INTERNATIONAL CORNER

ECTOPIC PREGNANCY – ADVANCES IN ULTRASOUND DIAGNOSIS

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ABSTRACT

Early and reliable diagnosis of ectopic pregnancy still remains a challenge but is essential to avoid life-threatening bleeding or consequent infertility. The introduction of transvaginal sonography has improved diagnostic accuracy, but using this technique in about half of ectopic pregnancies an ectopic gestational sac is not clearly visualized. Color Doppler ultrasound contributes to detection of hemodynamic changes in tubal arteries by enabling demonstration of high vascularity in approximately 94% of ectopic pregnancies. The appearance and the location of the blood flow relate to the gestational sac dimension and flow velocity waveform characteristics and are similar to those obtained from the spiral arteries in normal intrauterine pregnancies (RI = 0.42 ± 0.12). Color Doppler studies demonstrate a high quantity of color in ectopic pregnancies with vital trophoblast and/or a live embryo as well as those with relatively high beta hCG levels. Demonstration of the "hot flow pattern" shortens the diagnostic process and enables an easier clinical decision to be reached on the treatment of ectopic pregnancy. Based on our clinical experience in patients with less color signals and increased vascular resistance to blood flow, both indicating a non-vital trophoblast and/or long-standing demise, expectant management can be introduced. Our preliminary data suggest that three-dimensional sonography is an effective procedure for early diagnosis of ectopic pregnancies, which enables demonstration of hyperechoic border, an apparently specific feature not reported by conventional ultrasound studies. It seems that shortening diagnostic procedure process and proper selection of the patients based on color Doppler and 3D ultrasound evaluation enables introduction of more sufficient treatment options.

Key words: *ectopic pregnancy, color Doppler, 3D ultrasound.*

INTRODUCTION

Ectopic pregnancy represents implantation of the fertilized ovum outside the uterine cavity. In 95% of the cases it is localized in the Fallopian tube (95%), but sites like abdominal cavity, ovary, intraligamentous location, cornual, intramural or cervical sites are not unusual (1, 4). Increased incidence of ectopic pregnancy was found during the last decades (5, 6), mainly attributed to greater degree of socially acceptable sexual behavior, which led to increased incidence of the pelvic inflammatory disease (PID). Fortunately, the fatal outcomes have been reduced up to 75% for the reason of early diagnosis and less invasive treatment techniques. Mechanical factors predisposing pathomorphological site of implantation are: low-grade pelvic infection (main cause for the faulty implantation), peritubal adhesions (result of the previous PID), and salpingitis with the partial or total destruction of the tubal mucosa. It has been reported that ectopic pregnancies do occur in totally normal tubes, suggesting that abnormalities of the conceptus or maternal hormonal changes may act as etiological factors (7, 8).

Risk factors for ectopic pregnancy are STD – PID (sexually transmitted diseases – pelvic inflammatory disease) (9, 10), assisted reproductive techniques, abnormalities of the conceptus, maternal hormonal changes, surgical procedures in pelvis (11), IUD (intrauterine device) (12), previous ectopic pregnancy, fibroids, uterine malformations, cigarette smoking etc. In addition to providing an accurate description of the sites of implantation of ectopic pregnancy some authors showed that current IUD use 'protects' against interstitial pregnancies, which are the most difficult to manage and that subsequent fertility tends to be higher in women with distal EP (13). It is essential to identify the risk factors so we can provide patients with adequate information, diagnose and treat an ectopic pregnancy early, and possibly to develop preventive strategies (14-16).

The main problem of ectopic pregnancy is clinical presentation (17). Symptoms can vary from vaginal spotting to vasomotor shock with hematoperitoneum (18, 19). The classic triad of delayed menses, irregular vaginal bleeding and abdominal pain are most commonly not encountered, but the exact frequency of clinical signs and symptoms are hard to assess (1). Both typical and atypical clinical presentation can mimic all kinds of diseases, which have no connection with pathology of reproductive system, such as appendicitis, diverticulitis, non-specific mesenterial lymphadenitis, or diseases of the urinary system. In most cases ectopic pregnancy is confused with an early spontaneous abortion because of the similar symptoms in both processes (delayed menses, enlarged and softened uterus and bleeding). Other conditions that should be considered in differential diagnosis of ectopic pregnancy are: normal intrauterine pregnancy, salpingitis, torsion or rupture of the ovarian cyst, adnexal torsion, bleeding corpus luteum, endometriosis, appendicitis, gastroenteritis,

diverticulitis, conditions affecting urinary tract etc. Therefore, early and reliable diagnosis of ectopic pregnancy is major challenge for every clinician. Significance of early diagnosis lays in the possibility for application of the conservative methods of treatment, which are crucial for preserving further reproductive capability, and in severe cases the life itself (20). Diagnostic procedures are divided into two groups:

Non-invasive: history, general clinical and gynecological examination, hormonal and other laboratory markers and ultrasound diagnostics.

Invasive*:* culdocenthesis (21), curettage (22) and laparoscopy.

