Ectopic Pregnancy

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Ectopic Pregnancy

Thomas A. Molinaro, MD, and Kurt T. Barnhart, MD, MSCE

INTRODUCTION

Ectopic pregnancy refers to implantation of the embryo outside of the uterine cavity, typically (in 95% or more cases) within the fallopian tube, although unusual locations (cervix, ovary, abdomen, cesarean section scar) have been reported. Most ectopic pregnancies are located in the ampullary portion of the fallopian tube (80%), followed by the isthmic, fimbrial, or cornual (interstitial) segment. Regardless of the site of an ectopic pregnancy, there is always risk for life-threatening rupture and hemorrhage.

Although the current incidence of ectopic pregnancy is difficult to estimate, the Centers for Disease Control and Prevention (CDC) reported a steady increase between 1970 and 1992 and an overall incidence of 2% in 1992 (more recent data are not available). However, deaths due to ectopic pregnancy appear to be decreasing in the United States, presumably due to diagnosis before tubal rupture. According to CDC reports, 13% of all pregnancy-related deaths from 1970 through 1989 were associated with ectopic pregnancy; this number dropped to 7% for the years 1991 to 1997.

Advances in ultrasonography and rapid serum β-hCG assays have made it possible to diagnose ectopic pregnancy earlier and to implement conservative, nonoperative approaches to treatment. When surgery is indicated, laparoscopic approaches have significantly decreased the morbidity compared to laparotomy. Nevertheless, diagnosing a pregnancy of unknown location continues to be a challenge in early first trimester gestations. While some patients may present with symptoms that raise suspicion of an ectopic pregnancy, a large proportion of ectopic pregnancies are found in asymptomatic patients.

This manual begins with a review of risk factors for ectopic pregnancy, the recognition of which is important in raising suspicion and thus prompting evaluation for possible ectopic pregnancy. This is followed by a case-based discussion of currently recommended approaches to diagnosis and management of ectopic pregnancy.

RISK FACTORS AND PATHOGENESIS

The risk of ectopic pregnancy seems to be increased by factors that alter tubal morphology or function or that affect the hormonal milieu of early pregnancy, resulting in altered embryo transport. There is no evidence that abnormal embryos are more likely to implant in the fallopian tube. Early assessment of patients with risk factors increases the probability of diagnosing an ectopic pregnancy in a timely manner, allowing the use of less invasive, fertility-sparing treatments.

PREVIOUS ECTOPIC PREGNANCY

One of the most predictive risk factors is a previous ectopic pregnancy, which has been noted to increase the risk of a second ectopic pregnancy by up to 8 fold. Barnhart et al found that having 2 previous ectopic pregnancies increased this risk 16 fold. Epidemiologic studies of women with repeat ectopic pregnancies show that the risk is increased if the patient has tubal disease of infectious origin or infertility; this risk decreases after successful intrauterine pregnancies. Patients with a history of ectopic pregnancy should be counseled to seek medical care early in pregnancy.

PREVIOUS SURGERY

Any prior abdominal surgery may predispose to ectopic pregnancy. In a study of patients with repeat ectopic pregnancies, 93% had previous abdominal surgery. The risk of ectopic pregnancy is increased among women who conceive after a failed tubal ligation. Marchbanks et al found a 4.5 fold increase in the risk of ectopic pregnancy among women who had previous tubal surgery. A recent meta-analysis placed this risk even higher. When tubal ligation with electrocautery fails, the risk of ectopic pregnancy is increased 9 fold. Other methods of sterilization increase the risk from 1.2 to 10 fold, with the risk remaining constant over time.

SEXUALLY TRANSMITTED INFECTION

Sexually transmitted infections such as gonorrhea and chlamydia are well-known causes of tubal damage and infertility. The inflammation associated with upper genital...
tract infection with these pathogens leads to tubal obstruction and scarring. A previous history of pelvic inflammatory disease (PID) has been associated with a 3-fold increased risk of ectopic pregnancy. Patients with a repeat ectopic pregnancy are also likely to have had PID in the past.

