Three-dimensional Ultrasound Imaging in the Diagnosis of Ectopic Pregnancy

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ABSTRACT

Morbidity and mortality of ectopic pregnancy (EP) have been drastically reduced since the first successful surgical removal of a fallopian tube EP in 1884 by Tait. Diagnosis and treatment were revolutionized by the introduction of quantitative serum beta hCG assay, high frequency transvaginal ultrasound (TVS), laparoscopic surgery, and interventional radiology with uterine artery embolization (UAE). In this paper, the focus will be on TVS diagnosis of EP in various locations. With two-dimensional (2D) color Doppler TVS having established itself as state-of-the-art diagnostic tool for EP, it will be discussed whether the additional use of 3-dimensional (3D) TVS facilitates the diagnosis of EP.

Keywords: 3D ultrasound, Color/power Doppler, Ectopic pregnancy, Tomographic ultrasound imaging.

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INTRODUCTION

Ectopic pregnancy has remained a major cause of maternal morbidity and mortality. The incidence of EPs, denominated as the number of EPs per 1,000 pregnancies, varies from 6.4 to 20.7.^{1–3} EP is diagnosed in 6–16% of women seeking help in emergency departments with bleeding and/or pain in the 1st trimester.⁴

Reflecting the impact of socioeconomic factors on public healthcare, mortality rates of EP could be reduced by 50% in industrialized countries, while EP still remains a leading cause of maternal death in Africa and Asia.^{5,6} In 2009, an EP mortality ratio of 0.48 per 1,00,000 live births (0.08% of 100 EP) was established for the USA,³ compared to 1.4–2.79% in Nigeria and Ghana, probably resulting from delayed diagnosis and treatment.⁷ The lack of research productivity concerning EP in low-income countries and their missing presence in international scientific working groups in the field⁸ is another indirect sign that advances in diagnosis and management leading to earlier detection and better treatment of EP have reached developing countries only in urban areas. These advances include the serum beta hCG pregnancy test, TVS imaging, minimal invasive laparoscopic surgery, chemotherapy with methotrexate, and interventional radiology with UAE.

To date, TVS with high-resolution probes is an indispensable tool in any early pregnancy unit. One of its purposes there is to evaluate the spatial relationship of a suspicious mass—possibly representing an EP—to the inner genital organs, which is often difficult for nondynamic imaging such as CT and MRI. In contrast, TVS as a tool for “dynamic” investigation of structures within the pelvis can visualize whether the suspicious mass moves together or independently of ovary or uterus (sliding sign), by exerting gentle pressure with the tip of the US probe. Furthermore, with the tip of the TVS probe located in the topographic center of the pelvis/region of interest (ROI), image quality benefits from the ability to use close-range high frequencies with optimal resolution and image quality. Thirdly, TVS with color-, power-, and HD-flow Doppler technology is able to show increased blood flow in the ROI and to detect typical trophoblast flow characterized by low resistance indices and low velocities, with peak systolic velocity (PSV) greater at and above 20 cm/s, and pulsatility index (PI) lower than 1.⁹

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With serum beta hCG levels of 0–750 U/L at 1 week before the first missed period, and 200–7,000 U/L at 1 week after the first missed period, the threshold for sonographic visibility of the trophoblast is usually reached as early as 5 weeks after the last menstrual period (LMP).¹⁰

The term “visibility threshold” refers to visualization of an intrauterine trophoblast using TVS which is achievable transvaginally already at a serum beta hCG of 1,400 mIU/mL vs 4,500 mIU/mL with transabdominal ultrasound (TUS) probes (Fig. 1).

Given all these improvements, modern TVS has led to a diagnostic paradigm change from “negative for intrauterine GS” or “pregnancy of unknown location” (PUL) to a high percentage of positive identification of the site of the EP. High resolution TVS is able to visualize 75% of all EPs during the first assessment, and even 87–99% of tubal EPs.¹¹ Last but not least, transvaginal 3D ultrasound has created another diagnostic platform, with identification of new, equally efficient ways of diagnosing EP.

