

The Ectopic Pregnancy: A Well-Deserved Review

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An ectopic pregnancy results from a pregnancy following the implantation of a blastocyst at any location other than the endometrial lining of the uterine cavity. Although an ectopic pregnancy is more readily diagnosed due to improved testing techniques available today, it is a life-threatening condition and remains a major source of patient morbidity and mortality. Furthermore, the disease state can easily become more complex as the patient faces the loss of a child and fears for her own health.

Key words: sonography, ectopic pregnancy, serum quantitative beta human chorionic gonadotropin, color flow, pulsed Doppler

Ectopic pregnancy is the leading cause of pregnancy-related deaths in the first trimester. The most recent estimated death rate from an ectopic pregnancy is approximately 17 in 1000 cases,¹ and ectopic pregnancy has a relative risk of death 10 times as great as that of childbirth.² The fact that this condition can result in the death of women of childbearing age who are free of disease and for the most part otherwise healthy increases the personal tragedy and medical concern.

The early recognition of an ectopic pregnancy is of paramount importance in preventing maternal morbidity and mortality. In addition, early diagnosis may optimize treatment options, medical versus surgical, and may preserve the patient's fertility.

The following case presentations demonstrate that the condition of ectopic pregnancy can be readily dismissed. Ectopic pregnancy was not considered to be the primary diagnosis in any of the presented cases.

Case Report 1

A woman in her early 20s, gravida 7, para 2, spontaneous abortion 4, presented to a health care facility complaining of light but intermittent vaginal spotting for 1 month. Her last menstrual period was 1 month prior to the onset of her spotting. She stated that she had taken a home pregnancy test 2 days previously and

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FIG. 1. Echogenic fluid in the cul-de-sac indicating hemoperitoneum.

the results were positive. Her visit to the health care facility was prompted by the recent onset of left lower quadrant discomfort. A repeat urine pregnancy test was obtained and verified her positive results.

In view of the patient's symptoms and the positive urine pregnancy test, a pelvic ultrasound was performed. The study was reported as unremarkable, and the impression was a normal pelvic ultrasound without evidence of an intrauterine or ectopic gestation. The patient was discharged with the diagnosis of a spontaneous abortion and was informed that she needed to make a follow-up appointment with an obstetrician/gynecologist for follow-up management.

The patient presented to our clinic 1 week later for further evaluation. She still complained of intermittent vaginal spotting accompanied by left lower quadrant pain that had been steadily increasing in duration and severity. A bimanual pelvic examination revealed minimal vaginal bleeding and left adnexal tenderness with evidence of fullness. A quantitative serum beta human chorionic gonadotropin (β hCG) was obtained and had a resulting value of 6685 mIU/mL international reference preparation (IRP).

A repeat pelvic ultrasound was performed and demonstrated an empty uterus. Although there was a moderate amount of echogenic free fluid in the cul-de-sac (Fig. 1), there was no free fluid identified in the upper

abdomen. In the right adnexa, there was a normal-appearing ovary identified and no evidence of a mass. Ultrasound imaging of the left adnexa revealed a normal-appearing ovary containing a 1.2 cm corpus luteum cyst (Fig. 2). Just caudad to the left ovary was a 2.5-cm mass with an echogenic rim and a hypoechoic center. Suspicion was aroused that this may represent a tubal ring. Color flow demonstrated a bizarre pattern of flow, and Doppler interrogation of the vessels revealed a moderately low resistive index of 0.30. After reviewing the patient's clinical symptoms, quantitative serum β hCG results, and the ultrasound findings, a laparoscopy was performed on an emergency basis.

During laparoscopy, inspection of the pelvis revealed a moderate amount of blood in the left adnexa and cul-de-sac. A ruptured ectopic pregnancy was identified in the ampullary portion of the left salpinx. Active bleeding was seen in the surrounding tissues, and extensive involvement of the salpinx and vessels was present. Unfortunately, the fallopian tube had to be removed. The patient had an uneventful and full recovery.

Case Report 2

A woman in her early 30s, gravida 2, para 1, presented to a health care facility with complaints of



FIG. 2. Left ovary containing a 1.2 cm corpus luteum cyst. The location of an ectopic pregnancy is usually ipsilateral to the corpus luteum.

heavy vaginal bleeding with large clots and generalized pelvic cramping that had been continuing for the past month. The definite onset of her last normal menstrual period was unknown. Past pelvic surgeries included an appendectomy and a left ovarian cystectomy.