THE ROLE OF BIOCHEMICAL MARKERS IN ECTOPIC PREGNANCY

Beta hCG (human chorionic gonadotropin) is the glicoprotein hormone released into circulation by human placental trophoblastic cells. From the 8^{th} day after conception its concentration in blood rises 1,7 times every day (23). As soon as implantation occurs the trophoblast starts producing beta hCG. Common urine beta hCG tests react at concentrations higher or equal to 1000 IU/l of urine, which means that they become positive 10 – 14 days after conception (1). Falsely positive results may be obtained in the case of proteinuria, erithrocyturia, gynecological tumors, tuboovarian abscess (24), or some drug intake (e.g. tranquilizers). Embryo in cases of an ectopic pregnancy usually disappears, becomes reabsorbed and we usually visualize an empty gestational sac producing smaller amounts of beta hCG. Normal levels of beta hCG could be found only in cases of a still living embryo which occurs in 5 – 8% of ectopic pregnancies (23). For the reason of low concentrations of human chorionic gonadotropin only 40 – 60% of ectopic pregnancies have the positive urine test, therefore more sensitive blood test should be performed, which becomes positive already 10 days after conception (23). Absolute value of beta hCG levels in circulation are much lower than the levels of the same hormone in normal intrauterine pregnancies of the same gestational age (25, 26). Dynamics of the titer show slower increase of circulating concentrations and increases the time for doubling its values. The most important use of the quantitative beta hCG determination in conjunction with ultrasonography is that of understanding the value of "discriminatory zone" of beta hCG. The discriminatory zone represents the level of beta hCG above which all normal intrauterine chorionic sacs will be detected by ultrasound. There is now almost a consensus in considering the discriminatory zone to be about 1000 mIU/ml with the use of transvaginal probe of at least 5 MHz (27-30).

THE ROLE OF ULTRASOUND IN THE DIAGNOSIS OF ECTOPIC PREGNANCY

With recent technological development ultrasonography (but more precisely, transvaginal sonography) has become the "gold standard" diagnostic modality for the effective and fast detection of ectopic pregnancy. An important advantage of most currently used transvaginal transducers is the ability to perform simultaneous and spectral Doppler studies, allowing easy identification of the ectopic peritrophoblastic flow. In comparison to transvaginal sonography, transabdominal ultrasound, as a method for detecting ectopic gestation is restricted for a very small number of oddly located ectopic pregnancies, mainly high up in the pelvis – outside the effective reach of 5 MHz vaginal probe (31).

Transabdominal Ultrasound

The absence of gestational sac inside the intrauterine cavity at 6 weeks' gestation raises the suspicion of an ectopic pregnancy. Transabdominal ultrasonography cannot reliably diagnose ectopic pregnancy, except when a live fetus is demonstrated in the abdominal cavity. In only 3 – 5% of the cases an ectopic gestational sac with embryonic echoes and clear heart activity can be demonstrated (32). Probe with frequency of 3.5 MHz and large contact area is used for transabdominal ultrasonographic imaging and full bladder plays a role of an acoustic window. Resolution of this probe is somewhat lower, but the penetration is much deeper than one of the transvaginal probe.

The best results in confirming the intrauterine pregnancy are achieved using following criteria:

1. Normal size, shape and location of the gestational sac in the uterine cavity,
2. Double ring surrounding the gestational sac,
3. Embryonic parts with eventual,
4. Heart action.

Signs for ectopic pregnancy could be divided into uterine and extrauterine, some of them being diagnostic or just suggestive. Diagnostic signs include: absence of the intrauterine gestational sac surrounded with double ring, absence of the yolk sac and/or fetal structures inside the gestational sac and presence of extraovarian adnexal structure.

Suggestive signs are: uterine enlargement with thickened endometrium and blood or coagulum in the retrouterine space (32).

Low sensitivity, specificity, positive and negative predictive values for detection of ectopic pregnancy are shortcomings of transabdominal ultrasound (33, 34). This modality still has some value in successful detection of a small proportion of ectopic pregnancies with bizarre location, such as high in the pelvis.

Transvaginal ultrasound

In comparison with transabdominal approach, transvaginal ultrasound enables much better image of the morphological features in pelvis thanks to higher frequencies and probe location in immediate vicinity of the examined area. Sensitivity of transvaginal sonography was found to be 96%, the specificity reached 88%, the positive predictive value 89% and the negative predictive value 95%(35). Intrauterine gestational sac surrounded with double ring with clear embryonic echo is considered to be strong evidence against ectopic pregnancy because heterotopic, pregnancy (intrauterine and ectopic), coincide rarely, but should not be so easily ignored, especially in the patients undergoing some of the methods of assisted reproduction (36).

Intrauterine sonographic findings in women with ectopic pregnancy are variable. These include:

1. Empty uterus, with or without increased endometrial thickness,
2. Central hypoechoic area, or a sac like structure inside the cavity– the so called pseudogestational sac, and
3. Concurrent intrauterine pregnancy.

Early intrauterine pregnancy and recent spontaneous abortion may present themselves on transvaginal sonography with empty uterus and endometrial layer variable in thickness (3). Therefore, they are considered suggestive signs. Pseudogestational sac can be demon-

strated in 10 – 20% of patients with ectopic pregnancy (3) as a mixed echo pattern of endometrium that results from a decidual reaction, fluid, or both. Careful examination of the uterine cavity usually allows a reliable distinction to be made between the pseudogestational sac and normal gestational sac. The pseudogestational sac is detected in the middle of the uterine cavity, its shape changes, owing to myometrial contractions. In differentiating a real gestational sac from a pseudogestational one, transvaginal color and pulsed Doppler ultrasound proved to be very useful.