HISTORY

The first successful treatment of tubal pregnancy with salpingectomy was described in 1884 by Tait (1845–1899).¹² As a result of improvements of surgical techniques, changing the approach from open salpingectomy to laparoscopy,^{13,14} technological innovations in the field of ultrasonography (Fig. 2)^{15–17} and biochemistry with the production of an antiserum highly specific to the P-subunit of hCG,¹⁸ mortality rates could be reduced from 72 to 90% in 1880–0.14% in

Fig. 1: Trophoblast flow 2 weeks postconception in the endometrium

Fig. 2: First Obstetrics and Gynecology ultrasound publication in "The Lancet" 1958, Prof Ian Donald

1990,^{19,20} and this in spite of a six-fold increase of EP numbers, for example, in the US between 1970 and 1992.²¹

The increasing incidence of EP has to be attributed mainly to the following factors: more common pelvic inflammatory disease (PID) with tubal damage as a result of spreading chlamydia salpingitis,²² ever rising popularity of cesarean section,²³ and general availability and usage of assisted reproduction techniques.²⁴ Most tellingly, one of the first IVF attempts in history in 1976 resulted in an EP.²⁵

EP LOCATIONS

The sites of EP can be divided into two groups: 96% of EPs are found in the fallopian tubes, named after the 16th century Italian anatomist Gabriele Fallopio. The remaining 4% of EPs include uterine, ovarian, and abdominal locations.²⁶ It is this small group of nonfallopian EPs which is mainly responsible for morbidity and mortality: the mortality rate for interstitial pregnancy, for example, was found to be 15 times higher than the mortality rate of tubal ectopic.²⁷

TUBAL ECTOPIC PREGNANCY

The great majority of EPs (96%) implants within the fallopian tube. In 1,800 surgically treated cases, the distribution along the tube was found to be the following: 70% in the ampulla, 12% in the isthmus, and 11.1% fimbrial²⁶ (Fig. 3). Other than the uterus, the fallopian tube has limitations of both vascularization and compliance, which explains that tubal ectopic pregnancies (TEPs) have a lower percentage of viable embryos and rupture earlier, at 6–8 weeks after the LMP, than uterine EPs (12–16 weeks). Under normal circumstances, the tube cannot be visualized by ultrasound. If, however, the tube is dilated by an ectopic trophoblast, this section of the tube becomes visible, and trophoblast flow can be demonstrated using color Doppler. In 70–85% of cases, corpus luteum (C. luteum) and TEP are ipsilateral (Fig. 4).

The best approach to identification of the ectopic trophoblast is therefore visualization of the ovaries and determination of the site of the C. luteum. The next step consists in careful exploration of the surroundings of the ovary containing the C. luteum, looking for an adjacent inhomogeneous mass. Once this mass is seen, gentle pressure with the tip of the probe on the structures between ovary and the mass can provide knowledge whether or not the mass and the ovary are connected (sliding sign). Now color Doppler mode is activated and used to demonstrate C. luteum neoangiogenesis in the ovary, the "ring of fire." The adjacent mass is interrogated in the same way to verify a similar vascular ring signal representing the trophoblast flow. Finally, 3D mode can give an idea of the spatial arrangement of ovary and mass and deliver additional proof that

Fig. 3: Ectopic pregnancy sites and their distribution

Figs 4A to D: Ipsilateral tubal ectopic and corpus luteum

Figs 5A and B: (A) Tubal ectopic pregnancy, multiplanar; (B) Surface rendered 3-dimensional ultrasound with high-density flow Doppler

the mass, now identified as trophoblast, is not part of the ovary, but of the fallopian tube (Fig. 5).

OVARIAN ECTOPIC PREGNANCY

Ovarian ectopic pregnancy (OEP) results from the implantation of the trophoblast into the ovary, which happens in up to 3% of all EPs, or once in 7,000–15,000 pregnancies.²⁶ As per histological evidence, the implantation may occur intra- or extrafollicular;²⁸ however, this classification makes no difference for sonographic appearance and clinical manifestation. Like in other EPs, clinical symptoms may include vaginal bleeding and abdominal pain, with positive pregnancy test. Sonographic indicators for OEP are subtler

than in other EPs. With a positive pregnancy test and the provisional diagnosis “PUL” overshadowing this clinical scenario, successful management depends on the cooperation between the main responsible obstetrician, sonographer, laparoscopic surgeon, and pathologist,²⁹ the first three often being the same person. Ovarian ectopic pregnancy appearance in TVS can be misinterpreted as ovarian endometriosis or as C. luteum, and even during laparoscopy, it usually presents as a hemorrhagic or ruptured C. luteum cyst.³⁰ 3D ultrasound can demonstrate a small hypoechoic mass representing the gestational sac (GS), bulging from the ovarian cortex and being surrounded by a thick hyperechoic ring (“bagel sign”).³¹ The addition of color/power Doppler will highlight trophoblast flow

within this hyperechoic ring and will eventually visualize a “ring of fire” of an adjacent C. luteum graviditatis right next to it. Thus, 3D power Doppler ultrasound is able to establish OEP diagnosis by visualizing ectopic trophoblast and C. luteum within the same ovarian volume.³¹ The interested reader can find excellent images in the publication of Ghi, Banfi, Marconi, Pilu, *et al.* “Picture of the month—three dimensional sonographic diagnosis of ovarian pregnancy.” *Ultrasound Obstet Gynecol* 2005;26:102–104.³¹

UTERINE ECTOPIC PREGNANCIES

All uterine ectopic pregnancies have higher beta hCG levels and higher rates of embryonic viability in common compared to TEP and OEP, which is a limiting factor for the use of methotrexate in uterine ectopic pregnancies.