At the health care facility, a bimanual pelvic examination revealed a moderate amount of vaginal bleeding and generalized pelvic tenderness, although the exam was negative for masses. A urine pregnancy test was ordered, and the results were reported as positive. In view of this finding, a serum quantitative β hCG was requested. In addition, a transvaginal ultrasound was performed. The results were essentially normal other than a thickened endometrium and a very small amount of fluid in the left adnexa.

The serum quantitative β hCG results were reported as 88 mIU/mL IRP. Although a spontaneous abortion was suspected, a repeat serum quantitative β hCG was obtained 48 hours after the initial testing. The results were reported to be 72 mIU/mL IRP, which was felt to confirm the diagnosis of a spontaneous abortion.

Five days after the patient's initial visit to the health care facility, she presented to our clinic for further evaluation. She stated that her vaginal bleeding had de-

creased substantially although her pelvic pain was increasing in severity. Bimanual examination of the pelvis revealed a small amount of blood within the vagina and an extreme amount of cervical motion tenderness and discomfort in both adnexae. Due to this finding, repeat diagnostic testing was ordered.

The result of a repeat serum quantitative β hCG was reported to be 50 mIU/mL IRP. Transabdominal and transvaginal sonography demonstrated an anteverted uterus without evidence of an intrauterine pregnancy. The right adnexa demonstrated a normal-appearing ovary with a moderate amount of echogenic free fluid extending into the cul-de-sac. Just cephalad to the ovary, a 3.0 cm predominantly solid mass was identified. Color flow of the mass demonstrated a bizarre flow pattern (Fig. 3). Pulsed Doppler interrogation of the mass resulted in a moderately low resistive index of 0.33 (Fig. 4). The left ovary and adnexa appeared normal. There was no free fluid in the upper abdomen.

As a result of the ultrasound findings and the patient's increasing pelvic pain, a laparoscopy was immediately scheduled for the suspicion of an ectopic pregnancy.

During laparoscopy, inspection of the pelvis revealed a moderate amount of blood in the right adnexa



FIG. 3. Color flow of a solid mass in the right adnexa separate from the ovary. The demonstration of a bizarre flow pattern is highly suspicious of an ectopic pregnancy.

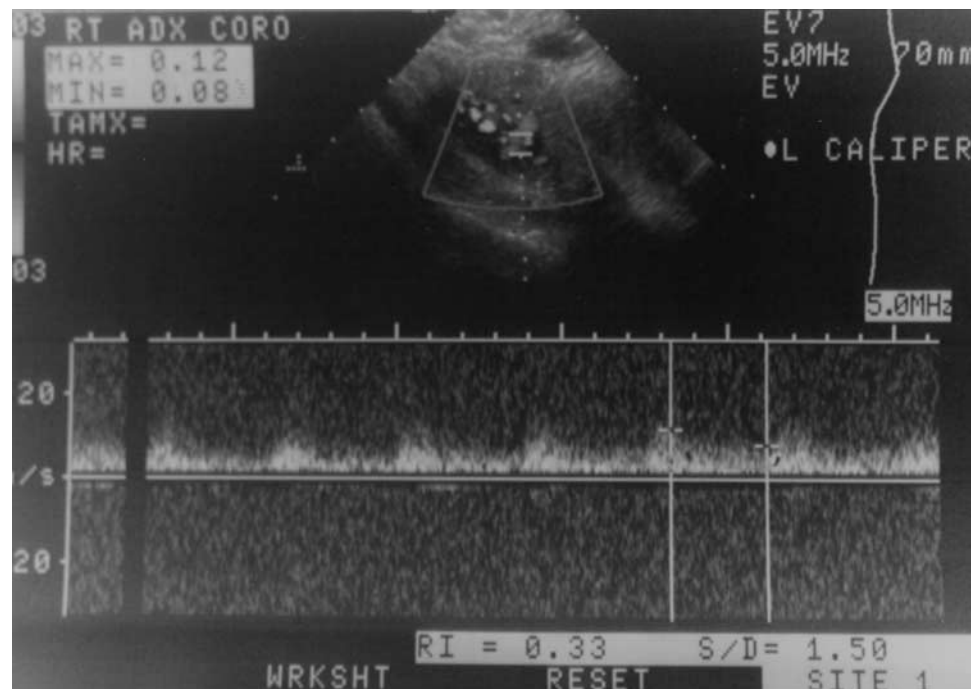


FIG. 4. Doppler interrogation of the solid mass seen in Figure 3 displaying a moderately low resistive index.

