Doppler Evaluation of the Ovary: Clinical Applications and Challenges

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Abstract: Transvaginal sonography has been shown to be an accurate technique for discriminating between benign and malignant adnexal masses. Accurate preoperative differential diagnosis of adnexal masses is essential for optimizing patients' treatment. The advancement and wider availability of therapies of assisted conception have occurred to a large extent as a result of developments in ultrasonography. Transvaginal color Doppler has opened up exciting new possibilities for the better understanding of the physiology and pathophysiology of ovarian blood flow, resulting in a number of completely new diagnostic parameters.

Key words: Doppler ultrasound, clinical application, ovarian tumor, angiogenesis.

INTRODUCTION

The ovary is one of the most active organs in the female body. It progresses through many changes, including puberty, pregnancy and menopause. It is complex in its embryology, histology and steroidogenesis. Furthermore, it is made up of germinal epithelium, germ cells of gonadal stroma, and mesenchymal cells—each with their own potential to form a tumor. The ovary is the site of origin for a larger variety of primary cancers than any other organ. In addition, the ovary is unique in that it not only gives rise to a great variety of malignancies but is also a favorite site for metastasis from other organs. Furthermore, there are many clinical entities in human medicine linked with ovarian changes, etiologically connected with abnormal quantity and quality of the human genome. Ultrasound, more than any other modern technique, has enabled the direct assessment of many of the ovarian functions. Transvaginal sonography has revolutionized the morphological evaluation of the ovary and its conditions, both benign and malignant. The advancement and wider availability of therapies of assisted conception have occurred to a large extent as a result of developments in ultrasonography. Transvaginal color Doppler has opened up exciting new possibilities for the better understanding of the physiology and pathophysiology of ovarian blood flow, resulting in a number of completely new diagnostic parameters.

TECHNIQUE

Ultrasound imaging has provided a unique method for the non-invasive study of ovarian structural changes. The measurements of blood flow velocity by ultrasound are based on the Doppler effect. This effect implies that the frequency of a sound wave emitted from a stationary source and reflected from a moving interference changes according to the velocity and direction of the moving interface. Velocity waveform shows the frequency shift vs. time. The major advantage of this analysis is angle-independence and there is no need for simultaneous vessel visualization and diameter measurements. More than ten indices have been used for velocity waveform analysis. The A/B ratio, resistance index (RI) and pulsatility index (PI) are predominantly used.

Doppler ultrasound has the potential to study patterns of ovarian blood flow and hence identify functional changes. The availability of pulsed Doppler instruments has made it possible to sample the signals at a chosen depth and thus to direct flow in any selected deep pelvic vessel. Transvaginal color Doppler is the system that uses pulsed Doppler that performs flow analysis at multiple points along each scan line of echo data. Flow information is than color-coded and displayed on the entire corresponding anatomical image. The main advantage of this color Doppler system is rapid and definitive determination of the position of the small vessel, accuracy of the measurements and precise indication of flow direction and velocity. After simultaneous visualization of morphological and blood flow

information, a pulsed Doppler gate is placed over the area of interests to provide flow velocity waveforms which may be analyzed in a conventional fashion.

OVARIAN DOPPLER

The ovarian artery is a tributary of the upper aorta and reaches the lateral aspect of the ovary through the infundibulopelvic ligament. In some patients, these vessels are not clearly visualized and the sample volume should be moved across the ligament and than through the substance of the ovary until the arterial signal is identified. Signals from the ovarian artery are characterized by the low Doppler shifts of a small vessel with low velocity. The waveform shape varies with the state of activity of the ovary. Studies of ovarian artery blood flow show the difference in the vascular resistance between the two ovarian arteries depending on the presence of the dominant follicle or corpus luteum. A longitudinal study of the ovarian artery throughout of the menstrual cycle usually will show decreased pulsatility and resistance indices, reflecting vascular impedance and implying increased flow to the ovary containing the dominant follicle or corpus luteum. The ovarian artery of the "inactive" ovary in this cycle would show low end-diastolic flow or absence of diastolic flow. A rise in end-diastolic flow in "active ovary" is most obvious around day 21 and suggests that the corpus luteum acts as a low impedance shunt. The increased blood supply to the functioning corpus luteum is essential for delivery of precursors involved in steroidogenesis and for distribution of progesterone.

