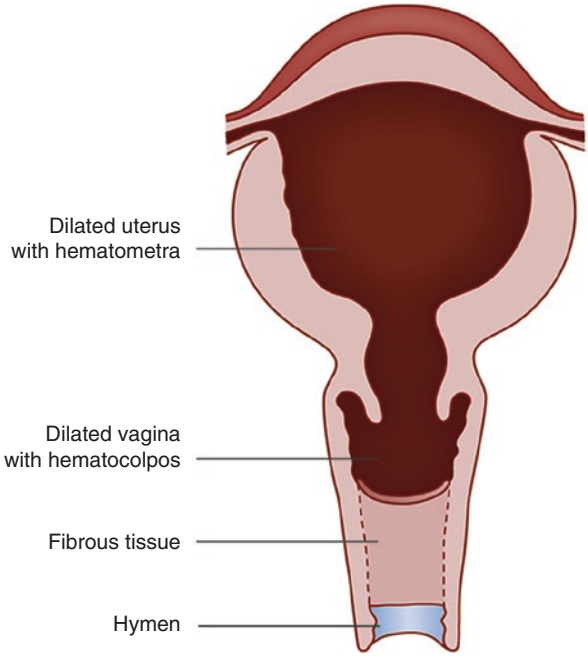

Fig. 3.4 Lower vaginal atresia. Reproduced with permission from [39]

depending on the patient's anatomy. An abdominal mass can be sometimes palpated and upon rectal exam a bulge is felt. 2D- and 3D-US and/or MRI confirm the presence of an obstructed upper vagina with hematocolpos and exclude the diagnosis of cervical agenesis [40]. Percutaneous drainage may be temporarily necessary to allow relief of pain and the facilitation of transfer of care to a tertiary center. Definitive surgical correction is the therapy of choice. This goal can be established by a vaginal pull-through procedure to create a new vaginal canal, with undermining and approximation of mucosal edges [41]. Postoperatively, wearing a vaginal mold or initiating early vaginal dilation may further decrease the risk of vaginal stenosis [10]. Incorrect diagnosis of the vaginal obstruction may result in excising of the obstruction without mucosal approximation. This will lead to local scar formation, recurrent partial or total obstruction, and difficulty in performing a second surgical procedure.

3.6.3 Cervical Agenesis/Atresia (Class I-b ASRM)

Congenital absence of the uterine cervix associated with a functioning endometrium is an extremely rare müllerian anomaly and occurs in 1 in 80,000 to 100,000 births [42]. Rock et al. have organized cervical agenesis (or atresia) and dysgenesis (or dysplasia) into four categories: cervical agenesis, cervical fragmentation, fibrous cervical cord, and cervical obstruction [43]. When this anomaly occurs, it is known to be associated in half of the cases with vaginal aplasia and with renal anomalies [44]. Amenorrhea and cyclic lower abdominal pain are the first symptoms presenting in an adolescent, and can be associated also with upper abdominal pain and fever if diagnosis is delayed. Endometriosis or pelvic infection may result from the chronic hematometra. In some cases, hematosalpinx may also be present. Transrectal ultrasonography and MRI can aid in defining anatomy [45]. Menstrual suppression with GnRH analogues may be helpful in controlling symptoms while planning surgery. The diagnosis and management of this Müllerian anomaly are both challenging and controversial. In the past, the surgical management of cervical agenesis has been debated and the solutions offered have gone from hysterectomy with the creation of a neovagina [46], to the recanalization around stents of the rudimentary cervix [47]. The surgical perspective in cases of cervical agenesis has evolved in time. Early literature reports different attempts of canalization of cervical atresia through cervical drilling or through catheter or pessary placement between the uterus and vaginal vault, with or without simultaneous vaginoplasty [48–50]. Some successful cases have been reported but the risks of conservative surgery (deadly peritonitis, high failure rates, and poor functional results) far outweighed the benefits. Consequently, it is not, thus, surprising that total hysterectomy with ovarian conservation still offers numerous benefits and is supported as a treatment option by several authors. Recent advances in reproductive technology and laparoscopic surgical techniques mean that conservative surgery is a possibility and perhaps should be considered as the first-line treatment option. Two series of patients treated for this rare Müllerian anomaly with uterovaginal anastomosis have been reported.

Deffarges et al. [51] described 18 patients with cervical atresia, 7 of whom had associated vaginal aplasia, and Chakravarty et al. [52] described 18 patients with cervicovaginal atresia. In both series, menstruation was restored in all the patients. In each of those series, two pregnancies were reported, both with delivery of viable neonates. Complications reported by Deffarges et al. were two low vaginal stenoses that were easily resolved and one cervical stenosis treated with multiple canalization procedures leading to a pyosalpinx requiring salpingo-oophorectomy. In the largest published series of 30 patients with cervical dysgenesis, Rock et al. [43] recommended hysterectomy, as first-line of treatment option, in patients with complete cervical agenesis and described successful creation of an adequate cervical outflow tract in the subset of patients with cervical obstruction. An Italian study performed in 12 adolescents (10 with complete cervical agenesis and 2 with cervical dysgenesis) confirmed that laparoscopically assisted uterovaginal anastomosis may be considered the treatment of choice for patients with cervicovaginal atresia [53]. The technique adopted by the authors was unique in performing hysterotomy at the caudal end of the uterine corpus to ensure direct communication of the vaginal mucosa to the endometrial lining. In conclusion, careful preoperative workup is essential so that an accurate diagnosis is made prior to surgery. This congenital condition is very rare and should be managed in specialist or tertiary centers with not only surgical expertise but also access to multidisciplinary and wide-ranging clinical support services.

3.6.4 Unicornuate Uterus (Class II ASRM)

The unicornuate uterus is caused by complete development of only one of the Müllerian ducts, with absent development of the contralateral side. In cases where the contralateral Müllerian duct develops only partially, the unicornuate uterus is associated with a rudimentary horn, which may be cavitated or not cavitated and may or may not communicate with the unicornuate uterus. A solitary uterine horn can be observed in up to 35% of patients. More commonly (in 65% of cases), a small rudimentary horn is seen arising from the primary single horn. A cavitated non-communicating rudimentary uterine horn (class II-b according to the ASRM classification) can be found in about 20–25% of women with unicornuate uterus. There is a higher incidence of unicornuate horns on the right side which is not fully understood [54]. A unicornuate uterine malformation is estimated to account for 5% of all uterine anomalies, occurring in 1 in 4020 to 5400 women [55, 56]. Patients can have an associated 40% risk of renal anomalies usually ipsilateral to the anomalous side [57], 15% endometriosis, and, rarely, extrapelvic or absent ovaries [56]. Patients with cavitated non-communicating rudimentary horn present shortly after menarche with increasing dysmenorrhea that is refractory to any treatment except complete suppression with either combination hormonal therapy or GnRH analogue with add-back therapy. Ultrasonographic imaging typically reveals a mass [58], but anatomical assessment of the uterine structures is best accomplished through MRI [59]; however, 3D-US has increased the sensitivity and specificity of this diagnosis

[60]. Laparoscopy is utilized to confirm the diagnosis and remove the non-communicating functional rudimentary horn as treatment for dysmenorrhea, and to prevent possible endometriosis caused by transtubal menstrual reflux and conception in an obstructed horn [55, 61].

3.6.5 Didelphys Uterus (Class III ASRM)

Didelphys uterus is a class III Müllerian anomaly based on the ASRM classification. In the general population, the true incidence is unknown, but has been reported to be between 0.1 and 3.8% [62]. For unknown reasons, anomalies of this type are more common in the Finnish population, with an incidence of 0.5% [63]. This disorder occurs as a result of a complete or near-complete failure of the Müllerian ducts to fuse. Each duct develops into an independent hemiuterus and cervix, although partial cervical fusion is generally seen. A longitudinal vaginal septum can be seen in up to 75% of cases [64] (see below Sect. 3.8). Without obstruction, didelphys uterus is asymptomatic. However, 6% of cases of vaginal septum with duplicated cervix and uterus are characterized by unilateral obstruction of one hemivagina by vaginal septum [65]. Didelphys uterus with obstructed hemivagina is associated with ipsilateral renal agenesis [66–68]. This association has been first described in the literature as Herlyn-Werner-Wunderlich syndrome. More recently, an acronym OHVIRA (Obstructed Hemivagina and Ipsilateral Renal Anomaly) has been proposed to describe this condition [69]. Patients may present at menarche with progressive dysmenorrhea secondary to hematometrocolpos, hematosalpinx, and endometriosis, [70]. Occasionally, patients present with fever, peritonitis, purulent vaginal discharge, and leukocytosis, leading to a presumptive diagnosis of PID [71]. It is only the finding of a double uterus and the absence of a kidney that will lead to the correct diagnosis. In general, examination reveals an anterolateral bulge in the vagina that makes it impossible to reach the cervix. In these cases, persistent postmenstrual hemorrhage (sometimes malodorous) is characteristic before the patient presents with pyocolpos in the obstructed vaginal canal. There is sometimes limited inter-uterine (at the level of the isthmus) or inter-vaginal (at the vaginal apex) communication. Furthermore careful examination of the vagina in these cases will sometimes reveal a small opening in the otherwise obstructed vaginal septum that may have allowed the migration of pathogenic bacteria. In the majority of cases, regular menses from the communicating hemiuterus result in misdiagnosis and increase the risk of unindicated procedures at the time of presentation [68, 69]. Occasionally, the condition can be diagnosed following acute urinary retention [72]. There are also some cases described in girls under 5 years of age [73]. Ultrasound has proven to be accurate in the differential diagnosis of double uteri. In a study of 39 patients with technically adequate sonographic visualization of the uterus, transabdominal US demonstrated a sensitivity of 100% and a specificity of 100% in reaching the correct diagnosis of double uteri [74] (Fig. 3.5). MRI has been demonstrated to be also accurate in discriminating between the various types of double uteri. Fedele et al. reported a sensitivity of 100% and a specificity of 79% when

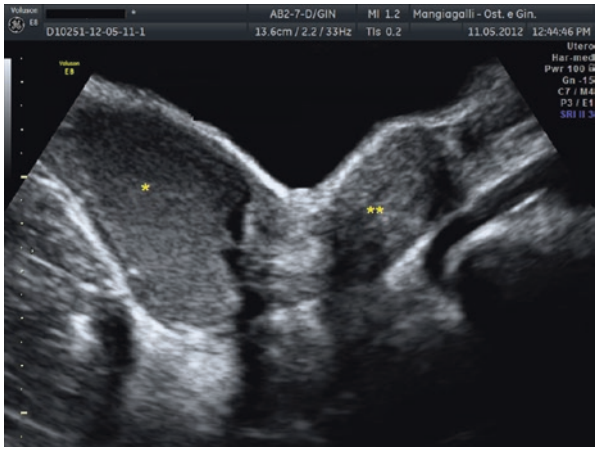

Fig. 3.5 2D Transvaginal US. Longitudinal US scan shows an hematocolpos (*) and a dilated right hemiuterus (**) in a 14-year-old girl with Herlyn-Werner-Wunderlich syndrome

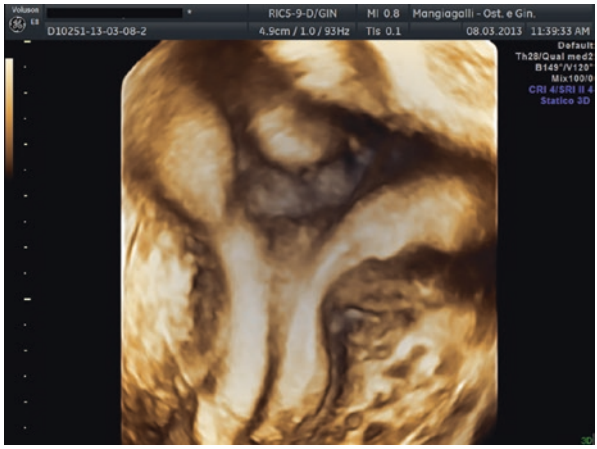

Fig. 3.6 3D Transvaginal US. Surface-rendered view of a didelphys uterus at volume ultrasound: on the coronal plane, two divergent independent hemiuteri and cervix are noted

using MRI to differentiate between bicornuate, didelphic, and septate uteri [75]. Currently, 3D-US and especially MRI are the primary diagnostic tools but they are limited to tertiary care centers (Fig. 3.6). In the meantime, MRI correctly anticipates the diagnosis, but it is unable to accurately assess the presence of endometriosis, pelvic infection, or adhesions that would affect future fertility. In these selected patients, laparoscopy is highly recommended. In general, a single transvaginal surgical procedure, including removal of the obstructed vaginal septum and marsupialization of the blind hemivagina, solves the symptoms of this pathology. After the septum has been excised (Fig. 3.7), laparoscopy can be performed for potential treatment of associated endometriosis, adhesions, or both. In certain cases, hysteroscopic metroplasty has been performed with simultaneous abdominal ultrasound to evacuate and correct a complete septate uterus with unilateral hematometra [76, 77]. More recently, to avoid damage to hymen or cervices, vaginoscopy with resectoscope has been suggested [78, 79]. Women with non-obstructed didelphys uterus

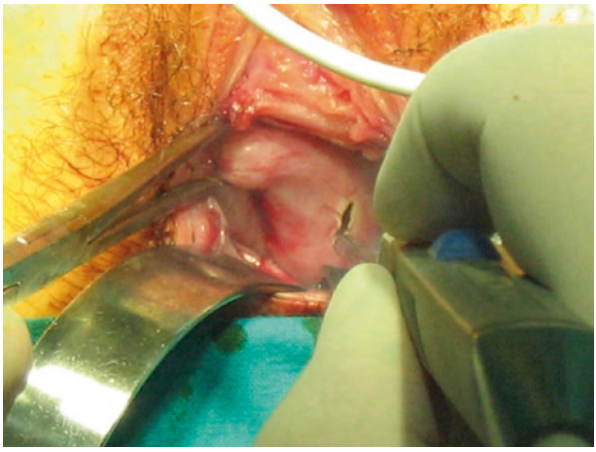

Fig. 3.7 Longitudinal incision of the vaginal septum in a young patient with OHVIRA

are usually not candidates for surgical unification. The decision to perform metroplasty should be individualized, and only selected patients may benefit from surgical reconstruction. Most reports of metroplasty in this setting are anecdotal and lack the statistical power of randomized studies. Therefore, the apparent benefits of surgery are not clear.

3.6.6 Transverse Vaginal Septum

TVS results from failure of fusion between the müllerian ducts and the urogenital sinus or abnormal vaginal canalization. A TVS can divide the vagina into two segments and thereby reduce its functional length. A TVS can be imperforate or perforate, and vary in its thickness and location in the vagina. Most of them are located in the superior vagina (46%). The next most common locations are the mid vagina, at a rate of 40%, and the inferior vagina, at a rate of 14% [80]. A TVS is relatively uncommon, with a reported incidence varying greatly from 1 in 2100 to 1 in 84,000 females [81–83]. Unlike other Müllerian duct anomalies, TVS is only occasionally associated with urologic defects but it has been associated with other structural anomalies, including imperforate anus, bicornuate uterus, coarctation of the aorta, atrial septal defect, and malformations of the lumbar spine. TVS is rarely diagnosed in the neonate or infant unless the obstruction causes a significant hydromucocolpos. Hydromucocolpos can be diagnosed in utero during a third-trimester transabdominal ultrasound. Early delivery and drainage of the obstructed vagina and uterus are indicated when other organs are compromised [84]. In infants, the vaginal septum is usually thin (<1 cm thick) and can be corrected without extensive procedures. Clinical follow-up is necessary because vaginal stenosis with subsequent accumulation of fluid may develop postoperatively. In adolescence, imperforate septum presents with obstructed menstruation and hematocolpos [85]. A presence of a palpable pelvic mass and a perineal bulge can be often revealed depending on level and location of the imperforation during the physical examination. In these patients, cyclic

abdominal pain, vaginal discharge, amenorrhea, or abnormal menstruation, and occasionally urinary retention may be present at the postpubertal stage. Moreover, retrograde blood flow through the uterus and the fallopian tubes resulting from imperforation may predispose these patients to develop severe endometriosis in 2–56% of cases [65, 86]. Women with a perforate septum often have normal menses and usually present with dyspareunia and difficulty in inserting tampons into the vagina [85]. Initial evaluations should include an abdominal US of the pelvis [87]. Imaging should include an assessment of the renal anatomy since up to 20% of cases have associated renal anomalies. The diagnosis can be confirmed on MRI, especially if a strong clinical suspicion exists. MRI can also be useful to determine the thickness of the vaginal septum preoperatively. It is also extremely important to identify a cervix on US or MRI in order to differentiate between a high septum and cervical atresia. The surgical approach to TVS excision depends on the character, thickness, and location of the septum. The TVS is most frequently less than 1 cm thick and can be treated by excision and end-to-end anastomosis of the vaginal mucosa. The TVS can be thick in the adulthood, rendering its removal more difficult than in the infant. While thick septa require complex surgery often necessitating reconstruction using grafts or flaps, thin TVS can be managed considerably more easily [88]. Treatment involves surgical resection of the septum and anastomosis of the upper and lower vaginal mucosa, usually followed by vaginal dilatation. It can be performed vaginally, laparoscopically, or via an abdominoperineal approach, depending on the location and thickness of the septum [80, 88]. Common problems of these techniques include shortening of the vagina due to septal tissue excision and postoperative stenosis of the vagina owing to the formation of constricting fibrous bands during the healing process. A Z-plasty technique may help to prevent circumferential scar formation [89–91]. More recently, Arkoulis et al. have proposed a simple technique for the surgical management of thin septa, utilizing two interdigitating Y-plasties, without the need for excision of any septal tissue. The authors presented their small series of eight consecutive cases where this technique was used, with no major complications or any case of vaginal re-stenosis [92]. In general, regardless of the technique used for postoperative dilation, it is very important to do an entire septum resection and to try to prevent stenosis and scarring, which is common after a transverse septum resection. For difficult cases, a probe can be passed transfundally through the uterus, down through the endocervical canal, and into the upper vagina so as to tent up the septum and aid in the resection. For more extreme and complex cases, vaginoplasty may be indicated. Complications may be significant and include vaginal stenosis and re-obstruction (recurrence), dyspareunia, endometriosis, infertility, obstetric complications, and psychological difficulties. It is essential that accurate information on the septum is available to ensure that the correct operative approach is chosen.

In conclusion, transverse vaginal septum should be managed within specialist centers for complex gynecology with experience in managing congenital gynecological anomalies. However, knowledge of the clinical presentation and management of these abnormalities is important, as it can prevent misdiagnosis and unnecessary delays in specialist referrals.

3.6.7 Longitudinal Vaginal Septum

Incomplete resorption of the Müllerian ducts and urogenital sinus may cause the formation of a longitudinal vaginal septum. A longitudinal vaginal septum is associated with a uterine anomaly (septate or didelphys uterus) in 95% of cases [86]. Conversely (as previously stated), patients with uterine duplication have a concurrent longitudinal vaginal septum in 75% of cases [64]. The presence of a duplicated cervix is indicative of either didelphys or complete uterine septum. The septum may be complete or partial. In some cases where the septum is complete, it may be bilaterally (uterus didelphys, bicollis, with complete vaginal septum with bilateral obstruction) or unilaterally imperforate and symptomatic (see didelphys uterus). Non-obstructed longitudinal partial vaginal septum is typically asymptomatic and, occasionally, the patient will complain of bleeding despite the placement of a tampon. Currently, it may not present at all until pregnancy when it is an incidental finding. In some cases the patient may complain of a hooked tampon or pain with coital activity, which may be secondary to bruising of the septum [83]. The partial septum should be removed only if symptomatic or if the woman desires restoration of a normal vaginal canal. Prior to initiating the surgery, a Foley catheter is placed in the bladder. Since these septa are typically well vascularized, Kelly clamps are systematically applied to the anterior and posterior portion of the septum and then cut with a knife or electrocautery device. It is not usually necessary to excise the complete septum as the tissue retracts and leaves a narrow ridge that is of no consequence. Hemostasis is secured by placing a continuous locking suture, absorbable (00) on each edge of the divided septum [93]. As the tissue can be very thick, attention to hemostatic control is always essential.

3.7 Asymptomatic Genital Malformations

3.7.1 Vaginal Agenesis (Class Ie ASRM)

Vaginal agenesis, also known as Müllerian aplasia or MRKHS, is the congenital absence of the vagina with variable Müllerian duct in otherwise phenotypically normal 46, XX females. The uterus and cervix in such patients are more often absent; however, 7–10% of such women have a rudimentary uterus with functional endometrium [94], and as many as 25% have cavitated müllerian remnants [95, 96]. The fallopian tubes are frequently normal; however, they may be hypoplastic or malformed [97]. The ovaries demonstrate normal endocrine function [98]. The prevalence of MRKHS is given as 1 in 4500–5000 newborn females [99]. This is based on a single study from Finland and does not allow similar predictions for other populations. MRKHS is generally divided into three subtypes: MRKHS (typical or type I), MRKHS (atypical or type II), and MURCS (Müllerian Renal Cervical Somite) association or type III. Anatomic examination is required for differential diagnosis of specific MRKHS types. MRKHS type I accounts for approximately 44% of MRKHS cases and is characterized by complete uterus aplasia in the

presence of two symmetric rudimentary horns linked by a peritoneal fold, normal fallopian tubes, ovaries, and renal system [100]. MRKHS type I is rarely associated with clinical signs of hyperandrogenism [101]. MRKHS type II is the most frequent form of MRKHS, accounting for approximately 56% of cases [100]. It is characterized by uterine symmetric or asymmetric hypoplasia, accompanied by aplasia of one of the two horns or by a size difference between the two rudimentary horns, with or without dysplasia of one or both of the fallopian tubes. MURCS association, which represents the most severe form of MRKHS, is characterized by Müllerian duct aplasia/hypoplasia, renal agenesis/ectopy (in 25–50% of patients), and cervicothoracic somite dysplasia (Klippel–Feil syndrome) (30–40%)[102]. In this form, other less common associated anomalies such as heart defects, hearing impairment, syndactyly or polydactyly are often observed [103]. MRKHS is mainly sporadic; however, familial cases have been described indicating that, at least in a subset of patients, MRKHS may be an inherited disorder [104, 105]. The syndrome appears to demonstrate an autosomal dominant inheritance pattern, with incomplete penetrance and variable expressivity. The etiology of MRKHS is still largely unknown, probably because of its intrinsic heterogeneity. Several candidate causative genes have been investigated, but to date only WNT4 has been associated in a few cases with MRKHS patients with hyperandrogenism [106]. The development of secondary sexual characteristics occurs normally, thus the diagnosis of MRKHS is generally made late, at the beginning of puberty, due to the lack of onset of menstruation (primary amenorrhea) or, seldom, due to the impossibility of sexual intercourse. Indeed, vaginal agenesis is the second most common cause of primary amenorrhea in adolescents [107]. Functional endometrial tissue in an obstructed uterine remnant can rarely cause cyclic pelvic pain from hematometra, hematosalpinx, and endometriosis [108]. When it is expected to have a suspicion of Müllerian anomalies, 2D-US and renal US represent the first assessment survey to exclude urinary tract anomalies [37]. An MRI may be more accurate in the evaluation of müllerian structures, but given the expense, it can be reserved for when ultrasound is indeterminate [19]. Because transabdominal 2D-US and MRI are not always reliable in providing a clear-cut diagnosis on the presence of endometrium in the uterine horns, Fedele et al. have recently demonstrated the use of an endoscopic ultrasound probe in the evaluation of the structure of the rudimentary uterine horns in MRKHS, with specific regard to the identification of the endometrial cavity and its localization inside the myometrial structure, as well as the identification of the vascular structures of the rudiment [108].

Laparoscopy is not usually indicated unless the diagnosis cannot be determined on findings from other studies or if a concern exists regarding the presence of a functioning uterus or rudimentary uterine tissue. Evaluation of the patient with near total or complete vaginal agenesis, like other Müllerian anomalies, begins with a genital examination (Fig. 3.8). Most patients will have a vaginal dimple or very foreshortened, blind-ending vagina. The hymenal fringe is usually present along with the small vaginal pouch, as they are both embryologically derived from the urogenital sinus. A pelvic mass will usually be absent and occasionally a peritoneal fold can be palpated on recto-abdominal bimanual examination. Management of these patients

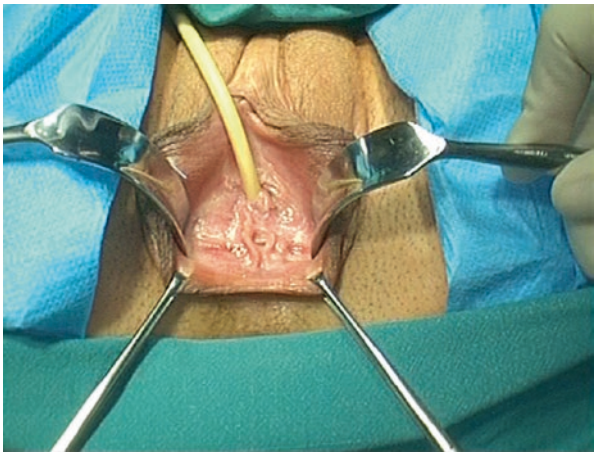

Fig. 3.8 A preoperative perineal photograph demonstrating the absence of the vaginal opening in a patient with MRKHS

requires attention to two distinct areas: (a) the management of the congenital anomaly itself, in order to allow the patients to become sexually active and (b) the management of the psychological impact of such condition [82]. For many reasons, psychological support and counseling are essential components of the preoperative evaluation and care. Young patients with MRKHS suffer from extreme anxiety and very high psychological distress when they are told they have no uterus and vagina. Thus, it is suggested that patients and their families attend counseling before and throughout treatment. Group programs and MRKHS associations are also of great help [109]. In addition to the inability to have sexual intercourse, these young women are usually infertile, resulting in psychological pain and self-esteem issues [110]. Initially, the management of this malformation is usually based on a nonsurgical method and then, if necessary, on a surgical approach. In the last 10 years, literature has significantly supported the nonsurgical approach as the first line for the creation of the neovagina [111]. The nonsurgical technique involves the repeated use of graduated vaginal dilators [112] over a period of 6–12 months (Fig. 3.9). This will be successful in about 95% of cases when appropriately selected [113]. This method must be tried initially in all girls with absent vagina and a 1 cm deep dimple. Historically, Ingram suggested the use of a dilator put on a modified bicycle seat [114], whereas D'Alberton et al. and Motta et al. have reported a success in 95% of the patients who have undergone a dilatation of retrohymenal pit by using coitus [115, 116]. Furthermore, particular care must be taken not to dilate the urethra, which can lead to urinary incontinence. For those girls with less than 1 cm of vagina or those in whom Frank's maneuver fails, surgery will be required. Surgical creation of a neovagina is an option not only for young women who fail nonoperative dilation therapy but also for those who choose surgery after a thorough discussion with the patient (and parents/guardians as indicated) regarding the advantages and disadvantages. Currently, there are multiple operations appropriate for the creation of a neovagina in patients with vaginal agenesis but there is no consensus on the best approach. The creation of a neovagina should certainly be performed in only a

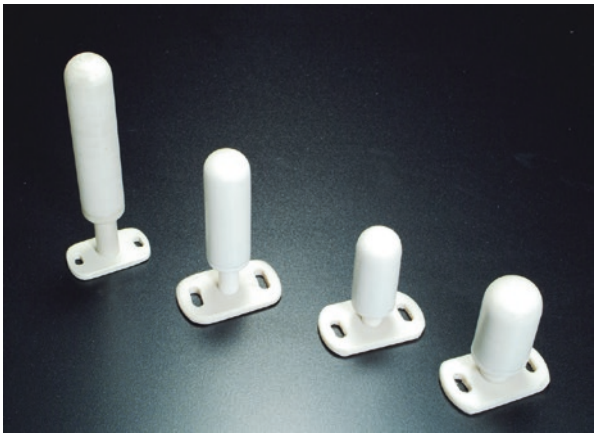

Fig. 3.9 A set of vaginal dilators

limited number of centers and the procedure of choice should also be determined by the surgeon's experience and success with the procedure because reoperation increases the risks of injury to surrounding organs. Among the historical operative procedures, the Abbè–McIndoe procedure [117, 118] (Fig. 3.10), the Williams vaginoplasty [119], the Creatsas' modified Williams vaginoplasty [120], the Vecchietti method [121] as well as the Davydov method [122] were frequently used. New surgical methods, in which laparoscopy has replaced traditional surgery, have recently been developed. Among these sigmoid colpopoiesis [123, 124] has been suggested, although Fedele's modified Vecchietti technique [125] and Davydov's method modified by Adamyan et al. [126] and by Soong et al. [127] are the two most adopted laparoscopic procedures. The modified laparoscopic Vecchietti procedure creates a dilation-like neovagina in 7–9 days. It involves placement of a pluggable segmented dummy onto the vaginal dimple that is gradually pulled superiorly by threads laparoscopically placed that are then connected to the traction device placed on the patient's abdomen (Fig. 3.11). The threads are then gradually tightened approximately 1.0–1.5 cm per day for a week. Postoperatively, the patients must comply with daily vaginal dilation until regularly sexually active. The main goal of laparoscopic Davydov's technique is to make a neovagina using the patient's own pelvic peritoneum as covering. It involves dissection of the perineum to create a neovaginal space while laparoscopically mobilizing the peritoneum. The peritoneum is then sutured to the introitus and a purse-string suture closes the cranial end of the neovagina. A soft vaginal mold is left in situ for 6 weeks and then vaginal dilators are kept for 30 min a day to maintain a suitable vaginal length until regularly sexually active. The Vecchietti's and Davydov's laparoscopic techniques have been recently compared in an Italian study [128]. Vecchietti's laparoscopic technique is definitely simpler and faster owing to its unique laparoscopic step, whereas the modified Davydov's procedure also requires a perineal step which can be complex. Epithelization of the neovagina at 6-month follow-up was 60% and 80%, respectively, and 100% in both groups at 12 postoperative months, as it has been previously suggested [129]. Davydov's procedure is particularly indicated for patients with abnormalities of the external genitalia, such as

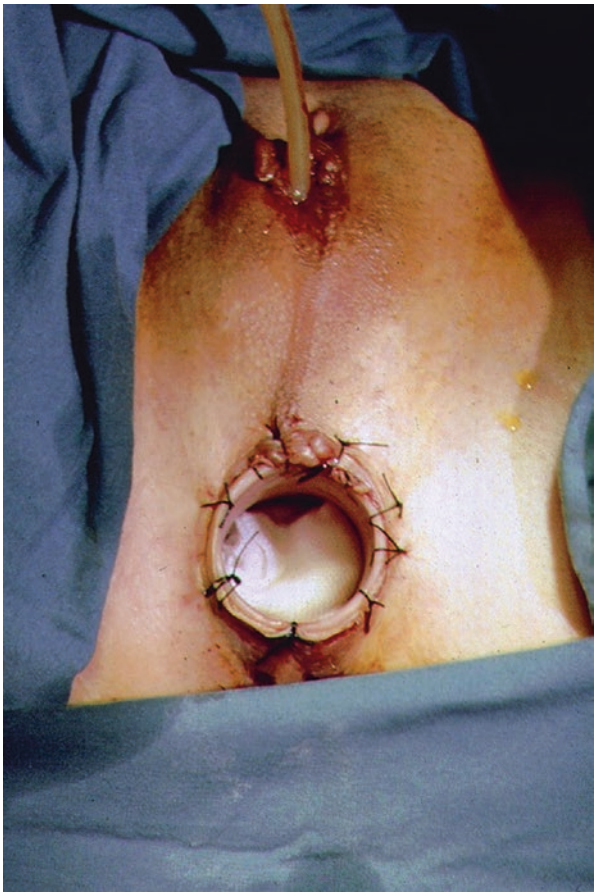

Fig. 3.10 Perineal photograph taken intraoperatively after creation of the neovagina with split-thickness skin graft (McIndoe procedure)

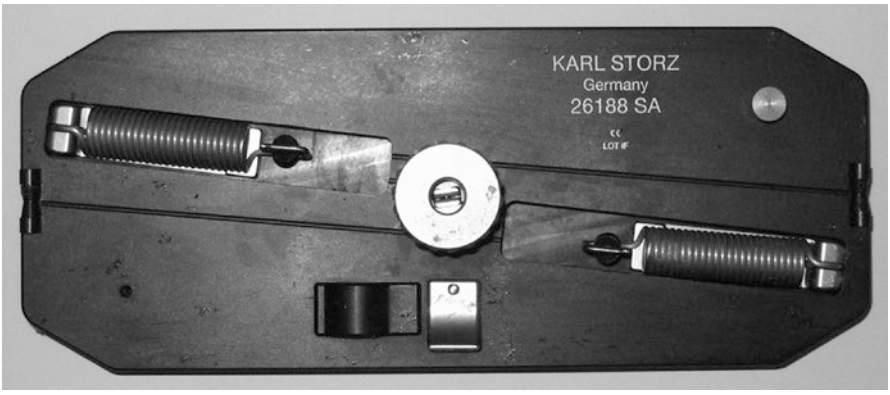

Fig. 3.11 The traction device required for Vecchietti laparoscopic operation

female hypospadia, which is a contraindication to the creation of a neovagina by vaginal pressure, such as in the laparoscopic Vecchietti technique and Frank method. Otherwise, patients with a pelvic kidney are not assigned to Davydov's procedure group but rather to Vecchietti's procedure owing to the risk of damaging the pelvic kidney or ureter during laparoscopic mobilization of the peritoneum. Similarly, previous pelvic surgery might be a relative contraindication to Davydov's technique because the presence of postoperative adhesions might complicate the surgical procedure and increase the risk of intraoperative complications. Finally, in view of the possibility of offering uterine transplantation to these patients, the disruption of the pelvic anatomy caused by Davydov's approach might likely preclude such procedure, whereas Vecchietti's technique leaves the anatomy of the intrapelvic structures unaltered. As previously reported, in patients with MRKHS, rudimentary uterine horns are frequently cavitated. In the majority of cases, there is no evidence of endometrial functioning (hematometra), and in fact only a small number of cases experienced cyclic pain symptoms. Such finding warrants a systematic search of this anatomic characteristic to provide, before corrective surgery, an adequate counseling on the therapeutic possibilities, i.e., the removal of cavitated and symptomatic uterine remnants or the attempt to anastomose them to the vaginal vestibulum. The latter procedure has been described by the same Italian research group in a recent report [130]. The traditional motherhood options for women with MRKHS are adoption or use of a gestational surrogate carrier with their own oocytes through IVF [131, 132]. Importantly, gestational surrogate pregnancies with MRKHS women as genetic mothers do not seem to have any increased risk of fetal uterine malformation, which would indicate that epigenetic changes may be behind this syndrome [133]. Up to now, there have been 11 human uterus transplantations with 5 successful deliveries [134]. So far, MRKHS has been the main indication for uterus transplantation with nine patients being transplanted [135, 136].

3.7.2 Bicornuate Uterus (Class IV)

The bicornuate uterus is classified as a class IV Müllerian duct anomaly. This condition is the result of the incomplete fusion of the two Müllerian ducts at the level of the uterine fundus and is characterized by two divergent uterine horns that fuse at the level of the lower uterine isthmus. A muscular uterine septum is also present and classification depends on its extent. When the septum extends to the internal os, the anomaly is considered complete; this is known as a bicornuate unicollis uterus. Another variant of the complete form of bicornuate uterus is the bicornuate bicollis uterus, in which the septum extends to the external os. This anomaly has been described in approximately 25% of patients with bicornuate uteri. When the septum is confined to the fundal region, it is considered a partial bicornuate uterus. The external uterine contour has an indented fundus, arbitrarily defined as more than 1 cm, and is sometimes referred to as "heart shaped"; the vagina is generally normal [19, 74, 75]. Bicornuate uterus is considered an incidental finding in child- and adolescenthood. Young patients are usually asymptomatic and have no difficulty becoming pregnant. Such anomaly is

associated with obstetrical complications including cervical incompetence, preterm labor, and malpresentation. Evaluation of bicornuate uterus should begin with ultrasound during the luteal phase of the menstrual cycle, when the endometrium is echogenic and thickened, resulting in a clear distinction between the endometrial cavity and the myometrium. In the past, 2D-US and hysterosalpingography did not effectively distinguish between septate and bicornuate uterus. Findings of the uterine fundus can also be achieved with abdominal US performed with a semi-full bladder in the secretory phase of the menstrual cycle visualizing the tubal ostia and the region of the internal cervical os. If there is no indentation of the perimetrial fundal profile, or when such an indentation is less than 5 mm below the imaginary line joining the two tubal ostia, then the uterus is septate. On the other hand, when such a fundal indentation is identified and is 5 mm or more below the abovementioned line, the uterus is bicornuate or didelphic [74, 137]. MRI is very effective in characterizing uterine anomalies; however, it is costly and has limited availability. More recently, transvaginal 3D-US has allowed the visualization of both the uterine serosa and the endometrium with less cost than an MRI. When compared with the gold standard of concurrent hysteroscopy and laparoscopy, 3D ultrasound has similar accuracy in correctly identifying the specific anomaly [138]. Otherwise, it is extremely important to correctly differentiate a septate uterus from a bicornuate one, for which surgical intervention is not indicated. Non-uterine causes of infertility must be ruled out before metroplasty is considered as last resort. The Strassman metroplasty should be reserved for selected women based on poor reproductive outcomes.

3.7.3 Septate Uterus (Class V)

Septate uterus is the most common uterine anomaly with a mean incidence of 35% [14]. It results from incomplete resorption of the medial septum after complete fusion of the müllerian ducts has occurred. The septum, which is located in the midline fundal region, is composed of poorly vascularized fibromuscular tissue [139]. Numerous septal variations exist: the septum is considered complete (Class V-a) if it extends to the internal os (and beyond), thus dividing the endometrial cavity, and partial (Class V-b) if it does not. A complete uterine septum is typically diagnosed in young adulthood. Such malformation can be associated with a longitudinal vaginal septum, in approximately 25% of cases, separating the vagina itself, either partially or all the way to the introitus [140]. In addition, septa may be segmental, which results in partial communication between the endometrial cavities [141]. As previously mentioned, visualization of the uterine fundus is crucial to reliably differentiate between a septate and bicornuate uterus. Today, the diagnosis of septated uterus is readily made with hysteroscopy and its accuracy is close to 100% [142]. 2D-US is a good noninvasive method to evaluate the uterine cavity. The sensitivity of this method to diagnose a septated uterus is 81% [143]. Three-dimensional US is more accurate and is better in distinguishing between septated uterus and bicornuate uterus. The accuracy of 3D-US in detecting uterine septa is 92% [142]. Using 3D-US with the injection of saline to the uterine cavity as contrast

medium has increased the sensitivity to 98% and specificity to 100% in the diagnosis of septated uterus [142]. When the abovementioned method fails, an MRI, which has a sensitivity of 100% and specificity of 79% in detecting intrauterine lesions, may be used [142]. A uterine septum affects female reproductive health in three ways: (a) obstetrical complications, (b) recurrent miscarriages, and (c) infertility [144]. Although clinical studies consistently demonstrate a poorer obstetric outcome in patients with septate uterus compared to women without uterine anomalies [9, 145], literature on septate uterus as the primary cause of female infertility is controversial. A septate uterus is generally amenable to hysteroscopic resection of the septum, whereas surgical intervention does not improve reproductive outcome in patients with bicornuate uterus. There are several minimal invasive surgical techniques available in order to remove the septum; the hysteroscopic metroplasty by resectoscopy is considered the first therapeutic option [146].

3.7.4 Arcuate Uterus (Class VI)

The arcuate uterus is classified as a class VI Müllerian duct anomaly. It is characterized by a small septate indentation at the superior aspect of the uterine cavity in the fundal region and it usually demonstrates a normal external fundal contour.

On 2D-US, a single endometrial cavity is frequently noted. Three-dimensional US permits to obtain planar reformatted sections through the uterus, which allow both the precise evaluation of the fundal indentation and the length of the septum. On MRI, the arcuate uterus demonstrates a normal external fundal contour and a smooth indentation of the endometrial canal by a broad-based myometrial prominence. The prominent fundal myometrium shows normal myometrial signal intensity, with no hypointensity to suggest fibrous tissue. Rarely symptomatic and rarely associated with adverse reproductive outcomes, arcuate uterus has been advocated by some authors to represent a true anomaly, whereas others consider it a normal variant rather than a true anatomical or developmental anomaly [147]. In the last years, hysteroscopic resection of subseptations has become routine in clinical practice, especially in fertility clinics, in which surgery is undertaken before performing costly fertility treatments in an attempt to decrease the risk of miscarriage in a future pregnancy. Otherwise, a recent retrospective study, as previously demonstrated for the first time by Fedele et al. [148], underscored the importance of subseptation resection in patients with infertility for the sole purpose of ameliorating fertility outcomes, independently from obstetric outcomes [149].

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Gonadal Failure

4

Maria Francesca Messina and Alfonsa Pizzo

4.1 Introduction

The gonads are the primary reproductive organs; in males, the gonads are the testes and, in females, the gonads are the ovaries. These organs are necessary for sexual reproduction, as they are responsible for the production of male and female gametes (a cell that fuses with another cell during fertilization).

Gonads also produce the sex hormones needed for the growth and development of primary and secondary reproductive organs and structures.

Gonadal activation starts in puberty with the pulsatile secretion of gonadotropin-releasing (GnRH) hormone that stimulates pituitary release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

This hormonal cascade results in gonadal maturation with subsequent production of sex steroids, nonsteroidal factors, and gametes. The physical changes in puberty culminate in sexual maturity and reproductive capacity [1].

During the first months of life, the hypothalamic-pituitary-gonadal (HPG) axis is active (termed mini-puberty) and results in sex hormone levels near adult concentrations [2]. The hormonal dynamics of the neonatal mini-puberty represent the first opportunity to observe the activity of the HPG axis before adolescence, as childhood is a period of quiescence with low GnRH secretion. Episodic GnRH secretion resumes in early puberty with nocturnal, pulsatile GnRH secretion that extends progressively through the day and is sustained throughout adult life.

Gonadal failure, also known as hypogonadism, is what occurs when the gonads cease functioning as efficiently [3, 4].

This diminished functioning may result, in females, in low estrogen levels, in addition to a decrease in other hormones produced by the gonads. Ovulation may be

M.F. Messina (✉) • A. Pizzo
Department of Human Pathology of Adulthood and Childhood, University of Messina, Messina, Italy
e-mail: Francesca.messina@unime.it; pizzoalfonsa@gmail.com

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impaired, and this may then result in partial or complete infertility. This deficiency of the sex hormones can also result in defective sexual development if gonads cease functioning in prepubertal age or in withdrawal effects (premature menopause) if it happens in adults. Mostly, these effects are permanent.

Hypogonadisms may be distinct in two main distinct entities: hypogonadotropic or central hypogonadism and hypergonadotropic hypogonadism (ovarian insufficiency) [5].

Moreover, the failure of the gonads may be caused by both congenital and acquired disorders.

4.2 Etiology

4.2.1 Hypogonadotropic Hypogonadism

Absent or partial puberty in association with low serum sex steroids in the setting of low or inappropriately normal serum gonadotropin levels defines hypogonadotropic hypogonadism (HH). It can be attributed to a variety of congenital origins including single gene mutations, idiopathic forms, and genetic syndromes [5]. Acquired causes of HH include central nervous system (CNS) insults such as trauma, irradiation, and intracranial tumors (Table 4.1). The most common cause of HH is transient and is termed constitutional delay of growth and puberty (CDGP), a variation of normal development, more frequent in males than in females, in which puberty and pubertal growth spurt occur at or later than the extreme upper end of the normal range.

Table 4.1 Causes of hypogonadism

Hypergonadotropic hypogonadism (ovarian insufficiency)	Hypogonadotropic hypogonadism (hypothalamic-pituitary defects)
Congenital	*Congenital*
– Turner syndrome	– Kallmann syndrome
– Primary ovarian insufficiency	– Isolated hypogonadotropic hypogonadism (IHH)
– Abnormalities in gonadotropin production or action	– Combined pituitary hormone deficiency
– Galactosemia	– Transcription factor mutations
– Gonadal dysgenesis	– Leptin and leptin receptor defects
– X chromosome abnormalities	– Syndrome (Laurence–Moon–Biedl, CHARGE)
Acquired	*Acquired*
– Autoimmune destruction	– Traumatic brain injury
– Chemotherapy	– Central nervous system diseases (tumors, infections, autoimmunity, infiltrative diseases)
– Radiation	– Functional hypothalamic amenorrhea (Eating disorders, athletes amenorrhea, stress, obesity)
	– Iatrogenic (irradiation, corticosteroids)
	– Medical condition (chronic diseases, hypothyroidism, Cushing syndrome, hyperprolactinemia, etc.)

Congenital forms are clinically characterized by absent or partial puberty and infertility. Biologically, HH is characterized by low or normal serum levels of LH and FSH in the setting of low sex steroids. Typically, patients with HH present in adolescence or early adulthood with delayed onset of puberty, primary amenorrhea, poorly developed sexual characteristics, and/or infertility.

4.2.1.1 Congenital Origins

Kallmann syndrome: This syndrome refers to the combination of hypogonadotropic hypogonadism and anosmia. The mutation of KAL1 gene results in a defect in the migration of GnRH and olfactory neurons. Individuals with KS have hypothalamic GnRH-secreting deficiency and aplasia of the olfactory bulb as noted on magnetic resonance imaging (MRI). The inherited mechanism may be X-linked or autosomal.

Isolated hypogonadotropic hypogonadism (IHH): One potential cause is loss of function mutations of the GnRHR, a G-protein coupled receptor (more than 25 loci have been shown and several European centers offer genetic screening, www.orpha.net and www.gnrhnetwork.eu). Genotype–phenotype variations exist even within members of the same kindred. Females typically present with primary amenorrhea. IHH has been noted to be reversible in 10–20% of HH patients.

Combined pituitary hormone deficiency: HH can be present as part of a broader pituitary deficiency disorder (CPHD). It is defined as the presence of two or more pituitary hormonal deficiencies. In some case, neonatal signs such as hypoglycemia can point to a CPHD diagnosis early in life, yet adolescents present for evaluation with absent/partial puberty and short stature.

Transcription factor mutations: Even with intact GnRH production and signal transduction, pituitary gonadotropin synthesis may still be deficient due to mutations in a variety of transcription factors. An important transcription factor is Prop-1, the prophet of the pituitary transcription factor Pit-1. Prop-1 gene mutations can result in familial combined pituitary hormone deficiency including growth hormone deficiency, central hypothyroidism, and hypogonadotropic hypogonadism. HESX-1 is a transcription factor needed for normal pituitary development; its deficiency can be responsible of septo-optic dysplasia and hypogonadotropic hypogonadism. Other transcription factors implicated in rare causes of hypogonadotropic hypogonadism are LHX4 and SOX2.

Leptin and leptin receptor defects: Leptin deficiency acts as a sign of nutritional deprivation and results in the suppression of the reproductive axis. Classical findings in individual with leptin deficiency include hyperphagia, obesity, and hypogonadotropic hypogonadism. Girls with LEP (leptin) or LEPR (leptin receptor) gene mutations present with delayed puberty, lack of a pubertal growth spurt, and reduced expression of secondary sexual characteristics.

Syndromes: Numerous syndromes include neuroendocrine dysfunction. The best known is Prader–Willi syndrome (PWS), caused by a genetic defect involving paternal chromosome 15 or maternal disomy. In these patients, hypogonadotropic hypogonadism is the expression of the hypothalamic dysfunction also evidenced by their hypotonia, hyperphagia, and intermittent temperature instability.

4.2.1.2 Acquired Origins

Traumatic brain injury: Traumatic brain injury (TBI) is an insult to the brain that results in neurologic dysfunction. TBI can determine anterior pituitary insufficiency and in particular gonadotropin deficiency may be found in 42% in the acute phase, at the 12-month follow-up many of these patients spontaneously recovered reproductive function. The final prevalence of hypogonadism is 7.7%.

Central nervous system diseases: Intracranial tumor is a common cause of acquired hypogonadism in adolescence (e.g., craniopharyngiomas and pituitary adenomas including prolactinoma). HH can result from the compression of pituitary tissue/stalk or secondary to inhibition of GnRH secretion in the case of prolactinoma or Cushing's disease. Clinically, visual disturbance or headaches may accompany pubertal arrest in these cases. Importantly, all patients with pituitary tumors should have a complete evaluation of anterior and posterior pituitary function.

In children, resultant hypogonadotropic hypogonadism can exist as a result of the primary cerebral tumor or due to the therapeutic regimen needed to treat the lesion (chemotherapy and radiotherapy). Gonadotropin deficiency and delayed puberty are most likely in those who receive 40 Gy or more of radiation. Gonadotropin deficiency may continue to evolve for many years after radiation, with rates of total incidence ranging from 20 to 50%. Therefore, all children who have CNS lesions should be monitored for gonadotropin deficiency and signs of pubertal delay. Central hypogonadotropic hypogonadism can be caused by previous central nervous system infection or autoimmune destruction of the pituitary.

Functional hypothalamic amenorrhea: Functional hypothalamic amenorrhea occurs when hypothalamic-pituitary-ovarian axis is suppressed due to an energy deficit stemming from stress, weight loss, excessive exercise, or eating disorders [6, 7]. So, it is commonly associated with eating disorders such as anorexia nervosa and bulimia, and also occurs in elite female athletes. It is characterized by a low estrogen state without other organic or structural disease. Patients with functional amenorrhea may demonstrate the features of the female athlete triad, which consists of insufficient caloric intake with or without an eating disorder, amenorrhea, and low bone density or osteoporosis. Laboratory tests usually reveal low or low-normal levels of serum follicle-stimulating hormone, luteinizing hormone, and estradiol; however these levels can fluctuate, and the clinical context is the discriminating factor. In these girls, suppression of GnRH secretion results in attenuation of LH and FSH release, decreased estrogen production, and low circulating leptin levels.

In addition, chronic, systemic illness can cause HH via deficits in nutritional intake creating a negative energy balance or chronic inflammatory states resulting from immunologic disorders (i.e., inflammatory bowel disease and celiac disease) or psychological stress.

Drugs such as opiates and steroids can also suppress the HPG axis.

4.2.2 Hypergonadotropic Hypogonadism

Delayed onset of puberty or stalled pubertal development can also be caused by gonadal defects that may first become evident in adolescence. In such cases, unresponsive defective gonads lead to increased serum gonadotropin levels that characterize hypergonadotropic hypogonadism [5].

Primary hypogonadism can be due to congenital origins such as chromosomal abnormalities, syndrome, or genetic mutations, but it can also be acquired later in childhood or adolescence due to autoimmunity or exposure to chemotherapy or radiation (Table 4.1).

