EMERGENCY MEDICINE PRACTICE
EBMEDICINE.NET
AN EVIDENCE-BASED APPROACH TO EMERGENCY MEDICINE

Complications In Pregnancy Part I: Early Pregnancy

It is Sunday evening and the place is dead. You're thinking about napping when the charge nurse lets you know about a new patient in room 9, the dreaded pelvic room. You go to see her and find a young female complaining of abdominal pain and vaginal bleeding. She claims her periods have been regular and that she is not sexually active. She has stable vital signs. She is extremely tender in the right lower quadrant, but does not have rebound. You're thinking appendicitis until urine is obtained and, low and behold, she has a positive urine pregnancy test. Blood is sent for a type and cross, and morphine is given for her pain. Your bedside ultrasound shows a single intrauterine sac (no yolk sac seen). A formal pelvic ultrasound is ordered and, as soon as the order is placed, the radiologist calls and asks, "What is the patient's β-hCG?" You knew this was coming since this isn't the first time he's asked this question; this time you have an answer as to why the beta is not needed to order the study……

Pregnancy-related complications are, unfortunately, a common experience for women and often require an evaluation at the local ED. Due to the very nature of pregnancy, these are always potentially high risk situations because they impact not only the mother but also the embryo or fetus. This review focuses on the common emergencies that are unique to the pregnant patient. Pregnancy-related complications may be classified as either early or late. Early complications usually occur in the first trimester prior to gestational viability. Late complications occur primarily in the third trimester and impact the fetus and the mother since the fetus is typically viable. Common medical problems may impact and affect the course of a pregnancy. This issue, which is Part One in a two-part series, focuses on the early complications of pregnancy. Part Two will focus on the late complications of pregnancy and the common medical conditions that can occur during pregnancy.

June 2007
Volume 9, Number 6

Authors

Deborah Houry, MD, MPH
Assistant Professor, Department of Emergency Medicine, Emory University School of Medicine, Atlanta, GA

Matthew Keadey, MD, FACEP
Chief of Service, Medical Director, Emergency Medicine, Emory University Hospital, Assistant Professor, Emory University School of Medicine, Atlanta, GA

Peer Reviewers

Thomas W. Lukens, MD, PhD, FACEP
Clinical Operations Director, Department of Emergency Medicine, MetroHealth Medical Center, Cleveland, OH

Joseph Toscano, MD
Attending Physician, Emergency Department, San Ramon Regional Medical Center, San Ramon, CA

CME Objectives

Upon completion of this article, you should be able to:
1. Describe the variety of presentations of early complications of pregnancy.
2. Elucidate the risk factors for miscarriage and ectopic pregnancy.
3. List the modalities for evaluating miscarriage and ectopic pregnancy.
4. Describe the treatment options for ectopic pregnancy and miscarriage.

Date of original release: June 1, 2007
Date of most recent review: May 10, 2007
See "Physician CME Information" on back page.

Commercial Support: *Emergency Medicine Practice* does not accept any commercial support. Drs. Keadey, Lukens, and Toscano report no significant financial interest or other relationship with the manufacturer(s) of any commercial product(s) discussed in this educational presentation. Dr. Houry has received research grant support from CDC, NIH, and UCB Pharma.

Critical Appraisal Of The Literature

A search of *Ovid MEDLINE* and *PubMed* for pregnancy-related emergencies between 1966 and 2006 was performed to obtain the references for this article. The searches were limited in all areas to English-language and human studies.

For the search on early pregnancy-related complications, key words included pregnancy, ectopic, abortion, miscarriage, methotrexate, vaginal bleeding, Rh immunization, and ultrasound. In addition, articles were obtained from the bibliographies of the identified articles in selective cases. A search of the Cochrane Database of systemic reviews specific to early pregnancy-related complications included one review on the interventions for tubal ectopic pregnancy.

The most credence was given to scientific articles, including clinical trials, prospective cohort studies, and aggregate studies including meta-analyses of clinical trials. Retrospective studies, case-controlled studies, and other meta-analyses provided secondary evidence for analysis, followed by panel consensus, cross-sectional studies, and case reports. In addition, the American College of Emergency Physicians (ACEP) has published two clinical policies relevant to the evaluation and management of pregnancy-related emergencies. In 1997, ACEP published *Clinical Policy for the Initial Approach to Patients Presenting with Chief Complaint of Vaginal Bleeding*. Realizing that this was a broad topic, ACEP published a more specific clinical policy in 2003 titled, *Critical Issues in the Initial Evaluation and Management of Patients Presenting to the Emergency Department in Early Pregnancy*. Both of these policies provide evidence-based guidelines in the treatment and management of pregnancy-related emergencies. For a list of clinical policies utilized, see **Table 1**.

Table 1. Clinical Policies On Emergencies Of Early Pregnancy

American College of Emergency Physicians	Vaginal bleeding	*Annals of Emergency Medicine.* 29(3):435-58, 1997 Mar.
American College of Emergency Physicians	Early complications of pregnancy	*Annals of Emergency Medicine.* 41(1):123-33, 2003 Jan.
American College of Obstetrics and Gynecology	Nausea and vomiting of pregnancy	*Obstetrics & Gynecology.* 103(4):803-14, 2004 Apr.
American College of Obstetrics and Gynecology	Treatment of tubal pregnancy	*International Journal of Gynecology & Obstetrics.* 65(1):97-103, 1999 Apr.
Society of Obstetricians and Gynecologists of Canada (SOGC)	Rh Alloimmunization and Rhogam administration	*Journal of Obstetrics & Gynecology* Canada 25(9):765-73, 2003 Sep.

Epidemiology, Etiology, And Pathophysiology

Complications of early pregnancy are common clinical conditions that often require emergency care. The patient may or may not be aware that she is pregnant at the time of ED evaluation**.**

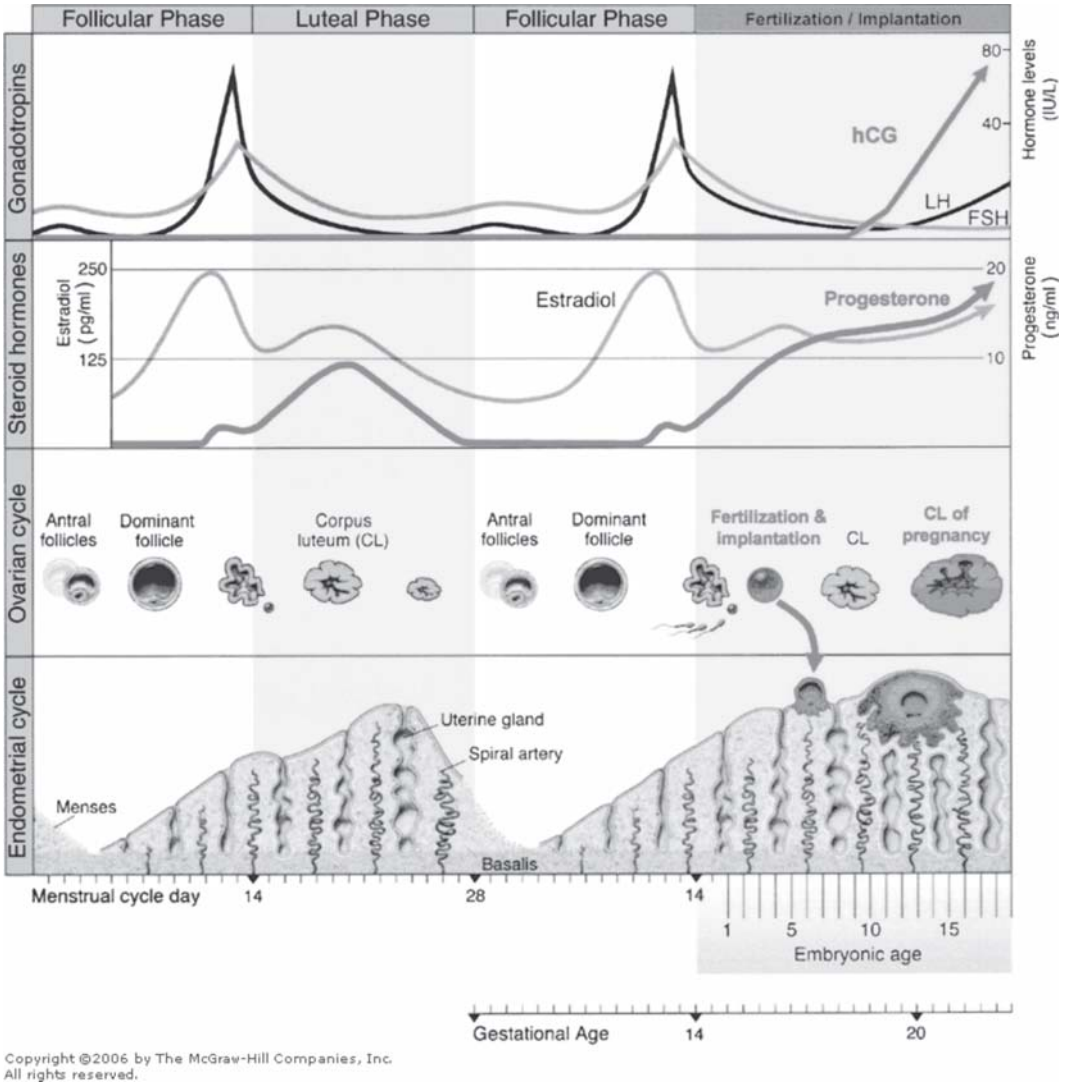
Hormones Of Early Pregnancy

Multiple hormones are involved in the support and growth of a normal pregnancy, see **Figure 1**. In a typical menstrual cycle, follicular stimulating hormone (FSH) and luteinizing hormone (LH) produced by the pituitary gland lead to egg maturation and ovulation about two weeks into the menstrual cycle. After ovulation, a corpus luteum develops that produces estrogen and progesterone. In a normal menstrual cycle without egg fertilization, the levels of FSH and LH decline, leading to involution of the corpus luteum, a decline in progesterone and estrogen levels, and menstruation. However, if the egg is fertilized and implants in the endometrium, the hormone β-hCG supports the corpus luteum, maintaining its production of estrogen and progesterone. As the embryo develops, the serum beta human chronic gonadotropin (β-hCG) level increases until 10-12 weeks of embryo gestational age, where it peaks at 150,000-200,000 mIU/mL.[1] As the levels of β-hCG decline, the placenta secretes multiple hormones, including progesterone, estrogen, and human placental lactogen, to maintain the pregnancy. In a nonviable pregnancy, inadequate levels of estrogen and progesterone lead to involution of the embryo and menstruation.

Ectopic Pregnancy

Ectopic pregnancy, or pregnancy implanted outside the uterus, is an increasingly frequent problem that poses a major health risk to females during their childbearing years. It is the second leading cause of maternal death, is responsible for 9% of maternal mortality, and is the nation's leading cause of first trimester maternal death.[2] It is estimated that 2% of pregnancies in the United States are ectopic; in patients presenting to the ED, the prevalence is estimated at 6-16%.[2-4] The incidence of ectopic pregnancy has quadrupled over the past 20 years. Between

Figure 1. Hormone Cycle



Reprinted with permission. Copyright © 2006 The McGraw-Hill Companies. All rights reserved

1970 and 1992, the number of ectopic pregnancies increased fourfold, from 4.5 per 1000 pregnancies in 1970 to 19.7 per 1000 pregnancies in 1992.[2,3] The increase in incidence is most likely due to the rising incidence of sexually transmitted diseases, earlier diagnosis of pelvic inflammatory disease resulting in tubal damage but not blockage, and the rise in the use of assisted reproductive technologies.

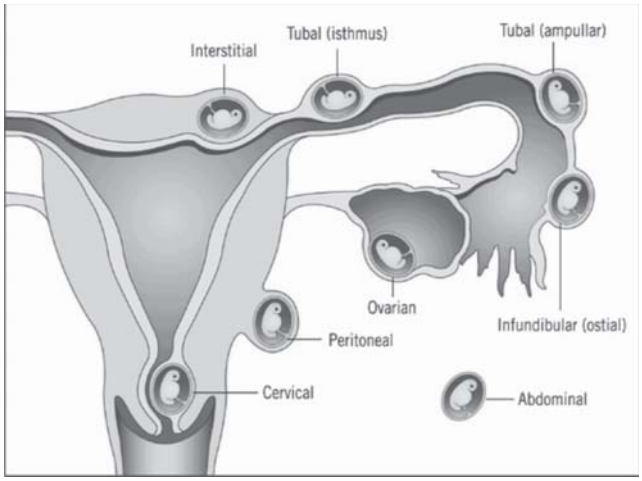
More recent data about the incidence of ectopic pregnancy have become unreliable and the CDC has reported that current estimates may not be accurate.[3] In the past, rates of ectopic pregnancy were estimated using hospitalization data since all cases were treated surgically. However, as medical treatment became more widely used, outpatient treatment of ectopic pregnancy has increased so hospitalization data is no longer representative. Consequently, one must question the validity of reports from managed care organizations and from Norway and the United Kingdom stating that there is a falling or stable incidence in ectopic pregnancies as well as a decrease in the ratio of live births to ectopics.[5,6] In addition, a large managed care organization reviewed their patient databases and found the rate of ectopic pregnancy to be similar to the reported data in 1992.[7]

There are several factors that increase the risk of ectopic pregnancy. Although most ectopic pregnancies are seen in females aged 25-34, the rate is highest among older females and minorities.[3] Most risk factors relate to a strong association between ectopic pregnancy and conditions that are thought to impede normal migration of the fertilized ovum to the uterus. High risk conditions that predispose to an ectopic pregnancy include previous tubal surgery, previous ectopic pregnancy, in utero exposure to diethylstilbestrol, and documented tubal abnormalities. Although an IUD and tubal ligation decrease a woman's chances of conceiving, the rate of ectopic

pregnancy is substantially increased if the patient becomes pregnant. More weakly associated risk factors include smoking, increasing age, and more than one lifetime sexual partner. No clear association has been documented between ectopic pregnancy and the use of oral contraception medication, previous pregnancy termination, spontaneous miscarriage, or cesarean delivery.[8-11]

Of all ectopic pregnancies, 97% occur in the fallopian tube. Of all tubal pregnancies, 55% are at the ampulla, 25% at the isthmus, and 17% at the fimbria, see **Figure 2.**[12] Other atypical implantation locations include (in decreasing order) cervical, ovarian, and abdominal. Depending on the site of implantation, the clinical presentation may vary.

Figure 2. Possible Anatomic Sites In Ectopic Pregnancies



Reprinted with permission from: Illustration: Seeber. Suspected Ectopic Pregnancy. Obstet Gynecol Volume 107(2, Part 1).February 2006.399-413.

Simultaneous intrauterine and extrauterine gestations (heterotopic pregnancy) have historically been rare. Original prevalence studies indicated a rate of 1:30,000 pregnancies. However, recent data suggest it is more frequent and occurs in 1 in 4000 pregnancies. This is believed to be due to the increasing utilization of assisted reproductive technologies which result in impeding tubal transport and increase the risk of multiple fertilized ova. *In vitro* fertilization pregnancies have demonstrated about a 1:100 rate for heterotopic pregnancy.[13-15]

Miscarriage

Approximately 20-25% of pregnant patients experience some bleeding during their pregnancies; it is widely estimated that almost half of all females who have bleeding during early pregnancy miscarry, although the risk is probably higher in the ED population.[16,17] About 70% of potentially fertile menstrual cycles produce an ovum that, when fertilized, implants in the endometrium. Of these "chemically" detectable pregnancies, up to one-third end before they are clinically recognized by a missed menstrual period, and another 9-14% are recognized as clinical miscarriages.[16] About 80% of miscarriages occur during the first trimester; the rest occur before 20 weeks of gestation.

Causes of miscarriage are shown in **Table 2.** Most early miscarriages are due to genetic abnormalities, but environmental causes predominate as the pregnancy progresses. Fetal loss after implantation ranges from one-third to one-half of all detectable pregnancies.[16-18] Gestational viability cannot be assessed by physical exam and β-hCG levels alone. Often, pelvic ultrasound in conjunction with β-hCG levels is needed to accurately assess fetal viability. The risk of miscarriage rises with increasing age, increased parity, and history of vaginal bleeding.[16-19]

Table 2. Etiology of Spontaneous Miscarriage

Genetic Causes (most common)
• Trisomy
• Aneuploidy
• Polyploidy
• Translocations
Environmental Causes
• Uterine
Congenital abnormalities
Lieomyoma
Intrauterine adhesions (Asherman's Syndrome)
• Endocrine
Progesterone deficiency
Thyroid disease
Uncontrolled diabetes
Luteinizing hormone hypersecretion
• Immunologic
Antiphospholipid antibody syndrome
Lupus
• Infections
Viral
Bacterial - genitourinary tract and systemic
Others

Several stages of miscarriage have been described.

- *Threatened miscarriage* - the patient has bleeding but a closed internal cervical os. The risk of miscarriage in this population is estimated at 35-50%, depending on the patient population and severity of symptoms.[20]

- *Inevitable miscarriage* - the internal cervical os is open.
- *Incomplete miscarriage* - products of conception (POCs) are present at the cervical os or in the vaginal canal.
- *Completed miscarriage* - the uterus has expelled all fetal and placental material, the cervix is closed, and the uterus is contracted.

