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REVIEW ARTICLE

Ultrasonographic and multimodal imaging of pediatric genital female diseases

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Abstract

Ultrasonography is the first-line imaging modality in the evaluation of the female pelvis in childhood and adolescence, because it is easy to perform, non-invasive and it does not require sedation. The transabdominal approach is preferred in children and adolescents, after filling the bladder to move away the bowel loops from the pelvis. The probe frequency must be adapted to age, thickness of tissues and depth of the structures under examination. High-frequency (4-12 MHz) linear or convex probes are used in newborns; high-frequency linear probes (4-12 MHz) in toddler, convex 5-7.5 MHz probes in girls and convex 3.5-5 MHz probes in teenagers. In this article, the main pathological conditions of the genital female tract in pediatric age are examined, such as congenital anomalies, disorders of sex development, ovarian cysts, ovarian tumors, adnexal torsion, primary amenorrhea, precocious puberty and pelvic inflammatory disease.

Keywords Ultrasound examination · Pediatric age · Genital female tract · Congenital anomalies · Disorders of sex development · Pelvic expansive masses

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Introduction and examination technique

The female genital tract consists of the uterus, the fallopian tubes, the ovaries and the vagina. The most common indications for pelvic imaging in childhood and adolescence include assessment of internal and external genitalia anatomy, ambiguous genitalia, congenital malformations and effects of hormonal stimulation and neoplastic diseases. Ultrasonography is the first-line imaging modality in the evaluation of the female pelvis in childhood and adolescence because it is easy to perform, non-invasive and it does not require sedation [1].

The probe frequency must be adapted to age, thickness of tissues and depth of the structures under examination.

High-frequency (4–12 MHz) linear or convex probes are used in newborns; high-frequency linear probes (4–12 MHz) in toddler, convex 5–7.5 MHz probes in girls and convex 3.5–5 MHz probes in teenagers [2, 3].

Using the color power Doppler increases the diagnostic accuracy in particular in case of ovarian masses, ovarian torsion and pelvic inflammatory disease. Nowadays, the enhanced ultrasonography is "off label" even though it might have a role when studying ovarian masses. The sonoelastography does not have a real application in the study of the pediatric pelvis.

Magnetic resonance imaging (MRI) is used when ultrasound findings are inconclusive, especially in congenital malformations and neoplastic diseases. Computed tomography (CT) is predominantly used in staging neoplastic diseases.

The different ultrasound approaches are:

1. The transabdominal approach is preferred in children and adolescents, after filling the bladder to move away the bowel loops from the pelvis. This approach allows an accurate evaluation of the uterus (presence, size, morphology and ecostructural features) with details of the endometrium (thickness and characteristics), vagina (morphology, size, possible obstruction) and of its continuity with the uterus. The ovaries (presence, site, volume, echostructural characters, stroma, number and distribution of follicles), the bladder (content, wall thickness), the parauterine and paravesical spaces and the presence of fluid collections are also evaluated. The exam must include the kidneys (site, number, size, echostructure) and the adrenal glands (size and echostructure) [4, 5] (Fig. 1). The probe frequency must be adapted to age, thickness of tissues and depth of the structures under examination.

   High-frequency (4–12 MHz) linear or convex probes are used in newborns, high-frequency linear probes (4–12 MHz) in toddler, convex 5–7.5 MHz probes in girls and convex 3.5–5 MHz probes in teenagers.
2. *Transvaginal* Transvaginal probes are only used in sexually active adolescents, sometimes to complete the transabdominal examination It allows a better visualization of the uterine cavity, in particular of the endometrium and ovaries [6, 7].
3. *Transrectal* Transrectal probes are rarely used, representing an invasive approach and in the study of the cervix, vagina, and bladder (in particular of the bladder trigonum, of the urethra and of the pelvic masses).
4. *Transperineal scans* Being non-invasive, transperineal scans can be performed even in newborns and children to evaluate the distal tract of the vagina and the urethra and is, therefore, useful in the study of abnormalities of the lower genital tract (urogenital sinus, obstructions or vaginal septa determining hydrohematocolpos hydrohematometrocolpos, expansive processes and hypertrophy of small or big lips) [8].

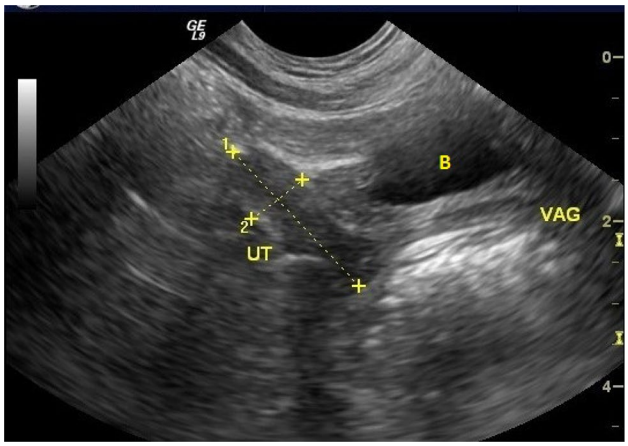

Fig. 1 Normal pre-puberal uterus of a 7-year-old girl, transabdominal approach. *UT* uterus, (++) length, *VAG* vagina, *B* bladder. The bladder is an important acoustic window

Normal anatomy and variants

The size and shape of the uterus and ovaries depend on age and hormonal stimulation. Maternal and placental hormones determine relative enlargement of the uterus and ovaries in newborns. Their size in early childhood remains relatively stable up to the first growth spurt, which occurs between 7 and 8 years. The neonatal uterus is prominent, usually showing a prevalence of the neck on the body, with well-visible endometrial rhyme and thickened myometrium (Fig. 2); its size decreases after the first weeks/months of life.

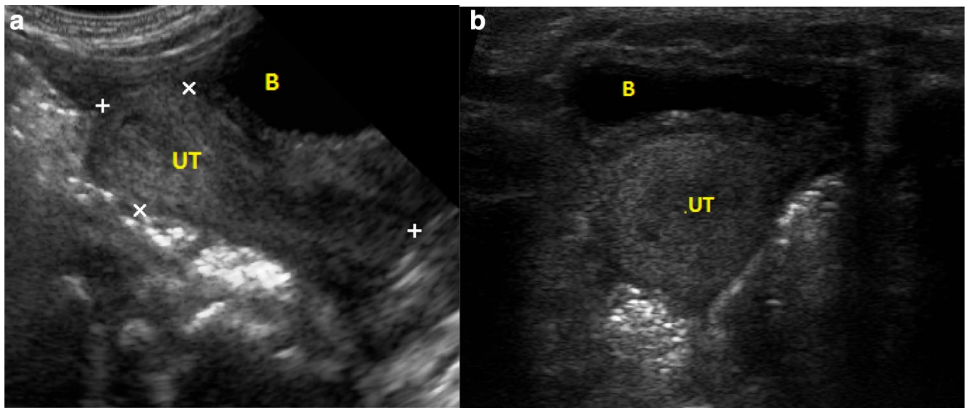

Fig. 2 Neonatal uterus of a 3-day-old child. The neonatal uterus shows a prevalence of the neck on the body and the endometrial rhyme is thickened. **a** Longitudinal section. **b** Axial section. *UT* uterus, *B* bladder, (++) length

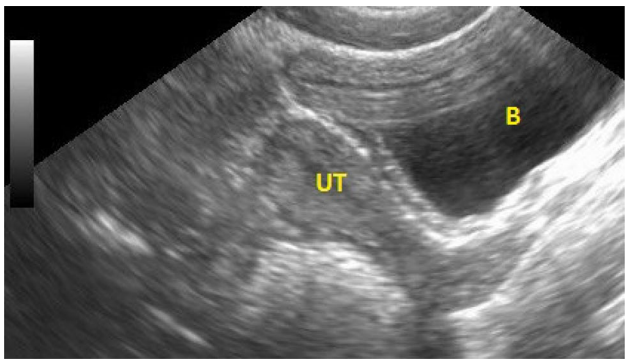

Fig. 3 Pubertal uterus of a 13-year-old-girl. The uterus has the classic pear appearance with a body:neck ratio of 2:1. *UT* uterus, *B* bladder

Table 1 Normal Ovarian Volume and Appearance by Life Stage (modified by Langer et al. [12])

Stage	Ovarian volume (cm^3)	Ovaria appearance
Neonatal	1–3.5	Follicles and cysts common
Pediatric	0.5–1.5	Fewer than six follicles; cysts uncommon
Prepuberal	1–4	Follicles and cysts common
Pubertal	2–6	Follicles and cysts common
Reproductive	4–16	Follicles and cysts common
Postmenopausal	1.2–5.8	Follicles and cysts in approximately 15–20%

There are no changes in shape and size until the age of 7 years: the uterus is cylindrical, the size of the cervix is bigger than the body with a body/neck ratio = 1:2 (infantile uterus). It is not possible to see the endometrial rhyme.