4.2.2.1 Congenital Origins

Turner syndrome: The most common cause of congenital primary hypogonadism is sex chromosome aneuploidy as is present in Turner syndrome [8]. It occurs in 1:2500 live born females. Diagnosis is suggested by characteristic physical features, including short stature, webbed neck, high palate, renal and cardiac malformations and confirmed by karyotypic analysis showing a partial or complete absence of an X chromosome or a chromosomal mosaicism. In adolescence, key diagnostic features include short disproportionate stature and ovarian insufficiency resulting in absent or incomplete puberty. In some instances, primary amenorrhea is the only presenting symptom. While most TS patients will require pubertal induction, about one-third of girls present with spontaneous initiation of puberty and 5% exhibit menarche and 2% spontaneous pregnancy.

Although intrinsically normal, the ovaries in girls with TS undergo accelerated atresia such that the timing of ovarian failure is variable and can occur anytime between childhood and young adulthood. FSH levels may be very elevated in TS in the first 2 years of life, revealing precocious gonadal insufficiency. Hypogonadism in these patients not only affects puberty and reproductive capacity but also has consequences on metabolic, hepatic, cardiovascular and bone health (density).

Gonadal dysgenesis: The second largest group of young women with primary ovarian insufficiency has a 46, XX karyotype (46, XX gonadal dysgenesis). Some of them have an autosomal recessive form of the disorder, and others have premutation for the fragile X syndrome.

Primary ovarian insufficiency: Primary ovarian insufficiency, a condition characterized by follicle depletion or dysfunction leading to a continuum of impaired ovarian function, is suggested by a concentration of follicle-stimulating hormone in the menopausal range, confirmed on two occasions separated by 1 month, and diagnosed in patients younger than 40 years with amenorrhea or oligomenorrhea [9, 10]. Other terms, including premature ovarian failure, are used synonymously with primary ovarian insufficiency. Up to 1% of women may experience primary ovarian insufficiency. More than 90% of cases unrelated to a syndrome are idiopathic, but they can be attributed to radiation, chemotherapeutic agents, infections, tumors, empty sella syndrome, or an autoimmune or infiltrative process.

Patients with primary ovarian insufficiency should be counseled about possible infertility, because up to 10% of such patients may achieve temporary and unpredictable remission.

There is evidence of genetic predisposition to primary ovarian insufficiency, and patients without evidence of a syndrome should be tested for FMR1 gene mutation [11].

X chromosome abnormalities: Other X chromosome abnormalities, including Xq deletion and Triple X, can cause varying degrees of hypogonadism. The proximal regions of both the p and the q arms of the X chromosomes are most critical for maintenance of the germ cell compliment and also terminal deletions at the telomeric regions of these arms are associated with oocyte depletion. Deletion of these regions is more likely to result in premature ovarian insufficiency after some period of ovarian function rather than a complete loss of germ cells evident at the start of the teenage years as is more commonly seen with the proximal deletions. Early molecular studies have identified two regions of the long arm of the X chromosome within the translocation breakpoints which were felt to harbor important ovarian determinant genes. POF1 (Xq26–q28) contains several candidate genes (HS6ST2, TDPF3, GPC3) and one known to be associated with POI, the Fragile Mental Retardation 1 (FMR1) gene. POF2 (Xq13.3–q22) contains several candidate genes for which one has been disrupted in POI.

Xq deletion can cause a phenotype similar to TS as well as isolated premature ovarian failure. Deletions in the critical region, Xq13–q26, can also lead to premature ovarian failure.

Abnormalities in gonadotropin production or action: Mutations within the beta-subunit of the gonadotropins, the gonadotropin receptors, or forms of resistance to gonadotropins can all result in hypergonadotropic hypogonadism. Females with mutations in the beta-subunit of FSH present with primary amenorrhea, delayed puberty, and poorly developed secondary sexual characteristics; they have low FSH levels, low estradiol levels, and high LH levels due to lack of feedback inhibition by estradiol. In females, LH resistance results in normal puberty but subsequent amenorrhea, infertility, and elevated LH levels, demonstrating that ovulation requires LH as well as FSH.

Galactosemia: Galactosemia results from a deficiency in galactose-1-phosphate uridyltransferase (GALT). In females, the disease can result in hypergonadotropic hypogonadism with varying degrees of primary and secondary amenorrhea and oligomenorrhea. Ultrasound studies of the ovaries showed streak gonads in most affected females, so the cause is premature ovarian failure, as demonstrated by elevated levels of FSH, although the pathophysiology is not well understood.

4.2.2.2 Acquired Origins

The most important acquired origins include treatment for pediatric cancer (radiation and chemotherapy) and autoimmune conditions.

Chemotherapy and radiation: Advances in the treatment of childhood cancer (surgery, chemotherapy/radiotherapy) have improved survival rates and growing

numbers of adolescents are presenting with acquired forms of hypogonadism secondary to treatment of pediatric cancers. The type of treatment, dosage/exposure, and age of treatment are important determinants of gonadotoxicity and patients treated at a younger age typically have lower risk for long-term, deleterious reproductive effects. In girls, the dose of intra-abdominal radiation needed to destroy more than 50% of developing oocytes in less than 2 Gy. In the 70% of patients who survive pediatric cancer, one in six female survivors develops primary ovarian failure and those who undergo spontaneous menarche have decreased ovarian reserve. If chemotherapy (vincristina, L-asparaginase, methotrexate, 6-mercaptopurina) is combined with total body radiation, the risk of developing premature ovarian failure is very high. Sporadic case of spontaneous recovery of ovarian function in childhood cancer survivors has been reported; although most common in older children and adults, recovery of ovarian function has occurred as long as 12 years post-exposure to radiation and alkylating chemotherapy.

Autoimmune gonadal failure: The most common cause of premature ovarian failure in adolescents with a 46, XX karyotype, for whom an abnormality has not identified, is autoimmunity. Autoimmunity can lead to ovarian failure, especially in those who have other types of autoimmune endocrinopathies. Autoimmune polyglandular syndrome (APS) I and II have been associated with premature ovarian failure at prevalence rates of 30–50%. APS I consists of a triad of hypoparathyroidism, mucocutaneous candidiasis, and adrenal insufficiency. The mutation is within the AIRE gene. Patients with one autoimmunity disease should be regularly screened for other endocrinopathies on routine basis.

4.3 Evaluation

If gonadal failure is congenital or starts before pubertal development (chronological age <8 years), it generally manifests with pubertal delay and primary amenorrhea [12]. So the clinical suspicion arises in peripubertal age when clinical signs of pubertal development are lacking (Table 4.2 and Fig. 4.1).

Primary amenorrhea is defined as the failure to reach menarche. Evaluation should be undertaken if there is no pubertal development by 13 years of age, if menarche has not occurred 5 years after initial breast development, or if the patient is 15 years or older (Figs. 4.1 and 4.2).

In these cases, clinical evaluation begins with a careful clinical history and physical examination (Table 4.2). Important elements on history include the parents' pubertal timing because late menarche in the mother or delayed completion of adult height in the father is strongly suggestive of CDGP. History should include attention to any CNS insult, symptoms of chronic disease or history of cancer and treatments with chemotherapy and/or radiotherapy.

Lack of sense of smell can be an important clue to the presence of Kallmann syndrome.

Table 4.2 Findings in the evaluation of pubertal delay and amenorrhea

History
1. Family history of delayed menarche or pubertal delay in the father
2. Chronic illness
3. Chemotherapy or radiation
4. Weight loss, excessive exercise, poor nutrition, psychosocial stress, diets
5. Galactorrhea
6. Menarche and menstrual history
7. Illicit drug use
8. Medications
9. Sexual activity
10. Significant headache and vision changes
11. Vasomotor symptoms
Physical examination
1. Anthropometric measurements (weight and height)
2. Evaluation of growth chart
3. Body mass index (nutritional status)
4. Dysmorphic features (webbed neck, short stature, low hairline)
5. Tanner staging for pubertal signs
6. Thyroid examination
7. Male pattern baldness, increased facial hair, acne
Laboratory testing
1. Complete blood count and metabolic panel abnormalities
2. Estradiol
3. FSH and LH
4. Free and total testosterone, DHEAS
5. Karyotype
6. Prolactin
7. Pregnancy test
8. Thyroid-stimulating hormone
Diagnostic imaging
1. Pelvic ultrasonography (presence of malformation of uterus, ovaries volume and structure)
2. Magnetic resonance imaging of head or sella turcica

The physician should measure the patient's height, weight, and body mass index, and evaluate secondary sexual characteristics according to Tanner staging. Short stature, dysmorphic features such as webbed neck or low hairline may suggest Turner syndrome.

If gonadal failure starts after menarche, it determines secondary amenorrhea that is defined as the cessation of previously regular menses for 6 months.

Breast development is an excellent marker for ovarian estrogen production. Thin vaginal mucosa is suggestive of low estrogen. Patients should be asked about eating and exercise patterns, change in weight, and previous menses (if any).

Neurological assessment should include evaluation of visual fields.

Gonadal failure may manifest with primary or secondary amenorrhea [13], so differential diagnosis should include all the conditions that can lead to primary and secondary amenorrhea (Figs.4.2 and 4.3).

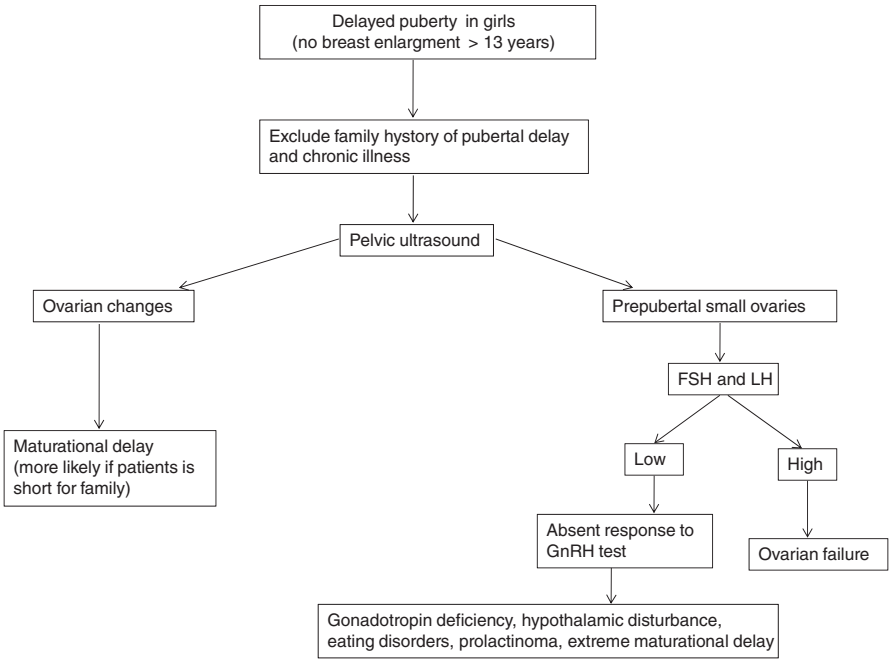

Fig. 4.1 Schematic algorithm for assessing adolescent females presenting with lack of pubertal development

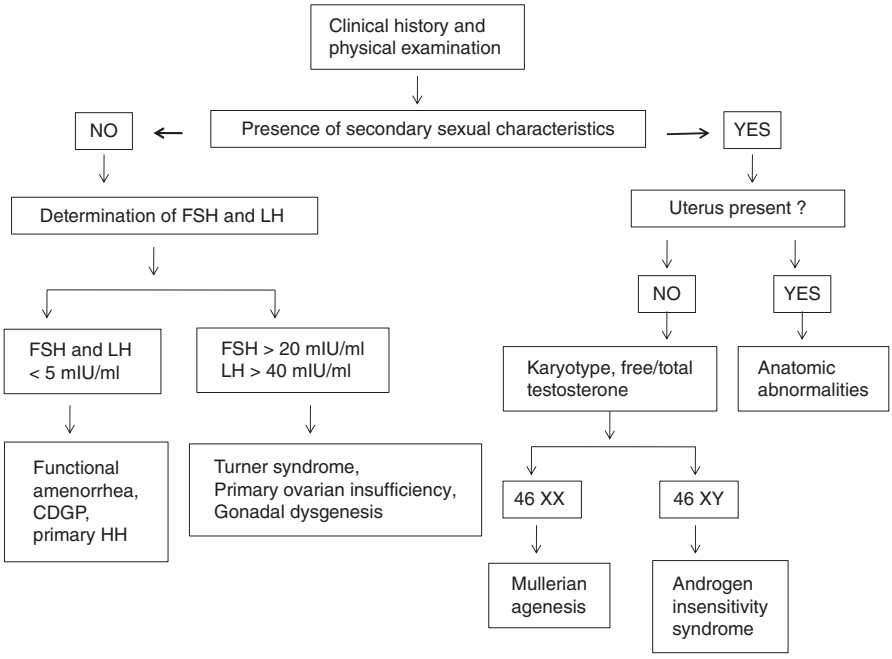

Fig. 4.2 A diagnostic approach to primary amenorrhea

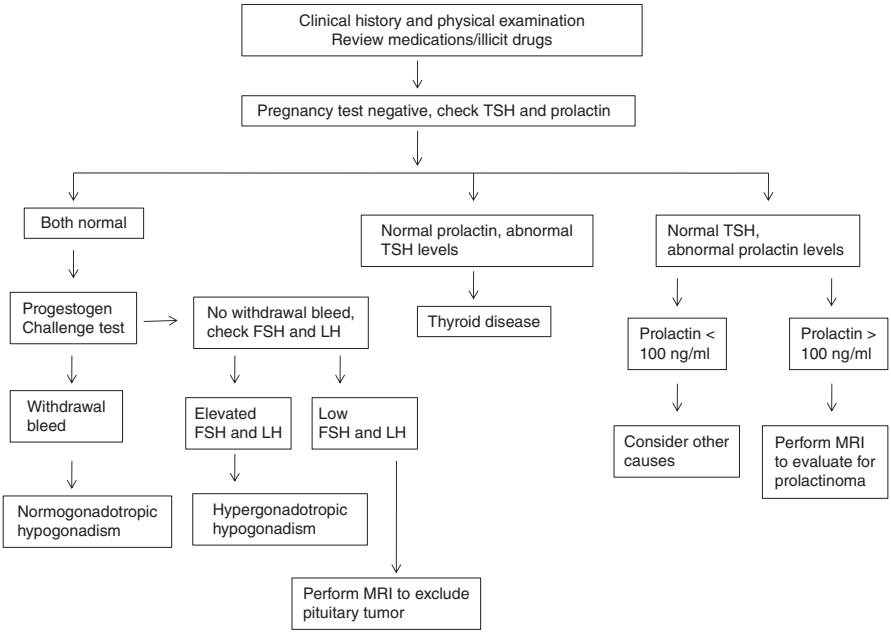

Fig. 4.3 A diagnostic approach to secondary amenorrhea

4.4 Diagnostic Workup

The initial workup includes serum luteinizing hormone, follicle-stimulating hormone, and estrogen levels.

Low gonadotropin levels suggest CDGP or pathologic hypogonadotropic hypogonadism and can be further evaluated with GnRH stimulation test [14, 15]. In contrast, elevated gonadotropins indicate primary gonadal failure. A bone age radiograph is an essential component of the evaluation; in fact in CDGP it is generally retarded in respect to chronological age, while in hypo- and hypergonadotropic hypogonadism it is correspondent to chronological age.

If the patient is short in stature, a karyotype analysis should be performed to exclude Turner syndrome. A complete blood count and a comprehensive metabolic panel may be useful if history or examination is suggestive of chronic disease. Autoimmune panel or molecular genetic analysis may be indicated if other possible causes have been excluded.

Pelvic ultrasonography can identify volume and anatomical abnormalities (streak gonads) of the ovaries.

If a pituitary tumor is suspected or elevated levels of prolactin have been detected, magnetic resonance imaging (MRI) may be indicated.

4.5 Treatment

In general, there are several goals for treating hypogonadism in adolescence: developing secondary sexual characteristics and growth as well as inducing gonadal maturation for future fertility [16].

The initiation of estrogen therapy at an age concordant with normal endogenous ovarian production (i.e., at least by ages 9–11 years) has always been considered important for normal psychosocial development of the adolescent.

All patients with premature gonadal failure need estrogen therapy for initiation and completion of pubertal progression and subsequently for the maintenance of a multitude of health processes [5, 12]. Remodeling of bone is of utmost importance, but other physiologic processes are dependent on normal estrogen status as well at least through 50 years of age. The findings and concerns for long-term hormone replacement of the Women's Health Initiative do not apply to these or any other patient prior to the age of 50 years and should not be used to prematurely stop their hormone replacement.

Counseling is of utmost importance for these individuals and should cover expectations.

Primary insufficiency can be corrected by hormone therapy according to the following schedule:

100 mcg of daily transdermal estradiol or 0.625 mg of daily conjugated equine estrogen on days 1 through 26 of the menstrual cycle + 10 mg of cyclic medroxyprogesterone acetate for 12 days (e.g., days 14 through 26) of the menstrual cycle.

This regimen should be administered until the average age of natural menopause and is recommended to decrease the risk of ischemic heart disease and osteoporosis.

Combined oral contraceptives (OCs) deliver higher concentrations of estrogen and progesterone than necessary for hormone therapy, may confer thromboembolic risk, and may theoretically be ineffective at suppressing follicle-stimulating hormone for contraceptive purposes in the population: thus a barrier method or intrauterine device is appropriate in sexually active patients.

For optimal bone health, patients with primary ovarian insufficiency need a supplement of calcium (e.g., 1200 mg daily) and vitamin D (e.g., 800 IU daily).

Treatment of functional hypothalamic amenorrhea involves nutritional rehabilitation as well as reduction in stress and exercise levels. Menses typically return after correction of the underlying nutritional deficit. The patient should take calcium and vitamin D supplements. Estrogen replacement without nutritional rehabilitation does not reverse the bone loss. Combined oral contraceptive pills will restore menses, but will not correct bone density. Leptin administration has been reported to restore pulsatility of gonadotropin-releasing hormone and ovulation in these patients, but its effect on bone health is unknown.

The physical development of puberty is accompanied by psychosocial and emotional changes, so disrupted puberty can carry a psychological burden as well as

anxiety and depression. Treatment inducing growth and development of secondary sexual characteristics may be helpful in alleviating some of the distress hypogonadal adolescents experience related to their lack of development. Frank discussion of patients' concerns, anticipatory guidance, and emotional support should be an integral part of their care.

Therefore, a holistic, collaborative approach including psychological counseling is a key component of managing hypogonadism in adolescence.

4.5.1 Transition of Adolescents to Adult Care

The transition from pediatric to adult care is a challenge for patients with chronic endocrine conditions with different disorders having condition-specific needs. Too often, the transition process is characterized by cracks and gaps in care as reported for patients with TS. Such disjointed care can negatively impact health and quality of life for adolescents with hypogonadism as periods without treatment result in decreased sexual function, diminished energy, and poor bone density. Special transition clinics where pediatric and adult endocrinologist work together are increasingly being created to bridge care and promote continuity and adherence to treatment [17, 18].

Conclusions

Hypogonadism in adolescence results from a variety of causes including congenital and acquired forms. Early diagnosis is important for initiating treatment to develop secondary sexual characteristics and growth as well as for inducing gonadal maturation for future fertility.

Furthermore, early treatment may help to minimize some of the psychosocial impacts of hypogonadism on adolescents.

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Dysmenorrhea

5

Gabriele Tridenti and Cristina Vezzani

Abbreviations

ACOG	American College of Obstetricians and Gynecologists
ESR	Erythrocyte sedimentation rate
FDA	Food and Drug Administration
Hz	Hertz
IRCCS	Istituto di Ricovero e Cura a Carattere Scientifico
LT	Leukotriene
NSAID	Non-steroidal anti-inflammatory drug
OC	Oral contraceptive
OHVIRA	Obstructed hemi vagina ipsilateral renal agenesis
PgE_2	Prostaglandin E_2
$PgF_{2\alpha}$	Prostaglandin $F_{2\alpha}$
PG	Prostaglandin
PID	Pelvic inflammatory disease
STD	Sexually transmitted disease
TENS	Transcutaneous electric nerve stimulation
VAS	Visual Analogue Score
VMS	Verbal Multidimensional Scoring System

G. Tridenti, M.D. (✉) • C. Vezzani, M.D.
Department of Obstetrics and Gynaecology, Santa Maria Nuova Hospital—IRCCS,
iale Risorgimento 80, 42123 Reggio Emilia, Italy
e-mail: gtride@tin.it; Cristina.Vezzani@ausl.re.it

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The term *dysmenorrhea* comes from the three ancient Greek words: δυς (difficult), μην (month), ρεω (flow), and its literal meaning is "difficult menstrual flow" [1, 2]. Dysmenorrheic women have a significantly reduced quality of life, poorer mood, and sleep quality during menses in comparison with non-dysmenorrheic women. Menstrual pain affects many aspects of life, such as family relationships, friendships, school/work performances, social/recreational activities, and physical activities as well [3]. Being reported by 15–85% women, dysmenorrhea is the most frequent genital complaints in teenage and it is the main cause of recurrent short-term absenteeism from school or work. Usually, appearing within 6–12 months after menarche, it is less frequent during the first 2–3 postmenarchal years, when menstrual cycles are mostly anovulatory, while its incidence grows in mid- and late adolescence, with the establishing of ovulatory cycles. Dysmenorrhea is very often misdiagnosed, untreated, or undertreated, with high percentages of self-medication, often in nontherapeutic dose to achieve a quick relief of pain [4, 5]. Sixty to seventy percent adolescents report painful menses; 15% interrupt daily activities because of pain, with school absenteeism in 14–52% of cases, with a six-fold higher incidence if a family history of dysmenorrhea is present [6, 7]. Dysmenorrhea may decrease after giving birth or with advancing age [8]. The perception of pain may be the result of strictly individual factors, such as attitude towards menses, pain threshold, and mood [4].

The typical clinical picture of primary dysmenorrhea includes *painful lower abdominal cramps*:

- Requiring medication or limiting normal activity
- Starting with menstruation or within a few hours before or after its onset
- Lasting no more than 24–48 h
- Strictly correlated with ovulatory cycles and duration and amount of menses [9]

On the contrary, in premenstrual syndrome symptoms start before menstruation, occur, and resolve shortly after the onset of menstrual bleeding [10].

Commonest risk factors of dysmenorrhea are:

• Family history	• Frequent life changes
• Young age	• Few social supports
• Precocious menarche	• Stressful close relationships
• Heavy and prolonged menstrual flows	• Low socioeconomic level
• Nulliparity	• Low fish intake
• Smoking and exposure to environmental tobacco smoking	• Poor physical activity
	• Underweight and overweight
	• Marked uterine retroversion
	• Low intake of polyunsaturated fatty acids
	• Vitamin D deficiency

Balbi et al. [11], Dei and Bruni [12]

Two different main clinical pictures exist among affected teenagers:

- *Primary Dysmenorrhea*: at postmenarchal onset, it accounts for the 90% of cases in teenagers and typically comprises recurrent abdominal painful cramps occurring with menses without any identifiable pelvic pathology.
- *Secondary Dysmenorrhea*, in 10% adolescent cases, at late onset depending on the underlying disease, with menstrual pains associated with well-defined pelvic pathologies, such as:

– Endometriosis	– Interstitial cystitis
– Mullerian obstructive anomalies	– Adenomyosis
– PID	– Pedunculate submucous myomas
– STDs	– Endometrial polyps
– Early pregnancy complications	– Pelvic adhesions
– Cervical stenosis	– Bowel inflammatory diseases
– Ovarian cysts and dermoids	– Pelvic tuberculosis
– Sequelae of genital mutilations	– Large ovarian cysts

Dei and Bruni [12], Harel [13], Sanfilippo, and Erb [14]

Secondary dysmenorrhea may be accompanied by other gynecological symptoms, such as intermenstrual bleeding and menorrhagia; moreover, the timing and intensity of pain during the menstrual cycle may be constant or diffuse, and not necessarily associated with menses [4].

Affecting 8–10% women of reproductive age, endometriosis, that is endometrial tissue in extrauterine locations, is the most frequent etiology of secondary dysmenorrhea and it is associated with obstructive genital anomalies in 11% cases [14, 15]. Another possible cause of secondary dysmenorrhea is adenomyosis, that is endometrial tissue within the myometrium, recently detected also in adolescents and more frequently than previously expected [16].

All Mullerian anomalies may give rise to secondary dysmenorrhea because of altered vascularity. Nevertheless, heavier and worsening clinical pictures may occur in obstructed uterine and/or vaginal anomalies, such as noncommunicating functioning rudimentary uterine horn and obstructed hemivagina. Most cases are part of complex asymmetrical uro-genital malformations with duplex uteri and vaginae with unilateral renal agenesis [12].

The pathophysiology of primary dysmenorrhea shows different steps, with a major role of defined inflammatory lesions occurring in the menstruating womb:

- Increase of ω-6 fatty acids (mainly arachidonic acid) in endometrial cell membrane after ovulation and their release with premenstrual progesterone withdrawal which activates lysosomal phospholipase.
- ω-3 fatty acids/ω-6 fatty acids ratio may play a role in the release of algogenic factors.
- Activation of prostaglandins (PGs) and leukotrienes (LTs) cascade in the uterine wall, with subsequent inflammation giving rise to cramps and systemic symptoms.
- Myometrial contractions, then ischemia and pain in the uterine muscle [17].

- Higher vasopressin and low nitric oxide blood levels may induce vasoconstriction and myometrial contractions [18, 19].
- Uterine flexion may play a pathogenetic role in dysmenorrhea: if the best condition is uterine body and cervix on the same axis, with an angle of 180° ± 30°, greater or lesser angles could impede menstruation with stronger myometrial contractions and pains: marked anteflexion and retroflexion both may rise menstrual pains [20].

Up to now, the overproduction of uterine prostaglandins is the most widely accepted explanation for primary dysmenorrhea. The severity of menstrual pain and associated symptoms is directly proportional to the amount of prostaglandins released, and their production is strictly connected to the endometrial exposure to luteal phase progesterone and therefore to ovulation. Among all prostaglandins, PgE_2 and $PgF_{2\alpha}$ are mainly involved in the pathogenesis of dysmenorrhea. While the former may result in either myometrial contraction or relaxation, the latter elicits both strong vasoconstriction of uterine blood vessels and myometrial contractions, lowering also pain threshold by sensitizing nerve endings to pain. In the pathogenesis of dysmenorrhea, a more and more relevant role of central factors was shown, even if their relationship with peripheral factors has still to be fully clarified. Unknown genetic or environmental factors and congenital variants in the pain processing of the central nervous system may predispose dysmenorrheic women to a greater pain perception, being mainly hypersensitive to deep muscle pain [4]. Dysmenorrheic women displayed a shift in the balance between pro-inflammatory cytokines and anti-inflammatory transforming growth factor-β, with up-regulation of genes coding for cytokines and down-regulation of the ones coding for transforming growth factor-β; therefore in dysmenorrheic women, the inflammatory response is different even without pain, with distorted hormonal and cytokine profiles [21]. Recurrent monthly dysmenorrhea may lead to the development of a central sensitivity to pain, with an abnormal augmentation of pain perception by mechanisms within the central nervous system [22]. Dysmenorrheic women are supposed to have central changes which persist beyond menses being possibly induced by the recurrent nociceptive stimuli into the central nervous system. Primary dysmenorrhea may therefore raise the risk for the development of other painful diseases later in life [23].

Signs and symptoms of *primary dysmenorrhea* are:

• Cramps	• Loss of appetite	• Diarrhea
• Nausea	• Weakness	• Facial blemishes
• Vomiting	• Headache	• Abdominal pains
• Bloating	• Backache	• Dizziness
• Flushing		• Depression
• Sleeplessness		• Irritability
• General aching		• Nervousness
		• Leg aches

The relationship between sleep and pain may be bidirectional, with pain disrupting sleep and disrupted sleep heightening pain perception [4].

Secondary dysmenorrhea more often shows

- Chronic pelvic pains
- Mid-cycle pains
- Dyspareunia
- Metrorrhagia
- Harel [13]

The main diagnostic symptom of primary dysmenorrhea is a colicky suprapubic abdominal pain, occurring as follows:

- Along the lower abdomen midline
- Also described as a "dull" pain in both lower abdominal quadrants, lumbar areas, and thighs
- Appearing with the onset of ovulatory cycles
- Starting just few hours before or after the onset of menses
- With frequent associated symptoms such as diarrhea, nausea, vomiting, weakness, lightheadedness, headache, dizziness, lipothymia, fever, etc.

Associated symptoms peak with maximum blood flow and usually last less than 1 day. Pains may last 2–3 days at most and are quite similar in every menstrual period [5]. Being a subjective symptom, the quantification of dysmenorrhea is difficult. Its intensity may be:

- *Mild*, not disturbing daily activities nor requiring painkillers
- *Moderate*, slightly interfering with daily routines but manageable with pain killers
- *Severe*, markedly preventing daily life activities [24]

To measure and to grade dysmenorrhea, the two most common tools currently in use rely upon girls' self-reporting, which is unavoidably subjective and inaccurate:

(a) *A verbal multidimensional scoring system*, such as the "Menstrual Distress Questionnaire" and the "Menstrual Symptom Questionnaire," both considering the impacts of pain on daily activities, systemic symptoms, and analgesic requirements (Table 5.1);
(b) *A linear visual analogue scale* (*VAS*): a 10 cm line drawn on a sheet of paper, representing a continuum of severity of pain from "no pain at all" at one extreme till "unbearable pain" at the opposite one. The patient is asked to rate pain with a mark on the line and the result is achieved by measuring the distance from zero to the mark (Fig. 5.1).

Table 5.1 Verbal multidimensional scoring system (VMS)

Grade	Working ability	Systemic symptoms	Analgesia
Grade 0: Non-painful menstruation Unaffected daily activity	Unaffected	None	Not required
Grade 1: Painful menstruation seldom inhibiting the woman's normal activity Analgesics seldom required. Mild pain	Rarely affected	None	Rarely required
Grade 2: Daily activity affected. Moderate pain Analgesics required giving relief Absence from school/work is unusual	Moderately affected	Few	Moderately required
Grade 3: Activity clearly inhibited. Severe pain Poor effect of analgesics. Vegetative symptoms (headache, tiredness, nausea, vomiting, diarrhea)	Clearly affected	Apparent	Poor effect

Gamit KS, et al. "International Journal of Medical Science and Public Health," (2014)

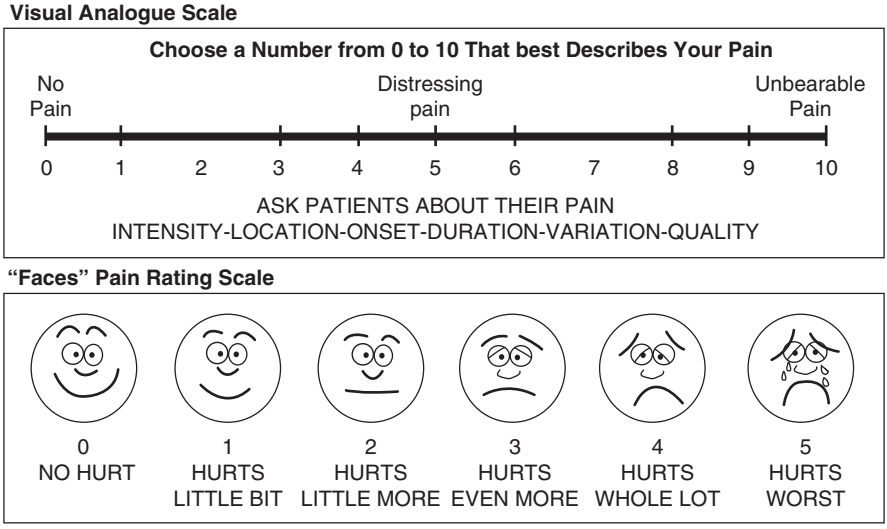

Fig. 5.1 Linear Visual Analogue Scale (VAS) (www.researchgate.net/publication/259499877)

Both tools lack validation and cannot be trustfully employed in teens [8].

Taking into account the onset of dysmenorrhea, different clinical pictures may be identified:

- *Early onset dysmenorrhea*, appearing within 6 postmenarchal months or in clearly non-ovulatory patients, it is very likely due to an underlying obstructive genital anomaly, and mainly Wunderlich/OHVIRA syndrome (uterus didelphys with obstructed hemivagina and ipsilateral renal agenesis).
- *Late onset dysmenorrhea*, arising after some years of painless periods, highly suggests secondary dysmenorrhea.
- *Sudden onset dysmenorrhea*, suddenly arising in non-symptomatic or oligo-symptomatic patients, makes PID and early pregnancy complications (miscarriage or ectopic pregnancy) suspected [25].

Clinical approach to dysmenorrheic patients must follow good medical practice recommendations:

MEDICAL HISTORY, properly focused on menstruation, allows for differential diagnosis between primary and secondary dysmenorrhea by considering:

– Age at menarche	– Associated symptoms
– Length and regularity of cycles	– Chronology of associated symptoms related to menses
– Dates of the last two menses	– Severity and duration of associated symptoms
– Duration and amount of flows	– Progression of associated symptoms over time
– Type, location, and radiation of pain	– Time between menarche and onset of symptoms
– Worsening of pain over time	– Degree of patient's disability
– Gastrointestinal and urinary functions	– Lifestyle (food, smoking, physical activity)

Bettendorf et al. [26]

Other items to be considered in medical history:

- Sexual activity, dyspareunia, contraception
- Past obstetric and gynecologic events, and mainly STDs, PID, pelvic surgery, infertility
- Other medical problems
- Family history of endometriosis in first degree relatives
- All previous treatments, ways of administration, and outcomes
- Other ongoing medical treatments
- Dei and Bruni [12], Harel [13]
- Meal skipping
- Less sleep
- Higher sugar intake

are other important risk factors for the occurrence of dysmenorrhea [6].

PHYSICAL EXAMINATION must follow several steps.

- *Abdominal evaluation* is always indicated to detect palpable masses.
- *Inspection of external genitalia* is mandatory in young girls to rule out abnormal hymens.

- *Pelvic exam* (*vaginal or rectal*), not indicated in virgins with mild to moderate dysmenorrhea, must be performed:
  - In sexually active girls
  - If organic diseases or genital anomalies are suspected
  - With no response to conventional treatments of primary dysmenorrhea

LABORATORY TESTING OR IMAGING, not required to diagnose primary dysmenorrhea, are advisable if secondary dysmenorrhea is suspected. Laboratory testing are not resolving, and they may be useful if a pelvic inflammatory disease is suspected, with a slight increase of both erythrocyte sedimentation rate (ESR) and protein C reactive and possible positive cervical swabs [12].

- *Ultrasonography*, first-step diagnostic tool to image the pelvis, including also the assessment of number and location of kidneys in girls, is widely performed even if no evidence exists about its routine application in primary dysmenorrhea. On the contrary, pelvic ultrasonography is mandatory:
  - In the diagnostic workup of secondary dysmenorrhea
  - With no response to first-line treatments
  - With an abnormal, impossible, or unsatisfactory pelvic exam

    The transabdominal approach is usually preferred in young patients. Nevertheless, it must be borne in mind that ultrasonography can never replace physical exam.
- *Magnetic resonance imaging* is unnecessary in the diagnosis of primary dysmenorrhea while it may be useful to detect adenomyosis, Mullerian anomalies, and-bladder lesions [27].
- *Hysteroscopy and sonohysterography* can highlight congenital anomalies of the uterine cavity and endometrial polyps and submucous myomas as well.
- *Laparoscopy* is still the gold standard in the diagnostic workup of secondary dysmenorrhea due to endometriosis, PID, and pelvic adhesions. It must be performed
  - With highly suspected organic pathologies
  - With failed first-line treatments.

It is not to be delayed in refractory to therapy teens if endometriosis is suspected; biopsies of lesions are mandatory if endometriosis is diagnosed [28].

5.1 Treatments

Different therapeutic approaches to dysmenorrhea exist, and they may be grouped as follows:

- Non-medical options
- Medical options, both hormonal and nonhormonal ones
- Surgical options
- Complementary and alternative medicine

Treatments of dysmenorrhea may also be classified into

Conventional therapies:
Non-steroidal anti-inflammatory drugs (NSAIDs)
Oral contraceptives (OCs)
Surgery
Nonconventional therapies:
Behavioral treatments
Physical exercise
Manipulation of the spine
Reflexotherapy
Heat therapy
TENS
Acupuncture
Magnetotherapy
Alternative medicine

Non-medical treatments include:

- *Diet*: by lowering animal fats intake in favor of ω-3 fatty acids provided food, such as fish [12].
- *Physical exercise* may act on dysmenorrhea by enhancing β-endorphins release and by bettering pelvic blood flows. The results are controversial but it must always be advised as a first-step therapy.
- *Transcutaneous electrical nerve stimulation* (*TENS*) may be distinguished in
  - *High frequency TENS* (50–120 Hz): with low effect, it is more effective than placebo
  - *Low frequency TENS*: not effective at all in fact

Self-regulated by the patient, it is a non-medicinal-no-risk procedure acting by activation of the large-diameter Aβ proprioceptive nerve fibers of the skin with no activation of both finer Aδ fibers and pain C fibers. TENS effectiveness relies on the rise of pain threshold, preventing pelvic painful stimuli to reach the spinal cord. Furthermore, it enhances β-endorphins secretion and it betters uterine blood flow. Positive effects, if present, are perceivable within few minutes from the application of the device [13, 29, 30].

- *Acupuncture*: well tolerated without side effects procedure, it has been approved by FDA. It significantly lowers pain in mild-to-severe dysmenorrhea, with a long-acting effect. More expensive than NSAIDs and OCs, it may be recommended when first-line treatments are rejected or contraindicated. To establish proper recommendations and administration, further data are required [29, 31, 32].
- *Manipulation of the spine*: as some Authors suggest, the rationale of this procedure relies upon the existing close relationship of pelvic sympathetic and parasympathetic nerve pathways with spine segments T10-2L and S2–S4. Possible vertebral mechanical dysfunctions, with lowered mobility of the spine, could alter sympathetic pathways regulating blood supply in pelvic organs, with subsequent vasoconstriction and dysmenorrhea. Vertebral manipulation could improve spine mobility and increase pelvic blood supply by action on vessels innervation,

thus bettering dysmenorrhea. According to Cochrane Library, the efficacy of this procedure has no evidence [33].

- *Behavioral treatments*, targeted to enhance central control of pain, include:
  - Relaxation exercises
  - Biofeedback
  - Counseling about management of pain

Their effectiveness is low, few data are available, the evidence is poor; therefore, they are not recommended by Cochrane Library [34].

- *Topical heat*, very likely the most traditional treatment of dysmenorrhea, can be supplied in different modalities:
  - Hot patches
  - Hot water bottle
  - Adhesive patches generating chemical heat.

Even if evidence is poor, their effectiveness is well known and it should be greater than Acetaminophen and equal to Ibuprofen [13].

- *Topical magnetic devices*, about which poor evidence is reported, are static magnets to be applied to the skin under the underwear.
- *Reflexotherapy*, with no evidence, like the above reported device, is mentioned for completeness and consists of two procedures:
  - Application of a seed to an ear by a plaster, following the belief the ear hosts trigger points connected with all body parts
  - Stimulation of the hands and mainly of the feet, which both should carry reflexion areas connected to other body organs. Putting pressure on specific trigger points should release energy activating the healing process [35, 36].

For the above-mentioned treatments, no evidence is reported [37].

The large variability in the reported outcomes of the various non-pharmacologic approaches suggests the efficacy of such methods to be personal, differing from one patient to the other [4].

Nonhormonal medical treatments display:

- *Over-the-counter medications* (*acetaminophen*): they increase the pain threshold but their effectiveness is not assessed conclusively.
- *Non-steroidal anti-inflammatory drugs* (*NSAIDs*), classified as prostaglandin synthetase inhibitors, are almost certainly effective by suppressing the endometrial prostaglandin synthesis. They are the first-line medical treatment of dysmenorrhea to be taken at the very onset of bleeding and/or associated symptoms. Naproxen sodium, zomepirac sodium, mefenamic acid, ketoprofen, ibuprofen, and diclofenac showed to be comparably effective on menstrual pain [38]. NSAIDs, mainly Diclofenac, are effective in restoring both pain-related reduction in physical activities and sleep disturbances in dysmenorrheic women. NSAIDs effects are mostly tolerable and gastrointestinal safety issues are generally less worrisome in acute

Table 5.2 Properties and side effects of most prescribed NSAIDs in dysmenorrhea

Active principle	Peak blood levels	Half-life (h)	Other effects
Acetosal	1 h	2–3	Increased menstrual flow
Ibuprofen	40′	2–4	Unchanged menstrual flow
Ketoprofen	1–2 h	2	Photosensitizer, increased menstrual flow
Naproxen	1 h	14	Increased menstrual flow
Indomethacin	2 h	2,5	Heavier gastric side effects
Sulindac	2 h	1	
Diclofenac	2–3 h	1–2	Increased menstrual flow
Etodolac	1 h	7	
Mefenamic acid	2–4 h	3–4	Inhibits LTs and synthesized PGs
Meclofenamate	1–2 h	2	Decreased menstrual flow
Piroxicam	2–4 h	45–50	Heavier gastric side effects
Piroxicam + β-cyclodextrin	30–60′	45–50	
Nimesulide	2 h	3	Decreased menstrual flow, hepatotoxicity

Dei and Bruni [12]

administration than in chronic one [4]. Usually, a 2–3 days treatment is needed. Maximum dosing is recommended, with twice the regular dose initial loading followed by the usual dosage divided during the day. If the treatment is ineffective, a different preparation is advisable even if the various NSAIDs formulations have comparable efficacy on dysmenorrhea. Pain relief is achieved in 64–100% cases. In non-responding women (15% of the whole), oral contraceptives may be offered as a second-line treatment [34] (Table 5.2).

- *Cox-2 inhibitors* (*Colecoxib*) are advisable in patients reporting peptic ulcer or intolerance to NSAIDs. According to FDA, they may be prescribed to over 18 patients.
- *Transdermal glyceryl trinitrate* relaxes the myometrium but it is less effective than diclofenac.

Hormonal medical treatments are:

- *Combined oral contraceptives* (*OCs*), which are effective on dysmenorrhea and safe in teenage, display also useful health benefits such as alleviation of acne and protection against unintended pregnancies. This is the reason why OCs are the first-line option in sexually active dysmenorrheic girls. In all patients, they may be considered if a 6-month NSAIDs therapy is ineffective to be initiated while continuing with NSAIDs and preferring extended regimens [39]. Their action on dysmenorrhea is performed by:
  - Limiting endometrial growth and thickness.
  - Lowering PGs, LTs, and cyclooxygenase 2 blood levels.

  - Inhibiting ovulation and progesterone secretion, thereby reducing volume of menstrual fluid, prostaglandins synthesis, and dysmenorrhea [39]. Very likely OCs also lower blood pressure of uterine vessels. If symptoms persist during the 7 days pill-free interval, an extended, interval-free, 3 months treatment is advisable because of its high effectiveness on associated symptoms. If no pain relief occurs with a 3–6 months OCs treatment, secondary dysmenorrhea must be suspected and laparoscopy is recommended to diagnose and treat possible endometriosis [13].
- *Progestin only pill* can decrease the amount of menstrual bleeding lowering also abdominal cramps but further studies in dysmenorrheic patients are requested [13].
- *Depot medroxyprogesterone acetate* (*map*) *contraceptive* is an efficacious, long-acting, progestin-only, injecting contraceptive of which either intramuscular and subcutaneous preparations are available (the latter is unavailable in Italy), both to be administered once every 12 weeks. It can mitigate dysmenorrhea but in adolescents concerns exist about possible side effects on bone mass density, mainly after a 2-years long treatment. It is not a first-choice option in teenage. (www.fda.gov/medwatch/SAFETY/DepoProveraLabel.pdf)
- *Levonorgestrel-releasing intrauterine system* can lower both menstrual blood flow and pains. Even if concerns existed about its insertion in nulliparous and adolescents, nowadays its administration in both of them is approved by ACOG. Further opportunities in teenage are displayed by the launching on the market of Jaydess. The copper intrauterine device was shown not to act on dysmenorrhea [40, 41].
- *Etonogestrel subdermal implant* can better dysmenorrhea while in use. Its effectiveness has been verified but further studies in adolescents are needed [42].
- *Combined estrogen and progestin transdermal patch* may mitigate the symptoms but available data are controversial. Further studies are required before it may be recommended as a treatment of dysmenorrhea [43].
- *Combined estrogen and progestins vaginal ring* was verified to be an effective treatment of dysmenorrhea. An extended 84 days regimen is possible. After a 6 months administration, a significant bettering of the clinical picture was seen [44].
- *GnRH agonists* showed to be effective for both primary dysmenorrhea and endometriosis. Nevertheless, they are not advisable in under 16 adolescents because of concern about bone demineralization, verified after a 6 months administration. In longer-lasting treatments, an estroprogestin “add back” therapy is recommended to prevent bone loss [45].

Even taking into account differences among various formulations and ways of administration, NSAIDs and oral combined contraceptives (OCs) are first-line treatments of dysmenorrhea.

5.2 Surgical Treatment

If dysmenorrhea is resistant to a 6 months NSAIDs treatment followed by a 6 months COC therapy, both diagnostic and therapeutic surgery is advisable.

Different surgical approaches are available:

- *Laparoscopy* is still the gold standard to diagnose and treat endometriosis, of which the prevalence in adolescents is unclear but it is much more frequent than supposed in the past.
  According to various experiences, endometriosis was detected in:
  62% girls undergoing laparoscopy because of pain.
  75% girls with chronic pelvic pains resistant to treatment.
  70% girls with dysmenorrhea.
  49% girls with chronic pelvic pains not necessarily resistant to treatment [46].
  Because of hesitation in performing laparoscopy in very young people, in aged under 20 the diagnosis is often delayed with 10 years average delay between early symptoms and diagnosis; therefore, serious damages and impairment of future fertility are possible [47, 48]. Adolescents mostly show minimal-to-mild endometriosis, but the disease may rapidly progress to more severe stages, not correlated with symptoms. Even seldomly, stage III or IV endometriosis with endometriomas were detected in teenagers too [49]. To prevent long-term sequelae in adolescents, early diagnosis and treatment of endometriosis are mandatory to be necessarily performed in the same surgical setting [50]. In teenage, the recurrence risk is quite high (>20% at 2 years, 40–50% at 5 years); therefore, affected adolescents deserve close follow-up for recurrences [49, 51]. Laparoscopy is also the gold standard to diagnose and remove a noncommunicating functioning rudimentary horn, which may give rise to nonrespondent worsening dysmenorrhea [52].
- *Laparoscopic uterosacral nerve ablation* does not lower dysmenorrhea, while it carries risks for complications.
- *Presacral neurectomy* is the total transection of presacral nerves and it showed good effectiveness in pain relief but complications are possible and evidence is uncertain.

Drainage of a hemihematocolps with transvaginal removal of an obstructing vaginal septum is the fully resolving surgical treatment of worsening secondary dysmenorrhea in patient affected by duplex uteri and vaginae with lonely kidney and obstructed hemivagina (ipsilateral to the renal agenesis) with hemihematocolpos frequently misdiagnosed as a pelvic mass. In 78% cases, a didelphic uterus was found (Wunderlich/OHVIRA syndrome), while the remaining 22% showed a fully septate uterus. Such complex malformations show an early onset worsening dysmenorrhea when hemihematolpos occurs. The “gold standard” resolving treatment

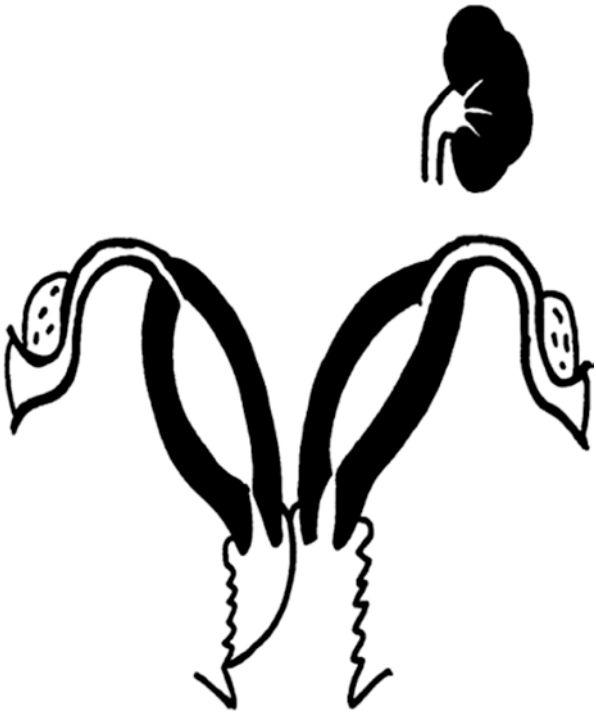

Fig. 5.2 Wunderlich/ OHVIRA syndrome

is transvaginal drainage of the retained blood and ricanalization of the genital tract by full removal of the vaginal septum. For completeness, didelphic uterus with unilateral renal agenesis and ipsilateral Garter's duct cyst (Herlyn-Werner Syndrome) is to be mentioned, even if very rare. An obstructive genital anomaly must always be suspected in an early onset non-respondent dysmenorrhea in adolescents. Early diagnosis and surgical treatment are mandatory to preserve fertility [53, 54] (Figs. 5.2 and 5.3).

- *Hysterectomy* is obviously not advisable in girls as a treatment of dysmenorrhea while it may be considered in parous dysmenorrheic women not seeking for further pregnancies and with an underlying uterine disease [55].

5.3 Complementary and Alternative Medicine

Such a definition groups different therapeutic proposals that are out of the conventional medical system. Considered by many people as a "natural" remedy of dysmenorrhea and equalized by the same lack of evidence according to Cochrane Library, these treatments suppose primary dysmenorrhea to be due to a poor assumption of fruits, eggs, and fish [37, 56–58].

Fig. 5.3 Septate uterus with obstructed hemivagina and ipsilateral renal agenesis

These therapies number:

- *Vitamin B1*, 100 mg daily 60 days long, with a verified bettering of the clinical picture of which the mechanism of action is unknown. Moderate evidence of lowered pain threshold and cramps was detected. Before prescribing Vitamin B1, adequate dietary intake of vitamins is to be checked.
- *Vitamin E*, 500 mg a day, from 2 days before till 3 days after the onset of menses. It acts by inhibiting protein kinase C, a membrane arachidonic acid release. It significantly betters symptoms but evidences are low.
- *Vitamin B6*, 200 mg a day, may lower symptoms but further studies are needed.
- *Fish oil*, from salmon, tuna fish, halibut may be effective on dysmenorrhea. It contains ω-3 polyunsaturated fatty acids (linolenic, eicosapentenoic, docosahexenoic acids) which, if dietary supplemented, may lessen dysmenorrhea by competition with membrane ω-6 fatty acids, released during menses and subsequently metabolized to prostaglandins. A dosage of 2.5 g daily may better symptoms but no evidence exists and further studies are required. Nausea, acne, dyspepsia, and fish flavor are possible side effects.