Although a completed miscarriage occurs spontaneously in some miscarriages, particularly those earlier in gestation,[17] establishing the diagnosis is difficult unless an intact gestational sac is seen. Cervical closure may occur after an episode of heavy bleeding and clot passage after partial expulsion of the products of conception. Unless an intact gestational sac is seen, completed miscarriage should be diagnosed only after a dilation and curettage (D & C) with pathologic confirmation of gestational products or by conversion of the pregnancy test to "negative," which may take up to four weeks.[21]

Differential Diagnosis

The spectrum of clinical pictures for patients with complications of early pregnancy varies greatly, so the differential diagnosis includes all first-trimester complications as well as those conditions found in non-pregnant patients, see **Table 3**. Of greatest concern is the possibility of ectopic pregnancy, which may masquerade as a threatened miscarriage in the early stages of an ectopic pregnancy. Even in the patient with painless vaginal bleeding, the diagnosis of ectopic pregnancy must be considered. For this reason, early sonography is imperative to locate the pregnancy in any patient for whom you are considering a diagnosis of ectopic pregnancy. Threatened miscarriage, the most common alternative diagnosis, can be diagnosed only if sonography determines that the pregnancy is intrauterine. Hypovolemia may be seen, particularly in incomplete miscarriage, if bleeding is substantial, but hypotension without obvious vaginal hemorrhage is highly suggestive of ectopic pregnancy. Identification of fetal parts or chorionic villi in tissue expelled or obtained during D & C is useful to confirm a complication of IUP, but is not sufficient to exclude ectopic pregnancy in a patient who has received infertility treatment and has a possible heterotopic gestation.

Table 3. Differential Diagnosis Of Early Pregnancy Complications

Pregnancy-Related Conditions	Non-Pregnancy-Related Conditions
Ectopic pregnancy	Pelvic or urinary infections
Spontaneous abortion	Urinary calculus
Molar pregnancy	Appendicitis
Ruptured corpus luteum cyst	Gall bladder disease
Hyperemesis gravidarum	Pancreatitis
Implantation bleeding	Hepatitis
	Ruptured ovarian cyst
	Hemorrhagic ovarian cyst
	Ovarian torsion
	Trauma to cervix

A ruptured corpus luteum cyst should also be considered in the patient who has first trimester bleeding associated with peritoneal pain or irritation. The corpus luteum normally supports the pregnancy during the first seven to eight weeks. Rupture causes sudden peritoneal irritation. Sonography is helpful in most cases if it reveals an IUP. If the patient is unstable (especially if an IUP cannot be identified by sonography), laparoscopy or laparotomy may be required. Uncontrolled hemorrhage from corpus luteum cyst rupture occurs in only 1% of cases.[22]

Other diagnoses should be considered but are less likely. A small amount of bleeding occurs at the time of implantation of the blastocyst into the endometrium and occasionally at the time of the first missed menses. Molar pregnancy is also characterized by vaginal bleeding, usually during the late first trimester or the second trimester, and can be identified by sonography. Cervical and vaginal lesions may also cause local bleeding and can usually be seen on vaginal inspection.

Prehospital Care

In the prehospital setting, the patient may present with varied complaints. Vaginal bleeding and abdominal pain may be clearly related to an early pregnancy-related emergency if the patient is aware she is pregnant. Often, the diagnosis of pregnancy is not known by the patient and, unfortunately, other undifferentiated complaints (such as syncope) and findings (such as hypotension) may be the initial presentation of a pregnancy-related emergency in a patient who may or may not know that she is pregnant.

Paramedics and emergency medical technicians should be primarily concerned with patient stabilization and transport. Immediate assessment and treatment of the ABC's is paramount. Two large bore IV's (18 gauge or larger) should be established and an infusion of an isotonic solution should be initiated in any hypotensive patient or actively bleeding

patient. Transfer to a local medical facility should be dictated by the urgency of the situation and the ability of a given facility to respond to the needs of the patient. In any acute emergency with a pregnant patient, optimal care of the fetus is dependent on appropriate management of the mother.

ED Evaluation

Initial Stabilization

As with any patient who presents to the emergency department, vital signs, airway, breathing, and circulation (ABC's) must be assessed first. If the patient has unstable vital signs or abnormal ABC's, these should be addressed and stabilized before further evaluation. Approximately 20% of ectopic pregnancies manifest signs and symptoms warranting immediate intervention.[23] For patients with significant signs of hypovolemia, rapid volume resuscitation should be instituted with isotonic intravenous fluids and blood products, as necessary. Focused abdominal ultrasounds (FAST scans) that identify hemoperitoneum may identify a subset of patients that will require surgical exploration, but prospective studies in this population are lacking.[24] Free fluid can be identified by transabdominal US and may warrant immediate exploration in the appropriate clinical situation.[25] For patients who remain unstable, immediate surgical exploration is the best method of management.

History

A good patient history provides the basis for the ED evaluation. Historical features specific to the patient with an early pregnancy include the estimated length of the gestation, time since last menstrual period, symptoms of pregnancy (or loss of pregnancy symptoms), presence, degree, and duration of vaginal bleeding, passage of tissue other than blood, fever, and attempts by the patient to induce miscarriage. Risk factors for ectopic pregnancy should be elicited, including a history of prior ectopic pregnancy, tubal surgery, history of an IUD or tubal ligation, prior pelvic infections, and use of assisted reproductive technologies. Recent trauma or intimate partner violence should also be considered.

Patients with ectopic pregnancy may present with a number of complaints, but it is important to realize that no specific complaint or historical feature is diagnostic. The classic triad of a history of amenorrhea, vaginal bleeding, and abdominal pain is present in less than half of the cases.[26] The most common complaint for ectopic pregnancy is abdominal pain, but other features, (e.g., syncope or vomiting) may be present, which mimic other conditions. When found together, significant abdominal pain and estimated gestational age of less than 70 days have a sensitivity of over 95% for ectopic pregnancy.[27-31] Therefore, if either or both of these historical features are absent, it makes the diagnosis of ectopic pregnancy less likely, but still possible.[27-31] Kerr's sign (referred pain to the shoulder from diaphragmatic irritation) or referred back pain can be seen in patients with significant hemoperitoneum, but its predictive value has not been extensively studied with ectopic pregnancy.

Patients with a miscarriage commonly present with vaginal bleeding and often complain of abdominal discomfort. This is problematic since patients with an ectopic pregnancy can often present with similar complaints. Although vaginal bleeding is the most common presentation, the severity of bleeding does not correlate with the risk of patients proceeding to a complete miscarriage. It is estimated that 50% of pregnant patients with vaginal bleeding will have a viable pregnancy.[10,27]

Physical Exam

A typical evaluation of a patient with a presumed complication of early pregnancy should focus initially on stability. This is often just an assessment of vital signs and observation of the patient. Signs of shock may be present whether compensated or not. Subtle signs, such as confusion or weakness, may indicate a more serious condition. Tachycardia, which is usually associated with stage II shock, may be absent.[32,151-154] A phenomenon known as *relative bradycardia*, although uncommon, has been found in multiple case studies of hemoperitoneum and can often lead to an alternative incorrect diagnosis. In an unstable patient, immediate interventions should be initiated to resuscitate the patient.

The assessment of the patient who experiences first trimester vaginal bleeding includes a careful abdominal examination to evaluate for tenderness or peritoneal irritation as well as to assess uterine size (often not palpable abdominally). Pelvic examination should be performed to evaluate the condition of the cervix (closed or open), the presence of clots or fetal tissue, the degree of vaginal bleeding, and the uterine size and tenderness. The cervix should be gently probed with ring forceps to determine

whether the internal os (1.5 cm deep to the external os) is open or closed. Parous females normally have an open or lax external os. This is unnecessary in the patient who has a clearly open os or visible POCs, but can be safely performed during the first trimester as long as the forceps are used gently and do not penetrate more than 2-3 cm. In the patient with second trimester bleeding, probing should not be done because the uterus is more vascular and the organized placenta may overlie the cervical os.

The adnexa may be enlarged, particularly unilaterally, either because the corpus luteum is cystic or because the pregnancy is located in the fallopian tubes. Significant adnexal or uterine tenderness should always raise the possibility of an ectopic pregnancy. However, when an adnexal mass is palpated, one-third of patients will have a contra-lateral ectopic pregnancy.[31] Much less commonly, pelvic infection may cause uterine and adnexal tenderness during early pregnancy, and this will usually present with a vaginal discharge.

Any tissue that is passed should be examined in saline suspension or under low-power microscopy to differentiate sloughing endometrium and organized clot from chorionic villi which form fronds and appear feathery in the saline suspension. Chorionic villi can be recognized in approximately one-half of miscarriage specimens by this simple means.[33] Except for the rare instance of heterotopic pregnancy, this reliably excludes an ectopic pregnancy.

Diagnostic Studies

Because there is no reliable historical or physical exam finding, ancillary studies should be conducted to locate the pregnancy in any patient who has abdominal pain or vaginal bleeding and a positive pregnancy test result. Recent technological advances have allowed accurate evaluation of pregnant patients in situations of clinical uncertainty. Hormonal assays and sonography are both useful for assistance in excluding ectopic pregnancy. A type and cross is an important test to obtain if you anticipate that blood will be needed (or to evaluate the risk of Rh incompatibility). In any unstable patient, the use of unmatched blood must be considered. A CBC may be helpful, but should not be relied upon since the hematocrit may be normal in the earlier stages of a ruptured ectopic. A urinalysis may be obtained to help elucidate other causes of abdominal pain. In addition, laparoscopy can be the most efficient diagnostic and management tool in some critically ill patients.

Hormonal Assays: β-hCG

hCG is a hormone secreted by syncytiotrophoblasts in early pregnancy. Serum testing can detect levels as low as 5 mIU/mL, whereas urine testing can detect levels as low as 20 mIU/mL.[34] This hormone can be detected as early as one week prior to the expected menstruation following conception. After the first trimester, the β-hCG level starts to decline as other hormones support the pregnancy. During the ED evaluation, an initial quantitative level can be drawn to aid in determining gestational age, but it is most useful in conjunction with sonography to determine whether the pregnancy is at a stage that it should be visualized, see **Table 4**.

Table 4. Landmarks For Gestational Age And β-HCG By Transvaginal Sonography

TVS findings	Weeks From LMP	β-hCG (mIU/mL)
"Discriminatory zone"	5-6	1500-2000
Yolk sac	6	2500
Upper "discriminatory zone"	6-7	3000
Fetal pole	7	5000
Fetal heart motion	8	17,000

Adapted from Dart RG. Role of pelvic ultrasound in evaluation of symptomatic first trimester pregnancy. Ann Emerg Med 1999; 33: 310-320.

Although women with ectopic pregnancies and miscarriages tend to have lower levels of β-hCG, intrauterine pregnancies may also present with these values. Therefore, reliance on one β-hCG level may lead to termination of viable pregnancies or missed ectopic pregnancies.[30,34] In addition, it cannot be assumed that very low levels of β-hCG (less than 100 mIU/mL) predict a benign course. In a review of 716 admitted patients with ectopic pregnancy, 29% of those with a very low level of β-hCG were found to have tubal rupture at laparoscopy, and the risk of tubal rupture has been found to be similar across a wide range of β-hCG levels.[35]

Serial β-hCG levels are more sensitive for detecting an abnormal early pregnancy. Serum levels normally double every 1.8 to 3 days for the first six to seven weeks of pregnancy, beginning eight to nine days after ovulation.[17] After an initial level is drawn, repeat values should be checked 48 hours later. An abnormal change in the quantitative β-hCG level is a nonspecific indicator of pregnancy failure during the first six weeks of gestation and does not differentiate between an ectopic pregnancy and miscarriage.[36]

More than 70% of patients with an ectopic pregnancy will have an abnormal rise or fall of the β-hCG level upon serial testing.[36] As with a single value, serial values cannot reliably predict the location of a gestational sac.

Decreasing levels of β-hCG clearly indicate a nonviable pregnancy but cannot reliably differentiate between a miscarriage and ectopic pregnancy; in an ectopic pregnancy, 8% will have a β-hCG level fall similar to that expected with a miscarriage.[36] A β-hCG decrease of less than 50% is always associated with an abnormal gestation and 19% of those are ectopic.[29, 37] In a prospective study of 353 consecutive patients presenting with a presumed ectopic and inconclusive ultrasound results, a fall in β-hCG of greater than 50% reduced the chances of an ectopic pregnancy to less than 3%.[29] Therefore, in the appropriate population, serial β-hCG levels, sonography, and expectant treatment may be appropriate.

Rising values significantly reduce the chances of a miscarriage, but the risk of an ectopic pregnancy persists. Normally, doubling β-hCG levels are commonly seen during early ectopic pregnancy. In early ectopic pregnancies, 21% will have an initial increase in β-hCG similar to an intrauterine pregnancy.[36] In two prospective cohort studies of 700 combined patients, a rise of β-hCG greater than 50% on serial testing suggested a normal pregnancy, but between 22-35% were found to eventually have an ectopic pregnancy.[29,31] However, a rise of less than 50% almost always indicated an abnormal pregnancy.[29,37]

Progesterone

Serum progesterone levels provide an additional or alternative marker to determine which patients need further evaluation and follow-up for possible ectopic pregnancy.[39,40] Progesterone levels can be problematic since they are not universally available in a timely manner and are not accurate enough in isolation to diagnose ectopic pregnancy. However, a single value that is very high or very low can be helpful. In a prospective study of 700 patients, a progesterone level greater than 22 ng/mL reliably (99% accuracy) excluded the diagnosis of ectopic pregnancy.[39] However, lower progesterone levels have a positive predictive value of only 18%. Very low levels of progesterone (less than 5 ng/mL) can reliably exclude a viable intrauterine pregnancy but do not differentiate miscarriage from an ectopic pregnancy.[38] In a hypothetical cohort study based on test characteristics to evaluate diagnostic strategies, the use of progesterone alone resulted in a miss rate of 2.5%, which was felt to be clinically unacceptable.[41] Therefore, progesterone should not be used alone unless it is over 22 ng/mL and only in conjunction with sonography.

Sonography

Sonography is the primary method used to locate an early gestation, establish gestational age, and assess fetal viability. Consensus opinion recommends starting with a transabdominal ultrasound (TAS) and progressing to a transvaginal ultrasound (TVS) if further images or evaluation is required.[42] A β-hCG may be helpful in correlating the US images, but does not need to be available prior to study completion. TAS image quality may be improved via a larger sonographic window if the patient has a full bladder; therefore, consideration should be given to intravenous or oral fluids to promote urine generation and instructions given to abstain from urination until the TAS is completed. On the other hand, TVS images are best with an empty bladder so, if a TVS is needed, ask the patient to completely empty her bladder prior to the study.

As the ovum is fertilized and the newly formed blastocyst travels down the fallopian tube, it is approximately 0.1 mm and too small to be visualized by TVS.[44,45] The use of color flow Doppler has allowed earlier identification of this structure through the demonstration of peritrophoblastic flow.[46] Others have described an intradecidual sign (an echogenic area located within a markedly thickened decidua on one side of the uterine cavity) as an early sign of an intrauterine pregnancy, but its sensitivity, specificity, and overall diagnostic accuracy have been questioned. [47,48]

The gestational sac is the first visible indication of a pregnancy as the chorionic cavity is created as early as 4.5-5 weeks of gestational age at a size of 2-3 mm, see **Figure 3 A-E** on page 9 for US images.[45, 49,50] At five weeks, a secondary yolk sac is first seen and disappears at the end of the first trimester. In normal gestations, the yolk sac should be visible by TVS when the gestational sac measures more than 8 mm.[51] If the gestational sac is greater than 8 mm and no yolk sac is seen, an abnormal gestation is most likely present.[52,53] An amniotic membrane may be seen as early as four weeks. An amniotic sac may be seen adjacent to the yolk sac; by 12-16 weeks, it should no longer be present as it fuses with the outer chorion.[54] An embryo is typically seen adjacent to

the yolk sac around six weeks, when the gestational sac reaches a size of greater than 16 mm on TVS. Embryonic cardiac activity should be seen when the embryo reaches a size of greater than 5 mm.[57,58] Although cardiac activity has been seen in embryos as small as 2 mm, 5 mm is the discriminatory value

Figure 3A.Yolk Sac At Five Weeks

Sagittal TVS of the uterus at menstrual age of five weeks demonstrates an intrauterine gestational sac with a yolk sac (arrow).

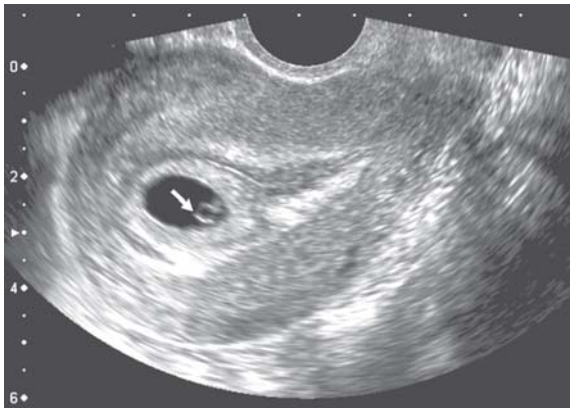


Figure 3B. Abnormal Intrauterine Gestational Sac - Threatened Abortion

A: Sagittal TVS demonstrates a gestational sac with thin decidual reaction (arrow).
B: Coronal TVS shows an irregular intrauterine gestational sac (arrowheads).

