Ultrasonographic Assessment of Ovarian Endometrioma

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Endometriosis is a common gynecologic disease that affects about 10% of women of reproductive age. Most women with endometriosis experience pelvic pain, dysmenorrhea, dyspareunia and infertility, all of which reduce their quality of life. Ultrasound examination is an easy and noninvasive method in the differential diagnosis of endometriosis, and is useful in planning surgical intervention of ovarian endometrioma, as well as preoperative and postoperative medical therapy. With advances in ultrasonography, the application of higher-frequency scanning probes can evaluate ovarian endometrioma to improve diagnostic accuracy. This includes morphologic assessment with two-dimensional ultrasound and other various ultrasound modalities such as three-dimensional sonography, color Doppler, and power ultrasound imaging. The aim of this review will focus on the ultrasonographic findings of ovarian endometrioma during diagnosis, in differentiating various benign and malignant tumors, and their functional role during treatment.

KEY WORDS — endometrioma, ovary, ultrasonography

Introduction

Endometriosis, which is defined as ectopic presence of endometrial tissue outside the uterus, is a common gynecologic disease that affects about 10% of women of reproductive age. Most women with endometriosis experience pelvic pain, dysmenorrhea, dyspareunia and infertility, all of which reduce their quality of life. Although the mechanism responsible for the development of endometriosis remains unclear, several hypotheses have been proposed to investigate the etiology of endometriosis [1]. Retrograde menstruation with additional factors, such as aberrant production of steroids from ectopic endometriotic lesions, and alteration and/or dysfunction of the immune system (especially macrophages) in the peritoneal microenvironment increases the susceptibility of endometriosis. Ovarian endometrioma is considered to be one entity of numerous component endometriotic lesions, and its pathogenesis may be either implantation or metaplasia theory from histogenesis of ovarian endometriomas. Continuum between the flat cells of the ovarian surface mesothelium and the endometriotyp
epithelium of the endometrioma has been histologically confirmed [2].

Conventional two-dimensional (2D) gray-scale ultrasound is a valuable diagnostic technique in the clinical practice of gynecology. The use of three-dimensional (3D) ultrasound can further help in the analysis of morphological anatomy and the measurement of the volume of the internal genital organs. Three-dimensional sonography with image reconstruction is less invasive than hysterosalpingography for the assessment of uterine anatomy, and it can visualize both the uterine cavity and the myometrium on a 3D scan. This facilitates the diagnosis of uterine anomalies, especially in the differentiation of septate from bicornuate uteri for preoperative surgical planning [3]. In the assessment of the ovaries, three perpendicular planes of the ovaries can be rotated to obtain the largest dimensions, increasing the ability to evaluate the ovary and follicles, especially in women with polycystic ovary syndrome [4]. The evaluation of stroma and volume determinations can be obtained more accurately by 3D images than by traditional 2D ultrasonography. Three-dimensional power Doppler ultrasound can also reveal blood flow and vascularity in the target organ or the region of interest, and quantify these for further evaluation. Such applications have been proved to be beneficial in the field of infertility and reproductive endocrinology [5].

Ultrasound examination is an easy and noninvasive method in the differential diagnosis of endometriosis, and is useful in planning surgical intervention of ovarian endometrioma, as well as preoperative and postoperative medical therapy. It is important to differentiate between the various gynecologic conditions arising from endometriosis due to the high prevalence of endometriosis with clinical symptoms. With the advance of ultrasonography, the application of higher-frequency scanning probes is providing greater resolution and improving the ability to evaluate ovarian endometrioma. Morphologic assessment with 2D ultrasound is the foundation of the evaluation of ovarian endometrioma. The use of various ultrasound modalities, such as 3D sonography, color Doppler, and power ultrasound imaging, in evaluating ovarian endometrioma will improve diagnostic accuracy. The aim of this review will be to focus on the ultrasonographic findings of ovarian endometrioma in the diagnosis differentiating different benign and malignant tumors, and in the functional role of power Doppler ultrasound during various treatments.

The Findings of Ultrasound in the Diagnosis of Ovarian Endometriomas

Endometriosis without the presence of endometriomas is almost invisible when viewed by ultrasonography. When an endometrioma is suspected with ultrasonography, the most characteristic finding is a cyst with diffuse homogeneous hypoechoic (ground-glass) appearance (Fig. 1). The cyst may be secondary to a hemorrhage. Ectopic endometriotic tissue is shed with menstruation and will increase the size and content of the cyst but will not disappear with each period. It is described as a chocolate cyst. The cyst may present in a solitary or multiple form in the ovaries (Fig. 2). Endometrioma may contain a fluid-fluid level (Fig. 3), which needs to be differentiated from a hemorrhagic functional cyst with heterogeneous content which shows as fine linear strands (“fish-net”) (Fig. 4). The ovaries will fix with adjacent

