Ovary and ultrasound: from physiology to disease

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Abstract

Gynecological ultrasound is one of the most accurate imaging technique in clinical practice. It is characterized by minimal invasiveness, tolerability, repeatability, fast execution and low cost, changing completely the methodological approach to diagnosis of adnexal pathology, in particular those one from ovary. Vaginal ultrasonography is a practical and reliable method to monitor structural changes in the ovaries during the physiological menstrual cycle, but it allows also early detection of pathological features. Correct characterization of ovarian/adnexal masses is important for optimal patient management. The morphological features of an adnexal mass can be used to indicate the likelihood of being benign or malignant. Ultrasound diagnostic accuracy is really high in distinguishing functional ovarian cysts from organic ones, thanks to also the possibility to observe these lesions as time goes on and to study them very well with a three dimensional approach. On the contrary, differential diagnosis between benign ovarian masses and malignancy is more complex, in particular identifying borderline tumors. Pattern recognition has been shown to be superior to all other ultrasound methods (e.g. simple classification systems, scoring systems, mathematical models). However, even when ultrasound don't make possible a diagnosis, this tool gives important information for correct management of every single case.

Key words: ultrasound, ovary, cysts, ovarian cancer, diagnostic imaging

Introduction

Gynecological ultrasound is one of the most accurate imaging technique in clinical practice. It is characterized by minimal invasiveness, tolerability, repeatability, fast execution and low cost. Thanks to these characteristics ultrasonography is an important tool in the diagnostic approach to gynecological pathology.

Ultrasound (US) has changed completely the methodological approach to diagnosis of adnexal pathology, in particular those one from ovary. It is the goal standard to study the ovary, as ovarian pathology is often asymptomatic and semeiologic signs are poor accurate.

When performed by an experienced operator, it can play an invaluable role in the primary diagnosis of gynecological cancers, in the assessment of tumor extent in the pelvic and abdominal cavity and in the evaluation of treatment effects as well as follow up after treatment. The use of ultrasound to evaluate important prognostic parameters makes possible the individualization of the best oncology treatment. In this way we can make maximum therapeutic impact with minimal patient morbidity. Ultrasound also enables the targeted biopsy of advanced tumors or metastatic lesions, allowing fast and minimally invasive establishment of the tumor histology.

Thanks to ultrasound it is possible to:

- report the presence of a mass,
- origin, dimensions, ultrasonographic features, to obtain a diagnosis,
- when it is not possible a certain diagnosis, ultrasound gives important information for a correct diagnostic/therapeutic approach (ultrasound accuracy ranges from 68% to 91%).

Transvaginal sonography (TVS) has greatly enhanced sonographic visualization of pelvic structure; in fact it affords better resolution of the uterus and ovaries than that obtained with the conventional transabdominal approach, and now it is the gold standard to examine the uterus and adnexal structures [1].

Besides, patients with pelvic pain, and in particular acute pain, are ideally suited to assessment by ultrasonography at the time of presentation. The use of the endovaginal probe should be thought of as a natural extension of the conventional bimanual examination and a scan should never be looked at in isolation. An accurate scan can enable the clinician to avoid surgery in some cases and select the correct surgical approach in others. TVS is also the least invasive investigative tool available in the assessment of women with chronic pelvic pain [2].

Ultrasonography is easy, rapid, and able to provide critical information for the evaluation of an adnexal mass. It can help determine whether the mass is ovarian or extra-ovarian, solid or cystic, simple or complex and vascular or avascular.

Ultrasonography can be used to evaluate material or fluid contained in a mass and it can be used to assess the surface of the ovarian capsule.

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In diagnostic approach, next to ultrasound, color-flow Doppler is useful for distinguishing between benign and potentially malignant lesions [3]. In most cases, CT scanning and MRI are unnecessary in the evaluation of an adnexal mass. Furthermore, serial or follow-up ultrasound examinations are helpful in monitoring the progression of an ovarian mass over time. Repeating an ultrasound in 6 weeks can delineate if the mass is enlarging or if the dimensions are diminishing. The presence of pelvic or abdominal ascites and/or pelvic or abdominal lymphadenopathy on CT scans or MRIs further raises the index of suspicion for ovarian malignancy.

Careful manipulation of a transvaginal probe during gynecological ultrasound imaging allows the operator to assess the mobility and elasticity of pelvic structures, and the analysis of these 'dynamic images' in the context of a patient's symptoms can lead to a more reliable diagnosis than is possible using still ultrasound images or static ultrasonography alone [4]. It is possible to:

- investigate the presence of pain and define the location of the most painful sites (pain mapping);
- examine the elasticity of the pelvic content (malignant masses are rigid, solid, non-compressible structures);
- assess spontaneous movement, such as peristalsis, of structures;
- detect the content of a pelvic mass with hypoechoic appearance;
- evaluate the mutual sliding of different tissue layers (e.g. bladder-uterine septum) or of the different pelvic organs (e.g. free movement of the ovaries in the pelvis);
- better define the outline of a pelvic lesion (regular or irregular adherence to surrounding organs.

