Ultrasound and MRI diagnosis of the developmental and functional abnormalities of the female reproductive tract.

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Learning objectives

To describe aetiology, pathophysiology, clinical features and role of Imaging procedures (especially ultrasound and MRI, with a special focus on some recent applications of the latter) in a wide range of congenital and acquired disorders of the female reproductive system.
Background

1) DISORDERS OF THE SEXUAL DIFFERENTIATION

Developmental abnormalities may occur at any stage of the normal sexual differentiation, as it is recalled in Figures 1 and 2. Attention must be drawn to the fact that a female differentiation of both internal and external genitalia, not being caused by any ovarian activity, just follows the absence of testicular products.

A) ABNORMALITIES OF CHROMOSOMAL SEX

- Turner's syndrome (genome: XO). In the absence of products of embryonic testis, the newborn has normal female genitalia. Usually located within the broad ligaments, the ovaries have a streak appearance (Fig. 3): their stroma is normal but no follicles or oocytes can be found. Without follicles no estrogen production will ever establish nor puberty occur; early diagnosis can however be made if mesenchymal disorders (lymphedema, pterygium colli, hypoplastic 4th metacarpal bone, etc.) associate.

- Mixed gonadal dysgenesis. Chromosomal mosaicism is frequent. Both a non-functioning testis and a streak ovary are present. The uterus, at least one Fallopian tube and the vagina develop due to the inactivity of the testis; the external genitalia are ambiguous.

- True hermaphroditism. The chromosomal situation may vary. One testis and one ovary (or at least one mixed gonad) usually develop. An uterus (sometimes hypoplastic and unicornuate) is generally present, with ambiguous external genitalia.

B) ABNORMALITIES OF GONADAL SEX

In the pure gonadal dysgenesis, the karyotype (either XX or XY) is normal. Two non-functioning streak gonads are present; the genitalia differentiate as female, without any puberty.

C) ABNORMALITIES OF PHENOTYPIC SEX

- Female pseudohermaphroditism. In an otherwise normal female fetus the deficiency of a steroidogenetic enzyme (21- or rarely 11-hydroxylase) causes excess of adrenal androgens, leading to virilisation and growth acceleration.

- Male pseudohermaphroditism. In a male fetus the external genitalia are ambiguous because of the absence of the enzyme (5a-reductase) necessary to the synthesis of dihydrotestosterone.
- Testicular feminilization (Morris' syndrome). In a male fetus with a normal testicular activity the receptor to testosterone and dihydrotestosterone is absent. Neither Wolffian nor Müllerian ducts develop; the external genitalia are female, with a short blind vagina.

- Abnormalities in the development of the Müllerian ducts [1].

* Mayer-Rokitansky-Kuster-Hauser syndrome. Female patients with normal ovaries are affected. Vaginal agenesis associates with uterine abnormalities ranging from a rudimentary bicornuate to a only slightly hypoplastic uterus, sometimes containing normal endometrium (in this case hematometra occurs at the age of menarch).

* Abnormalities of the "lateral" fusion between the right and left Müllerian ducts originate a spectrum of malformations ranging from uterus didelphys to bicornuate, arcuate and septate uterus, this latter representing the most common form.

* Abnormalities of the "vertical" fusion between the Müllerian ducts and the sinovaginal bulbs (which gives rise to the lower fifth of the vagina) cause the presence of obstructive or non-obstructive transverse vaginal septa.

2) PUBERTAL CHRONOLOGICAL ALTERATIONS

Figures 4 and 5 report the most common causes of both early and late puberty, whose main clinical manifestations are respectively a scarce final height and the many consequences of a deficient ovarian hormone production.

3) ABNORMALITIES OF OVARIAN HORMONE PRODUCTION

Besides providing oocyte maturation, the ovaries produce steroid hormones. Estrogens (although in varying quantity) and androgens are secreted through the whole menstrual cycle, while progesterone is produced only between ovulation and the subsequent menstruation.

The main abnormalities in the ovarian hormone production are summarized in Tab. 6. Other clinical manifestations may accompany the impaired fertility observed in all these circumstances. Amenorrhea or acyclic uterine haemorrhage occur when excess estrogen and/or progesterone is produced; amenorrhea or menstrual disorders and obstacles to oocyte maturation associate to a deficiency of estrogen or progesterone; an increased testosterone production causes virilisation.

4) ABNORMALITIES OF THE MENSTRUAL CYCLE

The relationship of endometrial anatomy and histology to the cyclic pituitary and ovarian hormone production (Fig. 7) is well known. The most important causes of abnormal menstrual cycles are reported in Fig. 8.