From 7 years onwards, the uterine growth is slow and progressive and the body:neck ratio is 1:1 (transitional uterus); if viewable, the endometrial rhyme is thin.

At puberty, a sudden acceleration of the uterine growth occurs and it is related to Tanner's stages, age, weight and height; the body grows more than the cervix causing the classic pear appearance with a body:neck ratio of 2:1 (post-pubertal uterus); the endometrial thickness is more than 2 mm (Fig. 3).

The pubertal uterus becomes as big as the adult one. The endometrium is visible as an echogenic line of variable thickness depending on the phase of the menstrual cycle. In the proliferative phase, it is thin and linear with central echogenic stria; it becomes echogenic in the secretive phase and inhomogeneous in the menstrual phase [9, 10].

It is possible to classify the morphology of the uterus according to the body:neck ratio:

infantile uterus: body:neck ratio = 1:2;
transitional uterus: body:neck ratio = 1:1;
post-pubertal uterus: body:neck ratio = 2:1;
adult uterus: body:neck ratio = 3:1.

The ovaries are visible with ultrasound at any age; after the menarche, they are more adequately evaluated in the early follicle phase. Volume, follicles, stroma and vessels must be evaluated during the exam.

The volume of the ovary is calculated using the ellipsoid formula: length × depth × height × 0.523.

In relation to the ovarian volume, it is possible to distinguish different stages (Table 1).

After 6 years of age, the ovarian volume increases with a gradual increase in the stroma and the number and size of the follicles, with a correlation with the stages of Tanner (Table 2).

In the newborn, the ovarian follicles can be voluminous. After a few days/months, the dimensions decrease and remain stable during the following years (Fig. 4). Small follicles can be seen within the ovary even in prepubertal stage; they arise in response to the pulsatile release of gonadotropins by the developing pituitary gland (Fig. 5).

At puberty, follicles respond to the stimulation of the follicle-stimulating hormone (FSH) (Fig. 6); during the proliferative phase some follicles are recruited but only one of

Table 2 Tunner's stages represent a scale of physical development of the children/adolescents based on the evaluation of primary and secondary sexual characteristics such as the size of the breasts and the development of pubic hair, divided into five stages, from stage 1 = impubation, to stage 5 = complete pubertal development

	Brests	Pubic hair
Stage 1 (prepubertal)	Elevation of papilla only	No pubic hair
Stage 2	Elevation of breast and papilla as small mound, areola diameter enlarged Median age: 9.8	Sparse, long, pigmented hair, along labia majora Median age: 10.5
Stage 3	Further enlargement without separation of breast and areola Median age: 11.2	Dark, course, curled hair sparsely spread over mons Median age: 11.4
Stage 4	Secondary mound of areola and papilla above the breast Median age: 12.1	Adult type hair, abundant but limited to mons Median age: 12
Stage 5	Recession of areola to contour of breast Media age: 14.6	Adult type spread in quality and distribution Median age: 13.7

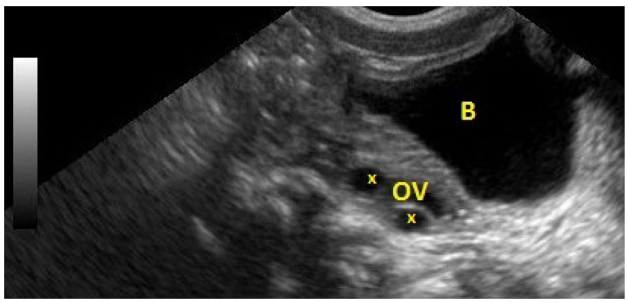

Fig. 4 Neonatal ovary of a 4-day-old child. There are usually some prominent follicles (x) which will disappear as the child grows. *OV* ovary, *B* bladder

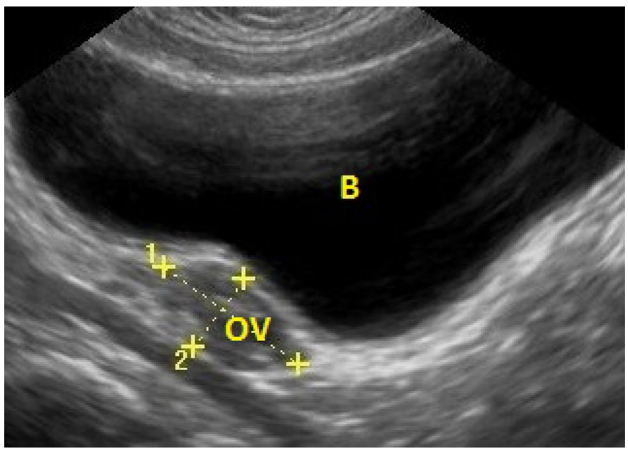

Fig. 5 Prepubertal ovary of a 6-year-old child. No prominent follicles are visible even though sometimes they can appear. *OV* ovary, (++) length

them (dominant follicle) comes to maturation and produces estrogen; if the luteotropic hormone (LH) is released, ovulation occurs and the follicle becomes the corpus luteum and

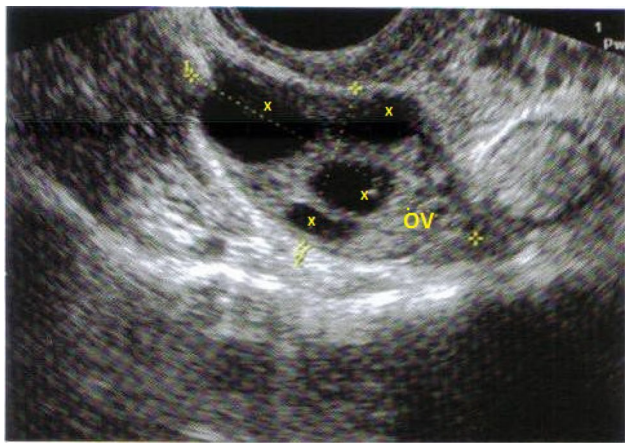

Fig. 6 Pubertal ovary of a 12-year-old girl. Some prominent follicles (++) are visible. *OV* ovary

produces progesterone until the beginning of the next cycle [11, 12].

Ecographically, it is possible to distinguish different types of ovaries depending on the number, size and location of the follicles:

- homogeneous ovary (normal or reduced volume, cortical and non-differentiated stroma);
- microfollicular ovary (normal volume, number of follicles < 4, not more than 3–5 mm in diameter);
- multifollicular ovary (normal or increased volume, number of follicles > 5, between 5 and 10 mm in diameter and diffused through the ovarian stroma);
- polycystic ovary (normal or increased volume; number of follicles > 10, between 3 and 8 mm in diameter; located in the periphery or inside the ovary);
- multifollicular/polycystic ovary with dominant follicles (it has the same characteristics as the previous one with 1 or 2 follicles > 13 mm in diameter).

In the ultrasonography of the ovarian development, the ovarian volume is the most significant parameter.

Congenital abnormalities

The development of the female reproductive tract includes cell differentiation, migration, fusion and subsequent canalization of the Mullerian ducts. The majority of female genital tract malformations are the result of developmental anomalies in Müller's (paramesonephric) and in a smaller part of Wolff's (mesonephric), urogenital and/or cloaca sinuses. The cranial parts of the paramesonephric ducts give rise to the fallopian tubes while the caudal ones merge on the midline in a process called "lateral fusion", forming the uterus and the upper 2/3 of the vagina. The lower part of the vagina develops from the urogenital sinus and is separated from the upper part by the hymen, which is thinned and perforated during the perinatal period. The close relationship between mesonephric and paramesonephric ducts means that various anomalies of the genital apparatus can be associated with abnormalities of the urinary tract; therefore, the ultrasound examination must be extended to the evaluation of the urinary tract too [13].

Abnormalities of Müller's ducts

Abnormalities of the reproductive system can occur at different stages of life. Most of the external genital anomalies are evident at birth. Non-obstructive abnormalities of Mullerian origin may be asymptomatic whereas obstructive forms may be evident causing hydro/mucocolpos or lack of menarche (primary amenorrhea) associated with pelvic pain.

In the evaluation of Mullerian anomalies, the diagnosis is made with ultrasound, MRI and vaginoscopy and/or laparoscopy.

Ultrasonography is the first-line instrumental investigation and it is made with transabdominal scans associated with transperineal scans for the evaluation of the lower genital tract and urinary and vaginal [14]. 3D–4D ultrasound is extremely useful for studying the morphology of internal genital organs.

Mullerian anomalies are classified as follows [15, 16] (Fig. 7; Table 3):

1. Agenesis/aplasia of Müller's ducts.
2. Lateral casting fault:
   (a) Symmetrical: bicornuate uterus, didelphic uterus, septate uterus and arcuate uterus;
   (b) Asymmetric: unicornuate uterus.
3. Vertical melting defect: cervical agenesis/dysgenesis, imperforate hymen and vaginal septum.