In the presence of ovarian pathology it is essential to determine the functional or persistent nature of a lesion. For example, the possibility of a diagnosis of a luteal or follicular cyst should always be considered, even if the adnexal lesion is strange in appearance or intra-peritoneal fluid is abundant. In addition to clinical information, and observing the presence or absence of typical sonographic features of the corpus luteum (vascular 'ring of fire'), a dynamic evaluation helps in the identification of the corpus luteum: by pushing the lesion with the transvaginal probe one can observe slow movement of internal echogenic spots in the presence of fluid, a jelly-like movement in the presence of a clot and firmness in the presence of a solid structure. In addition, the streaming phenomenon [5] can be observed: in the presence of acoustic streaming, the content of an ovarian lesion is usually mucinous or serous fluid, and not old blood, as in an endometrioma, which is characterized by higher viscosity of the chocolate-like fluid, although exceptions to this rule exist. If intra-cystic tissue is seen and the operator is not certain whether it is amorphous material or true solid tissue, pressure exerted using the probe will either move the amorphous material or confirm the fixed position of a papillary projection from the internal cystic wall. Moreover, movement of a pelvic lesion can help determine its precise origin; a paraovarian cyst slides with respect to the ovary (split sign), while fixed ovaries behind the uterus (kissing ovaries) may be indicative of severe endometriotic pelvic disease or pelvic inflammatory disease. When a dermoid cyst shows the same echogenicity as that of the surrounding bowel loops, the mass effect and the peristaltic movement of the bowel loops can help in recognizing the presence of the adnexal mass.

Ovarian physiology

Transabdominal sonography (TAS) and TVS can identify ovaries in the majority of premenopausal and postmenopausal women. Although it is true that in the postmenopausal patient the ovary may be difficult to identify by TAS, in over 60% of patients, both ovaries can be identified in postmenopausal women, particularly if scanning by TVS and using abdominal palpation [6].

TVS is a practical and reliable method to monitor structural changes in the ovaries and the uterus during the menstrual cycle. The results are of clinical importance also for a better understanding of the physiological changes and helpful when monitoring induction of in assisted reproduction [7]. Ovaries are typically depicted as oblong structures measuring approximately 3 cm in long-axis and 2 cm in antero/posterior (AP) and transverse dimension. On angled long-axis scans, they are immediately medial to the pelvic vessels. They are particularly well depicted when they contain a mature follicle that is typically in the 1.5 to 2.0 cm range. It is not unusual to depict multiple immature, or atretic, ovarian follicles in the 3 to 5 mm range that serve as US marker of the ovary. The size of the ovary is related to the patient's age and phase of follicular development. When the ovary contains a mature follicle, it can become twice as large in volume than one that does not contain mature follicles. In premenopausal women, the normal ovary typically measures 3 × 2 × 1 cm. It may be up to 5 cm in length in one dimension, but should remain oval in shape. Rounded ovaries typically are encountered in patients with polycystic ovarian disease.

Measurements of the long, short and A/P dimension of the ovary determines ovarian volume by the ellipsoid formula (length × height × width × 0.5 = volume in cm^3) [7]. In premenopausal women, the normal ovary ranges from 10 to 12 cm^3 in size, depending on the presence of a mature follicle, which can account for up to 2 cm or 4 cm^3 of volume.

The ovaries of postmenopausal women are usually smaller (2 × 2 × 1 cm) and featureless. The texture should be relatively featureless without presence of cystic or solid areas within the ovary [8].

Beginning with menarche, during spontaneous cycles there usually is development of one or sometimes two dominant follicles.

TVS can depict the developing follicle starting when they measure between 3 and 5 mm. In the spontaneous cycle, usually there is one, or two, follicles that develop to measure approximately 10 mm in size. As the follicle matures, more fluid is elaborated into its center, and the number of granulosa cells lining the inner wall of the follicles increases. The oocyte, which is less than a tenth of a millimeter, is surrounded by a cluster of granulosa cells. This complex is termed the cumulus oophorus. It measure approximately 1 mm and occasionally can be depicted along the wall of some mature follicles. Immediately before ovulation the cumulus separates from the wall and floats freely within the center of the follicle. Even with the enhanced resolution afforded by TVS, the attached or floating cumulus is only rarely visualized. Mature follicles typically measure from 17 to 25 mm in average inner dimension. Within the same individual, however, the size of a mature follicle is relatively constant cycle to cycle. Intra-follicular echoes may be observed within mature follicle, probably arising from clusters of granulosa cells that shear off the wall near the time of ovulation. After ovulation the follicular wall becomes irregular as the follicle walls becomes irregular as the follicle become "deflated". The fresh corpus luteum usually appears as a hypoechoic structure with an irregular wall and may contain some internal echoes corresponding to hemorrhage. As the corpus luteum develops 4 to 8 days after ovulation, it appears as an echogenic structure of approximately 15 mm and its wall is thickened by the process of luteinization. In addition to delineation of changes in follicle size and morphology, TVS can depict the presence of intraperitoneal fluid. It is normal to have approximately 1 to 3 ml on the cul-de-sac throughout the cycle. When ovulation occurs, there is between 4 and 5 ml of fluid within the cul-de-sac. The intraperitoneal fluid resulting from ovulation may be located outside of the posterior cul-de-sac, surrounding bowel loops in the lower abdomen and upper pelvis, or the anterior cul-de-sac superior to the uterine fundus [9].

Ovarian volume

The human ovary is an organ which changes in size and activity throughout life; at birth, the ovary is 1 cm in length. The ovary decreases slightly in volume at 1 month of age, probably due to the clearance of maternal estrogen from the female neonate.

There is a continuous slow growth of the ovaries throughout childhood: they enlarged, increase in weight 30-fold, and change in shape, so at puberty, they have reached the size, shape and weight of the adult ovary. In reproductive age ovaries are ovoid, they measure approximately 3-5 cm by 1.5-3 cm by 0.6-1.5 cm. After the menopause the ovaries shrink to a size approximately one-half of that seen in the reproductive era (weigh 3-4 g) [10].