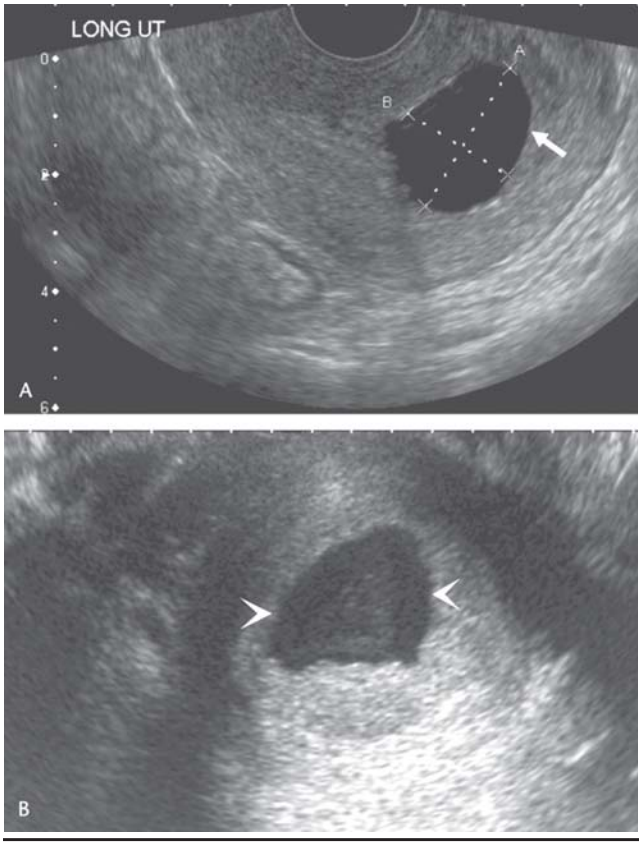


Figure 3C. Normal Gestational Sac

Sagittal TVS of the uterus shows a normal gestational sac (within calipers) with a thick echogenic rim representing chorionic villi and decidual reaction (arrowheads).

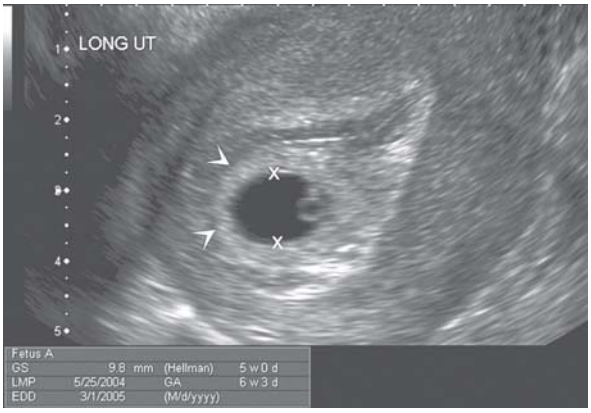


Figure 3D. Normal Six-Week Gestation

Coronal TVS at six weeks of menstrual age demonstrates an intrauterine gestational sac, yolk sac (curved arrow), and early embryo (within calipers).

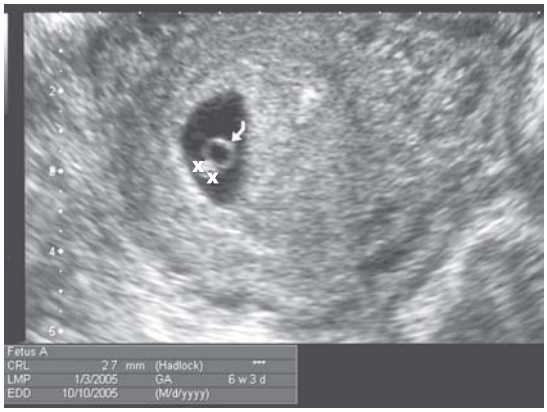
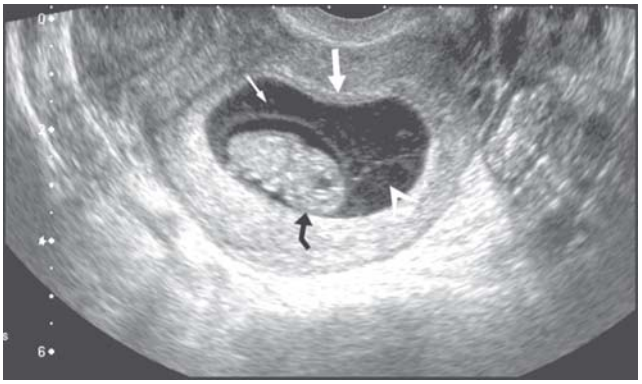


Figure 3E. Embryonic Stage Of Intrauterine Pregnancy

Coronal TVS of the uterus demonstrates intrauterine pregnancy with an embryo (black bent arrow), amniotic membrane (small arrow), which has not yet fused with chorion (white large arrow). Arrowhead points to low level echoes.



Figures 3 A-E are reprinted with permission from Dogra V. Paspulati RM. Bhatt S. First trimester bleeding evaluation. [Review] [125 refs] [Journal Article. Review] Ultrasound Quarterly. 21(2):69-85.

for cardiac activity.[59,60]

Historically, sonography has been performed by a radiologist. Focused sonography performed by emergency physicians to answer a specific question has increased in use and has become a core competency in emergency medicine residency training. Other tests may provide more detailed information, but a focused emergency ultrasound is non-invasive, allows a patient to stay in the ED, and is rapidly utilized, often without the delay in waiting for the radiology staff to be mobilized. These advantages make it a valuable addition to the diagnostic resources available to the emergency physician.

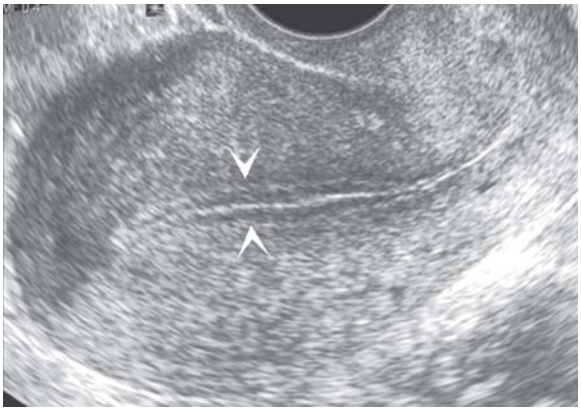
Use Of Ultrasound In Miscarriage

Sonography is the primary means of evaluating the health of the fetus as well as its location and age. In a prospective cohort study of 225 patients, if fetal heart beats were identified, the risk of miscarriage, even in the face of vaginal bleeding, was only 5.5%.[55]

The sonographic features of a miscarriage depend on the stage of development and should be correlated with β-hCG levels and gestational age. The gestational sac size and appearance are major criteria in determining outcome.[50,61] Mean gestational sac diameters of more than 8 mm on TVS or 18 mm on TAS without an embryo or a yolk sac are important predictors of a nonviable gestation, see **Figure 4**. A deformed shape, low position, and a thin decidual reaction are all markers for a poor outcome.[67] Demonstration of cardiac activity within the embryo should occur by the time the embryo reaches 5 mm crown-rump length; the finding of embryonic bradycardia (heart rate less than 100 prior to six weeks and less than 120 between 6.3-7 weeks) is associated with a poor outcome, see **Table 5**.[57] If a viable conception cannot be seen, serial ultrasound examinations and assessment of β-hCG should be arranged as an outpatient.

Figure 4. Normal Endometrium

Sagittal TVS of the uterus demonstrates a normal endometrial lining (arrowheads).



Reprinted with permission from: Dogra V. Paspulati RM. Bhatt S. First trimester bleeding evaluation. [Review] [125 refs] [Journal Article. Review] Ultrasound Quarterly. 21(2):69-85.

Table 5. Sonographic Criteria For Fetal Demise

- 15 mm crown-rump length with no fetal heart beats
- No fetus with gestational sac of 25 mm mean diameter
- Enlarged amniotic cavity greater than crown-rump length
- Abnormal hyperechoic material in the uterus
- No fetal heart tones after 10-12 weeks gestational age
- Empty amniotic cavity

Adapted from Cunningham et al. Williams's obstetrics, ed 20, Norwalk, Conn, 1997, Appleton & Lange.

Persistent vaginal bleeding after a miscarriage can be due to retained products of conception. On TVS, an endometrial thickness of greater than 8 mm may indicate retained products, see **Figure 5**.[63,64] Doppler imaging may differentiate free floating clots from retained trophoblastic tissue by demonstrating low resistance arterial flow.[65,66]

Use Of Ultrasound In Ectopic Pregnancy

The most definitive sign of an early ectopic pregnancy is the presence of a extrauterine gestational sac or an embryonic pole with cardiac activity, see **Table 6** on page 12 and **Figures 6 and 7**.[67] TAS may show direct evidence of ectopic pregnancy, but indeterminate results should be expected in almost 50% of cases.[22] As a result, indirect evidence for or against an IUP must be evaluated. The absence of an intrauterine gestational sac seen on TAS in the patient who has a quantitative β-hCG level greater than 6500 mIU/mL is highly predictive of an abnormal or ectopic pregnancy.[23] Unfortunately, levels this high develop in less than 25% of patients with ectopic pregnancies;[23] more commonly, only non-diagnostic findings or absence of IUP are seen.[68]

With transvaginal ultrasound, the percentage of indeterminate ultrasonographic findings is reduced to 18%.[69] If an intrauterine gestational sac is not seen on TVS when the β-hCG level is greater than 1400 mIU/mL, strongly suspect an ectopic pregnancy. A prospective study of 840 women with suspected ectopic pregnancy demonstrated that TVS had an 87% sensitivity and a 94% specificity in diagnosing ectopic pregnancy when compared to the gold standard of laparoscopy.[70] Additionally, up to 69% of ectopic pregnancies can be detected by TVS at the initial ED visit.[71] Landmarks with TVS

and corresponding β-hCG levels are seen in **Table 4** on page 7.

Laparoscopy

Although invasive, laparoscopy is extremely accurate as a diagnostic (and therapeutic) procedure for possible ectopic pregnancy; it is the diagnostic treatment of choice in patients with peritoneal signs and unclear results from ultrasography.[13,71]

Figure 5. Retained Products Of Conception

Sagittal (A) and coronal (B) TVS images in a patient with vaginal bleeding demonstrate heterogeneous intrauterine contents (arrowheads). C: Color flow Doppler (shown in grayscale) evaluation shows increased vascularity of the complex endometrial contents.

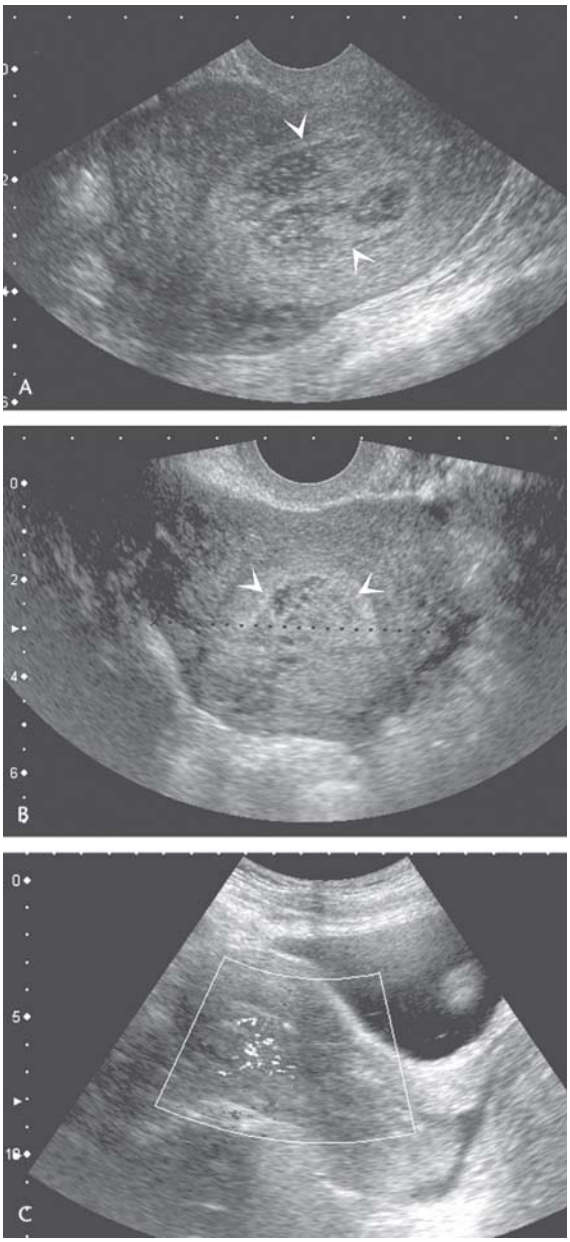


Figure 5 is reprinted with permission from: Dogra V. Paspulati RM. Bhatt S. First trimester bleeding evaluation. [Review] [125 refs] [Journal Article. Review] Ultrasound Quarterly. 21(2):69-85.

Treatment

The **Complications of Early Pregnancy Clinical Pathway** on page 16 presents a general management algorithm for the pregnant patient presenting to the ED in the first trimester with vaginal bleeding or abdominal pain. In rare cases where the patient cannot be stabilized, an immediate laparotomy may be indicated. However, the majority of patients who seek treatment can be systematically evaluated with management based on diagnostic findings.

In stable patients, the goal is to exclude ectopic pregnancy in a timely fashion. In stable patients suspected of having an ectopic pregnancy, two general outpatient approaches have been described, using either sonography or β-hCG as the initial screening tool.[72,73] Both of these are equally sensitive, but when TVS is performed first, fewer normal pregnancies

Figure 6. Transvaginal Sonogram Of Psuedo Sac Which Can Often Be Mistaken For Gestational Sac

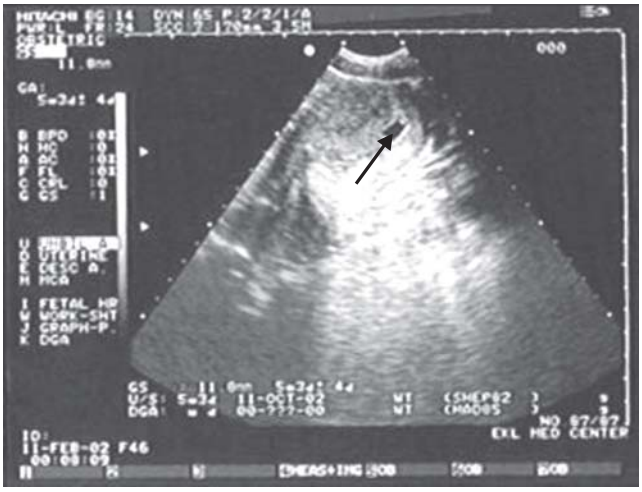


Figure 7. Transvaginal Sonogram Of Fetal Heart Motion In Fallopian Tube

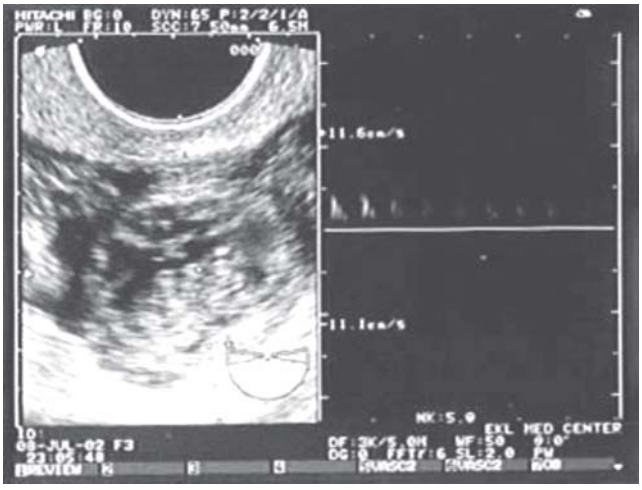


Table 6. Sonographic Findings In The Patient With Suspected Ectopic Pregnancy

Diagnostic of IUP
"Double" gestational sac
Intrauterine fetal pole or yolk sac
Intrauterine fetal heart activity

Diagnostic of ectopic gestation
Ectopic fetal heart activity or
Ectopic fetal pole

Suggestive of ectopic gestation
Moderate or large cul-de-sac fluid without IUP
Adnexal mass* without IUP
*Complex mass most suggestive of ectopic pregnancy, but cyst can also be seen with ectopic pregnancy

Indeterminate
Empty uterus
Nonspecific fluid collections
Echogenic material
Abnormal sac
Single gestational sac

Adapted from Dart RG. Role of pelvic ultrasound in evaluation of symptomatic first trimester pregnancy. Ann Emerg Med 1999; 33: 310-320.

were terminated in the evaluation of presenting symptoms. Data from two or more ancillary studies can be used together to evaluate the odds of ectopic pregnancy. Cost, availability, and convenience will drive the ordering of ancillary studies in different institutions. In all cases, if the patient is discharged, give careful instructions for symptoms that would require return to the ED, see **Table 7**.