1. **Agenesis/aplasia of Müller's ducts**

Mayer–Rokitansky–Küster–Hauser syndrome (*MRKH*) Its incidence is about 1:5000 and it is characterized by the absence of the vagina, hypo/aplasia of the uterus with the presence of uterine "anlages" and normal ovaries (which determine the appearance of normal secondary sexual characteristics). The diagnosis is generally made at puberty because of the primary amenorrhea, but it could also be done during childhood thanks to ultrasound examinations performed for other reasons. The karyotype is female 46, XX, normal. Renal, vertebral, auditory and more rarely heart abnormalities are associated with MRKH type II or MURCS (Müllerian Uditive Renal CervicoSomites) association.

The ultrasound is performed to confirm the presence of normal ovaries, to highlight and characterize any Müllerian derivation structures and to determine the presence, position and morphology of the kidneys. Conservative treatments are possible but neoplastic surgery may be performed with the implantation of autologous vaginal cells grown in vitro [17].

2. (A) **Symmetrical lateral fusion fault** Partial or complete fusion defect of the Mullerian ducts (bicornuate uterus, didelphic uterus) or a non-resorption of the septum between the two Mullerian ducts (uterus septum, uterus subsect or arcuate).

Didelphic uterus Doubling of the genital tract, with two separate well-developed uteri, each connected to an ovary. This condition is usually associated with the presence of a longitudinal vaginal septum.

Two-tone uterus (*uni- or bicollis*) Double bilobed uterine cavity with normal endometrium, partially fused at the medial wall, concave aspect of the base with incision > 10 mm, angle between the emicavities of at least 60°. The bicornuate uterus may have a single cervix (bicornuate unicollis) or double (bicornuate bicollis). A longitudinal vaginal septum can be associated.

Uterus septum Defect of reabsorption of the uterine septum, normal fund or with concavity < 10 mm, endometrial echoes separated by a septum, with an angle between the emicavities of about 30° (Fig. 8).

The differential diagnosis between bicornuate uterus and septum uterus is often difficult with the only conventional ultrasound. Therefore, it may require 3D and 4D ultrasound, which clearly displays the uterine fund profile.

Uterus subseptum or arcuate It is considered an anatomical variant. It has no clinical manifestations in childhood–adolescence and it can be suspected when the transverse uterine diameter is increased and the myometrium is thickened at the level of the fund.

(B) Asymmetric lateral fusion defect:

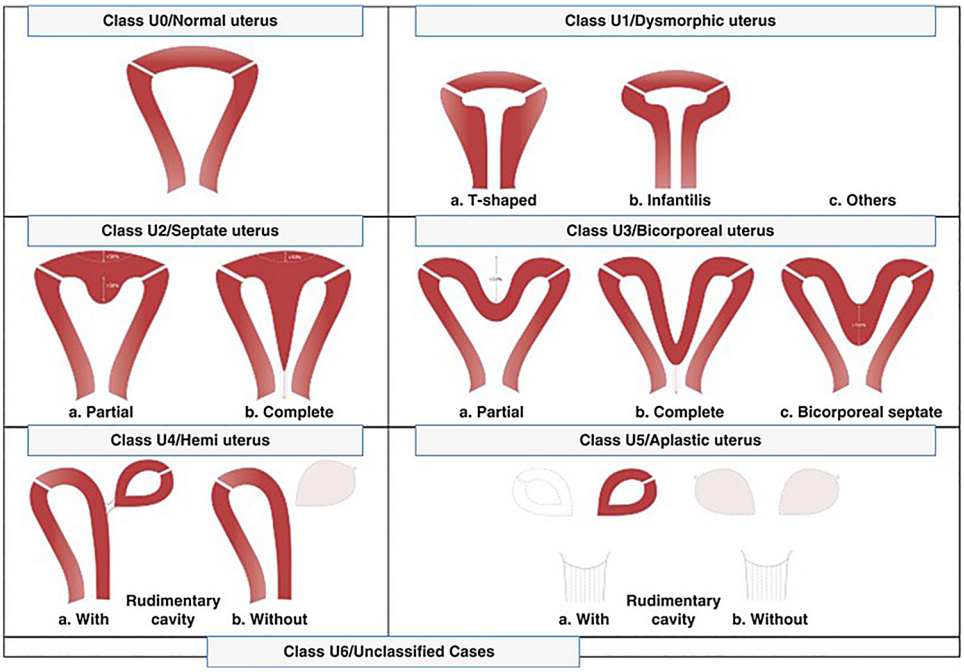

Fig. 7 Anomalies are classified into the following main classes, expressing uterine anatomical deviations deriving from the same embryological origin: U0, normal uterus; U1, dysmorphic uterus; U2, septate uterus; U3, bicorporeal uterus; U4, hemi-uterus; U5, aplastic uterus; U6, for still-unclassified cases. Main classes have been divided into sub-classes expressing anatomical varieties with clinical significance

Unicornuate uterus It is related to the arrest of the development of one of the Müller's ducts, with latero-deviation of the developed uterine horn. It has a "banana" morphology and it is connected to a single salpinge (Fig. 9). A rudimentary uterine horn may be found and it can lead to cryptomenorrhea, as it does not communicate with the vagina. Renal abnormalities are common, fertility can be reduced, as well as the ability to carry out pregnancy [18].

3. Vertical casting fault Fusion defect of the caudal portion of the Mullerian ducts and of the urogenital sinus or lack of vaginal canalization. It determines atresia of the cervix, distal vaginal atresia, vaginal segmental atresia or transverse septum. Since these are obstructive forms, they may become symptomatic at birth (hydro/mucocolpos) or at puberty (primary amenorrhea with hematocolpos/hematometrocolpos).

Cervical atresia: rare, it is associated with atresia of the upper part of the vagina. Patients have primary amenorrhea and cyclic or chronic abdomino-pelvic pain.

Distal vaginal atresia Developmental defect of the inferior part of the vagina derived from the urogenital sinus. It is replaced by fibrous tissue with dilatation of the upstream tract.

Patients have normal development of secondary sexual characteristics (the ovaries are normal) but absent vaginal orifice and, therefore, primary amenorrhea with cyclic or chronic pain because of the cryptomenorrhea which can lead to hematocolpos (Fig. 10) and hematometrocolpos.

The ultrasound examination can evaluate this situation, mostly with transperineal scans which better document the absence of the distal vagina.

Transverse vaginal septum Defect in fusion and/or canalization of Mullerian ducts and embryological urogenital sinus. The external genitalia appear normal. A vaginal septum may be in the upper (46%), middle (40%) or lower (14%) section of the vagina. The septum sometimes has a small central perforation.

Patients may present hydro/mucocolpos during childhood and hematocolpos/hematometrocolpos at puberty, with distention of the cranial portion of the vagina [19]. Infectious complications in adolescence are possible with piohematocolpos. It is important to identify the cervix during the ultrasonography to distinguish a high vaginal septum from a

Table 3 ESHRE/ESGE classification of uterine anomalies: schematic representation (modified by Grimbizis [15])

Uterine anomaly		
	Main class	Sub-class
U0	Normal uterus	
U1	Dysmorphic uterus	(a) T-shaped (b) Infantilis (c) Others
U2	Septate uterus	(a) Partial (b) Complete
U3	Bicorporeal uterus	(a) Partial (b) Complete (c) Bicorporeal septate
U4	Hemi-uterus	(a) With rudimentary cavity (b) Without rudimentary cavity
U5	Aplastic	(a) With rudimentary cavity (b) Without rudimentary cavity
U6	Unclassified malformations	

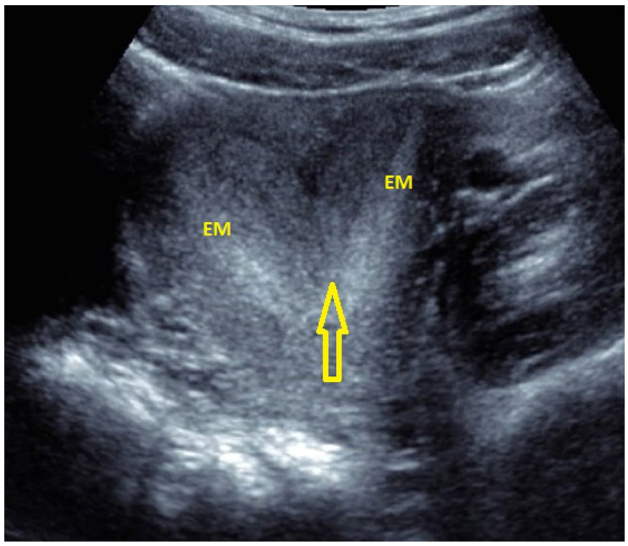

Fig. 8 Uterus septum of an 11-year-old girl. In this malformation, there is a normal fund, concavity < 10 mm and endometrial emicavities (*EM*) separated by a septum (↑)

cervical atresia. The transperineal scans better document the occluding vaginal septum and the downstream vaginal tract.