Adnexal sonographic findings in women with ectopic pregnancy are variable. Gestational sac located inside adnexa with clear embryonic echo and heart activity directly proves ectopic pregnancy, but is seen in only 15 – 28% of the cases. Less rare is visualization of an adnexal gestational sac with or without embryonic echo (without heart action) (37). Such a finding is detected in 46 – 71% of reported cases if tube is unruptured (38), while the most common finding is an unspecific adnexal tumor.

Accurate ultrasound diagnosis of ectopic pregnancy depends strongly on examiner's experience. Adnexal abnormalities may be difficult to identify because of confusion with loops of bowel or other pelvic structures (39).

There are four adnexal structures that may resemble an ectopic pregnancy and should be correctly identified (40). One is the corpus luteum, which is eccentrically located within the ovary, surrounded by ovarian tissue and possibly creating the impression of a sac – like structure. About 85% of ectopic pregnancies are formed on the same side as the corpus luteum (41). This is important to bear in mind while trying to distinguish tubal pregnancy from the ipsilateral corpus luteum. Corpus luteum is found in the ovary and its echogenicity is slightly (or at times even substantially) lower than that of trophoblastic tissue of the tubal ring. Furthermore, hemorrhagic corpus luteum usually shows a hypoechoic rather than a cystic central region (42). Other three conditions than need to be correctly differentiated from an ectopic gestation are a thick – walled ovarian follicle, the small intestine, and tubal pathology conditions, such as hydrosalpix containing fluid.

Using the protocol of combination of clinical examination, serum beta hCG assay and transvaginal ultrasound examination it is possible to diagnose ectopic pregnancy with a sensitivity of 100% and specificity of 99% (43).

Another problem in detection of an ectopic pregnancy in adnexal region arises in patients undergoing assisted reproductive procedures or simple hormonal superovulation. Besides the increased risk for ectopic pregnancy in these patients, a large number of artificial corpora lutea will be seen that resemble the tubal ring of an ectopic pregnancy. Sometimes cystic adnexal masses (ovarian cystadenoma, cystadenofibroma, endometrioma, teratoma and pedunculated fibroids) may also rise differential diagnostic problems.

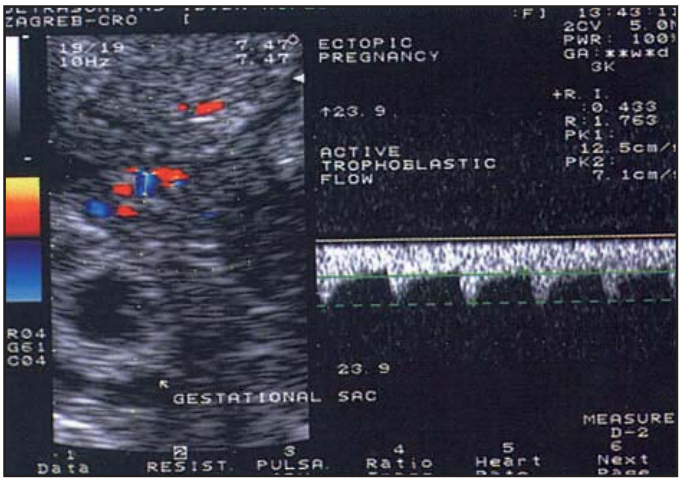
Free intraperitoneal fluid is seen in 40 – 83% the women with ectopic pregnancy, but also in up to 20% of normal intrauterine pregnancies (38). In case of tubal abortion echogenic echoes suggesting the presence of blood clots are demonstrated, while tubal rupture is associated with a homogeneous, hypoechoic retrouterine echo that represents blood collection. The possibility of an ectopic pregnancy increases if the amount of fluid is moderate to large, but the absence of blood does not exclude its diagnosis.

Serial serum beta hCG assay may rise a suspicion on ectopic pregnancy at a very early gestation, while transvaginal ultrasound scan may not be able to demonstrate the site of the pregnancy. Under these circumstances sometimes it is necessary to perform laparoscopic examination to exclude the possibility of ectopic pregnancy. However, even laparoscopic examination may not be able to achieve a precise diagnosis, especially when the ectopic pregnancy is very small or when there are co-existing pathologies such as hydrosalpinges, adhesions or fibroids. Some reports demonstrated that laparoscopic ultrasound can facilitate the diagnosis of the site of ectopic pregnancy intraoperatively, even if it is as small as 3,9 mm (44). The number of negative laparoscopies can be decreased and repeat laparoscopy avoided. Therefore, laparoscopic ultrasound should be used when the site of ectopic pregnancy cannot be determined or is obscured by other pathologies during laparoscopic examination.

Color Doppler facility

Ultrasound machine with color Doppler facility is an excellent guide in search for blood flow signals within the entire pelvis. The color flow pattern associated with ectopic pregnancy is variable. It usually presents randomly dispersed multiple small vessels within the adnexa (Figure 1), showing high-velocity and low impedance signals (RI = 0.36 0.45) clearly separated from the ovarian tissue and corpus luteum. The sensitivity of transvaginal color and pulsed Doppler in diagnosis of ectopic pregnancy reported in several studies ranges from 73 – 96%, and specificity from 87 – 100% (3, 4, 38, 45).

Figure 1. Transvaginal color Doppler imaging of ectopic pregnancy. Note color Doppler signals indicative of invasive trophoblast (left). Pulsed Doppler waveform analysis (right) demonstrates low resistance index (RI = 0.43).