Color Doppler study of the ovary

Color Doppler sonography combines the physiologic information obtained by Doppler assessment of vessels with anatomic depiction of the location of blood flow within or adjacent to a particular organ. Color Doppler assign a color to the frequency shift detected; red colors indicate flow toward the transducer, whereas blue indicates flow away from the transducer. Lighter shades of color indicate high frequencies usually found in area of stenosis. The information obtained can be processed to form a triplex image consisting of a real time image, color blood flow information, and a frequency waveform and spectral analysis displayed simultaneously. Basically, the amount of parenchymal flow is reflected in the size and shape of the diastolic portion of the waveform. The frequencies contained in a waveform can be quantitated using either calculation of a resistance index (RI) and/or pulsatility index (PI). In a study, about physiological changes in normal menstrual cycle, it was shown that on the side with the dominant follicle, follicular and ovarian stromal peak systolic blood flow velocity rose significantly during the menstrual cycle with no significant change in PI. The changes in blood flow velocity correlated significantly with changes in serum follicle-stimulating hormone, luteinizing hormone and progesterone concentrations. There are no significant changes in either blood flow velocity or PI in the contralateral ovary. Uterine artery time-averaged maximum velocity on the side of the developing ovarian follicle increased during the menstrual cycle with no significant change in the contralateral vessel. Uterine artery PI on the side of the de-

veloping follicle declined during the mid-luteal phase and was significantly lower than on the contralateral side. The changes in time-averaged maximum velocity correlated with the changes in serum estradiol and progesterone concentrations. The vascular changes in the wall of the dominant ovarian follicle and ovarian stroma during the menstrual cycle are consistent with activity of angiogenic-like factors. The decline in uterine artery resistance during the mid-luteal phase may reflect optimal vascularity for implantation of the blastocyst [11]. Three-dimensional power Doppler angiography (3D-PD) of cyclic ovarian blood flow evaluates the cyclic changes in the vascularity of normal ovaries, including those that were ovulating, non-ovulating, and hormonally suppressed. Hormonally suppressed ovaries have significantly lower vascularity throughout the cycle. Normal-appearing ovaries with vascular indices above the normal ranges established by these data may warrant further investigation. The vascular indices of ovulating ovaries were significantly higher than those of non-ovulating ovaries with the largest discrepancies during the luteal phase. Hormonally suppressed ovaries had significantly lower vascularity throughout the cycle [12, 13].

Ultrasound features of ovarian lesions

TAS has been for many years the first step in the diagnostic approach to gynecological diseases; today is a second line examination, with empty bladder, very useful for big adnexal masses or in the suspect of a malignancy. By using TAS is possible to have a panoramic view of the pelvis and to study extra-pelvic organs (liver, kidneys).

TVS represents the best methodological approach to study ovarian masses, because it is possible to obtain more clear images with high definition, easier to classify.

Diagnostic approach should be completed by color/ /power Doppler study of intra- and perilesional vascularization, with PI and RI, to analyze vascular structure of ovarian mass.

US features of ovarian masses are various and often not specific for a particular pathology. Although it is easy to recognize the presence of a mass, it is very difficult to make a specific diagnosis and a certain assessment of the ovarian mass histology: sonographic findings can't be separated from clinical evaluation.

Ultrasound scan shows:

- localization of the mass in the pelvis, its relationships with ovarian parenchyma and nearby organs;
- morphology, dimensions, US features, color/power Doppler evaluation;
- presence of fluid in the pouch of Douglas or ascites.

Often ovarian pathology is represented by an adnexal mass, so the lesion could be surrounded from normal looking ovarian stroma, or distinct from this, or the ovarian stroma is completely absent.

To understand the classification of ovarian masses it is necessary to analyze all these morphological features:

a) internal walls,
b) cyst content (solid/liquid),
c) presence of septa or papillary projections,
d) vascularization.

The **internal wall** of a cystic lesion is described as being smooth or irregular. If there is a solid papillary projection, then the wall is irregular by definition. In cases of solid tumors the description of the internal wall as being small or irregular is usually not applicable but the outline of the tumor is described as smooth or irregular.

The dominant features of the **cystic content** are described as: 1) "anechoic" (no echoes, "black"), 2) low level echogenic content (i.e. mucinous tumors), 3) "ground glass" appearance (homogeneously dispersed echogenic content, as in endometrioma), 4) hemorrhagic (with internal thread-like structures, representing fibrin strands as in hemorrhagic corpus luteum) [14].

"**Solid**" is a **content** exhibiting high echogenicity, suggesting the presence of tissue. Method to distinguish between blood clots and the presence of solid tissue involve pushing the transducer gently towards the structure and looking for internal movement and the use of color Doppler imaging. The presence of flow is diagnostic for solid tissue. The absence of flow is not informative.

A **septum** is defined as a thin strand of tissue running across the cyst cavity from one internal surface to the contralateral side. An **incomplete septum** is a thin strand of tissue running across the cyst cavity from one internal surface to the contralateral side, but which it is not complete in some scanning planes. It is thin or thick in relation to the dimension (more/less than 3 mm).

Papillary projections are an important US finding in morphological classification of ovarian masses. They are defined as any solid projection into the cyst cavity, from the cystic internal wall, with a height $\geq$ 3 mm. Papillary projections surface can be smooth or irregular; it is important to assess their vascularization by color/ /power Doppler.

Studies concerning the early diagnosis of ovarian cancer associated TVS with Color/power Doppler study to identify earlier the vascular changes that anticipate ovarian architectural modifications.

The rationale of the use of color Doppler is related to the fact that during the fast growth, the tumor spread through the neo-angiogenesis, characterized by a poor smooth muscular component: blood flow resistance in these vessels is less than that found out in vessel with normal wall components.

Color/power Doppler study of an ovarian mass enables to identify also small size vessel, characterized by slow flow and to define appearance, distribution and architecture.

It is suggested to use a semi-quantitative assessment of flow, describing the amount of blood (area and color scale) within the septa, cyst walls, or solid tumor areas. A score of 1 is given when no blood flow can be found in the lesion, a score of 2 is given when only minimal flow can be detected; a score of 3 when moderate flow is present and a score of 4 when the mass appears highly vascular [14].