- *Magnesium*, 500 mg daily, showed to be more effective than placebo but further studies are needed. Its mechanism of action is unknown: very likely it lowers prostaglandin sintesis. Diarrhea and creeps may occur. It is contraindicated with renal failure because of possible hypermagnesemia.

Complementary and alternative treatments of dysmenorrhea also include herbal preparations of oriental origin, among which:

- *Toki-shakuyaku-san*, coming from Japan and composed by different plants, such as angelica, peony roots, and ginger root stocks. Divided doses of 7.5 mg per day were shown to be effective on dysmenorrhea but the results are not completely reproducible and the evidence is poor.
- *Iranian herbal preparations*, using saffron, celery seeds, aniseed, with low and very low evidences.
- *Chinese herbal medicine*, following traditional prescriptions, proposes a decoction of four herbs, including peony and angelica, from which capsules are derived by watery abstraction. Fifteen capsules per day, during the first 5 days of menses or pains, lead to a persistent improvement of symptoms after a three-cycle administration, but evidences are few. Since long time ago in eastern countries a variety of herbal treatments have been used to relieve dysmenorrhea with beneficial effects. They mainly inhibit uterine contractions by reducing prostaglandin secretion, suppressing cyclooxigenase-2 activity, activating superoxide dismutase, stimulating somatostatin receptor with a decrease of intracellular Ca^{2+} and/or recovery of phospholipid metabolism [59, 60]

Further studies about safety, doses effectiveness and outcomes are required before recommending herbal approach [8, 61].

Anecdotally, it is worth mentioning:

- *Aromatherapy*, proposed in Korea using lavender, sage, and rose fragrances [62, 63].
- *Rose tea*, used in Taiwan to mitigate primary dysmenorrhea, improves symptoms, anxiety and stress, with psychological bettering just after a 1-month treatment [64].

To sum up, dysmenorrhea is an important disease affecting most women of reproductive age with important social repercussions. Even if it is difficult to quantify, in adolescents it is the main cause of absenteeism from school and, if resistant to treatments it may be an important pointer of an underlying pelvic disease [8]. Nonetheless, many adolescents don't seek medical care because of this condition. The subsequent algorithm summarized the most validated therapeutic approach to primary dysmenorrhea. As endometriosis was detected in 70% teenagers undergoing laparoscopy because of "resistant to treatment dysmenorrhea," diagnostic laparoscopy, if indicated, must not be delayed in adolescents, both to relieve pains and to preserve future fertility at most [49]. Future treatments of dysmenorrhea should

focus on the prevention of pain more than on its management of pain to its prevention [4] and clinicians should identify secondary dysmenorrhea as early as possible to minimize its possible negative outcomes. It must also be considered that information, education, and support, to be supplied by heath care providers both to adolescents and their families, are the foundations of prevention and treatment of dysmenorrhea [65].

5.4 Algorithm

PAINFUL MENSES:

Anterior 1–3 days long pelvic pains at the onset of menses → alleged primary dysmenorrhea

Other clinical pictures including menstrual pains → alleged secondary dysmenorrhea.

ALLEGED DIAGNOSIS OF PRIMARY DYSMENORRHEA

First-step approach → ***6 months treatment with NSAIDs***

- If successful → treatment to be continued unchanged
- If unsuccessful → shift to OCs

Second-step approach → ***6 months treatment with OCs***

- If successful → treatment to be continued unchanged
- If unsuccessful → alleged secondary dysmenorrhea

ALLEGED DIAGNOSIS OF SECONDARY DYSMENORRHEA

Signs and symptoms of STDs?

- Yes → ***Confirm diagnosis and treat***
- No → ***Laparoscopy***

Endometriosis?

- Yes → ***Confirm diagnosis and treat***
- No → ***Abnormal anatomy*?**

Abnormal anatomy?

- Yes →***Surgical treatment***
- No →***Inexplicable dysmenorrhea***

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Dysfunctional Uterine Bleeding

6

Tiziano Motta, Antonio Simone Laganà,
and Salvatore Giovanni Vitale

Abbreviations

AUB	Abnormal uterine bleeding
DUB	Dysfunctional uterine bleeding
ESHRE	European society of human reproduction and embryology
PT	Prothrombin time
PTT	Partial thromboplastin time
vWF:Ag	Von willebrand factor
FVIII:C	Factor VIII coagulant activity
FXI:Ag	Factor XI
VWF:RCo	Ristocetin cofactor activity
GnRH	Gonadotropin-releasing hormone
FSH	Follicle-stimulating hormone
LH	Luteinizing hormone
TSH	Thyroid-stimulating hormone
PRL	Prolactin
DHEA-S	Dehydroepiandrosterone sulphate
17-OHP	17-OH progesterone
OGTT	Oral glucose tolerance test
PBAC	Pictorial blood loss assessment chart
CBC	Complete blood count

T. Motta (✉)
Department of Obstetrics and Gynaecology, University of Milan—Fondazione IRCSS Cà Granda Ospedale Maggiore Policlinico, Via Commenda, 12, 20122 Milan, Italy
e-mail: teamotta@alice.it

A.S. Laganà • S.G. Vitale
Unit of Gynecology and Obstetrics, Department of Human Pathology in Adulthood and Childhood "G. Barresi", University of Messina, Via C. Valeria 1, 98125 Messina, Italy
e-mail: antlagana@unime.it; vitalesalvatore@hotmail.com

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vWD	Von willebrand's disease
SLE	Systematic lupus erythematosus
PCOS	Polycystic ovary syndrome
SHBG	Sex hormone-binding globulin
HAIR-AN	Hyperandrogenism, insulin-resistance and *acanthosis nigricans* syndrome
CAH	Congenital adrenal hyperplasia
COC	Combined oral contraceptive
NSAIDs	Non-steroidal anti-inflammatory drugs
MAP	Medroxyprogesterone acetate
GnRH	Gonadotropin-releasing hormone
SERM	Selective estrogen receptor modulator
DDVAP	Desmopressin
IUD	Intrauterine device
LNG-IUD	IUD containing levonorgestrel
ACOG	American congress of obstetricians and gynecologists

6.1 Introduction

Abnormal Uterine Bleeding (AUB) is an atypical loss of blood from the uterine cavity that occurs outside of the menstrual cycle. It is often a source of anxiety for adolescents as well as their parents, who will often consult their more knowledgeable medical doctor or gynaecologist in order to understand it better. Normal blood loss during menstruation has been estimated to be approximately 30–35 mL/cycle with a maximum amount of 60–80 mL/cycle [1]. The menstrual cycle commonly lasts 7 days in a young woman (if not less) with a frequency that varies between 21 and 45 days, usually requiring the use of sanitary towels/tampons for 3–6 days [2]. In the 3 years following menarche, the cycles often present characteristics of anovulation. However, these cycles will occur every 21–34 days in adolescents once this period has passed. Actually, numerous clinical studies have drawn attention to the fact that over 50% of cycles in the first 2 years post-menarche are anovulatory, while a further 20% continue to be so after 5 years [3–5]. AUB can therefore be considered as a form of bleeding that is irregular for quantity, duration or frequency. It can also be characterised by excessive uterine bleeding that appears regularly (menorrhagia), through massive irregular bleeding (metrorrhagia) or a combination of both (menometrorrhagia). Sometimes, it can appear through intermittent bleeding or moderate bleeding with a cyclical trend (oligomenorrhoea) (Table 6.1).

Instead, Dysfunctional Uterine Bleeding (DUB) represents a particular type of AUB, and is defined in the USA as an excessive, prolonged and irregular bleeding of the endometrium (frequency <21 days; duration >7 days; daily use of sanitary towels/tampons >1/1–2 h), that does not cause pain and does not have any organic cause, so much so that it is frequently considered to be a symptom of anovulatory

Table 6.1 Common terms used to describe abnormal bleeding

• Menorrhagia: regular menstrual loss per rhythm but prolonged (>7 days) or in excessive quantities (>80 mL per cycle)
• Metrorrhagia: non-cyclic menstrual flow
• Menometrorrhagia: irregular non-cyclic, heavy and prolonged menstrual flow.
• Polymenorrhoea: menstruation with a shortened rhythm (<21 days).
• Hypermenorrhoea: menstruation that lasts >7 days.
• Oligomenorrhea: menstruation with an extended rhythm (>45 days and <6 months).
• Hypomenorrhoea: menstrual flow which is low in quantity and short in duration
• Intermenstrual Spotting: Low blood loss between two menstruations

Table 6.2 Differential diagnosis of dysfunctional uterine bleeding

Non-endocrine causes:
• Coagulation disorders
• Hepatic and renal impairment
• Diabetes
• Enteric diseases
• Rheumatic diseases
• Cardiac diseases
• Neurological diseases
Endocrine causes:
• Thyroid disorders
• Hyperandrogenic alterations
• Hyperprolactinaemia

bleeding [6]. According to this definition, up to 95% of cases of adolescent AUB would be considered DUB [7]. Conversely, the European Society of Human Reproduction and Embryology (ESHRE) considers DUB as an excessive, intense, prolonged and frequent bleeding of uterine origin that cannot be attributed to any demonstrable pelvic pathology, complication during pregnancy or systemic disease. DUB can therefore be described, in accordance with the definition provided by the ESHRE, as either ovulatory or anovulatory, as well as presenting itself as either acute or chronic [8]. However, the immaturity of the hypothalamic-pituitary-ovarian axis is considered the main cause. Since DUB is a diagnosis of exclusion, other potential causes of AUB (organic AUB) must be considered. This would include non-endocrine (coagulation disorders, hepatic and renal impairment, diabetes, gastroenteric, rheumatologic, cardiac and neurological diseases) and endocrine (thyroid disorders, hyperandrogenic diseases, hyperprolactinaemia) causes (Table 6.2).

6.2 Adolescent Assessment

The initial assessment of an adolescent with DUB requires an accurate summary of the patient's medical history, both familiar (in order to exclude haemorrhagic diatheses) and personal (previous surgery, trauma with ecchymosis, epistaxis or gingival bleeding, previous or current pathologies, use of drugs, accurate menstrual and sexual history), in addition to an objective medical examination (body

Table 6.3 Adolescent assessment: the importance of clinical history

• Timing
• Menstrual history (age when menarche occurred; length of cycle; duration of bleeding)
• Sanitary towels/tampons (count and dimension of loss) (Pictorial blood loss assessment chart score)
• Presence of vaginal loss
• Presence of abdominal pain
• Remote anamnesis
• Use of drugs
• Personal/family history of easy bleeding (gingival) or epistaxis and endocrine disorders

N.B. The patient should be requested to provide (in private or in the presence of relatives) information regarding sexual history, use of contraceptives and previous sexually transmitted diseases

Table 6.4 Physical examination

• Assessment of stage of puberty; blood pressure, height, weight, body mass index
• Diagnosis of eventual clinical signs (hirsutism; petechiae or contusions)
• Thyroid (goiter)
• Breast (galactorrhoea)
• Abdomen (presence/absence of lumps)
• Pelvis (Development of pubic hair)

In a non-sexually active adolescent, vaginal examination is rarely necessary (abdominal ultrasound could be enough)
In a sexually active adolescent, vaginal examination is advised

mass index, stage of puberty, inspection of external genitalia with an eventual gynaecological examination for sexually active patients, abdominal examination). It can sometimes be useful, although not strictly necessary, to perform a pelvic ultrasound (abdominal/transrectal or transvaginal in a sexually active patient) (Tables 6.3 and 6.4).

Although the Italian situation differs from that of the USA, where around 62% of 17–18-years-old teenagers are sexually active [9], it is important to exclude pregnancy or a related complication (miscarriage or ectopic pregnancy): this can only be done through an accurate anamnesis of the adolescent. In the USA, statistics have drawn further attention to the fact that around 25% of adolescents will contract a sexually transmitted infection. Since cervicitis and endometritis are both frequent causes of heavy menstrual flow [10], if they are confirmed, it would be advisable to investigate (or to confirm) the presence of *N. Gonorrhoea* and of *Chlamydia trachomatis*.

A laboratory assessment should therefore be performed in accordance with the clinical history and physical examination of the patient. The initial laboratory tests should include pregnancy test, complete blood count (CBC), fibrinogen, Prothrombin Time (PT) and Partial Thromboplastin Time (PTT) [11, 12]. In adolescents with a history of heavy and prolonged bleeding, immunological dosage of von Willebrand factor (vWF:Ag), dosage of factor VIII coagulant activity (FVIII:C), factor XI (FXI:Ag) and ristocetin cofactor activity (VWF:RCo) could be required [11, 13]. In suspect cases, it is good practice to request a haematological consultation. In

Table 6.5 Factors linked with a daily loss >80 mL (National Institutes of Health Guidelines, 2008)

• Pictorial blood loss assessment chart score > 100
• Heavy bleeding (>1 sanitary towel/hour)
• Low levels of ferritin
• Blood clots that pass through the sanitary towel, with a diameter of >2 cm.

adolescents who have a medical history indicative of anovulation, plasma levels of follicle-stimulating hormone (FSH) and Thyroid-Stimulating Hormone (TSH) should be evaluated, while in those with DUB and evident hirsutism, prolactin levels (PRL), total testosterone, dehydroepiandrosterone sulphate (DHEA-S), 17-OH progesterone (17-OHB) and androstenedione levels should be measured in association with an oral glucose tolerance test (2 h OGTT) and the dosage of fasting insulin and lipids [11, 13]. In order to better quantify the extent of blood loss, some authors have suggested to use a simple and reliable semiquantitative method at home (Pictorial Blood Loss Assessment Chart: PBAC score) [14–16], besides the above-mentioned CBC, serum iron and ferritinemia. The daily menstrual graphic is based on the scores that are attributed to each tampon or sanitary towel used, in relation to the different levels of saturation observed (one use >3 towels/day in the first 3 days of cycle, with/without blood clots, together with a menstrual loss >80 mL/day) [17] (Table 6.5).

6.3 Blood Clotting Disorders

Adolescents who are not pregnant and do not have a sexually transmitted infection can reveal in around 20% of cases an underlying coagulopathy [18–20], especially if they suffer from a heavy menstrual flow. In particular, haematological causes of DUB can be divided into two groups:

1. As a result of deficiency of coagulation factors [von Willebrand's Disease (vWD), deficiency of factor II, deficiency of factor V, deficiency of factor VII, deficiency of factor X, deficiency of factor XI, fibrinogen alterations, haemophilia A and B]
2. As a result of alterations in platelet function (idiopathic thrombocytopenic purpura, leukaemia, aplastic anaemia, Fanconi anaemia, Glanzmann's thrombasthenia, Bernard–Soulier Syndrome, renal and hepatic impairment, platelet transfusion, cardiopulmonary bypass, drugs)

However, the most known haematological cause is vWD, whose prevalence in the general European and American populations is estimated to be near 1% [21, 22]. Not only is menorrhagia mainly prevalent in women who show blood clotting disorders, but these are also mainly prevalent in patients with menorrhagia. A prevalence of 3–36% of vWD has been reported in adolescents with menorrhagia [23]. Similarly, it has been shown that an alteration in coagulation was present in

25% of adolescents with severe bleeding or haemoglobin levels <10 g/dL [24]; such levels reached 50% in cases of adolescents with menorrhagia already present in successive cycles after the menarche [25]. Depending on the severity of symptoms and laboratory test results, the different variants of vWD have been classified by the International Society on Thrombosis and Haemostasis into three different subgroups: type 1, the less severe form of factor vW deficiency (70% of cases); type 2, in turn divided into four variants and the form due to a qualitative defect (20–30% of cases); and type 3, the most severe and rare form of factor vW deficiency (<5%) [26].

6.4 Renal and Hepatic Impairment

Chronic renal impairment can cause menstrual irregularities. In particular, it has been showed that around 80% of women with chronic renal impairment suffer from menorrhagia [27]. There are several factors that can cause the condition to arise: (a) an increase in azotaemia often leads to irregular secondary cycles, to central inhibition of gonadotropins and to a consequent reduction in serum oestradiol levels [28]; (b) elevated levels of prolactin, that occur in around 50% of patients undergoing dialysis (due to reduced clearance), can cause DUB in adolescents with renal impairment [27, 29, 30]; and (c) haematological alterations subsequent to renal impairment (normochromic anaemia, normocytic anaemia due to a reduction in erythropoietin production; increased bleeding time due to a reduction in fibrinogen, platelets and associated uraemia) can cause prolonged and severe bleeding [23, 27, 31].

Similarly, hepatic impairment, either chronic or slowly progressive, can be linked to blood clotting disorders (reduction in vitamin K-dependent blood clotting factors: factors II, VII, IX and X; reduction in levels of protein S, protein C, fibrinogen and platelets) [32] or alterations in hormonal levels.

6.5 Diabetes

Menstrual irregularities, including amenorrhoea, oligomenorrhoea and menometrorrhagia, have been observed in adolescents with diabetes [33, 34]. In fact, hyperglycaemia seems to have an effect on the hypothalamic-pituitary axis, leading to a progressive slowing-down of gonadotropin-releasing hormone (GnRH) pulsatility and a consequent reduction in the pulsatile production of luteinizing hormone (LH) [33–35]. DUB has been observed more frequently in adolescents with poor glycaemic control, especially in those with haemoglobin A1c levels above 12.8 mg/dL or glycaemia above 240 mg/dL [33–35]. In adolescents with insulin-resistant diabetes, DUB is the result of increased peripheral conversion of androstenedione into oestrone, which leads to an excessive oestrogenic response in the endometrium. Similarly, the stimulatory effects of insulin on the ovary increase androgen production, resulting in irregular bleeding of the endometrial mucosa.

6.6 Enteric Diseases

Alterations of the menstrual cycle have been described in patients affected by inflammatory intestinal diseases. In fact, menstrual alterations (oligomenorrhoea, polymenorrhoea, menorrhagia and metrorrhagia) were observed in a group of 360 women suffering from Crohn's disease and 251 suffering from ulcerative colitis in 60% and 53% of the cases, respectively [36, 37]. The aetiology of DUB associated with enteric pathologies is not well understood even though there is a recognised link with the severity of the illness, stress and malabsorption.

6.7 Rheumatic Diseases

Menstrual cycle disorders have also been described in women with rheumatic diseases. When compared with healthy subjects, women with juvenile chronic arthritis have a higher incidence of metrorrhagia: in particular, menstrual disorders generally appear after the onset of the disease [38]. Alterations in the menstrual cycle have also been observed in around 53% of women with Systematic Lupus Erythematosus (SLE) [39]. Increased serum levels of LH and PRL were also frequent in these subjects.

6.8 Cardiac Diseases

In adolescents, another pathological condition that has been associated with DUB is the cyanotic congenital heart disease [40, 41]. The mechanism through which other alterations of the menstrual cycle are induced is currently unknown, although surgical correction time with respect to the menarche period seems to be key. In fact, subjects under 10 years of age at the time of corrective surgery show higher regularity of the menstrual cycle than subjects undergoing correction post-menarche (menstrual cycle become regular only after 6 months following the surgery) [42]. In subjects where the surgical repair is postponed until 6–10 years post-menarche there is an elevated incidence of menstrual cycle alterations, with a predominance of amenorrhoea.

6.9 Neurological Diseases

Polycystic Ovary Syndrome (PCOS) has been increasingly described in adolescents suffering from Temporal Lobe Epilepsy (10–25%) in comparison with control subjects (4–6%) [43, 44]. Furthermore, numerous studies have reported that around 40% of adolescents treated with valproic acid suffer from PCOS and 30% have alterations in the menstrual cycle compared to adolescents treated with other anticonvulsants [43–46]. It is believed that an increase in PCOS and DUB incidence is a direct effect of epileptogenic lesions on the hypothalamic-pituitary axis in

addition to the known effects of some antiepileptic drugs. The exact mechanism involved is not understood, although weight gain linked to treatment with valproic acid could play a role, since it is associated with a reduction of sex hormone-binding globulin (SHBG) and insulin-like growth factor binding protein, which thereby leads to an increase in androgen and PCOS [44–47].

6.10 Thyroid Disorders

It has long been known that thyroid disorders are linked with menstrual cycle abnormalities. An increase in SHBG levels occurs during hyperthyroidism, which leads to a similar increase in serum levels of oestradiol, testosterone and androstenedione [48]. In subjects with DUB, hypomenorrhoea occurs in 52% of cases, polymenorrhoea in 32.5%, oligomenorrhoea in 11% and hypermenorrhoea in 4.5%. Conversely, in subjects with hypothyroidism a reduction in SHBG occurs, leading to a reduced elimination of androstenedione and oestrone and an increase of aromatase activity. The most frequently observed menstrual disorder is menorrhagia, due probably to irregular endometrium growth secondary to an excess of oestrogens [48]. In other cases, it can be caused by reduced levels of factors VII, VIII, IX and XI, thereby further increasing the risk of menorrhagia [48, 49].

6.11 Hyperandrogenic Alterations

It is widely known that androgen excess can cause DUB in adolescents. Sometimes, the presence of menstrual alterations can be the first sign of PCOS or other hyperandrogenic conditions. The most frequent cause of androgen excess in adolescents is PCOS: although the exact prevalence in this population is not known, it occurs in 3–6% of adult women [50, 51]. In addition to insulin resistance, often related to PCOS, two other extreme conditions of PCOS can occur (albeit more rarely): hyperthecosis of the ovary (a condition of hyperandrogenism in which androgen levels are higher while those of LH are lower), and hyperandrogenism, insulin-resistance and *acanthosis nigricans* syndrome (HAIR-AN) [52]. In addition to PCOS, other rare conditions of hyperandrogenism in adolescents are also recognised as a cause of DUB: late-onset Congenital Adrenal Hyperplasia (CAH), Cushing syndrome, androgen-secreting tumours, and hyperprolactinaemia.

6.12 Hyperprolactinaemia

Elevated levels of PRL are able to inhibit GnRH secretion: intermittent secretion of this peptide initially causes luteal phase deficiency together with polymenorrhoea, while amenorrhoea appears when the secretion of GnRH is completely suppressed.

As mentioned above, a hyperandrogenic condition is secondary to hyperprolactinaemia, but it is also possible for prolactin to have a direct effect on the adrenal gland and ovary.

6.13 Treatment

The treatment of DUB is mainly dependent on the cause (endocrine or non-endocrine). The simple correction of the cause is often enough to improve and correct menstrual alteration: it is widely known, for example, that treatment of thyroid disorders leads to a swift return to the normal menstrual cycle. The estimation and consequent correction of blood loss represents the second and crucial therapeutic objective. The most frequently proposed drugs for this specific purpose are listed in Table 6.6.

6.14 Oestrogenic and Combined Oestro-Progestogen Therapies

Oestrogens have long been used as initial therapy against acute DUB, especially since 1982 when a randomised controlled trial showed that 72% of patients who underwent two doses of oestrogen i.v. (12 h apart) stopped bleeding compared to 38% who received a placebo [53]. The single parenteral oestrogen therapy definitely has the advantage of inducing endometrial vasospasm, regenerating the endometrial mucosa and increasing blood clotting factors. Actually, at least in Italy, it is not possible to use it since more than a decade, due to its commercial unavailability. The alternative is the administration of an association of combined oral contraceptive (COC) containing at least 30 mcg of ethinylestradiol, starting with 2–3 pills per day and subsequently reducing it to one pill per day, when bleeding has reduced (after 3–4 days, on average). A review of six randomised controlled trials comparing cyclic and continuous administration of a COC has demonstrated their equivalent efficacy and compliance; however, a significantly reduced menstrual loss was observed in the group who underwent continuous treatment with COC [19, 54]. To date, there are no available data regarding the choice of a COC over another [23].

Table 6.6 Medical therapies used to treat dysfunctional uterine bleeding

• Combined oral contraceptives
• Progestogens
• Tranexamic acid and aminocaproic acid
• Non-steroidal anti-inflammatory drugs (NSAIDs)
• Danazol and GnRH Analogues
• Medicated I.U.D.
• Desmopressin

6.15 Single Progestogen Therapy

In patients with contraindications to oestrogens, progestogen is the only available option. Actually, according to Cochrane, the administration of oral progestogens from the 15th to 26th day of the cycle in subjects with ovulatory cycles does not offer advantages over other medical therapies [tranexamic acid, non-steroidal anti-inflammatory drugs (NSAIDs), Danazol, medicated intrauterine devices (IUD)]. However, their administration can be more effective if prolonged for at least 21 days, despite we should consider their side effects (swelling, weight gain, fatigue, headaches/migraines, mood changes and depression) that limit to three cycles their use [55]. According to National Institute for Health and Care Excellence guidelines, this last method of administration is particularly effective in women with anovulatory cycles and should represent a potential option after non-use of other medical therapies, as a result of intolerance or their failure [56].

As suggested by current literature, especially the American one, among the available progestogens is possible to use high doses of medroxyprogesterone acetate (MAP 20–40 mg × 3/day): the short half-life of the drug (14 h) requires, in effect, its administration at definitely higher dosage, as well as multiple doses spaced closer together. This however, once again, will lead to an unavoidable increase of side effects. For the specific pharmacological characteristics of both the molecules (long half-life: 25–50 h with elevated biological activity in terms of secretory endometrial transformation), an effective therapeutic alternative is the administration of nomegestrol acetate (2.5–5 mg) or of norethisterone (or norethindrone) acetate (5–10 mg). The latter also possesses a unique characteristic, since it can be converted into ethinylestradiol, which is able to enhance the action of endometrial stabilization [57]. In emergencies, high doses of both the molecules are recommended and initially spaced close together. Subsequently, in case of success, doses can be spaced further apart (Table 6.7).

Table 6.7 Emergency treatment for dysfunctional uterine bleeding (Haemoglobin <10 g/dL)

• Combined oral contraceptives containing 30–50 mcg of EE, 2–3 pills/day for 3–4 days, then 1 pill/day as part of an extended regimen
• Medroxyprogesterone acetate 10 mg (up to maximum 80 mg) every 4 h until the end of the bleeding, then every 6 h for 4 days, then every 8 h for 3 days, every 12 h for 2–14 days and every 24 h for the remaining period
• Nomegestrol acetate (2.5–5 mg) or norethisterone acetate (5–10 mg) every 4 h until the end of the bleeding, then every 6 h for 4 days and subsequently every 8 h for 3 days, every 12 h for 2–14 days and every 24 h for the remaining period
• Tranexamic acid: 10 mg/kg i.v. every 6–8 h for 2–8 days or 20–25 mg/kg as oral administration every 8–12 h, for 5–7 days
• Aminocaproic acid: 4–5 g i.v. in 60′ every 8 h until the end of the bleeding (maximum 30 g/day) then 50–100 mg/kg as oral administration every 3–6 h, for 5–7 days

6.16 Tranexamic Acid and Aminocaproic Acid

Due to their ability to inhibit plasminogen conversion into plasmin, these drugs reduce fibrinolytic activity in several body areas, including the endometrium, where they stabilize the blood clots that have formed; at high doses, a reduction of the uterine artery flow has also been described [58, 59]. At a dosage of 15–20 mg/kg, if started on the first day of bleeding in order to promote an immediate platelet and fibrin aggregation, it has favourable safety profile for the management of idiopathic metrorrhagia or for patients affected by coagulopathy [60], with a significant reduction (40–50%) of the menstrual flow [61]. Aminocaproic acid has also been successfully used in the reduction of excessive uterine bleeding, although it is less powerful and causes more significant side effects than tranexamic acid, such as gastrointestinal disorders (nausea and diarrhoea). These side effects are the main cause of treatment cessation or dose decrease, leading to an inevitable reduction in effectiveness. Both the drugs could be considered useful in association with other medical treatments [COC, progestogen, desmopressin (DDVAP)].

6.17 Non-steroidal Anti-inflammatory Drugs

A further non-endocrine therapeutic approach may be the use of NSAIDs (naproxen sodium, ibuprofen, mefenamic acid, etc.). Actually, their effectiveness in adolescent DUB has only been proven in comparison with placebo (600–1200 mg/day) [63], whereas it has not been proven with respect to tranexamic acid and medicated IUD [19, 63]. Aspirin or NSAIDs should never be administered to adolescents with DUB who had abnormal bleedings, until after a complete and accurate assessment (possibly also from the haematological point of view).

6.18 Danazol, Gonadotropin-Releasing Hormone Analogues and Clomiphene Citrate

Danazol and GnRH analogues are particularly effective in reducing heavy menstrual flow; however, due to their well-known side effects (respectively, hyperandrogenism and osteoporosis) they are little used in the adolescent population and only for limited periods, even in association with oestro-progestogen (add-back therapy) [19, 23, 54, 62].

Clomiphene citrate, a selective estrogen receptor modulator (SERM) used as first-line agent for anovulatory infertility in PCOS, was recently proposed as new method to stop and prevent DUB in adolescents. After three cycles of a low-dose therapy in 92% of the treated girls, a complete cessation of bleeding was obtained without any hormonal or ovarian side effects [64].

6.19 Medicated Intrauterine Devices

IUD containing levonorgestrel (LNG-IUD), in addition to their already known contraceptive properties, is currently considered as the most efficient medical treatment for heavy menstrual flow, particularly in women with blood clotting alterations [65, 66]. Since 2007, the American Congress of Obstetricians and Gynecologists (ACOG) [67, 68] has concluded that the available data in literature confirm the safety of IUD, even in adolescents; actually, the experience in the specific treatment of DUB is still scarce. One randomized trial developed in Finland on 200 young patients (18–25 years) with regular menstrual cycles and undergoing treatment with LGN-IUD or COCs found a significant reduction of bleeding in the LGN-IUD group (49.3 vs. 22%; $p < 0.001$), although by subjective evaluation [69]; another study developed in New Zealand on 133 adolescents (11–19 years) found 85% of maintenance rate of device and only 8% of expulsion, comparably with adult population [70], and reduction of bleeding in five adolescents affected by blood clotting disorders (100% of cases), without any relevant side effect apart from well-tolerated, moderate spotting [62]. Menstrual cycle control effectiveness was also described after the use of LNG-IUD in an adolescent suffering from vWD disease refractory to previous treatments with high dose COCs, GnRH analogue, etonogestrel subdermal contraceptive implant and aminocaproic acid [71].

6.20 Desmopressin

Desmopressin is a synthetic analogue of the antidiuretic hormone vasopressin. The molecule is able to increase platelet adhesiveness and plasmatic concentrations of circulating vWF:Ag and FVIII. Its administration is therefore suggested for the prevention and treatment of bleeding in patients affected by vWD and haemophilia. It is administered at home via nasal spray (150–300 μg) or in a hospital environment s.c. or i.v. at a dose of 0.3 μg/kg, however not for more than two consecutive administrations in a 12 h interval. Its administration is also limited to the first 2–3 days of heavy flow, especially for its secondary effects of tachyphylaxis on endothelial vWF deposits, tachycardia, headaches, nausea and fluid retention (risk of hyponatremia). Literature data suggest a greater therapeutic efficacy when administered (at lower doses and therefore with a lower risk of side effects) in association with tranexamic acid, rather than alone [72]. However, its effectiveness is considered to be similar both after single administration and together with COC [62, 73].

Only in case of real failure of the above-mentioned medical treatments, it is possible to perform dilation and curettage of the uterine cavity. Considering also that the risk of endometrial cancer during adolescence is approximately 0.1/100,000 women, this procedure is suggested by the ACOG only for obese adolescents with persistently anovulatory cycles for a period longer than 2 years [74]. Some authors suggest as an alternative to use intrauterine application of a Foley catheter (16–18 French) filled with at least 30 cc of water (Balloon) and maintained in situ for a period no longer than 24 h [75].

Some indications for the management of the differing degrees of DUB have been summarised below for further utility (Tables 6.7, 6.8 and 6.9).

Table 6.8 Treatment of adolescents with minimal or moderate bleeding

Entity of bleeding	Hb (g/dL)	Management/treatment
Minimal (flows longer than normal or shorter cycles for ≥2 months)	>12	• Reassurance. • Menstrual calendar. • Iron supplementation. • Periodic reassessment.
Moderate (moderately prolonged flows or short cycles with frequent flows—every 1–3 weeks)	10–12	• Reassurance. • Menstrual calendar. • Exclude sexually transmitted diseases and blood clotting alterations. • Iron supplementation. • Cyclic progesterone therapy or combined oral contraceptive at low doses. • Reassessment <6 months

Table 6.9 Treatment of adolescents with severe bleeding

Entity of bleeding	Hb (g/dL)	Management/treatment
Severe (without bleeding present)	<10	• Exclude coagulopathies. • Iron supplementation. • Hormone therapy (combined oral contraceptive/progestogen) • Tranexamic acid. • Reassessment <6 months.
Severe (acute haemorrhage)	<10	• Transfusion. • Integrate liquids. • Hormonal haemostasis (combined oral contraceptive 2–3/g for 3–4 days). • Tranexamic acid. • Uterine dilation and curettage if hormonal haemostasis fails (rare). • Follow-up with combined oral contraceptive/progestogen.
Hypovolemic shock	<5–6	• Stabilisation. • Transfusion. • Exclude coagulopathies. • Administration of combined oral contraceptive at higher doses until haemorrhage is blocked • Tranexamic acid • Dilation and curettage, or tamponing with *balloon* in extreme cases

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Menstrual Disorders in Post-menarcheal Girls

7

Francesca Pampaloni and Pina Mertino

Abbreviations

AAP	Atypical AntiPsychotics
ACTH	Adrenocorticotropic hormone
AMH	Anti-Mullerian hormone
BCM	Body cellular mass
BIA	Bioelectrical impedance assessment
BMD	Bone mineral density
BMI	Body mass index
CCK	CholeCystoKinin
CNS	Central nervous system
CRH	Corticotropin-releasing hormone
CVD	Cardiovascular disease
DM	Diabetes mellitus
DXA	Dual energy X-ray absorptiometry
D2	Dopamine receptors 2
E2	Estradiol
FHA	Functional hypothalamic amenorrhea
FMR1	Fragile X mental retardation protein
FSH	Follicle stimulating hormone
fT3	Free thyroxine 3
fT4	Free thyroxine 4
GALT	Galactose-1-phosphate-uridyl-transferase
GLP-1	Glucagon like peptide-1
GnRH	Gonadotropin-releasing hormone
HRT	Hormone replacement therapy

F. Pampaloni, M.D. (✉) • P. Mertino, M.D.
Pediatric and Adolescent Gynecology Unit, Careggi Hospital, Florence, Italy
e-mail: pampa@virgilio.it; pinamertino@gmail.com

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IBD	Inflammatory bowel disease
IGF-1	Insulinlike growth factors-1
LH	Luteinizing hormone
MRI	Magnetic resonance imaging
PCOS	Polycystic ovary syndrome
POI	Premature ovarian insufficiency
PRL	Prolactin
SLE	Systemic lupus erythematosus
TIDA	Tubero infundibular dopaminergic neurons
TRH	Thyrotropin-releasing hormone
TSH	Thyrotropin stimulating hormone
T2DM	Type 2 diabetes mellitus

7.1 Pathophysiology of Post-menarche Menstrual Function

Girls, during adolescence, go through the maturation of a complex endocrinological system, which involves the hypothalamus, the pituitary gland, the ovaries and their interactions. All the above should lead to a healthy reproductive function, but it doesn't occur immediately, so, in postpubertal girls we can find frequent menstrual disorders like polymenorrhea and oligomenorrhea (Tables 7.1 and 7.2) [1–4].

Menstrual irregularity is virtually always the result of anovulatory cycles. However, the opposite is not always true monthly, menstrual regularity does not necessarily indicate underlying regular ovulatory cyclicity. Within 1 year after menarche, menstrual regularity approximates adult standards in most girls, although there is considerable interindividual variation in the time it takes for menstrual cyclicity to mature [1, 4]. Average menstrual cycle length is 21–45 days in 75% of girls 1 year post-menarche, and further 5% falls within these bounds for each of the following 3 years [5, 6]. During the first 2 post-menarcheal years, about half of menstrual cycles are anovulatory, but the duration half of these anovulatory cycles is 21–45 days [2, 3, 6].

Table 7.1 Pathogenesis of menstrual disorders in girls

Functional immaturity	
Central (hypothalamic)	Physical/emotional stress
	Low energetic intake
	Chronic diseases
	CNS organic pathology
Prolactin excess	
Ovary	PCOS
	Hormone secreting ovarian cysts
	POI
Endocrinopathies	Hypo/hyperthyroidism
	Adrenogenital syndrome
	Cushing syndrome
Internal genitalia	Uterine synechiae
	Acquired vaginal stenosis
Pregnancy	

Table 7.2 Definitions

Secondary amenorrhea	Absence of bleeding in girls >180 days, Europe Absence of bleeding in girls >90 days, USA
Oligomenorrhea	Intervals between cycles >45 days (gynecological age > 2 years) Less than 8 cycles per year
Polymenorrhea	Intervals between cycles <21 days

Table 7.3 Normal period

What is a normal period?	Menarche before 15
	Last 1 week or less
	21–45 days from the first day of one period to the first day of the next period
	During bleeding, the girl fills less than one pad per hour

Reproduced with permission from [8]

Thus, normal menstrual frequency is much greater than ovulatory frequency. Within the first 5 gynecological years, 95% of menstrual cycles lasts 21–40 days, and about 75% of cycles are ovulatory; over the next several years the mature menstrual pattern is established with approximately an 80% ovulatory rate. During the following years the menstrual pattern is mature, and consequently ovulatory, in about 80% of cases [2, 3, 6]. As earlier age of menarche is associated with earlier ovulatory maturation, the opposite applies and late maturation [7]. Normally adolescent anovulation causes only minor menstrual cycle irregularity (Table 7.3).

7.2 Functional Immaturity

Normal, pubertal maturation, menstrual function requires a series of neuroendocrine steps involving numerous districts of the body that can provide a physiological latency. Ovarian follicular structures, i.e., granulosa cells and theca cells, may experience a period of mild dysfunction due to the immaturity of their cross-talk mechanisms and, probably, to the elevated stimulus on the ovary by physiologically increased insulin concentrations. In these cases of functional immaturity, androgen production by thecal cells (mainly androstenedione) is increased but their aromatization in estradiol is reduced, leading to a delay in follicular maturation with oligomenorrhea as clinical manifestation.

7.3 Functional Hypothalamic Amenorrhea (FHA)

FHA includes all clinical conditions characterized by stress, low energetic intake, intense physical activity, and chronic disease affecting metabolic homeostasis.

7.3.1 Mean Pathogenic Mechanisms

In a dangerous, acute situation the production of norepinephrine (also responsible for the feeling of fear) from locus coeruleus starts. In the same time, norepinephrine increases production of CRH with activation of hypothalamus–pituitary–adrenal axis and of sympathetic autonomous nervous system. The answer to stressing stimuli is mediated by β-endorphin, even if modulated by genetic variables. All physiological functions not fundamental for survival are restricted, as the ovarian function. The anatomic and functional proximity between GnRH-gonadotropin axis and CRH-ACTH axis allows rapid short inhibitory mechanisms on reproductive function in response to stress hormone hyperproduction. In a chronic stress state, the answer to chronic stimuli is modulated by feedback of rearrangement, acting through the same pathway of increased limbic–hypothalamic–pituitary–adrenal axis activity [9] and reduced central gonadotropin-releasing hormone (GnRH) drive [10–12].

Of note, stress and its resulting hormonal changes could trigger either undernutrition or overnutrition, depending on fuel availability, attitudes about food, and dietary behaviors such as bingeing, purging, overeating, or restricting. The answer to hormonal stress depends on age and weight, for this reason in adolescence it is stronger than in adults.

The energetic homeostasis is another crucial point to allow physiological reproductive function. Vagal nerve is the principal nervous input to central nervous system (CNS); this nerve is connected to gastric distension and cholecystokinin (CCK) and glucose production. Peripheral endocrine signals are various: leptin and adiponectin are signals produced by adipose tissue acting as feedback on hypothalamic nuclei regulating feeding and reproductive control. On the contrary, ghrelin, produced by cells of stomach fundus, is a short-term signal of energetic request. Both leptin and ghrelin play their role, respectively inhibitory and stimulating on appetite center, through arcuate nuclei, probably through pro-opiomelanocortin and the peptides derived from its cleavage. The feedbacks from other peripheral hormones produced by gastrointestinal tract are integrated at hypothalamic level: Peptide YY, GLP-1, Insulin, and Pancreatic polypeptide. These peripheral endocrine messages mix their information to hypothalamus with central afferences (as endocannabinoids and oxytocin).

The inhibitory effect of energetic deficit on hypothalamic function is a key point in menstrual dysfunctions of adolescent athletes, due to strenuous exercise sometimes associated to inadequate energy intake. This can be expressed by inappropriate luteal phase, anovulatory cycles, oligomenorrhea, or secondary amenorrhea. It is important to keep in mind that the same endocrine system that binds energetic restriction and menstrual alteration produces effects on bone turnover, increasing reabsorption and reducing neoformation in the adolescent age, causing a problem in reaching or maintaining peak bone mass.

Amenorrhea, low bone density, and eating disorders, the so-called “Athletic Triade,” expose these girls to high risk of stress fractures. Stress fractures are normally not due a single traumatic event, but to multiple bone stresses. The bones most frequently interested are tibia, metatarsi, and navicular, due to their particular exposure to micro traumatic events.

7.3.2 Diagnosis

Functional hypothalamic amenorrhea is a diagnosis established after exclusion of other conditions having similar manifestation. The diagnostic workup should be based on the history of menstrual disorders. In the majority of cases normal menses with ovulatory cycles are followed by gradual loss of ovulation, then the menses become rare till they completely disappear. A lack of menarche can also be the main manifestation of FHA in early pubertal girls (Chap. 2). A careful clinical history is essential for identifying these patients; familiar osteoporosis, low birth weight, bowel malabsorption, previous fractures, late menarche, and low sun exposition are also important factors for bone mineral density deficiency; the number of hours of physical activity per day or week, eating diary, and menstrual diaries are also useful. Family conflicts, problems with the peers, school difficulties, and stressful events should also be investigated. The measure of height and weight and body mass index (BMI) is fundamental. DXA (Dual energy X-ray Absorption) and BIA (Bioelectrical Impedance Assessment) are useful tools to assess body composition. The impedance assessment is based on low frequency electric energy modifications passing through the body. The attenuation (resistance) is mainly due to the presence of water, which is mainly related to muscle mass. This exam primarily evaluates hydration and nutritional state. Generally, a good hydration should be around 60% and lean mass 78–80%. The measure of fat mass is indirect and for this reason is not totally reliable. Athletic girls often present reduced levels of intracellular water due to thermoregulation induced by physical effort. The body cellular mass (BCM) expresses the metabolically active part of the body: a cutoff level of 7 is considered expression of undernutrition. The DXA total body is a more precise mean of studying body composition, even if it is expensive and minimally radiant. It consents the evaluation of Bone Mineral Density (BMD) using references for age. Ultrasound pelvic is a useful complementary examination because endometrial thickness is an indirect measure of estradiol levels. Ovary echo-structures can be extremely various: multi-follicular or micro-follicular with low vascularization to color Doppler (Table 7.4).

We can use progesterone challenge test to check the endometrial estrogenization [13]; performing the test blood sampling for hormonal profile can take place during bleeding. In the past medroxyprogesterone acetate 10 mg for 10 days has been extensively used: menstrual bleeding could be expected with an endometrial thickness >6 mm. Nowadays micronized progesterone 100 mg/day twice/day for 10 days is preferred, but it doesn't exist yet a definition of endometrial thickness related to the bleeding answer.

Table 7.4 Endocrine clues of FHA

Plasmatic cortisol towards elevated value
LH towards low level with FSH and PRL within normal range
IGF-1 towards low level
fT3 towards low level, fT4 and TSH within normal range
Insulin towards low level with normal glucose levels
FSH and PRL in the normal range

7.3.3 Management

Treatment of menstrual disorders, and secondary amenorrhea resulting from hypothalamic disorders should be aimed at the elimination of the primary cause, i.e., a decrease in psycho-emotional strain, avoidance of chronic stressors, reduction of physical exercise level, or optimization of BMI in patients who lose weight [14].

A cognitive-behavioral therapy can be proposed to help coping with stress response or modifying habits related to diet and physical exercise, working on body image difficulties or problem-solving skills. A reduction of stress response and the restoration of metabolic equilibrium is the main street to resume normal menses and ovulation. Usually, menstrual function resumes spontaneously as a result of lifestyle modification or of environmental changes (e.g., changing school).

If menses do not resume after a period of 6 months or primary causative treatment is not possible, e.g., in competitive athletes or ballet dancers, neutralization of hypoestrogenism consequences especially unfavorable effects on bone metabolism becomes the main issue. Hormonal preparations should be introduced into therapeutic protocol on an individualized basis; the patient's expectations with regard to treatment outcomes should also be considered. In situations with long-lasting low energy intake, the bone sparing effect of estroprogestins is probably ineffective.

7.4 Chronic Diseases

Systemic diseases affecting metabolic homeostasis can induce menstrual dysfunction and bone impairment.

Congenital bile atresia: Rare, inflammatory damage to intra-extra hepatic bile ducts with bile tree sclerosis and narrowing up to obliteration.

Celiac disease: The disease is an immune-mediated inflammatory enteropathy triggered by gluten exposure in genetically susceptible individuals. It has a high prevalence approaching 1% but it is very poorly diagnosed. The enzyme transglutaminase, through deamidation, modifies gluten, so the protein is presented like an antigen and triggers a systemic inflammatory reaction. Several studies have shown that celiac disease, mostly if not recognized, can impair women' reproductive life eliciting delayed puberty, infertility, amenorrhea, and early menopause [15]. Therapy is a gluten-free diet.

Systemic lupus erythematosus (SLE) is an autoimmune disorder; during its active phases, it may affect the hypothalamic–pituitary functioning and reproductive health status. Additionally, cyclophosphamide treatment can affect gonadal function [16].

Inflammatory bowel disease (IBD) is an autoimmune disease related to individual genetic susceptibility, modifications of gut microbiota, and trigger events that modify the physiological immune barrier inducing an inflammatory chronic condition. Menstrual disorders occur commonly in women with Crohn's diseases, linked both to malabsorption and to the elevated inflammatory reaction, present even in the years preceding the diagnosis. In these patients, we prefer the use of progesterone

with natural estrogen rather than hormonal contraceptive due to theirs higher level of thromboembolic risk, related to pathology. The treatment of the underlying condition is the main therapeutic aid.

Chronic kidney disease: Girls with kidney dysfunction often experience menstrual disorders especially patients in dialysis. Malnutrition and modification in body composition are probably the main pathogenetic factors. As a treatment it is possible to use progesterone or progestins.

7.5 Hyperprolactinemia

An increase in circulating prolactin (PRL) levels may reveal itself with menstrual disturbances. 5.5% of menstrual dysfunction in adolescents are due to hyperprolactinemia. Hyperprolactinemia is not a unique disease per se; rather, it has multiple etiologies [17–19] (Table 7.5).

PRL size is heterogeneous in terms of circulating molecular forms. The predominant form in healthy subjects and in patients with prolactinomas is monomeric PRL. Dimeric or big PRL (45–60 kDa), and big-big PRL or macroprolactin (150–170 kDa) correspond to less than 20% of the total PRL Though still controversial, studies indicate that macroprolactin has both low bioactivity and bioavailability [20–23], thus explaining why most patients with increases in macroprolactinemia lack typical symptoms related to hyperprolactinemia [22–24].

Considering prevalence, prolactinoma is the most common cause of chronic hyperprolactinemia, followed by drugs stimulating PRL production, pseudoprolactinoma, pregnancy, and primary hypothyroidism.

Prolactin secreting pituitary adenomas or prolactinomas represent the most common type of pituitary adenoma (about 40%) being the main cause of pathological hyperprolactinemia [17–19]. Pituitary adenomas secreting PRL can be distinguished in micro if they are <10 mm and macro if they are bigger than 10 mm.

The term pseudoprolactinoma is comprehensive of all compressive situations that disrupt or reduce inhibitory connections (Tubero Infundibular Dopaminergic neurons or TIDA) between hypothalamus and pituitary. They may be not functioning adenomas, tumors as craniopharyngiomas, traumatic lesions, infective, infiltrative or vascular pathologies that reduce the hematic flow or directly damage the neurovascular bundle.

Table 7.5 Causes of hyperprolactinemia

Pituitary macro/microadenoma	PRL secretion or multiple endocrine secretion
Pseudoprolactinomas	Tumors, infiltrative lesions, vasculitis, traumatic outcomes
Hypophysitis lymphocytic autoimmune	Consequence of inflammatory process
Empty sella syndrome	
Primary hypothyroidism	
Idiopathic	
Drugs	

Autoimmune lymphocytic hypophysitis is generally the consequence of an inflammatory process affecting the whole gland or only the infundibular-posterior region, with autoimmune partial parenchyma destruction and consequent hypofunction. It can alter menstrual cycle both through with hyperprolactinemia and low level of FSH and LH.

A primary empty sella syndrome is characterized by the increase of cerebrospinal fluid through a hole in the sella diaphragm, with compression of pituitary parenchyma. It is often asymptomatic, but it can sometimes appear with hyperprolactinemia and intracranial hypertension. Secondary empty sella is mainly related to hypophysitis.

In case of untreated primary hypothyroidism, we can register an increase of prolactin due to drag effect of TRH.

We define an idiopathic hyperprolactinemia if specific causes are not evident and the imaging is negative; in about 30% of cases, the levels of the hormone will reestablish spontaneously.

A high level of prolactin due to drugs is very common in the adolescent girls. Drugs act through different mechanisms: increased transcription of PRL gene (*estrogens*), antagonism of dopamine receptor (*risperidone*, *haloperidol*, *metoclopramide, domperidone, sulpiride*, etc.), dopamine depletion (*reserpine, methyldopa*), inhibition of hypothalamic dopamine production (*verapamil, heroin, morphine, enkephalin analogs,* etc.), inhibition of dopamine reuptake (*tricyclic antidepressants, cocaine, amphetamine, monoamine oxidase inhibitors*), inhibition of serotonin reuptake (opiates, fenfluramine, fluoxetine, sibutramine), etc. [19, 26–31].