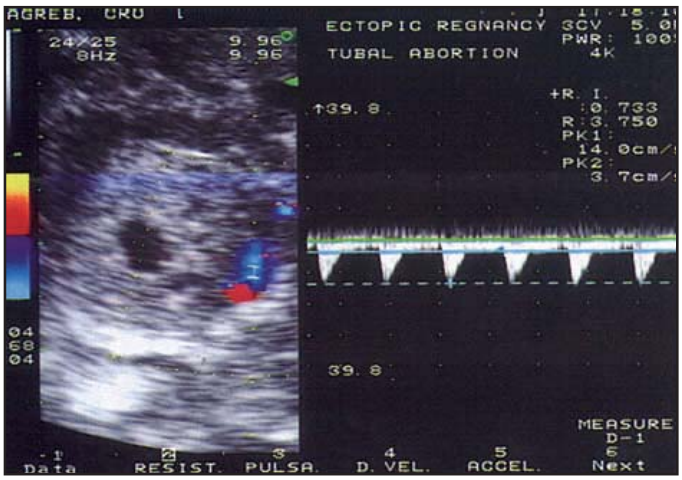


Visualization of ipsilateral corpus luteum blood flow may aid in diagnosis of ectopic pregnancy. The RI of luteal flow in the cases of ectopic pregnancy has been reported to be 0.48 ± 0.07, which is between the values of the non-pregnant women (0.42 ± 0.12) and those with normal early intrauterine pregnancy (0.53 ± 0.09) (46). In majority of patients with proven ectopic pregnancy, luteal flow is detected on the same side as the ectopic pregnancy. This observation could be used as a guide in searching for ectopic pregnancy.

The between-side difference in tubal artery blood flow can also be documented. There is a significant increase in the tubal artery blood flow on the side of tubal gestation. The mean reduction of the RI on the side with the ectopic pregnancy compared to the opposite side was 15.5% (4). These changes appear to be due to trophoblastic invasion, and show no dependence on gestational age. Bright color

on the screen is due to very high speed of the peritrophoblastic blood flow and low impedance. It should be stressed out that the patients with tubal abortion demonstrate significantly higher vascular impedance of peritrophoblastic flow (RI > 0.60), and less prominent color signals (Figure 2).

Figure 2. Gestational sac measuring 12 mm is visualized in the left adnexal region. Color Doppler depicts a small area of angiogenesis characterized by a high resistance index (RI = 0.73). This finding is indicative of tubal abortion.



The main diagnostic importance of transvaginal color and pulsed Doppler is in differentiating the nature of non-specific adnexal masses. Doppler blood flow indices in the uterine, spiral arteries and corpus luteum arteries in ectopic and intrauterine pregnancies showed that the mean uterine and spiral artery RI decreased with increased gestational age of the intrauterine pregnancies, but remained constantly high in ectopic pregnancies (47). The peak systolic blood flow velocity in the uterine artery increased with increasing gestational age in intrauterine pregnancies, and the values were significantly higher than in ectopic pregnancies (48). The difference in peak systolic velocity reflects a decreased blood supply to the ectopic pregnancy. Intrauterine gestational sac shows prominent peritrophoblastic vascular signals (RI = 0.44 – 0.45), while pseudogestational sacs do not demonstrate increased blood flow (RI>0.55). It has been suggested that velocities below 21 cm/s are diagnostic for pseudogestational sac and can successfully rule out trophoblastic flow of a normal intrauterine pregnancy (49).

The intravascular ultrasound contrast agent has a recognizable effect on Doppler ultrasonographic examination of the adnexal circulation. It appears to be helpful when the finding in color flow imaging is ambiguous. The use of the contrast agent may also facilitate localization of trophoblastic tissue in hemorrhagic adnexal lesions (50).

As with other diagnostic methods, transvaginal color and pulsed Doppler studies include both, false-positive and false-negative findings. A false-positive diagnosis arises predominantly from the corpus luteum, but in exceptional cases some adnexal lesions may mimic ectopic pregnancy. A false-negative result may arise from technical inadequacy, lack of experience or patients' non-compliance. The other possibility of fault diagnosis is non-vascularized ectopic gestation, as these are associated with low beta hCG values.

Some authors compared technical errors with improper setting of color flow parameters (51). The color velocity scale, color priority, color gain, color sensitivity and color wall filter should be adjusted to optimize color flow information. Technical errors may result in false diagnosis of ovarian torsion, malignancy and ectopic pregnancy. The diagnosis of ectopic pregnancy still remains a challenge to the clinician despite advances in ultrasound and biochemical technology. Frequently the diagnosis remains uncertain until laparoscopy or D&C are performed. With the increasing tendency towards conservative therapy, the distinction between ectopic pregnancies that will resolve spontaneously and those that will rupture is essential (52). Usually patients without acute symptoms and with declining beta hCG values are treated conservatively (53). However, secondary ruptures have been reported in patients with low initial beta hCG concentrations (54). The differentiation between viable ectopic pregnancies with trophoblastic activity and dissolving tubal abortions could facilitate the decision to proceed with conservative or operative treatment.