Three-dimensional ultrasound (3D-US) represent a technological evolution of traditional ultrasound: 3D images give a more realistic reconstruction of anatomical structure on three dimension. 3D-US enables a more detailed analysis of internal cyst walls, of borders, vascularization, so improving the diagnostic accuracy of US in the evaluation of the risk of malignancy, in particular towards small masses [15].

Ultrasound features of cystic ovarian lesions

Anechoic lesions. Ovarian cysts with internal fluid content (anechoic) are the most common with an a high prevalence both in fertile age and in menopause. The most common are functional cyst (follicular cyst, luteal cyst), the so-called "physiological cysts", but serous cystadenoma as well belongs to this group.

Malignancy risk is really low, in particular when they appear small size. They are characterized by clear and define borders, uniform anechoic internal echostructure, with posterior wall enhancement, are usually unilocular, single or multiple, unilateral. They appears like round masses, dimensions up to 6 cm; however it can happens to identify follicular cysts with 70-90 mm diameter. In color/power Doppler study they appears without any vascularization.

Probability of spontaneous resolution is estimated of 30-50%, higher in fertile age and in perimenopause, compared to late menopause. Only in 3-5% cyst grows, while in 40% of cases its dimensions remains stable. It has been demonstrate that the vanishing of the cyst is inversely related to its mean diameter: up to 70% if the cyst is 40-50 mm, only 10% with mean diameter of 70 mm.

Follicular cysts have define walls and uniform anechoic internal echostructure. They can have wrong images of septa, because of the presence of smooth strands of fibrin, and their vascularization is extremely weak and always perilesional.

Luteal cysts usually have thick walls, sometimes irregular. In color/Power Doppler it is possible to assess the typical perilesional vascularization, that marks the so-called "ring of fire".

Lesions with mixed characteristics (serous cystadenoma) are characterized by anechoic areas with endocystic solid areas (papillary projections). These projections can be small vascularized projections, that arise from internal capsula or from a septum or complex papillary projections, dimensions > 3 mm, often multiple, with a large implant base, that can make the suspect of a malignancy.

Hypoechogenic lesions. The content of these cysts can be homogeneous, more or less thick, with fibrin (as luteo-hemorrhagic cysts), ground-glass (as endometrioid lesions) or a cluster of mucus (as mucinous cysts).

Luteo-hemorrhagic cysts have thick walls, internal echostructure with a fishnet, lacy, cobweb, or "spider web" appearance, expression of the organization of internal hemorrhage.

Hypoechoic simple cysts are usually benign; they have regular and marked walls, with homogeneous content. Between these, the most frequent are endometriosic cysts, that have regular walls, with ground glass echogenicity and poor perilesional vascularization.

Hypoechoic complex cysts are characterized by several thin echogenic septations (as mucinous cystadenoma) or by the presence of thick confluent septa (as multiple endometriosic cyst). It is also possible to find out hypoechogenic lesions with papillary projections (as mucinous cystadenoma), often sign of malignancy. The most frequent cystic ovarian neoplasia, mainly hypoechogenic, are represented by mucinous cystadenoma, endometrioid cystadenoma, undifferentiated carcinoma, clear cell carcinoma and, less frequently, by serous cystadenocarcinoma [16].

Ultrasound features of solid ovarian lesions

Ovarian masses with solid content can be:

- benign lesions (ovarian fibroma, tecoma, fibrothecoma);
- primitive tumors (cystadenocarcinoma, undifferentiated ovarian carcinoma);
- metastatic tumors (gastro-intestinal, linfoma).

An ovarian solid mass appears on ultrasound like a lesion more or less echogenic.

Ovarian fibroma (fibrothecoma) can have a various appearance or it can be characterized by a prevalent internal solid component, uni- or multilocular. One of the main aspect is the presence of incomplete posterior acoustic enhancement in the mass, with a poor intralesional vascularization.

Ovarian malignant masses have sonographic features that can change in relation with histotype (epithelial or germinal), with invasiveness (borderline or infiltrating) and if it is primitive or not.

Solid malignant forms are: embryonal carcinoma, some tumors with endocrine activity, dysgerminoma and some metastatic neoplasms [16].

Ovarian complex masses

A lesion is defined as a "complex mass" when it has both solid and liquid components.

Ovarian neoplasms which have a prevalent solid component belong to this group. In general, like all epithelial neoplasms, malignancy probability is bigger if the mass is solid, irregular and highly vascularized.
More frequent type of complex ovarian mass is the **mature cystic teratoma** (dermoid cyst).

This benign ovarian lesion is complex because it contains various type of tissues: its US appearance is different according to the prevalence of each specific components (adipose tissue, bone tissue, calcifications, teeth, hairs, etc). As it is a benign lesion, it is important to assess the presence of a cystic teratoma when it is identifiable one of this features:

- complex mass, patchy, with hypo-echogenic and hyper-echogenic areas with posterior acoustic enhancement
- in a cyst with an anechoic content presence of linear echogenic reflectors
- presence of a raised protuberance projecting into the cyst cavity known as the Rokitansky nodule
- presence of a complex mass with strange ultrasound aspect, without any intralesional vascularization seen at Color/Doppler evaluation.

Malign type of dermoid cyst is **immature teratoma**, composed of tissues derived from the three germ layers. They represent < 1% of ovarian teratomas, affect a younger age group (usually during the first 2 decades of life) and they are only histologically distinguished by the presence of immature or embryonic tissues.