However, a role in menstrual disorders (and especially in dysmenorrhea) may be played by abnormalities of the physiological myometrial contraction [2]. Two different kinds of
contraction have been identified, thanks to recent advances in the Imaging procedures, in non-pregnant myometrium:

- the uterine peristalsis, an autonomous, myogenous activity originating in the junctional zone at a frequency of 2 to 3 per minute and extending from cell to cell for an average 4-10 millimeters [3]. Stimulated by estrogen and inhibited by progesterone [4], the uterine peristalsis has higher intensity and a cervix-to-fundus direction in the peri-ovulatory phase in order to help sperm transport, while it is fundus-to-cervix oriented in the menstrual phase, helping to expel mucosal debris [3-6]. Being part of the processes causing the onset of pregnancy and the menstruation, an abnormal uterine peristalsis may cause sterility, abortion, endometriosis and dysmenorrhea [5,6];

- the prolonged contractions are sporadic focal areas of myometrial thickening, during some minutes, without apparent biological effects [7,8].

5) IMPAIRED FERTILITY

Besides the abnormalities in the ovarian hormone production (Fig. 6) and the alterations of the patency of the Fallopian tubes, sterility may be also caused by anatomical and positional abnormalities of uterus and cervix, by intrauterine adhesions, inflammation, immunological disorders and production of cervical mucus inadequate to transportation and nutrition of sperms.

Fertility may also be impaired by abnormal uterine contractility, what can also be caused by leiomyomas. Leiomyomas may both interfere with the physiologic peristalsis and induce, in the adjacent myometrium, focal non-peristaltic movements, which may represent an attempt to expel the myomas [9]; moreover, submucosal leiomyomas may ulcerate and distort the endometrium, making implantation difficult.
**THE DETERMINATION OF SEX**

<table>
<thead>
<tr>
<th>Fecundation</th>
<th>2\textsuperscript{nd} to 5\textsuperscript{th} week</th>
<th>6\textsuperscript{th} to 11\textsuperscript{th} week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosomal sex</td>
<td>Gonadal sex</td>
<td>Phenotypic sex</td>
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**XY**  | Testicles | Testosterone  
| | | Dihydrotestosterone  
| | | Müllerian regression factor  

**XX**  | Ovaries | Nothing |

**Fig. 0:** The karyotype established at fecundation makes the gonads differentiate into either testicles or ovaries. The formation of male internal and external genitalia is induced by three different products of the embryonic testicles; in their absence, a female reproductive system develops.

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**Fig. 0:** The specific role of testosterone, dihydrotestosterone and Müllerian regression factor in the embryogenesis of the male reproductive system. No ovarian products are required to the development of the female internal and external genitalia.

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**Fig. 0:** A streak ovary in a patient with Turner's syndrome. Ovarian stroma (on the left) is normal; no follicles are present in the epithelial component (right). Hematoxylin-eosin stain, 100 x.

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Fig. 0: The causes of precocious puberty. In a true precocious puberty early activation of the hypothalamic-pituitary-ovarian axis occurs, which is absent in precocious pseudo-puberty.

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**DELAYED PUBERTY (> 14 YEARS)**

<table>
<thead>
<tr>
<th>Constitutional (normal late-onset puberty)</th>
<th>Hypothalamic/pituitary deficiency (hypogonadotropic hypogonadism)</th>
<th>Space-occupying lesions</th>
<th>Trauma</th>
<th>Functional abnormalities</th>
<th>Primary ovarian deficiency (hypergonadotropic hypogonadism)</th>
<th>Disorders of the sexual differentiation</th>
<th>Deficiency of steroid synthesis enzymes</th>
<th>Previous radio/chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hypothalamic/pituitary deficiency (hypogonadotropic hypogonadism)</td>
<td>Craniopharyngiomas</td>
<td>Histiocytosis X</td>
<td>Pituitary adenomas</td>
<td>Kallmann’s syndrome</td>
<td>Panhypopituitarism</td>
<td>Hyperprolactinemia</td>
<td>Abnormal body weight</td>
</tr>
</tbody>
</table>

**Fig. 0:** The causes of delayed puberty. Apart from a constitutional delay, a distinction must be made between the cases with a deficiency of the whole pituitary-ovarian axis (hypogonadotropic hypogonadism) and those with a normal pituitary function (hypergonadotropic hypogonadism).