CORNUAL/INTERSTITIAL PREGNANCY

Cornual/interstitial pregnancy (IEP) the term “cornual” is often used as synonym for “interstitial” EP. Strictly spoken, the cornual pregnancy (1% of all EPs) describes the location of an EP in the horn of a bicornuate or septate uterus, whereas an IEP (2–4% of all EPs) is defined as located in the interstitial or intra-myometrial section of the fallopian tube³² (Fig. 6). In an emergency laparotomy situs, this differentiation may be rather difficult (Fig. 7). This intramural section of the tube may under ideal sonographic conditions and careful

exploration of the 3D volume, for example, by 3D tomographic ultrasound imaging (TUI), be visualized as a hyperechoic thin line in the cornual area. In IEP, the medial section of this line can be seen connecting the apex of the cornual endometrial angle with the medial aspect of the ectopic GS, as the “interstitial line” (Fig. 8).³³

Another sonographic marker for IEP is the “claw sign”.³⁴ The myometrium, separating the central endometrium from the cornual mass in the lateral uterine fundus, forms a “claw” around this mass, with a remaining myometrial mantle of less than 5-mm thickness in the fundal area around the ectopic GS (Fig. 9). Particularly because IEP occurs significantly more frequently after assisted reproduction, a delay of diagnosis and treatment is unfortunately common and one of the reasons for a mortality rate 15 times higher (2–2.5%) than in TEP (0.14%),²⁷ (Fig. 7).

In analogy to the rather ominous naming of the arterio-arterial anastomosis of obturator artery and inferior epigastric artery as “corona mortis”, the severity of hemorrhage in IEP may be explained by the arterio-arterial anastomosis of the tubal branch of the ovarian artery and the uterine artery (Fig. 10).

Next to color Doppler mode for identification of cornual trophoblast flow (Fig. 11), 3D multiplanar (Fig. 9) and 3D tomographic imaging are excellent tools to deliver the decisive proof, which endometrium and trophoblast are separated by a layer of myometrium (Fig. 12).

Various treatment options have been described in the literature for IEP.²⁹ Of our three cases, one was ruptured and required

Fig. 6: Interstitial ectopic pregnancy

Figs 7A and B: (A) Emergency laparotomy situs with ruptured cornual/interstitial ectopic pregnancy; (B) Emergency laparotomy situs with ruptured cornual/interstitial pregnancy

Fig 8: Transvaginal ultrasound sonographic visualization of the interstitial line

Fig. 9: Three-dimensional multiplanar imaging of interstitial ectopic pregnancy. Note the interposition of myometrium in-between endometrium and trophoblast in the C-plane. 3D tomographic imaging of interstitial ectopic pregnancy, with evidence of a myometrial layer which separates trophoblast and endometrium and forms a “claw” around the trophoblast (“claw-sign”)

Figs 10A and B: Vascular supply of interstitial ectopic pregnancy within the anastomosis of uterine and ovarian artery. (A) Power Doppler image; (B) Schematic diagram

Figs 11A and B: Cornual trophoblast flow

Fig. 12: Three-dimensional tomographic imaging

Figs 13A and B: (A) Cornual resection per laparotomy. Situs with distended horn of the uterus containing the ectopic pregnancy; (B) Cornual resection per laparotomy. Demonstration of the embryo within the resected horn

emergency laparotomy with cornual resection. Of the other two, one was managed with laparoscopic cornual resection, the other with laparotomy and cornual resection (Fig. 13).

CESAREAN SCAR ECTOPIC PREGNANCY

Cesarean scar ectopic pregnancy (CSEP) occurs in up to 0.05% of all pregnancies and is found in 0.15% of women who had a previous

lower segment cesarean section (LSCS). In women after at least one LSCS, CSEP accounts for 6.1% of all EPs.³⁵ This rare form of uterine EP is defined by a trophoblast location in the niche of a lower segment cesarean scar, with the GS seen outside of the endometrium and surrounded only by myometrium and scar tissue (Fig. 14).