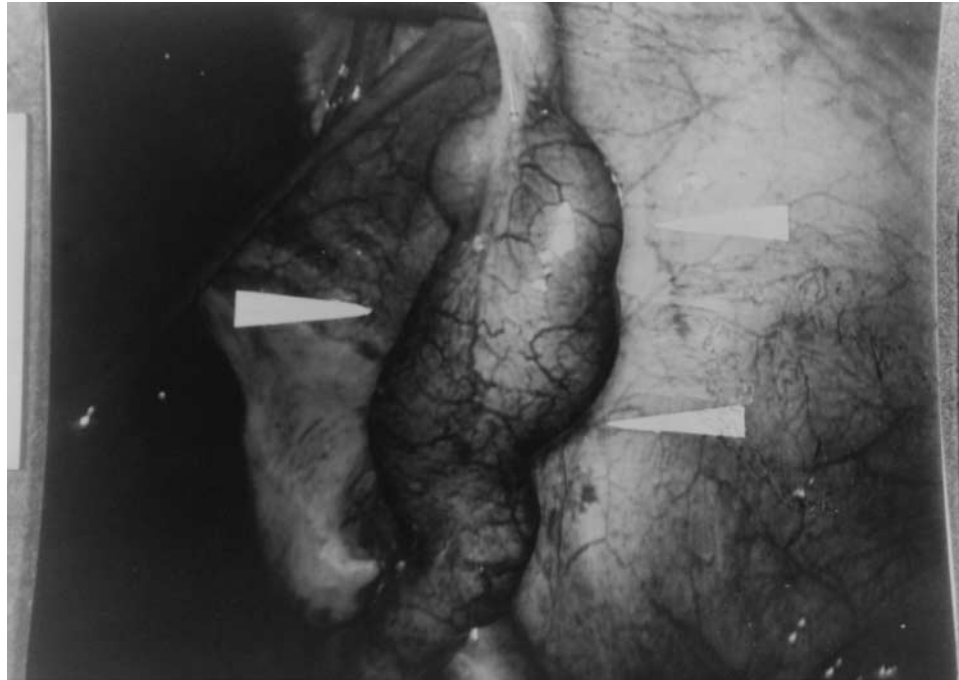


FIG. 5. An unruptured right ampullary ectopic pregnancy identified during laparoscopic surgery.

and cul-de-sac. The right salpinx contained an obvious ampullary ectopic pregnancy that was found to be unruptured (Fig. 5), although bleeding in the surrounding tissues was observed. The right fallopian tube was incised, and the ectopic pregnancy was removed with successful preservation of the patient's fertility. The patient recovered completely, without any complications.

Case Report 3

A woman in her early 20s, gravida 2, including a left ectopic pregnancy with a salpingectomy due to rupture, presented to our clinic for her first prenatal visit. She had performed a home pregnancy test with positive results. According to her last menstrual period, she was 5.5 weeks into her pregnancy. She had no complaints other than 1 day of very light vaginal spotting 1 week prior to her visit. A repeat urine pregnancy test was obtained at our clinic and confirmed her positive results. A routine bimanual examination was performed and was essentially unremarkable. Although asymptomatic, she was considered to be a high risk due to her previous ectopic pregnancy, and a pelvic ultrasound was ordered.

Transabdominal imaging was performed and revealed an empty uterus, normal-appearing adnexae,

and no evidence of free fluid within the pelvis. Transvaginal scanning was then performed and verified the absence of an intrauterine gestation. The left ovary and adnexa appeared normal. The right ovary was identified, and just slightly cephalad and separate from it was a 2.5-cm mass with an echogenic rim and a hypoechoic center. It was felt that this may represent a tubal ring (Fig. 6). Color flow suggested a disorganized and bizarre flow pattern, with increased flow seen in the echogenic rim.

Pulsed Doppler interrogation resulted in a resistive index of 0.44. There was no free fluid seen on transvaginal imaging. A stat serum quantitative β hCG was obtained and reported to be 3306 mIU/mL IRP. As a result of the ultrasound findings and the serum quantitative β hCG, the patient was treated with methotrexate.

Serial serum quantitative β hCG levels were obtained until the value was reported as less than 5 mIU/mL. Follow-up sonography was obtained and the results were normal, with resolution of the ectopic pregnancy. The patient had an uneventful recovery, and her fertility was able to be preserved.