Among antipsychotics, the most frequently involved are haloperidol, phenothiazine, and risperidone, while tricyclic drugs are the main observed among the antidepressants. Other studies [26] found the following rates of hyperprolactinemia associated with each therapeutic drug class: 31% neuroleptics, 28% neuroleptic-like drugs, 26% antidepressants, 5% H2-receptor antagonists, and 10% other drugs. The newer atypical antipsychotics (AAP) are characterized by increased antipsychotic efficacy, and fewer neurological and endocrine related side effects as compared to classical antipsychotic drugs. With the exception of risperidone, amilsulpride, and molindone that are often associated with high PRL levels [32], most of AAP elicit poor hyperprolactinemic response or no hyperprolactinemia at all [28]. Furthermore, addition of drugs like quetiapine and aripiprazole has been shown to reverse the hyperprolactinemia induced by other AAPs [29].

The evaluation of drug-induced hyperprolactinemia can be challenging; it is noteworthy to consider the concomitance of a pathologic cause. In an ideal situation, if the severity of the disease consents and is corroborated by a psychiatrist, it is recommended to perform repeated PRL measurements after discontinuing the medication for at least 3–4 days. When drug withdrawal is unsafe, an MRI should be performed to rule out a sella mass. If drug-induced hyperprolactinemia is confirmed, the switch to an alternative medication is the safer option [25, 30].

7.5.1 Diagnosis

The diagnosis of hyperprolactinemia is based on repeated findings (two at least) of an increase of PRL serum concentration (above 25 ng/ml or 600 UI/l in women). Blood samples should be collected in the morning in the patient in fasting state, who should be in a comfortable setting after a good night's sleep at least 2–3 h after waking up (samples drawn earlier may show sleep-induced peak levels). The TSH and IGF-1 dosage is a useful tool to confirm the diagnosis. Magnetic resonance imaging (MRI) with gadolinium as a contrast mean virtually visualizes all macroprolactinomas (diameter ≥10 mm) and pseudoprolactinomas, as well as most microprolactinomas (diameter <10 mm) [32–34]. In case of macroprolactinomas is worth a check of visual field.

7.5.2 Therapy

D2 receptor agonists induce the inhibition of stored PRL and the reduction of its synthesis and secretion through suppression of gene. A daily dopamine agonist administration can produce side effects such as nausea and vomiting; for these reasons it is worth starting with the lowest dose, monitoring the hormone plasma levels. Bromocriptine is less effective in adolescent microadenomas. Cabergoline is the drug of choice because it is characterized by a long half-life, low clearance and enterohepatic circulation.

The treatments with dopaminoagonist could, even if rarely, cause cardiac valves' lesions, so an echocardiogram in prolonged treatments is recommended. In patients with hyperprolactinemia, we can use also oral estroprogestin. In case of no symptoms, with negative imaging, the necessity of therapy is under debate.

7.6 Secondary Menstrual Disorders

In case of *Congenital Adrenal Hyperplasia,* menstrual cycles are irregular for higher levels of progesterone in follicular phase.

Cushing Syndrome is not so common in adolescent period and it is characterized by high level of cortisol. An increase in free urinary cortisol is required for the diagnosis.

7.6.1 Dysfunctional Thyroid

Hashimoto's thyroiditis (HT), the most common autoimmune thyroid disease at any age, is often associated with other autoimmune diseases.

Girls with hypothyroidism suffer from menstrual irregularity three times more than general population. In hypothyroid patients, TRH increases stimulation of both TSH and PRL and a deficit in LH production with inadequate luteal phase has also

been observed; reduction of SHBG, estradiol and testosterone circulating levels reduce endometrial growth.

In case of hyperthyroidism, we can find higher level of estrogen due to increase of SHBG and heavy menstrual bleeding.

7.7 Premature Ovarian Insufficiency (POI)

Numerous studies are available on the pathophysiology of premature ovarian insufficiency (POI). Spontaneous POI involves the precocious cessation of normal ovarian function, causing infertility, menopausal symptoms, and general health concerns. It affects approximately 0.1% of women under 30 years [35, 36].

There are multiple etiologies for primary POI, including genetic, autoimmune, and idiopathic presentations, but also iatrogenic related to chemotherapy or radiation, or pelvic surgery.

In adolescent girls, gonadal dysgenesis revealing after menarche is a frequent cause of gonadal defect (see Chap. 4). The most common genetic cause of POI is Turner syndrome, affecting about 1: 2500 girls [37] characterized by aneuploidy of X chromosome. But spontaneous 46, XX POI with ovarian insufficiency in girls with normal karyotype is frequent and related to various gene mutations related to X chromosomes or to autosomes.

A premutation in the Fragile X Mental Retardation 1 (FMR1) gene is responsible for an estimated 2–5% of cases of isolated sPOI and 14% of familial sPOI cases [37, 38]. The FMR1 gene contains a polymorphic trinucleotide (CGG): more than 200 CGG repeats cause fragile X syndrome, the most common heritable form of mental retardation. The FMR1 gene premutation, which may expand to the full mutation across generations, contains 55–199 CGG repeats, and entails about 24% risk of developing POI in carriers [37].

Approximately 4% of sPOI cases are due to lymphocytic autoimmune oophoritis caused by autoimmunity against steroidogenic cells, a process that may affect function of both the ovary and the adrenal glands [39, 40].

Classic galactosemia (ORPHA-79239) is caused by deficient activity of galactose-1-phosphate uridyl transferase (GALT), as a result of mutations in the GALT gene located on chromosome 9p13. GALT is the second of the three enzymes in the Leloir pathway, the main pathway of galactose metabolism. The incidence of classic galactosemia varies between 1:16,000 [41] and 1:60,000 [42] in Western countries. Galactose is needed for energy metabolism and glycosylation of complex molecules. It may be derived from exogenous (dietary) sources, most importantly lactose from dairy products, or endogenous production. Deficiency of the GALT enzyme leads to accumulation of galactose and its metabolites and results in secondary glycosylation abnormalities. Patients usually present in the first weeks of life with signs of liver and renal disease, cataracts, and an Escherichia coli sepsis. Diagnostic tests include elevated galactose and galactitol in body fluids, elevated Gal-1-P in erythrocytes, severely diminished enzyme activity in erythrocytes, and mutations in the GALT gene. A galactose-restricted diet quickly resolves the early

signs, but cannot prevent the development of later-onset complications, such as cognitive impairment, neurological sequelae, bone health abnormalities, and, in female patients, POI with subsequent infertility. Although POI in classic galactosemia represents a major concern for these patients and/or their parents [43], there are no published recommendations concerning fertility preservation in this group [44].

Symptoms of POI differ between affected women, varying from subfertility, to early development of irregular menstrual cycles and infertility, to primary amenorrhea and absence of spontaneous puberty [45]. The cause of POI in classic galactosemia is not yet understood. Several mechanisms have been postulated, including direct toxicity of metabolites (i.e., galactose-1-phosphate), altered gene expression, or aberrant function of hormones and or receptors due to glycosylation abnormalities [46–49]. It is also possible that not one, but several mechanisms act in unison to cause POI in classic galactosemia.

In general, POI can be caused by either the formation of a smaller primordial follicle pool or more rapid loss of primordial follicles [45] and there is evidence for both mechanisms in classic galactosemia. In classic galactosemia, there is some evidence that the follicle pool at birth is as large as in girls without this disease [44].

An immune-mediated premature ovarian insufficiency could be associated in some case of thyroidits immune-mediated, Addison and dyabets and many others immune-mediated disease. Many targets have been identified in the ovary: steroid secretion, gonadotropin, and oocyte. Many of the health complications associated with POI are directly related to ovarian hormone deficiency, primarily estrogen deficiency. They include menopausal symptoms (hot flashes, night sweats, insomnia, dyspareunia, decreased sexual desire, and vaginal dryness), decreased bone mineral density (BMD) and increased risk of fracture, infertility, increased risk of mood disorders, namely, depression and anxiety, cognitive decline, sexual dysfunction, increased rates of autoimmune disease, increased risk of cardiovascular disease, increased risk of type 2 diabetes mellitus (T2DM) or pre-DM, and dry eye syndrome [39].

7.7.1 Diagnosis

The most commonly applied definition of POI is 4 months of amenorrhea, with serum levels of FSH greater than 40 IU/L on two occasions. Dosage of FSH >30 UI/l twice, even if an FSH level >15 UI/l in adolescent, is already significant for an ovarian damage. The level of anti-mullerian hormone (AMH) produced by granulosa cells follicle can give us an estimate of ovarian reserve.

Pelvic ultrasound is useful to measure ovarian volume and to perform the antral follicle count. Ovarian volume in these patients is reduced, and cutoff is <6 cm^3; antral follicles are those with diameter between 2 and 10 mm; in a normal condition they should be between 3 and 8 per ovary. The minimum amount in both ovaries is 10 antral follicles.

In case of autoimmune etiology, we must check autoantibodies. Generally, we check autoantibodies directed to ovarian cell, against thyroglobulin, TRH, adrenal cells, and gastric mucosa.

In these patients it is also important to measure basal bone mineral density (especially in patients treated with chemotherapy during infancy), and to propose specific counseling for bone loss prevention: physical activity, diet, and vitamin D supplementation if required.

Genetic counselling, extended to other familiar, is particularly useful in case of FMR1 premutation; but it could be of interest also in X aneuploidies or other known mutations.

In subjects with previous antineoplastic treatment a thorough clinical and laboratoristic evaluation, considering also thromboembolic risk, is mandatory before choosing the hormonal therapy. A cardiological evaluation after chemotherapy in case of use of cardiotoxic drugs is also advised. In subjects recovered from Hodgkin disease extended to mediastinal area, we recommend strict mammary control for the well-known higher risk of breast cancer after radiotherapy.

If it is possible for a very precocious diagnosis we can suggest the patient an oocyte cryopreservation.

In case of POI, the communication of the diagnosis with the patient is very heavy, because they often do not accept their condition and can remove the information we give them. In our experience the possibility of a psychological counselling is precious.

7.7.2 Therapy

It is widely accepted that the mainstay of treatment of POI is hormone replacement therapy (HRT). The choice of HRT should closely mimic normal ovarian steroid hormone production and provide sufficient levels of E2 to reduce menopausal symptoms, maintain bone density, minimize psychologic impacts of estrogen deficiency, and protect against early progression of CVD and dementia [37]. In these patients it is very important for a very precocious start of hormonal therapy for ensuring a correct genital tropism and minimizing endothelial dysfunction due to hypoestrogenism. For these patients, especially those with presumptive autoimmune disorder, the possibility of pregnancy is very low but it exists and we have to inform them about it.

We usually prescribe oral or transdermal estradiol; the transdermal route is more advisable if a minimal venous risk is suspected. Risk of venous thromboembolism is increased by oral estrogen compared with transdermal estrogen use [35, 50–53].

An adequate dosage for estradiol in this age range is about 75–100 mcg transdermal and 1.5–2 mg per os daily. The individual variability of absorption, especially for oral route, is very wide. So we suggest to check the clinical answer through ultrasound examination evaluating uterus dimension and endometrial thickness and, in some cases, the dosage of 17 β estradiol in precocious follicular phase.

The progestin component of HRT for women with POI should be cyclical and will protect the endometrium by inducing regular withdrawal bleeds. Natural progesterone or dydrogesterone is preferable because of the low metabolic impact. HRT should be continued until the age of natural menopause, at which time the dose may be tapered to postmenopausal levels or stopped, depending on a woman's specific risks and needs.

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Eating Disorders in Adolescence

8

Vincenzina Bruni and Metella Dei

Abbreviations

ADH	Anti diuretic hormone
ALMI	Appendicular Lean Mass Index
AMH	Anti-Mullerian hormone
AN	Anorexia nervosa
ARFID	Avoidant/restrictive food intake disorder
ARP	Agouti-related protein
BCMI	Body Cell Mass Index
BIA	Body impedance assessment
BMC	Bone mineral content
BMD	(areal) Bone mineral density
BMI	Body Mass Index
BN	Bulimia nervosa
CCK	Cholecystokinin
DSM	Diagnostic and statistical manual of mental disorders
DXA	Dual X-ray absorptiometry
ED	Eating disorders
FFM	Fat free mass
FSH	Follicle-stimulating hormone
FT_3	Free 3-jodo-thyronin

V. Bruni
University of Florence, Florence, Italy
e-mail: vbruni@unifi.it

M. Dei, M.D. (✉)
Italian Society of Pediatric Adolescent Gynecology E.B,
Florence, Italy
e-mail: meteldei@alice.it

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Gh	Growth hormone
GI	Gastrointestinal
GLP-1	Glucagon-like peptide 1
GnRH	Gonadotropin-releasing hormone
IGF-1	Insulin-like growth factor
IGFBP	Insulin-like growth factor binding protein
LH	Luteotropic hormone
NPY	Neuro peptide Y
PP	Pancreatic polypeptide
REE	Resting energy expenditure
SGOT	Serum glutamic oxaloacetic transaminase
SHBG	Sex hormone binding protein
SRIs	Serotonin reuptake inhibitors
TBW	Total body water

8.1 Definition and Pathogenesis

There is increasing evidence that distress about shape and weight, behaviours of food restriction, and loss of control over eating are more common than previously thought in very young people [1]. The epidemiology and the real impact of these ED behaviours in pre-adolescents and adolescents is probably not clear because it is partially an underground phenomenon. Moreover, different behaviours such as food avoidance, strenuous exercising, and bingeing episodes are often mixed, so our current diagnostic categories could not be sensitive enough for this age group. For a general diagnostic framework, we refer to the DSM5 criteria [2] summarized in Table 8.1.

In adolescents strictly selective food intake, recurrent functional gastrointestinal symptoms impairing normal feeding and physical activity measured on estimated caloric intake are very common behaviours. Therefore, they often move in a "grey area" of eating disorders, sometimes presented as healthy habits, more difficult to discover.

From the point of view of the gynaecologists, the identification of an ED is pivotal in clinical situations where the reduced energy availability disrupts hypothalamus-pituitary-ovarian axis function inducing pubertal delay or amenorrhoea. It is important to stress that all eating disorders, especially bingeing, are associated with later overweight and gaining weight could promote the clinical expression of a polycystic ovary syndrome. The emergence of these disorders is mainly the consequence of several promoting factors acting during infancy, pubertal development, and early adolescent years. The knowledge of different pathogenic and risk factors is important to orient the history taking. Various studies have put in evidence the possible genetic transmission of vulnerability to ED, so girls coming from family where restrictive disorders or bingeing or struggling for being overweight are common are at risk for unhealthy relation with feeding. Recent

Table 8.1 DSM5 criteria for ED

Anorexia nervosa (AN)	Persistent restriction of energy intake leading to significantly low body weight. Intense fear of gaining weight or of becoming fat or persistent behaviour that interferes with weight gain. Disturbance in the way one's body weight or shape is experienced, undue influence of body shape and weight on self-evaluation, persistent lack of recognition of the seriousness of the current low body weight.
Bulimia nervosa (BN)	Recurrent episodes of binge eating: eating, in a discrete period, an amount of food that is definitely larger than most people would eat with a sense of lack of control over eating during the episode. Recurrent inappropriate compensatory behaviour to prevent weight gain (self-induced vomiting, misuse of laxatives, diuretics, or other medications, fasting, or excessive exercise). Self-evaluation is unduly influenced by body shape and weight.
Binge eating disorder (BED)	Recurrent episodes of binge eating not associated with the recurrent use of inappropriate compensatory behaviours. Binge Eating Disorder is associated with more subjective distress regarding the eating behaviour
Avoidant/restrictive food intake disorder (ARFID)	Persistent failure to meet appropriate nutritional and/or energy needs associated with: Significant loss of weight or failure to achieve expected weight gain or faltering growth in children Significant nutritional deficiency Dependence on enteral feeding or oral nutritional supplements Marked interference with psychosocial functioning
Other specified feeding or eating disorder (OSFED)	*Atypical Anorexia Nervosa*: all criteria are met, except despite significant weight loss *Night Eating Syndrome*: Recurrent episodes of night eating (…)

evidences pointed out the possibilities of epigenetic modifications occurring in the intrauterine life or related to adverse events in childhood. Sexual abuse, maltreatments, and neglect are frequent in the history of subjects with emotional feeding and tendency to loss of control [3, 4]. The genetic background and the family climate influence the development of typical personality traits that in subjects with tendency to restrictive eating are shyness, insecurity, cognitive rigidity, perfectionism, and respect for rules. In subjects with tendency to bingeing, depressed mood, low self-esteem, high stress reactivity are described. The comorbidity with anxiety disorders is elevated in all the cases. The increase of steroid hormones in post-pubertal years seems to facilitate the clinical expression of ED, with a critical peak between 13 and 17 years. Social pressure on thinness and fitness play a major role in the spread of attention to body image and caloric control. The current feminine dominant models ever-present in the messages of the mass media and the social networks magnify the difficulties with the changes of body image typical of adolescence.

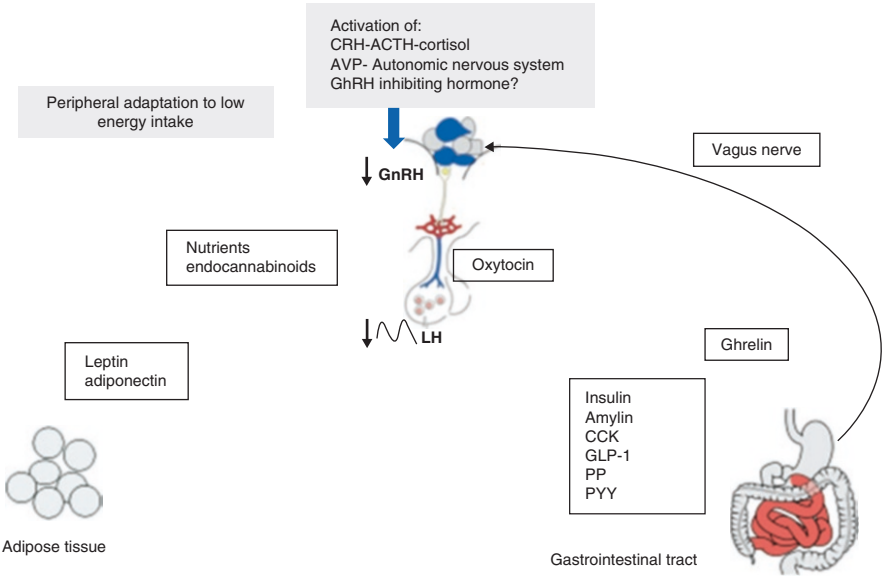

Fig. 8.1 Simplified overview of peripheral signs of energy availability to hypothalamic centres

The hypothalamus-pituitary centres are highly sensitive to energy availability. The evolution in all living beings has selected homeostatic mechanisms to avoid reproduction in circumstances at risk of failure. In humans, several sophisticated feedback mechanisms (Fig. 8.1) link growth, pubertal maturation, and menstrual function to signals coming from fat, GI tract, and stress response activation, in order to consent ovarian activity only when a metabolic equilibrium is present [5–7]. The same mechanisms, with similar thresholds, control the neo-apposition of bone mass and consequently reduce bone turnover. Oestrogen deficiency and hypercortisolism promote bone resorption. Physical hyperactivity, use of SRIs, specific nutritional deficiency, and genetic predisposition are additional pathogenic factors. These adaptive repercussions of energy deficiency are particularly evident in very young girls during puberty or in the first years of gynaecological age [8].

For the following hormones, a key role in response to food restriction is well documented in human beings:

1. Leptin a protein hormone [9] produced by adipocytes in a pulsatile fashion regulates food intake at hypothalamic level stimulating the production of anorexigenic hormones (NPYY, ARP) and indirectly inhibits the production of GnRH during pubertal maturation (threshold effect) and during the fertile period of life. This hormone displays multiple regulatory functions on ovarian folliculogenesis, bone marrow, bone turnover, and on liver triglycerides metabolism.
2. Ghrelin an orexigenic peptide [10] produced by specific cells in stomach and duodenum increases hunger and stimulates food intake. It acts on neuropeptide NPY and, unlike many other endogenous peptides, is able to cross the blood–brain

barrier. Moreover, Ghrelin produced inside the CNS, stimulates growth hormone and is involved in stress reaction; the peptide is also a stimulus on osteoblasts formation.
3. Insulin [11] the protein hormone produced by endocrine pancreas, besides the well-known effects on glucose cell uptake and fat deposition, acts at hypothalamic level as a sign of energy availability and is involved in the gratification related to food experience.

Other gastrointestinal peptides (PP, GLP-1, amylin, PYY), oxytocin, produced by neurohypophysis but not exclusively, endocannabinoids, adiponectin, and various nutrients (glucose, specific amino acids, long chain fatty acids) all interact [12] in the signalling of energy status to CNS. The adaptive response to energy deficiency is mainly based on:

1. The activation of autonomic nervous system, comprehensive of secretion of adrenalin by adrenal medulla, with imbalance of the sympathetic/parasympathetic physiological equilibrium (mainly reduced sympathetic/exaggerated parasympathetic nervous system activity)
2. The increased activity of CRH-ACTH-cortisol axis as a trigger of stress reaction, a modulator of behavioural and metabolic adjustments, an inhibitor of GnRH activity and of bone reabsorption
3. The reduction of peripheral conversion of thyroxine in 3-jodo-thyronin (FT_3 the bioactive form) in peripheral tissues
4. The uncoupling at hepatic level between Gh stimulus and IGF-1 production; the reduced IGF-1 concentrations slow down all mitotic processes in the body.

8.2 Diagnostic Work-Up

The assessment of an adolescent with suspected ED should start with a comprehensive history and a complete physical examination.

The history should focus on:

- Psychiatric disorders, weight concern, or food habits in the family
- Family conflicts or difficulties in recognizing and managing emotions
- Growth and nutritional problems in infancy
- Previous overweight and recent weight changes
- Stress, depression, or bereavement
- Perfectionism, obsessive traits
- Selective eating
- Functional or painful gastrointestinal disorders
- Diseases requiring food control (diabetes, coeliac disease…)
- Quality and quantity of physical activity
- Body reaction to cold (Raynaud phenomenon)
- Recent fainting fits
- Use of drugs or nutritional supplements

The physical examination can also be perfectly normal if the ED is at its beginning, but it is important to check, just with a handshake, the finger temperature, to consider the dryness of skin appendages, to look at the clothes (if baggy or layered). The signs of autonomic dysregulation are rather precocious: bradycardia, orthostatic hypotension.

The measurement of BMI is the starting point of body evaluation, but even if 18.5 has been proposed as a cut-off for menstrual function, this figure is only approximate. If the history does not give clear evidences, it is useful to propose an evaluation of body composition. A rapid, non-invasive and relatively low-cost method of orientation is the BIA. The technique determines the body tissue electrical impedance, which can be used to calculate an estimate of Total Body Water (TBW) and to derive Fat-Free Mass (FFM) and, by difference with body weight, Body Fat (BF). It must be kept in mind that dehydration is a recognized factor affecting BIA results and that moderate exercise before the measurements lead to an overestimation of fat-free mass and an underestimation of body fat percentage; an extremely reduced BMI is another limit to application of this method. BIA has a good accuracy in the prediction of resting energy expenditure (REE), the esteem of the energy required from the body in 24 h, always reduced as adaptation to negative energy balance, traditionally measured by calorimetry. As additional assessment the BCM, the measure of metabolically active body cells inside FFM, indexed to height, if lower than seven is a clue of catabolic phenomena. BIA (and BCMI) is also very useful for tracking body composition in an individual over a period [13, 14].

The US scan points out the degree of functional regression of internal genitalia. Reduced uterine size and endometrial thickness reveal the hypo-oestrogenization. Ovarian structure is often multifollicular (Fig. 8.2) in response to adaptation to reduced energy availability or during weight recovery. In situations of serious energy deficiency, the ovaries may appear compact; liver steatosis, evident as a diffuse increased echogenicity, is also often present due to the accumulation of triglycerides within hepatocytes. In anorexia nervosa can be useful to control the kidney to exclude a nephropathy linked to hypokalaemia and malnutrition.

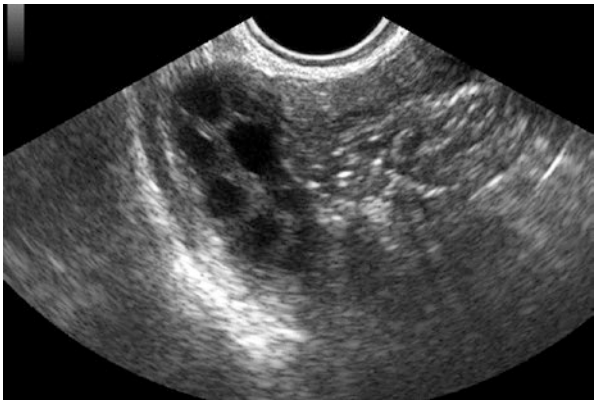

Fig. 8.2 Multifollicular ovary (slightly increase volume, multiple follicles of diameter >8 mm, without stroma visualization)

Routine blood tests can be normal if the metabolic situation is not particularly compromised; alterations are present when catabolic processes take place: an increase in albumin with a decrease in globulins, a relative increment in creatinine and liver enzymes, especially SGOT. A reduction in white blood cells and erythrocytes is present when the medulla function is impaired. Total cholesterol can be elevated because of mobilization of fat stores; high ferritin concentrations are a marker of inflammatory status. In special conditions, specific nutritional markers can be tested as retinol binding globulin and transferrin. The monitoring of plasma electrolytes is mandatory in case of suspect of purging behaviours (vomiting or laxative abuse) or during weight rehabilitation, together with amylase dosage. Standard urine analysis can show higher concentrations linked to dysregulation of ADH with altered osmoregulation.

The endocrine profile is typical of functional hypothalamic amenorrhoea, with low LH levels, normal FSH and, if tested, estradiol levels near the lower range. Prolactin is in the normal–low range and AMH is normal, as follicular reserve is intact. For diagnostic purpose, the profile of hormones involved in metabolic adaptations is more discriminating. Plasma levels of FT3, IGF-1, insulin (testing glucose concentrations at the same time) are generally reduced, while IGFBP 1 and 2 and SHBG are increased. Cortisol production is always increased, but the elevation is more evident if blood sample is collected in the late afternoon or using salivary assay at awakening [15]. The measure of Ghrelin and leptin is rarely disposable in clinical practice.

As previously mentioned, the adolescents with restricted eating experience a reduction in bone mass within 6–8 months; there is a preferential loss of trabecular bone which is more metabolically active and has a higher turnover, evident at the lumbar spine, but also cortical bone is involved. In pre-pubertal adolescents, ED can cause interruption of linear growth with reduction of bone size accrual. Therefore, an evaluation of bone mineral density is useful to control eventual bone loss. The lumbar spine and total body less head are the preferred skeletal sites for performing BMC and areal BMD measurements. In this age group, we refer to the *Z*-score, using a specific reference derived from a young, race, and sex-matched population. In girls with growth delay, the spine and total body BMC and BMD should be adjusted using the height *Z*-score or for spine using the volumetric BMD. In subjects with serious malnutrition too, the reduced periosteal bone apposition impair the vertebral body volume more than the area, requiring similar correction. Lean mass hypo hydration could be another variable affecting the measurement. Soft tissue measures (body fat and lean body mass) derived from whole body scans may be helpful for an evaluation of body composition more accurate than using BIA: according to guidelines, lean mass can be better estimated using appendicular lean mass divided by height square (ALMI) using specific *Z*-score [16].

Quantitative ultrasound bone evaluation is primarily a research technique and the results in this population are higher than in controls and unrelated to DXA measures.

Nail fold video-capillaroscopy is sometimes useful to distinguish hyperactive arteriovenous anastomosis due to adaptive response to energy deficiency from patterns related to connective tissue disorders.

8.3 Therapeutic Management

Menstrual dysfunction is sometimes the first sign of an eating disorder, especially when the restriction of food intake is not dramatic. Bulimia nervosa is more difficult to recognize because the repercussions on endocrine equilibrium are fainter; but the need for early diagnosis is anyway present for the high comorbid rates of mood disorders and suicidality. Therefore, the ability of the gynaecologist or the paediatrician that meet the girl to identify the real problem is paramount. The first rule is to leave enough time for listening to both the parents and the daughter, preferably not together.

When a clear diagnosis is made, it is important to find the words to explain the relationship between nutritional state and amenorrhoea as a sign of loss of equilibrium and to motivate the girl to start a therapeutic plan.

The management of an ED should always be multidisciplinary and co-ordinated. Weight restoration is the main therapeutic objective [21]. Nutritional advice and counselling can be the first step when the feeding control and the psychosocial impairment are not extreme, with ongoing medical monitoring. Outpatient supportive psychological counselling for the girl and, eventually, for her caregivers is generally advisable. For younger patients, family therapy and interventions are proposed.

In subjects with AN or significant nutritional deficiency or with frequent binge eating and purging, different levels of care are required. An initial assessment of the severity of the health repercussions of the disorder can require the cooperation of other physicians [17]. A cardiologic evaluation is generally necessary when the weight loss is significant, for the risk of precocious functional anomalies, as a minimal reduction of the heart output, a lengthening of QT, arrhythmia due to electrolytes disturbance, and secondary mitral valve prolapse. Severe physical and psychiatric conditions may suggest hospitalization (Table 8.2); intensive treatments in a residential facility or day treatment programmes in a specific ED Unit can be therapeutic options in less severe situations. We refer to specific references for the discussion of efficacy of treatment [18–20].

Reaching and maintaining a target weight (around 20–25th BMI percentile for age and for specific population) restoring physiological body composition is a fundamental step for the return of menses; subjects previously overweight need probably higher weight goals [22]. Metabolic hormones (FT3, IGF-1, cortisol) levels in the normal range are generally a prerequisite.

The bone mass restoration is a slower process and requires long time of follow-up (more than 1 year) to be detectable [23]. Situations of partial weight recovery with irregular menses and bone density long-lasting deficiency are quite frequent. Moderate bone-loading exercise after a certain weight rehabilitation can be useful. It is still a matter of discussion the opportunity to treat adolescents with hypo-oestrogenism related to energy deficiency with hormonal or non-hormonal treatments, mainly to contrast bone loss. In Table 8.3, we synthetized the therapeutic proposal and their results.

Moreover, few data point out that oestrogen substitution may facilitate response to psychiatric or pharmacological interventions [29], beyond its positive effects on urogenital atrophy. According to the current state of knowledge, oestrogen therapy

Table 8.2 Indications supporting hospitalization in a girl with ED

• BMI ≤ 75% for age
• EKG serious abnormalities
• Severe bradycardia and hypotension
• Dehydration
• Electrolytes disturbance
• Hypoglycemia
• Hypothermia
• Infections
• Uncontrolled vomiting
• Acute complications of malnutrition: syncope, seizures, pancreatitis …
• Food refusal
• Uncontrollable bingeing and purging
• Severe depression, suicidal ideation
• Necessity to be far from family
• Comorbid psychiatric conditions
• Failure of outpatient treatments

Table 8.3 Proposal for therapeutic options for contrasting bone loss in ED

Treatment	Efficacy and remarks	Reference
Combined hormonal contraceptives (20–35 mcg EE)	As monotherapy not effective on prevention of bone loss	Golden et al. [24]
DHEA 50 mg/day	More effective in association with oestrogens or oestroprogestin	DiVasta et al. [25]
Recombinant Human IGF-1	Effect dose dependent: 30 mcg/kg × 2 effective on markers of bone formation 100 mcg/kg × 2 effective on markers of bone formation and resorption	Grinspoon et al. [26]
Calcium and vitamin D supplementation	Effective only in case reports	
Alendronate 10 mg/day	Associated with calcium and vitamin D; effective but weight restoration remains a significant variable. Reserve for long-term safety in young people.	Golden et al. [27]
Physiological oestrogen-progestin replacement therapy: 100 mcg E2 patch twice weekly + MPA 2.5 mg 12 days every month	Transdermal estradiol therapy seems more effective than oral, probably because of the lack of suppression of hepatic IGF-1 synthesis. The bone catch-up in not complete.	Misra et al. [28]

alone cannot correct the multiple factors contributing to bone loss in subjects with energy deficiency, substituting to the effect of weight recovery. In few cases, it may provide a sense of reassurance because the patient has regular menstrual period and feels protected against osteopenia, which may reduce the efforts to rehabilitate her weight.

In conclusion, oestrogen-progestin replacement or physiological puberty induction in younger girls, with low dosages and always using transdermal estradiol, can be options to consider, if prescribed in agreement with the psychologist caring for the girl.

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Diagnosis of Polycystic Ovarian Syndrome in Adolescence

9

Anna Maria Fulghesu, Cristina Porru, and Elena Canu

Abbreviations

A	Androstenedione
AES	Androgen Excess Society
AFC	Antral follicular count
AMH	Anti-Mullerian hormone
CAH	Congenital adrenal hyperplasia
FAI	Free Androgen Index
FNPO	Follicle number per ovary
FNPS	Follicle number per ovarian scan identified as a median
MFO	Multifollicular ovary
NIH/NICHD	National Institute of Health/National Institute of Child Health and Human Development
OGTT	Oral glucose tolerance test
PCOM	Polycystic ovarian morphology
PCOS	Polycystic ovarian syndrome
S/A	Ovarian area in median section (A) and stroma area in the same picture (S)
T	Testosterone
US	Ultrasound

A.M. Fulghesu (✉) • C. Porru • E. Canu
Dipartimento di Chirurgia, Università degli Studi di Cagliari, Cagliari, Italy

Reparto di Ginecologia ed Ostetricia, Policlinico Duilio Casula, Monserrato, Cagliari, Italy
e-mail: fulgh@tiscali.it; c.porru82@libero.it; elena.canu@hotmail.it

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9.1 Introduction

The Polycystic Ovarian Syndrome (PCOS) is the most common endocrinopathy in the female population, interesting 5–10% of women during childbearing age.

The clinic manifestations are very heterogeneous, with rare or absent ovulatory cycles, leading to oligoamenorrhea, and hyperandrogenic signs as acne, seborrhea, alopecia and hirsutism [1].

Often are present also metabolic alterations, often independent by obesity, characterized by insulin resistance and/or hyperinsulinemia and tendency to put on weight. In certain cases, where insulin levels are particularly elevated achantosis nigricans is also present [2].

The pelvic ultrasound (US) shows big ovaries, multiple follicles ($n > 10$) of small size (average diameter 2–8 mm) arranged in the subcortical seat around a hyperechogenic stroma and with enlarged volume ovaries (>8 ml), in absence of dominant follicle [3].

The complexity of the syndrome depends from the fact that clinical features are variable, mild, or serious, depending from the age, differently evolving, differently influenced by lifestyles and diet-styles.

From the definition of the first authors, Stein and Leventhal [4], which in 1935 had discovered the existence of a precise association between some clinical elements (infertility, amenorrhea, hirsutism and obesity) and the morphology of the ovaries: increased volume and pearly appearance and texture, many other definitions have been proposed; the two main used by authors in the last 20 years are those of the NIH/NICHD (National Institute of Health—National Institute of Child Health and Human Development) of 1990, that of the Consensus of Rotterdam 2003 [5], and the last of Androgen Excess Society (AES) [6].

The definition proposed by NIH/NICHD envisages the presence of clinical hyperandrogenism or hyperandrogenemia, oligo or anovulation and the exclusion of other disorders that cause hyperandrogenism, as congenital adrenal hyperplasia, androgen secreting neoplasms, hyperprolactinemia, and thyroid dysfunction.

This definition excludes altogether the use of ultrasound in diagnosis and this view was not shared by many authors.

In 2003, the Consensus of Rotterdam [5] has reasserted the importance of ovarian morphology to the diagnosis of PCOS.

The consensus introduces the diagnosis of PCOS when there is the presence of at least two of the following symptoms (excluding other causes of hyperandrogenism):

- Oligoanovulation (oligoamenorrhea)
- Clinical hyperandrogenism and/or biological hyperandrogenemia
- Polycystic ovary morphology at ultrasound

More recently, the Androgen Excess and PCOS Society [6] proposed the hers guidelines which require the presence of:

- Hyperandrogenism biochemical and/or clinical
- Presence of chronic anovulation
- Polycystic ovarian morphology
- The exclusion of other disorders that cause hyperandrogenism

From "consensus," therefore, ovarian ultrasound evaluation becomes a crucial stage in the diagnostic workup, and the introduction of endovaginal probes with always best sharpness of the image has made it possible to study more precisely both the size and the ovarian morphology even in obese patients, in which the transabdominal scan was not sufficiently reliable.

On the other hand, all these lead to increased detection of PCOS compared with that found using the criteria of the NIH from 18 to 9% [7].

The real belonging to the large category of patients with PCOS of the last two phenotype, patients with anovulation and PCO ovary but without signs of hyperandrogenism, and patients with PCO ovary and hyperandrogenism but with normal ovulatory cycles, has done and is doing much to discuss.

A work published by Belosi, Fulghesu, Lanzone et al. [8]. has reclassified the population of patients for whom was made the diagnosis of PCOS by applying separately the two diagnostic criteria. Of 375 patients studied, 345 comply with the criteria Rotterdam and, of these, 273 also meet the criteria of NIH in 1990. Thus, there are 72 patients who have a diagnosis based solely on the Rotterdam criteria. For comparing the clinical and hormonal characteristics of these patients, it can be seen that the 72 "non-NIH" show BMI, androgens, and insulin to lower that patients "positive NIH."

Another study by Welt et al. [9], which analyzed the hormonal characteristics of PCOS patients, showed that patients NIH criteria negative (patients with menstrual irregularities and PCO) had levels of testosterone and androstenedione similar to that of the controls, and significantly lower than the two groups of patients affected by hyperandrogenism + menstrual dysfunction or hyperandrogenism + polycystic ovarian morphology (PCOM).

The diagnosis of PCOS still represents a research field for ultrasonographers, gynecological endocrinologists, and pediatricians, and represents a big problem in adolescence where apparently similar symptoms to those encoded as PCOS may represent evolutionary stages of sexual maturation.

In this chapter, following elements for PCOS will be discussed in relation to adolescence:

- Ultrasound
- Clinical symptoms
- Hormonal characteristics
- Metabolic aspects

We will examine the role of the distinct components of the syndrome in adolescence to discuss if adult diagnostic criteria are workable at a young age.

9.2 Ultrasound

For more than 15 years sonographic criteria which become more frequent reference to define the polycystic ovary was heavily influenced by the definition of Adams et al. [10]: multiple follicles ($n > 10$) of small size (average diameter 2–8 mm) arranged in the subcortical seat around a hyperechogenic stroma and with enlarged volume ovaries (>8 ml).

There is, nowadays, a paucity of data for ovarian morphology for normal and PCOS adolescents.

In 2003, the Consensus Conference of Rotterdam [5], after careful consideration of the studies in the literature, introduced the following sonographic criteria for the identification of PCO:

- Presence of at least 12 follicles in each ovary: the calculation must take account of all the follicles present, from the inner edge to the outer one, irrespective of their arrangement and, for a more exhaustive study, must evaluate different sections obtained on different planes.
- Follicular diameter between 2 and 9 mm: the follicular diameter corresponds to the average of the measured diameters in the three sections, or to the diameter of the follicle in the scan which appears circular.
- Increased ovarian volume (>10 mm^3): for the calculation of the volume, various formulae have been proposed, based on the preliminary identification of the three diameters; software of modern ultrasound devices are capable of performing precise calculations (we generally recommend the use of the ellipsoid formula $P/6 \times (D1 \times D2 \times D3)$).
- Even the mere presence in a single ovary of one of the characters described above constitutes a sufficient element for ultrasound diagnosis; otherwise ovarian cysts presenting pathological look are excluded from the diagnosis. The ultrasound examination should be also carried out in accordance with certain specific rules:
- The operator must have performed a sufficient training to ensure the careful evaluation of clinical picture and the correlation with the given endocrinology.
- Whenever possible, the transvaginal ultrasound should be preferred especially in obese patients.
- In women with regular menstrual cycles, the examination must be carried out in the early follicular phase (3rd–5th day); in oligo-amenorrheic women you can choose a random day or prefer the first 3–5 days following a bleeding induced by progesterone. This type of timing guarantees the optimal approach for the quantitative assessment of ovarian volume and area.
- If there is evidence of a dominant follicle (>10 mm) or of a corpus luteum, the ultrasound should be repeated in the next early follicular phase.

In clinical practice, for a proper diagnosis, mainly three aspects must be evaluated:

- Ovarian volume
- The dimension, number, and arrangement of follicles
- The evaluation of the stroma.

Ovarian volume is increased in PCOS. Technical volume assessment seems possible by both transvaginal and transabdominal route. Since the ovarian surface is irregular, the measurement of its volume as an ellipsoid is only approximate. The ovary should be visualized and measured in all three planes (longitudinal, sagittal, and transverse). Currently available ultrasound systems enable the assessment of ovarian volume by marking the outlines and calculating the result using appropriate software. Ovarian volume is traditionally calculated with a formula for an elongated ellipsoid ($\pi/6 \times$ the highest size in each of the three planes). Since $\pi/6 = 0.5233$, it is also possible to use a simplified formula: $0.5 \times$ the highest size in the longitudinal, sagittal, and transverse view) [11].

The recommended cutoff in 2003 has not changed over the years, the threshold value of 10 cm^3 has found general agreement among the various authors, even if the same group who had proposed in 2003 [12], in 2005 he proposed to reduce to 7 cm^3 the threshold value [13], while in 2013 the value of 10 is confirmed in the use of new technologies [14].

Ovarian volume changes over time. The highest values are observed in adolescents (1.3–3.8 years after menarche). Subsequently, this parameter gradually decreases [15].

The available studies indicate that ovarian volume does not change much between the age of 20 and 39 [14]. The results presented prove that there are natural, age-related changes in ovarian volume, which should be taken into account when diagnosing PCO in adolescents.

Three-dimensional ultrasound is a recognized diagnostic modality to assess ovarian volume. The mean volume in adult patients with PCOS ranges from 10.6 to 16.7 ml, whereas healthy women present values ranging from 5.2 to 8.7 [16]. The comparison of ovarian volume measured in two- and three-dimensional images has been the subject of numerous studies [7]. However, at present few data are present in adolescence [17].

As for the number of follicles the cutoff proposed in 2003 varies from 10 to 12 but detected on only one ovarian scan identified as a median (FNPS).

With the advance of US technology, recent guidelines, largely based on two studies in adults, recommended that the US features diagnostic for PCOM will be modified increasing the threshold of follicle number to 25 per ovary (FNPO), scanning by TV transducer frequency >8 MHz, and counting by a specific software but, perhaps, because of the low availability of such probes and software, this cutoff is disregarded in the clinical practice. From the results proposed as the basis for the guidelines, 10 ml would be confirmed as the best cutoff for FNSP realized in median ovarian section, with a sensitivity and a sensitivity equal to 81 and 84%, respectively.

The authors, however, suggest to apply these rules only above 18 years, and only if you have a probe of 8 MH, and suggest to stick to only ovarian volume in the other cases [14].

Another method of calculating and assessing follicles is the system enabling three-dimensional reconstruction with marking fluid-filled spaces (e.g., VOCAL, SonoAVC) [18].

In adolescence, the problem is more present because the follicular count may be difficult to do in TA ultrasound, and, often, the follicle number may be increased, than cutoff for adult, leading to overdiagnosis when applied to young girls [19, 20].

So that the workable parameter in the diagnosis of PCOS in adults could not be reliable in very young subjects.

About the follicle size, recent studies point out that the follicles including between 2 and 5 mm are more characteristic of the syndrome and more related to the presence of clinical symptoms [7]. The small size of the antral follicles reflects the arrest of follicular maturation. The description of the arrangement, even though impressive, is not reflected in the guidelines.

Figure 9.1 represents the classic PCOM morphology.

However, following these criteria, to have a polycystic ovarian morphology (PCOM), could happen to a 24% of women in the reproductive life, and this percentage could be doubled in adolescence [21], and do not permit to overcome very important diagnostic difficulties.

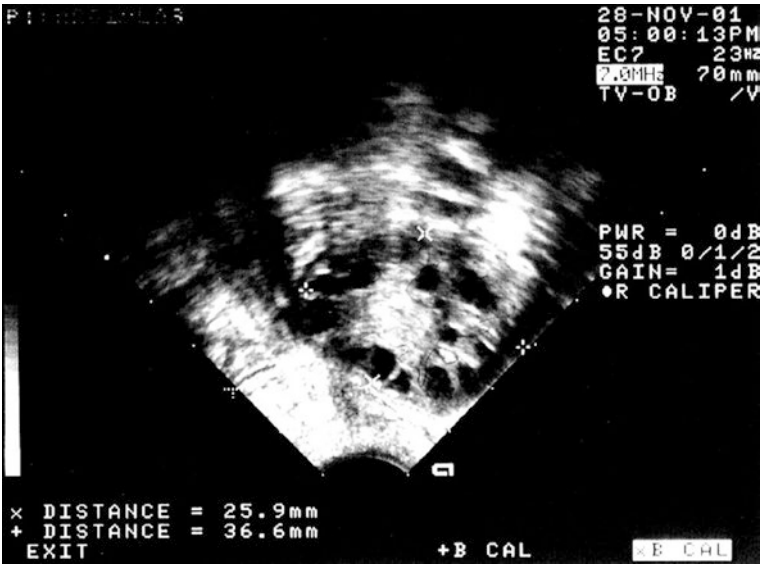

Fig. 9.1 The PCO morphology is characterized by the increased ovarian volume, by the increased number of follicles, by their peripheral arrangement, and by their small diameter

Our recent data on 302 healthy adolescents demonstrated that PCOM is present in 43% of group but is present in the 76% of them in the first 3 years from menarche.

After 3 years, this proportion is very different: disappears physiologically in 40% of subjects decreasing to 38%, whereas such morphology persists only in the 22% of girls after 5 years of menstrual cycle, which presumably could represent the subjects at real risk for menstrual dysfunction or PCOS (Fulghesu AM submitted for publication).

The spontaneous evolution versus the normal ovarian morphology suggests that PCOM in this age represents a developmental step in ovarian function.

Other US aspects, as increased ovarian stroma and higher stromal blood flow, whereas accepted as significant predictors of hyperandrogenism [22, 23], are not suggested in the official guidelines for the diagnosis of PCOM, but could be helpful in identifying the syndrome.

Indeed, excluding the evaluation of the ovarian stroma, it excludes the parameters that were already considered the most specific to the strong correlation with the circulating androgens [24]. In particular, in 1985 Adams and coworkers had reported the peripheral disposition of the follicles in the ovary PCO around a hyperechoic stromal tissue core. Dewailly observed that the choice of studying the ovarian volume is due to the fact that this parameter not only is easy to measure, but is also directly correlated with the hypertrophy of the stroma, of which discouraged the direct evaluation because it was considered subjective and difficult [25, 26]. For these reasons in recent years numerous studies have been undertaken to improve the diagnostic US specificity mainly focusing on evaluating stromal hyperplasia. Various systems have been proposed to define the increase of representation and echogenicity of stroma, normally slightly lower than that of the myometrium. None of these proposals has had large following because it is considered a highly subjective evaluation and operator-dependent instrumentation.

In 2001, my group has evaluated the measure of stroma compared to the remaining ovarian parenchyma, measuring the picture corresponding to the maximum ovary planar section, the area of the central stromal thickening zone (drawing obtained the peripheral profile of the stroma with caliper) and the total area of the ovarian parenchyma (drawing obtained with a second caliper, the outer limit of organ) and then calculating the ratio (S/A) (Fig. 9.2) [27].

With this kind of evaluation the diagnosis of ovary PCO corresponds to values of S/A > 0.34, more than a third of the ovary area in the median section (Fig. 9.2).

A subsequent multicenter study [24] indicated the S/A ratio, is gettable by standard technology, without inter-operator variations and provides great sensitivity and diagnostic specificity (96%). This index closely correlated with the plasma testosterone (R 0.731 $p < 0.001$) or/and androstenedione (R 0.734 $p < 0.001$).

The adoption of this new parameter finally could lead to a precise differentiation of PCO ovary already named multifollicular ovary. The multifollicular pattern (MFO) is described by several authors as an evolutionary step in adolescence [28] or as pathognomonic of amenorrhea or oligomenorrhea [29]. Such situations, from the pathogenic point of view, are characterized by gonadotropin pulsatility

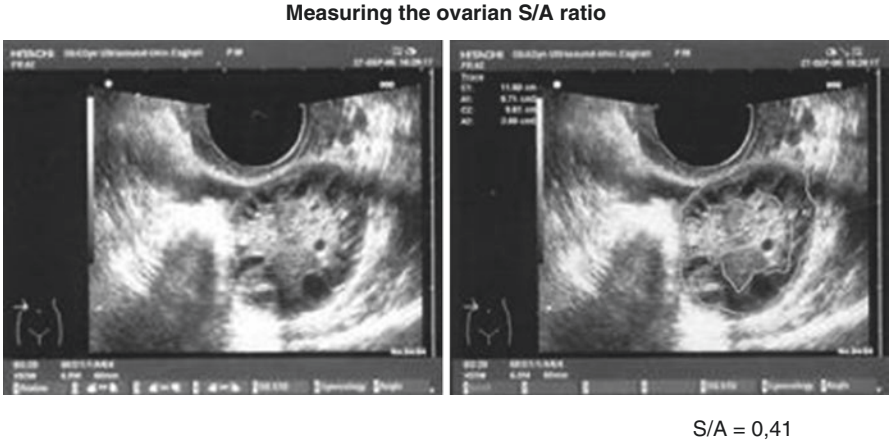

Fig. 9.2 A proportion between the ovarian area in median section (A) and stroma area in the same section (S), S/A ratio is obtained from two measures given by caliper

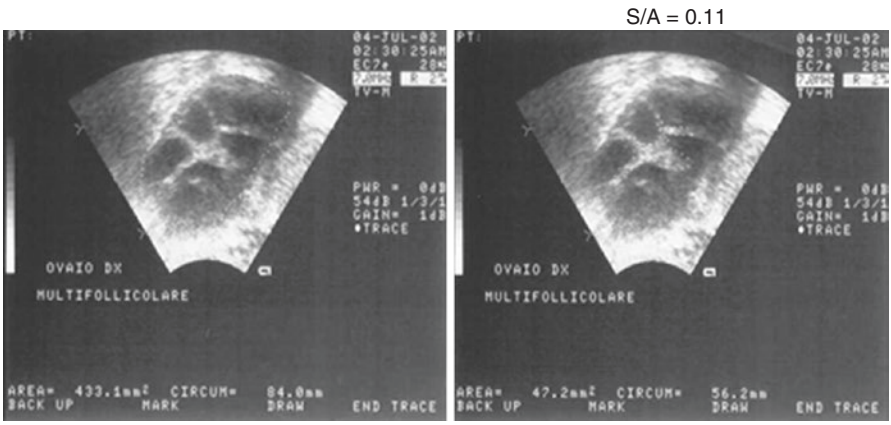

Fig. 9.3 A proportion between the ovarian area in median section (A) and stroma area in the same picture (S), S/A ratio is obtained from two measures given by caliper. Ovary PCOM in not PCOS girl: S/A 0.11

alterations due to eating disorders, or strong physical or psychological stress [10, 30] (Fig. 9.3).