The ovarian artery is a high-pressure system with blood flow characteristics very different from intraovarian circulation (Fig. 1). Near the ovarian hilus the penetrating vessels are coiled and tortuous. This type of vascularity demonstrates high-resistance blood flow. Every month during the women's reproductive life, one oocyte is released from the single mature follicle that has completed development. Increased vascularity on the innermost rim of the follicle may represent the dilatation of new vessels that have developed between the relatively vascular theca cell layer and the normally hypoxic granulose cell layer of the follicle. It is hoped that information on ovarian perfusion may be used both to predict ovulation and to investigate ovulatory dysfunction.

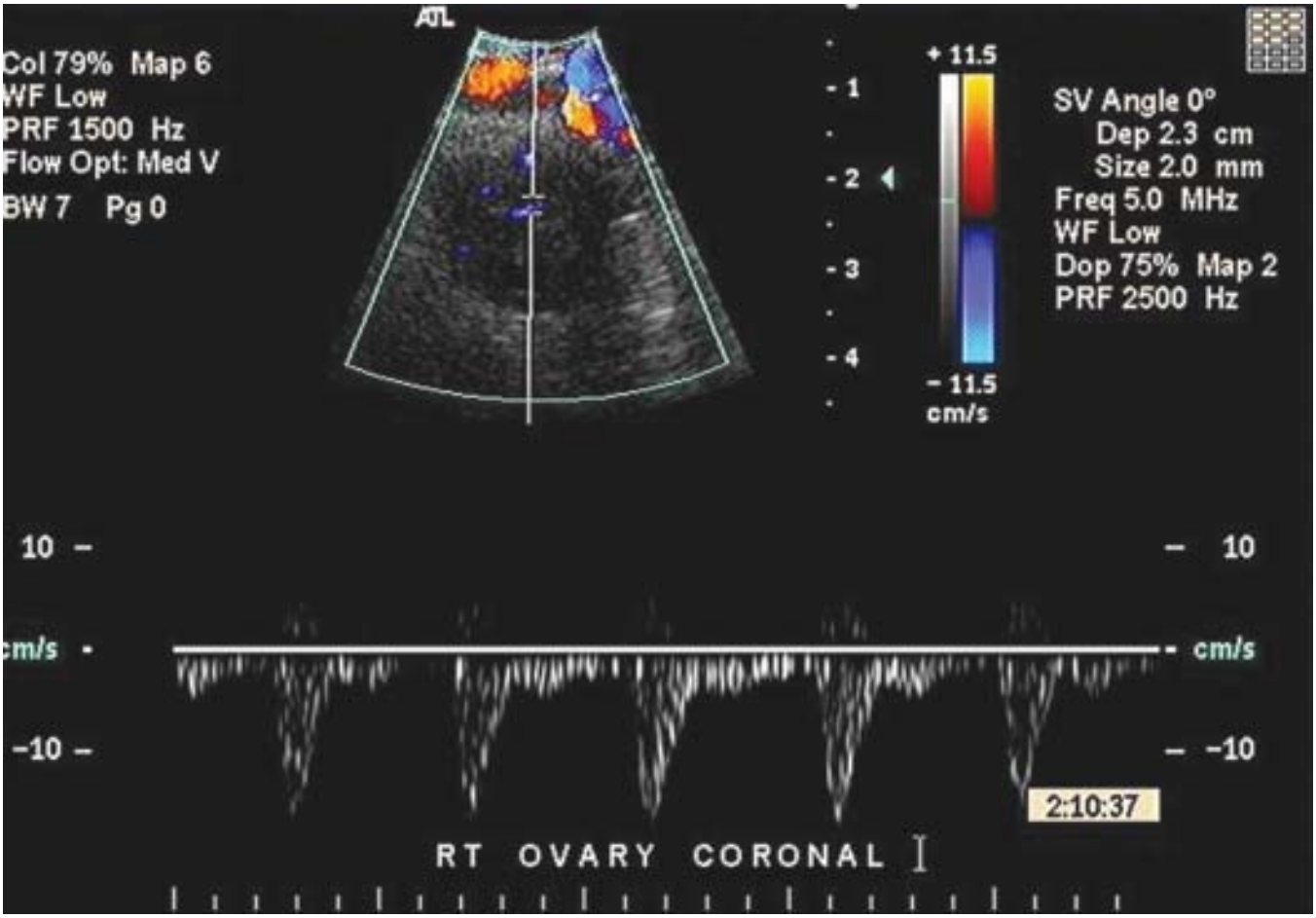

Fig. 1: The ovarian artery color and pulsed Doppler. Note the high resistance to blood flow

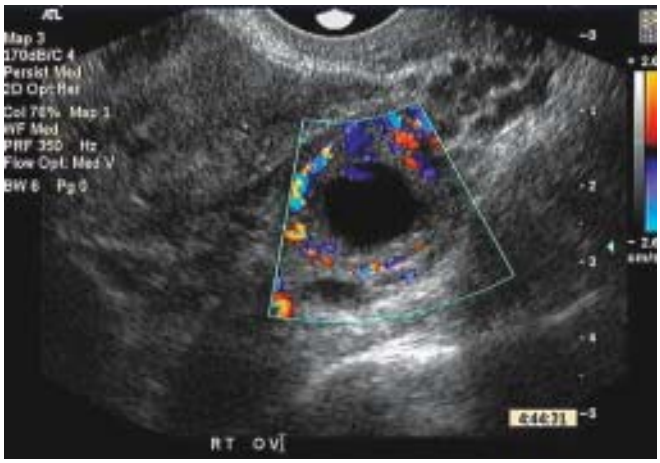

Fig. 2: Color Doppler image of the ovarian blood flow in the luteal part of the menstrual cycle

Color flow is more easily obtainable from ovarian tissue in the luteal phase (Figs 2 and 3). The qualitative postovulatory changes in intraovarian blood flow are characterized by increased turbulent flow accompanying morphological changes in the intraovarian vascular network and appearance of numerous arteriovenous shunts during the luteal phase. In summary, changes in the intraovarian blood flow occur before ovulation, implying a complexity of these changes that may involve both angiogenesis and hormonal factors, while postovulatory vascular accommodation is potentially important in the luteal phase. Using transvaginal color Doppler, corpus luteum blood flow, characterized by low impedance and high flow requirements, can easily be detected in normal early pregnancy, ectopic pregnancy and non-pregnant women.

It was long believed that simple dilatation of existing host blood vessels accounted for increased tumor vascularity. Tumor hyperemia could be related to new blood vessel growth. Angiogenesis and neovascularization are terms that are entering the vocabulary of every ultrasonographer. Angiogenesis occurs during embryonic development and during several physiological and pathological conditions in adult life. As mentioned before, angiogenesis is important in the process of ovulation and development of the corpus luteum. It accompanies numerous nonmalignant diseases such as acute or chronic inflammation and ectopic pregnancy. However, tumor angiogenesis differs at least in a temporal manner from other types of angiogenesis described.[1] In physiological conditions, angiogenesis is turned off once the process is completed. In nonmalignant processes, angiogenesis is prolonged, but still self-limiting. In contrast, tumor angiogenesis is not self-limiting. Malignant tumor microvasculature does not conform to the vasculature of normal tissues. It contains giant capillaries and arteriovenous shunts without intervening capillaries. Newly formed vessels contain no smooth muscle in their walls, but instead contain only a small amount of fibrous connective tissue. These vascular changes can be detected using color Doppler. Blood flow can be demonstrated throughout diastole, reflecting significantly decreased impedance to flow distal to the point of sampling.