Imperforate hymen The most common anomaly of the female reproductive tract. It is usually not associated with other malformations. It derives from the lack of canalization of the vaginal plate.

The diagnosis can be made at birth with the confirmation of hydro/mucocolpos or hydrometrocolpos (Fig. 11) and it is usually based solely on the clinical examination. Ultrasonography shows the distension of the entire vaginal lumen and sometimes of the endometrial lumen by corpuscular fluid content (secretions and mucus in newborns, blood and clots at puberty). The transperineal scans document the level of the obstruction, which is very low [20]. In obstructive abnormalities, reflux through the salpinges in the peritoneal cavity is possible. This situation increases the incidence of endometriosis (11–40% according to Brosens, 2013) [21].

Cloacal malformation

The cloacal malformation consists of a wide spectrum of serious non-hereditary anorectal malformations. Its incidence is 1:20,000 and it is more frequent in females.

The division of the cloaca or the urogenital sinus during the initial stages of embryogenesis may fail and it can lead to the confluence of the genital, urinary and intestinal tracts in a single channel (cloaca) or to the formation of two channels (a common genitourinary canal (urogenital sinus) separated from the intestine).

From an inspective/anatomical point of view we can distinguish:

- forms with only one perineal orifice, which include the classical form of the cloaca (the only common channel with orifice in the outlet of the urethra) and the posterior cloaca (the only canal with an outlet in the anus and urogenital sinus that opens anteriorly into the rectum);
- forms with two perineal orifices, which include the urogenital sinus (common outlet of the urethra or bladder with the vagina, with normal opposed anus), the variant cloaca (urogenital sinus and anterior), the posterior cloaca variant (urogenital sinus depilated posteriorly), at the front of the norman anus;
- a form without perineal orifices: sequence of cloacal dysgenesis.

The ultrasound examination is the first diagnostic approach in these patients. It should be performed preferably immediately after birth including the pelvic structures, the kidneys and the spinal canal. At birth, there is generally

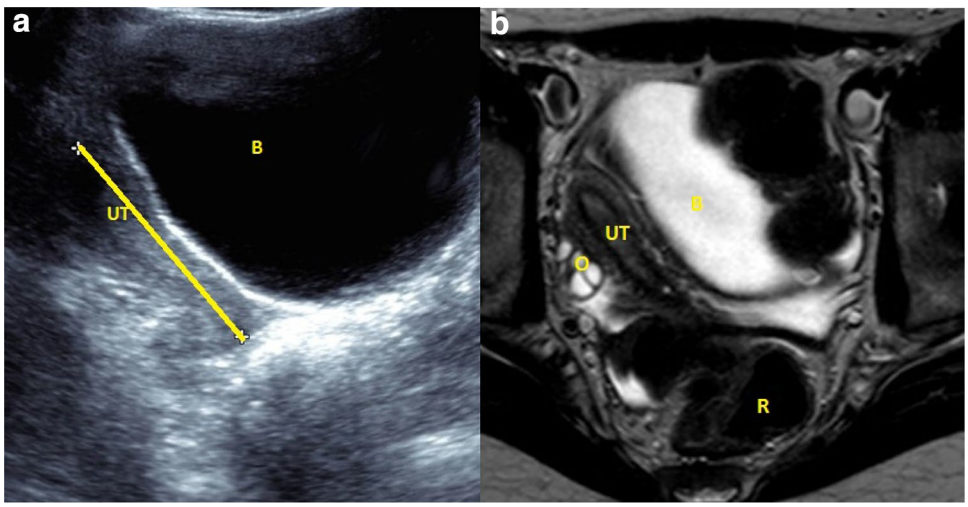

Fig. 9 Unicornuate uterus of an 11-year-old girl. **a** Ultrasonography. **b** MRI. The uterus has a "banana" morphology. *UT* uterus, *B* bladder, (xx) longitudinal diameter, *O* ovary, *R* rectus

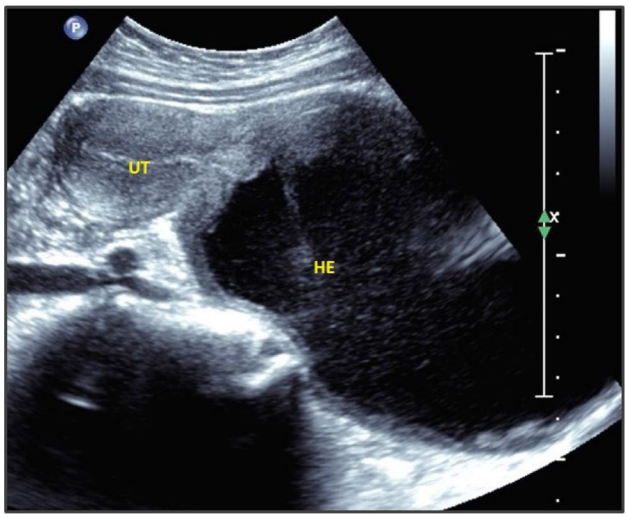

Fig. 10 Hematocolpos in a distal vaginal atresia of a 15-year-old girl. There is no vaginal orifice and this can lead to hematocolpos (*HE*). *UT* uterus

an abdominal mass with a non-homogeneous content caused by the accumulation of urine and meconium in the cloaca (Fig. 12). Sometimes it can lead to hydrocolpos [22].

Malformations associated with the urogenital apparatus are Mullerian anomalies, obstruction hydroureteronephrosis, multicyst kidney, kidney site abnormalities, meconial peritonitis and spine abnormalities.

Disorder of sex development (DSD)

They are a series of congenital affections characterized by atypical development of the chromosome, gonadal and/or phenotypic sex. It includes all those conditions characterized by the ambiguity of the genitals, discordance of the chromosomal/gonadal and/or phenotypic sex and by the major malformation anomalies of the genital ducts and/or the external genitalia. There has been a revision of the nomenclature of pathologies related to alterations of sexual development, following the 2005 Consensus Conference held in Chicago, jointly promoted by the European Society for Pediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society and stemmed from the new knowledge of molecular genetics [23] (Table 4).

The complexity of DSD spectrum requires a multidisciplinary analysis to allow the attribution of the most suitable sex for the development of the patient. The factors influencing this choice derive from a precise etiopathogenetic classification based on genetic and phenotypic sex, psychological and attitudinal orientation, possible surgical options, the possible need for replacement therapy, potential future fertility and the risk of neoplastic degeneration of the gonads [24, 25] (Table 5).

Sexual differentiation disorders may become evident at birth with the presence of ambiguous genitalia but may also occur during adolescence with amenorrhea, virilization of a female phenotype and infertility.

Imaging techniques play a key role in the evaluation of patients with DSD, which must be diversified according to age and clinical presentation [26].

In the newborn and infant with ambiguous genitalia, the goal is to define the anatomical condition of the genital apparatus. The first-line imaging technique is ultrasound, followed in some cases by genitography and MRI. The ultrasound examination must be performed with transabdominal and transperineal scans and must evaluate the internal and external genital organs, the retrovesical spaces and the inguinal regions. The study must be extended to the evaluation of the kidneys (anomalies of number, site and fusion), of the adrenal glands (hypertrophy) and the marrow (tethered cord).

If the ultrasound findings are not enough, an ultrasound genitography may be performed. It consists of the introduction of physiological solution through a catheter into the vagina, or into the urogenital sinus, and into the bladder. It

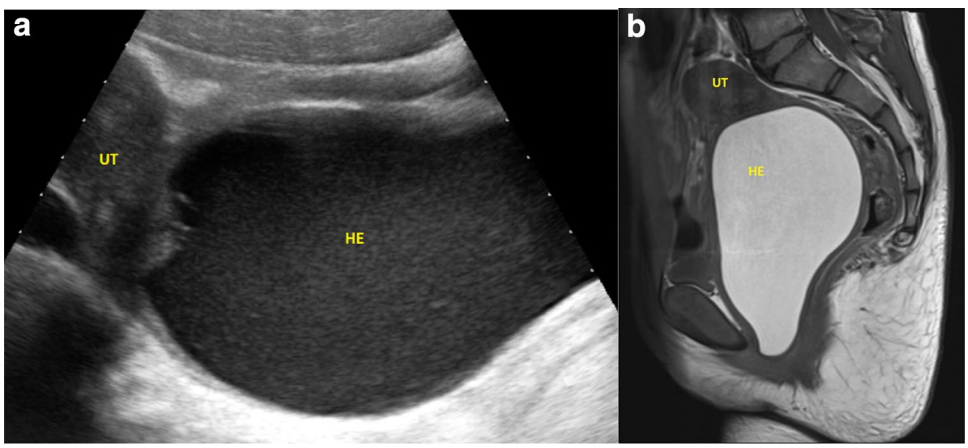

Fig. 11 Hematocolpos caused by imperforate hymen in a 14-year-old girl. **a** Ultrasonography. **b** MRI. There a massive distension of the entire vaginal lumen with hematocolpos (*HE*). *UT* uterus