**CONTRACEPTION**

A meta-analysis by Mol et al concluded that if a woman becomes pregnant while on an oral contraceptive, there is a slight increase in the risk of tubal pregnancy compared to women who conceive off oral contraceptives; that risk is significant in current IUD users when compared to pregnant control subjects. However, since the overall chance of pregnancy is lower among women using contraception, the risk of ectopic pregnancy remains considerably greater in nonusers of contraception.

**INFERTILITY AND ASSISTED REPRODUCTION**

Infertile women have a moderate increase in risk for ectopic pregnancy, regardless of whether they conceive unassisted or via assisted reproductive technology (ART). Some patients require ART because of prior damage to fallopian tubes, and this may be the basis of much of their increased risk. The hormonal alterations from ART have also been implicated as a potential mechanism for dysfunctional tubal motility and tubal implantation. In examining national registry data, Clayton et al found that ART-associated ectopic pregnancy rates were increased only among patients with tubal factor infertility.

**OTHER FACTORS**

In utero exposure to diethylstilbestrol (DES) also increases the risk of ectopic pregnancy, as tube and fimbrial morphology may be altered and embryo transport impaired. A systematic review of published studies found the risk to be increased 9 fold. Smoking has also been associated with an increased risk of ectopic pregnancy. In vitro experiments have demonstrated that cigarette smoke decreases the ciliary motion within the fallopian tubes and may interfere with an oocyte’s ability to enter the tubal lumen. Tobacco use has been shown to increase the risk of ectopic pregnancy from 1.4 to 5 fold, depending on the average number of cigarettes smoked.

**CLINICAL PRESENTATION AND DIAGNOSIS**

**CASE PRESENTATION**

A 28-year-old woman, G<sub>2</sub>P<sub>101</sub>, presents to the fertility clinic with complaints of abdominal pain and vaginal spotting. Her last menstrual period was 5 weeks and 2 days ago. The patient has a history of irregular periods suggestive of anovulation and has been undergoing ovarian stimulation with clomiphene citrate. She had an intrauterine insemination 21 days prior. Her first pregnancy resulted in a term infant delivered by cesarean section, and since that time she had 1 first trimester miscarriage. She has no significant past medical history and underwent an emergency appendectomy for a ruptured appendix 3 years ago. She smokes approximately 10 cigarettes per day.

On examination, the patient’s vital signs are stable, hematocrit is within normal limits, and serum quantitative β-hCG level is 1000 mIU/mL. Abdominal examination reveals minimal tenderness on suprapubic palpation; there is no rebound or guarding. Pelvic examination reveals a closed cervical os and scant old blood. Transvaginal ultrasonography shows a simple cyst on the right ovary, no adnexal masses, and no free fluid. No intrauterine pregnancy is visualized, and the endometrial stripe complex measures 12.5 mm.

- **Is this patient’s clinical picture concerning for possible ectopic pregnancy?**
- **What is the recommended approach to evaluating patients with symptoms during early pregnancy?**

The differential diagnosis of abdominal pain in early pregnancy should include gastrointestinal, genitourinary, gynecologic, and musculoskeletal sources. Gastrointestinal etiologies such as appendicitis, diverticulitis, gastroenteritis, or inflammatory bowel disease may present as abdominal pain. Urinary tract infections and nephrolithiasis should be entertained as possible sources of pain, and hematuria may be confused with vaginal bleeding. Nevertheless, in the case patient, the history of vaginal bleeding and recent fertility treatment make a gynecologic origin of her pain most likely. This patient’s symptoms raise concern about possible ectopic pregnancy, particularly given her risk factors (infertility, history of multiple abdominal surgeries, tobacco use). However, her serum β-hCG level is appropriate for her gestational age, and her ultrasonographic study is nondiagnostic. In a stable patient without symptoms or findings that definitely diagnose an ectopic pregnancy, the most appropriate next step would be to counsel the patient about warning signs and to repeat serum β-hCG testing in 48 hours.

