

Ectopic Pregnancy and Ultrasound: A Review

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Abstract: First trimester bleeding occurs in up to 30% of all diagnosed pregnancies. Important causes of first trimester bleeding include spontaneous abortion, missed or threatened abortion, ectopic pregnancy, and gestational trophoblastic disease. One of the greatest dilemmas for clinicians is to accurately diagnose the cause of pain or bleeding, and specifically to determine if an ectopic pregnancy exists due to its grave consequences. Ectopic pregnancy occurs in almost two percent of all reported pregnancies in the United States and is the leading cause of pregnancy-related death in first trimester. When an early pregnant patient is identified who has bleeding or pain, it is crucial step to determine where the pregnancy is located. Ultrasound as a first line diagnostic tool offers an excellent opportunity for pregnancy localization. The use of the beta subunit of human chorionic gonadotropin (beta-hCG) quantification is a valuable adjunct to help determine the course and possible outcome of an early pregnancy. The goal should be to preserve the health and future reproductive capabilities of our patients.

Key words: Ectopic pregnancy, ultrasound, beta-hCG, Doppler.

Learning objectives

- To know the accuracy of ultrasound in the diagnosis of ectopic pregnancy
- To understand the use of the beta-hCG subunit in the context of ultrasound.

INTRODUCTION

An ectopic pregnancy is any pregnancy that occurs outside the uterine cavity; and is a significant cause of morbidity and mortality in women. It occurs in nearly 2 percent of US pregnancies and is the leading cause of pregnancy-related death in first trimester. Ruptured ectopic pregnancies account for 10 percent of all maternal deaths. In addition, the incidence of ectopic pregnancies in the United States rose from less than 0.5 percent of all pregnancies in 1970 to 2 percent in 1992 and this number may be rising.¹⁻³

Risk factors associated with ectopic pregnancy include prior ectopic pregnancy, fallopian tube surgery, prior upper genital tract infection, and infertility especially if associated with assisted reproductive technologies. A more recent review⁴ summarizes the risks (Table 1).⁴⁻¹⁰ The clinician's challenge is to obtain an early diagnosis of ectopic pregnancy so that morbidity and mortality may either be eliminated or minimized.¹¹

With the increasing use of transvaginal sonography (TVS) since 1987 and more accurate beta-hCG tests, the mortality from ruptured ectopic pregnancies has been significantly reduced from a death rate of 35.5/10,000 ectopic pregnancies in 1970 to 3.8/10,000 in 1989.¹¹ High-resolution transvaginal ultrasound detects the gestational sac of an intrauterine pregnancy (IUP) by 32 to 35 days of gestation.¹² Early detection before rupture of the fallopian tube can offer the opportunity for outpatient treatment, reducing the risk of complications and impaired future fertility. A delay in diagnosis might result in tubal rupture, subsequent intra-abdominal hemorrhage, need for laparotomy, blood transfusion, and death.

Ultrasound Alone

Multiple studies have been performed to determine what criteria should be used to positively identify with the greatest accuracy, a woman's risk of having an ectopic pregnancy. The use of ultrasound alone has a sensitivity of nearly 100% in diagnosing an intrauterine pregnancy as early as 5.5 gestational weeks.^{13,14} Brown *et al* in 1994 found that using a less strict criteria of transvaginal sonography visualization of any adnexal mass other than a simple cyst had high specificity (98.9%) and positive predictive value (96.3%) and a better sensitivity (84.4%) and negative predictive value (94.8%) than using other ultrasound criteria such as an extrauterine gestation, gestational sac, yolk sac, or "tubal ring" sign in diagnosing an ectopic pregnancy (Figs 1 and 2).¹⁵ This is felt to be true due to the fact that only 20 to 25% of ectopic pregnancies present with visualization of an extrauterine embryo (Figs 3 to 5). In addition, the presence of