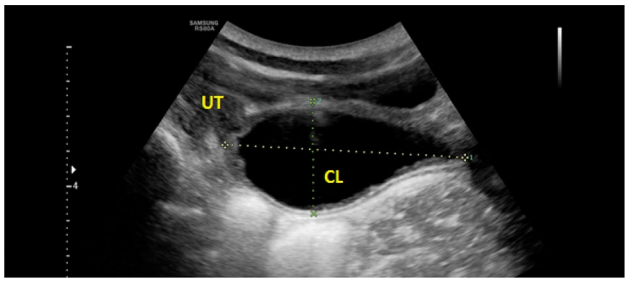

Fig. 12 Cloacal malformation of a newborn. There is an abdominal mass with a non-homogeneous content caused by the accumulation of urine and meconium in the cloaca. *UT* uterus, *CL* cloaca

Table 4 Revisede nomenclature from the consensus statement on management of intersex disorders LWPES/ESPE (modified by Lee et al. [23])

Previous	Revised
Intersex	DSD
Male pseudohermaphrodite, undervirilization of XY male, and undermasculinization of XY male	46, XY DSD
Female pseudohermaphrodite, overvilization of an XX female, and masculinization of an female	46, XX DSD
True hermaphrodite	Ovotesticular DSD
XX male or XX sex reversal	46, XX testicular DSD
XY sex reversal	46, XY complete gonadal dysgenesis

may allow the visualization of the vagina itself and of the cervix.

Genitography allows the differentiation between male and female urethra, the visualization of a vaginal cavity, the possible confluence of the vagina and of the urethra in a urogenital sinus and the recognition of Mullerian residues (prostatic utricle). The examination is performed with radioscopy through the injection of iodinated contrast to see the urogenital sinus, the urethra and the vagina. Sometimes it may be necessary to introduce two or more catheters in case of complex malformations (cloaca).

MRI can be used when ultrasonography is not enough. It does not use ionizing radiation and it is more sensitive in the definition of spatial relations and in the characterization of tissues. It also allows the evaluation of all the associated anomalies (renal, skeletal, bone marrow), but it may require sedation and it has lower tissue resolution.

The most frequent conditions of genital ambiguity are:

- Congenital Adrenal Hyperthrophy: is caused by the lack of one of the five genes necessary for the synthesis of cortisol (generally CYP21) which codes for the 21-hydroxylase enzyme;
- Partial Androgen Insensitivity Syndrome (Partial Androgen Insensitivity Syndrome): it is an X-linked condition caused by partial androgen receptor deficiency.
- CAH (46, XX DSD) may cause signs of virilization in female and non-palpable testicles in male. Some forms are characterized by inadequate synthesis of cortisol and aldosterone which can cause the death of the newborn. The affected girls have normal ovaries and uterus and but the vagina and the uterus are joined to form a single channel called urogenital sinus which may be better studied through genitography.

  In the newborn, the adrenal gland can be enlarged, globose, with a "cerebriform" appearance; with the introduction of substitution therapy (hydrocortisone) this finding tends to lessen.
- Complete Androgen Insensitivity (CAIS Partial Androgen Insensitivity Syndrome) is the most common cause of 46, XY DSD (1: 20,000). It is caused by the mutation of the gene that encodes the androgen receptor and it is X linked. The phenotype is female. The testes are located in the groin or in the labia majora and they are of normal size and echostructure. Mullerian, uterus, and salpinge-derived structures are absent, but there is a blind-ended vagina. Clinically, there is primary amenorrhea and sometimes an inguinal hernia containing a testicle.
- Gonadal dysgenesis or XY sex reversal (Swyer syndrome): it is caused by gene mutations (SRY in 15% of cases, DAX1, SOX9 and others). In the absence of testosterone, there is no virilization of the external genitalia; therefore, the phenotype is feminine, and there is no development of the male internal genital organs. In the absence of AMH (anti-Müllerian hormone), Müller's ducts give rise to the female internal organs even though the gonads are "streak" and, therefore, they do not respond to the increase of pituitary gonadotropins. This causes an incomplete expression of the secondary sexual characteristics. The uterus increases in volume with estroprogestin therapy, which allows the establishment of menstrual cycles.
- Turner syndrome: it is the most common cause of DSD associated with abnormalities of sex chromosomes. The karyotype is 45, X0, the phenotype is female with short stature, shield chest, palmate neck, pterygium, cubit valgus, shortness of the fourth metacarpus, possible aortic coarctation and aorta with bicuspid valve.

  The uterus is generally hypoplastic with persistent infantile characteristics, but it responds to supplemental hormone therapy. The gonads are often "streak like" but sometimes the patients have normal ovaries with follicles. Puberty is generally induced by hormone therapy, although in some cases, when the ovaries are normally represented, it can also occur spontaneously.

Table 5 Causes of DSDs (proposed classification) (modified from Pasterski et al. [24])

Sex chromosome DSD	46,XY DSD	46,XX DSD
47,XXY (Klinefelter syndrome and variants) 45,X (Turner syndrome and variants) 45,X/46,XY (mixed gonadal dysgenesis) 46,XX/46,XY (chimerism)	A: Disorders of gonadal (testicular) development 1. Complete or partial gonadal dysgenesis (e.g. SRY, SOX9, SFI, WT1, DHH etc) 2. Ovotesticular DSD 3. Testis regression B: Disorders in androgen synthesis or action 1. Disorders of androgen synthesis a. LH receptor mutations b. Smith–Lemli–Opitz syndrome c. Steroidogenic acute regulatory protein mutations d. Cholesterol side-chain cleavage (CYP11A1) e. 3 β-hydroxysteroid dehydrogenase 2 (HSD3B2) f. 17 β-hydroxysteroid dehydrogenase (HSD17B3) g. 5 a α-reductase 2 (SRD5A2) 2. Disorders of androgen action a. Androgen insensitivity syndrome b. Drugs and environmental modulators C: Other 1. Syndromic associations of male genital development (e.g. cloacal anomalies, Robinow, Aarskog, Hand-Foot-Genital, popliteal pterygium) 2. Persistent Mullerian duct syndrome 3. Vanishing testis syndrome 4. Isolated hypospadias (CXorf6) 5. Congenital hypogonadotropic hypogonadism 6. Cryptorchidism (INSL3, GREAT) 7. Environmental influences	A: Disorders of gonadal (ovarian) development 1. Gonadal dysgenesis 2. Ovotesticular DSD 3. Testicular DSD (e.g. SRY+, dup SOX9, RSP01) B: Androgen excess 1. Fetal a. 3 β -hydroxysteroid dehydrogenase 2 (HSD3B2) b. 21-hydroxylase (CYP21A2) c. P450 oxidoreductase (POR) d. 11 β –hydroxylase (CYP11B1) e. Glucocorticoid receptor mutations 2. Fetoplacental a. Aromatase deficiency (CYP19) b. Oxidoreductase deficiency (POR) 3. Maternal a. Maternal virilizing tumours (e.g. luteomas) b. androgenic drugs C: Other 1. Syndromic associations (e.g. cloacal anomalies) 2. Mullerian agenesis/hypoplasia (e.g. MURCS) 3. Uterine abnormalities (e.g. MODY5) 4. Vaginal atresia (e.g. KcKusick-Kaufman, Mayer- Rokitanski, Kuster-Hauser) 5. Labial adhesions

During the follow-up of these patients it is important to look for gonadoblastoma, whose incidence is about 30% in gonadal dysgenesis, 15% in PAIs, 0.8% in CAIS, and 2.6% in ovotesticular DSD.

Ovarian cysts

Fetal ovarian cysts may be occasionally found during prenatal ultrasound. They are usually unilateral and they originate from ovarian stimulation by chorionic gonadotropins of placental origin and maternal and fetal estrogens.

Ovarian cysts are often mobile and, therefore, they can dislocate in the abdomen. They can be simple or complex. Most of them are asymptomatic and undergo spontaneous regression after birth [27].

Intracystic hemorrhage is a relatively common complication of larger cystic formations during fetal life. It is causes by torsion of the appendage and it contains endocystic echogenic material with fluid–fluid images (Fig. 13). After self-amputation, the cyst can become free in the abdominal cavity ("wandering tumor") [28].

In pre-pubertal age, small follicles are frequently seen, but ovarian cysts are rare. If a single cyst with a diameter less than 1 cm is considered normal, the presence of more voluminous or multiple cysts will require the exclusion of precocious puberty or pseudopubertality; the assessment must also be correlated with the degree of maturation of the uterus, as well as with the levels of gonadotropins and estradiol [29].