These secondary amenorrhea are frequent in young age (adolescents often stressed and with mild eating disorders (DCA)), but with no signs of hyperandrogenism. This disorder is increasing and can be associated with normal BMI in the presence of conflicting attitudes towards food.

Other authors [16, 31, 32] confirmed the importance of S/A stroma in diagnosing PCOS. Battaglia and Sun found out exactly the same S/A ratio cutoff respectively in 3D and transrectal US studies, and, recently, the S/A ratio demonstrated the best

US PCOS diagnostic performance when associated with Total Ovarian Follicular count (FNPO) [33].

The increased stroma, until now, is studied mostly in adult population, for the difficult evaluation in TA. Further studies could confirm this possibility, considering that technical probe and software amelioration could overtake the problem of the TA US approach.

9.3 Additional Diagnostic Perspective

In recent years, to try to improve the ultrasound diagnosis of PCO, the application of color Doppler in the transvaginal US was studied in ovarian and uterine vessels highlighting an increase of pulsatily index of the uterine artery for effect of high levels of androgens and a reduction of uterine perfusion [33].

Subsequently the focus shifted on the vessels of the ovarian stroma noting the association between high levels of LH and increased stromal vascularization with a decrease of the intraovarian resistances and consequent stromal hyperplasia in patients with PCOS pattern [22].

Higher stromal blood flow, whereas accepted the significance as predictors of hyperandrogenism, actually is not suggested in the diagnosis of PCOS [7].

On the other hand, PCOS subjects presented increased Anti-Mullerian Hormone (AMH) levels [34, 35]. The number of follicles at all growing stages especially pre-antral and small antral follicles is increased in PCO. Thus elevated serum AMH level, as a reflection of this follicular stock, is two to fourfold higher in women with PCOS than in healthy women [35, 36]. Given its strong implication in the pathophysiology of PCOS, serum AMH had been considered the "Gold Standard" in the diagnosis of PCOS. Even though serum AMH would be theoretically more accurate than antral follicular count (AFC), as it reflects also the excess of small follicles non-visible on ultrasound [37], it is considered premature to make this diagnostic transition.

The robust association between AMH and AFC has led some authors to insert their performance in the diagnosis of PCOS [38], but it is found in all PCOM populations also in absence of hyperandrogenism [39].

In conclusion, therefore, we can say that the diagnostic ultrasound of PCOS cannot ignore the rules established in Rotterdam in 2003, which at present constitute the major criteria for identification of PCOS ovary; however, these guidelines are difficult to apply during the first 5 years after menarche when the physiological PCOM presence can reach 2/3 of the subjects.

9.4 Clinical Criteria

When PCOS is suspected in adolescence, a collection thoughtful and careful of medical history will be very useful for verifying the durability and authenticity of the described symptoms, and identify the presence of risk factors for PCOS

and insulin resistance as by low birth weight "sine causa," big weight gain in the first year of life, and finally pubarche premature and/or precocious puberty [40, 41].

Irregular menstrual cycles with oligoanovulation or secondary amenorrhea, is a very frequent symptom.

This event is to be considered normal in the first years after menarche, and is shrinking gradually from 2 to 3 years of gynecological life in normal girls, while it can stabilize with the passing years in individuals suffering from PCOS [42].

This clinical sign is present also in a great number of subjects stressed, athletes, too lean, or suffering from some form of eating disorders, as orthorexia, which presented menstrual dysfunction for alteration of gonadotropin secretion. For this reason, it is important to evaluate the lifestyle of subjects [43].

In adolescence, even the classic clinical criteria of hyperandrogenism such as acne, hirsutism, and alopecia should be considered with a different approach.

In fact, acne is a teenage phenomenon, physiological in both sexes. Its onset follows the adrenarche and adrenal androgen production, and physiologically tends to shrink after 2–3 years after menarche, to disappear in 6–7 years. In subjects really PCOS on the contrary, it is getting worse and as severity of injuries as an extension, but especially no signs of spontaneous improvement, and returns to the suspension of any treatment even up to 35–40 years [44].

On the contrary rarely hirsutism is a teenage temporary phenomenon. In fact, it needs a long time of hyperandrogenism to become a real problem. It may have different etiologies in addition to PCOS, first of all adrenal hyperfunction by enzyme deficiencies, but also a fair incidence of family forms.

For a correct assessment of hirsutism the Ferriman and Gallway [45] is the best scale, identifying nine body areas where hair follicles are hormone-dependent, with the exception of leg and forearm, where the familiar ethnic component is predominant. This scale assigns a value from 0 to 4 for each area and considers three levels of severity depending on the score achieved: <8 not relevant; Mild from 8 to 14; moderate 15 to 24; serious >24 (Fig. 9.4).

Hyperandrogenic alopecia is really rare in young girls, and the differential diagnosis with other familial forms or "sine causa" can be difficult. For this reason its use in the diagnosis of PCOS in adolescence is marginal.

9.5 Endocrine Criteria

The endocrine assessment must include androgens assay. Androstenedione and Testosterone, adrenal hormone 17OHP, and prolactin. Gonadotropins may be evaluated in suspicion of hypothalamic–pituitary axis disorders for example DCA or stress, or other primary ovarian disease.

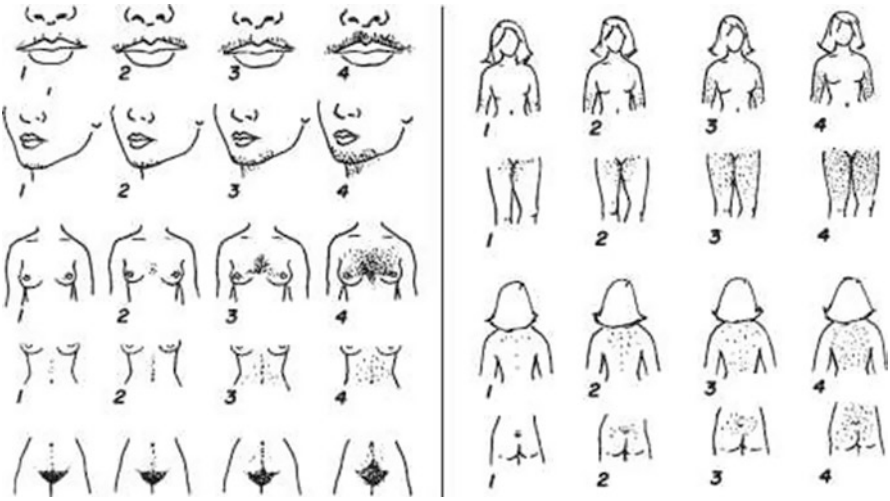

Fig. 9.4 Assignment of hirsutism score

Classically, the syndrome was attributed to altered LH/FSH secretion. Recent data have shown that the relative increase in the LH/FSH is only present in a minority of cases of PCOS [46], and does not alter either the prognosis or the therapeutic approach [47, 48].

The estradiol assay can be useful only in that it indicates the presence of follicular activation.

Prolactin is essential in the differential diagnosis of anovulation due to hyperprolactinaemia.

Ovarian androgens can be assessed only in early follicular phase, being involved in the production of progesterone, and therefore always high during ovulatory and luteal phase.

Often total testosterone (T) and androstenedione (A) are not so high in absolute values, or only one rose above normal cutoff (A > 3.5 ng/mL, *T* > 0.7 ng/ml), as a function of individual enzymatic pathways. Moreover, the dosage of the T is not technically simple and can be unreliable. It would be useful to combine it with the dosage of SHBG, which permits to calculate the Free Androgen Index (FAI) assessment, which replaces the direct determination of free testosterone (FT). FAI is direct active on receptors and is considered the most reliable marker of hyperandrogenism [47].

Among the adrenal androgens the most important is the 17OHP, which allows the exclusion of cases of classical and non-classical Congenital Adrenal Hyperplasia (CAH) and, in case of clinical adrenal hyperfunction, DHEAS.

9.6 Metabolic Aspect

The incidence of obesity, metabolic disorders, diabetes type 2, and the presence of metabolic syndrome was significantly increased in patients with PCOS [46].

Often the adipose tissue presents an android distribution, similar to an apple, which is put on relation with both insulin resistance and hyperandrogenism [49] and accounts for metabolic and cardiovascular disease. Obesity was observed in about half of women PCOS during childbearing age [50] and is considered one of the causes of insulin resistance and hyperinsulinemia.

Hyperinsulinemia, in response to food ingestion, however, affects also a 40–60% of normal-weight subjects presenting normal fasting insulin levels [51]. It's been suggested that normal-weight women with PCOS are suffering from a form of insulin resistance "intrinsic" to the syndrome while the obese patients present a state of insulin resistance in part inherent to the syndrome, and, in part, determined by increased body fat. Increased insulin secretion and peripheral insulin resistance may coexist in a heterogeneous way depending on the BMI.

Hyper-insulin secretion may be different, from a pathophysiological point of view, in lean and obese patients. From clinical observations in subjects presenting low birth weight and premature adrenarche and showing insulin resistance in childhood and young age, some authors consider this state a risk factor for development of PCOS at puberty [40, 41, 52].

In adolescence, fat deposits must reach 24% of the body mass to have menarche [43], and from a metabolic point of view, it is linked to a functional development of insulin resistance, which should be temporary and run out about 2 years after menarche. Often subjects with PCOS do not lose this metabolic characteristic and present multiple endocrine, skin, and biochemical effect of hyperinsulinemia [44]. However, despite this metabolic factor it is universally recognized as an important element of pathophysiology of the syndrome, to date it is not considered on Guidelines on Metabolic diagnosis.

This diagnosis should be made with both the determination of insulin and fasting glucose and HOMA calculation, which discloses peripheral insulin resistance and is increased especially in presence of body fat excess, and glucose and insulin under Oral Glucose Tolerance Test (OGTT) for evaluating the insulin response after load [53], which may be present also in lean subjects. In adolescence we find blood glucose curves almost always normal, in view of the large secretory capacity of the pancreas, except in cases of severe obesity, whereas the increased insulinemic response to glucose load is present in 70–90% of obese and 50% of lean subjects.

As regards the reference values of insulinemia, their interpretation is not easy; curves of normality for age and perhaps for ethnicity would be the gold standard [53], but the presence of values above 200 microU/ml is considered to be diagnostic.

In adolescence early diagnosis of hyperinsulinemia and the eventual normalization, with dietary interventions and insulin sensitizers treatment, can prevent the

onset of obesity and overweight in girls. The evaluation of hyperinsulinemia and insulin resistance can drive in the choose of therapeutic interventions to prevent the development of the metabolic syndrome [52].

Conclusions

Considering the psychological and clinical consequences of wrong diagnosis, in the adolescence the existing guidelines for adults cannot be applied as such, but some exceptions needed (Fig. 9.5).
The recommendations emerging are:

- Wait 2 years after menarche before making the diagnosis.
- Refrain from diagnosis in doubt to avoid the occurrence of anxiety and depression.
- Evaluation of metabolic status in presence of obesity and/or hyperandrogenism.
- Early treatment of hyperandrogenic and metabolic symptoms also before the diagnosis, in order to avoid psychological distress and long-time consequences of hyperinsulinemia.
- Consider carefully the ultrasound data, trying to get them with the best equipment, and use the TV when possible.

Based on these evidences I believe that we could improve, in predictive terms, our diagnosis of PCOS by inserting, where possible, the US evaluation of the stromal component (S/A index).

Proposed Criteria for the Diagnosis of PCOS in Adolescence:
Presence of menstrual irregularities
+

Diagnostic criteria for polycystic ovary syndrome in adolescents

Criterion	Hyperandrogenism[a]	Chronic anovulation[b]	Polycystic ovaries[c]
Diagnosis of PCOS	+	+	+
Diagnosis of PCOS probable but not confirmed	+	+	-
Diagnosis of PCOS not possible during adolescence	+	-	+
Diagnosis of PCOS not possible during adolescence	-	+	+
Not PCOS	+	-	-
Not PCOS	-	+	-
Not PCOS	-	-	+

PCOS, polycystic ovary syndrome. Carmina. The diagnosis of PCOS in adolescents. AM J Obstet Gynecol 2010.

a Hyperandrogenemia is primary criterion-acne and alopecia are not considered as evidence for hyperandrogenism-hirsutism may be considered sign of hyperandrogenism only when it has been documented to be progressive:

b Oligoamenorrhea (or documented anovulation) has to be present for at least 2 years:

c Diagnosis of polycystic ovaries by abdominal ultrasound has to include increased ovarian size (>10 cm^3).

Fig. 9.5 Shows the proposal of Carmina of 2010 [54]

Presence of clinical hyperandrogenism worsening after at least 2 years from menarche, or biochemical hyperandrogenism in the absence of adrenal disease
+
PCO ovaries with stromal hyperplasia (S/A > 0.33)

The presence of two-thirds of the above characteristics will place a suspect to be verified over time.

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Recommendations for the First Prescription of Hormonal Contraception in Adolescence

10

Floriana Di Maggio and Gilda Di Paolo

Abbreviations

BMD	Bone mineral density
BMI	Body mass index
CHC	Combined hormonal contraception
DMPA	Depot medroxyprogesterone acetate
EP	Estrogen progestogen
HC	Hormonal contraception
LARC	Long-acting reversible contraception
LNG-IUS	Levonorgestrel-releasing intrauterine system
OC	Oral contraception
POP	Progestogen Only Pill
SLE	Systemic lupus erythematosus
STI	Sexually transmitted infection
VTE	Venous thromboembolism

It is becoming more and more important to discuss the issue of contraception for adolescents, as national and international data have highlighted:

- The increasingly young age at which sexual intercourse begins
- The frequent lack of contraception during sexual debut (Table 10.1)

F. Di Maggio, M.D. (✉)
Adolescents Service A.S.L.Napoli1Centro, Naples, Italy
e-mail: florianadimaggio@virgilio.it

G. Di Paolo, M.D.
Pediatric and Adolescent Service, Pescara and Teramo, Italy
e-mail: gilda.dipaolo@alice.it

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Table 10.1 Risk factors in unprotected sexual intercourse

Young age at first sexual intercourse	Poor personal planning
Short relationships	Alcohol abuse
Lack of family cohesion and child monitoring	Psychotropic drug abuse
Older male partner	Binge eating
Poor school performance	Depression

Table 10.2 Resistance to contraceptive use

Insufficient information on how they work
Difficulties in speaking about it with partner
Perception of a foreign body or something that is "not natural"
"It won't happen to me" thinking about pregnancy or illness

- The rise in the pregnancy rate [1]
- Unchanged amount of abortions in adolescence [2]
- Increased incidence of STI [3]

10.1 Counseling

Contraceptive counseling is essential, during which it is often necessary to overcome a more or less explicit resistance to the use of contraceptives (Table 10.2).

We need to ensure the appropriate timing and language when supplying information on all the available contraceptive methods, with regard to their use, their additional benefits, and any side effects.

It is necessary to arrive at a shared decision.

We need also to have partner agreement; in these cases, the compliance is longer.

The agreement of the mother (where involved) is also important.

The importance of double Dutch contraception (condom plus hormonal contraception) should be stressed in the context of the prevention of STI.

To give more information about emergency contraception.

10.2 First Prescription

It is essential to fully investigate both family and personal medical history.

Family history:

Investigate:

Cardiovascular disease: ischemic stroke, myocardial infarction (MI)
Previous venous thromboembolism (VTE) <45 years *
Hyperlipidemia
Hypertension

Autoimmune diseases
Migraine

*at least 2 first-degree family members with VTE is a contraindication to EP use; grandparents should be included in the family medical history.

Other papers have pointed out that a family history from a female patient (mother or sister), in which that patient has experienced a CHC or pregnancy-related VTE, may further increase VTE risk in her female relatives [4].

There is no indication to screen thrombophilia on the basis of a risks/benefits assessment [5].

10.3 Clinical Examination

10.3.1 Personal Pathological History

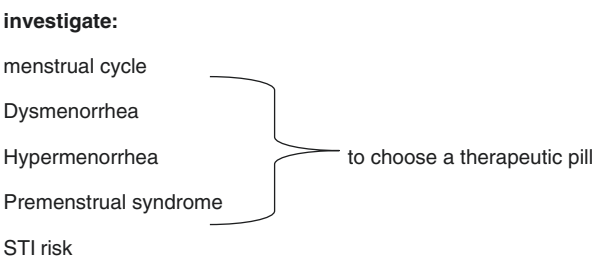
Investigate:

Current or previous illnesses *
Migraine
Autoimmune diseases (SLE, rheumatoid arthritis, thyroiditis, Sjogren syndrome, celiac disease) **
Raynaud syndrome
Drugs in use (exclusion of interactions)
Current or previous behavioral binge eating
Depression
Smoking (negotiate reduction in number of cigarettes)
Recreational drug use (alcohol, vasoactive substances)
Lifestyle (physical activity, sedentary, etc.)

*thrombophilic diathesis is an absolute contraindication for CHC use.
**in these cases it is useful to test for antiphospholipid antibodies.

10.3.2 Gynecological History

Investigate:



Clinical examination:
Always check

Blood pressure recording, Weight, Height, and BMI
Evaluate hyperandrogenic symptoms: acne, seborrhea, hirsutism

Not essential:

Gynecological examination
Pap Smear *
Breast examination
These can be carried out in a subsequent checkup

* <21 years: do not perform cytological screening independently of first sexual intercourse or risk behavior—ACOG 2012, US preventive services task force 2012, Canadian task force on preventive Health Care 2012.

All women who have been vaccinated against HPV should still follow the screening recommendations for their age groups (The American Cancer Society Guidelines for the Prevention and Early Detection of Cervical Cancer 2016).

10.4 Routine Laboratory Tests?

These are not recommended routinely as they do not contribute substantially to CHC safety. If there is a family history of metabolic diseases, autoimmune diseases, diabetes or dyslipidemias, then these can be carried out.

The expected advantages of the elimination of prescription blood tests are:

To improve access to effective contraception for the adolescent population
To separate screening procedures and contraceptive prescription
To dispel the widespread belief that contraception is hazardous for female health

Recommendations at first control after 3 months use:

To note side effects and/or problems
Verify proper use end stress instructions of use.
Check blood pressure.

Annual follow-up

Blood pressure monitoring
Body weight and BMI evaluation
Pelvic examination
Screening for STI*

Stress the importance of checkups or telephone calls any time in order to discuss side effects or to change contraceptive method.

*Recommendations ACOG-4-2012: screening for STI every year or every new partner.

10.5 Choice of Contraceptive

The options regard composition, means of administration, and system of drug intake.

Composition:

It is possible to choose between combined contraceptive and progestin only. Use of long-acting reversible contraception (subcutaneous etonogestrel or IUS with levonorgestrel, DMPA depot medroxyprogesterone acetate injection) is strongly recommended in adolescence for less risk of failure and greater compliance [6, 7].

Today we have several CHC that differ in progestin* or estrogenic** composition and they also (all) have noncontraceptive benefits. It is therefore important to choose an individualized CHC, examining the blood loss and therapeutic effects or suspicious clinical elements (overweight, migraine).

Way of administration: oral, transdermal, transvaginal, subcutaneous, intrauterine.

System of drug intake: 21 days, 28 days, continuous. Association with placebo pills for continuous use is probably simpler to use and facilitate compliance.

It is very important to point out:

Instructions for the correct use.
What to do if you forget the pill.
Interactions with other drugs, diarrhea, vomiting.
It is not advisable to interrupt administration of OC because of greater risk of pregnancy, more side effects in the first months or after 1 month interruption [8].

*Desogestrel, gestodene, drospirenone, Chlormadinone acetate, dienogest, levonorgestrel, norelgestromin, etonogestrel.

**Ethinyl estradiol, estradiol valerate, estradiol hemihydrate.

At the first prescription of HC, further information may be given regarding noncontraceptive benefits.

Positive effects on:

Pelvic pain and dysmenorrhea
Spotting and/or heavy blood loss
Endometriosis
Premenstrual syndrome
Signs of hyperandrogenism (seborrhea, acne, hirsutism)
Functional ovarian cysts and benign ovarian tumors

Iron-deficiency anemia
Pelvic inflammatory disease
Ectopic pregnancies

Protective effects:

Epithelial ovarian cancer
Endometrial cancer
Colorectal cancer

… .. how can we enhance contraceptive compliance?

Discussing any doubts and describing possible side effects:

Spotting, oligomenorrhea, breast tension, weight gain….

On many occasions, the real reason for low compliance is a concern about health and fertility in the future.

Moreover, several authors have pointed out the close relationship between side effects and the nonrational perception of a major health risk [9].

Categories of medical eligibility criteria for oral contraceptive use

1. **A condition for which there is no restriction for the use of the contraceptive method**
2. **A condition for which the advantages of using the method generally outweigh the theoretical or proven risks**
3. **A condition for which the theoretical or proven risks usually outweigh the advantages of using the method**
4. **A condition that represents an unacceptable health risk if the contraceptive method is used**

Category 1: Unrestricted use

- Age—from menarche *°
- Postabortion—immediately first and second trimester, and post-septic
- Non-migraine headaches—mild or severe
- Minor surgery without immobilization
- Severe dysmenorrhea
- Endometriosis
- Breast disease: benign breast disease or a family history of breast cancer**
- Anemias—thalassemia, iron deficiency
- Raynaud's disease—primary without antiphospholipid antibodies

*we have no data on the effect of OC assumption and post-menarchal growth.

°data concerning effects on bone mass are not univocal (possible reduction effect on bone mass growth in very young people, but there is catchup with interruption of the treatment) [10].

WHO (2009) guidelines point out a relation between an estrogenic level (20 mcg) and BMD (bone mineral density) lower then controls; on the contrary, if you use higher EE levels, there are no differences.

**in hormonal contraceptive users with a family history of breast cancer, there is no higher risk of breast cancer [11].

In girls with known BRCA1/2 mutations, there is a risk of earlier breast cancer onset in the OC users but there is another positive effect in terms of reduced incidence of ovarian cancer, [12] so an individual evaluation end possible use of POP is advised.

Category 2: The benefits generally outweigh the risks

Smoking—aged <35 years
Obesity—BMI ≥30–34 kg/m^2
Family history of VTE in a first-degree relative aged ≥45 years
Major surgery without prolonged immobilization
Superficial thrombophlebitis
Migraine headaches—without aura in women aged <35 years
Vaginal bleeding—suspicious for serious condition before evaluation
CIN
Raynaud's disease—secondary without antiphospholipid antibodies
Non-liver enzyme-inducing antibiotics

Category 3: The risks generally outweigh the benefits

Obesity—BMI 35–39 kg/m^2
Family history of VTE in a first-degree relative aged <45 years
Immobility (unrelated to surgery)—e.g., wheelchair use, debilitating illness
Known hyperlipidemias—e.g., family history of hypercholesterolemia
Symptomatic gallstones
Migraine headaches or a past history of migraine with aura at any age

Category 4: Unacceptable health risk and should not be used

Obesity—BMI ≥40 kg/m^2
Migraine headaches—with aura at any age
Known thrombogenic mutations
Raynaud's disease—secondary with antiphospholipid antibodies and thus a tendency to thrombosis
Hypertension—blood pressure ≥160 mmHg systolic and/or ≥95 mmHg diastolic; or vascular disease
VTE—current (on anticoagulants) or past history
Valvular and congenital heart disease—complicated by pulmonary hypertension, atrial fibrillation, history of subacute bacterial endocarditis
Hepatocellular adenoma
Angiopathic hereditary edema 3

Finally we must not forget adolescent girls with chronic diseases, which are nowadays increasingly frequent due to the better treatment of the underlying conditions; in these cases, the choice of contraceptive must consider the adolescents' needs and their clinical situation, determined in collaboration with their specialist, following specific guidelines. In the presence of estrogen-dependent diseases or increased risk of venous thromboembolism, it must be considered the possibility of using POP.

The guidelines refer to the writing of this work are:

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Ovarian Cysts in Adolescence

11

M. Chiara Lucchetti

11.1 Definition and Etiopathogenesis

The gold standard for the diagnosis of an ovarian neoplasm is the ultrasound definition provided by the IOTA (International Ovarian Tumor Analysis) criteria: It is the part of an ovary or the total ovary that is not part of the normal ovarian physiology [1].

Functional ovarian cysts: Ovarian cyst is an ultrasonographically anechoic space, round or oval shaped, with smooth, thin wall, acoustic posterior reinforcement, in absence of solid components, sepiments, and internal flow at Color Doppler. If these features are present in formations lesser than 3 cm in diameter, these are considered follicles. For diameters more than 3 cm, the appropriate definition is follicular cysts, that is greater expanding follicles, generally not bursted for lack of ovulation, which is a frequent event in adolescence; for this type of cysts, regardless the age group, incidence of malignancy is less than 1%.

During adolescence, ovarian cysts are generally due to failed follicular involution: Lack of ovulation induces follicular overgrowth, sometimes reaching huge dimensions and, possibly, acute symptoms due to intracystic bleeding, rupture, or torsion (of the cysts but even of the whole ovary). For this reason, such cysts are also named "functional" and only a conservative approach is required, with ultrasonographic re-evaluation with time. Only when a torsion is suspected a surgical approach is mandatory.

There are also cysts with features due to a bloody content inside (hemorrhagic cysts): They are the consequence of a bleeding inside a corpus luteum or a follicular cyst. These cysts have the appearance of a cystic complex mass, with a net-like distribution of internal echoes (fishing net-like, web-like, etc.) or, when resorption is present, like a solid area with concave edges (retracting clot); at Color Doppler they have no internal flow, but generally a circumferential flow along the cystic wall is present (fire-ring sign); the wall thickness may be variable.

M.C. Lucchetti
Bambino Gesù Children's Hospital, Rome, Italy
e-mail: mchiara.lucchetti@opbg.net

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This kind of cyst, being functional (it would be better to call them "dysfunctional") in their nature, tend to spontaneously disappear in 6–8 weeks.

Endometriosic cysts: Besides the rarity of this pathology in adolescence (especially if the "endometrioma" stage is considered), it has to be suspected that a complex cyst could be an endometrioma, particularly in patients with previous mullerian obstructive malformations and chronic dysmenorrhoea. Ultrasonographically, the appearance may be not different from that of an hemorrhagic cyst (scattered homogeneous echoes, groundglass-like, sometimes with a fluid level, no internal flow at Color Doppler, without solid internal nodules or neoplastic characteristics), but at a 6–12 weeks follow-up, not spontaneously disappearing, it becomes evident its real nature. If not surgically removed, endometriomas require at least a yearly ultrasonographic follow-up.

Complex cysts or masses: The majority of persistent ovarian solid or complex masses (strictly defined as neoformations or neoplasms) are mature teratomas or dermoid cysts, which are germinal tumors. Other neoplasms can be also present in the pediatric–adolescent age, but are relatively rare. Malignant tumors represent 1–20% of all ovarian masses in pediatric age, keeping in mind that the variability is due to the influence, on reported series, coming from pediatric general hospital or pediatric oncological hospital.

The ultrasonographic appearance of teratomas is characterized by the presence of hyperechogenic solid components (focal or diffuse, also named "Rokitansky nodule"), by thin lines or "spots" as well as hyperechogenic, by the possible presence of floating spheric structures and by the absence of internal flow at Color Doppler. At the first glance, these formations may be undistinguishable by some luteal/hemorrhagic formations, but at ultrasonographic follow-up the fail to resolve give the confirm of their neoplastic nature. Mature teratomas are bilateral in 12–15% of cases, which is an important consideration to remind during the initial evaluation and, most of all, during follow-up.

Epithelial tumors tend to assume the appearance of voluminous cystic formations (serous or mucinous cystadenomas), with a similar aspect to that of follicular cysts, but with dimensions usually exceeding 10 cm.

There is no uniformity of opinions, in the Literature, about dimensions to consider "at risk" for the torsion of an ovarian mass. It is well known that neoformations with a diameter between 5 and 8 cm are often present in case of ovarian torsion, suggesting to act like a "trigger" point predisposing to torsion.

Therefore, when a mass with such dimensions is addressed to a "wait and see" approach, it is important to be aware (and to tell the parents) that an ultrasonographic evaluation is mandatory in case of acute abdominal and/or pelvic pain. Moreover, dimensions greater than 8–10 cm of diameter have been recently reported to be one of the predictable factors indicating malignancy risk, either for cystic or solid masses.

11.2 Epidemiology

The estimated prevalence for ovarian masses in the pediatric–adolescent age is 2.6 cases out of 100,000 each year. Between 2008 and 2012 in the USA only 1.3% of all ovarian cancers have been diagnosed in patients below the age of 20, giving the idea

Table 11.1 Classification of ovarian tumors according to the WHO classification and their frequency in the pediatric and adolescent population

Epithelial	Serous		15–20%
	Mucinous		
	Endometrioid		
	Clear cell		
	Transitional cell		
	Epithelial-stromal (adenosarcoma, carcinosarcoma)		
Nonepithelial	Germ cell	Dysgerminoma	60–80%
		Yolk sac	
		Monodermal	
		Mixed	
		Teratoma	
	Sex cord stromal	Granulosa cell	10–20%
		Sertoli-Leydig	
		Mixed	
	Metastases		

of how rare and difficult to study this pathology could be. In a recent review of the Literature [2], the risk of malignancy of adnexal masses in children has been estimated around 19%, with a range from 2 to 59%, being the differences due to referral bias (specialized pediatric oncologist or not) and ages of studied population.

Epithelial carcinomas, which prognosis remains poor, account for 90% of all ovarian cancers in adults, while in children the most frequent ovarian cancer is nonepithelial, being epithelial in less than 20% of cases (Table 11.1), with a predominance of serous and mucinous histology [3, 4]. Most often, pediatric ovarian cancers arise from germ cells and have a good prognosis: Mangili et al. [5] reported results from the largest database on ovarian germ cell pathologies and stated that there are two important contributing factors to the prognosis of germ cell tumors (GCT): first, the majority (71%) is detected at stage I, and second they respond well to surgery and chemotherapy, leading to a 5-year survival of 95.6% and 73.2% in stage I and advanced stages, respectively. Because of this excellent prognosis of GCT, overall outcome of ovarian cancer in children is excellent compared with that in adults.

The malignancy risk has been evaluated in an epidemiologic study including more than 1000 cases [6] in which the risk stratification has clearly showed that, related to the frequency of onset of ovarian masses, the malignancy rate is proportionally higher in the 1–8 years group; in this age group, in fact, it is extremely rare the presence of an ovarian neoformation of functional nature and therefore the risk to be in the presence of a neoplasia is significantly higher. This is why in this age group the clinical approach, in case of ovarian mass, has to be more prudent.

Other studies have put in evidence that, besides patient's age, other characteristics are related to malignancy risk: clinical and hormonal features of precocious puberty or virilization (abnormal hormonal function), dimensions >8–10 cm, presence of solid components inside the formation, higher level of one or more tumor

markers. However, in the pediatric age it doesn't exist yet a reliable and validated tool able to distinguish, like in the adult population, a benign from a malignant ovarian mass. In fact, while a number of such tools (risk indexes, diagnostic algorithms) have been developed for the reproductive and menopausal age (RMI, ROMA; OVA1, LR2 and, recently, a new algorithm involving the use of protein HE4), in the pediatric age similar efforts have not allowed similar results, perhaps due to the eterogeneicity of the studied populations and to the small number of ovarian malignancies: with these premises, so that whatever complex diagnostic tool requires very difficult and time-consuming validation.

Box 1: Differential Diagnoses of Ovarian Cysts
- Hydrosalpynx
- Paraovarian cyst
- Hematometra/hematocolpos
- Salpyngitis
- Pelvic abscess
- Extrauterine pregnancy
- Abdominopelvic cysts not ovarian

11.3 Diagnosis

Symptoms associated with the presence of an ovarian mass are extremely variable, coming from the total lack of any symptom (it is frequent their occasional detection during imaging studies for other reason) to pelvic/abdominal pain (chronic/recurrent or acute), until clinical signs of abnormal hormonal secretion (precocious puberty, virilization, dysfunctional uterine bleedings, etc.). There have also been reported rare clinical manifestations associated to the presence of mature teratomas, very similar to paraneoplastic syndromes, such as autoimmune hemolytic anemia and immune-mediated limbic encephalitis [7, 8].

Generally, complex masses and in particular mature cystic teratomas can become symptomatic because of their related complications: torsion (3–16%), rupture (1–4%), infection (1%), malignant degeneration (0.17–2%).

Since presenting signs and symptoms of ovarian masses (either benign or malignant) are so heterogeneous, in recent years many authors have looked for clinical and/or imaging features in order to exclude the risk of malignancy and to increase the number of patients candidates to ovarian preservation (wait-and-see policy, re-evaluation, laparoscopic surgery, reduced number of oophorectomy).

Ultrasonography: In the diagnostic approach, it remains the primary tool either for the precocious diagnosis or the follow-up, offering the possibility to reassess in a reasonable time masses potentially suspicious so avoiding aggressive treatments. Ultrasonography has, in fact, the basic requirements of spread, ease of use,

and to repeat. Ultrasonographically, the mass is considered for its main features that are dimensions, appearance, and content, which should help in choosing the best therapeutic approach. When the cyst is unilocular, unilateral, with thin and smooth wall, smaller than 8 cm and without ascitic fluid, the risk of malignancy is very low (<1%).

US is the initial modality to confirm the presence of adnexal masses and provides their approximate size. In some cases, it characterizes the mass, such as a dermoid cyst, by showing calcification and fat-fluid level.

Malignancies are more often complex masses with irregular edges, not well defined, often with necrotic central areas, sepiments, and papillary projections. When ultrasonography, even repeated after 6–8 weeks, is not diriment, the second diagnostic step is represented by Magnetic Resonance Imaging; the use of Computed Tomography is only reserved for the staging of histologically proven malignancies.

Traditionally, masses greater than 5 cm have been used as cutoff suggestive of malignancy, with some studies using 7.5 and 8 cm. A recent study by Papic et al. [9] showed that 56% of benign masses were >8 cm so the cutoff value of >10 cm has been proposed as a malignancy predictor, as well as the presence of solid components seen on imaging. Neither of these predictors was independently 100% sensitive for malignancy, as 11% of malignant masses were <10 cm and 22% of malignant masses were cystic (complex) with no solid components.

Magnetic resonance imaging: Preoperative pelvic MRI findings might change the surgical management of pediatric patients with adnexal masses, so it is considered a valuable addition to the conventional workup in the clinical management, especially when an extraovarian origin of the mass is suspected or a malignancy has to be ruled out. In a study of Marro et al. [10], MRI correctly suggested benign nature in 24 of 28 (85.7%) benign masses while US was indeterminate in 19 of these 28 (67.8%) masses. MRI is required for better characterization of ovarian masses, for assessing likelihood of malignancy, and for staging the tumor. It is chosen for staging of malignancy over CT scan to reduce ionizing radiation exposure in this young and more vulnerable population.

Tumor markers: Their diagnostic significance is controversial for the possibility of higher plasmatic values either in malignant or in benign masses: in the Literature the rate of benign lesions associated with markers elevated values varies from 3.4 to 20%, while no more than half of the malignant forms have a higher value of one or more markers. It creates the risk to underestimate the possibility of malignancy, but even that of planning a too aggressive approach toward a benign lesion.

A recent paper dealing with pediatric age [9] has evidentiated that alpha-fetoprotein and beta-HCG are highly specific for neoplastic masses since in the analyzed series no benign mass was associated with elevated values of these markers. But the same study has identified 17% of patients with malignancies showing the absence of any marker elevation, coming to the conclusion that the absence of tumor markers modifications does not allow to exclude the presence of malignancy.

On the basis of such considerations, it appears reasonable to always program an extemporaneous histologic examination when tumor markers are elevated, in order to offer the most appropriate surgical approach, but never to plan an aggressive surgical approach only relying on tumor markers.

However, their use is always considered useful during follow-up of malignancies, either to evaluate the answer to therapy or to early detect recurrences.

Hormones: Hormonal samples are mandatory when an abnormal hormonal production is suspected (precocious puberty, virilization, hyperthyroidism, etc.). Inhibin-B, progesterone, and Anti-Mullerian Hormone (AMH) are other hormones actually under validation as possible pre- and postoperative "markers" of reduced ovarian reserve, coming from the mass itself and/or from its surgical treatment (open surgery or laparoscopy).

11.4 Therapy

About 60% of ovarian masses are treated surgically. Nowadays, more than 50% of surgeries for ovarian masses in adolescents are performed laparoscopically, and most of the patients (71–84%) undergo cystectomy rather than oophorectomy. However, of the small number of patients who undergo oophorectomy, the majority have benign lesions, and this has to be considered unacceptable, although still performed.

The best practical treatment of pediatric and adolescent ovarian masses is not a well-defined topic because of the lack of markers or validated indicators of malignancy. Considering neoplastic masses, very different approaches are described and followed, particularly for stadiation of germ cell tumors compared to epithelial and stromal, having developed in recent years extremely conservative strategies for the first ones (such as laparoscopy, ovary-sparing surgery, tumorectomy with preservation of residual ovarian tissue) and more aggressive for the others. In recent years, preservation rates in girls with benign ovarian masses have increased from 15% in 1999 to 39–61%, but as stated by Papic et al. [9] it is likely less than it could be.

Besides, it is always dutiful to consider that for many ovarian neoplasms the surgical treatment is needed as an emergency procedure because of a secondary torsion or rupture.

The main target in the management of an ovarian mass in pediatric and adolescent age should be to preserve the ovary, without betraying the oncological principles, most of all as far as it regards the stadiation, considering that during surgery the histology is not known until pathologic exam is performed.

The general basic rules in the management of ovarian masses in this age group should therefore be the following:

1. To establish cyst/mass main features
2. To avoid any surgery for functional cysts
3. To exclude the presence of neoplasms

Laparoscopic surgery is considered the gold standard in the treatment of benign ovarian masses. There are still existing controversies regarding malignancies, and for this reason a lot of "suspected" masses are still treated with laparotomies by gynecologists and pediatric surgeons. While there is general agreement about the use of laparoscopy when a malignancy is reasonably excluded during preoperative

Table 11.2 2014 FIGO ovarian cancer staging

Stage I. Tumor confined to ovaries or fallopian tube(s)
IA: Tumor limited to one ovary (capsule intact) or fallopian tube; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
IB: Tumor limited to both ovaries (capsules intact) or fallopian tubes; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
IC: Tumor limited to one or both ovaries or fallopian tubes, with any of the following:
IC1: Surgical spill
IC2: Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface
IC3: Malignant cells in the ascites or peritoneal washings
Stage II. Tumor involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer
IIA: Extension and/or implants on uterus and/or fallopian tubes and/or ovaries
IIB: Extension to other pelvic intraperitoneal tissues
Stage III. Tumor involves one or both ovaries or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes
IIIA1: Positive retroperitoneal lymph nodes only (cytologically or histologically proven):
IIIA1 (i) Metastasis up to 10 mm in greatest dimension
IIIA1 (ii) Metastasis more than 10 mm in greatest dimension
IIIA2: Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes
IIIB: Macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes
IIIC: Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ)
Stage IV. Distant metastasis excluding peritoneal metastases
Stage IVA: Pleural effusion with positive cytology
Stage IVB: Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

evaluation, there are not precise rules to achieve this "reasonably exclusion," although some authors have published data aimed to this.

There are two main stadiation systems for ovarian pediatric masses: one from the International Federation of Gynecology and Obstetrics (FIGO) and one from the Children's Oncology Group (COG), regarding only germ cell tumors (Tables 11.2 and 11.3). The Children's Oncology Group (COG) established also the current consensus guidelines for appropriate staging procedures among pediatric patients with ovarian germ cell tumors [11] (Table 11.4).

Regarding cystic mature teratomas, the Literature based on adult age suggests that laparoscopic excision is a safe procedure, without an increase in the number of recurrences when compared with laparotomy [12]. The decision to use the same approach for the pediatric age has been more cautious, and it is still considered as depending on the laparoscopic experience of the single surgeon and on the patient's age. The standard treatment of a cystic mature teratoma is still reported as ovariectomy by "open" surgery, but recently many authors have proposed the excision of the lesion (open or laparoscopically) without considering oophorectomy.

Table 11.3 Staging system for pediatric ovarian germ cell tumors (COG)

Stage I
Limited to ovary (ovaries); peritoneal washings negative; tumor markers normal after appropriate half-life decline (AFP 5 days, HCG 16 h)
Stage II
Microscopic residual or positive lymph nodes (2 cm)
Peritoneal washing negative for malignant cells, tumor markers positive or negative
Stage III
Lymph node involvement (2 cm) gross residual or biopsy only; contiguous visceral involvement (omentum, intestine, bladder); peritoneal washings positive for malignant cells; tumor markers positive or negative
Stage IV
Distant metastases, including liver

Table 11.4 2004 COG guidelines for GCT staging

– Collection of ascites or peritoneal washings
– Examination of peritoneum and biopsy of any abnormality encountered
– Gross examination of retroperitoneal lymph nodes by visual inspection and direct palpation with subsequent biopsy of abnormalities encountered
– Examination of the omentum with removal of abnormalities encountered
– Gross examination of the contralateral ovary with biopsy of abnormalities encountered
– Complete resection of ipsilateral ovary without tumor spill or capsule violation

In 2014, the Gynecologic Cancer Intergroup (GCIG) formulated a consensus on ovarian germ cell tumors [13]; since most tumors are unilateral and diagnosed as stage I disease, fertility-sparing surgery appears to be safe. In case of FIGO stage II disease or higher, surgery has to be extended, keeping in mind that the uterus usually can be preserved even in case of a bilateral tumor. The administration of neoadjuvant chemotherapy, prior to debulking surgery (as is accepted in widespread epithelial ovarian cancer in adults), can be considered in children with widespread dysgerminomas since the tumor is highly chemosensitive. Standard chemotherapy for advanced or incompletely resected GCT is based on bleomycin, etoposide, and cisplatinum; in carboplatinum replacing cisplatinum is also suggested, or even with ifosfamide replacing bleomycin. It is expected that more than 90% of children will survive their disease.

The majority of epithelial ovarian cancers in children reported in the Literature are mucinous ovarian cancers or low-grade serous ovarian cancers. Both for children and for adults, serous ovarian cancer will present most often at stage III or IV, with the typical features of a bloated abdomen, dyspnea, and abdominal pain. Epithelial ovarian cancer in children is not restricted to serous and mucinous carcinoma; there have been described cases of clear cell ovarian carcinomas, Brenner tumor, endometrioid ovarian carcinomas, small cell ovarian cancers of the hypercalcemic type, sarcomas. In contrast to the balanced and well-reported treatment schedule for children with GCTs, epithelial ovarian cancer in children is treated as adults with a combination of surgery and platin-based chemotherapy. Fertility sparing surgery is not an option, because it is very important that all macroscopic tumor is resected, particularly for stages II–IV.

The mainstream surgical treatment (open surgery or laparotomic surgery) is now considered appropriate only when there is the suspicion of a neoplastic, malignant mass. In this case, the open surgery allows that oncological stadiation is performed easier and correctly (evaluation of limphnodes, mesenter, peritoneum, ascitic fluid aspiration for citology), that the radical resection of the mass is verified, and that contralateral ovary is properly palpated (little internal neoformations may result hardly palpable, so not recognizable at all at laparoscopy). Traditional surgery is also associated with lesser incidence of ruptures or "spillages." On the other hand, surgical operation results, in the majority of cases, much more aggressive than needed, mostly considering the small number of malignancies in this age group.

An open approach is commonly used when malignancy is suspected, and it has also been recommended for large cysts owing to better visualization which may lead to decreased tumor rupture and improved ovarian preservation. However, in a study by Papic et al. [9] laparoscopy demonstrated to be an effective approach for ovarian preservation even with large benign masses. Additionally, there was no increase in tumor spillage rates between laparoscopic and open groups, and the length of stay was shorter in the laparoscopic group. The overall ovarian preservation rate for benign masses in that study was 24%, which is lower than other recent series reported (39–61%).

The complete ovarian resection (oophorectomy or salpingo-oophorectomy) is indicated on the basis of the tumor extension. In germ cell tumors not macroscopically involving the Fallopian tube, the tube of the affected side can be preserved without risk. Stage IA tumors (serous borderline, stromal sexual cords and germ cel tumors) also have been demonstrated to be safely treated with cystectomy/tumorectomy and strict follow-up. It is also possible to plan a possible second surgical procedure aimed to stadiate a patient initially treated with cystectomy alone, but this option has to be formulated on individual basis, considering the type on neoplasms, the pathologic stage, the grade, the risk that a chemotherapy will be needed and the compliance. It has to be discouraged, indeed, the routine biopsy of the contralateral ovary to avoid a further damage to future fertility.

Recurrences and mortality have been reported with variable values in different series: from 4% for both [11] to 16% for recurrences and 11% for mortality [14] to 0% for both [15, 16].

For stage I germ cell tumors surgical resection alone seems to be the best approach in order to accomplish the oncologic management and the fertility preservation. For more advanced stages, chemotherapy with bleomycin, etoposide, and cisplatinum gives generally optimal results; after three to four chemotherapy cycles, a second-look surgery is required to document the local answer and to eventually remove residuals of disease. Survival is good even in such cases (more than 90% after 5 years).

Even for stromal sexual cords in stage IA and low histologic grade, surgical treatment alone is proposed. Chemotherapy is reserved for more advanced stages, higher histologic grade or evidence of tumor rupture during surgery. Survival is good for stage I lesions (more than 90%), while for higher stages and grades survival after 5 years can be lower than 60%.

Malignant epithelial tumors are generally unusual before menarche and are mainly represented by serous borderline tumors with low malignancy potential and very good prognosis (89% survival at 20 years); the evolution to adenocarcinoma has only seldom been described. Proposed treatment is monolateral salpingo-oophorectomy and subsequent strict follow-up. For the very rare cases of adenocarcinoma, surgery has to be radical with rigorous adherence to FIGO guidelines.

When a cyst (of unknown origin) is associated with ovarian torsion, suggested treatment is always derotation and cystectomy (either in traditional surgery or laparoscopically); when the ischemic state of the ovary is severe (black-bluish ovary) or there is the suspicion of a solid mass inside the enlarged ovary, it seems appropriate to schedule a "second-look" surgery, avoiding unnecessary oophorectomies. The need for oophoropexy is a very discussed topic, either for the torsed ovary or for the contralateral one.

Cass et al. [15] and Bristow et al. [17] reported an 85% and 100% of ovarian masses with torsion treated with oophorectomy, respectively. Irreversible ischemic damage to the ovary and the concern for malignancy have been attributed to the high rates of oophorectomy in these masses. With increasing evidence of complete ovarian recovery after detorsion and low rate of malignancy (only 2% of ovarian masses with torsion were malignant in the study of Papic et al. [9]), current recommendation includes detorsion and cystectomy, without complete oophorectomy, followed by postoperative surveillance, regardless of how ischemic or necrotic the ovary appears intra-operative.

In the treatment of ovarian masses (either cystic or solid) is not indicated any hormonal therapy. It has been well demonstrated, in fact, that estroprogestinic therapy has no effect in the resolution of cystic masses (when their nature is functional, they are spontaneously disappearing) nor in time of resolution, as recently shown in a Cochrane's review by Grimes et al. [18].

Finally, aspiration of ovarian cysts has no indication and is considered obsolete because of its very low specificity (32%); if masses are complex there is the risk to spread teratomas and to induce a chemical peritonitis. If masses are cystic, unilocular, simple, according to their dimensions, the only treatment option is observation or excision (laparoscopic or open surgery) [19].

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Female Genital Mutilations

12

Lucrezia Catania, Omar Abdulcadir,
and Jasmine Abdulcadir

Abbreviations

AOU	Azienda Ospedaliera Universitaria
DAIMI	Dipartimento Materno infantile
FGM/C	Female Genital Mutilation/Cutting
WHO	World Health Organization

12.1 Introduction

WHO defines Female Genital Mutilation (FGM) as all procedures that involve the partial or total removal of external genitalia or other injury to the female genital organs for non-medical reasons [1]. The practice is still being reported in 30 countries in Africa and in some countries in Asia and the Middle East (Yemen, Iraqi, Kurdistan, Indonesia and Malaysia; there is a high prevalence of FGM in some specific geographical areas) [1, 2]. Some forms of FGM have also been reported in specific ethnic groups in Central and South America [1].

In the last decades, because of international migration, the number of affected or at risk of FGM girls and women has increased in high-income countries [3, 4].

L. Catania, M.D. (✉) • O. Abdulcadir, M.D.
Regional Referral Centre for the Treatment and Prevention of FGM, Health Promotion of Immigrant Woman, DAIMI, AOU-Careggi Florence, Florence, Italy
e-mail: lucreziacatania@yahoo.it; oabdulcadir@aou-careggi.toscana.it

J. Abdulcadir, M.D.
Department of Obstetrics and Gynecology, Geneva University Hospitals, Geneva, Switzerland
e-mail: jasmine.abdulcadir@hcuge.ch

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Unicef has estimated that over 200 million girls and women worldwide live with some forms of FGM and the negative health consequences [2]. Every year almost three million girls and women are at risk of FGM [4].

Healthcare providers in all countries may face the need to provide healthcare to this population. Unfortunately, health workers often do not know the different types of genital mutilations; they are unaware of the real health consequences and are inadequately trained in diagnosing and treating these properly. The opportunities to identify FGM are frequently missed [5]. Paediatricians/gynaecologists have to be able to identify children/girls who have had some forms of FGM to offer appropriate care, treatments and information and to protect girls at risk. Better-trained personnel will lead to improved communication, higher rate of accurate diagnosis and better health care offer. This could also have an impact on prevention of the practice for future generations [5]. An appropriate training can also avoid stigmatization and misdiagnosis, with possible serious legal, social and psychological consequences for families that may be unjustly persecuted after the incorrect reporting to the court [6].

12.2 Classification and Description

According to the World Health Organization (WHO), female genital mutilation is classified into four types and subdivided into subtypes (Table 12.1).