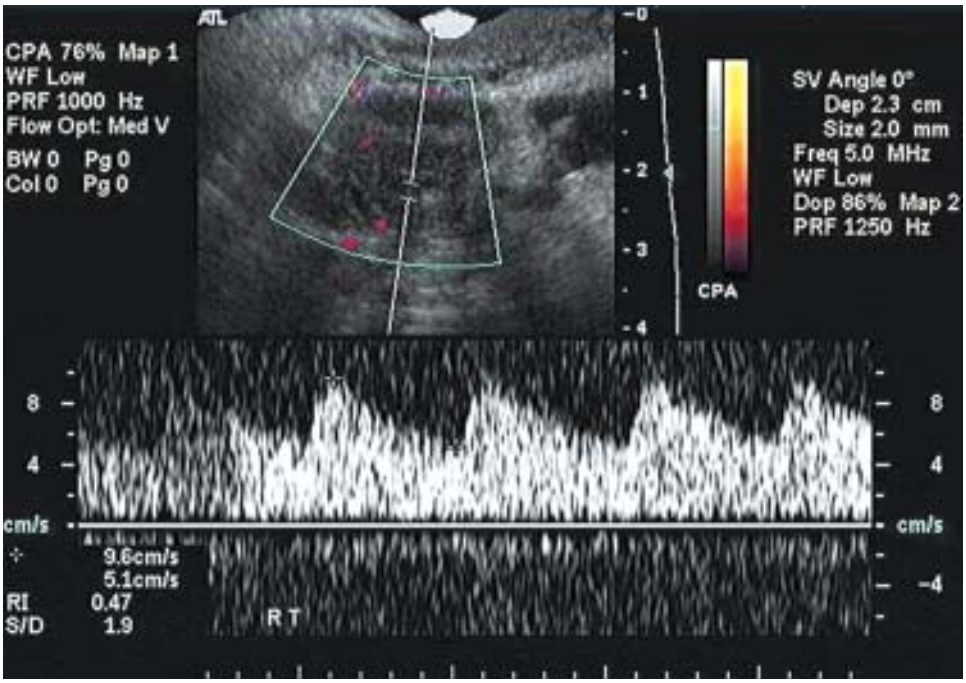

Fig. 3: Pulsed Doppler waveform analysis of the luteal blood flow. Note the low resistance to blood flow

Because very similar indices of impedance to blood flow are seen from the preovulatory follicle and corpus luteum, vascular information derived from the premenopausal ovary must always be related to the patient's menstrual cycle. Accordingly, physiological ovarian angiogenic activity could be excluded by carrying out the examination during the early proliferative phase (from the 3rd to the l0th menstrual day). In ovarian lesions that demonstrate low impedance and high diastolic flow, it is important to determine whether the waveform has a diastolic notch. Existence of a notch indicates persistence of an initial resistance from the muscular lining of pre-existing arterioles, and is typical of benign tumors. Small vessels that feed growing ovarian tumors or metastases could not be seen before the transvaginal application of color Doppler. The clinical application of this new modality and characterization of benign and malignant ovarian lesions on the basis of their vascularity have opened exciting avenues in the field of gynecological oncology.

ANGIOGENESIS IN BENIGN OVARIAN TUMORS

Functional cysts are the most common source of adnexal masses in women of reproductive age. The two main types of functional cyst, follicle and corpus luteum cysts, are benign and derived from either an unruptured follicle or the cystic degeneration of a corpus luteum, respectively. Typically, these cysts are unilateral and are less than 6 cm in diameter, and during pelvic examination, they feel smooth and cystic. On sonograms, the cysts appear unilocular and fluid-filled, without evidence of solid components or excrescences. It seems that transvaginal color Doppler is helpful in differential diagnosis of different causes of acute abdomen and detection of torsion of the functional cyst.[2] Torsion affects blood supply to the ovary both from the ovarian artery and the ovarian branch of the uterine artery. Below a morphologically recognized point, no blood supply was detected. Hemorrhage from a ruptured corpus luteum cyst can be severe enough to be mistaken for a ruptured ectopic pregnancy. This new technique enhances our ability to distinguish between these two conditions, and select the patients for surgical intervention when necessary.