**DIAGNOSTIC EVALUATION**

Early pregnancy symptoms most frequently associated with ectopic pregnancy include vaginal bleeding and/or abdominal or pelvic pain. The presence of
these symptoms should trigger immediate evaluation for possible ectopic pregnancy. Prompt evaluation also should occur as soon as pregnancy is confirmed in a woman with 1 or more risk factors. Women with a history of ectopic pregnancy should be evaluated immediately, as their risk of repeat ectopic pregnancy is increased at least 3 fold. Fortunately, these patients frequently present earlier in pregnancy because of their concern for a repeat ectopic pregnancy.9

History and Physical Examination

Initial evaluation of the patient with suspected ectopic pregnancy should include a thorough history and physical examination. Detailed medical, surgical, and social histories are important to uncover potential risk factors for ectopic pregnancy. An accurate menstrual history provides valuable information regarding gestational age, particularly in women with regular menstrual cycles. Women with irregular cycles and those who conceive while using hormonal contraception will not have predictable dates of conception.

Physical examination should include a review of vital signs, speculum examination, and abdominal examination. Vital signs at the time of presentation provide insight into the patient’s hemodynamic status; a tachycardic, hypotensive patient may be anemic or hypovolemic from acute intra-abdominal bleeding. Abdominal examination that reveals distention, rebound, or guarding may point to intra-abdominal bleeding and requires immediate action. Speculum examination may reveal vaginal bleeding or cervical dilation, which may point to a threatened abortion. A digital vaginal examination may not offer additional information.21 Most often, patients with an unruptured ectopic pregnancy will present with mild abdominal tenderness and vaginal spotting, findings that are not specific from other threatened intrauterine pregnancies. Nevertheless, all women with these first trimester symptoms should be evaluated for the possibility of ectopic pregnancy or threatened abortion, as a large number of these patients will have a nonviable gestation.7,22

Recommended Diagnostic Tests

Early diagnosis of ectopic pregnancy is now possible through the use of high-resolution transvaginal ultrasonography combined with serum quantitative β-hCG levels. The β-hCG level at which an intrauterine pregnancy should be seen is known as the discriminatory zone.23,24 This level varies among institutions depending on the β-hCG assay and resolution of ultrasound equipment but for transvaginal ultrasonography most often is between 1500 and 2000 mIU/mL, which corresponds to approximately 5.5 weeks gestational age.24,25 Using a lower discriminatory zone increases the sensitivity of the test but increases the chances of interrupting a viable pregnancy. A higher cutoff is therefore preferable. A serum β-hCG level above the discriminatory zone in the absence of an intrauterine gestation on transvaginal ultrasonography indicates a nonviable pregnancy. In patients who have conceived via ART, the presence of an intrauterine pregnancy is reassuring; however, the possibility of heterotopic pregnancy should always be entertained in symptomatic patients. The most recent rate of heterotopic pregnancy is 152 per 100,000 ART-assisted pregnancies; these pregnancies occurred most frequently in patients with tubal factor infertility.14,26

In some cases, a tubal pregnancy can be visualized by transvaginal ultrasonography as an inhomogeneous adnexal mass (blob sign), a hyperechoic ring surrounding the gestational sac (bagel sign), or a gestational sac with yolk sac, a fetal pole, or even fetal heart activity.27 Condous et al27 reported that of 152 cases of ectopic pregnancy diagnosed on transvaginal ultrasonography, a blob sign was seen in 88 (57.9%) and the bagel sign was present in 31 (20.4%). Sonographic evidence of free fluid in the pouch of Douglas is another finding often associated with ectopic pregnancy, indicating probable intra-abdominal bleeding.25,28 Despite the ability to detect ectopic pregnancy on transvaginal ultrasonography, the utility of screening all pregnant patients with early ultrasound is unclear as most studies have involved symptomatic patients.29