An agreed-upon classification and a corresponding correct morphology for each type of female genital mutilation are important for clinical practice, management, recording and reporting, as well as for research on prevalence, trends and consequences of female genital mutilation. A visual reference and learning tool for

Table 12.1 World Health Organization classification of female genital mutilation

Type I: Partial or total removal of the clitoris[a] and/or the prepuce (clitoridectomy)
Type Ia: Removal of the clitoral hood or prepuce only
Type Ib: Removal of the clitoris[a] with the prepuce
Type II: Partial or total removal of the clitoris[a] and the labia minora, with or without excision of the labia majora (excision)
Type IIa: Removal of the labia minora only
Type IIb: Partial or total removal of the clitoris[a] and the labia minora
Type IIc: Partial or total removal of the clitoris,[a] the labia minora and the labia majora
Type III: Narrowing of the vaginal orifice with creation of a covering seal by cutting and apposition of the labia minora and/or the labia majora, with or without excision of the clitoris (infibulation)
Type IIIa: Removal and apposition of the labia minora
Type IIIb: Removal and apposition of the labia majora
Type IV: Unclassified All other harmful procedures to the female genitalia for non-medical purposes, for example, pricking, piercing, incising, scraping and cauterization

Reprinted from [1]

[a]In the World Health Organization classification, when there is reference to removal of the clitoris, only the glans or the glans with part of the body of the clitoris is removed. The body or part of the body and the crura of the clitoris remain intact as well as the bulbs, two other sexual erectile structures [7]. This anatomic notion is very important in education and in treatment of sexual dysfunction

healthcare professionals is now available. This tool can be consulted by caregivers when unsure on the type of FGM diagnosed, used for training and surveys for monitoring the prevalence of female genital mutilation types and subtypes and be used in legal disputes Figs.12.1, 12.2, and 12.3 [8].

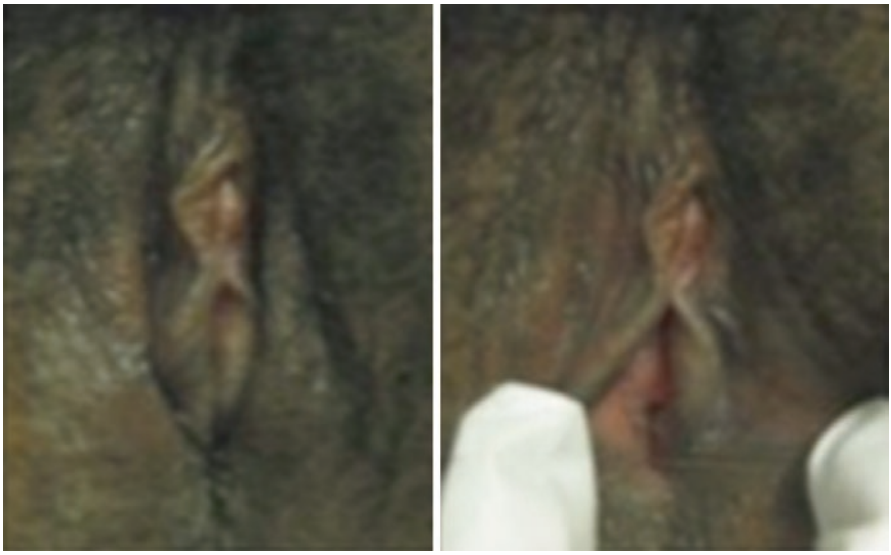

Fig. 12.1 Female genital mutilation type Ia: removal of the prepuce of the clitoris or clitoral hood (female circumcision). Courtesy of Jasmine Abdulcadir

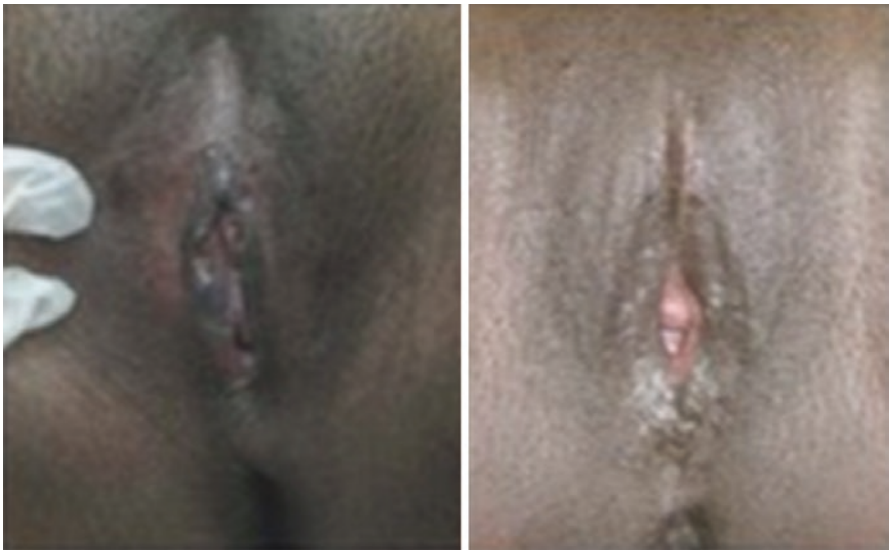

Fig. 12.2 Female genital mutilation type IIc: partial or total removal of the clitoris, the labia minora and the labia majora. Courtesy of Jasmine Abdulcadir

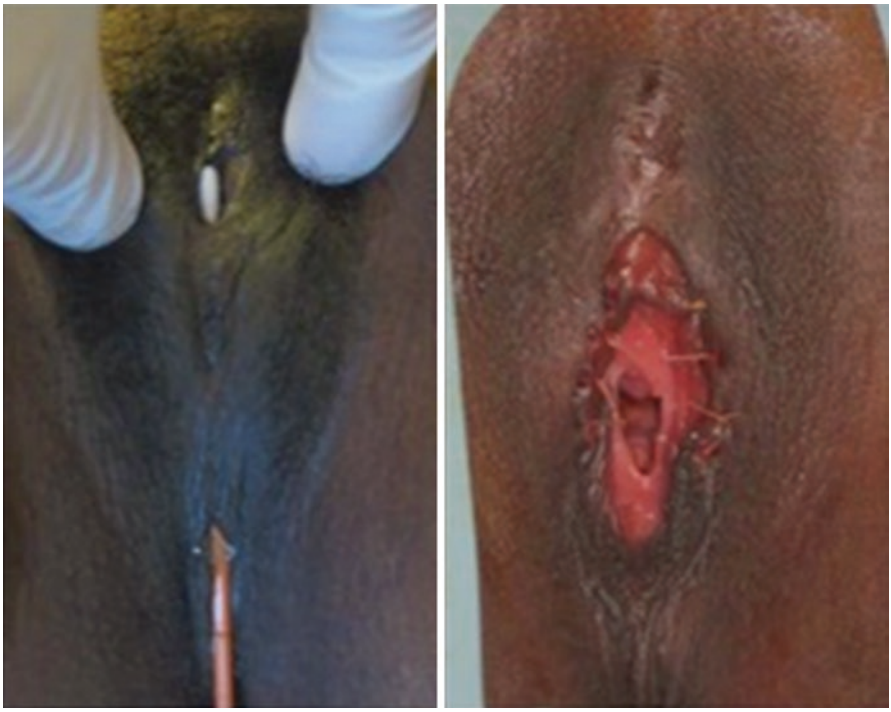

Fig. 12.3 Female genital mutilation type IIIb without cutting of the clitoris before and after defibulation. Courtesy of Jasmine Abdulcadir

12.3 FGM, Religion and Social Factors

FGM is not prescribed by any religion even if it is often thought that they are a religious obligation. Women and children with FGM/C can have Islamic, Christian, Jewish or Animist religion depending on their ethnicity.

Factors used to justify and perpetuate FGM are multiple and diverse: social and peer acceptance, preparation for adulthood and marriage, removal of dirty, masculine and impure parts of the genitalia, reduce sexual impulses to ensure chastity and overall maintain cultural identity [9].

The young girls who come from these cultures have to go through this painful experience, painful both physically and psychologically, to become part of the female group, and to be worthy of becoming wives and mothers 1 day.

While FGM leaves the ability for procreation intact, FGM mutilates the female body in the most intimate and sensitive parts which have the only function, so far discovered, of giving sexual pleasure. Furthermore, in the majority of cases, the subjects who are subjected to FGM are not in a position to oppose. This practice is recognized as an abuse and violence against minors and a violation of human rights [1].

FGM is practiced at different ages depending on the country of origin. It may be performed from few days after birth to 15 years, usually before the first period [2].

Among certain ethnic groups, it can be performed after the marriage or after giving birth. Most of girls examined for a study on FGM in a London safeguarding clinic were less than 10 years old when FGM was performed [10].

12.4 Complications

FGM can be responsible for heath complications, the severity of which depends on different factors such as quantity of removed tissue (types and subtypes of FGM), pre-existing health and nutritional condition of female baby/child, childhood feelings and emotions (often fear coexists with pride), hygienic and sanitary modalities and instruments used for the practice (unhealthy or sanitary tools, traditional practitioner or physician or nurse, etc.).

Although FGM is carried out during childhood, the available medical literature, often coming from countries of the diaspora, has mainly focused on the obstetric and gynaecological impact on adults. However, FGM is illegal and in many countries it is mandatory for health professionals to report to the police when a case of mutilation has been disclosed or when physical signs or symptoms of FGM are seen in a minor [9, 10].

FGM can be responsible for short- and long-term health complications [1].

The short-term effects of FGM afflict children/girls immediately after the procedure.

Haemorrhage, infection of the wound, pain, and shock are reported as common. Anaemia has been reported in 38% of girls after FGM [11]. Because of the use of unsterile tools, cases of tetanus, transmission of blood-borne infections such as Hepatitis B and C and HIV have been described. The real number of children who died for the operation is not officially registered [12].

Long-term complications may afflict women with FGM for long life. Their care and treatment require specific medical attention and sensitivity as women can be unaware that their symptoms are caused by FGM or that they underwent the practice. The most frequent complications are well described in the medical literature. Some others of them are frequent and unknown. The most serious complications concern FGM type II and III, which has also been more investigated compared with type I and IV.

Recurrent vaginal-urinary tract infections and dysuria (including prolonged micturition, drop by drop urinary stream flow through the tiny orifice of the infibulation) have been reported in up to 22% of women following FGM [9, 13]. When in the scar of FGM type III there are several orifices, urination is rainy. With the stagnation of the urine behind the infibulation scar, small stones can be hidden behind it. A prolonged bladder outlet obstruction caused by the infibulation (urethral meatus is covered by the scar) can cause myogenic, morphological and neurogenic changes which lead to detrusor overactivity, urinary urgency, with incontinence, frequency and nocturia [14].

Cysts in the scar are frequent and sometimes may evolve in abscesses or grow very much [15].

Post-traumatic clitoral neuroma (benign tumour arising after a section or injury to a nerve caused by the regenerative disorganized proliferation of the lesioned nerves) can be a consequence of FGM. Sometimes neurinomas are asymptomatic or they cause chronic pain or severe pain during sexual activity. In that case, the

treatment seems to be surgical excision. Considering the high frequency of clitoral cysts in case of infibulation, clitoral neuroma should be considered in the differential diagnosis when a cyst is painful [16].

Haematocolpos/haematometra has to be suspected in girls coming from countries with tradition of FGM when the absence of the menarche coexists with developed secondary sexual characteristics. The excessive tightness of the vaginal introits caused by an infibulation could be the cause. In that case, a defibulation can solve such complication.

Mental health problems such as anxiety, post-traumatic stress disorder and depression have been linked to FGM [17, 18].

The first sexual intercourses can be painful and sometimes remain so for life if not treated appropriately. In women with FGM type III, penetration is difficult or even impossible and a defibulation should be offered. When there is a sexological problem, it should not be assumed that the mutilation is the only cause responsible for it. Other factors may cause a sexual dysfunction, including other past traumatic events, and it is necessary to provide sexual education, information and proper treatment, involving the partner if necessary.

It is important to support adolescents with FGM because the social stigmatization and the negative messages from the media regarding FGM may provoke negative expectations on the possibility of experiencing sexual pleasure creating sexual dysfunction. They should have correct information on anatomy, sexual functioning, and appropriate treatment [1, 19, 20].

Negative impact on obstetric outcomes for the mother and baby has been described (increased risks of post-partum haemorrhage, C-section, perineal trauma and perinatal death) [1, 9, 21]. Risks were increased with more extensive FGM.

WHO (2016) has published the guidelines on the management of health complications from female genital mutilation to provide up-to-date, evidence-informed recommendations on the management of health complications from FGM and to provide standards that may serve as the basis for developing local and national guidelines and healthcare provider training programmes [1].

12.5 Defibulation and Clitoral Reconstruction

Defibulation is a surgical procedure for reversing infibulation and opening the vaginal introitus, uncovering the urinary meatus and, when not excised, the clitoris. The operation improves the urinary and menstrual flow, reduces the dysmenorrhea and dyspareunia, solves the urinary and vaginal infections, and facilitates instrumental examination and the spontaneous delivery. It can be partial (opening of the scar up to the urethral meatus) or total (opening up to the clitoris). Defibulation is the most important treatment of the infibulation. It is recommended to give appropriate briefing and psychological support before and after the operation [1].

Clitoral reconstruction is a relatively new surgical technique which implies the resection of the scar covering the clitoral stump, sectioning the suspensory ligament, removing the fibrosis surrounding the mobilized stump, and repositioning it as a neoglans. Even if recent reports claim that surgical clitoral reconstruction may restore

sexual function and reduce pain [22], available studies of this technique are flawed with lack of long-term follow-up and psychosexual assessment [1, 23, 24]. In absence of conclusive evidence on its safety and efficacy, at present it is not recommended by the available guidelines. When performed, post-op management should be multidisciplinary and guarantee adequate analgesia. Some authors reported that genital pain after clitoral reconstruction can recall memories of the genital mutilation [25].

12.6 Clinical Management of FGM

In high-income countries, it is not usual to see children who have acute symptoms due to a recent mutilation of the genitals. There is also a trend towards less invasive types of FGM with less tissue damage and lower acute health pathologies. A pricking or a small incision of the prepuce (Type IV FGM) or a little excision of the prepuce (Type Ia) is difficult to be diagnosed once healed, as there is no or a very small scar. Creighton states that while gynaecological operators are not familiar with the range of normal genitals in children, paediatricians have more experience but they usually tend to concentrate on the hymenal and anal findings and often do not examine the clitoris in detail unless specifically looking for FGM [9]. Paediatricians may also be unfamiliar with the different types of FGM particularly where physical signs are minimal or absent [9, 26, 27]. The examiner should be trained on these subjects and in the use of the colposcope. Detection of type IV FGM might be easier and documentation for peer review or to seek a second opinion from an expert would be possible. In addition, photo documentation for all Types of FGM will be required in the case of any subsequent legal proceedings. In presence of a child with FGM just arrived from the original country (because of migration or adoption), general assessment of the complications should be made. If she is infibulated, a deinfibulation to open the vaginal scar tissue can be offered. Girls who are asymptomatic may defer the operation until adulthood and should be given contact to access the appropriate service prior to sexual activity or marriage. Defibulation procedures are usually performed under local anaesthetic in adult women but in children a brief general anaesthetic would be more appropriate. Evidence is lacking but the psychological impact of a surgery performed on the site of the ancient trauma may be severe with flashbacks and memories. Input from a child psychologist with experience in working with children with FGM and their families should be available [10, 27, 28]. When a child is confirmed to have FGM, it is a professional requirement to report it and it is important to safe other younger sisters or other young female relatives. Parents should be made aware of the law against FGM [27].

Conclusion

The health needs of children with FGM are different from those of adults for whom there are official guidelines for a correct management of the physical and mental consequences. Skills needed for diagnoses and treatment of FGM in children should be specific. Paediatricians need to be familiar with the health implications and physical findings in children with FGM. They must also be aware of the legal status of FGM and their own responsibilities with regard to recording

and reporting FGM. Paediatricians working within safeguarding clinics are likely to be increasingly called upon to assess whether or not a child has had FGM. Confirmation of FGM in young children may be difficult. Genital findings may be subtle and this may be due to the performance of less invasive types of FGM in girls at a younger age.

In conclusion, when receiving children from communities with tradition of FGM it is important to confirm or not a FGM and its eventual complications; offer appropriate treatment or referral; assess the real risk of FGM in a child and her relatives who did not undergo genital mutilation; inform and communicate with them and their parents belonging to different cultures, avoiding stigmatization. In case of language barriers, family members or friends should never translate. Certified interpreters should be used. It is also useful to be familiar with safeguarding procedures, multiagency working and the legal implications [27].

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Sexual Abuse and Genital Trauma

13

Maria Rosa Giolito, Giulia Mortara, and Monica D'Amato

13.1 Definition

> "Sexual abuse occurs when a child is engaged in sexual activities that the child cannot comprehend, for which the child is developmentally unprepared and cannot give consent, and/or that violate the law or social taboos of society. The sexual activities may include all forms of oral-genital, genital, or anal contact by or to the child, or non-touching abuses, such as exhibitionism, voyeurism, or using the child in the production of pornography. Sexual abuse includes a spectrum of activities ranging from rape to physically less intrusive sexual abuse" [1].

13.2 Introduction and Epidemiology

Child sexual abuse is a social and public health problem, with potentially devastating and expensive consequences. Latest studies report that over one billion children from 2 to 7-years-old experienced violence; worldwide, the World Health Organization estimate that every year 1,500,000 people lose their life due to violence [2–4].

Child abuse outcomes can be both physical and/or psychological reflecting on social costs. Each abuse can leave indelible signs willing to persist, signs that if not

M.R. Giolito (✉)
Dipartimento Materno Infantile ASL Città di Torino, Turin, Italy
e-mail: mariarosa.giolito@aslto2.piemonte.it

G. Mortara
S.C. Consultori Familiari e Pediatrici ASL Città di Torino, Turin, Italy
e-mail: giulia.mortara@aslto2.piemonte.it

M. D'Amato
S.C. Legal Medicine, A.O.U. "Città della Salute e della Scienza", Turin, Italy
e-mail: damato.monica@libero.it

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properly detected and treated can determine permanent physical and psychological damages [5–8].

The mechanism that tries to explain how childhood negative events influence in a significant way people's health and welfare it's well represented by the Adverse Childhood Experiences (ACEs) Pyramid (Fig. 13.1) [9].

Among the many possible symptoms we mention: growth disorder, cognitive disorder, sleep and food-related disorder, psychosomatic disorder, anxiety and depression, alcohol and substance abuse, smoking, post-traumatic stress disorder, psychiatric disorder, self-injuring behaviors, suicide, cardiovascular pathologies, and cancer [10–12].

Not less important is the trans-generational transmission: from a 2005 study has been found especially in poly-victimization cases, abused children tend to become abusers in adulthood [13].

The most suitable approach consists of four fundamental steps:

- Investigate and identify problem extension
- Highlight causes and risk factors
- Actuate treatment programs
- Identify prevention programs [4, 14–17]

It's extremely important to identify the phenomena extension, in order to define and apply customized and efficient strategies to face the problem. Face means being

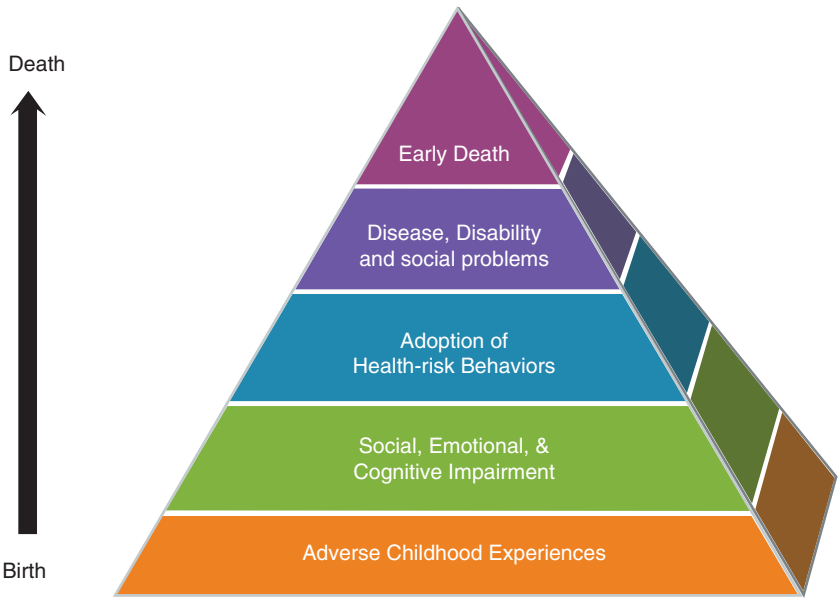

Fig. 13.1 The impact of adverse childhood experiences on the lifespan

able to detect, have the medical competences to assist the victim, and provide the most adequate treatments, but also implement prevention strategies [18].

The exact child abuse prevalence is unknown. This is due to several factors: absence of unified and shared protocols, victim's difficulties in disclosing due to the own nature and dynamics of the sexual abuse, low conviction rate in judiciary paths [19, 20].

Many times sexual abuse histories are revealed in adulthood. The NSPCC (National Society for the Prevention of Cruelty to Children) performed many studies, and from one of them, conducted on 2869 adults from 18 to 24-years-old, and the 11% of them reported to have been abused in childhood. Furthermore, comes out that 16.5% of the people from 11 to 17-years-old and the 24.1% of the people from 18 to 24-years-old, experienced sexual acts during childhood [21].

It's important, for the detection, to know the risk factors, in particular the environment around the child and his relationships. A recent research on child abuse in Malaysia shows that a low socioeconomic status, dis-harmonies or familiar conflicts, and substance abuse of parents psych disorders can be related to an increase in sexual abuse risk for little girls [22, 23].

Prevention programs have been applied by several world organizations (WHO, UNICEF) involving health, social, educational and justice services, summarized with the acronyms THRIVES (Training in parenting—Household economic strengthening—Reduced violence through legislative protection—Improved services—Values and norms that protect children—Education and life skills—Surveillance and evaluation) that have the potential to reach and sustain the efforts to prevent violence against children [2, 3].

13.3 Medical Examination

Victims usually can't give a name to what had happened to them and they can't explain the feelings in words, but their body can tell their stories even if children can't. Victims do not always receive the type of help they really need and each and every therapy is going to be relatively inefficient if the underlying traumatic experience is not detected and faced.

The medical examination usefulness is undisputed for the identification of the clinical situation and/or the various injuries of nature and a treatment program launch.

It's vital to detect the sexual abuse as soon as possible to prevent consequences. At this point, clinicians have a key role in the identification, management and report of suspected sexual abuse, and many health organizations promote training programs for clinicians in order to support sexual abuse detection and improve the victim taken in charge.

Clinicians must be able to identify abuse signs and symptoms, diagnose, and provide medical treatments in case of injuries, infections, or other pathological conditions related or not related to the abuse. It's important that they perform a complete and accurate medical evaluation, examining the little girl from the head to the toes, reassuring her when it's possible, on her health status [24–26].

The minor victim of sexual abuse can in fact perceive her own body as "damaged," thus the psychological reassurance related to her body's status and her integrity represents a fundamental moment along the recovery path in order to avoid the victim to keep saying "I still feel like I am not normal" [27, 28].

During the medical examination, the clinician has to accurately collect the documentation, also photographs, that could be helpful in court site, where he could be asked to give testimony [29].

The testimony in court needs competences that are not always obtained in clinical practice. Guidelines are available in literature and essential indications for a correct and adequate testimony for the doctors that are usually asked to explain why the physical examination alone does not prove or disprove that sexual abuse occurred [30, 31].

It is the clinicians' duty to report to the court the child prejudice status according to the state legislation and he must activate, if needed, protection measures to avoid further abuses, also, if necessary, with hospitalization or urgent admission foster care homes.

Even though the importance of specific timing is widely documented in literature, often clinicians don't have adequate knowledge and technical and emotional skills to deal with a suspected sexually abused girl. Therefore, to limit diagnostic errors (false positive/false negative) and further traumas for the child, it's important that medical examination is performed by professionals with specific skills [21, 30, 32, 33].

13.4 Reception

It is not always possible to schedule the first medical examination for a little girl suspected of sexual abuse, thus usually the first examination can't be performed in the best context.

It is fundamental to try to ensure a quiet and discreet environment, not to traumatize the little girl further, ensuring a second clinician's presence to support both the clinician and the child.

It is important to perform the examination at the presence of a trusted adult—unless the girl prefers he/she doesn't stay—who remains with her during the clinical evaluation and assists her while she gets undressed and dressed. It is fundamental to have time to be able to obtain the girl's trust and agreement, providing explanations on examination modalities and reasons, and using a proper language suitable for her age. It is important to ensure privacy, not to use strength or deceits during the exam. In particular, it's recommend to reschedule the visit if the child is not calm while examining the genital area and she doesn't cooperate [25, 34–36].

It is also recommended not to touch the genital area and breast, unless if needed for the clinical evaluation: in this case, the little girl must be informed and her agreement obtained. It is important to observe and report the behavior and the emotional state during the examination [37].

Sedation is performed very rarely, when the benefits are doubtfully higher than potential risks, for example, in case of vaginal and/or anal injuries that need surgical treatment, in case of foreign vaginal and/or ano-rectal bodies, and in case of important bleeding or of nature to be diagnosed.

13.5 Medical History

The medical history data collection and the reported child story are the base for the medical evaluation.

It is important that professionals are competent, empathic, not judging and objective. Often the sexual abuse diagnosis is exclusively based on the medical history so the data collection accuracy is fundamental. Inductive questions should never be asked; instead, the spontaneous story should be reported paying attention to transcribe the girl's sentences integrally and to avoid making her repeat the story many times. Congruence check is necessary between the dynamic facts, timing and observed clinical status, scheduling possible further investigations (blood exams, pharynx/vaginal/rectal swabs, instrumental exams) [27].

13.6 Objective Examination

During the medical examination, the little girl must be examined "from the head to the toes" analyzing each single part of her body and paying attention to cover the different areas as the examination proceeds. During the objective examination, the genital area evaluation has to be done. It's good practice to examine also the oropharynx because oro-genital contacts are recurring in sexual abuse. It is fundamental to report any careless signs, paying special attention to the body, hair, and oral hygiene. Weight and height have to be measured as well as the pubertal stage according to Tanner's stages. It is important to perform a complete evaluation giving back to the little girl, if possible, the "body integrity" concept that could be precluded if the examination is limited to the anal-genital area only [38–41].

13.7 Ano-genital Area Examination

To examine the ano-genital area, the three positions shown in the figure are used (Fig. 13.2):

In Figure 13.2 the supine position, usually well accepted, gives a good visualization of the vulvar area, the vaginal orifice (a). It's possible to examine the youngest little girls kept in this position by a trusted adult on his arm. To visualize clearly the hymenal ring, the little and big lips pull technique is used (b). In the genupectoral position, the little girl leans on her hands and knees (c). This position is sometimes less appreciated because the clinician stands behind her, out of her sight, but it's fundamental to confirm signs identified in the supine position [42]. To visualize clearly the anus, a light traction is applied to the gluteus (d); the little and big lips pull technique is used for the hymenal ring visualization even in the genu-pectoral position (e).

It is important to know very accurately the ano-genital area anatomy of the prepubertal girl, its anatomic variants, and the typical pubertal age estrogenization. The vaginal orifice is surrounded by a tissue ring called hymen. The hymen and the anus

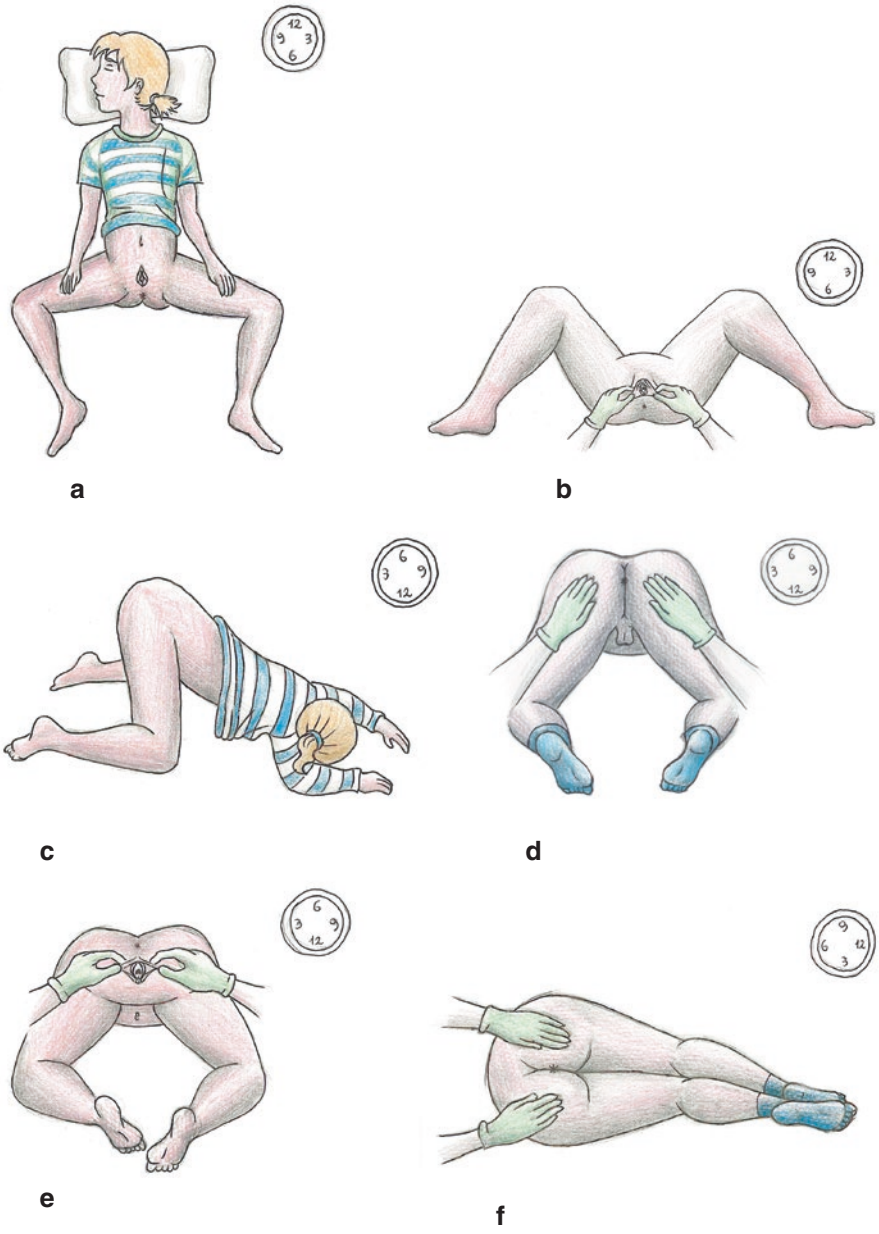

Fig. 13.2 (**a**, **b**) Supine position, (**c**–**e**) genupectoral position, (**f**) left lateral decubitus position

are described using the comparison with the clock quadrants (12 o'clock corresponds to the suburethral zone and 6 o'clock to the rectum medial line in supine position (Fig. 13.3a, b)).

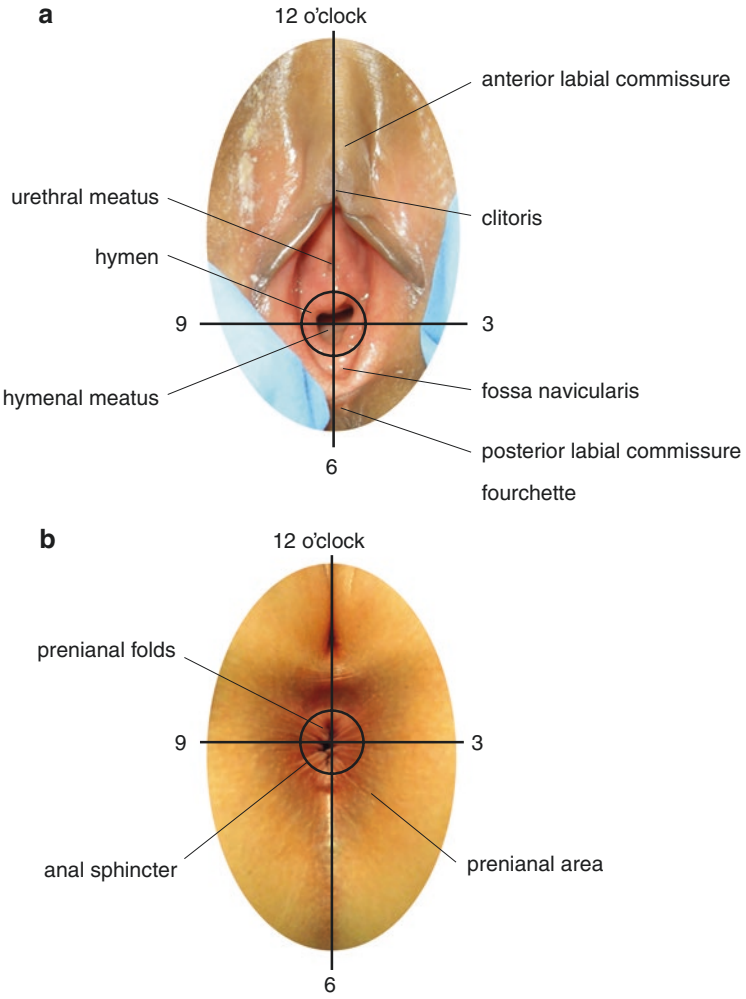

Fig. 13.3 Ano-genital area

In prepubertal girls, hymenal tissue can be completely absent in the suburethral area approximately from 10–11 o'clock to 1–2 o' clock. The posterior tissue portion can be more or less represented thus the posterior edge can be more or less high, configuring crescentic hymen, a frequent configuration. In another common hymen configuration, the tissue completely surrounds the vaginal orifice (annular hymen).

The hymen, like the other genital organs, is under the sexual hormones influence. The estrogens, for example during neonatal (due to mother hormones' presence) and puberal period, make hymen tissues more redundant, in a way that often fold on themselves making edges wavy and frequently covering vaginal orifice.

The myth the hymen "breaks up" during the first sexual intercourse leads to the preconception that it's possible to determine whether there has been sexual activity

at least ones with the medical examination; actually, it is evident that health professionals without specific experience often expect that penetrative acts always leave clear physical signs and believe that a doctor can determine through the medical examination if an adolescent is "virgin" or not [43, 44].

In this regard, Kellogg's review on 36 pregnant adolescents is very interesting: only 2 of the 36 girls presented hymenal complete transection[1] of the posterior half. The scientific explanation is that penetration doesn't always cause visible tissue damages and/or that acute injuries can heal without leaving any sign.

13.8 Medical Examination Timing

Sexual abuse often doesn't produce evident signs and many of the injuries are superficial. For this reason, it is fundamental to perform the medical examination as soon as possible. Literature recommends to carry out the examination within 72 h from the sexual abuse or anyway as soon as the minor protection safety measures have been applied.

Latest studies indicate the need to perform the medical examination in prepubertal girls within 24 h from the event and within 72 h in adolescents. Furthermore, still for prepubertals, it has been confirmed that DNA research provide positive results especially when the medical examination is executed within 24 h [30].

The early medical examination objectives are numerous [25, 27, 33]:

- Identify ano-genital injuries and sexually transmitted diseases
- Prevent pregnancies through emergency contraception in pubescents
- Collect evidences for forensic medicine purpose
- Safeguard victim's physical integrity and psychological wellness reassuring on her health state

Medical examination should be postponed only in case the girl is not cooperative and she doesn't agree with the exam execution despite the reassurances. We restate that the doctor who is going to perform the clinical examination must have specific competences. In case a competent professional isn't available, it's recommended to send the child to the closest specialized hospital or territorial center [30, 34, 45].

13.9 Injures Recovery Time

Traumatic ano-genital injuries heal rapidly, often leaving no trace [46].

The more often damaged structures during a penetrative sexual abuse are the hymenal membrane, the fossa navicularis, and the fork [47].

[1] Clefts/notches up to hymenal base are known as transections.

The healing process of these injuries is not different from the recovery of any other injuries of the same nature in other body regions. The healing stages consist of:

- Thrombosis and inflammation cells activation
- Damaged cells regeneration
- New cells multiplication
- New epithelium differentiation

The healing process of the more superficial injuries proceeds with formation of new epithelium at a rate of 1 mm in 24 h. For deeper injuries, the damaged cells regeneration process is fully active between 48 and 72 h, and the multiplication and differentiation processes begin from the fifth and seventh day. The complete tissue recovery takes from 4 to 6 weeks; the scarring tissue maturation might need at least 60–180 days [33, 47, 48].

These healing processes explain the usual absence of genital injuries in little girl victims of sexual abuse if the medical examination is performed too far in time from the last suspected violence episode.

13.10 Physical Signs

The evaluation of possible signs of sexual abuse can be accomplished during the medical examination performed for other reasons or asked by a parent reporting a suspect. In this case, it is the doctor's duty to activate the services and/or report to the Court according to the state legislation in the different countries.

Physical signs in case of sexual abuse are caused by traumas, mechanical actions characterized by rubbing, stretching, and compressing. The sexual trauma effects, and thus physical signs, can be: bruises, hematomas, abrasions, grazes, injuries.

Generally speaking, this signs vary depending on several factors [21, 46, 47, 49]:

- Abusive action type
- Force used
- Girl's age and pubertal status
- Abusive events frequency
- Elapsed time from last abusive episode

It is fundamental to reaffirm that in the majority of cases, anal and genital injuries become undetectable in a short time period from when they have been produced and consequently it's very recurring that injuries are not detectable anymore, not because the episode didn't happen but because the healing process leaves no cues. Thus, conclusions that exclude with absolute certainty that the event happened must be avoided [50–52].

The doctor can rarely formulate a definitive diagnostic hypothesis based on the objective examination alone; therefore, the diagnosis of sexual abuse must be

multidisciplinary to avoid, due to a wrong medical valuation, a not-guilty adult is unfairly accused or a minor victim of abuse isn't safeguarded by the abuser [53–56].

The observed signs have more or less probative consistency through the integration with other acquired evidence findings [25, 57].

Many studies demonstrate that 90–95% of children who declared in believable way they have been abused have normal clinical finds or not specific physical signs. In fact, the answer to the question "Has the girl been abused?" it is not usually on the body [27, 33, 58].

Related to the physical signs only, several indications are provided by scientific literature and the classifications proposed can lead to the correct interpretation of what is observed during the medical examination [21, 30].

The evaluation path for a little girl victim of sexual abuse (Fig. 13.4) is complex and must be anyway complete and multidisciplinary.

13.11 Sexually Transmitted Infections

Victims of child sexual abuse are at risk of contracting sexually transmitted infections (STI), even though the transmission is quite rare, due to the modalities that characterize the majority of sexual abuses.

Actual literature does not recommend an STI screening for all the victims of sexual abuse, but it is necessary to be able to evaluate how and when to proceed with further diagnostic exams (Fig. 13.5).

It is recommended to submit to screening the little girls with anal and/or vaginal penetration history, those living in high STI prevalence area, those who have been abused by a stranger or by a high STI risk person keeping in mind the elapsed time from the contact, the incubation time, and the window period.

Screening is also mandatory for little girls who have been diagnosed an STI in the past and for those presenting suggestive STI signs and symptoms, such as vaginal discharge, vulvovaginitis, genital ulcers, or condyloma acuminata [59].

The risk of contracting a sexually transmitted disease is related to the infection prevalence itself in the local adult population, to the abuse modalities and duration, to the girl's age, and to the possible coexistence of genital and/or perianal injuries [60].

The type of exam and the examined area depend on the sexual contact modes and are case-dependent: blood exams, pharyngeal, anal, vulvar, transhymenal or vaginal swabs, or first urine exam.

Asserting that sexual abuse is the infection's source with a certain degree of confidence implies the consideration and exclusion of other possible transmission ways.

Many of the sexually transmittable infections can be vertically transmitted from the mother to the child during pregnancy, the childbirth, or during the perinatal period. For some others, it is exceptionally described that the transmission is through fomite, by self-inoculation or for very close physical contact, with modalities varying from one infection to another.

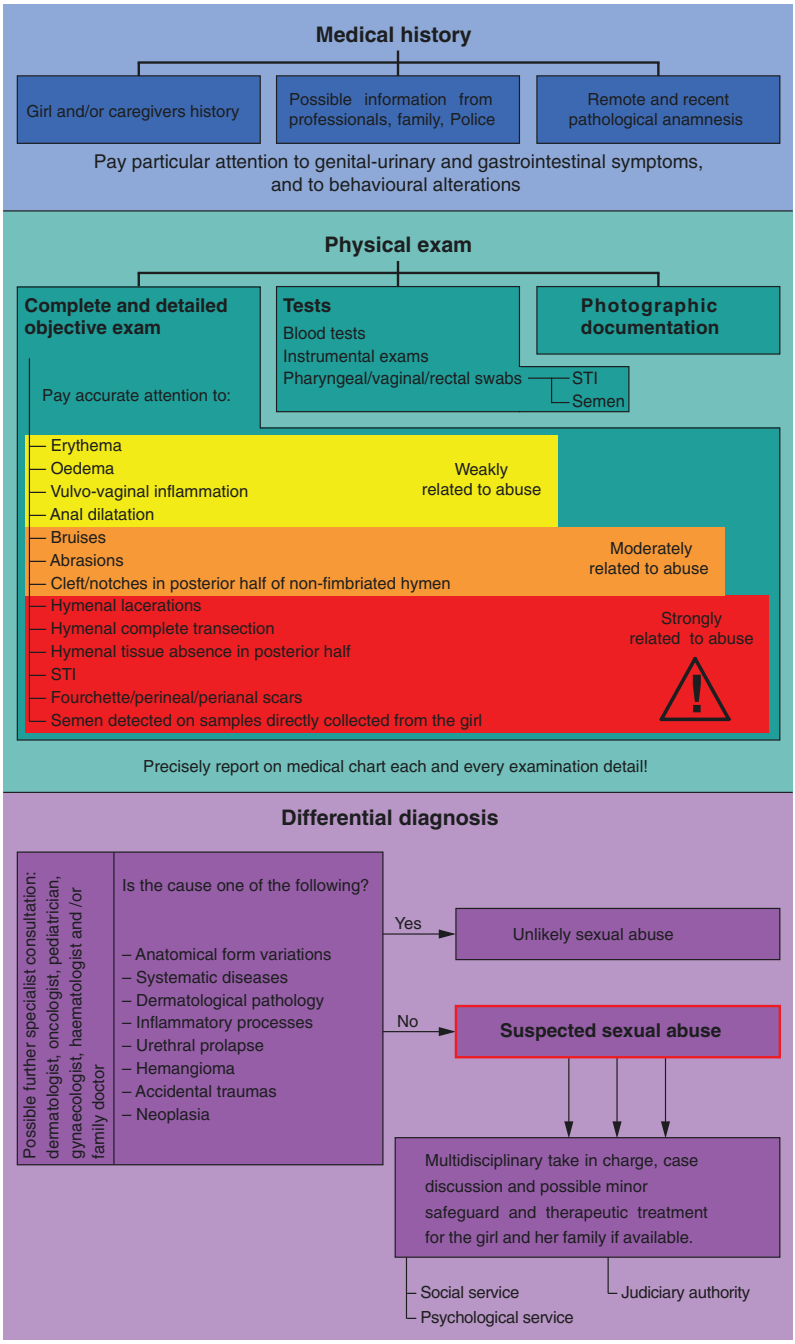

Fig. 13.4 The evaluation path for a child victim of sexual abuse: medical history, physical exam and different diagnoses

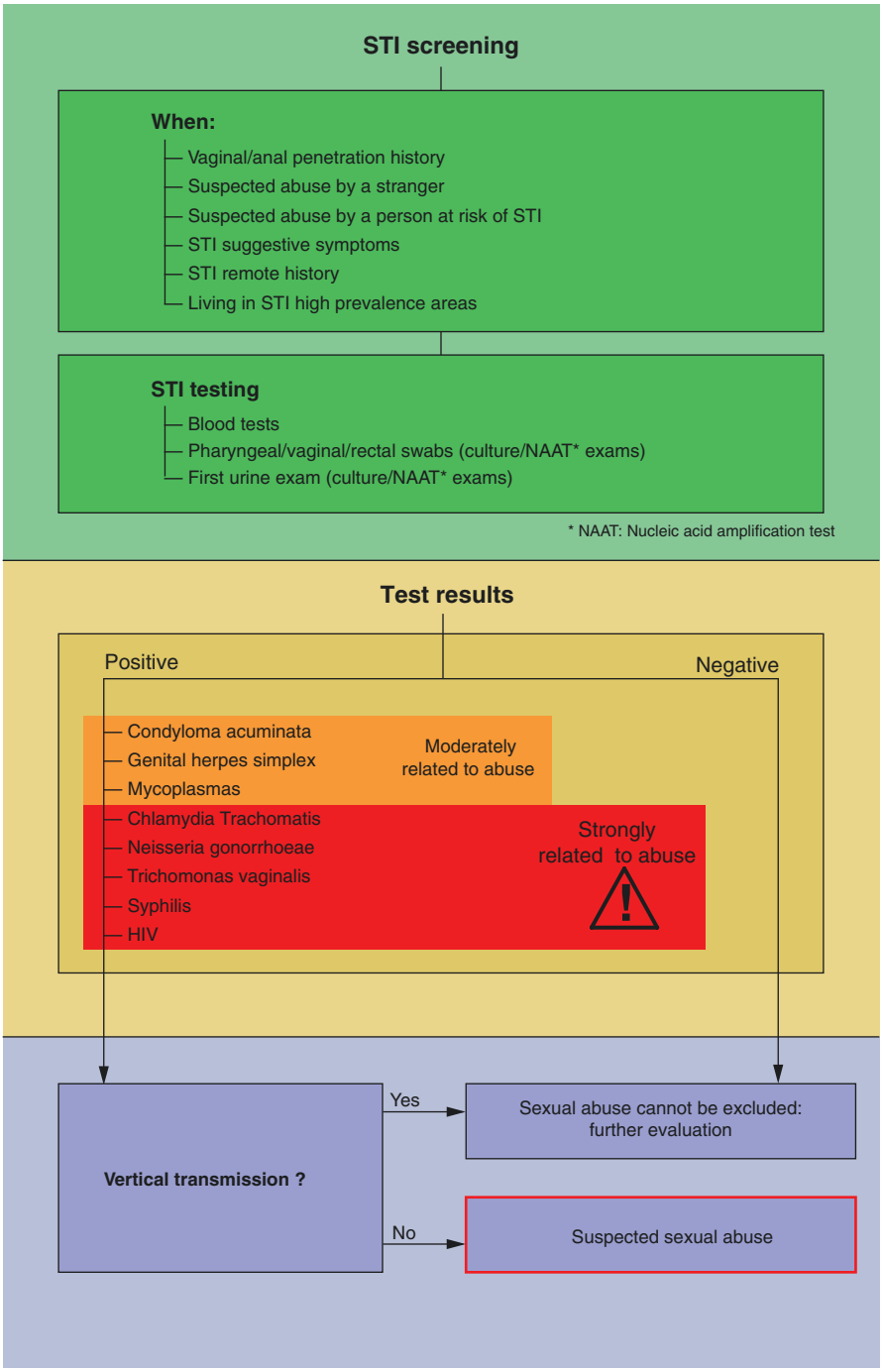

Fig. 13.5 Sexually trasmitted diseases and child sexual abuse

We remind that while taking in charge a little girl victim of suspected sexual abuse, it is also to be considered the possibility to submit to screening her brothers and sisters (possible victims of abuse as well) too, the parents (to check vertical transmission too) and any possible cohabitants.

Scientific evidences do not help to determinate at which age the vertical transmission can be excluded and there is no research study providing a defined cut-off age after which it cannot be considered.

From the literature analysis results the following:

- Gonococcal anal and genital infections are rarely acquired in perinatal age and beyond the neonatal period and are considered as probable sexual abuse consequences [21, 30, 61].
- Chlamydia infections in children older than 3 years have to be considered as a probable consequence of sexual abuse [21, 30, 62].
- HIV infections in children not exposed to the virus in perinatal age, with no previous contacts with blood products or needles have high probability of being consequences of sexual abuse [30, 62].
- Trichomonas has to be considered as possible consequence of sexual abuse [21, 62].
- Herpes and condyloma acuminata can be sexually transmitted to children but are not diagnostic of abuse by themselves and experts' opinions are controversial [30, 62].
- The mycoplasmas' presence is also controversial [63].

The vertical transmission must always be considered, but we remind that sexual abuse can happen at any age, even in infants. It is then important to highlight that the identification of a vertically transmitted infection does not necessarily exclude that the child could have been a victim of sexual abuse.

Literature studies indicates that, when the vertical transmission can be excluded, Gonorrhea, Chlamydia, Trichomonas, Pox, Condyloma acuminata and HIV are found more frequently in victims of sexual abuse than in non abused population. Sexual abuse is the most probable transmission modality of sexually transmitted infections in prepubertal girls [21, 30, 62].

We underline that the meaning of a sexually transmitted infection in a prepubertal girl with history of suspected sexual abuse requires a careful interpretation and always needs the urgent activation of the childhood protection services.

The answer to the question "is the presence of a sexually transmitted infection in young girls a consequence of a sexual abuse?" is "almost always".

"Almost always" is supported by literature and international guidelines, but almost is a qualifying adjective that admits the possibility of rare or unusual transmission mechanisms that don't involve sexual abuse. So, in any case, the certainty in concluding that a little girl has been or not sexually abused depends on the quality of the path to make the diagnosis [64].

This path always must guarantee an expert professional intervention, a high quality laboratory analysis, including taking samples correctly. Furthermore, it is

important to pay great attention to the safety and wellness of the girl and her family through a multidisciplinary care with excellent communication flows between institutions and a continuous comparison among professionals avoid achieving easy and rushed conclusions, both supporting or against the sexual abuse hypothesis [21, 30].

13.12 Documents

It is fundamental to collect all the medical examination data precisely and correctly in the medical report. Terms and words must be not ambiguous or results of self-interpretation, especially regarding the minor's and caregivers' history. It is recommended to report the exact words used by the minor telling her history, transcribing them in inverted commas.

The photographic data collection should be a standard procedure, especially in case of evident physical injuries, due to its low frequency even when the sexual abuses have been confirmed. The photographic data are fundamental to support the clinical examination and to avoid submitting the little girl to multiple repeated examinations in case of doubtful injuries. Moreover, they allow successive analysis by other specialists, when injuries are already healed [21, 27, 30, 58, 65].

We reaffirm the importance of asking for girl's agreement before performing any act, including the photo shots.

Data to be collected and reported in the medial report are:

- Child and accompanist's personal data
- Reason why the medical examination is asked for
- Minor and accompanist's tell
- Familiar, physiologic, remote pathological, and recent pathological medical history
- General and genito-anal exam examination
- The photographic material
- Minor's behavior during the medical examination
- Instrumental/laboratory tests and specialists consultation if executed
- Possible therapy and preventive care

The medical report, based on the specific country legislation, in case of sexual abuse has to be sent to the judiciary authority and/or to the childhood protection services for the multidisciplinary care.

The detection, diagnosis, taking in charge, and treatment of sexual abuse constitute complex problems where medical, psychological, social, and juridical aspects intersect each other; this makes the involvement of many professional roles indispensable and therefore the only possible and adequate tool to face them is the teamwork made of professionals with specific competences on child sexual abuse.