After implantation in the mucosa of endosalpinx, the lamina propria and then the muscularis of the oviduct, the blastocyst grows mainly between the lumen of the tube and its peritoneal covering (55). Growth occurs both parallel to the long axis of the tube and circumferentially around it. As the trophoblast invades surrounding vessels, intensive blood flow and/or intraperitoneal bleeding occur. The intensive ring of vascular signals could be a criterion for viability of an ectopic pregnancy that can be determined rapidly and easily and seems to be independent of beta hCG values (56). In patients with a viable ectopic pregnancy who demand a conservative treatment, this method could provide an aid, in addition to beta hCG values; for supervising the efficiency of treatment, especially in those cases where beta hCG levels slowly normalize. In this way duration of hospitalization could be shortened, the patients uncertainty diminished, and the cost of the treatment reduced. In cases of persisting high beta hCG levels after operative removal of the ectopic, color Doppler sonography can provide evidence for the presence of viable trophoblast remnants. On contrary, in asymptomatic patients with hypoperfused and/or avascular ectopic gestational sac and decreased values of beta hCG expectative treatment can be established.

3D Ultrasound in the assessment of tubal ectopic pregnancy

Three-dimensional (3D) ultrasound technology offers some advantages over conventional two-dimensional (2D) sonographic imaging (57, 58). Modern systems are capable of generating surface and transparent views depicting the sculpture-like reconstruction of surfaces or the transparent images structure's content.

Planar mode tomograms are helpful in distinguishing the early intraendometrial gestational sac from a collection of the fluid between the endometrial leaves (pseudogestational sac).

A prospective follow up study was conducted in order to evaluate the potential utility of 3D ultrasound to differentiate the intrauterine from ectopic gestations (59). Fifty-four pregnancies with a gestational age < 10 weeks and with an intrauterine gestational sac < 5 mm in diameter formed the study group. The configuration of the endometrium in the frontal plane of the uterus was correlated with pregnancy outcome. After exclusion of three patients with a poor 3D image quality, the endometrial shape was found to be asymmetrical with regard to the median longitudinal axis of the uterus in 84% of intrauterine pregnancies, whereas endometrium showed symmetry in the frontal plane in 90% of ectopic pregnancies. Intrauterine fluid accumulation may distort the uterine cavity, thus being responsible for false-positive, as well as false-negative results. The evaluation of the endometrial shape in the frontal plane appeared to be a useful additional mean of distinguishing intrauterine from ectopic preg-

nancies, especially when a gestational sac was not clearly demonstrated with conventional ultrasound. Similarly, preliminary data of other authors suggested that 3D sonography is an effective procedure for early diagnosis of ectopic pregnancy in asymptomatic patients before 6 weeks of amenorrhea (60).

The possible use of 3D power Doppler is the monitoring of the vascularity of ectopic pregnancy. The hypoperfusion, quantified by indices of vascularity (VI) and flow (FI), could indicate that the ectopic pregnancy is spontaneously being resolved, and that laparoscopy should be postponed. This way, the conservative approach to ectopic pregnancy would rely on more precise and easily obtainable data. Vice versa, in case of hyperperfusion, the patients should be subjected to laparoscopy or medical treatment immediately.

Shih and colleagues (61) described the use of 3D color/power angiography in two cases in which an arteriovenous malformation of mesosalpinx was diagnosed following involution of an anembryonic ectopic gestation. The diagnosis of arteriovenous malformations has traditionally been made by arteriography. Recently, it has also been diagnosed by non-invasive methods such as contrast enhanced CT, MRI and color Doppler ultrasound. The advantage of 3D reconstruction of color/power angiography images is better spatial and anatomic orientation and quick demonstration of the vessels, usually within one minute, especially in the areas where complex structures are present. Therefore, unlike MRI, digital subtraction angiography or contrast enhanced CT, 3D color/power angiography allows the physician to examine vascular anatomy immediately and without radiation exposure.

Most tubal gestations are not ongoing viable gestations. They are usually in the involutional phase of abortion within a confined area which results in the extrusion of products of conception through a ruptured site or fimbriae. In the two reported cases, the serum assays of beta hCG in both patients increased to significant levels which precluded intrauterine missed abortion (61). Besides, there were neither retained products of conception in utero nor heavy vaginal bleeding (indicating process of abortion in progress) prior to the diagnosis of arteriovenous malformation. Therefore, authors speculated that there might be an ectopic gestation occurring somewhere, although they could find only a pelvic arteriovenous malformation rather than an adnexal gestational sac.

The major difference between uterine implantation and tubal gestation is that endosalpingeal stroma usually falls to undergo decidualization. The chorionic villi of the tubal implantation may than invade into the tubal wall and mesentery (mesosalpinx) more directly and rapidly. The vascularization within the ectopic pregnancy is an analog of placenta increta (62). In such situations cytotrophoblast may invade the contiguous artery and vein of mesosalpinx with destruction of these vessels' walls, and thus may induce an arteriovenous malformation in situ or nearby. Possibly, the secretion of angiogenic factors (by trophoblast) and the increasing afterload of an arterioventricular shunt existing in the tubal gestation can induce the rapid growth of a small pre-existing congenital arteriovenous malformation. However, two unusual cases of adnexal arteriovenous malformations associated with "vanishing" ectopic gestation where congenital etiology seemed unlikely have also been reported (61). B-mode ultrasound and color Doppler provided information on the hemodynamics of the vascular tumor and led to the diagnosis of arteriovenous malformation. Three-dimensional color/power angiography further improved understanding of the complex vascular anatomy and refined the diagnosis.