Clinical symptoms can occur already around 5 weeks post menstruation in form of painless vaginal bleeding. Cesarean scar ectopic pregnancy might be mistaken for an isthmic intrauterine

Fig. 14: Lower segment cesarean section scar pregnancy. B-Mode and power Doppler

pregnancy or an incipient miscarriage of an initially regularly placed intrauterine pregnancy, though an inevitable spontaneous abortion is usually accompanied by lower abdominal cramps. In abortion, TVS presents images of a deformed or collapsed GS and vertical sliding movements of products of conception along the long axis of the lower uterine and cervical segment during uterine contractions (sliding sign) which can be provoked by gentle pressure on the myometrium. In contrast, the ultrasonographic evidence of an immobile trophoblast located atypically in the level of the cesarean scar and surrounded by rich blood flow in 3D power Doppler has to be taken as unmistakable sign of a viable CSEP.³⁶ Demonstration of embryonic heart action within the GS, rather common, given the excellent blood supply in vicinity of the uterine arteries, is additional proof. More differential diagnostic clues will be provided by 3D surface rendering of the uterus in the sagittal axis: the ballooning of the cervix, as typically seen in a cervical pregnancy (see section “cervical pregnancy”), is absent in CSEP. Since the CSEP expands within the cesarean scar niche, the main mass of the GS is not placed centrally in the uterocervical axis but anteriorly of it. Finally, the myometrial layer between GS and Bladder is very thin or absent (Fig. 15).

CERVICAL ECTOPIC PREGNANCY

Cervical ectopic pregnancy (CEP), defined as the implantation of a fertilized ovum in the endocervical canal below the inner cervical os, is a rare condition, with an incidence below 0.1% of all EPs³⁴ (Fig. 16). This ectopic implantation happens to be in the level where the uterine arteries reach the side of the uterus. Clinicians have to be cautioned that clinical and sonographic presentation of miscarriage and cervical pregnancy often have such features in common as early pregnancy vaginal bleeding, speculum examination in both cases revealing an open external cervical os with a fleshy mass protruding,²⁹ a positive serum beta hCG test, and TVS demonstration of a dilated cervical canal with heteroechogenic content. The response however to an attempt of evacuation of alleged “retained products of conception” could be deleterious in a CEP, disrupting placentation, and causing massive hemorrhage and even emergency hysterectomy. On the contrary,

there is also need to differentiate between isthmic pregnancy with intraendometrial implantation just above the inner cervical os, and cervical pregnancy, because of opposite prognosis of the two: while a viable isthmic pregnancy is likely to have a normal outcome, cervical pregnancy—as uterine ectopic pregnancy—has no chances of going to term and implies a high risk of maternal morbidity and mortality due to severe hemorrhage (Fig. 17).

3D vaginal sonography in combination with color Doppler has redefined the sonographic criteria of cervical pregnancy: 3D surface rendering with three orthogonal planes (sagittal, transversal, and coronal) shows an hourglass appearance of cervix, isthmus, and corpus uteri in the reconstructed image. The ballooned cervix contains the trophoblast, clearly located below a constricted isthmus.³⁶ With color/power Doppler mode added, atypically intense blood flow in the cervical area around the trophoblast can be demonstrated³⁷ (Fig. 18). The inclined reader may find further study material online: TheFetus.net.³⁸

ABDOMINAL ECTOPIC PREGNANCY

Against the backdrop of a positive serum beta hCG, the heteroechogenicity of a thickened endometrium, indicating a collection of debris and blood in the uterine cavity, resembles images of retained products of conception with a collapsed GS (pseudosac), in approximately 20% of all EPs.³⁹ It has therefore been argued that in the case of high and/or increasing serum beta hCG, a (diagnostic) curettage could provide histological clues—by demonstrating presence or absence of trophoblast villi within the endometrial tissue—to eventually abandon wrong assumptions of incomplete abortion, and in doing so, help to focus on the search for a PUL.^{40,41} Depending on its location, an abdominal ectopic pregnancy (AEP) can be accompanied by various symptoms, ranging from renal or gallbladder colic to symptoms of appendicitis. In clinically symptomatic PUL, careful transabdominal sonographic exploration of perihepatic and perisplenic spaces, and of the paracolic gutters, is always required to look for and to quantify free fluid, i.e., hemoperitoneum, but also to identify a possible AEP. Besides a good ultrasound equipment, sonographic skills, and

Fig. 15A: (a–d) Lower segment cesarean section scar ectopic pregnancy, 3D power Doppler