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Sexually Transmitted Diseases in Adolescence

14

Gilda Di Paolo

Abbreviations

BV	Bacterial vaginosis
DES	Diethylstilbestrol
CDC	Centers for Disease Control and Prevention
CIN	Cervical intraepithelial neoplasia
ELISA	Enzyme-linked immunosorbent assay
FTA-ABS	Fluorescent antibody absorbed treponemal
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HSV	Herpes simplex virus
LGV	Lymphogranuloma venereum
MSM	Men who have sex with men
NAAT	Nucleic acid amplification test
RPR	Rapid plasma reagin
SIL	Squamous intraepithelial lesion
STD	Sexually transmitted disease
STI	Sexually transmitted infection
TP-PA	*T. pallidum* particle agglutination
VDRL	Venereal Disease Research Laboratory
VIN	Vulvar intraepithelial neoplasia
WHO	World Health Organization

G. Di Paolo, M.D.
Pediatric and Adolescent Gynecology Service, UOSD of Gynecology and Obstetrics, Santo Spirito Hospital, Pescara, Italy
e-mail: gildipa55@gmail.com

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The term "Sexually transmitted diseases" (STDs) refers to a variety of clinical syndromes and infections that involve a great number of people all over the world [1, 2] and are caused by pathogens that can be acquired and transmitted through sexual activity [3]. Symptoms related to the infection usually involve the genitalia and urinary tracts, but there are some conditions that may have systemic manifestations.

The World Health Organization's fight against sexually transmitted diseases which is among the main concerns of worldwide public health [4]:

- 499 million curable sexually transmitted infections (gonorrhoea, chlamydia, syphilis, and trichomoniasis) are diagnosed in patients between 15 and 49 years old every year, many of which may be asymptomatic.
- Around 2/3 of these occur in under 25s
- At least 1 in 20 adolescents contracts STDs each year and the average age of infection is decreasing in relation to the ever younger age of first sexual intercourse in early adolescence (already 7% between 13 and 14 years old) and in relation to the increasing number of occasional partners.
- USA: 20 million new STDs are diagnosed each year, 50% among 15–24 year olds (mainly gonorrhoea and chlamydia)
- STDs represent one of the main reasons of both male and female infertility (USA: each year undiagnosed STDs cause infertility in 24,000 women)
- Drug resistance (especially in gonorrhoea) represents a great challenge for the overall control of the STDs in the world

The possibility of contracting an STD in young women is particularly high both due to the biological risks of the age group and due to the behaviour of adolescents (Table 14.1).

The biological vulnerability of the STDs in adolescents is related to:

- The immaturity of the immune system with lower local production of IgG and IgA
- Less dense cervical mucus due to the lack of progesterone as a consequence of anovulatory cycles
- Physiological extension of the columnar epithelium from the cervical canal to the vagina, with a higher susceptibility of the cylindrical cells to the STDs
- Alteration in vaginal flora caused by menstruation, use of contraceptives, vaginal douching, antibiotics, sexual intercourse, and stress

Factors of adolescent behaviour which expose them to greater risk of contracting an STD include:

- The ever younger age at which they have their first experience of sexual intercourse
- Promiscuity
- Number of sexual partners

Table 14.1 Sexually transmitted pathogens and related infections

Aetiological agents	Infection, disease, or related syndrome
Bacteria	
Calymmatobacterium granulomatis	Inguinal granuloma
Chlamydia trachomatis	Urethritis, cervicitis, epididymitis, proctitis, pharyngitis, MIP, lymphogranuloma venereum, neonatal conjunctivitis
Gardnerella vaginalis	Vaginitis, urethritis
Haemophilus ducreyi	Chancres ulcers or chancroid
Neisseria gonorrhoeae	Urethritis, cervicitis, epididymitis, proctitis, pharyngitis, conjunctivitis, neonatal conjunctivitis, MIP
Mycoplasma genitalium	Urethritis, cervicitis
Streptococcus type B	Vaginitis, balanoposthitis
Treponema pallidum pallidum	Syphilis
Ureaplasma urealyticum	Urethritis, prostatitis, MIP
Virus	
Cytomegalovirus (CMV)	Congenital malformations
Herpes Simplex Virus-HSV1 and 2	Primary and recurrent genital herpes, neonatal herpes
HAV, HBV, HCV	Acute and chronic viral hepatitis
Human papillomavirus	Genital warts, cervical and anal dysplasia
Molluscum contagiosum virus-Pox	Molluscum contagiosum
HIV-1	HIV disease/AIDS
Zika Virus	Microcephaly, neurological complications
Protozoa	
Entamoeba histolytica	Amebiasis
Giardia lamblia	Giardiasis
Trichomonas vaginalis	Vaginitis, urethritis, prostatitis, epididymitis
Ectoparasites	
Phthirus pubis	Pediculosis pubis

- Oral sex [5]
- Abuse of drugs and alcohol
- Smoking
- Failure to use any form of protection
- Limited use and/or negative perception of the health service [6]
- Inadequate knowledge and/or awareness of STDs

14.1 *Chlamydia trachomatis* Infection

Chlamydia trachomatis is the most common cause of curable bacterial sexually transmitted infection (STI) worldwide. Prevalence is higher among under 24s and in most cases is an asymptomatic infection (75% in women, 30% in men) and for this reason there is widespread transmission of the disease.

Chlamydia trachomatis is an obligate intracellular parasite of which 18 serologically distinct variants exist (these have been categorized by identifying monoclonal antibodies). These serotypes are:

- Serotypes A, B, Ba, and C cause ocular trachoma, a major cause of blindness in many developing countries.
- Three serotypes L_1, L_2, and L_3 are associated with lymphogranuloma venereum.
- Serotypes B, D, E, F, G, H, I, J, and K are associated with infection of the genital tract—cervicitis, urethritis, salpingitis, proctitis, and epididymitis. Major complications of female genital tract disease include acute pelvic inflammatory disease, ectopic pregnancy, infertility, and infant pneumonia and conjunctivitis.

Chlamydia is spread by sexual contact (vaginal, anal, or oral sex) and as vertical transmission at birth from mothers to infants.

The higher the number of sexual partners is, the greater the risk of contracting the infection is.

Indeed, the principal risk factor for contracting Chlamydia is having had a new sexual partner in the last 6 months.

Any clinical symptoms appear 1–3 weeks after infection. In women, Chlamydia infects the cervix, and, in most cases, the urethra, causing vaginal discharge, coital bleeding, and dyspareunia. On physical examination, mucopurulent or purulent discharge from the endocervical canal and cervical friability are common (Fig. 14.1). In an elevated number of cases, the infection can involve the urethra and the symptoms are characterized by dysuria, bladder tenesmus, and urinary frequency. Infection can cause pelvic inflammatory disease with abdominal pain, fever, backache, intermenstrual bleeding, and possible persistent fallopian tube damage.

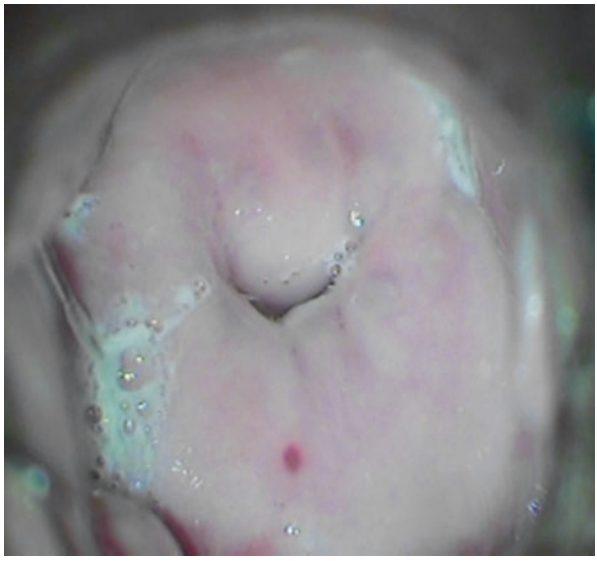


Fig. 14.1 Mucopurulent or purulent sichard from the portio (Chlamydia infection)

Men may act as disease carriers, spreading the condition, but rarely developing long-term health problems. Infection could be silent for months or years. In this case, the condition may be identified during a screening programme and/or routine testing. In men, chlamydia infection causes urethritis and epididymitis (from 30 to 50% of non-gonococcal urethritis is caused by chlamydia). The symptoms are dysuria and discharge when squeezing urethral meatus. If the infection is transmitted by anal sex, the symptoms are characterized by proctitis with pain and bleeding. If the transmission is by oral sex, the manifestation is a pharyngeal infection.

Despite the fact that symptoms are tolerable and are often not diagnosed, the consequences for the reproductive organs, and especially for women infected with Chlamydia, may be very serious. Untreated chlamydia infections put women at an increased risk (40–67%) of developing pelvic inflammatory disease. The involvement of the fallopian tubes, the uterus, and of other adjacent tissues can cause permanent damage (tubal occlusion being the worst possible consequence), or lead to peri-hepatitis (Fitz-Hugh-Curtis syndrome). Additional negative outcomes include chronic pelvic pain, tubaric infertility, and ectopic, or "extra-uterine", pregnancy. Tropism from Chlamydia in the cylindrical epithelial cells of the endo-cervix causes an inflammatory reaction which attracts polymorphonucleated cells and consequently leads to the development of a humoral immune response. Replication of the micro-organism in the host leads to cellular lysis with associated tissue damage which is worsened by the immune response. Several studies demonstrated that tubal damage pathogenesis is prevalently caused by the host immune reactivity, and, in particular, by the prolonged production of cytokine and chemokine by the tubaric epithelium. Immune reaction reactivation, is also possible, however, in the case of persistent infection, or re-infection, which trigger fibrotic responses towards Chlamydia antigens, among which is the Hsp60 (CT-Hsp60) protein which shares common amino acid sequences with man and with other bacteria, such as *Escherichia coli* [7].

In men, permanent damage seems less probable, although Reiter's syndrome has a higher incidence, which is a form of sero-negative arthritis that includes skin lesions, urethritis, and iridocyclitis.

Chlamydia infection may also increase susceptibility to HIV, which, in adolescents, has been shown to increase by a factor of 5. Moreover, a persistent Chlamydia infection can increase the risk of infection by oncogenic types of HPV, thus increasing the risk of cervical cancer [8, 9].

Urogenital infections caused by Chlamydia may be diagnosed using endocervical tampon samples (in women) and endo-urethral tampon sample (in men) or by testing "first emission" urine samples.

Nucleic acid amplification tests (NAATs) are the most sensitive tests and are recommended for detecting *Chlamydia trachomatis* infection [10].

NAATs can be performed on endocervical, urethral, vaginal, pharyngeal, rectal, or urine samples. The accuracy of NAATs on urine samples has been found to be nearly identical to that of samples obtained directly from the cervix or urethra [11].

Treating Chlamydia infections prevents adverse reproductive health complications and continued sexual transmission, and treating their sexual partners can prevent re-infection and infection of other partners.

Recommended treatment:
- Azithromycin 1 g, orally in a single dose
  Or
- Doxycycline 100 mg, orally, twice a day for 7 days

Alternative treatment:
- Erythromycin 500 mg, orally, four times a day for 7 days
  Or
- Erythromycin ethyl succinate 800 mg, orally, four times a day for 7 days
  Or
- Levofloxacin 500 mg, orally, once daily for 7 days
  Or
- Ofloxacin 300 mg, orally, twice a day for 7 days

A meta-analysis of 12 randomized clinical trials of azithromycin versus doxycycline for the treatment of urogenital chlamydial infection demonstrated that the treatments were equally efficacious, with microbial cure rates of 97% and 98%, respectively [12].

A high prevalence of *Chlamydia trachomatis* infection has been observed in previously treated patients. Most of these post-treatment case are not due to the inefficacy of the treatment, but rather, are usually caused by re-infection following unprotected sexual intercourse with, either, an inadequately treated partner, or with a new, partner who is also infected. For this reason is very important to treat the partner, or partners, whether or not they are asymptomatic, and, even, following a negative test. Complete abstention from sexual activity is recommended until 7 days after therapy with single-dose azithromycin or until after treatment with doxycycline has been completed. The use of barrier contraception (e.g. a condom) significantly reduces the risk of transmission but does not eliminate it completely. Given the wide diffusion of asymptomatic Chlamydia infections, an annual chlamydia screening programme would be opportune for sexually active women below the age of 25, as well as for all sexually active women with frequent new or multiple sexual partners, having a partner with a sexually transmitted infection, and for all pregnant women. In some European countries, the annual report of the National Chlamydia Screening Programme has registered a reduction in the episodes of pelvic inflammatory disease [13, 14].

14.2 Lymphogranuloma Venereum

It is a sexually transmitted infection caused by some serotypes of *Chlamydia trachomatis* ($L_1L_2L_{3,}$) which cause a chronic disease. It is endemic in Asia, Africa, and South America and was observed among male homosexuals in Europe (especially if infected HIV), where is a relatively common cause of proctitis [15–17].

The heterosexual transmission has been attributed to asymptomatic women carriers whereas in male homosexuals, the asymptomatic rectal infection is the likely source of transmission [18]. The contagion can only be contracted through vaginal, oral, and anal sexual intercourse. The infection is manifested by a vesicle in urogenital or rectal region that may erode, with the formation of a small painless ulcer that heals in a week with no results, and that often goes unnoticed. In the next phase, for the spread of the bacterium in the lymphatic system, the typical symptoms are a unilateral lymphadenitis (potentially involving the iliac, perirectal, and inguinal lymph nodes) associated with fever, malaise, and arthralgia. If not treated in good time, the infection may complicate with peri-rectal abscesses, fistulas, and scars that requiring surgery.

The diagnosis of lymphogranuloma venereum is based on history, on epidemiological information, after excluding other clinical conditions of proctitis, lymphadenopathy, and rectal ulcers; it is confirmed by the identification of the type-specific DNA LGV, if you detect *Chlamydia trachomatis*, and rectal levy is the best procedure.

Treatment [19]
- Doxycycline 100 mg orally two times daily for 21 days
- Erythromycin 500 mg orally four times a day for 21 days
- Was proposed azithromycin in single or multiple doses

14.3 Chancres Ulcers or Chancroid

It is an infection caused by Gram-negative bacillus *Haemophilus ducreyi*, rare in Europe, but particularly common in tropical countries, although the prevalence of chancroid appears to have decreased worldwide. Transmission occurs as a result of a trauma during sexual intercourse, and after an incubation period of about 3–10 days, the infection is manifested by the appearance of a papule with erythematous edge on the skin or on mucosal of the genitals. After about 24–28 h, the papule develops first in pustule and then in soft, bleeding, and painful ulcer. Clinically, an inguinal lymphoadenopathy and general symptoms may be associated. The combination of painful genital ulcer with inguinal adenopathy suppurative could be indicative of chancroid, especially after excluding other diseases responsible for genital ulcers (syphilis, herpes, lymphogranuloma venereum); the diagnosis can be confirmed by identifying the *H. ducreyi* even if the culture is difficult to perform [20].

As with other sexually transmitted infection leading ulcers in the genitals, the chancroid increases the risk of HIV transmission, and therapy in HIV-infected subjects is more complex.

Recommended treatment regimens [21]:
Azithromycin 1 g orally in a single dose
or
ceftriaxone 250 mg IM as a single dose
or
Ciprofloxacin 500 mg orally two times daily for 3 days
Sexual partners should also be treated even in e absence of clinical manifestations.

14.4 Gonorrhoea

Gonorrhoea is a sexually transmitted disease caused by infection with the *Neisseria gonorrhoea* bacterium. The incubation period varies from 3 to 10 days. *N. gonorrhoea* infects the mucous membranes of the reproductive tract, including the cervix, uterus, and fallopian tubes in women, and the urethra in women and men and can also infect the mucous membranes of the mouth, throat, eyes, and rectum. The organism adheres first to the epithelial cells, infects the epithelial layer, then penetrates into the sub-epithelial space, initiating the inflammatory process and its complications. Trans-luminal spread in males can lead to prostatitis orchiepididymitis and in females leads to PID (10–20% of the cases) and peritonitis. The bacterial dissemination can also cause bacteraemia, cutaneous lesions, fever, arthralgia, arthro-synovitis, especially of knee, hip, and wrist. Transmission can occur through sexual contact with the penis, vagina, mouth, or anus of an infected partner. Gonorrhoea can also be spread perinatally from mother to baby during childbirth. Highest reported rates of infection are among sexually active teenagers and young adults (15–29 years old). Gonorrhoea infection, in particular, is also concentrated in specific geographical locations and communities. Subgroups of MSM are at high risk of gonorrhoea infection.

Asymptomatic infection of the genital tract is very frequent in women, occurring in about 90% of cases, and does occur in males, but in only about 5% of cases.

Rectal and pharyngeal infections are generally asymptomatic.

In women, symptoms are generally correlated with endocervical and urethral infections and include an increase or a variation in the characteristics of vaginal secretions, intermenstrual spotting, dysuria, menorrhagia, dyspareunia, mucopurulent urethral or cervical discharge. Gonorrhoeal infection should be excluded proactively in young females presenting with lower abdominal pain, pain during uterus and adnexa mobilization and in women with a significant sexual history. Pelvic inflammatory disease is thought to affect one in five women who remain

untreated for gonorrhoea. The gonococco bacterium can cause Bartholin's abscesses and can lead to inflammation of the para-urethral glands. In males, gonorrhoea infection generally causes acute urethritis, displaying profuse mucopurulent urethral discharge, dysuria, and meato-urethral erythema [22, 23].

The diagnosis is based on the identification of *N. gonorrhoea* in genital, rectal, pharyngeal, and ocular secretions [10].

Culture testing is a cheap, specific diagnostic test which permits rapid identification of the bacteria and also permits testing for antibiotic susceptibility. The use of selective culture terrains with the addition of antibiotics is recommended. Culture testing is recommended for samples which have been taken from the endocervix, urethra, rectum, and pharynx, and samples should be taken according to the information contained in the sexual anamnesis of the girl. The sensibility of culture testing is elevated for samples taken from the genital area as long as collection, transport, and storage of the sample itself are appropriate.

Instant microscopic evaluation with Gram, or methylene blue has good sensitivity (>95%), and good specificity, as a rapid diagnostic test in symptomatic men with urethral secretions. Microscopy has poor sensitivity (<55%) in asymptomatic men and in identifying endocervical infections (<55%) or rectal infections (<40%). Microscopic evaluation cannot be recommended as a diagnostic test in these circumstances.

Nucleic acid amplification tests (NAATs) for the detection of Neisseria gonorrhoeae have a sensitivity >95% compared with microbiological culture although sensitivity varies from one type of NAAT to another. In the case of confirmation of diagnosis, or on failure of therapy, an antibiogram culture should be performed. NAAT can be used on endocervical swabs, vaginal swabs, urethral swabs, and urine samples. In women, NAAT sensitivity on urine is lower than that of NAAT performed on endocervical and vaginal swab. A single vaginal or endocervical specimen evaluated with NAAT has a sufficient sensibility (90%) when used as a screening test. Collection of urethral, urine, rectal, and pharyngeal specimens should be directed by the anamnesis and from the personal sexual habits.

Test indications:

- Vaginal discharge associated with risk factors for STD (<30 years old, new or multiple sex partners)
- Mucopurulent cervicitis
- Sex partner who has been recently diagnosed with an STD or a PID
- Symptoms or signs of urethral discharge in males
- Acute orchiepididymitis in males <40 years old
- Acute PID
- STD screening in adolescents
- Screening for subjects with multiple sex partners
- Purulent conjunctivitis in newborns.

Gonorrhoea treatment is complicated by the ability of Gonorrhoea to develop resistance to antimicrobials, and this causes grave limitations to the therapeutic approach [24, 25].

However, there is a geographical variability of the diffusion of the resistant types. For this reason, it is useful to consider different therapeutic options established by the national surveillance system.

In Europe, cephalosporins are mainly used because of the recurring resistance of *N. gonorrhoea* to fluoroquinolones.

Recommended treatment
- Ceftriaxone 250 mg IM, in a single dose
  or
- Cefixime 400 mg, orally, in a single dose.

Increasing bacterial resistance also extends to these antibiotics and makes it essential, whenever persistent symptomatology is encountered, to repeat microbiological culturing with antibiogram of the isolated strain.

The Centre for disease control recommended a possible dual therapy by the addition to Ceftriaxone of Azithromycin 1 g, orally, in a single dose. Recent sex partners (i.e., persons having sexual contact with the infected patient within the 60 days preceding onset of symptoms, or gonorrhoea diagnosis) should be referred for evaluation, testing, and for treatment.

The therapy must be extended to any partners with the strong recommendation to abstain from any sexual activity until the therapy has been completed and the symptoms have disappeared.

All new cases of *N. gonorrhoea* infection should be notified to local, regional, and national authority.

14.5 Syphilis

It is a complex sexually transmitted infection caused by the bacterium Treponema pallidum.

It develops in several stages, each characterized by different symptoms and course and is considered a chronic systemic disease marked by alternating active phases and periods of latency.

According to data provided by the WHO, there is an increased prevalence of syphilis in the general population, and men are affected more than women.

Transmission is by sexual contact or by vertical, mainly transplacental (congenital syphilis).

14.5.1 Primary Syphilis

From infection, the onset of symptoms may take 10–90 days (average 20 days).The first stage is characterized by the appearance of a papule at the place where the bacterial infection occurs (vulvar region, cervix, mouth, penile, anal canal), which later

after abrasion becomes an ulcer with raised edges, which are not painful (syphiloma) and which heals spontaneously after 3–6 weeks. If the infection is not treated at this stage, it progresses to the secondary stage.

14.5.2 Secondary Syphilis

Begins, about 2 months after the healing of the syphiloma, with the onset of rash that affects the palms of the hands, soles of the feet or other body parts; these lesions type macules, papules, or pustules are not associated with pruritus and are concomitant with a systemic not painful lymphadenopathy. In the mouth and in the vulvar region appear erosions painless but contagious. Characteristic of this stage are non-specific general symptoms (fever, headache, weight loss, patchy alopecia, sore throat). Even this stage may resolve spontaneously without any treatment.

14.5.3 Lag Phase

Stage without clinical manifestations is detected only by serology and the evolution can be towards recovery, asymptomatic carrier state or tertiary syphilis.

14.5.4 Tertiary Syphilis

At this stage can begin internal organs damage (brain, nervous system, eyes, heart, liver, bones, blood vessels). On the skin and mucosa appear painless papules that evolve into ulcers and scarring (Syphilitic gumma). Tertiary syphilis occurs in not treated subjects even after decades and is fortunately rare evolution.

The diagnosis of syphilis can be performed using material taken from a patient's excoriation or wound, isolating treponema, that is easily recognizable by optical microscopy or with direct immunofluorescence techniques, reliable methods for the diagnosis of early syphilis.

Serological diagnosis is based on using two types of tests: non-specific and specific for treponema. Among the first, there are the Venereal Disease Research Laboratory (VDRL) that identifies cardiolipin antibodies; it becomes positive after 3–4 weeks after infection, becomes negative after therapy, and is used to evaluate the effectiveness of treatment, and rapid plasma reagin (RPR); the specific treponema tests are the Fluorescent Antibody Absorbed treponemal (FTA-ABS) and *T. pallidum* Particle Agglutination (TP-PA).

The non-specific tests are widely used as inexpensive, but their use is not sufficient for diagnosis since they can result in a false negative in patients tested during primary syphilis and can result in a false positive in people without syphilis but affected by other diseases: infectious (malaria, tuberculosis, viral fevers, leprosy), collagen vascular disease, pregnancy, age, drug addiction. Therefore, the subjects tested with a non-treponemal test should always be assessed with a treponemal test to confirm the diagnosis. Specific tests positivity persists for all life.

Recently, specific new generation tests like ELISA have become available for use on a large scale.

The *treatment* is simple and involves the use of penicillin. Preparation, dosage, and treatment duration depend on the stage and clinical manifestations of disease:

- Benzatin penicillina G 2.4 million in single dose IM in the first and second stage and in early latent phase
- Benzatin penicillina G 2.4 million units IM three times, in latent syphilis and in the third stage.

The treatment of primary and secondary syphilis in allergic subjects includes an attempt to desensitization before using the drug of second choice, Doxycycline (100 mg orally twice a day for 14 days) [26].

Since latent syphilis is not transmitted sexually, the goal of treating people in this stage is the prevention of complications of disease and vertical transmission.

However, a careful examination of all accessible mucosa (oral cavity, perianal area, perineum, vagina in women, and under the foreskin in men) should always be performed in people with latent syphilis.

The infected person should refrain from any sexual activity with new partners until complete wound healing. Shall be performed diagnostic tests and therapy on sexual partners and, also, patients with primary and secondary syphilis should be tested for HIV infection.

14.6 Bacterial Vaginosis

Bacterial vaginosis (BV) is among the most common causes of vaginal secretions of reproductive age. It is characterized by an abundant proliferation of anaerobic bacteria (Gardnerella, Mycoplasma, Bacteroides, Mobiluncus, Atopobium) and a reduction of the Lactobacillus normally found in the vagina with a consequent increase in vaginal pH.

Bacterial vaginosis is not a sexually transmitted infection but it facilitates the transmission of several (HIV, Gonorrhoea, Chlamydia, HSV-2). The vaginosis appears most often after the first sexual intercourse, after having changed partners and in case of multiple partners. Vaginosis risk factors are: the use of vaginal douches and lubricants, dripping related to IUD, the cigarette smoke.

The complications of bacterial vaginosis are pelvic inflammatory disease, post-surgery infections, and obstetric complications (late abortion, preterm delivery, PROM, postpartum endometritis).

BV is the most frequent cause of malodorous leucorrhoea, but women with VB have mostly no symptoms.

The diagnosis is based on the presence of at least three of the following clinical manifestations. (Amsel criteria)

- Presence of whitish vaginal homogeneous secretions, which cover the vaginal walls
- Vaginal pH > 4.5
- Presence of "clue cells" at microscopic examination of vaginal exudate samples
- Fish smell by whiff test (secretion on slide +10% KOH)

It is also possible to use the Nugent score, which consists in finding the depletion of the normal Lactobacillus flora (It is assigned a score, which ranges from 0 to 10 and is based on the presence of different bacterial morphotypes observed on Gram-stained smears; Lactobacillus (L), Gardnerella (G), and Mobiluncus (M) are quantified).

Bacterial vaginosis requires treatment only in these cases: if it is symptomatic, if it appears during pregnancy or before the insertion of an IUD or before a gynaecological operation.

Treatment
Metronidazole 500 mg × orally daily for 7 days
0.75% Metronidazole gel for intravaginal application (5 g) of the 2× for 7 days
Or
Clindamycin Gel 2% or from 100 mg ova for 7 days
Or as a second choice
Tinidazole os × (2 g × 2 days)

While taking metronidazole, alcohol must be avoided since it can provide nausea, vomiting, abdominal cramps (disulfiram-like syndrome).

The use of probiotics and intestinal acidifying can rebalance the vaginal flora [27].

The benefit of the therapy may also include a decrease in risk of acquisition of *C. trachomatis*, *N. gonorrhoeae*, *T. vaginalis*, HIV, and HSV-2. In the presence of a high colonization of Mycoplasma or Ureaplasma, it must be evaluated the association with a specific therapy.

14.7 Herpes Virus Infection

Genital herpes is a chronic viral infection. Two types of HSV may cause genital herpes: HSV-1 and HSV-2; most cases of recurrence of genital herpes are caused by HSV-2.

A higher percentage of ano-genital herpes infections are ascribed to HSV-1, which is particularly evident among young and MSM women [28], as a consequence of oral sex. In 50% of cases, infection is asymptomatic and, thus, favours the diffusion of the virus.

The primary infection (first contact with the virus) is transmitted through close cutaneous and mucosal contact and, thus, the virus may enter the epithelial cells and replicate.

The symptoms of the infections, after a few days from the contact, are pain, vulvar pruritis, vaginal discharge, burning sensation associated with the appearance on vulva, anus, and cervix of vesicles, which rapidly form ulcerative lesions. Cutaneous ulcerative lesions may be covered by scabs.

Generally, genital lesions are associated with satellite lympho-adenitis and a global reduction in well-being. In some cases, lesions may involve only the cervix (Fig. 14.2), and there may be cases in which clinical manifestations appear after 6–12 months after first infection.

In adolescence, in 20% of cases of herpes infection, pharyngo-tonsillitis infection is present.

After a few weeks, after the visible lesions have healed, the virus no longer reproduces and it retreats through the peripheral terminations to the sacral ganglion with an absence of symptoms (asymptomatic phase, or latent infection).

Recurrences appear when the viral replication is reactivated, which may be caused in various ways, but above all by a weakening of the immune system of the host.

The diagnosis of genital herpes is mainly clinical, and the identification of specific antibodies is useful in case of primary infection (anti-HSV antibodies are

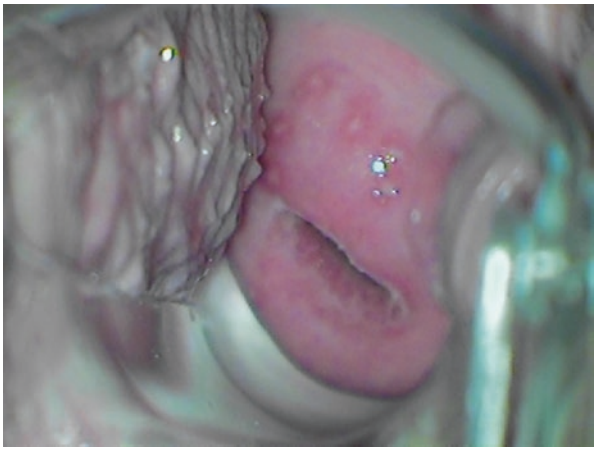


Fig. 14.2 HSV lesion of the cervix

produced during the first weeks after the infection and persist) or in case of atypical manifestations.

It is important that a differential diagnosis which considers other possible causes of genital ulcers (cancroid, Crohn's Disease, Lipschutz ulcers, Behcet's disease, pemphigus, secondary ulcers caused by pharmacological reaction).

HSV-2 infection leads to an increased risk of bacterial vaginosis. In particular, this gives rise to an increased risk, about three times greater, of contracting HIV and may accelerate the progression of AIDS.

Most pharmacological treatments involve the use of oral antiviral drugs that inhibit the viral DNA polymerase of the HSV. Systemic therapy should be given both in the case of primary infection, and in recurrences, but does not fully eliminate the infection, nor does it reduce frequency. Once the treatment has been interrupted, the risk, frequency, and the severity of recurrences is unaltered. Topical antiviral drugs give poor results.

Maintenance of suppressive treatment, reduces the frequency of recurrence in patients that have had more than six episodes in a single year and also reduces the risk of transmission to a partner.

Recommended treatment for first clinical episode:
- Acyclovir 400 mg, three times/day for 7–10 days,
  or
- Acyclovir 200 mg, five times/day for 7–10 days
- Famciclovir 250 mg, three times/day for 7–10 days
- Valacyclovir 1 g, twice/day for 7–10 days

Suppressive treatment:
- Acyclovir 400 mg twice/day
- Valacyclovir 1 g once/day
- Famciclovir 250 mg twice/day

In case of herpes virus infection, counselling is important in order to reduce the risk of transmission; therefore, it is necessary for the patient to:

- Be informed of the nature and course of the disease, of the possibility of recurrence, and of the risk of transmission even in asymptomatic phases
- Inform the partner of the presence and potential infection of the disease
- Recognize recurrence and avoid sexual activity during that phase
- Use a condom during any kind of sexual activity and, be aware that, if used correctly, a condom can reduce the risk of transmission
- Be informed of the therapies available in order to prevent or reduce the possibility of recurrence

14.8 Human Papillomavirus

Human papillomavirus (HPV) is the most common sexually transmitted viral disease: about 111 million new cases/year in younger under 25 years old. Approximately 150 types of human papillomavirus infection (HPV) have been identified by genome, at least 40 of which can infect the genital area [29], other types present a specific tropism for the oropharyngeal and laryngeal area or for the skin. The different types of HPV are separated into high- and low-risk types for malign transformation: some are responsible for benign transformations (condilomatosis, papillomatosis), whereas others produce pre-invasive lesions (dysplasia) and invasive lesions (tumours). Two types of HPV (HPV16 and 18) cause 70% of the tumours of the neck of the uterus and precancerous cervical lesions; there is also evidence to link HPV with tumours of the anus, the vulva, the vagina, the penis, the head, and the neck (tongue, tonsils, and throat).

HPV 16 is the most frequent virus type and is diagnosed in about 30% of all the HPV infections; it is associated to cervical carcinoma, both as squamous cell carcinoma and adenocarcinoma. It is also associated to 90% of vulvar intraepithelial neoplasia (VIN) and 85% of vaginal, anal, and oropharyngeal cancers.

HPV is transmitted sexually through contact with skin and mucous membranes and the micro-traumas which occur during sexual intercourse could favour transmission. Infection may also occur just through genital contact, and it is important to know that the use of a prophylactic does not totally eliminate the risk of infection if the virus has infected the skin area which is not protected by the condom [30]. In rare cases, vertical transmission may occur (from infected mother to baby during birth) or self-contamination may spread the infection to other parts of the body. Transmission by fomites has been hypothesized (as indirect transmission on towels, diagnostic instruments, and underwear) although to what degree the virus is able to survive outside the body, and its consequent capacity to infect, is not known.

Risk factors for HPV transmission and infection are [31]:

- Young age at first sexual intercourse
- Multiple sexual partners
- Sexual intercourse without using barrier methods
- Immunodeficiency condition
- Partner with high risk for STD.

Most genital HPV infections (70–90%), whether caused by low-risk or high-risk type HPV, are transient, asymptomatic, and have no clinical consequences. The reason is that the immune system can remove the virus before it causes pathogenic damage. In fact at 18 months from infection, 80% of women become HPV negative [32], and this percentage is higher in adolescents.

There are three possibilities of evolution for the HPV infection: regression, persistence, and progression.

It is hypothesized that, despite the apparent clearance, the virus can persist in the epithelium with a small charge and the disease can recover again if the immune host defences decrease.

The virus within the host cell can remain silent in episomal form; it can also induce its replication through the proliferation of squamous epithelium and produce vegetative form or it can integrate into the host cell genome, where it induces carcinogenesis processes.

The persistent (more than 18–24 months) HPV infection at high risk is the most important risk factor for the development of high grade CIN or invasive cancer.

Regarding host-related factors, these may include: alterations of immune status, pregnancy and, especially in young women, the presence of both herpes virus infections 2 and Chlamydia, cigarette smoking (nicotine derivatives are concentrated in the cervical mucus and act as immunosuppressants), the use of oestrogen-progestin contraceptive pills which facilitates the persistence of HPV 16 virus (in addition to reduction of the use of barrier methods).

The evolution of HPV infection to invasive cancer goes through lesions confined to the epithelium-defined SIL (squamous intraepithelial lesions). SIL were divided into:

- LSIL which includes the cytopathic changes of HPV infection and mild dysplasia (CIN I) (Figs. 14.3 and 14.4)
- HSIL which includes moderate dysplasia, severe dysplasia, and carcinoma in situ (CIN II, CIN III, CIS).

CIN (cervical intraepithelial neoplasia) is a histological term that considers the epithelial involvement by the lesion. Then, depending on the severity, following grades of CIN can be distinguished:

- CIN I The mild dysplasia: lesion involving the basal third of the epithelium
- CIN II moderate dysplasia: lesion involving up to 2/3 of the epithelium
- CIN III severe dysplasia: lesions involving the entire epithelium without exceeding the basement membrane

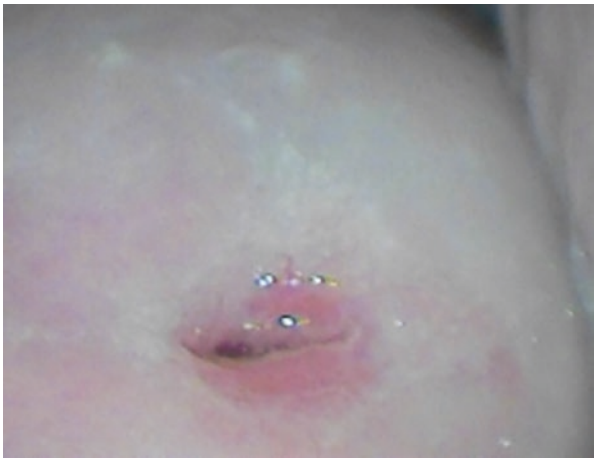


Fig. 14.3 L-SIL of the portio

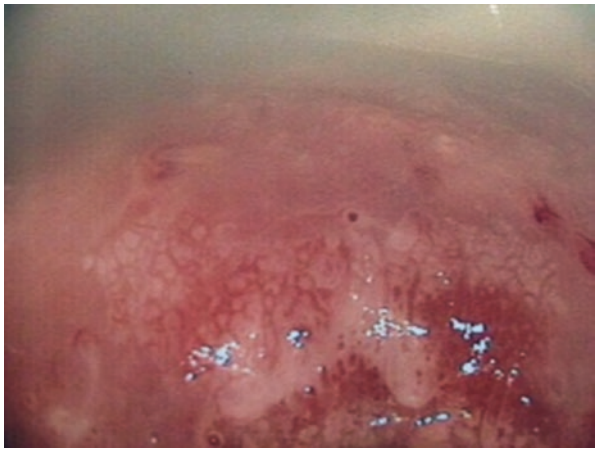


Fig. 14.4 H-SIL of the portio

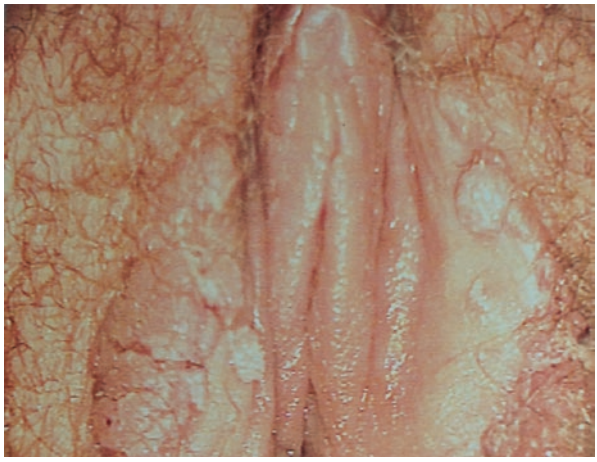


Fig. 14.5 Florid vulvar condylomatosis

These lesions have all the opportunity to regress, those of low grade with a higher percentage.

In adolescence, the most common clinical manifestation of HPV infection is ano-genital warts (florid ano-genital condilomatosis) (Fig. 14.5).

Epidemiological studies have found a low-risk HPV DNA in 100% of ano-genital condyloma, attributable in most cases to HPV 6 and HPV 11. The lesions appear after about 2–4 months from infecting sexual intercourse. Concerned areas may be vulva, vagina (Fig. 14.6), anus, the perineum, the urethra, and also the cervix.

Diagnosis of ano-genital warts is easily detectable with genital examination: the lesions appear as white-pinkish growths, sometimes with the typical cauliflower shape; they may be multiple and affect even large areas. It is necessary to resort to the use of the colposcope in case of micro-warts (Fig. 14.7) or of sub-clinical lesions or in suspected involvement of portio (Fig. 14.8). Normally, condilomatosi is asymptomatic and the detection can be casual. The presence of itching, burning, and vaginal discharge is caused by bacterial or fungal superinfection.

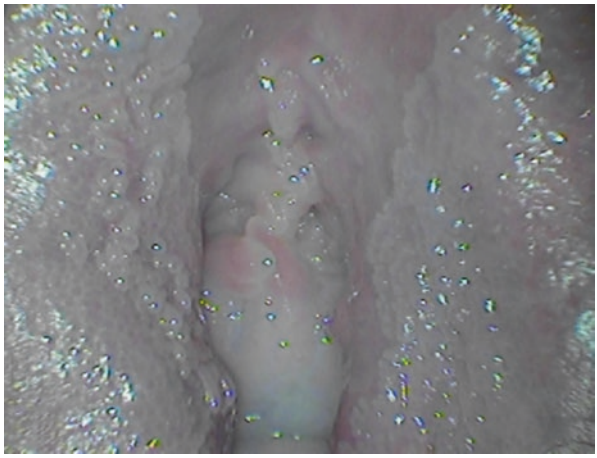


Fig. 14.6 Condylomatosis vaginalis

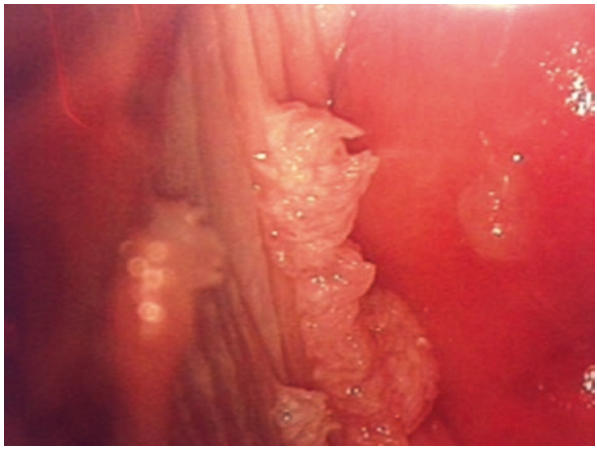


Fig. 14.7 Vulvar microwarts (evident only with colposcopy)

Therapy for HPV depends on the type of wound that the virus determines and from its seat; even if the benign genital lesions may resolve spontaneously, they often require specific treatments. Those pathologies have multiple consequences in teenager life: number of relapses, resistence to the therapies and scarrig sequelae may have a negative psycological and sexual impact.

Genital warts can be treated with both medical and surgical therapies.

For vulval-perineal condylomatosis, cytotoxic and immunomodulating medication can be used:

- Podophyllotoxin 0.5% solution, in two times per day × 3 consecutive days, up to a maximum of 6 weeks.
- Imiquimod, an application three times a week up to a maximum of 16 weeks

One alternative is sinecatechin ointment (derived to 15% from green tea).

The surgical therapies are: diathermy, laser vaporization, cryotherapy with liquid nitrogen.

It has been demonstrated that in young women (younger than 20 years old) there is a predominance of low-risk HPV infections and in the cervical area are found mainly paintings of condilomatosis and of low grade CIN, with risk of disease recurrence and not of progression; in fact, cervical cancer is very rare in adolescence.

Secondary prevention based on screening of cervical lesions is not recommended in this age group, as a result of evidence shown in several studies that cytological abnormalities detected in adolescents are predominantly low grade (97.4%) [33].

It is considered that submit teenagers to screening can lead to unnecessary treatment of cervical precancerous lesions that have a high probability of regressing spontaneously within 2 years of presentation. By contrast, the overtreatment is a real risk for damage on reproductive health [34].

ACOG, ACS, USPSTF Guidelines recommend to start at age 21, with different indications and case by case in immunocompromised patients, unreliable girls, multiple partners, pregnant patients, HIV positive, adolescent exposed in utero to DES [35].

Given the above considerations, there are no common protocols for the treatment of intraepithelial lesions in adolescents; however, in cases where the cytological

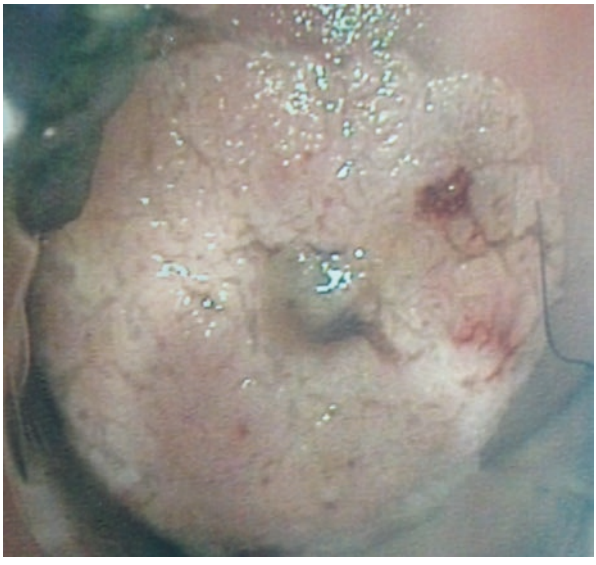
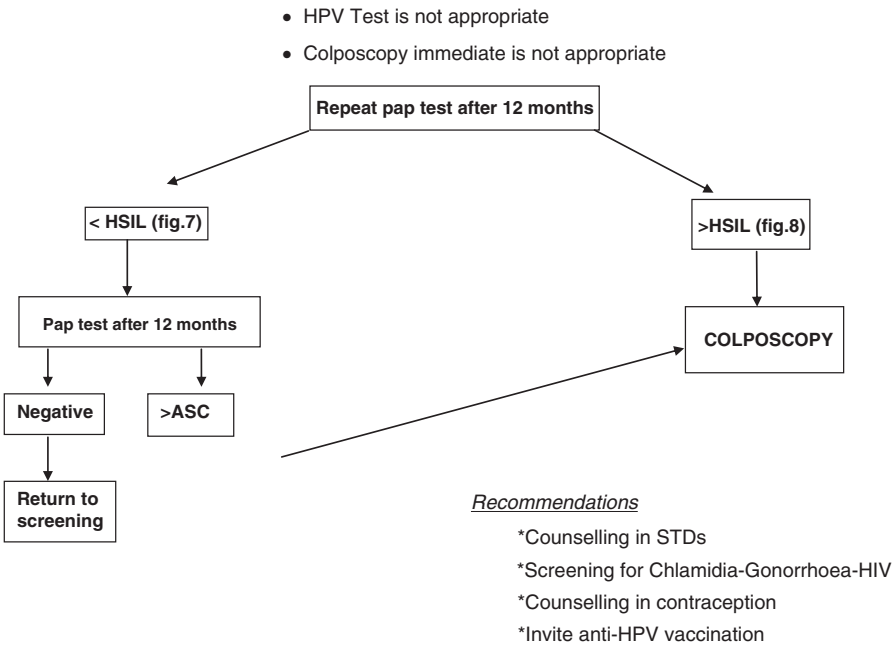


Fig. 14.8 Condyloma of the portio

Table 14.2 Protocols for the treatment of intraepithelial lesions in adolescents



examinations were performed, procedure for higher risk assessments is reported in Table 14.2 [36].

In the case of HSIL, referral of all to colposcopy is recommended. If CIN1 is diagnosed, follow-up with cytology is recommended at 12-month intervals. If CIN2 is diagnosed, observation is also recommended with 6-month intervals using cytology and colposcopy for up to 2 years. If CIN2 is persistent at 2 years, then treatment is recommended [37].

Prevention and Profilaxis

The WHO recommends a comprehensive and integrated approach for the prevention and control of uterine cervical cancer. The set of recommended actions includes measures that should be taken during the course of life, starting from education for informed sexuality. Primary prevention begins with vaccination against HPV in girls aged 9–13 years, that is, before they become sexually active.

Vaccines against HPV are composed of purified proteins derived from certain types of HPV, which form virus-like particles associated with adjuvant substances. Vlp mimic the viral capsid, but do not contain genetic material of the virus; therefore, they are able to induce a specific antibody response for HPV type, depending on the protein used, but are not able to cause infections.

Two kinds of preventive vaccines are available against HPV: bivalent and quadrivalent; both protect against HPV 16 and 18, which are responsible for about 70% of cervical cancers. The quadrivalent vaccine also protects against HPV 6 and 11, responsible for 90% of genital warts. Both vaccines have shown a certain level of cross-protection to other oncogenic HPV types, but not complete towards oncogenic genotypes. In June 2015, it was authorized in Europe a new 9-valent vaccine, which in addition to HPV 6, 11,16, and 18, protects against other oncogenic serotypes 5 (31, 33, 45, 52 and 58).

Many clinical studies have described a good safety profile of these vaccines [38], and in particular it has not found an increased risk of developing autoimmune diseases in vaccinated subjects [39].

The efficacy of vaccination does not seem to be significantly reduced by the passage of time and various meta-analyses have shown that, in countries where 50% of women have been vaccinated, there is a notable reduction in HPV 16–18 infections (68%) and in ano-genital condilomatosis in the pre- and post-vaccination period in girls between 13 and 19 years of age [40].

The bi-valent, quadrivalent, or 9-valent vaccine is recommended for females, while the quadrivalent or 9-valent is recommended for males [41].

HPV vaccination does not replace cervical cancer screening. In countries where HPV vaccine is introduced, screening programmes may still need to be developed or strengthened. All women who have been vaccinated against HPV should still follow the screening recommendations for their age groups [42].

14.9 HIV (Human Immunodeficiency Virus) Infection

The human immunodeficiency virus (HIV) is still one of the most serious infective diseases. It is associated with a serious, permanent disease of the immune system, which is expensive to treat and cure and which still causes a significant number of deaths and leads to reduced life expectancy.

The incidence of HIV infection in the world is still high: it is estimated that there is a 46–70% chance of infection following sexual intercourse with an infected partner and that chance is even greater if the partner is unaware of being seropositive for HIV. One in seven people with HIV does not know that they have been infected and a high proportion of patients only discover that they are ill after a significant period of time has elapsed. Consequently, there is a greater risk to their health and more risk of them spreading the virus themselves.

HIV is only transmitted in three ways:

- Through unprotected sexual intercourse, without using a condom (sexual transmission)
- Through shared use of needles and other material means of injection (transmission by blood)
- From mother to child during pregnancy, birth, or breastfeeding (vertical transmission)

Table 14.3 Trend in means of transmission 2006–2015 (ECDC data)

Means of infection	Percentage
Children infected by mother	−18
Injection of drugs	−38
Heterosexual intercourse	+19
Sex between men	+25

The data shown highlight how men who have sex with other men are disproportionately struck by HIV, as they are with other sexually transmitted infections (gonorrhoea, syphilis, chlamydia, and hepatitis B and C) (Table 14.3).

The probability of infection through sexual contact depends both on the characteristics of the virus and on the condition of the immune system; lesions and genital inflammation caused by the various STDs considerably increase, by about ten times, the risk of contracting HIV and it is estimated that these interactions come into play in at least 40% of the cases of HIV transmission. 2.8% of young people who had been diagnosed with an STD also resulted positive for HIV against an average in the general population of about 0.1%.

HIV screening is recommended for:

- People diagnosed with an STD
- People who have used injected drugs
- People who have had sexual intercourse with subjects who are seropositive for HIV
- People with anamneses featuring previous sexual abuse or violence
- People originating from countries where there is a high incidence of the HIV virus
- Women in the first 3 months of pregnancy

THE HIV TEST:

- Must be voluntarily taken without any form of coercion. Patients must not be tested without their knowledge.
- Routine use of HIV screening (notifying patients that an HIV test will be performed) is recommended in all health facilities.
- Specific written consent for HIV testing should not be requested—informed general consent for medical treatment is considered to be sufficient.
- Positive preliminary screening tests for HIV infection must be followed by further tests to confirm the diagnosis with certainty.
- People who are suspected of having recently contracted HIV must be immediately sent to a specialized treatment unit.