In post-pubertal age as well as in adulthood, ovarian cysts are common (Fig. 14). Cysts are defined when their diameter is more than 3 cm. Functional cysts generally derive from an ovulatory dysfunction. Follicular cysts are due to gonadal hyperstimulation by the pituitary gland; in the absence of the LH peak, the follicle does not break and continues to grow. They are generally unilocular, thin walled and anechoic. Small cystic formations are sometimes seen inside or outside the main cysts ("daughter cysts sign", sign of the daughter cysts: a finding that confirms the ovarian origin of a cyst) (Fig. 15). They do not cause symptoms and generally undergo spontaneous regression with menstruation.

The luteal cysts derive from the non-involution of a corpus luteum. They have fluid content, septa, internal trabeculation and heterogeneous aspects (such as "ground glass" or

ground glass, "mesh-like" or reticular, "fish-net or mesh) so that the lutein cyst is often referred to as the "great simulator" (Fig. 16). Lutein cysts usually disappear after menstruation. Sometimes, bleeding within the cyst can occur and this leads to the hemorrhagic corpus luteum. It shows corpuscular content, peripheral echogenic halo and the characteristic "ring of fire" in color Doppler (intense flow signal at the periphery); the painful symptomatology is linked to peritoneal irritation.

In hemorrhagic cysts, bleeding can cause a heterogeneous pattern with irregular trabeculation which leads to a "moth-eaten" or "worm-eaten" aspect. In the retraction phase, they have concave margins (Fig. 17).

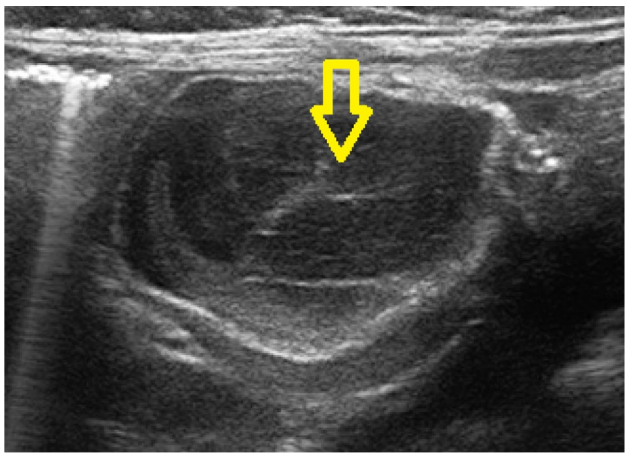

Fig. 13 Intracystic hemorrhage due to torsion of the appendage in a newborn. It contains echogenic material (↑) with fluid–fluid images

Paraovarian and paratubal cysts

They arise from the mesonephric ducts and from the mesothelium separated from the ovary, with the salpinge that appears as "stretched" on the upper profile of the cyst (Fig. 18). They have variable dimensions and tend to increase very slowly in volume, but they are not related to the ovarian cycle and are not under hormonal control. They are generally asymptomatic.

Peritoneal inclusion cysts

They are pelvic cystic masses, which arise from mesothelial proliferation. They occur in the presence of peritoneal adhesions with altered reabsorption of the peritoneal fluid related to the ovarian activity. They can sometimes reach large dimensions.

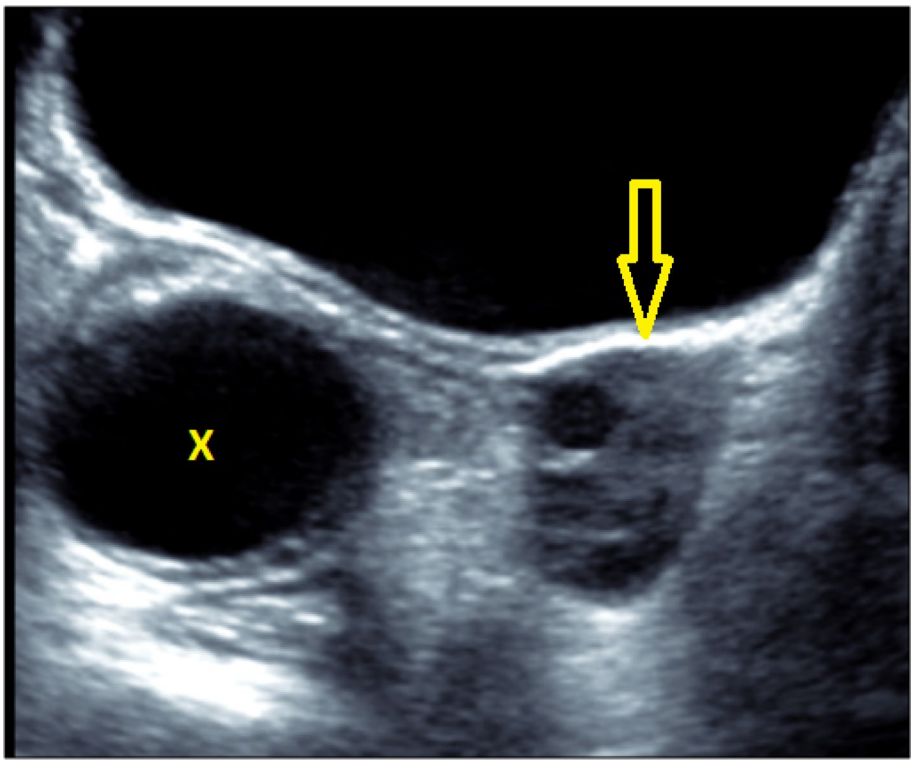

Fig. 14 Right ovarian cyst (x); left multifollicular ovary (↓) of a 7-year-old girl. A cyst is defined when its diameter is more than 3 cm

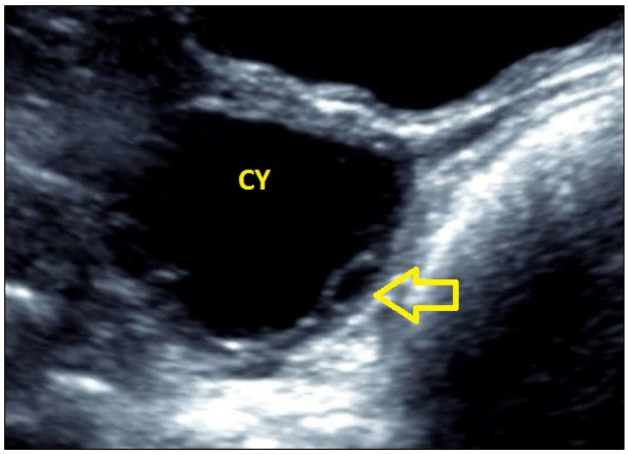

Fig. 15 "Daughter cyst" sign in a 5-year-old girl. It consists of a small cystic formation seen within an ovarian cyst (CY)

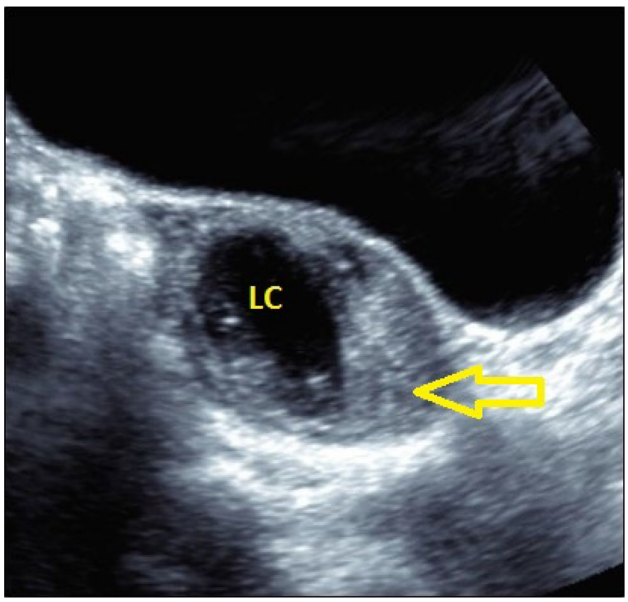

Fig. 16 Luteal cyst (LC) in a 13-year-old girl. It contains fluid, septa, internal trabeculation and it has a heterogeneous aspects ("ground glass") (←)

Ovarian neoplasms

Ovarian neoplasm is rare during childhood as it comprises 1–2% of all pediatric neoplasms. They are usually asymptomatic but can sometimes cause an abdomino-pelvic mass or endocrine alterations [30–32].

Ultrasonography is the first-line exam as it allows an evaluation of the dimensions, ecostructural characteristics (solid, cystic, calcific areas) and lesion vascularization [33].