**Fig. 1.** An endometrioma in a 34-year-old woman viewed with Doppler ultrasound. This cyst demonstrated diffuse low-level internal echoes without any normal ovarian tissue on this transvaginal sonogram. It had poor vascularity around the cyst without any solid or papillary mass.
pelvic structures, even demonstrating the ‘kissing ovaries’ feature on the ultrasonography. When pressure is applied to the ovaries with a transvaginal probe, the ovaries are not movable. Endometrioma will contain solid-appearing echoic nodulations (secondary to reactive fibrosis) without vascularity on color Doppler imaging. Using color Doppler ultrasound imaging evaluation of vessel distribution, a round-shaped homogeneous hypoechoic ‘tissue’ of low-level echoes without papillary proliferations associated with ‘poor’ vascularization, or a round-shaped homogeneous hypoechoic cyst with an echogenic portion without vascular flow detected indicates the likely presence of ovarian endometrioma [6]. The typical vascular pattern of ovarian endometrioma is presented as a pericystic flow at the level of the ovarian hilius (arrowhead) [7]. However, the use of color Doppler imaging does not improve the diagnostic accuracy of transvaginal ultrasonography alone in the diagnosis of ovarian endometrioma.

Ovarian Endometrioma and Infertility

There is still controversy over whether endometriosis is associated with infertility and the outcome of pregnancy. The mechanism of infertility associated with endometriosis may include hormonal, chemical, and immunological changes leading to impaired folliculogenesis, luteal phase defects, reduced fertilization
and abnormal embryogenesis [8]. The gold standard for the diagnosis of endometriosis is laparoscopic examination. Surgical removal of endometriomas and/or in vitro fertilization (IVF) is indicated for women who desire pregnancy. Surgery may lead to a decreased ovarian reserve, but it does not impair fertility outcomes of IVF in women previously operated for ovarian endometriomas [9]. Conversely, direct controlled ovarian hyperstimulation and IVF treatment is suggested in women with asymptomatic ovarian endometriomas, because removal of endometriomas before IVF does not improve fertility outcome [9]. Lower peak estrogen levels, higher gonadotropin injection doses, lower oocyte yield, and a higher cancellation rate of IVF cycles are demonstrated in women with advanced-stage endometriosis who have undergone previous surgery compared with tubal-factor infertility subjects, but no differences in fertilization, cleavage, implantation, pregnancy, miscarriage, and delivery rates are found between two groups [10]. However, the IVF outcome is significantly affected in women who previously underwent bilateral endometriomas cystectomy [11]. It still needs higher doses of gonadotrophins during controlled ovarian hyperstimulation and has a higher withdrawal rate for poor response, but the follicular number of follicles, oocytes retrieved, embryos obtained, clinical pregnancy rate and delivery rate per cycle are all significantly lower than in women without surgery [11]. In our previous study, lower body mass index, higher LH levels in baseline day 2 data, lower oocyte retrieval numbers and lower pregnancy rates were found in women with endometriosis [12]. Nearly half of our cases had large endometriomas and bilateral involvement [12]. The clinical pregnancy rate per started cycle in our endometrioma cases was slightly higher than women operated on for bilateral ovarian endometriomas [11]. Although fertilization rates were similar, our results suggested that embryo quality and uterine receptivity may still affect women with large and/or bilateral endometriomas [12].

We used 3D power Doppler ultrasonography to investigate the differences of ultrasound findings between cases with endometriosis and control [12]. There were significantly decreased intra-ovarian stromal blood flow parameters, including vascularization index (VI), flow index (FI) and vascularization flow index (VFI), in the patients with endometriosis who did not have any evident difference in total ovarian volume on the day of human chorionic gonadotropin. There was also significantly decreased uterine artery velocimetry (RI and PI) values as determined by Doppler analysis between two groups. Therefore, a deficient intra-ovarian vascularity potentially may be an initial marker of a reduced ovarian reserve before the increase of serum follicle stimulating hormone (FSH) levels in early follicular phase, and an important predictor of ovarian response. The above results all demonstrated that women who underwent previous conservative surgery for endometriomas showed signs of a diminished ovarian reserve. Ovarian damage during surgery may lead to decreased intra-ovarian vascularity in the endometriosis group. It was interesting that there were no significant differences in stromal blood flow parameters of 3D power Doppler ultrasound between the endometriomatous ovaries post-endometrioma surgery and the contralateral control ovaries in the same individuals, which may be compatible with decreased ovarian reserves in both ovaries of the patients with previous endometriomas after surgery in our study [12]. Therefore, 3D power Doppler can be used to demonstrate the dynamic vascularity of the IVF process and may provide a prognostic tool for IVF outcomes in patients with endometriomas.