Table 7. Ectopic Precautions For Expectant Management

Indications to seek immediate medical attention include:
- Worsening abdominal pain
- Worsening vaginal bleeding
- Weakness, shortness of breath, or passing out
- Unable to make defined 48-hour follow-up for repeat β-hCG testing

An alternative strategy using β-hCG determination prior to ultrasound has been used.[41] However, waiting times for the serum assay can increase length of stay in the ED. In addition, sonography can be diagnostic of ectopic pregnancy even if the β-hCG level is less than 1000 mIU/mL.[30] Finally, the diagnosis may be missed in those patients with a β-hCG lower than the discriminatory threshold who are not assessed with sonography.[30]

A subset of patients has indeterminate ultrasonographic results and β-hCG levels less than 1500 mIU/mL. When the β-hCG levels never rise to the discriminatory zone, the differential diagnosis includes intrauterine fetal demise and ectopic pregnancy. Early D & C with identification of POCs can be useful to the patient with flat β-hCG levels to detect chorionic villi and confirm a failed IUP.[74] Alternatively, expectant management may be utilized to follow β-hCG levels until they reach zero, particularly if initial levels are low. Expectant management is not recommended in patients who have received infertility treatment because the risk of heterotopic pregnancy is so high.[75]

All patients who are at risk for a fetomaternal transfusion in early pregnancy (pregnancy with vaginal bleeding, miscarriage, significant trauma, or an ectopic pregnancy) require assessment of their Rh antigen. Although the classically described Kleihauer-Bethke test has been purported as the standard of care for identifying fetomaternal hemorrhage, some studies have found it to be unreliable. In any patient at risk for fetomaternal hemorrhage, anti-D immune globulin (RhoGam®) should be administered if the patient is Rh-negative (unless the father is also Rh-negative) regardless of the results of the Kleihauer-Bethke test. A 50 μg dose is used during the first trimester and a full 300 μg dose after the first trimester.[13,76] Although it has never been prospectively studied, retrospective analysis shows that anti-D immune globulin prevents the alloimmunization of Rh-negative.[77,78]

Miscarriage Management

In the stable patient with a threatened miscarriage, as long as ectopic pregnancy has been excluded, observation over time may be sufficient to determine when intervention is needed. Serial quantitative β-hCG levels may be used to assess the health of the fetus if ultrasonography is indeterminate or if the gestational age is less than six to seven weeks. The sonographic "discriminatory zone" occurs when the quantitative β-hCG level is high enough to indicate that a normally developing IUP should be seen. This has been set at 1500-2000 mIU/mL for transvaginal sonography, and 6500 mIU/mL for transabdominal sonography.[13,23,79] 3000 mIU/mL should be used as the upper limit of the "discriminatory zone" for TVS, the level at which normal intrauterine pregnancies should always be visualized.[80] Sonography should be performed or repeated when β-hCG levels rise to 3000 mIU/mL. If β-hCG levels are flat or decline or if sonographic criteria for fetal demise are demonstrated, refer the patient to a specialist for follow-up. Patients with such findings must be followed closely. When β-hCG levels are falling, a D & C may be performed, especially if β-hCG levels are less than 250 mIU/mL. The tissue removed should be examined

for chorionic villi. Chorionic villi will be identified after D & C in approximately 70% of patients with indeterminate sonography.[74] If chorionic villi are not found, the risk of ectopic pregnancy increases.[74]

After assessment of hemodynamic status and management of blood loss, a patient with a threatened miscarriage requires very little specific medical treatment. Ectopic pregnancy should always be considered and sonography performed if risk factors for ectopic pregnancy are present or if the patient has pain. Although ectopic pregnancy can be associated with painless bleeding,[81] this occurs less frequently. Sonography can be scheduled more routinely at a later time as long as the patient is aware that the potential for ectopic pregnancy still exists. In the patient who is planning pregnancy termination, prompt referral should be encouraged and chorionic villi confirmed at the time of uterine evacuation.

Fifty percent or more of women with threatened miscarriage who are seen in ED's ultimately miscarry.[82] Treatment to "prevent" miscarriage is not useful because most fetuses can be shown to be nonviable one to two weeks before actual symptoms occur.[17] In the vast majority of cases, spontaneous miscarriage is the body's natural method of expelling an abnormal or undeveloped (blighted) pregnancy. Thus a major goal of ED management should be patient education and support. Patients should be advised that moderate daily activities will not affect the pregnancy. Tampons, intercourse, and other activities that might induce uterine infection should be avoided as long as the patient is bleeding, and she should return immediately for fever, abdominal pain, or a significant increase in bleeding. If tissue is passed by the patient, it should be brought for analysis for the presence of products of conception, because differentiation of fetal parts from decidual slough (decidual cast) is difficult.

Treatment of the patient with *inevitable miscarriage* includes dilation and evacuation (D & E) or D & C to remove the remaining intrauterine contents. When the os is open, the uterus is unable to contract adequately to limit bleeding from the implantation site, and simple removal of tissue from the cervix usually allows contraction to occur. Bleeding may be brisk, and gentle removal of fetal tissue from the cervical os with ring forceps often slows bleeding considerably.

Management of patients with *presumed completed spontaneous miscarriage* is more complicated. If the patient brings tissue with her, this should be preliminarily inspected in the ED and then sent to the pathology department for evaluation. Recent studies have shown that, in women with a history consistent with miscarriage who have minimal remaining intrauterine tissue as determined by sonography, expectant management is safe if ectopic pregnancy can be excluded.[83] If endometrial tissue is not seen with ultrasonography, bleeding is mild, and gestational age is less than eight weeks, curettage is frequently unnecessary and the patient may be safely followed-up by a gynecologist for serial hormonal assays.[84] In contrast, in women with significant remaining intrauterine tissue, the risk of complications may be decreased by uterine curettage.[83] Consultation with a specialist is advised and, if D & C is not performed, the patient should be instructed to return if increased bleeding, cramping, fever, or tissue passage occurs. Follow-up is required in one to two weeks to assure that the miscarriage is complete.

After miscarriage, the patient should be advised that fetal loss is associated with significant psychological stress, even during the first trimester. Follow-up in one to two weeks with a gynecologist should be provided.[85] Some physicians prescribe antibiotics after D & C (usually doxycycline or metronidazole), particularly in patient populations at high risk for genital tract infections. Ergonovine or methylergonovine (0.2 mg PO twice daily) may also be used to stimulate uterine involution. The patient should receive careful advice to return if signs of infection (fever or uterine tenderness) occur, if bleeding resumes, or if further tissue is passed. As noted in the previous section, anti-D immune globulin may also be indicated.

Ectopic

The primary goal of accurate and early identification of ectopic pregnancy is to limit morbidity and eliminate mortality resulting from this condition. If diagnosed early, the patient is potentially a candidate for either minimally invasive surgery or medical therapy. In early stages, these therapies have been found to be just as effective as the traditional laparotomy with salpingectomy. However, newer therapies have the advantage of salvaging the fallopian tube. In unstable patients with a high suspicion of tubal rupture, the choice of treatment is still laparotomy.

Medical Therapy - Methotrexate

Non-operative management has become standard care for the stable patient with an ectopic pregnan-

cy.[43,77] Methotrexate is the most commonly used drug and belongs to a class of drugs called folic acid antagonists.[86] It works by inhibiting the enzyme dihydrofolate reductase, leading to a depletion of the cofactors required for DNA synthesis. Initially, methotrexate was used to treat leukemia but gained wide acceptance in the treatment of choriocarcinoma. In pregnancy, methotrexate causes destruction of rapidly dividing fetal cells and involution of the pregnancy.[87] Methotrexate may be given orally, intramuscularly, or by continuous infusion. For the treatment of ectopic pregnancy, the intramuscular route is currently preferred.[87] However, success has been reported with the oral route alone in a few studies.[87] Stovall et al performed the largest study of methotrexate, which involved 100 patients, 96 of whom responded successfully.[91] Several smaller studies had success rates ranging from 83-100%.[86-90] With the exception of the study by Stovall et al, ectopic pregnancies with cardiac activity were excluded from methotrexate treatment.

Methotrexate may be given with citrovorum (Leucovorin®) rescue as a therapy for ectopic pregnancy. Citrovorum, which is a reduced form of folate, blocks the effects of methotrexate. Given after administration of methotrexate, it appears to rescue cells from additional adverse effects of the drug.

The use of methotrexate is associated with several complications, the most common of which is lower abdominal pain.[92-96,98] The pathophysiology of the abdominal pain is unclear, though it is probably related to bleeding and/or expulsion of the ectopic resulting in peritoneal irritation. These patients can be managed conservatively if they have a stable hemoglobin and no evidence of significant free fluid in the cul-de-sac by ultrasound. Twenty percent of patients in the study by Stovall et al had an increase in abdominal pain managed as an outpatient, and an additional 4% were subsequently hospitalized for observation.[91]

Other complications included transient elevation of transaminase levels, mild stomatitis, dermatitis, pleuritis, and nausea.[86-91,97] These side effects appear to be dose-related, occurring with higher doses of methotrexate received, without significant morbidity or mortality.

The most serious complication of the methotrexate regimen is tubal rupture, the pathophysiology of which is unclear, see **Table 8**. In six studies reviewed, there were seven ruptures among 275 treated patients.[92,96,99] In addition, there was one case report of tubal rupture despite falling β-hCG levels.[100] The possibility of rupture exists until complete resolution of the ectopic is documented (β-hCG less than 10-20 mIU/mL). There is no correlation between β-hCG levels and risk of rupture that can aid the clinician. Due to the extended time until resolution of the ectopic pregnancy, the symptoms of tubal rupture need to be monitored on a continuous basis.[86-91]

Table 8. Signs Of Treatment Failure For Ectopic Pregnancy and/or Tubal Rupture

- Significantly worsening abdominal pain
- Significant hemoperitoneum visualized via ultrasound
- Hemodynamic instability
- Lack of a decrease in β-hCG after day four of treatment
- Increasing or plateauing levels after the first week of treatment

Adapted from American College of Obstetrics and Gynecologists. Medical management of tubal pregnancy, ACOG Practice Bulletin 3. Washington DC ACOG 1998.

All patients presenting with worsening abdominal pain after receiving methotrexate should be carefully evaluated for tubal rupture. When a patient presents with abdominal pain after methotrexate administration, she should be evaluated with a repeat hemoglobin, an ultrasound to detect free fluid, and consultation with an obstetrician. Patients with increased abdominal pain who are hemodynamically stable with no fluid in the cul-de-sac and a stable hemoglobin may be managed as outpatients. Admission for continued observation despite negative studies may be required if her pain is not controlled or her vital signs are abnormal.

The success of higher dose methotrexate protocols with citrovorum rescue led to trials of lower single dose intramuscular (IM) methotrexate without citrovorum rescue. Success rates with this protocol have ranged from 85 to 100%.[83-86] In the largest study, which treated 120 patients, there was a 94% rate of ectopic termination (defined as a β-hCG of 10-20 mIU/ml).[87] Ectopic termination and resolution times range in various studies from a mean of 23.1$\pm$2.9 days to 38.4$\pm$6.4 days.[83-87] Low dose treatment is reported to result in longer resolution times, but higher initial β-hCG levels where found in these studies. It is unclear why initial levels where higher, but it could represent a selection bias in these studies.[87,13,15] Predictors for success of methotrexate treatment are listed in **Table 9**.[92] Of these markers, a low β-hCG level has proven to be most predictive. In a retrospective study of 60 patients, Tawfiq et al found that failure occurred in 65% of the cases where the β-hCG level was greater than 4000 mIU/mL.[102] In a review of 350 ectopic pregnancy patients, the

methotrexate failure rate rose to greater than 13% when the pretreatment β-hCG level was greater than 5000 mIU/mL.[103] However, despite these studies, there is not an accepted absolute β-hCG level where use of methotrexate is contraindicated.[104,105]

Table 9: Predictors For Success Of Methotrexate Treatment For Ectopic Pregnancy

- Low serum β-hCG levels
- Low progesterone levels
- Small size and volume of gestational mass
- Absence of cardiac activity
- Lack of peritoneal blood

In addition to the primary treatment of ectopic pregnancy, methotrexate is also indicated for the treatment of persistent ectopic after salpingostomy, prophylaxis for suspected persistent products of conception after conservative surgery, and in cases of unusual ectopic pregnancy, such as abdominally implanted pregnancies.[104] Absolute contraindications can be seen in **Table 10**. Relative contraindications include a gestational sac of greater than 3.5 cm and embryonic cardiac activity. In addition, any patient who receives methotrexate must be compliant, understand the importance of follow-up, and be able to return for surveillance and possibly further care.[105] Any patient receiving methotrexate should be screened with a complete blood count, liver function tests, and an electrolyte panel with a serum creatinine.[96] In addition, if the patient has a history of pulmonary disease, a baseline chest x-ray must be obtained due to the risk of interstitial pneumonitis.

The ability to conceive after the use of methotrexate for ectopic pregnancy has been addressed in several studies. One weakness in these studies is that the tubal patency rates were not established prior to methotrexate use, possibly leading to lower percentage of patency than expected. Of the patients attempting to conceive after methotrexate therapy, a success rate of about 80% has been reported.[96,106] The recurrent ectopic pregnancy rate is about 10% in patients treated with intramuscular methotrexate versus 13% in patients treated with linear salpingostomy, but this is not a statistically significant difference.[96,106]

Table 10. Absolute Contraindications To Methotrexate Use

- Breast feeding
- Immunodeficiency
- Alcoholism
- Pre-existing liver disease or dysfunction
- Blood dyscrasias or hematologic dysfunction
- Know hypersensitivity to methotrexate
- Active pulmonary disease
- Peptic ulcer disease
- Renal dysfunction

Adapted from American College of Obstetrics and Gynecologists. Medical management of tubal pregnancy. ACOG Practice Bulletin 3. Washington DC ACOG 1998.

Methotrexate Dosing Regimens

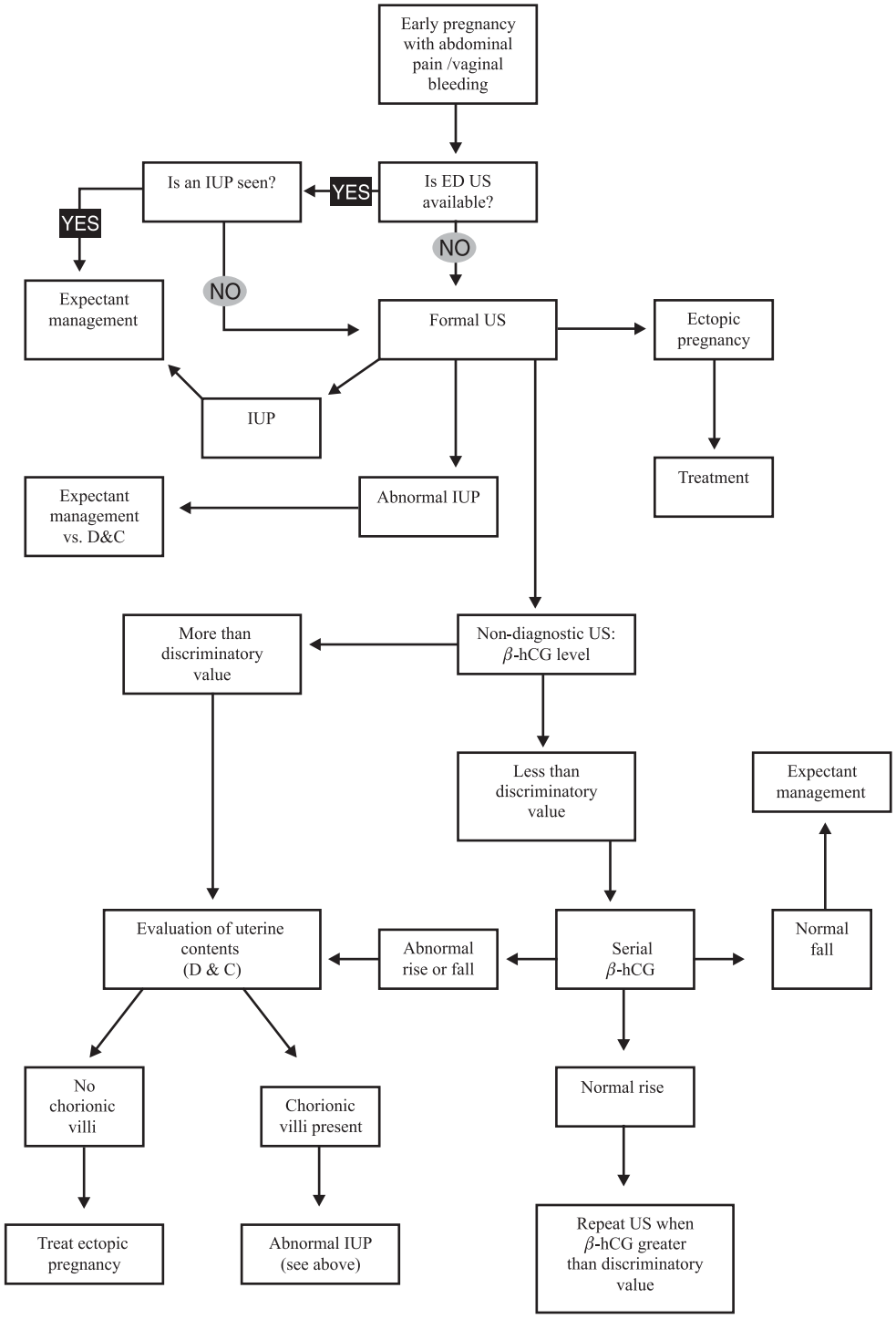
Traditionally, multi-dose IM methotrexate has been the treatment of choice, but single dose methotrexate is becoming more popular, see **Table 11** on page 18. These two regimens have never been directly compared, but a recent meta-analysis was conducted to compare efficacies.[119] In qualifying cases, the overall success rate for IM methotrexate was 89%. The success rate for multi-dose IM methotrexate was 92.7% while the success rate for the single dose regimen was only 88.1%. This was found to be statistically significant. When controlling for β-hCG levels, the failure rate with single dose therapy was almost five times greater than the multi-dose regimen. The success rates found in this meta-analysis mirrors what other studies have found regarding successful treatment rates in single dose and multi-dose regimens. A new two dose IM methotrexate protocol has been developed which attempts to balance efficacy as well as convenience, see **Table 12** on page 18. A dose of methotrexate is given on day one and day four without leucovorin rescue, and the prior single dose follow-up protocol is then followed. Due to the risk of failure with increasing β-hCG levels, some have advocated the use of the two dose protocol with β-hCG levels greater than 1000 mIU/mL, but this has not been prospectively studied to date.[104]