Functional ovarian pathology

Ovarian functional cysts can be visualized by US in women of all ages. The presence of a simple (unilocular, anechoic, thin-walled) cystic mass, related to either ovary measuring less than 3 cm is considered within normal limits. US and clinical follow up, however, is recommended when the dimensions of a cyst exceeded 3 cm. Approximately 60% of ovarian cyst resolve spontaneously. Several types of benign cysts exist and they are functional, that result from the stimulation of ovarian follicle by estrogen. It is the most common cause of ovarian enlargement in young women. They range in size from 0.5-2.5 cm. Functional cyst change in appearance during the course of the menstrual cycle. They include follicular, luteal and luteo-hemorrhagic cysts. The usually measure less than 5 cm in diameter. Basically, functional cysts regress spontaneously after one/three menstrual cycle or after a treatment with estro-progestins: this is very important from a clinical point of view, because it is possible, thanks to ultrasound monitoring, to avoid surgery.

Follicular cysts. Follicular cysts are the most common cystic structures found in healthy ovaries. These cysts arise from temporary pathologic variations of a normal physiologic process and are not neoplastic. The lesion result from either non rupture of the dominant mature follicle or failure of an immature follicle to undergo the normal process of atresia. The cysts have also been associated with a short menstrual cycle. Many follicle cysts lose the ability to produce estrogen; in other instances, the granulosa cells remain productive, with prolonged secretion of estrogen. Solitary follicle cysts are common and occur during all stages of life, from the fetal stage to the postmenopausal period. The cysts are thin walled, well-defined borders, anechoic lumen, posterior acoustic enhancement. They are usually unilateral and unilocular, usually ranging from several millimeters to 8 cm in diameter (average, 2 cm). The cyst regresses spontaneously usually within 2 cycles and can be monitored with US. If the cyst remains for 3 cycles it is likely not functional. If a cyst less than 6 cm persists in the premenopausal patient it's likely simple and can be monitored by US [16].

Luteal cysts. It is important to recognize the corpus luteum (CL) as a normal finding. CL occurs when the dominant follicle ruptures successfully. In the absence of a pregnancy, the CL normally collapses and becomes the corpus albicans. Sometimes it continues growing and/or an hemorrhage may create a cyst (luteo-hemorrhagic). It measures 1.5-2.5 cm in diameter and may contain internal echoes representing blood [17-19]. It may appear as a cystic lesion with a slightly thick, crenulated wall and internal echoes or as a subtle iso-echoic, or minimally

hypoechoic, solid-appearing area, due to hemorrhage and/or wall thickening. While the CL is usually avascular centrally, color or power Doppler will often depict hypervascularity around its periphery, referred as "ring of fire" [20].

While the US features of the CL have been described and are reasonable based on its physiology, the reliability of US features to distinguish a CL from other lesions has not been established.

Given the common occurrence of corpora lutea, however, when they have one of the typical features described above, we do not feel that US follow-up is needed [17]. CL cysts are less prevalent than follicular cysts. They are hormonally inactive but may tend to rupture with intra-peritoneal bleeding. Doppler evaluation reveals prominent diastolic flow in CL cysts. This low-velocity waveform is present throughout the luteal phase of the cycle [20].

Hemorrhagic Cysts. Hemorrhagic cysts are likely caused by bleeding into a corpus luteum. A reticular pattern of internal echoes due to fibrin strands is a strong predictor of a hemorrhagic cyst. This pattern has also been referred to as having a "spider web" appearance. While a clot may occasionally simulate a solid nodule, it is usually recognizable by its concave outer margin and/or absence of detectable flow at color or power Doppler US. Blood clot can sometimes be recognized on a gray-scale US scan by its "jellylike" movement when pressure is applied on the transducer. If imaged before fibrin strands or a retracting clot develops, a hemorrhagic cyst can be partly, or completely, filled with heterogeneous echoes that may simulate a solid mass [17].

Theca-Lutein Cysts. Theca-lutein cysts appear as bilateral enlarged ovaries with multiloculated cystic masses. This condition is associated with high levels of hCG. Theca-lutein cysts are seen most frequently in association with gestational trophoblastic disease (30%), PCOS or clomiphene therapy. The abnormality may resolve after treatment in a few months.

Polycystic Ovarian Syndrome (PCOS)

The normal adult ovary measures 3 cm in length, 1 cm in thickness, 2 cm in width. In females with PCO ovaries are usually bilaterally enlarged, contain multiple follicles and demonstrate increased stromal echogenicity. The diagnosis of PCOS has been recently simplified. Currently, 2 of 3 criteria are required to diagnosis PCOS. The 3 criteria are: (1) polycystic ovaries (multiple small cysts, often around the periphery of the ovary, the classic "string of pearls" appearance); (2) signs of androgen excess (acne, hirsutism, temporal balding, male pattern hair loss, clitoromegaly, etc), and (3) menstrual irregularities (oligomenorrhea or polymenorrhea). Note that a diagnosis of PCOS does not require multiple ovarian cysts or polycystic ovaries [21, 22].

The current ultrasonography guidelines, supported by the ESHRE/ASRM consensus group define the polycystic ovary as containing 12 or more follicles measuring 2-9 mm and/or an increased ovarian volume of $> 10\ cm^3$. Unlike previous definitions, this requires no subjective assessment of stromal echogenicity and/or follicle distribution pattern. The cut-off value for increased ovarian volume was based on cumulative evidence reporting a larger mean volume of $>10\ cm^3$ for polycystic ovaries. The cut-off of ≥ 12 follicles *throughout the entire ovary* was based on a single report demonstrating this value to have 99% specificity and 75% sensitivity in distinguishing between polycystic and normal ovaries [23]. Increased stromal echogenicity and/or stromal volume are specific to PCO, but it has been shown that the measurement of ovarian volume is a good surrogate for quantification of the stroma in clinical practice. A woman having PCO in the absence of an ovulation disorder or hyperandrogenism ('asymptomatic PCO') should not be considered as having PCOS, until more is known about this situation. Three-dimensional and Doppler ultrasound studies may be useful research tools but are not required in the definition of PCO [21, 24]. In a study they demonstrated that measurement of the ovarian volume yields good diagnostic accuracy to distinguish normal ovaries from PCO. However, it shows that the best compromise between sensitivity and specificity is obtained with a threshold set at $7\ cm^3$, instead of the $10\ cm^3$ threshold proposed by the Rotterdam Consensus Conference [25].