Discussion

The occurrence of ectopic pregnancy has vastly increased over the past 25 years.³ This increase in inci-



FIG. 6. A tubal ring of an ectopic pregnancy demonstrating an echogenic rim with a hypoechoic center.

dence has been thought to be the result of the rise in the rate of salpingitis, tubal microsurgery, in vitro fertilization, and laparoscopic tubal coagulation. Women with endometriosis, with tubal ligations, and who use intrauterine devices are also at an increased risk. The risk of maternal death has declined, but unfortunately it has not been eliminated.¹ The encouraging aspect is that an ectopic pregnancy is diagnosed earlier than it had been in the past.⁴ This is attributed to a combination of proper clinical management, the highly sensitive serum quantitative β hCG testing and the more recent advancements in sonology. Even with more thorough testing in diagnosing an ectopic pregnancy, time is of essence. The average duration from the last menstrual period to the time of medical treatment or surgery is 7.5 weeks.² To complicate matters, once the fallopian tube (being the most common site for an ectopic pregnancy) has ruptured, it usually cannot be salvaged.⁴

The presentation of an ectopic pregnancy is not always straightforward, and symptoms can be nonspecific. An ectopic pregnancy is missed by the initial examining physician in up to 70% of cases.⁵ A common error is misdiagnosing an ectopic pregnancy for pelvic inflammatory disease.⁶ Ectopic pregnancy and pelvic inflammatory disease share symptoms of pain and imaging criteria of free fluid and an adnexal mass.

An ectopic pregnancy will also frequently present with manifestations similar to an intrauterine pregnancy: threatened, inevitable abortion; ruptured ovarian cysts; adnexal torsion; appendicitis; and a vast array of other medical conditions involving the pelvis.

The classical symptoms of an ectopic pregnancy, which include abnormal vaginal bleeding, pain, and a palpable adnexal mass, are not always present. The diagnosis is not easily made clinically, and symptomatology and laboratory findings are not independently diagnostic. Laparoscopy, which by many is considered the standard of reference, is invasive and does not have 100% sensitivity.⁷ Pelvic sonology used in conjunction with clinical and laboratory testing has become an invaluable tool for the diagnosis of an ectopic pregnancy. Sonographers have a responsibility to search for the subtle signs that may indicate an ectopic pregnancy and to investigate new techniques to enhance the detection rate and optimize treatment.

The diagnostic evaluation of an ectopic pregnancy should always begin with a reliable laboratory test to include or exclude a pregnancy.^{2,5,6,8-13} One of the most important advances in the management of an ectopic pregnancy has been the development of the highly sensitive radioimmunoassay to quantitate the presence and levels of β hCG in the serum. A glycoprotein that is

composed of 2 subunits, alpha and beta, hCG is produced by the placental trophoblastic tissue soon after the pregnancy implants. Although the alpha subunits of luteinizing hormone, thyroid-stimulating hormone, and hCG are identical, their beta subunits are partially different. The antibodies employed in the hCG tests are specific for the beta subunit of hCG, which is diagnostic of pregnancy. The enzyme-linked immunosorbent assays (ELISA) that detect β hCG are the most sensitive and widely used.⁴

The binding sites of the β hCG can first be detected in the serum within 24 to 48 hours after the implantation of the pregnancy.¹⁰ This does not indicate where the implantation has occurred. Assuming that an intrauterine pregnancy is progressing normally, the serum quantitative β hCG levels should increase an average of 66% every 48 hours or double every 3 days.¹⁰ If the quantitative β hCG level does not follow this pattern, this may not be a normal intrauterine pregnancy. Caution should be taken, however, and the diagnosis of an ectopic pregnancy should not be based solely on serum quantitative β hCG levels. The laboratory test result values only represent guidelines and are not absolute.⁹ A viable intrauterine pregnancy may exhibit a low serum β hCG level representing slow but normal progression.¹⁴ Multiple gestations, heterotopic pregnancy, or trophoblastic disease may demonstrate an uncharacteristic increase in serum β hCG levels for any gestational age. Conversely, a normal rise in serum β hCG levels may sometimes be associated with an ectopic pregnancy.¹⁴ In most instances of ectopic pregnancy, due to the limited space and inadequate nourishment, the growth of trophoblastic tissue is not as rapid as in an intrauterine pregnancy. The resulting serum β hCG levels will increase only slightly, as ectopic pregnancy is usually associated with impaired β hCG production.^{1,2,9} An ectopic pregnancy can also exhibit a decreased or declining level of serum β hCG that may easily be misinterpreted as a spontaneous abortion. The declining levels may indicate that there is indeed an ectopic pregnancy that is already dead and then reabsorbed without any clinical recognition.^{2,8,9} Because the half-life of serum β hCG is brief, a fully infarcted ectopic pregnancy can cause hemorrhage even after measurable levels of the glycoprotein have disappeared. The chronic ectopic pregnancy, thought to constitute 85% of the cases, may elude diagnosis for many weeks.^{2,6,8-10}