Mature teratomas (dermoid cysts) occur commonly in women of reproductive age. They contain elements of mature adult structures derived from all three embryonic layers: endoderm, mesoderm, and peripherally ectoderm. These structures include hair, teeth, bone, skin, and calcified components that give focal, high-amplitude reflectors with acoustic shadowing. Unfortunately, these high-amplitude reflectors may simulate bowel gas; therefore, these lesions may be camouflaged and sometimes even large lesions can go undetected on sonograms.

Serous and mucinous cystadenomas are also common lesions. Serous cystadenomas may be unilocular but they are mostly multilocular, with or without papillary growth into the cavity. Mucinous cystadenomas may attain a huge size, and several have been reported to weigh 45-90 kg. Grossly, they present as rounded or ovoid masses with a smooth capsule that is usually translucent or bluish-whitish gray. Mucinous cystadenomas are thin-walled and mostly multilocular. Papillary formations may be present, but they are less common than in serous cystadenomas. Sonographic evaluation whether alone or in combination with tumor markers cannot determine the nature of the lesion before Doppler assessment. This is not surprising, because it can be difficult to distinguish a benign ovarian tumor from a malignant or borderline one by macroscopic inspection of the specimen or even by microscopic evaluation.

Fibromas, thecomas and Brenner's tumors are solid, benign tumors found in premenopausal and postmenopausal patients. Small, solid tumors are difficult to detect on sonograms because they are similar in echo texture to the normal ovary. If a solid lesion is observed in the adnexa of a premenopausal woman, it is more likely to be a pedunculated or broad ligament leiomyoma than a solid ovarian neoplasm. Transvaginal color Doppler is useful in differentiating fibroids from solid ovarian masses on the basis of their vascularity. Within or on the periphery of the uterine mass, even when it is out of the contour of the uterus, it is possible to detect waveform signals that are typical for the uterine vascular network. In such cases, blood flow is usually similar to normal myometrial perfusion, originating from terminal branches of the uterine artery. On the other hand, small vessels that feed a growing ovarian tumor are of ovarian vasculature origin.

ENDOMETRIOSIS

Endometriosis is a condition in which abnormal growth of tissue, histologically resembling endometrial tissue occurs outside the uterus, including on the surfaces of the bowel, bladder, or abdominal wall. The ovary represents a relatively unique site of implantation, as the levels of steroids surpass those in the circulation, and hence this affords an ideal environment for implantation of endometrial growth. It seems that the surface epithelium and the proximity of the tubal ostia influence transplantation production. When endometrial cells enter the ovarian stroma, large endometrial cysts filled with viscous chocolate colored liquid may be formed. There is usually a well-demarcated separation between the endometrial cyst wall and the normal adjacent ovarian stroma. The most prominent vascular area in these common benign cysts is at the level of the ovarian hilus. This type of neovascularization was often seen with endometriomas. It seems that low impedance/high diastolic flow is present when there is a hemorrhage during the menstrual phase of the cycle. Therefore, it is recommend studying ovarian endometrioma vascularity during the late

follicular phase. It is postulated that the effect of medical treatment is highly dependent upon the metabolically active implants arriving via a blood-supplying network. Conservative treatment has encouraging potential and can be successfully used in patients with an optimal vascular pattern. Surrounding inflammation and fibrotic changes that may disturb this process can be detected by transvaginal color Doppler. Based on some experience avascular ovarian lesions could be best removed surgically.