Operative Care

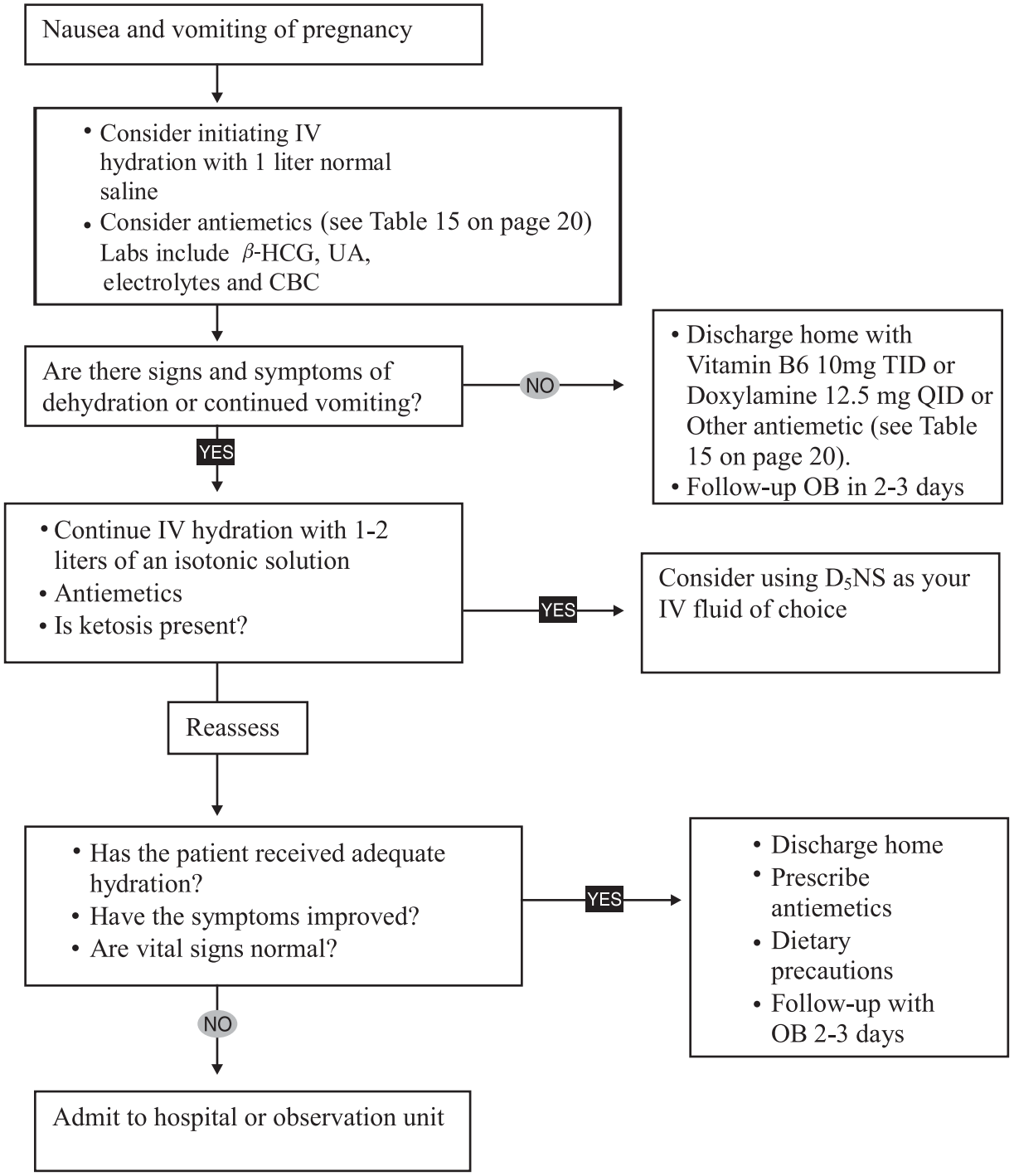
Historically, laparotomy was the treatment of choice for ectopic pregnancy. With the advent of methotrexate therapy and laparoscopy, laparotomy has become significantly less frequent. Laparotomy still has a role in patients who are unstable and unable to be emergently resuscitated as well as those with evidence of extensive intraperitoneal bleeding. In addition, in hemodynamically unstable patients with an open cervical os, D & C may be useful to obtain tissue that will either confirm an IUP or show a decidual cast suggestive of ectopic pregnancy.

For hemodynamically stable patients, those with peritoneal signs, or those who cannot receive methotrexate, use laparoscopy.[71,72] It is associated with decreased blood loss, fewer analgesic requirements, and shorter hospital stays. It has also been found to be cost effective when compared to the tra-

Clinical Pathway: Complications of Early Pregnancy



Clinical Pathway: For Nausea And Vomiting Of Pregnancy



This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient's individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

Table 11. Single Dose vs. Multi-dose Methotrexate Regimen For Treatment Of Ectopic Pregnancy

Multi-dose Regimen	
Treatment Day	**Intervention**
Pretreatment	CBC, LFT's, electrolytes, serum quantitative hCG
Day 1	Methotrexate 1 mg/m^2 IM Serum hCG
Day 2	Citrovorin 0.1 mg/m^2
Day 3	Serum hCG If serum hCG decreases less than 15% from day 1 to 3, provide methotrexate 1 mg/m^2 IM. If decrease is greater than 15%, start surveillance and stop treatment
Day 4	Citrovorin 0.1 mg/m^2
Day 5	Serum hCG If serum hCG decreases less than 15% from day 3 to 5, provide methotrexate 1 mg/m^2 IM. If decrease is greater than 15%, start surveillance and stop treatment
Day 6	Citrovorin 0.1 mg/m^2
Day 7	Serum hCG If serum hCG decreases less than 15% from day 5 to 7, provide methotrexate 1 mg/m^2 IM. If decrease is greater than 15%, start surveillance and stop treatment
Day 8	Citrovorin 0.1 mg/m^2
Surveillance	Serum hCG checked weekly until level is less than 5 mIU/mL
Single Dose Regimen	
Treatment Day	**Intervention**
Pretreatment	CBC, LFT's, electrolytes, serum quantitative hCG
Day 1	Methotrexate 50 mg/m^2 IM Serum hCG
Day 4	Serum hCG
Day 7	If serum hCG decreases less than 15% from day 4 to 7, provide methotrexate 50 mg/m^2 IM. If decrease is greater than 15%, start surveillance

ditional approach of laparotomy.

Traditionally, salpingectomy was the surgical procedure of choice, but with the newer laparoscopic techniques, tubal salvage procedures in hemodynamically stable patients are commonly used. Although the rate of persistent ectopic is 5-20% higher in the salpingostomy group, the use of methotrexate has abated most concerns. In general, it is thought that the risk of future ectopic pregnancy is increased by

Table 12. "Two dose" Intramuscular Methotrexate Regimen For Treatment Of Ectopic Pregnancy

Treatment Day	**Intervention**
Pretreatment	CBC, LFT's, electrolytes, serum quantitative hCG
Day 1	Methotrexate 50 mg/m^2 IM Serum hCG
Day 4	Methotrexate 50 mg/m^2 IM Serum hCG
Day 7	If serum HCG decreases less than 15% from day 4 to 7, provide methotrexate 50 mg/m^2 IM. If decrease is greater than 15%, start surveillance

the use of salpingostomy, but this is balanced by an increased rate of future fertility.[107-110] Salpingostomy is preferred to salpingectomy if the patient is stable and the procedure is technically feasible.[72]

Controversies/Cutting edge

Other Markers For The Diagnosis Of Ectopic Pregnancy

The search for novel markers for the diagnosis of ectopic pregnancy has yielded many potential candidates, but none of them have proven reliable and easily available. Elevated levels of vascular endothelial growth factor (VEGF) are reported in ectopic gestations but are neither sensitive nor specific.[111,112] Other placental markers (such as pregnancy associated plasma protein A (PAPP-A), pregnancy specific B1 glycoprotein, and human placental lactogen) and non-placental markers (such as glycodelin) have been studied.[113] In one study, the combination of VEGF, PAPP-A, and progesterone was able to discriminate ectopic from intrauterine pregnancy with a sensitivity of 99.7% and a specificity of 92.4%. In a study by Gerton et al, specific proteins were identified that were potentially able to discriminate between ectopic and intrauterine pregnancies.[114] Further study and characterization of these proteins is required, followed by prospective validation.

Other chemical markers studied include serum creatine phosphokinase (CK), myoglobin, smooth muscle heavy chain myosin, fetal fibronectin, leukemia inhibitory factor, and cancer antigen 125 (CA-125). Serum CK is generally increased in ectopic pregnancies (mean 56.7 mIU/mL; range 46.5 to 61.3 mIU/mL) relative to IUP (mean 41.0 mIU/mL; range 38.8 to 45.4 mIU/mL), but it is not sufficiently discriminative to be of clinical value in

the diagnosis of ectopic pregnancy.[115] In addition, recent studies have indicated that increased CA-125,[116] and urinary hCG expression of certain molecular components[117] can also be predictors of early pregnancy loss, although they are not in widespread use. Use of these objective means to identify fetal demise may help the mother accept the loss and allow consideration of D & C, if necessary.

Modeling For The Diagnosis Of Ectopic Pregnancy

An alternative approach to the diagnosis of ectopic pregnancy is the use of clinical decision rules and mathematical modeling. In a logistic regression model predicting ectopic pregnancy, the β-hCG ratio at 0 and 48 hours was found to best predict the subsequent outcome of a pregnancy with an unknown location.[118] However, ectopic pregnancies can have ratios that appear to be normal, especially in the early stages of an ectopic pregnancy.[40] Conversely, some intrauterine pregnancies that have a lower than normal rise in β-hCG would be misclassified as abnormal gestations. Of the models studied, none demonstrated a higher sensitivity for predicting ectopic pregnancy than clinical judgment.

Special Circumstance Of Early Pregnancy

Hyperemesis Gravidarum

Nausea and vomiting is a common problem affecting 50-70% of pregnant patients.[120-122] It usually starts during the first month of pregnancy and tapers off toward the middle of the second trimester. Hyperemesis gravidarum is a severe form of nausea and vomiting of pregnancy that causes starvation metabolism, weight loss, dehydration, and prolonged ketosis. In general, cohort studies have shown an incidence of 0.5-2%.[123] The cause of hyperemesis gravidarum is not clear; associations have been made with rapidly increasing estrogen and β-hCG levels.[124] A recent study also reported an increased infection rate with *Helicobacter pylori*.[125] For a list of risk factors associated with the development of hyperemesis gravidarum, see **Table 13**.

Evaluation and management of hyperemesis gravidarum should focus on the fluid status of the patient and identifying other causes of nausea and vomiting.[126] The history should focus on ruling out other causes in the differential diagnosis, see **Table 14** on page 20. Most patients typically have some symptoms prior to nine weeks. If a patient presents after nine weeks, give careful consideration to other diagnoses. Fever should lead the clinician to search for possible causes of infection that may lead to alternate diagnoses. Other than mild abdominal discomfort with retching, abdominal pain should not be a prominent feature and should be a clue for the clinician to search for other causes.

Table 13. Risk Factors Associated With The Development Of Hyperemesis Gravidarum

- Advanced placental mass
  - Multiple gestations
  - Molar pregnancy
- Genetics
  - Family history of hyperemesis gravidarum
  - Prior history of hyperemesis gravidarum in prior pregnancy
- Female gestations
- Hyperthyroidism
- Nullparity
- Young age
- History of migraine headaches
- History of motion sickness

Risk Factors That Reduce The Development Of Hyperemesis Gravidarum

- Smoking
- Male gestations

Adapted from American College of Obstetrics and Gynecology. Nausea and vomiting of pregnancy. ACOG Practice Bulletin. 103(4):803-14, Apr.

Initial laboratory and radiologic evaluation is minimal. Guidelines based on consensus opinion from the American College of Obstetrics and Gynecology suggest that, if a patient presents with only severe nausea and appears hydrated, no work-up may be required. Send an electrolyte panel, BUN and creatinine, urinalysis, and a complete blood count in any patient who requires intravenous hydration.[126] Further work-up should be directed toward abnormal findings in the history or physical exam. Significant pain on abdominal exam may lead the clinician to order liver function panels, amylase or lipase, and an abdominal US. In some patients, bilirubin, amylase and alkaline phosphatase can be mildly elevated, but should return to normal levels after delivery. Findings of a goiter should lead to tests for thyroid function.

Initial management involves rehydration with either oral or intravenous fluids and antiemetics, see **Clinical Pathway For Nausea And Vomiting Of Pregnancy** on page 17.[126] Patients who present with severe nausea and appear hydrated may be managed as outpatients with no further work-up in the ED. However, if the patient presents with persistent or prolonged vomiting or has signs and symptoms of dehydration, rehydration should be accomplished

Table 14. Differential Diagnosis Of Nausea And Vomiting Of Pregnancy

Gastrointestinal Conditions
Appendicitis
Pancreatitis
Biliary colic or cholecystitis
Peptic ulcer disease
Intestinal obstruction
Achalasia
Gastroesophageal reflux disease
Hepatitis
Gastroparesis
Genitourinary Conditions
Kidney stone
Ovarian torsion
Urinary tract infections
Degenerating uterine leiomyoma
Metabolic Disorders
Diabetic Ketoacidosis
Hyperthyroidism
Addison's Disease
Porphyria
Neurologic Conditions
Migraines
Brain tumors
Encephalopathy
Pseudotumor cerebri
Vestibular dysfunction
Other Conditions
Psychiatric illness
Drug toxicity
Pregnancy-Related Conditions
Acute fatty liver of pregnancy
Cardiomyopathy of pregnancy
Preeclampsia

Adapted from American College of Obstetrics and Gynecology. Nausea and vomiting of pregnancy. ACOG Practice Bulletin. 103(4):803-14, 2004 Apr.

with an isotonic crystalloid solution. Severely dehydrated patients often present with starvation metabolism which can be identified by ketones in the urine. Although it has never been studied, it is generally recommended by consensus opinion that glucose be added to the solution to reverse ketotic metabolism.[126] Electrolyte abnormalities, such as hypokalemia and hyponatremia, are common and should be replaced when identified. If a patient has had prolonged vomiting (more than three weeks) or weight loss (more than five pounds), a multivitamin and thiamine 100 mg IV should be considered to prevent the rare cases of Wernicke-Korsakoff Syndrome that have been reported in the literature.

In addition to hydration and calories, antiemetics provide the most symptomatic relief. Most standard antiemetics are in Food and Drug Administration (FDA) category C and are used successfully to treat hyperemesis gravidarum, see **Table 15**.[126] Although infrequently used in the ED, pyroxidine (vitamin B6) and doxylamine have been shown to improve symptoms of nausea and vomiting of pregnancy and have been found to have no significant teratogenic risk.[128-130] Although ondansetron (Zofran®) has been used with some success, no studies to date have looked at its efficacy compared to other antiemetics.[131] In animal studies, ondansetron has been shown to cause cranio-facial abnormalities.[132] In humans, there is only one small prospective cohort study evaluating embryogenic safety with ondansetron use; it showed no difference compared to other patients receiving typical antiemetics.[133] A short course of oral methylprednisolone has been reported to be therapeutic for intractable hyperemesis, but has recently been found to be associated with an increased risk of craniofacial abnormalities when used early in pregnancy.[134-137] Alternative therapies that are safe for the fetus and may provide some symptomatic relief include the use of ginger and P6 acupressure (located at the palmar aspect of the distal wrist).[138,139,156]

Most patients can be discharged from the ED after typical treatment, but often require prolonged stays (more than six hours). If a prolonged ED stay is anticipated or the patient has persistent symptoms despite adequate hydration, admission to an ED observation unit or an obstetric unit is appropriate.

Table 15. Common Antiemetics Used In Pregnancy

Agents	Effectiveness	Teratogenesis
H-1 Blockers Doxylamine Meclizine Hydroxyzine Diphenhydramine	Multiple RCT's show effect in reducing nausea and vomiting of pregnancy. No trials of effectiveness for diphenhydramine	No increased risk of malformations
Anticholinergics Scopolamine	No effectiveness trials reported to date	No increased risk of malformations
Dopamine Agents Metoclopramide Trimethobenzamide	Trimethobenzamide has shown effectiveness in RCT, no studies with metoclopramide	No increased risk of malformations
Phenothiazines Promethazine Prochlorperazine Chlorpromazine	Promethazine has shown effectiveness in RCT, no studies with prochlorperazine and chlorpromazine	Bulk of evidence shows no increased risk of teratogenesis
Butyrophenones Droperidol Haloperidol	No RCT's showing effectiveness	One small study of limited power showing no increased risk of teratogenesis
Steroids Solumedrol	Mixed results of RCT with no clear benefit	Possible risk of increased cleft palate abnormalities with use in early pregnancy
5-hydroxytriptamine 3 Receptor Antagonists Ondansetron	One RCT showing equal effectiveness with promethazine	No increased risk of malformations noted
Alternative Therapies Ginger Pyridoxine P6 acupressure	Multiple small RCT's show improvement in nausea and vomiting compared to placebo	No increased risk of malformations

Adapted from Jewell D, Young G. Interventions for nausea and vomiting in early pregnancy (Cochrane Review). In: The Cochrane Library, Issue 4, 2003. Chichester, UK: John Wiley & Sons, Ltd. and Magee LA, Mazzotta P, Koren G. Evidence-based view of safety and effectiveness of pharmacologic therapy for nausea and vomiting of pregnancy (NVP). Am J Obstet Gynecol 2002;186:S256-61.

Criteria for discharge may include:

- Signs and symptoms of volume depletion have resolved
- Tolerating oral fluids
- Urine ketones have cleared (starvation metabolism has been reversed)
- Close follow-up in one to two days with obstetrician

Typical discharge instructions may be seen in **Table 16**.[126]

Most cases of hyperemesis gravidarum resolve by mid second trimester with no significant sequelae, but the long term effects are not known. However, if the mother is not able to gain weight appropriately as the pregnancy progresses due to hyperemesis gravidarum, the fetus is at risk for low birth weight.[140-142,157,158]

Table 16. Discharge Instructions For A Patient With Nausea And Vomiting Of Pregnancy

- Rest and avoid situations that lead to symptoms
- Drink clear fluids for the first 24 hours and slowly advance your diet
- Eat at least six small meals a day
- Dietary modification with meals high in protein and low in carbohydrates may improve your symptoms
- Take medicines for nausea early when symptoms start
- Return for inability to tolerate anything by mouth, intractable vomiting, fever, severe weakness or dizziness upon standing, abdominal pain, blood in your vomit or stool, or black tarry looking stools

Adapted from: American College of Obstetrics and Gynecology. Nausea and vomiting of pregnancy. ACOG Practice Bulletin. 103(4):803-14, 2004 Apr.