Even though the exact role of 3D ultrasound in the pathology of early pregnancy is yet to be established, a promising results of already published papers are encouraging. Unlimited numbers of sections are easily obtained without the need for excessive manipulation with the probe. Additional progress has been made, owing to the permanent possibility or repeated analysis of previous stored 3D volumes and Cartesian elimination of surrounding structures and artifacts. Three-dimensional reconstruction of stored image without any degradation is the most impressive benefit of 3D scanning.

OTHER SITES OF IMPLANTATION

About 5% of ectopic pregnancies implant in sites other than the tubes (1). These are at times more difficult to detect and some, owing to strategic sites of implantation, may cause rupture, significant bleeding and higher morbidity and mortality than the tubal gestations.

Interstitial pregnancy occurs in 1.1 – 6.3% of all ectopic pregnancies (1, 63). This location of ectopic pregnancy usually occurs following in vitro fertilization (IVF) and previous salpingectomy (63), but in most cases there are no apparent risk factors. Interstitial pregnancy clinically presents with abdominal pain and a tender asymmetrically enlarged uterus. The major problem of this location lies in late diagnosis, because it is commonly diagnosed after the rupture of the cornu has occurred and this may result in massive hemorrhage. Previously, interstitial pregnancies were diagnosed only at laparotomy following the rupture. For the reason of major hemorrhage, hysterectomy rate was as high as 40% (60). In recent years, the routine use of ultrasound for the assessment of women with early pregnancy complications has enabled a non-invasive diagnosis of interstitial pregnancy to be made. Earlier diagnosis made before serious complications, allows the use of more conservative management, such as medical treatment or laparoscopic surgery.

A viable interstitial pregnancy may occasionally be misinterpreted as a normal intrauterine pregnancy. Therefore, it is important that strict diagnostic criteria are used in every case (64):

1. empty uterine cavity, and
2. chorionic sac that is seen separately and more than 1 cm from the most lateral edge of the uterine cavity and surrounded by a thin myometrial layer.

It is worth to mention that approximately 15% of patients with interstitial pregnancy have heterotopic pregnancy (64). In these cases, intrauterine findings may be misleading and should be interpreted with caution, rather than being used as primary diagnostic criterion. Visualization of the interstitial part of the tube in close proximity of the endometrium and depiction of the trophoblastic tissue improves the diagnosis of interstitial pregnancy (65). It also confirms that pregnancy is located outside the uterine cavity, facilitating the differential diagnosis between an interstitial pregnancy and unusual forms of intrauterine pregnancy such as angular pregnancy or pregnancy in the cornu of an anomalous uterus. This sign is particularly helpful in women with small intramural fibroids located in vicinity of the interstitial part of the tube, which may be misinterpreted as a solid interstitial pregnancy (66). In women with fibroids, the intramural part of the tube is displaced and can be visualized bypassing the mass, thus preventing the false-positive diagnosis of the interstitial pregnancy. Color Doppler facilitates the diagnosis of a cornual pregnancy by exposing low resistance peritrophoblastic flow.

Three-dimensional ultrasound has the advantage of providing views of the uterus, which can rarely be obtained by conventional 2D ultrasound scan (67). In the coronal section, the position of the

interstitial pregnancy in relation to the uterine cavity could be studied in detail. Visualization of the proximal section of the interstitial tube is facilitated, which increases diagnostic confidence (65). It is believed that 3D ultrasound is a helpful diagnostic tool in women with suspected interstitial pregnancy and should be considered in the cases where the diagnosis is not certain on conventional 2D transvaginal ultrasound scan (68).

Most cornual/interstitial ectopic pregnancies are treated by laparoscopy and laparotomy using various surgical procedures (excision, suturing, etc.). Lately, transvaginal sonographic puncture and local injection of methotrexate, has been used to treat both viable and non-viable interstitial pregnancies (64, 65). There have been very few reported side-effects after treatment with low-dose local injection of methotrexate (69). Data reported in the literature suggest the superiority of local therapy, with regard to both safety aspect and the success rate. In general, a likely explanation for the increased effectiveness of local injection is in higher concentration of therapeutic agent achieved in the target tissue. Although absorption of methotrexate into the circulation occurs after both local and systemic administration, a lower dose of methotrexate is used locally, leading to lower systemic levels and therefore fewer side-effects (70). Color Doppler plays an extremely important role providing an aid in approaching the cornual pregnancy from the medial aspect and traversing the thicker myometrial layer so rupture or bleeding are less likely to occur (71). In these cases, color Doppler guidance during the instillation of methotrexate enables better visualization of blood vessels and avoidance of intraprocedural complications.

Viable heterotopic/interstitial pregnancies are often treated by local injection of potassium chloride, as this is not teratogenic. All six reported cases of heterotopic pregnancies in the literature were successfully treated in this way, with three (50%) intrauterine pregnancies progressing normally to full term (4).

Expectant management of the interstitial pregnancy has also been reported (64, 66). All three non-viable interstitial pregnancies managed in this way were resolved spontaneously without any need for intervention. Expectant management can therefore, be useful option in selected cases.

Cervical pregnancy is defined as the implantation of the conceptus below the level of the internal os. It is the rare condition that occurs in one in 50.000 (4). Intrauterine adhesions, uterine anomalies, previous Cesarean sections, fibroids, previous therapeutic abortions and IVF treatment have all been associated with cervical implantation. Traditionally the diagnosis of cervical pregnancy was based solely on clinical findings and history reports after hysterectomy. Therefore, it is likely that only the most severe cases were diagnosed, and a number of cervical pregnancies went undiagnosed or were treated as incomplete miscarriages. In the past two decades, ultrasound has become the method of choice for diagnosis of early pregnancy disorders and certainly contributed to the recent increase in number of reported cervical pregnancies.