Fig. 15B: (Left, Right) Lower segment cesarean section scar ectopic pregnancy, 3D power Doppler

Fig. 15C: (a and b) Lower segment cesarean section scar ectopic pregnancy, laparoscopic situs, and postoperative B-mode image

experience, a high degree of suspicion is needed in dealing with EPs. Abdominal pregnancy sites can be—in decreasing order of frequency—the pouch of Douglas (PoD), mesosalpinx, omentum, spleen, liver, and appendix.^{42,43}

Abdominal ectopic pregnancy occurs as rarely as once in 8,000–10,000 pregnancies and makes up for 1–1.5% of all EPs.^{44,45} Maternal mortality rates are high, which is explained by an often advanced gestational age at discovery, severe hemorrhage at any time in case of placenta separation, and predominance of occurrences in developing

countries with limitations of infrastructure and medical equipment. The following case presentation shall illustrate the specific challenges of an AEP (Fig. 19).

SUMMARY

Transvaginal high frequency 2D/3D ultrasound with color Doppler has emerged as the most important tool in diagnosing an EP. Applied in a dynamic real-time study of the pelvic organs, the TVS

Figs 16A and B: B-Mode plus power Doppler, cervical ectopic pregnancy

Figs 17A and B: Sonographic differences between: (A) Cervical ectopic; (B) Supraisthmus pregnancy

Fig. 18: Power Doppler 2D and 3D visualization of cervical ectopic pregnancy

probe becomes the “seeing finger” of the examining clinician. The need of an experienced operator for the ultrasound machine in this encounter should not be conceived as disadvantage. If this operator is the gynecologist in charge himself, he may find the answers to all his diagnostic questions, while interrogating the ROI methodically using all diagnostic modalities from 2D over color Doppler to 3D and 3D color Doppler. Tomographic imaging with postprocessing of

volumes in different planes can be very useful as shown in section “interstitial ectopic pregnancy”. Nevertheless, in analogy to CT and MRI, offline analysis of TVS generated 3D data sets does not match with the performance of 2D–3D real-time examination incorporating anamnestic data and clinical information during scanning.⁴⁶ Again: the excellent diagnostic potential of TVS, with 3D mode added, is based on interactive dynamic real-time examination.⁴⁷

DIAGNOSTIC HINTS AND PITFALLS

Corpus Luteum

The C. luteum, also called “the great imitator,” can mimic not only ovarian malignancy but also an EP. Its prominent vascularity (physiological benign neoangiogenesis) can be easily visualized by color/power/HD flow Doppler as “ring of fire” using a low pulse repetition frequency (PRF). Likewise, the (ectopic) trophoblast, equally capable of neoangiogenesis, exhibits similar features in

color Doppler imaging. It should be well-noted that the majority of fallopian tube EPs is found on the same side as the C. luteum.

Transabdominal Approach

Clinically symptomatic PULs with high and/or increasing serum beta hCG suggest an abdominal pregnancy. Transabdominal ultrasound with high resolution probes is the only way to detect such pregnancies, if they are not located within the small pelvis. Transvaginal ultrasound in cases of suspected EP should therefor

Fig. 19A: (a and b) Case presentation of abdominal ectopic pregnancy

Fig. 19B: Case presentation abdominal ectopic pregnancy

Fig. 19C: (a and b) Case presentation abdominal ectopic pregnancy

Fig. 19D: (a to c) Case presentation of abdominal ectopic pregnancy

always be complemented by TAS, not only for risk classification (free fluid) but also not to miss an AEP.

Pseudosac

As a response to pregnancy hormones produced by an EP, the endometrium proliferates and may bleed. The resulting arrangement of proliferated endometrium with fibrin and serum in between the endometrial layers can mimic a GS within the uterine cavity, termed “pseudosac”. 3D TVS can give additional clues: while a normal implantation is eccentric within the endometrium of either the posterior or the anterior face, a pseudosac is found centrally in between the two endometrial layers. With color Doppler applied, this pseudosac lacks surrounding peritrophoblast flow.

Unexplained Positive Pregnancy Test

When dealing with elevated serum beta hCG levels above the “visibility threshold” in patients with “empty uterus” in TVS, a status after spontaneous abortion, and an EP are the most likely explanatory causes and can be confirmed by follow-up examinations. Should these two have been ruled out, differential diagnosis should be widened to include other possible sources of beta hCG production such as gestational trophoblastic neoplasia (GTN), ovarian germ cell tumors, tumors of the pituitary gland, and nontrophoblastic neoplasms of stomach, liver, pancreas, breast, as well as myeloma and melanoma.⁴⁸

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