PELVIC INFLAMMATORY DISEASE

Ultrasonography is often used to exclude intrauterine and ectopic pregnancy or to document the presence of an adnexal mass. Sonography shows a predominantly cystic collection with internal echoes that may have multiple loculations. Occasionally, distinction from fluid filled loops of bowel may be difficult. In this instance, a water enema may be helpful because the movement of water through the bowel will be observed on real-time ultrasound. Because the inflammatory process in the ovary involves both structural and vascular changes, color Doppler ultrasound can be a useful tool in its diagnosis and management. The early phase of the disease is characterized by edema of the fallopian tubes and dilatation of the blood vessels in their walls. The inflamed ovaries were enlarged and filled with multiple cysts which represented infected follicles or corpus luteum cysts. Intraovarian vessels could easily be identified and show usually moderate resistance to blood flow.

It is well known that the sonographic appearance of a complex adnexal mass should be interpreted in the context of the clinical setting. For example, in the febrile patient, a thick-walled mass containing echogenic fluid is likely to be an abscess. In this advanced and most severe form of pelvic inflammatory disease, it is difficult to identify the pelvic anatomy. Ovaries are usually adherent to the pelvic sidewall or to the uterus, and the scarring process can alter their endocrine function and circulation. Based on our experience, dynamic use of color Doppler ultrasound in patients affected with pelvic inflammatory disease is important for accurate diagnosis, follow-up and evaluation of the ovulatory function and ovarian perfusion.

Color Doppler ultrasound is a useful tool in the diagnosis of PID. It helps distinguish between dilated vessels and a fluid-filled hydrosalpinx, and it can be useful in the differential diagnosis of tubo-ovarian abscess. Measurements of the intra-ovarian resistance in the acute phase of the disease reveal the ovarian involvement and function, as these relate to the rapidly changing pattern of the disease. An increased resistance to blood flow in the chronic phase is probably related to the extensive scarring. This condition of reduced perfusion may have long-term effects on the endocrine function of the ovary.

INFERTILITY

The true possibilities of transvaginal color and pulsed Doppler sonography in research into the ovarian circulation, PCOS and corpus luteum function are yet to be discovered. Ovarian blood flow velocity seems to be the main determinant of follicular responsiveness and risk of OHSS. Therefore, ovarian stromal perfusion should be evaluated prior to IVF treatment, to identify patients with an altered response to hormonal stimulation and those with increased risk of hyperstimulation. It is hoped that further research on promoters of angiogenesis will improve ovarian responsiveness and IVF outcome in patients with diminished ovarian stromal blood flow.[3,4]

ANGIOGENESIS IN BORDERLINE TUMORS

Ultrasonography has been widely used to detect, characterize, and evaluate ovarian tumors. The principle of the diagnostic imaging study is based on macropathology. Thick septae, irregular solid parts within a mass, indefinite margins and presence of ascites are regarded as malignant patterns. Some authors have reported that ovarian tumors of low malignant potential presented the same patterns as malignant tumors. On the other hand, other authors mentioned that borderline tumors had an appearance similar to that of benign tumors and it was difficult to differentiate them from their benign counterparts. Therefore, assessment of vascular changes and the resistance to blood flow would be required in the ovarian tumor presenting either benign or malignant features by conventional ultrasound.[5] Blood flow velocity waveforms obtained from borderline tumors are relatively of high diastolic flow and low resistance. Doppler features are extracted from large arterioles or sinusoids with no muscles in their walls. This is a possible homodynamic response to the tumor angiogenesis factor produced from low malignant-potential cells. Therefore, the preoperative assessment of the adnexal mass by ultrasonography would include the size, consistency and blood flow to determine the likelihood of malignancy.[6-8]