The diagnosis of cervical pregnancy can be made on the following criteria:

1. No evidence on intrauterine pregnancy,
2. An hour glass uterine shape with ballooned cervical canal,
3. Presence of a gestational sac or placental tissue within the cervical canal, and
4. Closed internal os.

Early diagnosis may also explain the milder clinical symptoms and better prognosis of cervical pregnancy today as compared to pre-ultrasound era.

Transvaginal ultrasound approach has become the accepted standard for the examination of patients with suspected early pregnancy abnormalities. Apart from providing superior images of pelvic anatomy, addition of color Doppler enables simultaneous visualization of the pelvic blood vessels. The level of the insertion of the uterine arteries may be used to identify the internal os and thus facilitate the diagnosis of cervical pregnancy (71). The extensive vascular blood supply to the trophoblastic tissue originating from the adjacent maternal arteries at the implantation site (within the cervix) is easily visualized by transvaginal color Doppler. The products of conception in transit through the cervix after the failure of a normally implanted pregnancy are detached from their implantation site and maternal vascular supply. It is therefore impossible to detect any peritrophoblastic blood flow in these cases (72). Conversely, even a small amount of placental tissue in a true cervical pregnancy remains highly vascularized on color Doppler examination (73). This facilitates the differential diagnosis between the cervical pregnancy and incomplete miscarriage. Color Doppler analysis may also improve selection of the patients for primary surgical removal of cervical pregnancy and assist in planning D&C following medical treatment. It is necessary to stress out the potential of 3D sonography in diagnosis of cervical gestation: better anatomic orientation and multiplanar sections of the investigated area.

Local injection of methotrexate or potassium chloride appears to be most effective way of treating an early viable cervical pregnancy regardless of the gestational age. There are no data on the use of local injection in non-viable pregnancies, and it is uncertain whether the treatment would be as effective as in viable pregnancies. Systemic treatment in these cases is simple and highly effective and local injection would offer a very little advantage.

The regiments and dosages of methotrexate used for systemic therapy have varied considerably. There is no clear correlation between the dose and therapeutic success, and it is therefore logical to use as little methotrexate as possible to minimize side-effects. The usual regiment should be two intramuscular injections of 1 mg/kg methotrexate followed by folic acid. For local injection, 25 mg methotrexate into gestation sac appears to be sufficient. Potassium chloride 3 – 5 mEq is equally successful and less likely to cause side-effects (4).

The place of surgery should be limited to those cases where medical treatment has failed. Dilatation and curettage in combination with cervical cerclage or the insertion of a Foley catheter is probably the best choice for a general gynecologist and is as effective as more complicated and expensive methods for the prevention of uncontrollable hemorrhage (71).

The sonographic diagnosis of **ovarian pregnancy** is extremely difficult to establish. It has been calculated that ovarian pregnancy accounts for less than 3% of ectopic pregnancies (1, 2). The sonographic diagnosis is made upon the finding of a hyperechoic trophoblastic ring detected within ovarian tissue, and the fact that it is impossible to separate the ectopic gestational sac from the ovary by transabdominal pressure from either examiner's hand or transvaginal ultrasound probe (2). Color Doppler facilitates detection of the peritrophoblastic flow, which can speed up the entire diagnostic procedure.

Intra-abdominal pregnancy is a rare condition, constituting only 1% of all ectopic gestations (74). Its complications, however, can be devastating. These include massive hemorrhage due to disseminated intravascular coagulation (DIC) and placental separation complicating fetal demise, or infection with abscess formation. The outlook for the fetus is even worse, and perinatal mortality may reach 75%

with up to 90% of the surviving infants having serious malformations (75). The diagnosis of the abdominal pregnancy is not easy, especially in the early stages. Characteristically, patients present with abdominal pain, vaginal bleeding and gastrointestinal complaints. Ultrasonography together with beta hCG estimations have made early diagnosis easier. The problem still exists, however, as a patient subgroup with an ambiguous presentation remains (76).

Ultrasound seems to be the most valuable diagnostic tool to localize this rare type of ectopic pregnancy (2). Primary abdominal pregnancy is condition where fertilized egg implants itself directly into the peritoneal surface of abdominal cavity. If, however, an early tubal pregnancy dislodges and aborts into the pelvis, adhering to peritoneal surface, it is termed a secondary abdominal pregnancy through the secondary nidation. The sonographic presentation of abdominal pregnancy is no different from any other ectopic pregnancy, i.e. showing a hyperechoic ectopic gestational sac containing embryonic/fetal structures and extraembryonic structures with or without active heart beats. Oligohydramnion is the rule and there is no uterine mantle around the fetus.

Surgery is a time-honored treatment for abdominal pregnancy following its diagnosis, with placenta left in situ. This is mainly because, in many instances, the placenta is attached to the vital organs or vascular sites, which could be seriously damaged during placental separation. No serious complications occur when it's left in situ (77). An additional important factor is that most abdominal pregnancies are diagnosed relatively late in pregnancy, when the placenta and its area of attachment are larger. Recently, abdominal pregnancies have been diagnosed earlier and in one case the diagnosis was made at 6 weeks of amenorrhea (74). This made it possible for these pregnancies to be removed laparoscopically. The possible advantages of such therapeutic approach include lower morbidity and mortality, as well as better fertility outcome. However, only a limited number of cases of abdominal pregnancy have been reported early in pregnancy and the safety of operative laparoscopy can be guaranteed only in appropriately selected cases (74). Similar cases demonstrate further the importance of first-trimester ultrasound examination in diagnosing early pregnancy complications. The importance of sonographic imaging in cases of acute abdomen in pregnancy cannot be over-stressed (78).