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**ABNORMALITIES OF OVARIAN HORMONE PRODUCTION IN THE ADULT**

<table>
<thead>
<tr>
<th>Excess of estrogen and progesterone</th>
<th>Ovarian tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypogonadism (see delayed puberty)</td>
<td>Sheehan’s syndrome</td>
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<tr>
<td>Panhypopituitarism</td>
<td>Empty sella syndrome</td>
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<td>Ovarian autoimmune disorders</td>
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<td>Idiopathic precocious menopause</td>
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<td>Prolonged oral contraceptives intake</td>
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<tr>
<td>Excess of testosterone</td>
<td>Polycystic ovaries</td>
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<td></td>
<td>Stromal hyperplasia</td>
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<tr>
<td></td>
<td>Ovarian tumors</td>
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</table>

**Fig. 0:** In adult women the production of ovarian steroid hormones may be quantitatively abnormal. Clinical symptoms are observed both in case of excessive estrogen, progesterone or testosterone secretion and if the production of estrogen or progesterone decreases.

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Fig. 0: A well-known relationship links the changes observed in the endometrium during the menstrual cycle and the secretion of pituitary gonadotropins and ovarian steroid hormones.

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**Fig. 0:** Besides pregnancy-related disorders and systemic diseases, hormonal abnormalities and organic uterine alterations are the main causes of abnormal menstrual cycles.
Imaging findings OR Procedure details

1) DISORDERS OF THE SEXUAL DIFFERENTIATION

Besides a diagnostic definition (in cooperation with the ascertainment of the karyotype and the dosage of hormones), in these patients the Imaging procedures have to identify the gonads (gonadal dysgenesis, especially with a male genome, is associated with high risk of cancer [10]) and to direct the surgical procedures.

Ultrasound diagnosis may be difficult, also because of the impossibility to perform in many cases a trans-vaginal approach and of the frequent gonadal ectopia [11-13]. Its efficiency in the workout of the abnormalities of the Müllerian ducts ranges from 90 to 92% [14,15].

MRI proves useful [16]: the gonadal signal intensity is usually low in T1 and high in T2-weighted sequences [17], although their histological structure may alter the signal and in some cases make them indistinguishable from the abdominal content (Fig. 1). The overall reported accuracy of MRI in the abnormalities of the Müllerian ducts is up to 100% [14,18]. MRI can easily depict the different stages of defects of "lateral" fusion between the right and left Müllerian ducts (Figures 2-3) and accurately evaluate an unicornuate uterus (Fig. 4) ruling out the presence of endometrial tissue within a rudimentary uterus (which must be removed); in case of uterine hypoplasia the presence and patency of the cervix can be ascertained and the length of atresic vaginal segments and their distance from the introitus can be measured (Figures 5-6); Müllerian remnants in the Mayer-Rokitansky-Kuster-Hauser syndrome can be identified (all these informations being necessary to a successful surgical planning [1,12,13,16,19]).

2) PUBERTAL CHRONOLOGICAL ALTERATIONS

The pubertal development of uterus and ovaries and their possible diseases can be evaluated in the vast majority of cases by means of trans-abdominal ultrasound; MRI is useful when ovarian masses need further characterization (Fig. 7).

MRI exploration of the encephalic sellar and supra-sellar regions (Fig. 8) is crucial in order to diagnose the disorders reported in the Figures 4 and 5 of the Background section.

3) ABNORMALITIES OF OVARIAN HORMONE PRODUCTION

Combined trans-abdominal and trans-vaginal ultrasound gives adequate information regarding the ovaries (Fig. 9A): the follicular evolution (especially when a medical support to fertilization is administered) can be easily followed and most ovarian diseases can be diagnosed. Like in the case of precocious or delayed puberty, MRI can add information about complex ovarian disease (Fig. 9B-E) and demonstrate pituitary and/or hypothalamic abnormalities.

4) ABNORMALITIES OF THE MENSTRUAL CYCLE
Trans-vaginal ultrasound is the best Imaging method to assess the endometrial thickness; MRI is necessary only in case of endometrial or cervical carcinoma in order to define the stage and direct the therapy.

Cine-MRI (single-shot fast spin-echo T2 sequences [2,7,8]) may identify both the uterine peristalsis (a low signal intensity area moving within a focally thickened junctional zone [7,20]: Fig. 10) and the prolonged contractions (small low signal intensity myometrial foci, enlarging and then disappearing [20]). In the fast spin-echo T2 sequences commonly used in the MRI evaluation of the female pelvis a prolonged contraction may mimic a leiomyoma or adenomyosis [7,21], while cine-MRI may avoid this pitfall (Fig. 11); moreover, some Authors believe that an abnormal uterine peristalsis in the first days of the menstrual cycle can be detected by cine-MRI in dysmenorrhoic women [2].