Benign and malignant ovarian lesions: ultrasound findings

Endometriomas Several studies have described the US characteristics of endometriomas and defined their typical US features [26-31]. A 'typical' endometrioma is a unilocular cyst with a regular wall and homogeneously low-level echogenicity ('ground glass' appearance) of the cyst's content. Hyperechogenic wall foci can be seen in up to a third of endometriomas and are quite distinctive, as they are rarely found in other benign non-resolving ovarian cysts [32].

Almost half of endometriomas show US characteristics other than 'unilocular cyst with ground glass echogenicity'; moreover, endometriomas may look different in pre- and postmenopausal patients. Masses in post-

menopausal women whose cystic content has a ground glass appearance have a high risk of malignancy. The optimal rule to detect endometriomas was "an adnexal mass in a premenopausal patient with ground glass echogenicity of the cystic fluid, one to four locules and no papillae with detectable blood flow" [33].

Guerriero and Dogan were the first to perform studies to characterize "atypical endometriomas" that can lead to diagnostic problems and, in rare cases, the differential diagnosis with an ovarian malignancy can be difficult [34].

Septations are a frequent finding in endometriomas, giving the cyst a multilocular appearance. The wall of an endometrioma is usually smooth and clearly visible, but irregularity of the profile or even papillary projections can be present as a result of several processes involving the cystic wall, including inflammation, necrosis, hemorrhage and decidualization.

In particular, Guerriero published a diagnostic algorithm which defines an endometrioma as either a unilocular mass with ground glass echogenicity and a color score between 1 and 3 (i.e. no vascularization to moderate vascularization) or a unilocular-solid mass with ground glass echogenicity with a papillary projection, a color score of 1 to 2 and no flow inside the papillary projection [35]. However, as recently reported in a large series of cases, 'atypical' ultrasound features have been described in up to 50% of endometrioid cysts, indicating that sometimes a specific preoperative diagnosis might be challenging.

Endometrioma and ovarian cancer. Several publications report that the estimated prevalence of the association between endometriosis and ovarian cancer ranges between 0.3 and 0.8%. A strict association between endometriosis and clear-cell and endometrioid ovarian carcinoma has been documented. However, considering the discrepancy between the low prevalence of endometrioid and clear-cell cancers and the high prevalence of endometriosis, the hypothesis that endometriosis represents an exclusive premalignant condition remains to be verified [36].

Ovarian cancer

Ovarian tumors represent the third most frequent neoplasm of female reproductive tract and the fifth cause of death in women. The incidence, in the last ten years, has grown up to 30%; despite the improvement of therapeutic protocols, there is still a high mortality linked to a late diagnosis: approximately 70% of ovarian cancers is found out in late stages (III-IV stage).

Ovarian cancer is not so amenable to screening. It has no recognized premalignant phase; benign ovarian cyst do not develop into ovarian cancer if untreated.

The natural history is known, but the majority of women present with symptoms once the cancer has spread. It is serious, but the majority of women present with advanced disease, which carries a poorer prognosis [37].

Ovarian pathology is represented by benign neoplasms, borderline tumors and malignancy; they can arise from every cellular types of the ovary:

- Epithelial cells: celomatic origin, which give origin to Mullerian epithelium,
- Germ cells: totipotent cells that migrate from yolk sac to the ovary,
- Ovarian stroma: sex cord, for ovarian endocrine function.

Most of ovarian neoplasm arise from the surface of the ovary (60-65%) and 80-85% of this is a malignancy. Germ cell tumors account for 15-20% of ovarian cancer and 3-5% is a malignancy. Sex cord stromal tumors represent the 5-10% and 3-5% is a malignant neoplasm.

Mixed cystic and solid masses are the most frequent presentation of the common epithelial tumors of the ovary. Ultrasonography can describe the tumor morphology but cannot (with the exception of dermoid cysts) distinguish definitely benign from malignant tumors.

Epithelial Tumors. Of epithelial tumors, 70% are benign and 30% malignant. The two most common types are serous and mucinous tumors. The benign or low-malignant potential form is termed "adenoma" and the malignant form is termed "adenocarcinoma". The prefix "cyst" is added if the lesion is cystic, and "fibroma" is added if the tumor is more than 50% fibrous. Serous and mucinous tumors can be very large. They often fill the pelvis and extend into the abdomen.

Serous Cystadenoma. It comprises 30% of ovarian tumors, making it the most common benign tumor of the ovary in middle aged. It is usually unilateral (7-30% bilateral). Sonographically the benign masses are thin walled, unilocular with thin septa and may have papillae.

Serous Cystadenocarcinoma. It comprises 60-80% of all ovarian carcinomas. More than half of these tumors are bilateral (50-70%). Their size is smaller than the mucinous cysts; borders are irregular with a loss of capsular definition. The tumor may be accompanied by bilateral ovarian enlargement. Multilocular cysts contain chambers of varying size with septated, internal papillary projections. Calcifications may be present. Solid elements

or bilateral tumors suggest malignancy. Ascites forms secondary to peritoneal surface implantation.