Table 1: Risk factors for ectopic pregnancy⁴⁻¹⁰

	Adjusted OR (95% CI)	OR (95% CI)
Previous tubal surgery	4.0 (2.6-6.1)	4.7-21.0
Infertility (risk increases with length of infertility)	2.1-2.7	2.5-21.0
Previous genital infection confirmed	3.4 (2.4-5.0)	2.5-3.7
Previous miscarriage	3.0 (> 2)	—
Previous induced abortion	2.8 (1.1-7.2)	—
Past or ever smoker	1.5 (1.1-2.2)	2.5 (1.8-3.4)
Current smoker (risk increase with amount smoked per day)	1.7-3.9	2.3-2.5
Age 40 years and older	2.9 (1.4-6.1)	—
Intrauterine device use (> 2 years)	2.9 (1.4-6.3)	4.2-45.0
Previous IUD	2.4 (1.2-4.9)	—
Sterilization	—	9.3 (4.9-18.0)
Previous ectopic pregnancy	—	8.3 (6.0-11.5)
Documented tubal pathology	3.7 (1.2-4.8)	2.5-3.5
More than one sexual partner	—	2.1-2.5
Diethylstilbestrol exposure	—	5.6 (2.4-13.0)

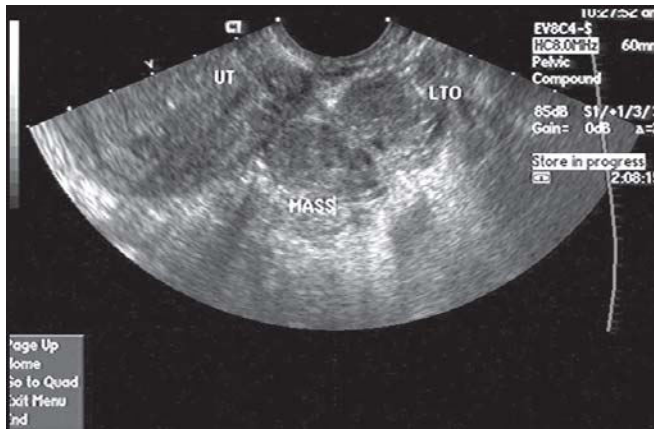


Fig. 1: Transvaginal sonography of the “blob sign” seen as a heterogeneous adnexal mass adjacent to a normal left ovary and situated in-between the uterus

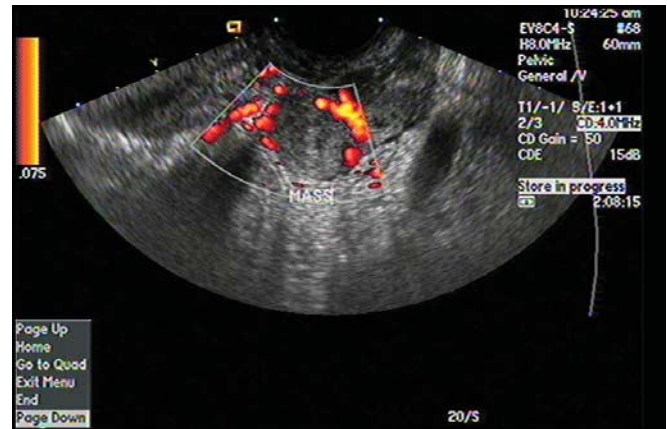


Fig. 2: Same patient as Figure 1 with power Doppler flow demonstrating the “tubal ring” sign surrounding the adnexal mass/ectopic pregnancy

a pseudosac has also come into question as a criterion for presumed ectopic pregnancy. Ahmed’s study in 2004 showed that a number of patients with a pseudosac did not have an ectopic pregnancy, and conversely, a number of patients with an ectopic pregnancy did not have a pseudosac.¹⁶

A brief mention should be made on heterotopic, cervical and abdominal pregnancies. 95% of all ectopic pregnancies are tubal in location but 2% are interstitial or cornual, 2% are ovarian and 1% are cervical or abdominal.¹⁷ There are now more reports in the literature on cesarean section scar pregnancies as well as heterotopic pregnancies which also have increased (0.3 to 1% of all pregnancies) due to assisted reproductive technologies.¹⁸⁻²⁴ Women who have histories that might increase their

risk for these types of pregnancies should have special scrutiny during ultrasound as they tend to be diagnosed later in gestation.