Other Diagnostic Tests

Endometrial stripe thickness. Several authors have examined the use of endometrial stripe thickness as a means of predicting ectopic pregnancy. A thin endometrial stripe offers some assistance in identifying abnormal pregnancies in women who present with pain or bleeding in early pregnancy.30 However, endometrial stripe thickness alone does not predict the presence of all ectopic pregnancies, as some patients may have an increase in endometrial proliferation from elevated estrogen levels.31 The addition of gestational age to endometrial stripe thickness has not proven helpful in the diagnosis of ectopic pregnancy.32 Nevertheless, a recent study found that an endometrial thickness greater than 25 mm is a relatively good indicator of an intrauterine pregnancy in most situations.33

Serum progesterone. Serum progesterone has been studied as a marker of nonviable pregnancies. A meta-analysis of 26 studies evaluating accuracy of a single serum progesterone measurement in diagnosing ectopic pregnancy found that a level less than 5 ng/mL is
highly (but not 100%) predictive of a nonviable pregnancy, but it cannot distinguish ectopic pregnancy from failed intrauterine pregnancy in all cases. Performing a diagnostic dilation and curettage at this progesterone level may interrupt a small number of viable pregnancies. Serum progesterone levels also can be normal in ectopic pregnancy. Therefore, there is no progesterone value that distinguishes an ectopic pregnancy from a failing intrauterine pregnancy with 100% specificity.

Serum markers. Several serum analytes also have been evaluated as potential markers of ectopic pregnancy but will require large-scale trials to further characterize their efficacy. Serum vascular endothelial growth factor (VEGF) is elevated in women with ectopic pregnancy, but there is no consensus regarding the appropriate cut-off level. Most recently, the combination of decreased pregnancy-associated plasma protein A, elevated VEGF, and decreased progesterone was found to have promise as a serum-based tool for distinguishing between normal intrauterine and ectopic pregnancy. Serum proteomics have also been used in an attempt to characterize serum protein profiles and to identify potential markers of ectopic pregnancy for future research.

Pregnancies of Unknown Location

Most often, patients who present with first trimester cramping and bleeding are found to have a serum \( \beta \)-hCG level below the discriminatory zone and a nondiagnostic ultrasound on initial evaluation. The expectant management of these patients is a critical component of early prenatal care. Follow-up evaluation of these patients should include serial \( \beta \)-hCG levels and repeat transvaginal ultrasonography (Figure).

Kadar et al\(^{41}\) showed that, in viable intrauterine pregnancies, the lower limit of rise in serum \( \beta \)-hCG was approximately 66% over 2 days. More recently, Barnhart et al\(^{42}\) found that the minimum rise may be as low as 53% over a 2-day period. These redefined serial \( \beta \)-hCG curves have been validated in a large cohort of women with symptomatic early pregnancies and in a small cohort with pregnancies conceived by in vitro fertilization.\(^{43,44}\) The decision to follow a patient with serial \( \beta \)-hCG levels requires that the patient be hemodynamically stable, relatively pain free, and able to comply with return visits. If \( \beta \)-hCG levels fall or fail to rise appropriately, the diagnosis of nonviable pregnancy is made.\(^{45}\) It is reassuring that more than 70% of ectopic pregnancies will have an

Figure. Approach to the patient with symptomatic early pregnancy and suspected ectopic pregnancy. D&C = dilation and curettage. (Adapted with permission from Seeber BE, Barnhart KT. Suspected ectopic pregnancy [published erratum appears in Obstet Gynecol 2006;107:955]. Obstet Gynecol 2006;107[2 Pt 1]:402.)
abnormal rise between 2 consecutive serum β-hCG levels. Studies have shown that the appropriate drop in β-hCG levels in complete spontaneous abortions should be at least 23% over 2 days. Nevertheless, ectopic pregnancies can have serum β-hCG curves that are appropriate, rise inappropriately, or fall, thus making these pregnancies difficult to distinguish from normal or abnormal intrauterine pregnancies.