There are no prospective data on the long term risks for women and children regarding hyperemesis gravidarum. It is appropriate to reassure patients that nausea and vomiting of pregnancy as well as hyperemesis gravidarum often portends well for the pregnancy.[126] Severe cases of hyperemesis gravidarum have been found in case reports to be associated with Mallory-Weiss tears, Boerhaave's Syndrome, Wernicke-Korsakoff Syndrome, spontaneous pneumothorax, splenic rupture, and acute tubular necrosis.[143-146]

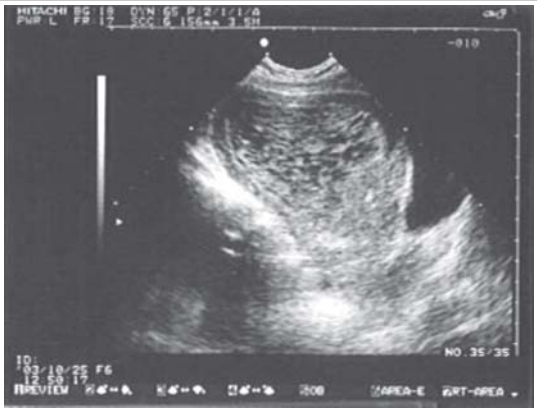
Molar Pregnancy

Gestational trophoblastic disease (molar pregnancy) comprises a spectrum of diseases characterized by disordered proliferation of chorionic villi. In the absence of fetal tissue, the pregnancy is termed a *complete* hydatidiform mole. More rarely, if fetal tissue is present and trophoblastic hyperplasia is focal, it is called an *incomplete* mole. In approximately 15% of molar pregnancies, neoplastic gestational disease develops, with persistence of molar tissue after the pregnancy has been evacuated.[147,148,159] Metastatic disease can develop, requiring chemotherapy and intensive oncologic management.[16]

Early molar pregnancy is usually not clinically apparent, but patients may seek care for persistent hyperemesis gravidarum due to high circulating levels of β-hCG. Vaginal bleeding, intermittent bloody discharge, or failure to hear fetal heart beats during the second trimester are the typical presenting signs. If spontaneous abortion occurs with molar pregnancy, it is usually during the second trimester (before 20 weeks), and the patient or physician may note passage of grapelike hydatid vesicles. Uterine size is larger than expected by dates (by more than four weeks) in approximately 40% of patients.[147] Theca lutein cysts may be present on the ovaries as a result of excessive hormonal stimulation, and torsion of affected ovaries can be seen.

The diagnosis of hydatidiform mole is based on the characteristic sonographic appearance of hydropic vesicles within the uterus, called the "snowstorm" appearance, see **Figure 8** on page 22. Alternatively, cystic changes are seen in partial molar pregnancies.[148] In some cases, partial molar pregnancy may be detected only on pathologic examination of abortion specimens.[148,149] Sonography usually provides the diagnosis of complete molar pregnancy.[149]

Figure 8. Typical Snowstorm Appearance Of A Uterus With Molar Pregnancy



Disposition

Once an IUP is diagnosed, the patient with threatened miscarriage may be discharged, but should be given careful instructions to return if she has signs of hemodynamic instability, significant pain, or other symptoms that might indicate ectopic pregnancy. Proactively developing protocols with OB-GYN as to when follow-up sonographic evaluation and serial

β-hCG measurements should be obtained can greatly facilitate patient care. It is often thought that bed rest should be prescribed for any threatened miscarriage; however, it has never been found to be of value in preventing a miscarriage from progressing.

Treatment of the patient with an *inevitable miscarriage* may include observation or dilation and evacuation (D & E) to remove the remaining intrauterine contents. The patient may be admitted, but discharge with close outpatient follow-up may also be suitable in select cases after OB-GYN consultation.

Management of patients with *presumed completed spontaneous miscarriage* is more complicated. Recent studies have shown that, in women with a history consistent with miscarriage who have minimal remaining intrauterine tissue as determined by sonography, expectant management is safe if ectopic pregnancy can be excluded.[83] If endometrial tissue is not seen with ultrasonography, bleeding is mild, and gestational age is less than eight weeks, curettage is frequently unnecessary and the patient may be safely followed-up by a gynecologist for serial hormonal assays.[84] In contrast, in women with significant remaining intrauterine tissue, the risk of complications may be decreased by uterine curettage.[83] Consultation with a specialist is advised and, if D & C is not performed, the patient should be instructed to return if increased bleeding, cramping, fever, or tissue passage occurs. Consensus opinion is that follow-up is required in one to two weeks to assure that the miscarriage is complete.

Traditionally, patients with ectopic pregnancy were admitted to the hospital; however, with the advent of methotrexate, outpatient treatment has become common. If a patient qualifies for methotrexate and is reliable, they may be discharged with clear instructions to return for worsening pain, bleeding, or fever. Unstable patients with a known ectopic pregnancy, patients with ultrasonographic results suggestive of ectopic pregnancy, and patients with a high risk for an ectopic pregnancy should be admitted for serial examinations and further diagnostic studies until a definitive diagnosis can be made.

Key Points

1. Do not rely on a single β-hCG level as a marker for a viable pregnancy.
2. Low levels of β-hCG do not reliably exclude an ectopic pregnancy alone.
3. Do not ascribe abdominal pain, nausea, and vomiting as side effects of methotrexate therapy without proper evaluation.
4. Do not assume a patient with abdominal pain has a normal pregnancy solely because they do not have vaginal bleeding and vice versa.
5. In patients who have undergone assisted reproduction, finding an IUP does not exclude the diagnosis of an ectopic pregnancy (heterotopic pregnancy).
6. The degree of bleeding and severity of symptoms do not predict which patients will progress from a threatened to inevitable to complete miscarriage.
7. Any patient who is Rh-negative with a miscarriage or ectopic pregnancy must be given anti-D immune globulin to prevent alloimmunization.
8. A patient with an ectopic pregnancy may be treated as an outpatient with methotrexate, but treatment failures do occur and close outpatient follow-up is required.
9. With initial methotrexate therapy, the β-hCG level may increase before it starts to decrease.
10. Do not rely solely on one test or study to make a definitive diagnosis. Often, multiple tests and US are needed to truly make a diagnosis with certainty.

Case Conclusion

The clinician was asked to justify the ordering of a formal pelvic ultrasound without first obtaining the results of the β-hCG. This article has provided evidence that the β-hCG can be useful in helping to interpret ultrasound findings but should not limit obtaining the test. In this case, the intrauterine sac ended up being a reactive sac to the ectopic that was found in the right salpinx. An obstetric (OB) consultation was obtained. After discussion with the patient and OB colleagues, the patient was treated with 50 mg/m² of methotrexate IM and discharged home to follow up with the OB physician in four days.

Summary

The complications of early pregnancy may vary in presentation. Ectopic pregnancies and miscarriage may be very difficult to differentiate from one another. The primary objective of the emergency physician should be to rule out an ectopic pregnancy since it is a major cause of maternal morbidity and mortality. Often, the diagnosis is left in question even with appropriate lab testing and ultrasound results. Patients may require serial evaluations and specialty consultation. Any patient at risk for feto-maternal transfusion should receive anti-D immune globulin for prophylaxis.

If an ectopic pregnancy is diagnosed, methotrexate should be reserved for those patients who qualify, and their ability to follow-up should be considered. Laparoscopy with salpingostomy or salpingectomy is typically the surgical procedure of choice,

but laparotomy is still used in unstable emergency cases.

Although a miscarriage is not usually life threatening, it can be a particularly stressful time for the patient and her significant other. Giving the patient and family a realistic understanding of the risk of miscarriage is helpful. Counseling and other resources should always be made available. Outpatient referral is usually required in cases of complete or inevitable miscarriage; a D & C is often required.

References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study, such as the type of study and the number of patients in the study, will be included in bold type following the reference, where available.

1. Widman's clinical interpretation of Laboratory Tests, 10th Ed. Sacher RA, Mcpherson RA, Campos JM, FA davis and Co., Philadephia, PA.1991. **(Textbook)**
2. Goldner TE, Lawson HW, Xia Z, et al. Surveillance for Ectopic Pregnancy- United States, 1970-1989. *MMWR CDC Surveill Summ* 1993;42: 73-85. **(Retrospective systematic national cohort review)**
3. Centers for Disease Control and prevention. Current Trends Ectopic Pregnancy- United States, 1990-92. MMWR Morb Mortal Wkly Rep. 44: 46-48. 1995 **(Retrospective systematic national cohort review)**
4. Zane SB, Keike BA, et al. Surveillance in a time of Changing Health Care Practices: Estimating Ectopic Pregnancy Incidence in the United States. *Matern Child Health J* 2002;6:227-36. **(Retrospective systematic national cohort review)**
5. Why Mothers Die 1997-99. The Fifth Report of Confidential Enquiries into maternal Deaths in the United kingdom 1997-99. *London: RCOG Press* 2001. **(Retrospective systematic national cohort review)**
6. Sowter MC, Farquhar CM. Ectopic Pregnancy: An Update Current Opin Obstet. *Gynecol* 2004;16:289-93. **(Review article)**
7. Van Den Eeden SK, Shan J, et al. Ectopic Pregnancy Rate and Treatment utilization in a Large Managed care Organization. 2005;105(5):1052-57. **(126,451 pregnancies reviewed, retrospective cohort study)**
8. Mol BW, Van Der Vee F, et al. Screening for Ectopic Pregnancy in Symptom Free Women at Increased Risk. *Obstet Gynecol* 1997;81:661-72. **(143 pregnancies, prospective cohort study)**
9. Ankum WM, Mol BW, et al. Risk Factors for Ectopic Pregnancy: a meta-analysis. *Fertil Steril* 1996;65:1093-9. **(Systematic review, meta-analysis)**
10. Barnhart K, Esposito M. et al. An Update on Medical Treatment of Ectopic Pregnancy. *Obstet Gynecol Clin North Am* 2000;27: 653-67. **(Review article)**
11. Fylstra DL. Tubal Pregnancy: A Review of current Diagnosis and Treatment. *Obstet Gynecol Surv* 1998;53:320-8. **(Review article)**
12. Atri M, Leduc C, et al. Role of Endovaginal Sonography in the Diagnosis and Management of Ectopic Pregnancy. *Radiographics* 1996;16:755-74. **(Review article)**
13. Ory SJ. New options for diagnosis and treatment of ectopic pregnancy, *JAMA* 1992;267:534. **(Review article)**
14. Maymom R, Sshulman A. Controversies and Problems in the Current Management of Tubal Pregnancy. *Hum Reprod Update* 1996;2:541-51.**(Review article)**
15. Tal J, Haddad S. et al. Heterotopic Pregnancy after Ovulation Induction and Assisted Reproductive Technologies: A Literature Review from 1971 to 1993. *Fertil Steril* 1996;66:1-12. **(Systematic review)**
16. Wilcox AJ et al: Incidence of early loss of pregnancy. *N Engl* J Med 1988;319:189. **(221, prospective cohort study)**
17. Cunningham FG et al. Williams obstetrics, ed 20. *Appleton & Lange* Norwalk, Conn, 1997. **(Textbook)**
18. Pandya PP et al. The prevalence of non-viable pregnancy at 10-13 weeks of gestation. *Ultrasound Obstet Gynecol* 1996;7:170. **(17,870, prospective cohort)**
19. Papulati RM, Bhatt s, et al. Sonographic Evaluation of First Trimester Bleeding. *Radiol Clin North Am* 2004;42:297-314. **(Review article)**
20. Karim SA et al. Effects of first and second trimester vaginal bleeding on pregnancy outcome. *J Pak Med Assoc* 1998;48:40. **(268, retrospective cohort)**
21. Steier JA et al. Human chorionic gonadotropin in maternal plasma after induced abortion, spontaneous abortion, and removed ectopic pregnancy, *Obstet Gynecol* 1984;64:391. **(105, retrospective comparative study)**
22. Hallatt JG et al. Ruptured corpus luteum with hemoperitoneum: a study of 173 surgical cases. *Am* J *Obstet Gynecol* 1984;149:5. **(173, retrospective cohort)**
23. Barnhart K et al. Prompt diagnosis of ectopic pregnancy in an emergency department setting. *Obstet Gynecol* 1994;84:1010. **(1263,Prospective cohort study)**
24. American College of Emergency Physicians: Emergency ultrasound imaging criteria compendium. American College of Emergency Physicians. *Annals of Emergency Medicine* Oct 2006;48(4):487-510. **(Editorial. Practice Guideline)**
25. Brooks A. Davies B. Smethhurst M. Connolly J. Prospective evaluation of non-radiologist performed emergency abdominal ultrasound for haemoperitoneum. *Emergency Medicine Journal* Sep 2004;21(5):5. (Duplicate Publication. Evaluation Studies. Journal Article) **(100, prospective cohort)**
Original reference: Brooks A. Davies B. Connolly J. Prospective evaluation of handheld ultrasound in the diagnosis of blunt abdominal trauma. *Journal of the Royal Army Medical Corps* Mar 2002;148(1):19-21. **(Evaluation Studies. Journal Article. Research Support, Non-U.S. Gov't)**
26. Stovall TG, Kellerman AL, Ling FW, Buster JE. Emergency department diagnosis of ectopic pregnancy. *Ann Emerg Med* 1990;19:1098-1103. **(2157, prospective case series)**
27. Ramakrishnan K, Scheid DC. Ectopic Pregnancy: Forget the Classic Presentation if You Want to Catch it Sooner. *J Fam Prac* 2006. 55: 388-95. **(Review article)**
28. Buckley RG, King KJ, et al. Derivation of a Clinical Prediction Model for the Emergency Department Diagnosis of Ectopic Pregnancy. *Acad Emerg Med* 1998;5:951-960. **(486, prospective cohort)**
29. Mol BW, Hajenius PJ, et al. Serum Human Chorionic Gonadotropin Measurement in the Diagnosis of Ectopic Pregnancy when Transvagional Sonography is Inconclusive. *Fertil Steril* 1998;70:972-981. **(350, prospective cohort)**
30. Kaplan DC, Dart RG, et al. Ectopic pregnancy: Prospective Study with Improved Diagnostic Accuracy. *Ann Emerg Med* 1996;28:10-17. **(481, prospective cohort)**
31. Dart RG et al. Predictive value of history and physical examination in patients with suspected ectopic pregnancy. *Ann Emerg Med* 1999;33:283. **(481, prospective cohort)**
33. Lindahl B, Ahlgren M. Identification of chorionic villi in abortion specimens. *Obstet Gynecol* 1986;82:858. **(272, prospective cohort)**
34. Brennan DF. Ectopic Pregnancy- Part I: Clinical and Laboratory Diagnosis. *Academic Emerg Med* 1995;2:1081-9. **(Review article)**
35. Saxon D, Falcone T, et al. A Study of Ruptured Tubal Ectopic Pregnancy. *Obstet Gynecol* 1997;90:866-7. **(693, retrospective cohort)**
36. Seeber BE, Barnhart KT. Suspected Ectopic Pregnany. *Obstet Gynecol* 2006;107:399-413. **(Review article)**
37. Dart RM, Mitterando J, Dart LM. Rate of Change of Serial Beta-Human Chorionic Gonadotropin values as a Predictor of Ectopic Pregnancy in Patients with Indescriminate Transvaginal Ultrasound Findings. *Ann Emerg Med* 1999;34:703-710. **(331, retrospective cohort)**
38. Mol BW, Lijmer JG et al. The Accuracy of a Single Progesterone Measurement in the Diagnosis of Ectopic Pregnancy: a meta-analysis. *Hum Reprod* 1998;13:3220-7. **(Systematic review)**
39. Buckely RG, King KJ, et al. Serum Progesterone Testing to Predict Ectopic Pregnancy in Symptomatic First-trimester Patients. *Ann Emerg Med* 2000;36:95-100. **(716, prospective cohort)**
40. Dart R, Ramanujam P, Dart L. Progesterone as a predictor of ectopic pregnancy when the ultrasound is indeterminate. [Evaluation Studies. Journal Article] *Am J Emerg Med* 20(7):575-9,2002 Nov. **(160, prospective cohort)**
41. Garcia CR. Barnhart KT. Diagnosing ectopic pregnancy: Decision