Serum Beta-hCG Alone

Following serial beta-hCGs alone has also been studied and the previously accepted 15% decline in 7 days (which is used to follow treated ectopic pregnancies) is probably too slow of a decline to be considered normal in a spontaneous miscarriage or tubal miscarriage.²⁵ Barnhart found the slowest rate of decline—described by the 95th percentile—ranged from 21 to 35% decline in 2 days and 60 to 84% in 7 days.²⁶ This led the authors to conclude that for patients whose pregnancies were expected to resolve spontaneously, a 15% decline in 7 days



Fig. 3: Transabdominal sagittal view of the uterus with a cul-de-sac mass (ectopic pregnancy)

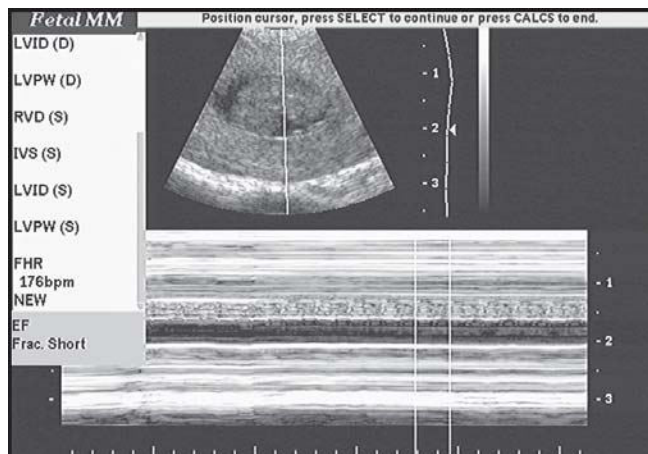


Fig. 5: Same patient as Figures 3 and 4 ultrasounds with live embryo's fetal heart tone demonstrated

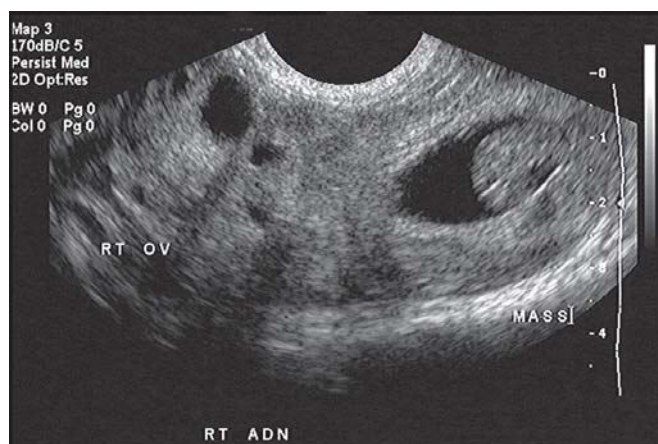


Fig. 4: Transvaginal view of the same patient as Figure 3 with a normal right ovary and adjacent ectopic pregnancy with live embryo

was slower than the newly graphed expected rate and should prompt intervention to eliminate the possibility of an ectopic pregnancy.

Most recently, the study of beta-hCG levels in a large population has shown that the slowest increase associated with a viable intrauterine pregnancy is 53% after 48 hours rather than the traditionally quoted 66% rise in 48 hours.²⁷

COMBINING ULTRASOUND AND BETA-hCG LEVELS

Due to the above controversies and fallibilities of using ultrasound alone or serum testing alone, many authors now conclude that a combined approach of using measurements of beta-hCG and incorporating transvaginal sonography may have an improved sensitivity of 97% and 96% specificity which could significantly decrease the need for invasive tests and unnecessary laparoscopies/laparotomies.^{4,28,29}

The advent of highly sensitive testing of serum beta-hCG levels has led us to accept that when the level was greater than or equal to 2,000 mIU/ml and an intrauterine pregnancy was not visualized by transvaginal sonography, an ectopic or nonviable pregnancy could be safely and accurately diagnosed.³⁰

This assumption has been put to the test, since Barnhart retrospectively looked at women who had presumed diagnoses of ectopic pregnancy due to a beta-hCG above 2000 mIU/ml without evidence of an intrauterine pregnancy by ultrasound or due to an abnormal rise or fall of serial beta-hCGs.³¹ They found that the presumed diagnosis of ectopic pregnancy was incorrect in nearly 40% of the cases, especially in women with hCGs above the discriminatory zone and no IUP visualized by ultrasound. These women had an equal chance of having a miscarriage or an ectopic pregnancy. Women who had plateaus in the hCG below the discriminatory zone were more likely to be diagnosed with an ectopic pregnancy, with the presumed diagnosis being wrong 30% of the time.