5) IMPAIRED FERTILITY

Ultrasound, "conventional" MRI and cine-MRI are useful in the diagnosis of the causes of impaired fertility mentioned above.

A work-in-progress which might clarify some aspect of uterine physiology and maybe disease is represented by the MRI evaluation of the speed of water diffusion within the endometrium in the different periods of the menstrual cycle (in normal women the diffusion is slower in the peri-ovulatory phase: Fig. 12).
**Fig. 0:** Turner's syndrome. Axial T1-weighted MRI scans. A very small, poorly differentiated, low signal intensity right ovary (arrows) can be detected. Bladder (B); rectum (R); ureter (U).

**Fig. 0:** Defects of "lateral" fusion between the right and left Müllerian ducts. Coronal oblique fast spin-echo T2-weighted MR images. A) Partial uterine septum (prominent upper myometrial component: short arrow) and small lower fibrous component (long arrow). B) Complete uterine septum with two distinct cervices (arrow).

Fig. 0: Defects of "lateral" fusion between the right and left Müllerian ducts. Axial fast spin-echo T2-weighted MR images. A) Arcuate uterus. Nonspecific low signal intensity of fundal myometrium (arrow). B) Bicornuate uterus. Divergence of uterine horns, with communication of endometrial cavities in the lower uterine body (arrow).

Fig. 0: Unicornuate uterus. Axial fast spin-echo T2-weighted MR image.

Fig. 0: Cervical atresia and vaginal agenesis. Sagittal fast spin-echo T2-weighted MR image.

Fig. 0: Uterine hypoplasia. A) Sagittal fast spin-echo T2-weighted MR image. A small uterine remnant can be seen (arrow). B) Sagittal longitudinal ultrasound scan in a different patient with Mayer-Rokitansky-Kuster-Hauser syndrome. No uterus can be identified cranial to a subtle cervix.

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Fig. 0: Mixed (solid and cystic) ovarian mass. A) Axial gradient-echo fat saturated T1-weighted MR image. The liquid component shows high signal intensity due to its mucoid or hematic content. B) Coronal fast spin-echo T2-weighted MR image.

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**Fig. 0**: Encephalic sellar/supra-sellar disease interfering with pubertal development. A) Contrast-enhanced CT scan. A roundish 3 cm-diameter solid non-enhancing mass with multiple small calcifications occupies the hypothalamic region (craniopharyngioma). B) Sagittal T1-weighted MR image after administration of paramagnetic contrast medium. An enhancing lobulated mass 4 cm in diameter occupies both the sellar and the supra-sellar region. C-D) Sagittal (C) and coronal (D) fat saturated T1-weighted MR images after administration of paramagnetic contrast medium. A small rounded enhancing lesion (prolactin-secreting macroadenoma) can be identified in the left portion of the pituitary gland.

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Fig. 0: Ovarian disease. A-B) Multiple small peripheral follicles (polycystic ovary) can be identified at both trans-abdominal ultrasound (A) and fat saturated coronal STIR T2-weighted MRI scan (B). C) Coronal T2-weighted MR image. Fatty-content ovarian mass. D) Axial T2-weighted MR image. A predominantly cystic mass, with thick walls and solid peripheral components, can be seen in the right ovary. E) Axial fat saturated T2-weighted MR image. Solid right ovarian mass.

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**Fig. 0:** Effects of the uterine contractility on MRI findings. The size of a leiomyoma (boxes) is overestimated in the sagittal T2-weighted Cine-MR image (A) taken during a superimposing myometrial contraction.

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Fig. 0: Sagittal T2-weighted Cine-MRI demonstration of the uterine contractility. The thickness of the junctional zone (arrows) decreases (B) some minutes after the reference MR scan (A).

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**Fig. 0:** Effects of the menstrual phase on the endometrial speed of diffusion. The diffusion is much slower in the diffusion-weighted MR image taken in the peri-ovulatory phase (upper row) than at the third menstrual day (lower row).

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Conclusion

The knowledge of the pathophysiological background of the anatomical and functional disorders of the female reproductive system is crucial in order to understand the many different alterations that can be found at Imaging exploration (especially with ultrasound and MRI) of uterus, ovaries, adrenals, hypothalamus and pituitary. An eye must be kept by Radiologists on the newest diagnostic procedures (e.g. cine- and diffusion-weighted-MRI) which may improve our comprehension of some mechanisms of physiology and disease.
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References