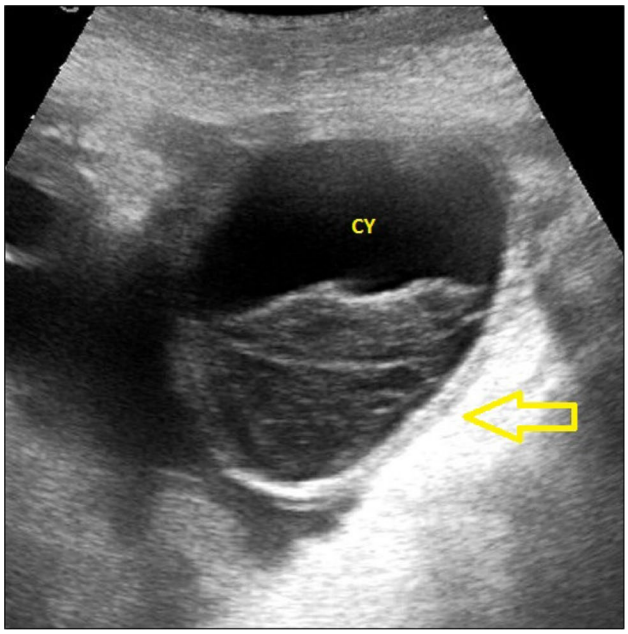

Fig. 17 Hemorrhagic cyst (CY) of an 18-year-old girl. It shows a heterogeneous pattern with irregular trabeculation which leads to a "moth-eaten" or "worm-eaten" aspect (←)

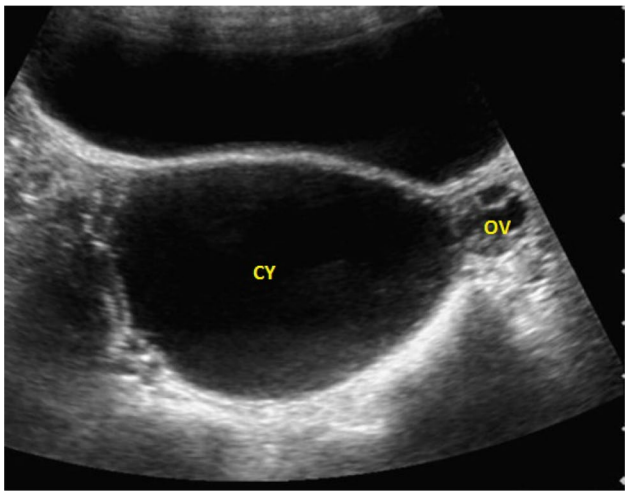

Fig. 18 Paraovarian cyst (CY) of a 10-year-old girl. They arise from the mesonephric ducts and the mesothelium and they are separated from the ovary (OV)

MRI provides further details regarding tissue characterization, extension, involvement of other organs, differential diagnosis and operative planning. However, in smaller or non-collaborating girls, it sometimes requires sedation [34–36]. CT is, therefore, often preferred because in non-collaborating patients it can be performed more quickly, without the need for sedation.

Elements of malignancy are the large size, the prevalence of the solid component, the irregularities of the contours, the thickness of the septa, the presence of papillary projections, the pattern of calcifications and the extension of necrosis. The values of serum tumor markers (αFP, βHCG, LDH) are useful for the diagnosis [37–40].

Germ neoplasms arise from the primordial germ cells of the urogenital ridge and are more frequent in girls and adolescents. They represent 2/3 of the neoplasms of the ovary and in 1/3 of the cases, and are malignant.

They include

- mature teratoma (mature cystic teratoma or dermoid cyst) is the most common form, representing 50% of pediatric ovarian tumors. In 10% it is bilateral. It is a congenital lesion deriving from germinal leaflets: endoderm, ectoderm and mesoderm. It is generally unilocular with a capsule of variable thickness and a predominantly sebaceous content with calcifications [41]. The echogenicity is variable in relation to the content: hyperechogenicity is due to sebum and fat; the Rokitansky nodule or dermoid plug or mural nodule is a mixture of tissues (bone, teeth, fat, and hair). The hair determines the thin echogenic bands (dermoid mesh); the calcifications generate the rear shadow cone, which if very extensive is called "tip of the iceberg" sign; images of fat/fluid level are possible.
- immature teratoma represents the 10–20% of ovarian tumors in patients with less than 20 years. It is an aggressive form, in which αFP and βHCG are indicative serum markers. It consists of immature embryonic tissue, deriving from all the germinal sheets (endoderm, ectoderm, and mesoderm) mixed with mature tissue; the amount of immature neuroepithelial tissue determines the histological degree. It appears in ultrasonography as a voluminous and heterogeneous mass, predominantly solid or mixed solid cystic, with thick and irregular septa, minute calcification, punctiform foci of adipose tissue and sometimes hemorrhagic areas.
- dysgerminoma is the most frequent malignant germ line tumor of childhood and adolescence, equivalent to the seminoma in the male. It is sometimes associated with gonadoblastoma in the dysgenetic gonads; in 10-15% of cases, it can be bilateral; it is an aggressive form, in which LDH and βHCG are indicative serum markers. It appears at ultrasonography as a solid, polylobulated and capsulated mass, with prominent, intensely vascularized fibro-vascular septa, areas of necrosis, hemorrhagic foci, "patchy" calcifications; ascites may be present.
- endodermal sinus tumor or yolk sac tumor is a rare, very aggressive, fast-growing form, with abdomino-pelvic diffusion and metastases; the indicative serum marker is αFP. It appears at ultrasonography imaging as a voluminous solid mass, inhomogeneous, with areas of necrosis and hemorrhage; ascites are frequently present. At imaging, it appears as a voluminous solid mass, inhomogeneous, with areas of necrosis and hemorrhage.

Epithelial tumors represent the 95% of ovarian tumors in adults, but only 15–20% of pediatric ovarian tumors; they are rare before the menarche as their development could be triggered by the hormonal stimulation. Cystadenoma is the most common epithelial tumor in children and adolescents.

Two variants are possible: the serous cystadenoma, more frequent, cystic, unilocular or multilocular, with thin walls and septa; and the rare mucinous, cystic, multilocular cystadenoma, with thick walls and septa and fibrous stroma.

Vaginal and uterine neoplasms

Rhabdomyosarcoma of the female genital tract usually arises from the vagina and the vulva during the first years of life or from the uterine cervix in older girls. It causes vaginal bleeding with palpable mass [42].

In ultrasonography, it appears as an inhomogeneous, lobulated formation, with hypo-anechogenic central areas caused by necrosis or colliquation. MRI is indicated for tissue characterization and for the local invasion, while CT is useful for the staging [43, 44].

Other rare forms of vaginal/uterine neoplasms in children are leiomyosarcoma, clear cell adenocarcinoma, and endodermal sinus tumor [45].

Adnexal torsion

It is a typical condition of the fertile age, but it can also affect the pediatric age (15% of cases), especially in the first years of life and puberty.

Pain is the most constant symptom, sometimes associated with nausea and vomiting, it is poorly differentiated from other urgent conditions that affect the genitourinary and gastro-intestinal system; therefore, the role of imaging is fundamental [46, 47].

It is caused by the partial or complete rotation of the appendage on its vascular peduncle and usually affects the ovary and the fallopian tube. Predisposing factors are the length and the laxity of the uterus-ovarian ligaments.

The torsion is usually one sided, and it is more frequent on the right one, due to the less mobility of the left gonad from the presence of the sigma.

The ultrasound examination documents the increase in volume of the ovary, which appears medialized, ascended, with an inhomogeneous echostructure, a central hyperechogenic stroma due to edema, small peripheral distribution follicles (perhaps due to fluid transudation caused by vascular

congestion). The pathognomonic finding is, however, the identification of the twisted vascular pedicle ("whirl" sign) (Fig. 19). Vascular signals to color Doppler in the gonadal tissue are generally absent; however, the presence of flow does not exclude torsion.

The uterus deviation from the torsion side and the presence of effusion in the Douglas is common [48–51].

Ovarian torsion can occur in 50% of cases in normal gonads, or it may be secondary to expansive diseases such as large cysts or neoplastic pathologies [52]. Torsion is the most common complication of pediatric ovarian tumors (approximately 3–16% of cases).

When ultrasonography is not enough, its MRI may be useful as it allows a better evaluation of the vascular vortex, the hemorrhagic content of the tube and the features of the expansive formation [53].

Primary amenorrhea

Primary amenorrhea is the absence of menarche over 15 years. The causes include gonadal dysgenesis (50%), hypothalamic hypogonadism (20%), the absence of the uterus, of the cervix and/or of the vagina (15%), the transverse vaginal septum or the imperforate hymen (5%), pituitary changes (5%); other conditions include polycystic ovary syndrome (PCOS), congenital adrenal hyperplasia (CAH), and complete androgen congenital insensitivity (CAIS) (5%) [4]. Ultrasonography is usually the first-line imaging method.