In addition to the highly sensitive serum quantitative β hCG levels, pelvic sonology has become the imaging modality of choice demonstrating sonographic signs of an ectopic pregnancy.⁴ The most important role of sonology in this clinical setting is to prove the presence of an intrauterine pregnancy, which usually dismisses the presence of an ectopic pregnancy. The exception to this finding is the coexistence of an intrauterine pregnancy and an ectopic pregnancy. According to recent statistics, this condition may occur in 1 in 4000 pregnancies.² Despite the rarity of the heterotopic pregnancy, the sonographer should always be aware of this possibility. This is especially true of patients who have conceived after assisted reproduction, where the occurrence of heterotopic pregnancy may be slightly increased.⁴

Although sonology is essential in the diagnosis of ectopic pregnancy, it is absolutely imperative to correlate the sonography examination with the results of the serum quantitative β hCG test(s) and to know the type of test that was used and its relative sensitivity.⁴ The "discriminatory zone" in which the serum quantitative β hCG level is reported to be above 2000 mIU and an empty uterus is identified on ultrasound, the chance of the existence of an intrauterine pregnancy is virtually zero.¹

The use of transabdominal scanning (TAS), transvaginal scanning (TVS), color flow Doppler, and pulsed Doppler has markedly increased the ability for detection of an ectopic pregnancy. All imaging techniques should be performed, as the use of a single technique alone may not be sufficient for a thorough evaluation of the entire pelvis.⁵ One study indicates that in 20% of proven ectopic pregnancies, the sonographic appearance of the uterus and adnexae was reported as normal when only TAS was performed.¹⁵ An additional study indicated that between 8% and 28% of the patients imaged with only conventional TVS (no color flow or pulsed Doppler) had results reported as normal when there was an ectopic pregnancy present.¹⁶

Sonographic evaluation of the pelvis should begin with TAS. This technique allows for mapping of the pelvic anatomy and familiarizes the sonographer with the uterus and adnexal structures and their physical relationship to one another. The most cephalic aspect and the far lateral margins of the pelvis can be evaluated with TAS, which would otherwise be missed when imaging with TVS only.⁵ TAS is a valuable tool

in attempting to locate a corpus luteum cyst and to assess the extent of a hemoperitoneum should it exist.

TVS should also be performed to evaluate the pelvic anatomy. The main objective is to demonstrate an intrauterine pregnancy that virtually eliminates an ectopic pregnancy, although the existence of a heterotopic pregnancy should be kept in mind. In addition, an intrauterine pregnancy can usually be identified 1 week earlier than with TAS only.⁴ If an intrauterine pregnancy is not demonstrated, careful evaluation of the endometrium should follow. A pseudogestational sac may be present, which is reported to be associated with 8% to 29% of ectopic pregnancies.^{14,17,18} The thickness of the endometrium should be evaluated, although by itself it is not a reliable sonographic sign for the diagnosis.¹⁶ It may be thickened and/or contain irregular collections of fluid. In the majority of cases, an ectopic pregnancy will present with a thickened endometrial interface due to decidualization.⁴ One study, however, has reported that there was no significant difference in endometrial thickness between patients with an ectopic pregnancy and those with a spontaneous abortion.¹⁶ Blood in the endometrial cavity can increase endometrial thickness measurements, and conversely a thin endometrial measurement cannot be used to exclude an ectopic pregnancy.¹⁶

The adnexae and cul-de-sac should be thoroughly imaged with TVS, as subtle sonographic findings may be detected to aid in the diagnosis. TVS is superior to TAS scanning in identifying small amounts of free fluid and characterizing its echogenicity. Free fluid is characterized as echogenic if any echoes are present regardless of the degree of echogenicity and the amount of fluid present.¹⁹ There has been a reported accuracy of 98% for detecting a hemoperitoneum with TVS, and it is known that there is a significant risk factor present for ectopic pregnancy when echogenic fluid is identified.¹⁹ Small amounts of free fluid can occur in both ruptured and unruptured ectopic pregnancy; however, caution must be taken, as it can also occur with an incomplete or a spontaneous abortion accompanied by a ruptured corpus luteum cyst.