ANGIOGENESIS IN MALIGNANT OVARIAN MASSES

The advent of vaginal ultrasound screening methods for ovarian cancer has made the ovaries more accessible.[9] Dramatic changes in ovarian tissue vascularity during oncogenesis are mediated by numerous angiogenic factors and can be detected by using flow data from color Doppler. Malignant tumor vessels are usually dilated, saccular, and tortuous, and may contain tumor cells within the endothelial lining of the vessel wall. Other features include the presence of arteriovenous shunting (large and direct communications, or microscopic communications in the tumor microcirculation) and bizarre thin-walled tortuous

vessels lined by tumor cells that end in amorphous spaces constituting 'tumor lakes' with or without associated necrosis. Arteriovenous shunts are remarkable because of extreme velocities that occur at sites of high-pressure gradients. This type of vessel is usually situated on the periphery of the tumor. New vessels are continually produced on the periphery of the tumor, creating the potential for its proliferation and growth. The second type of signal, exhibiting little systolic-diastolic variation, is usually present in the central vessels within the malignant tumor. This is, most probably, their response to the angiogenic activity of tumor cells. These vessels have a relative paucity of smooth muscle in their walls in comparison with their caliber and 'behave' more like capillaries than true arteries or arterioles. Vessels deficient in their muscular elements present diminished resistance to flow and thereby receive a larger volume of flow than vessels with high impedance. It seems that distribution of the vessels and impedance to blood flow is dependent on tumor type and size. Tumors gradually begin to compress their own blood vessels when they continue growing beyond a certain size. The absence of functional lymphatic vessels in the tumor stroma, and the increase in cell mass and tumor vessel permeability result in an increase in the interstitial pressure in the tumor core and lead to the occlusion of centrally located tumor vessels. This causes prolonged cessation of flow in the center of the tumor, followed by central necrosis. It seems that low resistance in centrally located vessels is a consequence of a response to the angiogenic activity of the tumor cells and to the differences in necrotic processes. Another important parameter for the assessment of tumor vascularity is the vascular arrangement. Randomly dispersed vessels within the solid part of malignant tumors were seen four times more than regularly separated vessels.

Color and pulsed Doppler sonography demonstrates the vascularity of an adnexal mass. Blood flow data should be considered to indicate the angiogenic intensity of a tumor, rather than indicating malignancy itself.[10-12] It seems clear that initial attempts to classify ovarian tumors solely on the basis of their impedance to blood flow have been too simplistic. This problem has been partly solved by the introduction of other 'vascular parameters' such as blood vessel arrangement and location, shape of the pulsed Doppler waveform and appearance of an early diastolic notch, as well as assessment of blood flow velocities. However, the difference in flow parameters in benign vs. malignant lesions may not always be sufficient to form the basis of a firm diagnostic impression.[13-16] A common criticism of color Doppler is that the operator is never blind to the B-mode image: there is a tendency to search harder for low-impedance blood flow patterns in lesions with a malignant appearance rather than in simple adnexal cysts. However, when applied by expert operators and in a disciplined fashion, it may significantly add to diagnostic information about an adnexal mass and its morphological appearance. If blood flow data are treated as providing an insight into the pathology of a tumor, they give reassurance when masses have a benign appearance, while giving confirmation of malignancy in adnexal masses with suspicious morphological features.

It is important to emphasize that the areas of overlap in benign versus malignant pelvic lesions tend to involve non-neoplastic masses that contain vasodilated vessels, owing to local or general hormonal imbalances, whereas some malignant tumors elicit sparse angiogenesis and may appear avascular, and therefore benign, in terms of color Doppler sonography. Obese women and women with irregular cycles and hormonal disturbances may produce ovarian blood flow patterns with typical low vascular resistance to blood flow. Therefore, measurements of estradiol and progesterone serum levels on the day of the transvaginal color Doppler examination should be performed when low vascular impedance to blood flow is found. It is possible that, with further improvement of color and pulsed Doppler sensitivity, and in conjunction with clinical findings, gray-scale ultrasound imaging and serum hormonal levels when necessary, a better distinction between malignant and benign pelvic tumors will be made. Contrast agents are another possibility for enhancing both color and power Doppler examinations by increasing the detection rate of small vessels.[17]