Polycystic ovarian syndrome (PCOS) is the most common endocrinopathy in premenopausal women and affects 6–8% of women of reproductive age [54]. Despite its high prevalence, diagnostic criteria and treatment are not universally agreed. The 2006 Androgen Excess Society criteria for PCOS include hyperandrogenism (hirsutism and/or hyperandrogenemia) and ovarian dysfunction (oligo-anovulation and/or polycystic ovaries on ultrasound) [55]. The diagnosis of PCOS in young adolescents is particularly difficult since transient oligomenorrhea and mild hyperandrogenism are common in the early years after the start of the menarche. In these cases, the recognition of polycystic ovaries becomes an important finding.

The ultrasound characteristics of PCOS are variable; the ovaries may appear normal or polycyclic, enlarged, with more small follicles. According to the 2003 ESHRE/ASRM Consensus Conference in Rotterdam, two of the following signs are required for the definition of PCOS: (1) oligo-anovulation; (2) clinical and/or biochemical signs of hyperandrogenism; (3) polycystic ovaries. Therefore, the finding of polycystic ovaries is one of the signs, but it is not fundamental for classification purposes. For the definition of polycystic ovaries, according to the Consensus Conference, it is necessary to find 12 or more follicles with a diameter between 2 and 9 mm, regardless of the location or an increased ovarian volume (> 10 ml), even if present in only one ovary [56].

More recently, according to the 2010 Amsterdam Consensus Conference, it was considered necessary to take into account all the three criteria of Rotterdam and, therefore, oligo/amenorrhea for at least 2 years after menarche, or primary amenorrhea at 16 years, ovarian increase in volume, over 10 cm^3 and biochemical hyperandrogenism, rather than clinical signs of androgen excess [57].

The number of follicles is an easily detectable finding by transvaginal ultrasound. However, this examination cannot be used in most adolescents. The MRI provides a better definition of follicles and an optimal evaluation of the ovarian volume. It can be used in adolescents, when the penetration power of the US bundle is reduced, e.g., for the thickness of the subcutaneous fat.

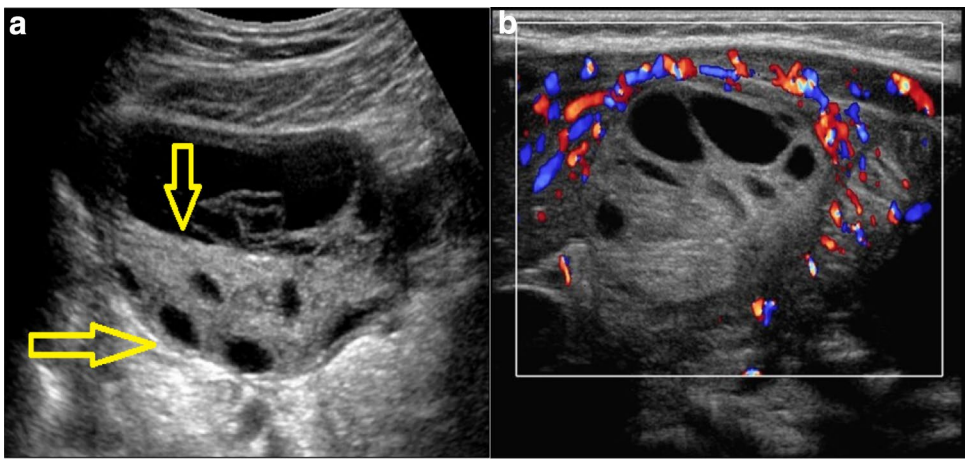

Fig. 19 Ovarian torsion in the newborn. **a** The ovary appears medialized with an inhomogeneous echostructure, a central hyperechogenic stroma (↓), small peripheral distribution of the follicles (→). **b** The twisted vascular pedicle ("whirl" sign) is a pathognomonic sign of this condition

Precocious puberty

Precocious puberty is defined as the appearance of secondary sexual characteristics, including the menarche, before the age of 8 in the female and before the age of 9 in the male. It can be central or true precocious puberty (dependent on gonadotropins) or peripheral or precocious pseudo-puberty (independent of gonadotropins). There are also incomplete forms of precocious puberty, including premature thelarche, premature pubarche and premature menarche without other signs of puberty. In central precocious puberty, activation of the hypothalamic–hypophyseal–gonadal axis with secretion of the hormone of gonadotrophin release by the hypothalamus leads to pubertal development.

At the ultrasound examination, the uterus and ovaries are increased in size, with characters of advanced maturation. Although the cause of central precocious puberty is in most cases (> 80%) idiopathic, forms secondary to CNS lesions are also possible.

In precocious peripheral puberty or early pseudo-puberty, serum gonadotropin levels are low. An autonomous follicular ovarian cyst (as in McCune–Albright syndrome) or a secreting tumor (such as juvenile granulosa cells) can autonomously produce elevated estrogen levels and induce rapid pubertal development and vaginal bleeding. In McCune–Albright syndrome, which is associated with patches of milk coffee and mono- or polyostotic fibrous dysplasia, the cystic formations appear discontinuous together with vaginal bleeding and then regress. Sertoli–Leydig cell tumors are more often non-secretory, or may produce androgens, as well as some adrenal tumors and, therefore, induce virilization. Exposure to estrogens or androgens (topical or ingested) also induces similar stimulation effects [58, 59].

Ultrasonography is used to assess the degree of stimulation of the uterus and ovaries and to identify the cause of inappropriate stimulation (in the case of early pseudo-puberty). Ultrasound can also be used to monitor the effect of medical or surgical treatment.

Pelvic inflammatory disease

Pelvic inflammatory disease affects girls in reproductive age. It is usually due to an ascending sexually transmitted infection which progressively involves the uterine cavity, the salpinge and the ovaries ascending from the vagina and the cervix. Then it spreads to the entire pelvis. The inflammatory process can resolve or become chronic with permanent compromise of the tubal architecture (sactosalpinge) and/or formation of adherent pseudocysts. This disease is usually caused by *Neisseria gonorrhoeae, Chlamydia trachomatis* and other endogenous anaerobic organisms [60].

The diagnosis is based on the clinical presentation which includes fever, pelvic pain, tenderness and vaginal discharge.

Anatomo-pathological changes are

- **Acute adnexitis** In the initial phase of the acute inflammatory process the tubas show thickened walls due to mucosal edema; it produces an exudate that pours into the pelvis. The progression of the infection can lead to the occlusion of the tubal ostia with consequent collection of purulent material and distention of the tubal lumen (*pyosalpinx*) [61]. If the inflammatory process progresses, it passes to the *tube-ovarian complex stage*, characterized by the simultaneous involvement of the ovary. If the infection progresses, it can lead to the formation of an abscess with the simultaneous involvement of tuba, ovary and pelvis (*tube-ovarian abscess stage*).
- **Chronic adnexitis** If the acute adnexitis does not resolve completely, it can evolve to the chronic form. The tube dilates due to the presence of inhomogeneous fluid in the lumen, with a tubuliform convoluted conformation, thin walls and mucosa and fibrous and flattened folds. It is often associated with adhesion phenomena with pseudocyst formation.
- Transvaginal ultrasound is useful for identifying complications of pelvic inflammatory disease (such as pyosalpinx, tube-ovarian abscesses and other abdominal-pelvic collections) and for differential diagnosis [62].

In the initial phases, there is an adnexal tumefaction adjacent to the ovary, isoechoic to the myometrium, tubular or ovoid, pain to the targeted pressure of the endocavitary probe, discrete or rich vascularization at the color Doppler examination [63].

In the pyosalpinx phase, the tuba becomes tubuliform and convoluted, due to the presence of inhomogeneous liquid and the accumulation of pus and blood; the walls thicken due to edema resulting from the inflammation. In the transverse section, hyperechogenic endoluminal protrusions are observed, linked to the edema of endosalpingeal folds. This gives rise to a characteristic echographic sign called “cogwheel” which consists of the presence of incomplete, hypoechoic, thick septa which do not reach the opposite tubal wall (a sign always linked to convolution). Sometimes pelvic effusion might be associated [64].

In the tube-ovarian complex phase, a single mass in which the tube and the ovary are not well distinguishable is appreciable.

In the tube-ovarian abscess phase, the mass becomes no longer recognizable with markedly inhomogeneous content. The abscess can be surrounded by free fluid in the purulent type of pelvis or can be combined with collected collections.

In endometritis, the endometrium is thickened, inhomogeneous and/or hyperechoic.

In the acute phases, there is an intense tubular/ovarian vascularization with low-resistance flow in color Doppler.

In the chronic phases, hydrosalpinx or sactosalpinx with thin tubular walls of <5 mm thickness may be present. They are convoluted and dilated, with incomplete septa, flattened folds with small echogenic nodules ("beads on a string" sign), poor wall vascularization and pelvic effusion usually in the form of peritoneal inclusion cysts [65, 66].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, and its later amendments.

Human and animal rights This article does not contain any studies with human or animal subjects performed by any of the authors.

Informed consent Additional informed consent was obtained from all the patients for whom identifying information is not included in this article.

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