Although there are no available data on the use of color Doppler and 3D ultrasound in this field, we believe that these modalities may add additional information on the implantation site and attachment of the placenta to surrounding structures.

THERAPY

Throughout the years, the treatment of ectopic pregnancy has been emergency laparotomy, including salpingectomy. In order to preserve fertility, alternatives to laparotomy and salpingectomy include observation, laparoscopic removal of ectopic pregnancy and systemic or local use of methotrexate or other feticidal agents. As medical therapy for ectopic pregnancy becomes a common practice, familiarity with its side effects may lead to greater success rates. The decision to abandon medical treatment and proceed with surgery should be based on defined guidelines, such as development of peritoneal signs, decreasing hemoglobin levels, or hemodynamic instability (79).

Methotrexate may be administered systemically (80), locally (81, 82) or in combination. Local application is performed either laparoscopically or transvaginally under ultrasound needle puncture (40). In the latter approach, methotrexate is injected directly into the gestational sac. The success rate of systemic, single-dose methotrexate (83 – 96%) is similar to that of local administration under laparoscopic guidance (89 – 100%), but the success rate of methotrexate under ultrasound guidance seems to be lower (70 – 83%) (83). Local injection of methotrexate under control of color Doppler imaging may increase the success rate (4). The use of color and pulsed Doppler enables visualization of the trophoblastic adnexal flow with high-velocity and low impedance pulsed Doppler (RI<0.40). The needle can be inserted into the area of maximum color signal, which marks trophoblastic invasiveness and vitality.

Pharmacological management of an unruptured, size-appropriate ectopic pregnancy is now an established standard of care. The present protocol recommends systemic use of methotrexate in a single-dose (84). This form of methotrexate has proven to be successful and cost-effective alternative to traditional surgical management of ectopic pregnancy (85). In view of the risk of standard therapy and patients desire for fertility, methotrexate treatment may be a therapeutic alternative in cervical pregnancy as well. Recent reports have affirmed that ectopic pregnancy has become, a medical rather than a surgical disease (2, 4, 69, 72, 79, 83, 84, 86).

Puncture injections are valid and reasonable alternative to a traditional surgical approach, especially in patients with an interstitial, cervical or heterotopic pregnancy. In these particular cases, puncture procedures guided by transvaginal ultrasound can efficiently replace surgical treatment and save the patient from unnecessary hysterectomy.

Early diagnosis is the key to effective non-surgical treatment. Diagnostic algorithms using serial beta hCG measurements and transvaginal ultrasound examinations make definitive diagnosis possible without laparoscopy. As stated before, with help of color Doppler it is possible to identify the activity, invasiveness and vitality of trophoblast. These represent the most important characteristics for making the decision for more selective management of ectopic pregnancy. Three-dimensional ultrasound seems to be an even more effective procedure for early diagnosis of ectopic pregnancy in asymptomatic patients, even before 6 weeks of amenorrhea (59).

Laparoscopic salpingostomy, the surgical gold standard, is an effective therapy in patients who are hemodynamically stable and wish to preserve their fertility. The reproductive performance after salpingostomy appears to be equal to, or better than salpingectomy, but the recurrent ectopic pregnancy rate is slightly higher (3). A variable systemic dose of methotrexate produces outcomes close to those of laparoscopic salpingostomy in similar patients (87). Methotrexate treatment is recommended in the asymptomatic patient with serum beta hCG levels of less than 2000 IU/ml, a tubal diameter of < 2 cm, and absence of fetal heart activity. The patient's understanding of her condition and compliance are mandatory. However, in many cases, ectopic pregnancy does not meet suitable medical criteria and still requires surgery. In cases suspicious of tubal abortion with a high impedance signal (RI>0.55) and beta hCG below 1000 IU/ml, local administration of methotrexate is not advised.

CONCLUSION

The introduction of beta hCG testing and transvaginal ultrasound has changed our approach to the patient suspected of an ectopic pregnancy. Important advantage of the most currently used transvaginal transducers is the ability to perform simultaneous color and spectral Doppler studies, allowing easy identification of the ectopic peritrophoblastic flow. Therefore, color Doppler may be applied

whenever a finding is suggestive of ectopic pregnancy.
Further progress in diagnostic procedures is made with introduction of 3D ultrasound. Transvaginal 3D ultrasound enables the clinician to perceive the true spatial relations and thus easily distinguish the origin of an adnexal mass, while 3D power Doppler allows detailed analysis of the vascularization.
Transvaginal color and pulsed Doppler imaging may be used for detection of the patients with less prominent tubal perfusion, suitable for the expectant management of ectopic pregnancy. It is expected that increased sensitivity of the serum beta hCG immunoassay and the quality of transvaginal B-mode, color Doppler ultrasound and more recently 3D with color and power Doppler facilities will allow even earlier detection and conservative management of ectopic pregnancies. Diagnostic advances are becoming very important since fertility outcomes and number of women attempting to conceive after ectopic pregnancy will further increase.

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