It is possible that restricted blood supply to the ovarian stroma in endometrioma after conservative surgery might be associated with impaired embryo quality. Leptin is considered an angiogenic factor and may serve as a sensitive marker of IVF outcomes. The angiogenic effect of leptin is equivalent to that of vascular endothelial growth factor (VEGF), but the angiogenic response is evident earlier compared with VEGF [13]. It means leptin plays a possible role in conditions where new blood vessel growth is crucial, such as a decreased ovarian reserve in patients with endometriosis after surgery. Elevated levels of serum leptin are associated with poor ovarian response, as well as decreased follicle maturation,
embryo quality and pregnancy outcomes [12,14].

In our previous study, follicular fluid leptin (14.38 ± 1.74 ng/ml) was higher than serum samples (5.36 ± 1.37 ng/ml) examined on ovum pick up day in normal control, which is compatible with the data from Anifandis et al [14], but there were no significant differences in follicular fluid or serum leptin concentrations between the patients with endometriosis and the control group [12]. The value of follicular fluid leptin demonstrated a negative correlation with ovarian stromal FI in the control group, but there was an absence of this effect in the endometriosis group in our study [12]. Reduced blood flow (such as decreased FI in our study) through the ovarian stroma may lead to a follicular hypoxia followed by the secretion of several angiogenic factors, such as leptin, in ovarian follicles. The reduced ovarian response may then be found through negative feedback of leptin to the ovaries. Loss of the negative correlation between follicular fluid leptin and intra-ovarian FI in the endometriosis group may represent deficient angiogenic responses in ovarian cortices after surgery.

Postmenopausal Endometrioma

Endometriosis is uncommon in postmenopausal women, because it depends on estrogenic stimulation for its continued growth during reproductive ages. In asymptomatic postmenopausal women, the risk of malignancy of simple adnexal cysts is low (0.6%). Almost half of these women, whose menopause tended to occur more recently and they tended to be younger, resolve spontaneously during close ultrasound follow-up and avoid unnecessary surgical intervention for physiological cysts [15]. However, many cysts still persist and/or remain unchanged. Color Doppler ultrasound is usually recommended for screening for ovarian cancer. Vuento et al suggested that the evaluation criteria for abnormal ovarian findings in asymptomatic postmenopausal women were an ovarian volume of 8 cm³ or greater, nonuniform echogenicity, and/or a pulsatility index (PI) of the ovarian artery or tumor vessel, if present, of 1.0 or less [16]. The conventional 2D sonography seems to be sufficient as a primary screening modality when a malignant tumor is suspected. However, they found that transvaginal color Doppler ultrasound is an effective method for detecting ovarian cysts in asymptomatic postmenopausal women. In our previous study, 3D power Doppler sonography has proved that the flow intensity of the ovarian stroma, including VI, FI and VFI, decreased in the order of the aging process: premenopause, perimenopause, then postmenopause [17]. There were a significant increase in ovarian stromal flow indices in postmenopausal women receiving continuous-combined hormone replacement therapy, but not in the control group [18]. Introducing 3D ultrasonography with power Doppler facilities as a secondary screening test for ovarian cancer in asymptomatic peri- and postmenopausal women will further improve the accuracy of ovarian cancer screening studies. Kurjak et al detected malignant tumors early and accurately using 3D ultrasonography and power Doppler imaging, in multiloculated, complex or solid ovarian mass, or persistently cystic mass > 5 cm in diameter, in which the echo architecture and/or blood flow pattern was not highly suggestive of a benign histology according to 2D morphologic and Doppler ultrasonic criteria of the ovarian malignancy and related cut-off scores [19]. Up until this point there has been little discussion in the differential diagnosis of ovarian endometrioma with malignancy in postmenopausal women using 3D ultrasonography.

Accuracy of Ultrasonography in the Differential Diagnosis of Suspected Adnexal Tumors

Sometimes, the clinical features and biological behavior of ovarian cancer might be closely related to endometrioma and/or endometriosis. About 0.7% of ovarian endometriosis cases demonstrate malignant transformation [20]. In contrast, the frequency of endometriosis that occurred in benign, borderline malignant, and malignant ovarian tumors is 9.7%,
12.5%, and 11.4%, respectively [21]. The most frequent ovarian cancer closely related with endometriosis is endometrioid adenocarcinoma. It is important in clinical practice that surgeons should be aware of the possibility of ovarian cancer employing careful preoperative evaluation when laparotomy or laparoscopic surgery is arranged in ovarian endometrioma cases.