Mucinous Cystadenoma. This is a type of epithelial tumor that is lined by the mucinous elements of the endocervix and bowel. It comprises 20% of all benign tumors and is the second most common benign epithelial neoplasm of the ovary after serous cystadenoma. In 75% of patients, the mucinous tumors show simple or septate thin-walled multilocular cysts. The mass often contains internal echoes (cyst filled with sticky, gelatin-like material) with compartments differing in echogenicity. This tumor is large, measuring 15-30 cm in diameter, the tumor is usually unilateral (5% bilateral).

Mucinous Cystadenocarcinoma. The invasive form of the tumor is found in 10% of menopausal women. This mass may be unilateral or bilateral (20%). It can also become very large and it's more likely than the benign form to rupture. If it ruptures, is associated with pseudomyxoma peritonei that causes loculated ascites with mass effect. On ultrasound, the mucoid ascites appears as hypoechoic fluid with bright punctate echoes. Malignant cysts tend to have very thick, irregular walls and septations.

Germ Cell Tumors. Germ cell tumors include teratoma, dysgerminoma, embryonal cell carcinoma, choriocarcinoma, and endodermal sinus tumor. With the exception of teratomas, all are rare.

They often occur as mixed tumors with elements of two or three varieties of germ cell tumors. This tumor usually in found in adolescents. They are associated with elevated AFP and hCG levels. Clinical symptoms include pelvic and/or abdominal pain and a palpable mass (average diameter is 15 cm). The tumor is usually unilateral; 40% of tumors will calcify. The tumor ranges in texture from homogeneously solid (3%), predominantly solid (85%) to predominantly cystic (12%).

Dermoid tumor (teratoma) is the most common germ cell tumor, comprising 20% of ovarian tumors. The tumor has been found in young children although about 80% occur in women of childbearing age. Approximately 30% are malignant, especially if found in the pre-adolescent female. This tumor is usually unilateral. Dermoids have a wide spectrum of US appearances depending on which elements (ectoderm, mesoderm or endoderm) are present. On US there may be fat-fluid levels, calcification, or an echogenic mass with shadowing and bright linear bands that represent hair. It is important to perform both TAS and TVS examinations to evaluate for a dermoid tumor [38]. Ultrasonography may demonstrate a completely cystic mass, a cystic mass with an echogenic mural nodule, a fat-fluid level, high-amplitude echoes with shadowing (e.g. teeth or bone), or a complex mass with internal septa. Echogenic dermoids often are confused with bowel. If a palpable pelvic mass is present that is not identified on ultrasonography, an echogenic dermoid must be considered. Indentation on the bladder wall will be a clue that a mass is present. The calcification within the pelvic cavity is also shown on the Rx.

Immature teratomas occur in adolescents (10-20 years). They are rapidly growing solid malignant tumors with many tiny cysts. AFP is elevated in 50% of cases. The tumor is unilateral and small in size, although it may grow to a larger dimension. On US the texture ranges from cystic to complex; it usually is solid with internal echoes.

Struma ovarii defined those rare ovarian tumors that are composed entirely or predominantly of thyroid tissue. They constitutes 3% of all ovarian teratomas, 2% of all germ cell tumors and 0.5% of all ovarian tumors. Using pattern recognition, the most specific feature of pure struma ovarii was the 'struma pearl' (a smooth roundish solid area) [39].

Ovarian dysgerminoma comprise 1-2% of all malignant ovarian tumors. In 75% of cases they are diagnosed in the 2nd and 3rd decades of life. They are characteristically solid and well-encapsulated with an average diameter of 15 cm. Dysgerminoma is the most common malignant ovarian germ-cell tumor diagnosed in pregnancy. It may produce hCG simulating a pregnancy, and patients with ovarian dysgerminoma may have elevated serum levels of LDH. The US features are: a purely solid tumor divided into different lobules with irregular internal echogenicity, smooth lobulated contours and well-defined borders. They are richly vascularized at color/power Doppler examination [40].

Granulosa Cell Tumors are a rare type of ovarian cancer and little is known about their morphological appearances on ultrasound examination. Most of them are large multilocular-solid masses with a large number of locules, or solid tumors with heterogeneous echogenicity of the solid tissue. Hemorrhagic components are common and increased vascularity is demonstrated at color/power Doppler examination. The hyper-estrogenic state that is created by the tumor often causes endometrial pathology with bleeding problems as a typical associated symptom [41].

Fibroma and fibro-thecomas of the ovary are benign tumors arising from the stromal component. According to the WHO classification they represent a subgroup of

the granulosa-theca cell tumors and belong to the thecoma-fibroma group. Most are round, oval or lobulated solid tumors that cast stripy shadows and that many are associated with fluid in the pouch of Douglas. Variability in US morphology of fibromas/fibrothecomas might be explained by the varying degrees of cellularity, collagen content and stromal edema that characterize these lesions. Hemorrhage, edema and necrosis may explain the varying echogenicity of the fluid in the cystic spaces. Color Doppler findings are variable, but most fibromas/fibrothecomas manifest minimal to moderate vascularization. Some fibromas/fibrothecomas are atypical, very few being mostly cystic [42].

Ultrasound based Scoring Systems

Correct characterization of ovarian/adnexal masses is important for optimal patient management. Masses felt to be benign can be managed expectantly or with minimal-access surgery. Malignant pathology will require referral to an appropriately trained gynecological oncologist. The morphological features of an adnexal mass can be used to indicate the likelihood of it being benign or malignant [29, 43].

In several years of studies about diagnostic accuracy of ultrasound in adnexal masses, to face the limits due to morphological variability of adnexal masses and to variability linked to operator experience in assessing different ultrasound appearance, several scoring systems have been developed, together with models of logistic regression and artificial neural networks [44-49]. These systems have the aim to detect cut-off values to distinguish a benign mass from a malignant one.