analysis comparing six strategies. *Obstetrics & Gynecology* Mar 2001;97(3):464-70. **(160, prospective cohort)**
42. American College of Emergency Physicians. Emergency ultrasound imaging criteria compendium. American College of Emergency Physicians. *Annals of Emergency Medicine.* Oct 2006;48(4):487-510. **(Editorial. Practice Guideline)**
43. Stovall TG, Ling FW. Ectopic pregnancy: Diagnostic and therapeutic algorithms minimizing surgical intervention. *J Reprod Med* 1993;38:807. **(Prospective cohort)**
44. Bree RL, Edwards M, et al. Transvaginal Sonography in the Evaluation of Normal Early Pregnancy: Correlation with HCG level. *AJR Am J Roetgenol* 1989;153:75-79. **(75, prospective cohort)**
45. Rempen A. Diagnosis of Viability in Early Pregnancy with Vaginal Sonography. *J Ultrasound Med* 1990;9:711-16. **(363, prospective cohort)**
46. Emerson DS, Cartier MS, et al. Diagnostic Efficacy of Endovaginal color Doppler Imaging in an Ectopic Pregnancy Screening Program. *Radiology* 1992;183:413-20. **(Prospective serial case reports)**
47. Yeh HC, Goodman JD, et al. Intradecidual sign: US criterion of Early Intrauterine Pregnancy. *Radiology* 1986;161:463-7. **(36, prospective cohort)**
48. Laing FC, Brown DL, et al. Intradecidual Sign: Is it Effective in Diagnosis of an Early Intrauterine Pregnancy? *Radiology* 1997;204:655-60. **(102, prospective cohort)**
49. Coulam CB, Brfitten S, et al. Early (34-56 Days from Last Menstrual Period) Ultrasonographic Measurements in Normal Pregnancies. *Hum Reprod* 1996;11:1771-74. **(361, prsopective cohort)**
50. Levi CS, Lyons EA, et al. Early Diagnosis of Non viable Pregnancy with transvaginal *US. Radiology* 1988;167:383-85. **(62, prospective cohort)**
51. Jauniaux E, Jurkovic D, et al. Development of a Secondary Human Yolk Sac: Correlation of Sonographic and Anatomic Features. 1991;6:1160-66. **(180, prospective cohort)**
52. Stampone C, Nicotra M, Muttinelli C, Cosmi EV. Transvaginal sonography of the yolk sac in normal and abnormal pregnancy. [Journal Article. Research Support, Non-U.S. Gov't] *J Clin Ultrasound* 24(1):3-9, 1996 Jan. **(117, cross sectional study)**
53. Lindsay DJ, Lovett IS, et al. Yolk Sac Diameter and Shape at Endovaginal US: Predictors of Pregnancy Outcome in the First Trimester. *Radiology* 1992;183:115-8. **(481, propspective chort)**
54. Yeh HC, Rabinowitz JG. Amniotic Sac Development: Ultrasound Features of Early Pregnancy-Double Bleb sign. *Radiology* 1988;166:97-103. **(Retrospective cohort)**
55. Goldstein SR, Wolfson R. Transvaginal Ultrasounagraphic Measurement of Early Embryonic Size as a Means of Assessing Gestational Age. *J Ultrasound Med* 1994;13:27-31. **(143, prospective cohort)**
56. Wisser J, Dirschedl P, et al. Estimation of Gestational Age by Transvaginal Sonographic Measurement of the Greater Embryonic Length in Dated Human Embryos. *Ultrasound Obstet Gynecol* 1994;4:457-62. **(160, prospective cohort)**
57. Goldstein SR. Significance of Cardiac activity on Endovaginal Ultrasound in Very Early Embryos. *Obstet Gynecol* 1992;80: 67-72. **(92, prospective cohort)**
58. Levi CS, Lyons EA, et al. Endovaginal US: Demonstrationof Cardiac Activity in Embryos less than 5.0mm in Crown Rump Length. *Radiology* 1990;176:71-74. **(91, retrospective cohort)**
59. Hertzberg BS, Mahoney BS, et al. First Trimester Fetal Cardiac Activity: Sonographic Documentation of a Progressive Early rise in Heart Rate. *J Ultrasound Med* 1988;7:573-5. **(124, prospective cohort)**
60. Doubilet PM, Benson CB. Embryonic Heart Rate in Early First Trimester Pregnancy: What is Normal? *J Ultrasound Med* 1995;13:431-4. **(Retrospective cohort)**
61. Tongsong T et al. Pregnancy outcome of threatened abortion with demonstrable fetal cardiac activity: A cohort study. *J Obstet Gynaecol* 1995;21:331. **(255, prospective cohort)**
62. Nyberg DA, Liang FC, et al. Threatened Abortion: Sonographic Distinction of Abnormal and Normal Gestational Sacs. *Radiology* 1986;158:397-400. **(126, retrospective cohort)**
63. Wong SF, Lam MF, et al. Tarnsvaginal Sonography in the detection of retained Products of Conception after First Trimester Spontaneous Abortion. *J Clin Ultrasound* 2002;30:428-32. **(113, prospective cohort)**
64. Sudan O, Golan A, et al. Role of Sonography in the Diagnosis of Retained Products of Conception. *J Ultrasound Med* 2004;23:371-74. **(124 retrospective cohort first author name should be sadan)**
65. Zale Y, Gamzu R, et al. Color Doppler imaging in the Sonohystographic Diagnosis of residual Trophoblastic Tissue. *J Clin Ultrasound* 2002;30:222-5. **(25, prospective cohort - first author name is zalel)**
66. WolmanI, Hartoov J, et al. Transvaginal sonohysterography for the Early Diagnosis of Residual Trophoblastic Disease. *J ultrasound Med* 1997;16:257-61. **(29, prospective cohort)**
67. Dogra V, Paspulati RM, et al. First Trimester Bleeding Evaluation. *Ultrasound Quarterly* 2005;21:69-85. **(Review article)**
68. Wong TW et al. Efficacy of transabdominal ultrasound examination in the diagnosis of early pregnancy complications in an emergency department. *J Accid Emerg Med* 1998;15:155. **(151 prospective cohort 840, prospective cohort)**
69. Barnhart KT et al. Diagnostic accuracy of ultrasound above and below the â-hCG discriminatory zone. *Obstet Gynecol* 1999;94:583. **(331, prospective cohort)**
70. Shalev E et al. Transvaginal sonography as the ultimate diagnostic tool for the management of ectopic pregnancy, *Fertil Steril* 1998;69:62. **(840, prospective cohort)**
71. Kontoravdis A et al. The diagnostic value of laparoscopy in 2365 patients with acute and chronic pelvic pain. *Int* J Obstet Gynecol 1996;52:243. **(2365, prospective cohort)**
72. Carson SA, Buster JE. Ectopic pregnancy. *N Engl* J Med 1993;329:1174. **(Review article)**
73. Dart R, Howard K. Subclassification of indeterminate pelvic ultrasonograms: stratifying the risk of ectopic pregnancy. *Acad Emerg Med* 1998;5:313. **(248, retrospective cohort)**
74. Dart R et al. Utility of a dilatation and evacuation procedure in patients with symptoms suggestive of ectopic pregnancy and indeterminate transvaginal ultrasonography. *Acad Emerg Med* 1999;6:1024. **(255, retrospective cohort)**
75. Dimitry ES et al. Nine cases of heterotopic pregnancies in 4 years of in vitro fertilization. *Fertil Steril* 1990;53:107. **(9 serial case reports)**
76. Von Stein GA et al. Fetomaternal hemorrhage in threatened abortion. *Obstet Gynecol* 1992;79:383. **(Prospective cohort)**
77. Anti-D administration in pregnancy for preventing rhesus alloimmunisation. Cochrane Database of Systematic Reviews. (2):CD000020, 2000. **(Systematic review)**
78. Bowman JM. Chown B. Prevention of Rh immunization after massive Rh-positive transfusion. *Canadian Medical Association Journal* Sep 7 1968;99(9):385-8. **(Case report)**
79. Olshaker JS. Emergency department pregnancy testing. *J Emerg Med* 1996;14:59. **(Review article)**
80. Dart R et al. Normal intrauterine pregnancy is unlikely in emergency department patients with either menstrual days >38 or â-hCG >3,000 but without a gestational sac on ultrasonography. *Acad Emerg Med* 1997;4:967-971. **(194, retrospective cohort)**
81. Abbott JT et al. Ectopic pregnancy: Ten common pitfalls in diagnosis, *Am* J *Emerg Med* 1990;8:515. **(Review article)**
82. Paspulati RM. Bhatt S. Nour S. Sonographic evaluation of first-trimester bleeding.Radiologic. *Clinics of North America* Mar 2004;42(2):297-314. **(Review article)**
83. Hurd WW et al. Expectant management versus elective curettage for treatment of spontaneous abortion. *Fertil Steril* 1997;68:601. **(152, retrospective cohort)**
84. Schiff E, Ben-Baruch G, Moran O. Yahal I, Oelsner G, Mashiach S. Menczer J. Prediction of residual trophoblastic tissue in first-trimester abortions and low levels of human chorionic gonadotropin beta-subunit. *Am J Obstet & Gynecol* 162(3):797-801, 1990 Mar. **(174, retrospective cohort)**
85. Brier N. Understanding and managing the emotional reactions to a miscarriage. *Obstet Gynecol* 1999;93:151. **(Review article)**
86. Stovall TG, Ling FW, Carson SA, Buster JE. Nonsurgical diagnosis and treatment of tubal pregnancy. *Fertil Steril* 1990;54:537-538. **(Prospective cohort)**
87. Sauer MV, Gorrill MJ, Rodi IA, Yeko TR. Nonsurgical management of unruptured ectopic pregnancy: An extended trial. *Fertil Steril* 1987;48:752-755. **(26, retrospective cohort)**
88. Redi IA, Sauer MV, Gorrill MJ, et al. The medical treatment of unruptured ectopic pregnancy with methotrexate and citrovorum rescue: preliminary experience. *Fertil Steril* 1986;46:811-813. **(7, prsopective cohort (the first authors name is rodi)**
89. Ory SJ, Villanueva AL, Sand PK, Tamura RK. Conservative treatment of ectopic pregnancy with methotrexate. *Am J Obstet Gynecol* 1986;154:1299-1306. **(6, prospective cohort)**
90. Ichinoe K, Wake N, Shinkai N, Shiina Y, Miyazaki Y, Tanaka T. Nonsurgical therapy to preserve oviduct function in patients with tubal pregnancies. *Am J Obstet Gynecol* 1987;156:484-487. **(23, prospective cohort)**
91. Stovall TG, Ling FW, Gray LA, Carson SA, Buster JE. Methotrexate treatment of unruptured ectopic pregnancy: A report of 100 cases. *Obstet Gynecol* 1991;77:749-753. **(100, propsective cohort)**
92. Stovall TG, Ling FW, Gray LA. Single-dose methotrexate for treatment of ectopic pregnancy. *Obstet Gynecol* 1991;77:754-757. **(31, prospective cohort)**
93. Gross Z, Rodriguez JJ, Stalnaker BL. Ectopic Pregnancy: Nonsurgical, outpatient evaluation and single-dose methotrexate treatment. *J Reprod Med* 1995;40:371-374. **(17, prospective cohort)**
94. Glock JL, Johnson JV, Brumsted JR. Efficacy and safety of single-dose systemic methotrexate in the treatment of ectopic pregnancy. *Fertil*

Steril 1994;62:716-721. **(82, retrospectiove cohort)**
95. Henry MA, Gentry WL. Single injection of methotrexate for treatment of ectopic pregnancies. *Am J Obstet Gynecol* 1994;171:1584-1587. **(61, prospective cohort)**
96. Stovall TG, Ling FW. Single-dose methotrexate: An expanded clinical trial. *Am J Obstet* 1993;168:1759-1765. **(120, prospective cohort)**
97. Kadar N, Caldwell BV, Romero R. A method of screening for ectopic pregnancy and its indications. *Obstet Gynecol* 1981;58:162-165. **(Retrospective cohort)**
98. Ankum WM, Van der Veen F, Hamerlynck JVThH, Lammes FB. Laparoscopy: A dispensable tool in the diagnosis of ectopic pregnancy? *Human Reproduction* 1993;8:1301-1306. **(100, prospective cohort)**
99. Wolf GC, Nickisch SA, George KE, Teicher JR, Simms TD. Completely nonsurgical management of ectopic pregnancy. *Gynecol Obstet Invest* 1994;37:232-235. **(12, prospective cohort)**
100. Abbott J, Abbott R. Ruptured ectopic pregnancy after medical management: current conservative management strategies. *Am J Emerg Med* 1993;11:480-482. **(Case report)**
101. Lipscomb GH, Stovall TG, et al. Nonsurgical treatment of Ectopic Pregnancy. *N Eng J Med* 2000;343:1325-9. **(Review article)**
102. Tawfiq A, Agameya AF, et al. Predictors of treatment failure for Ectopic Pregnancy Treated with Single Dose Methotrexate. *Fertil Steril* 2000;74:877-80. **(60, retrospective cohort)**
103. Lipscomb GH, McCord ML, et al. Predictors of Success of Methotrexate Treatment in Women with Tubal Ectopic Pregnancies. *N Eng J Med* 1999;341:1974-78. **(350, retrospective cohort)**
104. Seeber BE, Barhhart KT. Suspcted Ectopic Pregnancy. *Obstet Gynecol* 2006;107:399-414. **(Review article)**
105. American College of Obstetricians and Gynecologists. Medical Management of Tubal Pregnancy. ACOG Practice Bulletin 3. Washington DC: ACOG 1988. **(Practice Guideline)**
106. Stovall TG, Ling FW, Buster JE. Reproductive performance after methotrexate treatment of ectopic pregnancy. *Am J Obstet Gynecol* 1990;162:1620-1624. **(57. prospective cohort)**
107. DiMarchi JM, Kosasa TS, et al. Peristent Ectopic Pregnancy. *Obstet Gynecol* 1987;70:555-60. **(625, retrospective cohort)**
108. Vermesh M, Silva PD, et al. Persistent Tubal Ectopic Gestations: Pattenrs of Circulating beta-Human Chorionic Gonadotropin and Progeterone, and Management Options. *Fertil Steril* 1988;50:584-8. **(329, retrospective cohort)**
109. Seifer DB, Gutmann JN, et al. Comparison of Persistent Ectopic Pregnancy after Laparoscopic Salpingostomy vs. Salpingectomy at Laparotomy for Ectopic Pregnancy. *Obstet Gynecol* 1993;81:378-82. **(157, retrospective cohort)**
110. Graczykowski JW, Mishell DR Jr. Methotrexate Prophylaxis of Persistent Ectopic Pregnancy after Conservative Treatment by Salpingostomy. *Obstet Gynecol* 1997;89:118-22. **(129, randomized controlled trial)**
111. Daniel Y, Geva E, et al. Levels of vascular Endothelial Growth Factors are Elevated in Patients with Ectopic Pregnancy: Is this a Novel Marker? *Fertil Steril* 1999;72:1013-7. **(20, prospective case control)**
112. Fasoulitis SJ, Spandorfer SD, et al. Maternal Serum Vascular Endothelial Growth factor Levels in Early Ectopic and Intrauterine Pregnancies after in vitro Fertilization Treatment. *Fertil Steril* 2004;82:309-13. **(159, prospective cohort)**
113. Muller RD, Raio L, et al. Novel Placental and Non-Placental Serum Markers in Ectopic vs. normal Intrauterine Pregnancy. *Fertil Steril* 2004;81:1106-11. **(Prospective case control)**
114. Gerton GL, Fan XL, et al. A Serum Proteonomics approach to the Diagnosis of Ectopic Pregnancy. *Ann N Y Acad Sci* 2004;1022:306-16. **(140, prospective cohort)**
115. Duncan WC et al. Measurement of creatine kinase activity and diagnosis of ectopic pregnancy. *Br* J *Obstet Gynaecol* 1995;102:233. **(120, retrospective cohort)**
116. Azogui G et al. CA-125 is elevated in viable pregnancies destined to be miscarried: a prospective longitudinal study. *Fertil Steril* 1996;65:1059. **(25, prospective cohort)**
117. O'Connor JF et al. Differential urinary gonadotropin profiles in early pregnancy and early pregnancy loss. *Prenat Diagn* 1998;18:1232. **(Prospective case controlled)**
118. Condous G, Okaro E, et al. The Use of a New Logisitic Regression Model for Predicting Outcome of Pregnancies of Unknown Location. *Human Reprod* 2004;19:1900-10. **(185, prospective cohort)**
119. Barnhart KT, Gosman G, et al. The Medical Management of Ectopic Pregnancy: A meta-Analysis comparing Single dose and Multidose Regimens. *Obstet Gynecol* 2003;101:778-84. **(Systematic review)**
120. Jewell D,Young G. Interventions for nausea and vomiting in early pregnancy. *The Cochrane Library* 2003(4). **(Cochrane Review)**
121. John Wiley & Sons, Ltd.; Gadsby R, Barnie-Adshead AM, Jagger C. A prospective study of nausea and vomiting during pregnancy. *Br J Gen Pract* Chichester, UK 1993;43:245–8. **(363, prospective cohort - start with gadsby - delete that prior to it in reference regarding john wiley and sons)**
122. Vellacott ID, Cooke EJ, James CE. Nausea and vomiting in early pregnancy. *Int J Gynaecol Obstet* 1988;27:57–62 **(500, epidemiologic survey)**
123. Klebanoff MA, Koslowe PA, Kaslow R, Rhoads GG. Epidemiology of vomiting in early pregnancy. *Obstet Gynecol* 1985;66:612–6. **(9098, retrospective cohort)**
124. Glick MM, Dick EL. Molar pregnancy presenting with hyperemesis gravidarum. *JAOA* 1999;99:162. **(Case report)**
125. Frigo P et al. Hyperemesis gravidarum associated with *Helicobacter pylori* seropositivity. *Obstet Gynecol* 1998;91:615. **(105, prospective cohort)**
126. American College of Obstetrics and Gynecology Practice Bulletin: nausea and vomiting of pregnancy. *Obstetrics & Gynecology.* Apr 2004;103(4):803-14. **(Practice guideline)**
127. Dickson MJ. Management of hyperemesis in pregnant women. *Lancet* 1999;353:325. **(Letter to the editor)**
128. Sahakian V, Rouse D, Sipes S, Rose N, Niebyl J. Vitamin B6 is effective therapy for nausea and vomiting of pregnancy: a randomized, double-blind placebo-controlled study. *Obstet Gynecol* 1991;78:33–6. **(59, randomized, double blinded study)**
129. Vutyavanich T, Wongtra-ngan S, Ruangsri R. Pyridoxinefor nausea and vomiting of pregnancy: a randomized, double-blind, placebo-controlled trial. *Am J ObstetGynecol* 1995;173:881–4. **(342, randomized, double blinded study)**
130. Neutel CI, Johansen HL. Measuring drug effectiveness bydefault: the case of Bendectin. *Can J Public Health* 1995;86:66–70. **(Review article)**
131. Tincello DG, Johnston MG. Treatment of Hyperemesis Gravidarum with 5-HT3 anatagonist Odansetron (Zofran). *Post Grad Med* 1996;72:688-9. **(Case report)**
132. Moiseiwitsch JR, Lauder JM. Regulation of Gene Expression in Cultured Embryonic Mouse Mandibular Mesenchyme by Serotoin Antagonists. *Anat Embryol* 1997;195:71-8. **(Bench research, non blinded controlled study)**
133. Einarson A, et al. The Safety of Odansetron For Nausea and Vomitting of Pregnancy. *BJOG* 2004;111:940-3. **(176, retrospective case control)**
134. Safari HR et al. Experience with oral methylprednisolone in the treatment of refractory hyperemesis gravidarum. *Am* J *Obstet Gynecol* 1998;178:1054. **(44, prospective, double blinded study)**
135. Carmichael SL, Shaw GM. Maternal corticosteroid use and risk of selected congenital anomalies. *Am J Med Genet* 1999;86:242–4. **(1299, retrospective case control)**
136. Park-Wyllie L, Mazzotta P, Pastuszak A, Moretti ME, Beique L, Hunnisett L, et al. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. *Teratology* 2000;62:385–92. **(Systematic review)**
137. Rodriguez-Pinilla E, Martinez-Frias ML. Corticosteroids during pregnancy and oral clefts: a case-control study. *Teratology* 1998;58:2–5. **(Retrospective, Case control)**
138. Fischer-Rasmussen W, Kjaer SK, Dahl C, Asping U. Ginger treatment of hyperemesis gravidarum. *Eur J Obstet Gynecol Reprod Biol* 1991;38:19–24. **(30, double blind randomized, cross over trial)**
139. Vutyavanich T, Kraisarin T, Ruangsri R. Ginger for nausea and vomiting in pregnancy: randomized, doublemasked, placebo-controlled trial. *Obstet Gynecol* 2001;97:577–82. **(70, randomized, double blinded, placebo controlled)**
140. Chin RK, Lao TT. Low birth weight and hyperemesis gravidarum. *Eur J Obstet Gynecol Reprod Biol* 1988;28:179–83. **(Retrospective cohort)**
141. Godsey RK, Newman RB. Hyperemesis gravidarum. A comparison of single and multiple admissions. *J Reprod Med* 1991;36:287–90. **(140, retrospective cohort)**
142. Gross S, Librach C, Cecutti A. Maternal weight loss associated with hyperemesis gravidarum: a predictor of fetal outcome. *Am J Obstet Gynecol* 1989;160:906–9. **(64, retrospective cohort)**
143. Togay-Isikay C, Yigit A, Mutluer N. Wernicke's encephalopathy due to hyperemesis gravidarum: an under-recognised condition. *Aust N Z J Obstet Gynecol* 2001;41:453–6. **(Case report)**
144. Spruill SC, Kuller JA. Hyperemesis gravidarum complicated by Wernicke's encephalopathy. *Obstet Gynecol* 2002;99:875–7. **(Case report)**
145. Kim YH, Lee SJ, Rah SH, Lee JH. Wernicke's encephalopathy in hyperemesis gravidarum. *Can J Ophthalmol* 2002;37:37–8. **(Case report)**
146. Eroglu A, Kurkcuoglu C, Karaoglanoglu N, Tekinbas C, Cesur M. Spontaneous esophageal rupture following severe vomiting in pregnancy. *Dis Esophagus* 2002;15: 242–3. **(Case report)**
147. Liang SG, Ooka F, Santo A, Kaibara M. Pneumomediastinum following esophageal rupture associated with hyperemesis gravidarum. *J Obstet Gynaecol Res* 2002;28:172–5. **(Case report)**
148. Mungan T et al. Hydatidiform mole: clinical analysis of 310 patients. *Int J Obstet Gynecol* 1996;52:233. **(310, retrospective cohort)**
149. Goldstein DP, Berkowitz RS. Current management of complete and partial molar pregnancy. *J Reprod Med* 1994;39:139. **(Review article)**
150. Lindholm H, Flam F. The diagnosis of molar pregnancy by sonography and gross morphology. *Acta Obstet Gynecol Scand* 1999;78:6. **(135, retro-**