14.10 Hepatitis

Hepatitis B (HBV) and C (HCV) must still be considered diseases with serious social impact. It is necessary to identify preventative instruments and management techniques to better control this pathology which represents a serious public health

problem, striking 400 million people around the world, of whom 95% are unaware that they have contracted the disease.

Subjects who result as being positive from the test for hepatitis should be informed of measures to be taken that are adequate to prevent transmission which occurs principally by blood contact.

The campaign to vaccinate against Hepatitis B must be promoted.

14.11 The Zika Virus

The principal means of transmission of the Zika virus is by means of the bite of the Aedes mosquito. It has recently been demonstrated that sexual transmission of the virus is possible and very common [43].

A study on the persistence of the Zika virus in bodily fluids has demonstrated that the virus may remain in the sperm of infected men until up to 6 months after the onset of symptoms [44].

The presence of the virus does not automatically imply a risk of infection, but the possibility is not excluded. In order to inhibit this means of diffusion of the Zika virus, the WHO has released new guidelines to prevent the transmission of the virus by sexual intercourse. These guidelines are valid not only for those countries directly affected by the epidemic, but also for those in which cases of infection could only be imported. The document requires that both men and women abstain from sex, or use a condom for at least 6 months, even if no symptoms are detected.

The WHO also states "presently, knowledge of the Zika virus is limited and our guidelines will be re-examined and updated according to the latest research available" [45].

14.12 *Trichomonas vaginalis*

Infection by Trichomonas is a very common sexually transmitted disease; it is asymptomatic in 50% of cases in females and 90% males. Transmission is primarily through sexual contact; in women, the most affected parts are vagina and cervix with occasional involvement of the urethra, Bartholin's glands, and Skene's glands. In men, the infection involves urethra, prostate and seminal vesicles. The more evident symptoms of acute trichomoniasis are leucorrhoea in significant amounts, itching, vulvar and vaginal erythema, dyspareunia, dysuria, and inflammation of the uterus. The gynaecological examination showed the characteristic malodorous leucorrhoea and hyperaemia of the vaginal mucosa (Fig. 14.9); the colposcopic examination can reveal the typical "strawberry" aspect of Tricomonas infection.

The fresh microscopic examination of vaginal secretion allows to identify the protozoa, but the most widely used method for the diagnosis of trichomoniasis is represented by culture in a selective medium, whose sensitivity is significantly high (90.95%) and whose specificity is absolute (100%).

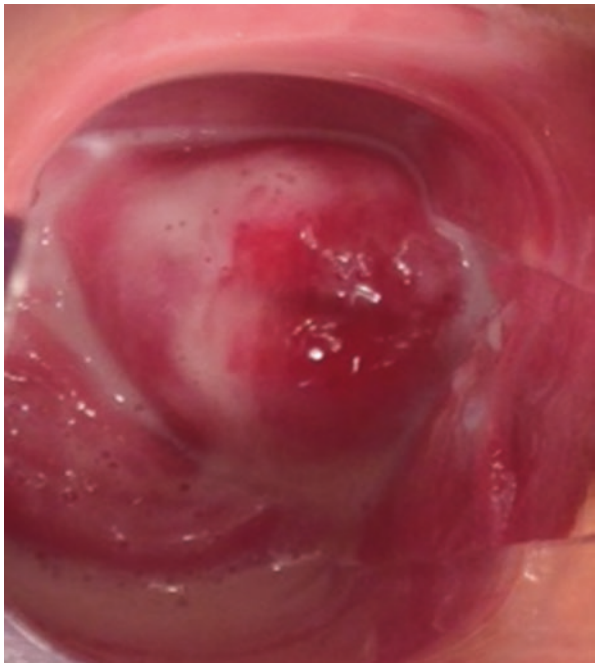


Fig. 14.9 Leuchorrhoea and hyperemia of the vaginalis mucosa and portio (Trichomonas Vaginalis)

14.12.1 Treatment

Therapy should be extended to the partner even if he has no symptoms:

- Metronidazole 2 g × os single dose
  or
- Tinidazole 2 g orally as a single dose

Alternative scheme:

- Metronidazole 500 mg × 2 orally twice daily for 7 days.

Metronidazole for topical use is not recommended because it does not reach therapeutic levels in the urethra and perivaginal glands.

The prevention and control of STDs is based on the following five strategies:

- Risk evaluation, education, and counselling of people at risk of STDs, favouring the use of preventative instruments
- Pre-exposure vaccination of people at risk of STDs, which may be prevented by vaccination
- Identification of people with asymptomatic infections and with symptoms associated with STDs
- Diagnosis, treatment, counselling, and follow-up of persons with an infection
- Evaluation, treatment, and counselling of the sexual partners of people infected with an STD [3]

In dealing with adolescents, it is fundamental to facilitate access to health facilities, to guarantee privacy, and to offer adequate space and time for effective prevention which permits the integration of sex education even in clinical practice.

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Pregnancy in Adolescence

15

Gabriele Tridenti and Cristina Vezzani

Abbreviations

ADHS	Attention deficit hyperactivity syndrome
BMI	Body mass index
CNS	Central nervous system
EU	European Union
FASD	Fetal alcohol spectrum disorders
GD	Gestational diabetes
HCG	Human chorionic gonadotrophin
IUD	Intra uterine device
IUFD	Intra uterine fetal death
IUGR	Intra uterine growth retardation
LARC	Long acting reversible contraception
LBW	Low birth weight
NICU	Neonatal intensive care unit
pPROM	Preterm prelabor rupture of membranes
PTB	Preterm birth
SCOG	Canadian Society of Obstetrics and Gynaecology
SIDS	Sudden infant death syndrome
UK	United Kingdom
US	United States
USD	United States dollar
WHO	World Health Organization

G. Tridenti, M.D. (✉) • C. Vezzani, M.D.
Department of Obstetrics and Gynaecology, Santa Maria Nuova Hospital—IRCCS,
Viale Risorgimento 80, 42123 Reggio Emilia, Italy
e-mail: gtride@tin.it; Cristina.Vezzani@asmn.re.it

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Although teen pregnancy is more frequent in the developing countries, it is a major public health issue all over the world with significant medical, emotional, and social consequences for the adolescent mother, her child, and her family [1, 2]. According to WHO, adolescence is the period of human life between childhood and adulthood ranging from ages 13 to 19, so adolescent pregnancy is defined as "any pregnancy occurring among adolescent girls aged 19 or younger" [3].

Worldwide teenage gestations are mostly unplanned. They account for 16 million births a year from ages 15 to 19 girls and one million from 12 to 15 year olds, with also five million abortions a year, of which three millions "unsafe." Complications of pregnancy and delivery are still the second cause of death in adolescent girls. Even if a declining pattern is ongoing in developed countries, up to now teen pregnancies are 11% of whole births in the world. Ninety-five percent of them occur in low–middle income countries, mostly in sub-Saharan Africa, India, Bangladesh, and mainly in rural areas with poorly educated women. Early marriage and childbirth are more common in developing parts of the world, leading to different social circumstances and possibly different pregnancy outcomes [2]. With 7% of the whole national births, the USA shows the highest rate of teen pregnancy in Western countries, costing 9.4 billion USD a year and defined by President Clinton in 1995: "Our most serious social problem" [4].

Three main indicators are in use to monitorize teen pregnancy:

- *Teenage birth rate*: the annual number of reported live births among 13–19 years per 1000 women aged 13–19
- *Teenage abortion rate*: the annual number of reported induced abortions among <20 years per 1000 women aged 13–19
- *Teenage pregnancy rate*: the annual number of reported teenage live births + induced abortions per 1000 women aged 13–19. Being often unavailable, data about miscarriages and ectopic pregnancies are not included [5]

207,000 teenage live births a year took place in EU countries in 2011, occurring in 15/1000 of 15–19 year olds on the average. The highest birth rates were detected in Bulgaria (46.7/1000) and the UK (25/1000) while the lowest ones were observed in the Netherlands (5.2/1000) and Italy (7/1000), with a general decrease of 1.3% annually since 1996. In 2011 also 160,000 induced abortions in ages 15–19 were performed in Europe, with the highest abortion rates in Sweden, the UK, and Estonia (20/1000) and the lowest ones in Greece, Italy, and the Netherlands (<10/1000), with a general decline since 1996. Reliable data about teen abortion are not always available because of different legislations among EU countries. As previously ascertained, teenage pregnancy outcome differs across the continent with higher abortion rates in Northern countries [6].

In Italy, teen pregnancy is a niche event, occurring in 50% cases during the first year of intercourses. About 10,000 deliveries in minors were recorded every year from 1998 to 2008, i.e., about 1.7–2% total Italian births (514,308 in 2013). They are mostly grouped in Southern Italy and the main islands (Sicily and Sardinia), with higher pregnancy rates among foreigners (www.istat.it/it/archivio/nascite). In

2015 about 3200 teen abortions, of which 530 in foreigners, were performed legally in Italy, i.e., 3.4% all legal abortions, with a constant declining since 2006 [7]. It was also verified that the lower the maternal age, the higher the abortion rate [8].

Adolescent pregnancy is a very unique situation involving both social and medical issues; its management deserves appropriate skills and devoted health caregivers. Main risk factors of teen pregnancy are mostly socioeconomic. Belonging to a low-income family, promiscuity, unemployment, low educational attainment, poor school results, living in a disadvantaged neighborhood, belonging to ethnic minorities: all these social conditions promote teen pregnancy, along with medical and behavioral risk factors: mental deficits, early sexual debut, risky behaviors, unprotected sex. In fact, peer pressure to engage in sexual activity, low self-esteem, low educational ambitions or goals, poor information and education about sexual health, lack of access to contraception, inconsistent or incorrect use of contraceptive methods also contribute to adolescent pregnancy [1]. If compared with older women, smoking, drug addiction, and alcohol misuse during pregnancy are more frequent among adolescent mothers [9]. Teen pregnancy is mostly connected with poverty: the lower the socioeconomic level, the higher the risk of early pregnancy [10]. It must always be kept in mind that a strong association exists between sexual and physical abuse and early pregnancy [11].

To sum up, "4 steps" in adolescent pregnancy may be identified:

RISKY BEHAVIORS → TEEN PREGNANCY → DELIVERY / ABORTION

Even if adolescent pregnancy rates are declining in the western world, a health care provider approaching an adolescent girl seeking for medical assistance must always be aware that she could be at risk of early pregnancy and the subsequent practical suggestions must be considered:

- *Pregnancy test*: it is mandatory in cases of amenorrhea, abdominal pains, nausea, vomiting, weight gain, urinary dysfunctions, menstrual disorders *whatever sexual history is reported*
- *First-trimester ultrasonography* is necessary to check gestational age if pregnancy test is positive
- *Careful counselling about all available options*: to be supplied with a nonjudgmental attitude if a pregnancy is diagnosed. The gestational age being verified, health care provider must deal with all possible choices (parenting, termination, fostering, adoption) according to the current laws of the country
- *Privacy and confidentiality* should be guaranteed at most
- *Close follow-up and support*: they must be supplied by devoted facilities and specialized health care providers whatever the choice is
- *Multidisciplinary approach* is advisable at most, considering adolescence is a distinct physical and developmental stage in woman's life and teen pregnancy worldwide shows higher maternal, obstetrical, and neonatal risks. Therefore, adolescent gestations should be managed as high risk ones. Gynecologist and devoted midwives, social workers, psychologists, and support groups should take care of the adolescent mothers [12, 13]

- *Postpartum or post-termination contraception planning* is mandatory to be already established when the pregnancy is still in progress [14]

Abortion in adolescents is differently regulated in various countries according to local laws; therefore, a comprehensive dissertation of its management is almost impossible and beyond the scope of the present treatise, which is mostly focused on the continuation of pregnancy and the connected items.

If the adolescent's choice is parenting, it is worth stressing that teen pregnancy entails heavy risks both for the mother and the fetus because of typical biological, social, environmental, and behavioral features (mostly predisposing to preterm delivery and low birth weight infants), all of which deserve special consideration. Teen pregnancy should therefore be managed as a high risk one in programs taking care of its unique features and concerns [15]. The subsequent typical adolescent biological items must be carefully considered.

- *Maternal age at conception*: even if previous experiences highlighted adolescent mothers aged less than 16 years to be at high risk of preterm delivery and low birth weight neonates [16] more recent researches defined:
  - "*Young maternal age*" as low gynecological age (≤2 years since menarche) or as a chronological age ≤16 years at conception or delivery
  - "*Very young maternal age*" as gynecological age <2 years postmenarche or as a chronological age <15 years at conception or delivery
  - Very young maternal age was shown both to increase the risk of maternal anemia and to have a detrimental effect on infant health and survival by raising the risk of preterm delivery and low birth weight [17]. The birthrate is higher among older adolescents than in younger ones [18].
- *Gynecologic age*, mentioned above, is defined as: age at last menstrual period minus age at menarche. Considering 2–3 postmenarchal years are required to reach full reproductive maturation; reproductive immaturity was defined as gynecologic age less than 3 years [19], now updated as a gynecologic age less than 2 years. In fact, body height and pelvic development are almost complete by 2 years after menarche [17]. During this interim, a conception may occur in still growing reproductive organs, predisposing to preterm delivery [19].
- *Maternal prepregnant size*, i.e., BMI, is a reliable predictor of infant size at birth, with small mothers delivering small offsprings. Defining low prepregnant weight as <45 kg and short prepregnant stature as <157 cm, a less than 19.8 kg/m^2 BMI reveals a thin body habitus, with an increased risk of low birth weight babies, possibly due to a deficit in both visceral adiposity, which is a determinant of insulin resistance, and in subcutaneous truncal adipose tissue during the first 2 postmenarchal years [16].
- *Cervix length*, defined as the shortest distance between the internal cervical os and the external one, in adolescent mothers may be shorter than in older women because of still incomplete development, thus predisposing to preterm delivery when a distance <25 mm is detected prior of 29 weeks gestation [17, 20]. Shorter cervices may also predispose to lower genital tract infections, which are more frequent in

adolescents with a further increased risk of preterm delivery. During pregnancy, cervical length should be verified by serial transvaginal ultrasonic scans.

- *Gravidity and parity*: as opposed to what happens in adults, repeated adolescent pregnancies show a growing risk of preterm delivery [19].
- *Fetomaternal competition for nutrients*, occurring between the still growing mother and her fetus, may explain the reason why pregnant teens gain more weight during pregnancy and deliver smaller babies than older women do. The needs of both growing mother and fetus cannot simultaneously be satisfied and a competition for nutrients occurs between each other resulting in higher incidence of both poor fetal growth and maternal anemia [17]. Leptin surges in the third trimester, hyperinsulinemia, insulin resistance may lead to continuous storage of maternal fat reserves, making less energy available for the fetus with subsequent smaller placenta, less placental nutrient transfer, and reduced uterine/umbilical cord blood transfer and IUGR [21].

To prevent preterm delivery and low birth weight babies, health care providers dealing with pregnant teens must focus their attention on the below reported items:

- *Gestational weight gain*, defined as the difference between the last measured weight gain in pregnancy and the reported prepregnant weight is a reliable predictor of the infant birth weight mainly in adolescents because of their typical perimenarchal weight gain at central body areas [16].
- *Past history of preterm delivery*: it raises the risk of a subsequent premature birth mainly if repeated pregnancies occur in under 18 year olds [22].
- *Genitourinary tract infections* are well-known preterm delivery inducers in all ages pregnancies by favorising chorioamnionitis and by damaging the connective tissue of the cervix and the placental membranes through microbic proteases, elastases, collagenases, and mucinases leading to pPROM. In pregnant teens, the alkalinity of the peripubertal vagina may increase their susceptibility to bacterial vaginosis; the eversion of the squamocolumnar junction of the adolescent cervix may foster Chlamydia infections, of which the incidence is quite high in this population group, ranging from 11.8 to 31% [23]. Finally, the typical shorter cervix may enhance the ascending of vaginal organisms to the upper uterus [19]. Besides the physiological features of pubertal status, the adolescent sexual behaviors, typified by serial unprotected monogamous sexual relations with low condom use, make pregnant teens frequently acquire the sexually transmitted diseases fostering preterm prelabor rupture of membrane (pPROM) and subsequent preterm delivery [24]. Besides the reported higher risk of pPROM and preterm delivery, in pregnant teens STDs increase also the risk of HIV acquisition and transmission [25].
- *Trauma* is the main cause of death in adolescence. Pregnant teens suffer from accidental and non-accidental traumas more than older women do [26]. In pregnant teens, abdominal traumas are very frequent, rising the risk of placental abruption and preterm delivery, making it mandatory to screen for recent traumas in a teen pregnancy care setting [19].

As previously stated, social and demographic features, as well as behavioral and psychological variables, are important factors in the risk assessment of a pregnant teen and in the subsequent follow-up.

- *Ethnicity* is closely related to early pregnancy, with American black and hispanic women having the highest pregnancy rates and white non-hispanic women having the lowest ones [27]. Black race also strongly raises the risk of preterm and very preterm deliveries both in adults and adolescent mothers (while hispanic ethnicity does not), possibly because of increased, ethnicity-connected, susceptibility to bacterial vaginosis, group B streptococcal infection, and premature cervical effacement [28].
- *Socioeconomic status* plays a main role both in fostering teen pregnancies and in conditioning their outcome, with higher rates of preterm delivery among poor teen mothers. Some experiences showed that pregnant teenagers were more likely to be single and to live in a rural area [2], other researches detected higher pregnancy rates among ethnic minorities living in deprived metropolitan areas [10], among underachievers in school and among young women with mental health problems [29]. Very often teen mothers belong to a single-parent family or have parents poorly interested in their education. Having a low educated mother or being herself a teen mother increases the risk of adolescent pregnancy, the same as being a younger sibling of an adolescent mother [30]. Unemployment and child poverty are also strong predisposing factors, and the trend is "the lower the deprivation rank, the higher the risk of teenge pregnancy" [31].
- *Inadequate nutrition*: Even if a proper nutrition is of utmost importance during teenage because of growth and physical changes, the diet quality is usually poor in adolescents, whose primary sources of macronutrients are often foods lacking nutritional properties [32]. Pregnant teens show the same food preferences, eating behaviors, and lifestyle habits of their nonpregnant peers [33]. If compared with women aged 19–64, girls aged 11–18 consume less fruits and vegetables with higher intakes of sugar-sweetened beverages and inadequate intake of key vitamins and minerals. Such dietary patterns are similar across highly developed countries [34]. Adolescent girls are at particular risk of iron deficiency anemia due to both the rapid growth in teenage and the onset of menarche [35]. The iron needs linked to adolescence coupled with the increased iron demand in pregnancy makes pregnant adolescent particularly vulnerable, and iron deficiency is aknowledged to be implicated in adverse birth outcomes such as prematurity and low birth weight [32]. As well known, good pregnancy nutrition plays an important role on birth outcomes, fetal growth, and infant survival. Nutritionl needs change during the course of pregnancy with increasing requirements for several micronutrients as the pregnancy progresses [36]. Conversely, pregnant adolescents were shown to have intakes of energy, iron, folate, calcium, Vitamin E, and magnesium below the dietary recommendations [37, 38]. If compared with older teens, "very young adolescents" (under 15 years or under 2 years gynecological age) may be at even greater nutritional risk due to competing growth needs between mother and fetus [17]. Smoking teen gravidas and those from deprived

backgrounds may also be at greater risks of nutritional issues [39, 40]. Compliance for supplements may be low in pregnant teens [32].

- *Substance abuse*: According to large cohort studies, tobacco smoking, drugs, and alcohol misuse are more frequent among teen mothers than in pregnant women aged 25–30 [10]. *Sigarette smoking* during the first trimester entails an increased risk of miscarriage and labio-palatoschisis while smoking during the whole pregnancy (the same as heavy second hand smoke) implies higher incidences of preterm delivery, low birth weight babies SIDS and future smoking offsprings, mainly if they are females. Attention-Deficit/Hyperactivity Disorder (ADHD) and asthma are also more frequent among children of smoking pregnant teens. Smoking reduction programs for pregnant adolescents were more successful when smoking partners are also involved [41]. *Alcohol misuse* is epidemic among adolescents, and it is quite common also among pregnant teens. Both alcohol moderate daily assumption and occasional drunknesses during the first trimester raise the risk of miscarriage, intra uterine fetal death, and a range of lifelong physical, cognitive, and behavioral birth defects, such as IUGR, microcephaly, facial dismorphologies (short palpebral fissures, thin upper lip, smooth filtrum), and various central nervous system dysfunctions, all grouped under the umbrella name of fetal alcohol spectrum disorders (FASD) [42, 43]. Considering FASD are mostly due to a fetal alcohol exposure between the sixth and 12th week of gestation, they are only partially preventable at the first antenatal visit. International guidelines recommend temperance during the first trimester of gestation but even in the subsequent trimesters a security threshold is not specified because of individual alcohol metabolization [41]. Pregnant teens may be multiple *illicit substances* addicts, each one with different dangerous effects (summarized in the Table 15.1), but all of them sharing a common increased risk of preterm delivery and IUGR.
- *History of childhood abuse*: A history of sexual and physical abuse places female adolescent at increased risk of becoming pregnant, fostering early sexualization, initiation, sexual risk-taking behaviors, and promiscuity [11]. In the main, exposure to all types of abuse increases the likelihood to start intercourses at early age and promotes low self-esteem and association with deviant peer groups: all factors leading to premature pregnancies [1]. The strength of this association varies with abuse type. Higher risk of adolescent pregnancy was verified following sexual and physical abuse but not in cases of emotional abuse and neglect. The co-occurrence of both physical and sexual abuse was even stronger than any single kind of abuse, with a fourfold increased risk of early pregnancy [11]. Among previously abused adolescents pregnancy may be not unplanned: a desire to escape from an abusive or dysfunctional family and to create a new family environment may lead to early pregnancy [44]. Previously abused pregnant adolescents are more likely to be cigarette smokers and alcohol or illicit substances addicts. They are also more often sexually promiscuous and involved in coercive sex, with higher risks of STDs and injury-mediated preterm delivery [16, 19]. Teen mothers who have been victims of abuse show higher risk of seeking late antenatal care, poorer obstetrical outcomes, increased neonatal morbidity and of

Table 15.1 Effects of prenatal exposure to abuse substances [41]

Substance	Effects on fetus and pregnancy	Neonatal effects	Neurodevelopmental disorders	Other long-distance effects
Cannabis and cannabinoids	Ectopic pregnancy, IUGR, preterm delivery	Risk of SIDS	Short term and visuo-spatial memory defects	Higher risk of tobacco and cannabis smoking offsprings
			Defective verbal and attentive abilities	
			Hyperactivity	
Cocaine	Acute hyperthermia	Low body length and weight	Higher sensitivity to stressors	Overweight in babyhood
	Altered placental vessels with preeclampsia and abruptio placentae	Risk of necrotizing enterocolitis	Hyperexcitability	
	IUGR, preterm delivery	Urogenital and cardiac anomalies	Cognitive disorders	Low linear growth in second childhood
			Teen impulsiveness	
Amfetamine and derivates	Hyperthermia	Low birth weight	Higher emotivity	
	IUGR	Low APGAR score	Anxiety and depression in childhood	
	Preterm delivery	Low motor ability	ADHS	
			Low verbal memory	
Opioids	Abruptio placentae due to untreated withdrawal	Neonatal withdrawal syndrome	Visual defects	
	IUGR	SIDS	Neurodevelopmental and behavioral disorders	
	Preterm delivery			
Inhalants: gases, solvents, aerosols, nitrites	Miscarriages	Skeletal anomalies	Neurodevelopmental delay	
	IUGR	CNS anomalies		

committing sexual abuse during their own child's life [45–47]. Moreover, if a history of previous sexual abuse doubles, the risk of adolescent pregnancy in a girl, a fivefold increase of pregnancy involvement was verified in previously abused boys [48]. Sexual abuse and violence before and during pregnancy should routinely be asked in an adolescent pregnancy setting [49].

- *School dropout*: Undereducation is a sign of a set of psychosocial and medical risk factors; in fact, recreational drugs addiction, alcohol abuse, deviant behaviurs, preterm delivery are more common among pregnant teens who dropout of school. By leaving school, these girls also loose an important source of support which could help them to develop the sense of mastery required to face motherhood [16, 19].

- *Mood disorders*: Psychopathology in teenagers is a risk factor for early pregnancy. Sixteen to 44% pregnant teens show depressive symptoms which worsen between the second and the third trimester, with an incidence twice as high as among adult gravidas and nonpregnant adolescents [50, 51]. Adolescent perinatal depression is strongly associated with low socioeconomic status and lacking social support [52]. Furthermore, previous experiences revealed postpartum depression in half adolescent mothers, i.e., twice the rate of adult mothers [53]. If untreated, maternal depression is associated with adverse maternal, neonatal, and childhood outcomes, with higher incidence of preterm delivery, SGA infants and behavioral and cognitive disorders in children as well. Postpartum depression, unresponsive mothering, and rapid repeated pregnancy often occur in depressed pregnant teens [54, 55] with frequent postpartum smoking, alcohol misuse, and substance abuse [56].

Adolescent pregnancies have a higher risk of adverse outcomes [57] and besides age-related risk factors pregnant teens show typical maternal, obstetric, and neonatal complications during gestation and at delivery, of which it is worth mentioning:

- *Anemia and nutritional deficiencies*: Because of feto-maternal competition for nutrients and increased postmenarchal needs anemia is very frequent among pregnant adolescents, being detected in 50–66% cases [58]. Besides the above-mentioned deficiencies of micronutrients, because of mostly unplanned gestations, precoceptional counselling and folic acid supplementation are often missed in pregnant teens, whose age implies a slowly higher risk of spina bifida. Eating habits, cigarette smoking, alcohol consumption, and some gastrointestinal diseases, such as celiac disease, atropic gastritis, Crohn's disease, and ulcerative colitis, may impair the intestinal absorption of folate, the same as the administration of trimethoprim, pyrimethamine, antiepileptic drugs, aminopterin, methotrexate, sulfasalazine, and isotretinoin [41]. All the above-mentioned clinical and behavioral situations, and also MTHFR gene polymorphism, require an implemented 5 mg daily folic acid supplementation instead of the usually recommended 400 μg daily administration [59]. Furthermore, because of poor outdoor activities, Vitamin D blood levels were shown to be low in many adolescents, mainly if they are black, vegan, on a low fat diet, overweight, or obese. Type 1 diabetes, inflammatory bowel diseases, liver diseases, cystic fibrosis, African or Southern Asian ethnicities, long lasting treatments with heparine, isotretinoin, glucocorticoids, antituberculous, and antiepileptic drugs may also lower Vitamin D availability, and its deficiency could promote preeclampsia and impair the skeletal and dental development of the fetus. Daily Vitamin D 100 UI, equal to 10 μg, is needed in pregnancy. Either daily 15 minutes sun exposure of arms and face or Vitamin D supplementation are recommended in pregnancy [60].
- *Eating habits and BMI*: Teen pregnancies may occur in girls suffering from eating disorders while they improve their food supply. A low BMI, as defined by proper age-related diagrams, raises the risk of LBW newborns and preterm delivery due to pPROM. Eating habits must be strictly monitored in pregnant teens,

Table 15.2 Total and average physiologic weight gain related to preconceptional BMI

Preconceptional BMI (kg/m$^{2)}$	Total weight gain	Second and third trimester average weight gain (kg/week)
<18.5 → underweight	12.5–18	0.51
18.5–24.9 → normal weight	11.5–16	0.42
25–29.9 → overweight	7–11.5	0.28
>30 → obesity	5.9	0.22

Dei and Bruni [41]

considering also a high preconceptional BMI and high-fat diets raise the risk of both macrosomia and preeclampsia [41]. Total and average physiologic weight gain related to preconceptional BMI is reported in Table 15.2.

- *Insufficient prenatal care*: if compared with older pregnant women, adolescents were shown to start their prenatal care significantly later in pregnancy, with delayed or missed first trimester antenatal visits and also significantly lower attendance rate of prenatal classes [2, 46]. Reasons for delay in seeking care lie on lacking knowledge about the relevance of prenatal care and about the consequences of its missing. Previous violence, desire to hide pregnancy, doubts about continuation, concerns about lack of privacy or judgmental attitudes from health care providers, financial problems may be further reasons behind the delay. Absent or delayed prenatal care worsens maternal, obstetrical, and neonatal outcomes [61].
- *Preeclampsia and hypertensive disorders of pregnancy*: available data about their incidence in teens are controversial. Some studies reported a higher incidence than in adults, possibly connected to the reproductive and physiologic immaturity of pregnant adolescents [16, 19, 62]. Other experiences do not demonstrate any difference [46] or even showed reduced rates after potential confounders being controlled [9]. Very common risk factors of preeclampsia in teens are nulliparity and first pregnancy with a partner [41]. Screenings of preeclampsia are available at first trimester by combining blood pressure assessment, ultrasonography, and seric PAPP-A levels at the second trimester by performing Doppler ultrasonography of maternal uterine arteries.
- *Gestational diabetes*: in pregnant teens, lower rates of GD were detected than in adults [9, 63].
- *Congenital anomalies* are more common in adolescent pregnancies, with higher rates of CNS anomalies (anencephaly, spina bifida, hydrocephaly, microcephaly), gastrointestinal anomalies (gastroschisis, omphalocele), and musculoskeletal anomalies (cleft lip, cleft palate, polydactily, syndactaly) [64], possibly due to pre- and postconceptional risky behaviors or to nutritional deficiencies [41]. A careful second trimester ultrasonographic screening of fetal anomalies must be supplied.
- *Molar pregnancy*: complete hydatidiform mole shows a biphasic trend, with higher incidence at both extreme reproductive ages. In under 20 year olds, a sevenfold higher rate was detected (4–6/1000 cases), which further worsens in oriental girls. On the contrary, invasive mole and choriocarcinoma are very rare

in teens. Nausea, vomiting, bleedings, pelvic pains, and signs of hyperthyroidism are common symptoms but the diagnosis is mostly made by β-HCG evaluations, showing much higher serum levels than expected according to gestational age (>100,000 UI), and ultrasonography, with the typical "snowstorm pattern." Suction curettage is the treatment of choice and subsequent β-HCG monitoring is mandatory [41, 65].

- *Preterm delivery (PTB) and IUGR* are the main issues dealing with adolescent pregnancies. Higher risks of PTB (<37 weeks), very PTB (<32 weeks), and extremely PTB (<28 weeks) are reported in pregnant teens, as well as LBW babies (<2500 g), very LBW babies (<1500 g), IUGR (<3rd centile for gestational age), stillbirths, NICU admissions, and neonatal deaths [9, 61]. Typical teen risk factor of PTB and IUGR are summarized in Table 15.2. The younger the adolescent in terms of chronologic and gynecologic ages, the higher the rate of preterm labor and delivery. Advisable interventions are based on close follow-up, appropriate weight gain, cervical cerclage (when suggested by the clinical picture), screening of urogenital infections, psychologic and social support, screening of sexual abuse and careful timing of delivery [19] the gestational age being verified, a careful follow-up of fetal growth is mandatory in the third trimester. Serial biometric ultrasonography with also maternal and fetal Doppler velocimetry should be preferred to symphysial fundal height measurements [41].
- *Multifetal pregnancies* are a further risk factor of PTB and IUGR. Accurate estimates of multiple pregnancies in adolescents are lacking but a threefold higher rate was detected in black girls, possibly because higher baseline FSH levels in black women. Adolescent multiple gestations carry an even higher incidence of preterm birth (81%), IUFD and IUGR than teen singletons and adult twin pregnancies (Table 15.3). Moreover, most infants are LBW ones. [66].

Table 15.3 Risk factors of preterm birth and IUGR

Risk factors of preterm birth	Risk factors of IUGR
Maternal age <16 years	Low maternal height and weight
Gynecologic age <2 years	Low preconceptional maternal BMI
Parity	Low central fat stores
Previous preterm deliveries	Still ongoing maternal growth
Urogenital infections	Gestational hypertension
Traumas	Defective placentation
Black race	Smoking during first trimester
Poverty	Missed folic acid supplementation
Smoking and substance abuse	Maternal DHA and Vitamin D deficiencies
Lacking perinatal cares	Anemia
Poor school attendance	High caffeine intake
Previous sexual abuse	Malaria
Stress and depression	Hyperthyroidism
Poor social support	Disadvantaged socioeconomic status
Multiple pregnancy	Domestic violence and sexual coercion

Steven-Simon et al. [19], Dei and Bruni [41]

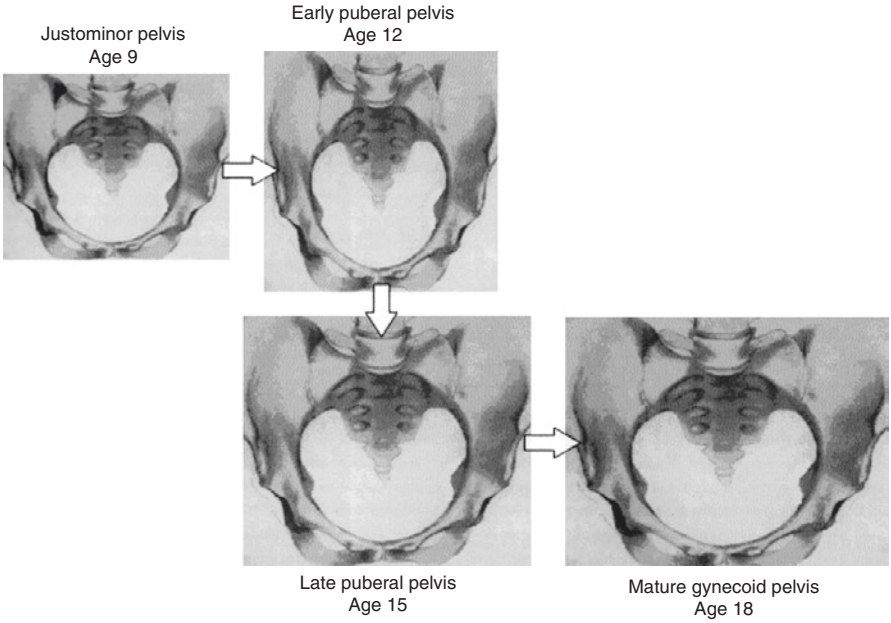

Fig. 15.1 Reshaping of the pelvis at puberty [67]

Labor and delivery have peculiar features in teenage, requiring appropriate care and management. The adolescent pelvis, mainly at very young ages, is incompletely developed, transversely narrowed and anthropoid shaped, with small capacity. A reshaping of the pelvic inlet and outlet takes place during puberty, with a tranverse enlargement leading to a rounded mature, gynecoid-shaped pelvis (Fig. 15.1). At the same time, a remodeling of the subpubic arch occurs, from the pointed arch of the immature pelvis to the rounded arch of the mature gynecoid pelvis (Fig. 15.2). The closer is the menarche, the less adequate is the pelvis to deliver [67]. Furthermore, during pregnancy the still growing pregnant adolescents show a three-fold bigger bone mineral impoverishment than adult gravidas. This accelerated bone mineral loss is not fully counterbalanced by the physiologic increase in calcium absorbtion normally occurring in pregnancy. This event reveals the continuing unmet maternal skeletal needs during pubertal development and growth, further amplified by fetal skeletal mineralization. Osteopenia is rather frequent in pregnant teens, while osteomalacia is more common in adult multiparas and osteoporosis typifies other clinical pictures [68].

According to Friedman's curve, the average labor in adolescents progresses slower than in older gravidas. All steps of both cervical dilation and fetal descent are significantly delayed, as depicted in Fig. 15.3 by matching adolescent and adult Friedman's curves [69]. Teen parturients in labor show slower rates of dilation and descent, longer latent, active and deceleration phases, and longer second stages; therefore, oxytocic drugs are more often required. Even if macrosomia is rare in adolescence, teen labors associated with macrosomic fetuses display a significantly

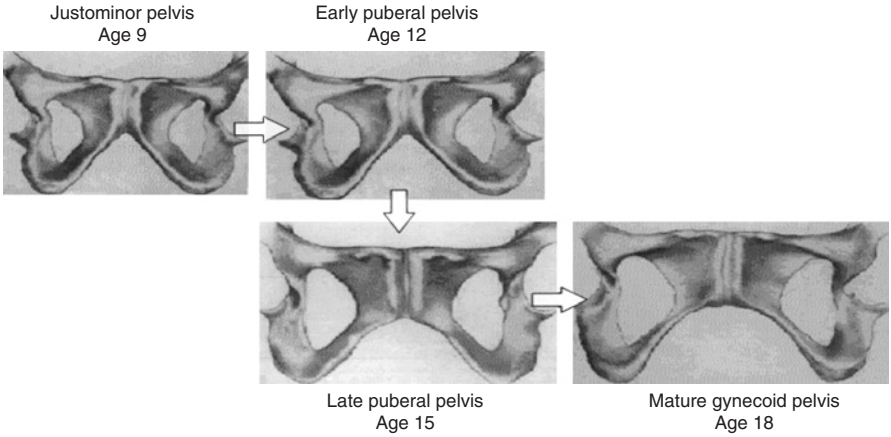

Fig. 15.2 Reshaping of the pelvis at puberty [67]

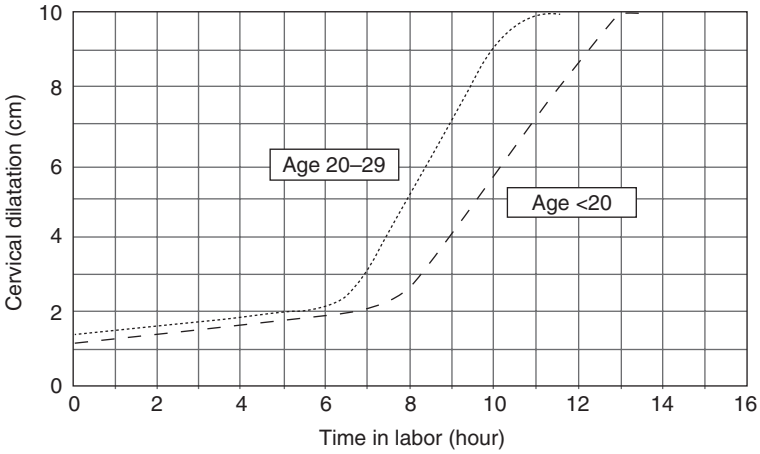

Fig. 15.3 Plot of cervical dilation vs. elapsed time in teens and adults [60]

longer active phase and a higher incidence of distocias. Very likely, the still immature pelvis increases the risk of abnormal labor progression and cephalopelvic disproportion [67]. In contrast with older woman, adolescents revealed lower rates of assisted delivery and cesarean section, varying from 2 to 14% [70]. Because of the higher incidence of preterm delivery, IUGR, SGA neonates, abnormal labor, IUFD, and the higher neonatal mortality (inversely correlated with maternal age), teen gravidas should deliver in tertiary care hospitals [67].

Postpartum deserves special considerations in teenage mothers because of its proper risk factors. It is a period of female life characterized by psychological vulnerability for every woman and mainly for adolescent mothers, who may have more difficulties in fulfilling their maternal role. Teen mothers are more likely to suffer

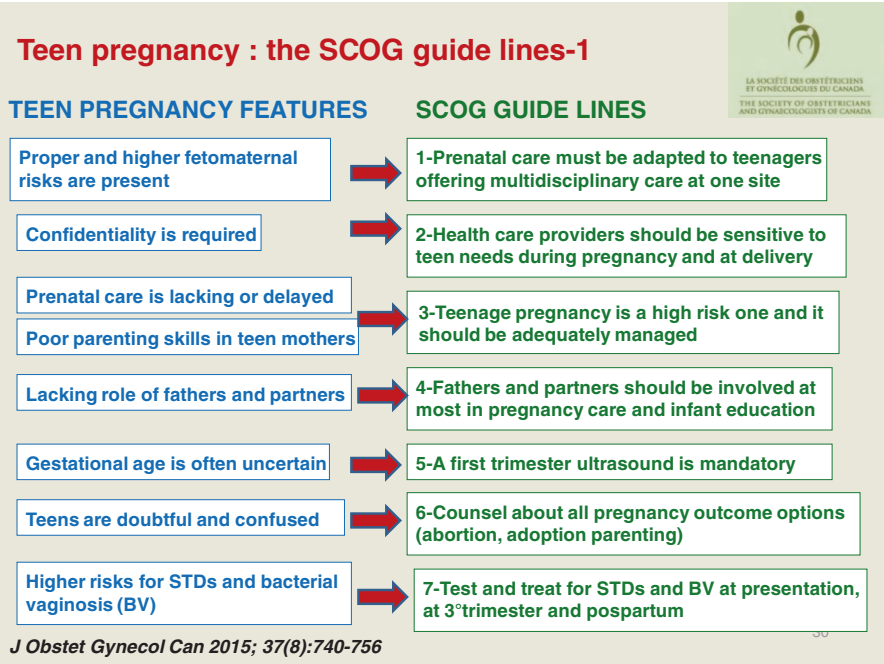

Fig. 15.4 Synopsis of the SCOG Adolescent Pregnancy Guidelines - 1

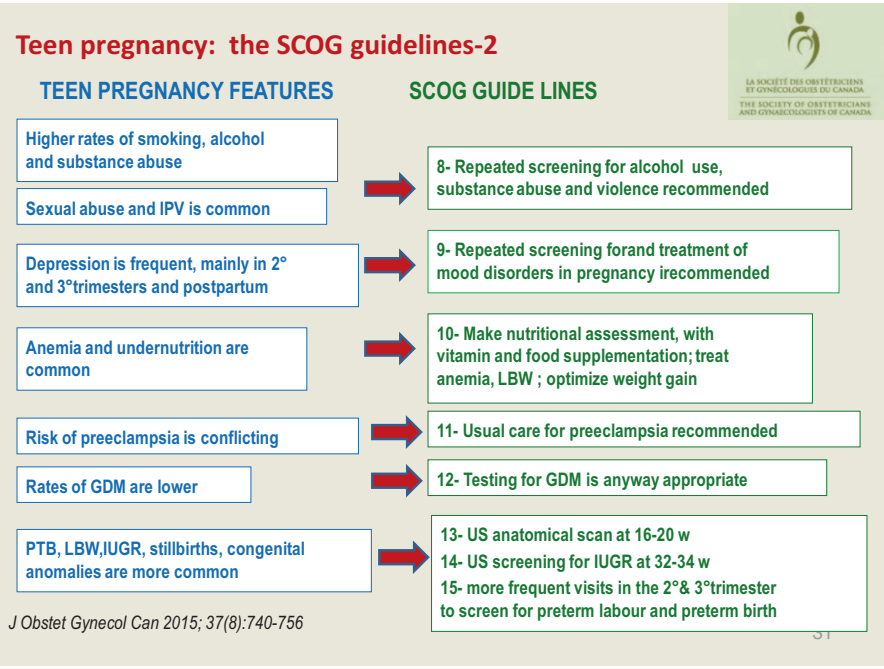

Fig. 15.5 Synopsis of the SCOG Adolescent Pregnancy Guidelines - 2

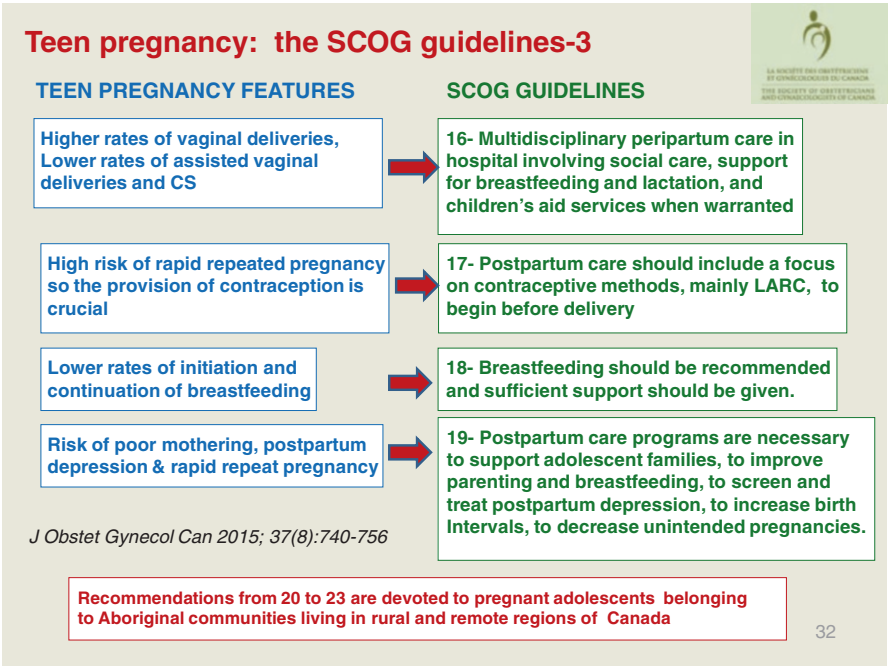

Fig. 15.6 Synopsis of the SCOG Adolescent Pregnancy Guidelines - 3

from depression, to dropout from school, and to have low educational attainment, to live in poor housing, to be unemployed or low paid, and to require social assistance. They may be abandoned by the partner and lack family support. The child of a teen mother is more likely to live in poverty, to grow up without a father, to be negleted or abused, to attain poor school results, to be involved in drug and alcohol addiction, crime, or abuse and, last but not least to become a teen parent itself [1, 41, 71]. Health caregivers dealing with adolescent mothers in postpartum period should focus their attention on the following main issues.

- *Breastfeeding*: Teen mothers have a lower initiation and continuation rate of breastfeeding than adult women [72], possibly due to multiple socioeconomic factors. Age, race, educational level, marital status, and economic conditions may be determinant, as well as poor knowledge and lack of breastfeeding support from family, friends, and partner. Social care and support should be given to foster breastfeeding for at least 6 months, according to joint WHO/UNICEF global recommendations for optimal infant feeding [73]. Proper information should be given to drug-addicted teen mothers about substances excreted in breast milk [41].
- *Nutrition*: It should be properly addressed to support breastfeeding teen mothers whose calorie needs exceed pregnancy ones. Hundred grams of breast milk require 90 kcal energy intake and a daily 2.7 L watery intake is needed. To maintain maternal bone mass, adequate nutritional calcium intake is recommended [41].

- *Depression*: It is very frequent in postpartum. In teen mothers, it is highly more common than in adult ones, influencing parental behaviors and intefering with maternal sensitivity and discipline. Significant depressive symptoms were reported in up to 45% of teen mothers after 1 month and till 1 year from delivery [74]. Multiple pathogenetic factors are involved, mostly based on previous depressive features, obstetrical complications, stressing events during pregnancy, or prolonged absence of the child because of NICU hospitalization. First pregnancy, difficult breastfeeding, lacking partner, conflicting family and intimate relationships, domestic violence, lacking social support, sense of neglect, and parenting stress may promote the onset of postpartum depression, affecting both the teen mother and her developing infant [41, 75]. In fact, depressive symptoms in adolescent mothers are associated with problem behavior and poorer academic achievements in their offsprings, from toddlehood through adolescence [51]. Indeed, lower rates of postpartum depression were observed when family or partner's support is available while lacking support increases stress and depression, raising the risk of abuse, neglect, and violence [76]. Early diagnosis and treatment of teen postpartum depression is recommended. Screening of postpartum depression is therefore mandatory and variations of the Edinburgh Postnatal Depression Scale were shown to be accurate screening tools [77]. Postpartum care programs, social workers, and local midwives should be available to provide the adolescent mother with the support she needs.
- *Education*: Fostering the continuity of education of pregnant teens and teen mothers is the main goal to avoid subsequent social marginalization, poverty, and neglect. Proper laws and school programs should be available [71].
- *Rapid repeated pregnancies*, i.e., within 2 years from delivery, occur in 35% cases, two-third of them are unplanned and they are more frequent among ethnic minorities. School attendance and living alone or with a parent as opposed with a partner are protective factors against rapid repeated pregnancies [78]. Adolescent mothers should be informed that lactation is not a reliable contraceptive method and a barrier method may be employed at any time. The provision of contraceptive options is crucial in postpartum care and contraceptive counselling should be started during pregnancy. Oral contraception and a subdermal contraceptive implant may be supplied 6 weeks postpartum while an IUD may be inserted 2 months after delivery [41]. In teen mothers, LARC methods, such as subdermal implant, Depot Medroxyprogesterone Acetate (not available in Italy), and IUDs, are a far better prevention of repeated pregnancies than are shorter term methods such as oral contraception, contraceptive patches, or barrier methods [79]. LARC methods are first choice in teens and they should be suggested after delivery before the patient is dismissed from hospital. A non-LARC method could be supplied temporarily and barrier methods are always advisable to prevent STDs [80].

15.1 Final Remarks

Teen pregnancy is risky for both the mother and the fetus. While approaching a pregnant adolescent, all possible outcomes must be discussed with a nonjudgmental attitude, assuring privacy and confidentiality. Whatever the choice is, a very close

follow-up must be provided, preferably by a multidisciplinary team. If parenting is choosen, appropriate nutrition and weight gain should be strictly monitored. PTB, IUGR, STDs, substance abuse, and sexual abuse should be screened. Delivery in a tertiary care hospital is recommended. Postpartum depression should always be screened and treated. Prevention of rapid repeated pregnancies is mandatory by early contraceptive counselling. LARC methods are the first choice in adolescents.

Appendix 1: WHO Guidelines for Developing Countries

Considering early childbearing mostly occurs in developing countries, it also reflects broader forms of social and economic marginalization of girls. To prevent early pregnancy, WHO suggests the following guidelines:

• Prevent early marriage	→ by extending school age for girls
	→ by prohibiting marriages in under 18 year olds
• Foster prevention	→ with sex education in school
	→ in connection with sexual health services
• Improve contraception	→ by including contraception in sex education
	→ by organizing "youth friendly" health services
	→ by supplying contraception after deliveries or abortions
	→ by fostering tolerant laws and policies
• Punish forced sex	→ by banning it by law
	→ by making the perpetrator punishable
• Reduce unsafe abortion	→ with educational campaigns
	→ by admitting teens to family planning services
	→ by providing post abortion care and contraception
• Supply proper pre- and post-natal cares	→ with laws taking care of adolescents

World Health Organization [81]

Appendix 2: SCOG Adolescent Pregnancy Guidelines

In August 2015, the Canadian Society of Obstetrics and Gynecology published a guideline about adolescent pregnancy which still may be considered the most comprehensive and updated one. Published on the Canadian Journal of Obstetrics and Gynaecology [12], it has been summarized in the following pictures:

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