Ultrasound examination is a useful tool for preoperative differential diagnosis of adnexal lesions. The gray-scale ultrasound parameters for predicting malignancy include the size of the largest solid component, wall irregularity and lesion size, with a sensitivity of 100% and a false positive rate of 10% [22]. The presence of normal ovarian tissue adjacent to the ovarian cyst (the ‘ovarian crescent sign’) on an ultrasound scan is also a useful morphological feature to exclude the possibility of an invasive ovarian malignancy in the preoperative evaluation [23]. Ovarian cancer is diagnosed with a sensitivity of 96% and a specificity of 76% when no normal ovarian tissue is demonstrated by ultrasound. Several parameters are used in the evaluation of adnexal masses by transvaginal color Doppler sonography, including a number of vessels detected in each tumor, tumor vessel location (central vs. peripheral), peak systolic velocity, lowest resistance index, mean resistance index, lowest pulsatility index and mean pulsatility index [24]. Most parameters demonstrate an overlap between benign and malignant tumors with a high false-positive rate. The parameters which best differentiate malignant cancers from benign tumors are the lowest resistance index with a cut-off value of 0.45 (sensitivity 100%; false-positive rate 11.4%) and central tumor vessel location (sensitivity 90%; false-positive rate 11.4%). Using 3D ultrasoundography, the central localization of vessels in an adnexal mass can be easily observed (Fig. 6). In addition, the mean gray index and the flow index are potentially important parameters in differential diagnosis [25]. The use of 3D power Doppler ultrasound can help to discriminate between benign and malignant ovarian tumors. VI in a 5 cm³ ovarian tumor improves diagnostic performance in the 3D flow index, and is superior to that of the color content of the tumor scan (with sensitivity 93% vs. 78%, and a false positive rate 16% vs. 27%) [22].

Furthermore, borderline malignant tumors increase the diagnostic difficulties with only 47% being correctly classified as malignant [26]. About 8% of pelvic masses are difficult to correctly classify on the basis of ultrasound findings. Papillary projections, ten or more locules existing in a cyst without solid components, low-level echogenicity of cyst fluid, and moderate vascularization as assessed subjectively at color Doppler examination are independent ultrasound variables associated with unclassified mass. The diagnostic findings of ultrasound in borderline ovarian tumors are highly specific using the tumor pattern recognition method [27]. The morphologic features viewed through ultrasonography are a unilocular cyst with a positive ovarian crescent sign and extensive papillary projections arising from the inner wall, or a cyst with a well defined multilocular nodules. However, typical ultrasound features are only present in two thirds of cases, the others being misdiagnosed as benign lesions. The most frequent diagnostic ultrasound feature of borderline ovarian tumors is the presence of papillae, defined as a small number of solid tissue projections into the cyst cavity from the cyst wall measuring 1–15 mm in height and 1–10 mm in both width (base) and length (base) [28]. Intracystic solid tissue measuring more
than 15 mm in height or 10 mm in width or length would favor invasive malignant masses.

**Serum CA-125 for Ovarian Endometrioma**

CA-125 levels are often used in differentiating ovarian endometriomas from adnexal masses. The levels are significantly higher in patients with endometriotic masses, and increase with the stages of endometriosis [29]. Recently, a multiple-marker screening test for endometriosis involving a four-marker panel consisting of CA-125, macrophage chemotactic protein-1, leptin, and macrophage migration inhibitory factor, could diagnose 48% of subjects as to the presence of endometriosis with 93% accuracy, which may be useful in the workup of patients with suspected endometriosis [30]. Using a cut-off at ≥ 35 U/mL, elevated CA-125 levels demonstrates 79.3% sensitivity, 84.6% specificity, 79.3% positive predictive value, and 84.6% negative predictive value in the diagnosis of ovarian endometrioma in patients scheduled for surgery [7]. In our department's previous study in women undergoing surgery for endometriosis [29], CA-125 levels higher than 65 IU/mL, with a sensitivity of 76%, a specificity of 71%, a positive predictive value of 76%, and a negative predictive value of 93.2%, might help in the preoperative diagnosis of advanced stages of endometriosis or severe pelvic adhesions in women undergoing surgery for endometriosis, meaning that these patients require preoperative bowel preparation. The serum level of CA-125, which is also considered as a useful parameter to predict follicular loss before surgery in patients with ovarian endometrioma, is directly correlated to the histologic score and to cyst diameter [31]. However, transvaginal ultrasonography used alone is a more cost-effective method in the preoperative differential diagnosis of ovarian endometrioma than tumor marker values, such as CA-19.9 and CA-125 plasma levels [32]. Pattern recognition, using color Doppler ultrasound examinations, can further correctly discriminate between benign and malignant adnexal masses, and is also superior to serum CA-125 [33].

**Conclusion**

Ultrasound examination is an easy and noninvasive tool in the evaluation of ovarian endometriomas. It is useful in the analysis of morphologic anatomy and conventional 2D sonography seems to be sufficient as a primary screening test for ovarian endometriomas, even when a malignant tumor is suspected. Color Doppler and 3D power sonography will provide substantial assistance in detecting the functional role of ovarian endometriomas, and in discriminating ovarian endometriomas from malignant adnexal masses in preoperative differential diagnosis.

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