Logistic regression and statistical modeling have recently been introduced as adjunctive tools in the management of pregnancy of unknown location. A decision analysis model by Gracia et al concluded that the combination of ultrasonography and serum β-hCG was the most efficient manner to diagnose ectopic pregnancy. Condous et al have developed several models to predict the presence of an ectopic gestation. These authors also concluded that serum β-hCG, ultrasonography, and a patient’s individual risk factors could be combined to reasonably predict the presence of an ectopic pregnancy. Nevertheless, these models are not yet widely used in clinical practice.

**MANAGEMENT**

**CASE CONTINUED**

The patient is informed that she has been diagnosed with a pregnancy of unknown location. Because of her risk of ectopic pregnancy, she is cautioned regarding signs of tubal rupture, including abdominal pain, dizziness, and tachycardia. The patient is sent home from the clinic with instructions to return in 2 days for a repeat β-hCG level. When she returns 2 days later, she reports that her pain has subsided; her serum β-hCG level is now 1850 mIU/mL. The patient is instructed to return once again for testing and 2 days later is found to have a serum β-hCG of 2275 mIU/mL. Transvaginal ultrasonography at this time shows no evidence of an intrauterine pregnancy but reveals a right adnexal mass, without evidence of a gestational sac, yolk sac, or fetus.

- **What is the appropriate next step in the management of this patient?**

As evidence of a normal pregnancy, we would expect at least a 53% rise in this patient’s β-hCG level 2 days after the first measurement (ie, from 1000 mIU/mL to approximately 1530 mIU/mL) and another 53% increase 2 days later, to roughly 2200 to 2300 mIU/mL. Above a level of 2000 mIU/mL, we would expect to see evidence of an intrauterine pregnancy, and since we do not, the diagnosis of nonviable pregnancy is made. The adnexal findings on ultrasonography are sufficient to suspect ectopic pregnancy.

Once a pregnancy is deemed nonviable, the eventual diagnosis will be either ectopic pregnancy or spontaneous abortion. Barnhart and colleagues advocate uterine evacuation prior to methotrexate treatment to differentiate an ectopic pregnancy from a miscarriage and thus avoid unnecessary treatment of the estimated 40% of these pregnancies that are actually intrauterine. When suction curettage or manual vacuum aspiration is performed in the operating room or office, the sensitivity of frozen section for chorionic villi is approximately 87% to 93%. Endometrial biopsy has been shown to have a poor sensitivity of approximately 30% in detecting the presence of chorionic villi. If the frozen pathology fails to reveal chorionic villi, methotrexate can be given prior to discharge, or the patient can return the following day for a repeat serum β-hCG measurement. Patients with a completed abortion should have a decrease in β-hCG within 24 hours but should be followed until β-hCG is undetectable. When the quantitative β-hCG level continues to rise or plateaus, the diagnosis of ectopic pregnancy is made.

**CASE CONTINUED**

The patient is told that, regretfully, her serum β-hCG level and ultrasound findings indicate that the pregnancy is abnormal and that ectopic pregnancy is likely. A discussion of treatment options ensues, during which the patient expresses a desire for future fertility.

- **What treatment options would be appropriate to discuss with this patient?**

**TREATMENT OF ECTOPIC PREGNANCY**

**Medical Management**

In clinically stable patients, medical treatment of ectopic pregnancy may prevent the need for surgical intervention. Appropriate patients should have no evidence of tubal rupture and be capable of close follow up. Currently, the mainstay of medical management for ectopic pregnancy is systemic methotrexate, a folic acid antagonist that interferes with DNA synthesis and inhibits cell division. Absolute contraindications to methotrexate therapy include hemodynamic instability, hypersensitivity to methotrexate, active peptic ulcer disease, active pulmonary disease, intrauterine pregnancy, breastfeeding, immunodeficiency, alcoholism, blood dyscrasias, and chronic liver or kidney disease (Table 1). Relative contraindications include the presence of fetal cardiac activity, ectopic pregnancy size greater than 4 cm, serum β-hCG level greater than 5000 mIU/mL,
and free fluid in the pelvis suggestive of intra-abdominal hemorrhage.\textsuperscript{53,54}