3D ULTRASOUND

The three-dimensional capability has been extended to various diagnostic ultrasound modalities. In the case of ovarian tumor vascularity, the three-dimensional display allows the physician to visualize multiple overlapping vessels and to establish their relationship to other vessels and tumors or other surrounding tissues. The implementation of the three-dimensional display permits the physician to view structures in three-dimensions interactively, rather than assembling the sectional images mentally. The three-dimensional power Doppler system may enable physicians to study the region of interest in more detail. Although power Doppler has several advantages over conventional color Doppler ultrasound, it is still a kind of color Doppler imaging and therefore subject to some of the limitations of the conventional technique. For example, various parameters of color Doppler ultrasound, such as pulse repetition frequency, wall filter, priority, power gain, color persistence and frame rate must be optimized for three-dimensional display, as well as for qualitative and quantitative analysis of these power Doppler data. A change in color setting may lead to a totally different three-dimensional vascular image and dissimilar quantitative results. In addition, since now both color and power Doppler can be combined with more complex computing, the frame rate will be significantly reduced when the power/color Doppler mode is active. Therefore, if a mechanical three-dimensional probe is used, some very small vessels may escape from image capture. The effects of ultrasound attenuation can

sometimes cause different 'power intensity' and hence vessel detection between nearer and deeper parts of the tissue being explored.

Morphological analysis of the blood vessel system represents another approach to tumor diagnosis that, so far, has not been extensively evaluated. Nevertheless, there is a distinct impression from some reports that the distribution and branching pattern of blood vessels that supply fast-growing tumors differ from those of the normal blood supply to normal organs. This means that the blood vessel distribution seems to carry additional information that is missed by the present diagnostic approaches. However, describing branching structures such as the blood vessel tree is a mathematically complicated task. Microvessel density in ovarian cancers has been correlated with the likelihood of recurrence. The density (determined histologically) of microvessels, irrespective of their distribution, was found also to have significant implications for recurrence. In color Doppler studies the density can be determined by counting the number of color spots in a tumor area.

Different types of angiogenesis in different physiological and pathological conditions have been described. Physiological angiogenesis is seen in folliculogenesis, embryogenesis and implantation, chronic inflammation and some benign neoplasm. According to some authors the luteal vessels are usually fewer and seldom have complicated branching or encircle the cyst, in contrast to the findings in a malignant neoplasm. In simple cysts the vessels are usually straight and regularly branching, whereas in 'chocolate' cysts vessels usually branch from a hilar vessel then run along the surface of the tumor. Similar vascular anatomy is detected in dermoid cysts. In cases of malignant ovarian neoplasm the tumor vessels are usually randomly dispersed within the stroma and periphery, and some of them form several tangles or coils around the surface. The course of the main tumor vessel is usually irregular with more complicated branching. The diameter of these vessels is felt to be more uneven and 'thorn-like'. These findings can be compared to previous studies with conventional color Doppler ultrasound. However, the appeal of the three-dimensional display is that it is more comprehensive and allows physicians to understand the three-dimensional architecture of the microcirculation interactively. In addition, the resolution of current power Doppler is sufficient to detect vessels of around 1 mm in diameter. In an attempt to systematize the extent of perfusion, four regions of different perfusion states can be recognized: a necrotic region (central portion); a seminecrotic (ischemic) region; a stabilized microcirculation; and the hyperemic region within the outermost area. Different pathological types, tumors with different growth rates, primary tumors or metastases can all exhibit different perfusion patterns.

The results reported in the recent literature on three-dimensional color and/or power Doppler raise many new questions about the regulation of tumor angiogenesis, the density of tumor vessels and the differences between vessel architecture in benign and malignant ovarian growths. Improved detection and classification of tumor architecture after instillation of contrast agents might contribute to better diagnostic accuracy.

FUTURE CHALLENGES

The results reported in the recent literature on three-dimensional color and/or power Doppler are indeed provocative and, not surprisingly, raise many new questions about the regulation of tumor angiogenesis, the density of tumor vessels and the differences between vessel architecture in benign and malignant growths.[18,19] Three-dimensional power Doppler depiction of tumor angiogenesis has many clinical implications, including early detection of ovarian and endometrial cancers. Improved detection and classification of tumor architecture after instillation of contrast agents might contribute to better diagnostic accuracy.

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