There is also some debate over the so-called discriminatory level at which an intrauterine pregnancy should be visualized by transvaginal sonography.²⁸ Using the combined approach, this level may vary. It has been suggested that in the absence of a mass or fluid in the cul-de-sac, the discriminatory level of 2000 mIU/ml should be utilized and where there is the risk for multiple gestations, the level of > 2000 mIU/ml should be used before visualizing gestational sacs.³²

As to what order of testing might be the most cost effective and accurate, Gracia and Barnhart looked at 6 different algorithms using transvaginal sonography and quantitative hCG values.³³ The six algorithms involved the following: (i) ultrasound followed by quantitative hCG, (ii) quantitative hCG followed by ultrasound, (iii) progesterone followed by ultrasound and quantitative hCG, (iv) progesterone followed by quantitative hCG measurement and ultrasound, (v) ultrasound followed by repeat ultrasound, and (vi) clinical

examination. They found that the best decision tree was to perform transvaginal sonography on all women who presented with abdominal pain or bleeding in the first trimester. If the TVS was inconclusive, a beta-hCG was quantified and women were treated according to this level. This method produced the best outcome in that no ectopic pregnancies were missed and the smallest number (1%) of potential intrauterine pregnancies was interrupted. In addition, the average time to diagnosis was 1.46 days. This algorithm was found to be equally effective in high and low-risk populations.

DOPPLER/3D ULTRASOUND

Doppler ultrasound has been investigated since 1990 as an adjunct to two-dimensional transvaginal sonography with the potential to make earlier diagnosis of ectopic pregnancies possible. Doppler studies of peak flow velocities and resistive indices have been investigated in both uterine and tubal arteries and corpus lutei. Jurkovic in 1992 performed a prospective study of women with a singleton intrauterine pregnancy and women with an ectopic pregnancy and found that there was no difference in blood flow impedance in the uterine and spiral arteries and corpus luteum.³⁴ The peak flow velocities in the uterine arteries were significantly higher in women with ectopic pregnancies, however; reflecting decreased blood supply to the uterus in ectopic pregnancies. Kirchler evaluated blood flow via Doppler on the tubal arteries on both sides in women with and without ectopic pregnancies. The results showed statistical significance in the mean between-side difference of tubal blood flow; meaning, there was a larger difference between the side of the ectopic pregnancy and the normal side as compared to between-side differences of two normal fallopian tubes in women with an intrauterine pregnancy.³⁵ Salim looked at blood flow in the corpus lutei of normal, abnormal intrauterine pregnancies and ectopic pregnancies and found no statistical significance between ectopic, anembryonic or molar pregnancies and normal pregnancies.³⁶ Atri also studied pregnancies to see if there was a difference in the resistive indices of an ectopic pregnancy and a corpus luteum cyst of pregnancy—both entities which can be confused with one another.³⁷ He found that both high and low resistive indices discriminate ectopic pregnancy from a corpus luteum. Megier looked at 100 color and pulsed Doppler studies of tubal ectopic pregnancies and found that color Doppler facilitated the diagnosis of small ectopic pregnancies (gestational sacs < 1 cm and echogenic adnexal masses < 2 cm) by detecting high impedance flow (diastolic index < 0.35).³⁸ Most recently Ramanan described a new sign by Doppler ultrasound called the “leash sign” that has a sensitivity of 100% and specificity of 99%, PPV 95% and NPV of 100% in the early diagnosis of ectopic pregnancy.³⁹ It is described as an eccentric leash of vessels on color Doppler that showed a low resistance placental type of flow.

Transvaginal three- and four-dimensional sonography has had limited use thus far for visualizing ectopic pregnancies.

There have been case reports of using this modality for confirming the diagnosis of interstitial and cornual ectopic pregnancies as well as for the growing number of ectopic pregnancies in a cesarean section scar. This is due to the ability to see the uterus and endometrial cavity in the coronal plane view.^{40,41} The improvement in the spatial orientation is inherent in the use of three-dimensional sonography and has also been described as being useful in evaluating the endometrial stripe in cases of pregnancies of unknown location. Rempen described the presence of persistently distinct symmetry with regard to the median longitudinal axis of the uterus in the coronal plane in 90% of extrauterine pregnancies. This symmetry was lost in intrauterine pregnancies.⁴²

CONCLUSIONS

It is clear that efforts to identify an ectopic pregnancy at an earlier stage will have an important impact on the morbidity and mortality of reproductive aged women. There have been tremendous life-saving changes in the diagnosis, management and outcome of ectopic pregnancies over the last 20 years due to improved technologies and on-going studies that evaluate newer technologies. Transvaginal sonography with or without the use of serum markers or Doppler has become the mainstay in the first-line evaluation of women suspected of having an ectopic pregnancy or in cases of pregnancies of unknown location.

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