spective cohort)
151. Hurd WW et al. Expectant management versus elective curettage for treatment of spontaneous abortion. *Fertil Steril* 1997;68:601. **(63, retrospective cohort)**
152. Ruptured heterotopic pregnancy presenting with relative bradycardia in a woman not receiving reproductive assistance. *Ann Emerg Med* Mar 2004;43(3):382-5. **(Case report)**
153. Snyder HS. Lack of a tachycardic response to hypotension with ruptured ectopic pregnancy. *Am J Emerg Med* 1990;8:23-26. **(154, retrospective cohort)**
154. Johnsen RPS. Relative bradycardia: a sign of acute intraperitoneal bleeding. *Aust NZ Obstet Gynecol* 1978;18:206-208. **(Case report)**
155. Adams SL, Greene JS. Absence of a tachycardic response to intraperitoneal hemorrhage. *J Emerg Med* 1986;4:383-388. **(Case report)**
156. Roscoe JA, Matteson SE. Acupressure and acustimulation bands for control of nausea: a brief review. *Am J Obstet Gynecol* 2002;186:S244–7. **(Review article)**
157. Kallen B. Hyperemesis during pregnancy and delivery outcome: a registry study. *Eur J Obstet Gynecol Reprod Biol* 1987;26:291–302. **(3068, retrospective cohort)**
158. O'Brien B, Zhou Q. Variables related to nausea and vomiting during pregnancy. *Birth* 1995;22:93–100. **(126, Retrospective cohort)**
159. Nguyen N, Deitel M, Lacy E. Splenic avulsion in a pregnant patient with vomiting. *Can J Surg* 1995;38:464–5. **(Case report)**

CME Questions

The CME six-month print semester starts with the January issue and restarts with the June issue. The CME questions are numbered consecutively. Current subscribers can take the test in print every six months or online monthly.

75. All of the following are considered risk factors for ectopic pregnancy EXCEPT:
a. History of pelvic inflammatory disease
b. An IUD
c. Oral contraceptives
d. Prior history of ectopic pregnancy
e. In-utero exposure to diethylstilbestrol

76. The most common cause of early first trimester spontaneous miscarriages is:
a. Alcohol use
b. Inborn genetic errors
c. Tobacco use
d. Viral infections
e. Bacterial infections

77. A patient presents to the emergency department with lower abdominal cramping and mild vaginal bleeding after intercourse. A urine pregnancy test reveals that she is pregnant and her last menstrual period was seven weeks ago. All of the following should be reasonably considered in the differential diagnosis EXCEPT:
a. Ectopic pregnancy
b. Threatened miscarriage
c. Cervical trauma
d. Placental abruption
e. Vaginitis

78. A 25-year-old female presents with mild LLQ abdominal pain and vaginal bleeding. Her vital signs are stable and show no signs of orthostasis. Her physical exam reveals tenderness in the LLQ without peritoneal signs. Her pelvic shows the cervical os to be closed with no adnexal masses, slight cervical motion tenderness, and left adnexal tenderness. Her urine pregnancy test is positive. A transvaginal ultrasound shows an empty uterus, slight fluid in the cul de sac, and no direct or highly suggestive evidence of an ectopic pregnancy. A β-hCG level is found to be 400 mIU/mL. Which of the following are appropriate management options in this patient?
a. You deem the patient is at no risk for an ectopic pregnancy since the β-hCG is so low and discharge her to home
b. You call the OB-GYN and tell them you have an ectopic pregnancy they need to take to the operating room
c. The patient may be discharged with "ectopic precautions" and can follow-up with an obstetrician in 48 hours for a repeat β-hCG and possible repeat ultrasound
d. The patient is a clear candidate for methotrexate therapy
e. You diagnose miscarriage and set the patient up for a D & E with her gynecologist

79. All of the following are true statements regarding progesterone EXCEPT:
a. A progesterone level of less than 5 ng/mL is highly sensitive in identifying a nonviable pregnancy
b. A progesterone level of greater than 25 ng/mL is highly sensitive for identifying a normal pregnancy
c. Progesterone values between 5 and 25 ng/mL are typically of little value
d. Progesterone is not universally available, thus it is often little help to those providing care in the ED
e. A progesterone level of less than 5 ng/mL clearly identifies an ectopic pregnancy

80. Contraindications to the use of methotrexate in an appropriately selected patient with an ectopic pregnancy include all of the following EXCEPT:
a. History of focal glomerulosclerosis
b. History of pneumonia six months ago
c. Immunosuppression
d. Drinks about a six-pack a day
e. Diagnosed with a bleeding ulcer two weeks ago by EGD and still on proton pump inhibitors

81. An 18-year-old female presents with severe abdominal pain. She has no prior history and the pain is acute in onset. She is afebrile, but her heart rate is 142 and her blood pressure is 78/palpation. Her abdominal exam shows clas-

sic peritoneal signs. She receives immediate resuscitation with 2 liters of isotonic saline. Her blood pressure slightly improves to 85/palp, but her pulse remains tachycardic in the 140's. You obtain a cath urine specimen, which you are able to do a point of care urine pregnancy test on; it is positive. Her hematocrit comes back at 7 mg/dL. The next most logical action in this case is:

a. Order a type and cross for four units and call the obstetrician for an immediate consult for probable ruptured ectopic in an unstable patient
b. Obtain an ultrasound in radiology to confirm the diagnosis of ectopic pregnancy
c. Give Zosyn and Flagyl with the presumptions that this a septic abortion
d. Call the general surgeons with the presumption that this could still be an appendicitis
e. Question the patient regarding the contraindications to giving methotrexate

82. Of the following tests in a patient with a confirmed ruptured ectopic pregnancy, the most important laboratory test to send off is:

a. An electrolyte panel with bun and creatinine
b. Wet prep
c. Tests for gonorrhea and chlamydia
d. Type and cross
e. Quantitative β-hCG

83. A patient presents to the ED who is pregnant with vaginal bleeding and lower abdominal pain. You see a gestational sac via ultrasound but no fetal pole. You diagnosed the patient with a threatened miscarriage. All of the following are appropriate to tell the patient at discharge, EXCEPT:

a. She must be admitted for D & C
b. 50% of women still have normal pregnancies
c. Restriction in physical activity has no effect on the pregnancy
d. She should refrain from douching, tampons, or intercourse while she is bleeding
e. She should follow-up with her gynecologist in two days for a repeat β-hCG level

84. All of the following are true regarding a patient with a molar pregnancy EXCEPT:

a. A patient with a molar pregnancy is typically diagnosed after the 20th week of conception
b. The typical ultrasound appearance of a molar pregnancy is described as a "snowstorm appearance" in the uterus
c. Patients with a molar pregnancy may present with symptoms of hyperemesis gravidarum
d. Molar pregnancies may present with the passage of grape-like vesicles from the vagina
e. Molar pregnancies often have a uterus size that is greater than expected age

85. A patient presents to the ED with vomiting for the last three days. She was recently diagnosed with a pregnancy of about eight weeks. Her vital signs are stable and, other than some mild signs of dehydration, her physical exam is normal. Her laboratory work-up shows only some ketones in her urine. The mostly likely diagnosis is:

a. Viral gastroenteritis
b. Small bowel obstruction
c. Morning sickness
d. Hyperemesis gravidarum
e. Ectopic pregnancy

86. A patient presents to the ED with abdominal pain and vaginal bleeding. She has been trying to get pregnant for years and is under the care of a fertility specialist. She has a positive pregnancy test in the ED, and an ultrasound shows an IUP. What do you tell her regarding the risk of having an ectopic pregnancy?

a. It is impossible to have both an ectopic pregnancy and an intrauterine pregnancy at the same time
b. It is highly unlikely that the she has an ectopic pregnancy and the chances are 1:50,0000
c. Given her prior problems getting pregnant, it is inevitable given her symptoms that she will develop an ectopic pregnancy during this conception
d. Although it is highly unlikely, her risk of developing a dual intrauterine and ectopic pregnancy is still a consideration at a chance of 1:4000
e. If she has had any form of assisted reproduction, her risk of a heterotopic pregnancy is significantly increased at 1:100

Coming In Future Issues:

Critical Care Monitoring
Abnormal Vision
Shoulder Fractures

Class Of Evidence Definitions

Each action in the clinical pathways section of *Emergency Medicine Practice* receives a score based on the following definitions.

Class I
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II
- Safe, acceptable
- Probably useful

Level of Evidence:
- Generally higher levels of evidence
- Non-randomized or retrospective studies: historic, cohort, or case-control studies
- Less robust RCTs
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

Indeterminate
- Continuing area of research
- No recommendations until further research

Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

Significantly modified from: The Emergency Cardiovascular Care Committees of the American Heart Association and representatives from the resuscitation councils of ILCOR: How to Develop Evidence-Based Guidelines for Emergency Cardiac Care: Quality of Evidence and Classes of Recommendations; also: Anonymous. Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part IX. Ensuring effectiveness of community-wide emergency cardiac care. JAMA 1992;268(16):2289-2295.

Physician CME Information

Accreditation: This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Mount Sinai School of Medicine and Emergency Medicine Practice. The Mount Sinai School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation: The Mount Sinai School of Medicine designates this educational activity for a maximum of 48 *AMA PRA Category 1 Credit(s)™* per year. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Credit may be obtained by reading each issue and completing the printed post-tests administered in December and June or online single-issue post-tests administered at EBMedicine.net.

Target Audience: This enduring material is designed for emergency medicine physicians.

Needs Assessment: The need for this educational activity was determined by a survey of medical staff, including the editorial board of this publication; review of morbidity and mortality data from the CDC, AHA, NCHS, and ACEP; and evaluation of prior activities for emergency physicians.

Date of Original Release: This issue of *Emergency Medicine Practice* was published June 1, 2007. **This activity is eligible for CME credit through June 1, 2010.** The latest review of this material was May 10, 2007.

Discussion of Investigational Information: As part of the newsletter, faculty may be presenting investigational information about pharmaceutical products that is outside Food and Drug Administration approved labeling. Information presented as part of this activity is intended solely as continuing medical education and is not intended to promote off-label use of any pharmaceutical product. Disclosure of Off-Label Usage: This issue of *Emergency Medicine Practice* discusses the off-label use of methotrexate.

Faculty Disclosure: It is the policy of Mount Sinai School of Medicine to ensure objectivity, balance, independence, transparency, and scientific rigor in all CME-sponsored educational activities. All faculty participating in the planning or implementation of a sponsored activity are expected to disclose to the audience any relevant financial relationships and to assist in resolving any conflict of interest that may arise from the relationship. Presenters must also make a meaningful disclosure to the audience of their discussions of unlabeled or unapproved drugs or devices.

In compliance with all ACCME Essentials, Standards, and Guidelines, all faculty for this CME activity were asked to complete a full disclosure statement. The information received is as follows: Drs. Keadey, Lukens, and Toscano report no significant financial interest or other relationship with the manufacturer(s) of any commercial product(s) discussed in this educational presentation. Dr. Houry has received research grant support from CDC, NIH, and UCB Pharma.

For further information, please see The Mount Sinai School of Medicine website at www.mssm.edu\cme.

ACEP Accreditation: *Emergency Medicine Practice* is approved by the American College of Emergency Physicians for 48 hours of ACEP Category 1 credit per annual subscription.

AAFP Accreditation: *Emergency Medicine Practice* has been reviewed and is acceptable for up to 48 Prescribed credits per year by the American Academy of Family Physicians. AAFP Accreditation begins August 1, 2006. Term of approval is for two years from this date. Each issue is approved for 4 Prescribed credits. Credits may be claimed for two years from the date of this issue.

AOA Accreditation: *Emergency Medicine Practice* has been approved for 48 Category 2B credit hours per year by the American Osteopathic Association.

Earning Credit: Two Convenient Methods

Print Subscription Semester Program: Paid subscribers with current and valid licenses in the United States who read all CME articles during each *Emergency Medicine Practice* six-month testing period, complete the post-test and the CME Evaluation Form distributed with the December and June issues, and return it according to the published instructions are eligible for up to 4 hours of CME credit for each issue. You must complete both the post test and CME Evaluation Form to receive credit. Results will be kept confidential. CME certificates will be delivered to each participant scoring higher than 70%.

Online Single-Issue Program: Current, paid subscribers with current and valid licenses in the United States who read this *Emergency Medicine Practice* CME article and complete the online post-test and CME Evaluation Form at EBMedicine.net are eligible for up to 4 hours of Category 1 credit toward the AMA Physician's Recognition Award (PRA). You must complete both the post-test and CME Evaluation Form to receive credit. Results will be kept confidential. CME certificates may be printed directly from the Web site to each participant scoring higher than 70%.

Emergency Medicine Practice is not affiliated with any pharmaceutical firm or medical device manufacturer.

CEO: Robert Williford **President and Publisher:** Stephanie Williford **Director of Member Services:** Liz Alvarez **Director of Marketing:** Lisa Malcolm

Direct all editorial or subscription-related questions to EB Medicine: **1-800-249-5770** • Fax: 1-770-500-1316 • Non-U.S. subscribers, call: 1-678-366-7933

5550 Triangle Parkway, Suite 150 • Norcross, GA 30092

E-mail: **ebm@ebmedicine.net** • Web Site: **EBMedicine.net**

Emergency Medicine Practice (ISSN Print: 1524-1971, ISSN Online: 1559-3908) is published monthly (12 times per year) by EB Practice, LLC, 5550 Triangle Parkway, Suite 150, Norcross, GA 30092. Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement. This publication is intended as a general guide and is intended to supplement, rather than substitute, professional judgment. It covers a highly technical and complex subject and should not be used for making specific medical decisions. The materials contained herein are not intended to establish policy, procedure, or standard of care. *Emergency Medicine Practice* is a trademark of EB Practice, LLC.

Subscription price: $299, U.S. funds. (Call for international shipping prices.)