Tanaka et al\textsuperscript{55} first used systemic methotrexate to successfully treat an interstitial pregnancy in 1982. Initial efforts at using methotrexate for the treatment of ectopic pregnancy involved direct injection of the drug into the gestational sac under ultrasound guidance.\textsuperscript{60} Shortly after, systemic administration was attempted using a multiple-dose regimen of 1 mg/kg of intramuscular (IM) methotrexate every other day, alternating with leucovorin “rescue” to prevent bone marrow suppression and toxicity.\textsuperscript{57,58} Patients were followed closely and serum β-hCG levels were checked every 2 days, with additional doses of chemotherapy given (up to a total of 4) until the β-hCG level decreased by 15%.\textsuperscript{59} In a study of 100 patients with an unruptured ectopic pregnancy treated on an outpatient basis, Stovall et al\textsuperscript{60} reported a 96% success rate with a multiple-dose regimen of methotrexate and leucovorin. Single-dose therapy with one 50 mg/m\textsuperscript{2} dose of IM methotrexate without leucovorin rescue was attempted soon after. Stovall et al,\textsuperscript{61} the first to publish results with a single-dose protocol, reported a 97% success rate among a selected population of 30 patients. Nevertheless, the potential for tubal rupture and possible need for emergency surgery was shown to be higher with single-dose therapy.\textsuperscript{62}

There are few direct comparisons between methotrexate protocols. In a large retrospective cohort (643 patients with medically treated ectopic pregnancy), the success of multiple-dose methotrexate therapy was approximately 95%, compared to 90% with single-dose therapy.\textsuperscript{63} A small, prospective randomized trial comparing the 2 protocols was underpowered to detect equivalence.\textsuperscript{64} Barnhart et al,\textsuperscript{65} in a 2003 meta-analysis summarizing the available observational studies of methotrexate regimens, reported an overall success rate of 88% for single-dose therapy compared to 93% with multiple-dose therapy. Many studies have examined factors that may increase the risk of failing methotrexate treatment. The only factor that predicted a decrease in treatment success in a large observational study (350 patients) was a serum β-hCG level greater than 10,000 mIU/mL before treatment.\textsuperscript{66} A systematic review including more than 500 patients found the risk of failure to be increased in patients whose initial serum β-hCG was greater than 5000 mIU/mL.\textsuperscript{67} In the meta-analysis by Barnhart et al,\textsuperscript{65} when controlling for baseline β-hCG values and the presence of embryonic fetal activity, the relative risk of failure was 4 times higher with single-dose protocols. Also, while the single-dose protocol was associated with significantly fewer side effects, 20% of patients required at least 2 doses.

### Table 1. Contraindications to Methotrexate Therapy

<table>
<thead>
<tr>
<th>Absolute contraindications</th>
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<tbody>
<tr>
<td>Intrauterine pregnancy</td>
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<tr>
<td>Evidence of immunodeficiency</td>
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<tr>
<td>Moderate to severe anemia, leukopenia, or thrombocytopenia</td>
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<tr>
<td>Sensitivity to methotrexate</td>
</tr>
<tr>
<td>Active pulmonary disease</td>
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<tr>
<td>Active peptic ulcer disease</td>
</tr>
<tr>
<td>Clinically important hepatic dysfunction</td>
</tr>
<tr>
<td>Clinically important renal dysfunction</td>
</tr>
<tr>
<td>Breastfeeding</td>
</tr>
</tbody>
</table>

Relative contraindications

- Embryonic cardiac activity detected by transvaginal ultrasonography
- High initial β-hCG concentration (> 5000 mIU/mL)
- Ectopic pregnancy > 4 cm in size as imaged by transvaginal ultrasonography
- Patient refusal to accept blood transfusion
- Inability to participate in follow-up


Recently, a 2-dose methotrexate protocol without leucovorin rescue was tried in 101 patients and found to have an efficacy of approximately 87%, with side effects similar to those experienced with single-dose therapy.\textsuperscript{68} Patient satisfaction was greater than 92%. Importantly, only 3% experienced tubal rupture. Larger studies may prove the 2-dose methotrexate protocol to be the most efficacious, with minimal side effects.