To study ovarian masses it is possible to use scoring systems, to gain a high predictive value of benignity or malignancy; these systems differ one to each other for considered characteristics and for chosen diagnostic algorithm.

There are systems based only on sonographic features at bidimensional scan and systems which consider also Doppler indices (as PI, RI, A/B), to assess intensity and vascular pattern distribution at color/power Doppler study [50].

An example of scoring system is the one introduced by Sassone [51], according to a score model, based on four variables: internal structure, wall thickness, septum thickness, echogenicity. This model has a high sensibility (100%) towards neoplasms, even if there is a high frequency of FP (PPV 37%). When this model has been modified, including the variable "posterior acoustic enhancement", typical feature of mature cystic teratomas, the model has improved, with a sensibility of 98,6% and a specificity of 77%.

Further improvement of scoring systems has been made by an Italian group, introducing some criteria that enable to distinguish dermoids and luteinic hemorrhagic cysts from ovarian neoplasms. This is possible using a nonlinear scale of scoring, which increases predictive value of septa, solid tissue and projections, when they are more than 3. This model is accurate when is applied to small adnexal masses, with a sensibility of 92% and specificity of 77% [52].

Subjective evaluation of the grey-scale ultrasound image, i.e. *pattern recognition*, for discrimination between benign and malignant tumors, can almost certainly be learnt by anyone performing gynecological ultrasound examinations on a regular basis, but diagnostic accuracy increases with increasing experience [53, 54]. An experienced ultrasound examiner can very confidently discriminate between benign and malignant pelvic tumors using pattern recognition (sensitivity 88-100% – specificity 62-96%).

Adding Doppler examination to the grey-scale ultrasound imaging does not seem to yield much improvement in diagnostic precision but it may increase the confidence with which a correct diagnosis of benignity or malignancy is made. Absence of solid components and absence of irregularities in an adnexal mass at US examination suggests benignity, whereas any irregularity (in the outline, the cystic wall or in the echogenicity of a tumor) suggests malignancy. Unilocular and multilocular cysts, without solid components, can be considered benign, even though some cysts with an extremely large number of locules may be malignant even in the absence of irregularities or unequivocal solid components.

In cystic tumors with solid components, the larger and more irregular the solid components are the greater the risk of malignancy.

In solid tumors, the more irregular the outline and echogenicity of the tumor the greater the risk of malignancy. Using these simple rules, the detection rate of malignant tumors, including borderline tumors, is 88% with a specificity of 96% .

Papillary projections (a solid projection into a cyst cavity from the cyst wall of 3 mm in height) are an important sign of malignancy. They seem to be more common in borderline ovarian tumors than in benign ovarian tumors and primary invasive ovarian tumors. Papillary projections seem to be particularly common in ovarian adeno-fibromas, but they are also often seen in serous cystadenomas and mucinous cystadenomas. Pa-

pillary projections in benign tumors explain many FP ultrasound diagnoses of malignancy. Many FP and FN diagnoses with regard to malignancy are also explained by mucinous cystadenomas/mucinous borderline tumors because of their overlapping ultrasound morphology [54].

In preoperative discrimination between benign and malignant adnexal masses, specialist ultrasound examination is superior to CA125 for preoperative discrimination between benign and malignant adnexal masses, irrespective of the diagnostic confidence of the ultrasound examiner [55]; adding CA125 to ultrasound does not improve diagnostic performance, as previous confirmed in a study which considered the inclusion of CA125 in mathematical models [56].

Borderline ovarian tumors (BOTs) constitute only 10-15% of all malignant ovarian tumors, but they are enigmatic neoplasms that have caused confusion and apprehension disproportionate to their incidence [57]. The favorable prognosis of BOTs, which occur mostly in young women of reproductive age, supports the adoption of conservative surgical treatment. Therefore, accurate diagnosis is essential for planning appropriate patient management. Using pattern recognition, it is possible to establish a correct preoperative diagnosis of borderline ovarian tumors with an accuracy of 69%. In particular, the accuracy of ultrasound diagnosis of borderline tumors is lower in comparison with benign and invasive malignant lesions [58].

In 1999 a prospective, European multicenter study including nine centers from five countries (Belgium, Sweden, Italy, France, UK) was set up, the so-called International Ovarian Tumor Analysis (IOTA) study. Its aim was to minimize the limitations of previous work by prospectively collecting the history and US findings of more than 1000 patients with a persistent mass following a standardized protocol (1999-2002). A Logistic Regression (LR) model with 12 variables was created to calculate the risk of malignancy in an adnexal mass. It had a sensitivity of 93% and a specificity of 76% [59]. However, recent study demonstrated that the prediction of malignant adnexal masses can be improved by considering different ultrasound-based subgroups of tumors (four subgroups: unilocular cyst; multilocular cyst; presence of a solid component but no papillation; presence of papillation), constructing a scoring system for each subgroup instead of using a risk estimation model applicable to all tumors [60].

In the framework of the IOTA Study simple ultrasound based rules were developed to correctly classify as benign or malignant most adnexal tumors. They selected *five simple rules to predict malignancy* **(M-rules)**: (1) irregular solid tumor; (2) ascites; (3) at least four papillary structures; (4) irregular multilocularsolid tumor with a largest diameter of at least 10 cm; and (5) very high color content on color Doppler, and *five simple rules to suggest a benign tumor* **(B-rules)**: (1) unilocular cyst; (2) presence of solid components where the largest solid component is < 7 mm in largest diameter; (3) acoustic shadows; (4) smooth multilocular tumor less than 10 cm in largest diameter; and (5) no detectable blood flow on Doppler examination. These 10 rules were applicable to 76% of all tumors, where they resulted in a sensitivity of 93%, specificity of 90% (LR+ 9.45 – LR- 0.08) [61, 62].

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