TAS and TVS should always be correlated with each other to evaluate the information obtained by both techniques. In addition to the conventional sonographic imaging techniques, color flow and pulsed Doppler should be included to interrogate the adnexae and cul-de-sac. The 2 imaging techniques should always be combined, as they complement each other and

may detect a previously unseen ectopic pregnancy.² These techniques will also improve specificity when compared to concurrent serum β hCG levels.⁴

Soon after ovulation occurs and there is a progression into early pregnancy, the flow in the ovarian arteries transfers from a high resistant waveform to a low resistant waveform.⁴ If no intrauterine pregnancy is identified, then bilateral evaluation of the ovarian arteries should be obtained and a comparison of the contralateral blood flow and waveforms should be made. This is of utmost importance, since the ovarian artery with the higher velocity usually will define the most probable side of the location of an ectopic pregnancy.⁴ An additional adnexal finding to aid in the diagnosis of an ectopic pregnancy is the identification of a corpus luteum cyst. Color flow and pulsed Doppler should be applied to interrogate the adnexa to help in identification. The characteristic luteal flow around the corpus luteum can be demonstrated even when it is barely seen or not detectable with conventional TAS and TVS. The side on which the corpus luteum is identified is the usual site for the ectopic pregnancy.^{14,15}

To make the diagnosis of an ectopic pregnancy even more likely is the identification of a tubal ring and, rarely, an embryo and/or yolk sac within it. The characteristics of a tubal ring are usually a concentric echogenic ring with a hypoechoic center located in the adnexa separate from the ovary. The echogenicity represents the viable trophoblastic tissue and muscle layers of an ectopic pregnancy.³ Any questionable mass, regardless of the sonographic appearance, should be thoroughly investigated.

The pulsed-Doppler signals of an ectopic pregnancy are typically of low impedance and high diastolic flow, although a significant range of Doppler waveforms may be observed. There may be low impedance to high impedance and also reversed diastolic flow. Color flow may also vary widely, and any bizarre pattern of flow that is observed should arouse suspicion. The vascularity of an ectopic pregnancy can change depending on the viability of the trophoblasts. It has been observed that in a chronic ectopic pregnancy where trophoblasts become necrotic, color flow may be decreased or even absent. With a history of medical treatment for an ectopic pregnancy, an increase in vascularity has been observed.^{4,8} A thorough sonographic evaluation of the pelvis and clinical correlation is essential and must be carefully analyzed and reviewed.

In the past, and currently, there have been several studies on low-resistance endometrial arterial flow to confirm or exclude the presence of an intrauterine pregnancy to aid in the diagnosis of an ectopic pregnancy.^{4,7,20} The efficacy of this technique in early pregnancy in relation to ALARA principles has not been fully investigated. In general, in any situation where there is a potential diagnosis of an ectopic pregnancy, the benefits would outweigh the risks, although specific studies in the future might provide further information on this issue.

Sonology findings, including the size of the adnexal ring, the presence or absence of the fetal pole and cardiac activity, and the presence or absence of echogenic free fluid, along with information about stable or falling values of hematocrit and β hCG, are assessed by practitioners and may help to determine medical or surgical treatment of ectopic pregnancy.

Conclusion

As previously described and demonstrated in the presented case reports, the diagnosis of an ectopic pregnancy can be extremely complex and challenging due to the vast range of presentations of the disease. The use of TAS, TVS, color flow Doppler, and pulsed Doppler combined with the highly sensitive serum quantitative β hCG testing has demonstrated an increased ability to detect an ectopic pregnancy. As sonology becomes more sensitive and specific in the diagnosis of an ectopic pregnancy, delays in recognizing the disease should lessen.

Women with the suspicion of an ectopic pregnancy are frequently encountered by sonographers. (This usually seems to occur on a late Friday afternoon, late hours of the evening, or very early in the morning.) Regardless of the time period, knowledge is always beneficial, and it is the responsibility of the sonographer to be informed of the patient's medical history, clinical symptoms, and laboratory testing results. Because pelvic sonography plays a key role in diagnosing the life-threatening condition of an ectopic pregnancy, all imaging techniques and variations should be thoroughly performed and applied to the fullest extent of their capabilities. When a sonographer is presented with a patient with the potential diagnosis of an ectopic pregnancy, the only safe rule to bear in mind is the fact that all women of childbearing age are at risk for harboring an ectopic pregnancy.²

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