Potential side effects of methotrexate therapy include pelvic pain or cramping, nausea, diarrhea, elevated liver transaminases, stomatitis, and pneumonitis.\textsuperscript{69,70} Risk factors for treatment failure are shown in Table 2.\textsuperscript{53} Patients should be counseled regarding the risks and benefits of treatment with methotrexate, including the potential need for emergency surgery in the event of tubal rupture or persistent ectopic pregnancy. Proper patient selection of relatively asymptomatic patients with lower serum β-hCG concentrations is essential for minimizing risk of tubal rupture.\textsuperscript{71}

### Surgical Management

In the hemodynamically stable patient, surgery may be indicated if medical management with methotrexate is contraindicated or has failed. In most cases, a laparoscopic approach is preferable. Compared with laparotomy, laparoscopy has been shown to reduce
methotrexate with laparoscopic salpingostomy and also found that surgery was more successful (93% vs 85%). Saraj et al found single-dose methotrexate to be 91% effective versus 95% for laparoscopic salpingostomy. Another randomized trial comparing single-dose methotrexate therapy with laparoscopic salpingostomy found no difference in success rates; however, this study allowed investigators to use either systemic methotrexate or local injection. A recent systematic review found no evidence to support the superiority of medical management over laparoscopic salpingostomy. A study of women who underwent these procedures found that although methotrexate therapy had a greater negative impact on quality of life, women were more likely to choose medical therapy because of their desire to avoid surgery.

In terms of cost-effectiveness, recent studies examining the health care costs associated with ectopic pregnancy show that conservative management with methotrexate offers cost savings compared with surgical intervention. The majority of these studies used a single-dose methotrexate protocol in their analysis. However, presumptive treatment with methotrexate was found to be more costly than performing a dilation and curettage and treating only patients with proven ectopic pregnancy.

- Is it possible to predict tubal rupture if ectopic pregnancy is diagnosed before rupture? In the event that rupture occurs, what is the treatment?

Prevention and Treatment of Tubal Rupture

Tubal rupture is associated with increased morbidity and mortality, including the need for emergency surgery, blood transfusion, and prolonged hospitalization. Several authors have proposed risk factors to predict spontaneous tubal rupture or rupture subsequent to methotrexate therapy. While higher levels of β-hCG may place patients at higher risk, rupture may occur at any serum β-hCG level and is difficult to predict. Bickell et al found that most ruptures occurred in the first 48 hours following initial symptoms. While this risk declined with time, it never reached zero. Tubal rupture may also be higher in patients without risk factors, as clinicians may not be as clinically suspicious. In women treated with methotrexate, pregnancy located in the isthmus, normally rising serum β-hCG levels before treatment, or an increase in serum β-hCG after medication administration increases the risk of tubal rupture. Lipcomb et al suggest that a serum β-hCG level greater than 10,000 mIU/mL is the strongest risk factor for tubal rupture. More recently, Dudley et al found that the initial level was not as important as the rate of rise before methotrexate (risk of rupture increased

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### Table 2. Predictors of Methotrexate Treatment Failure

<table>
<thead>
<tr>
<th>Adnexal fetal cardiac activity</th>
<th>Size and volume of the gestational mass (&gt; 4 cm)</th>
<th>High initial β-hCG concentration (&gt; 5000 mIU/mL)</th>
<th>Presence of free peritoneal blood</th>
<th>Rapidly increasing β-hCG concentrations (&gt; 50% in 48 hr) before methotrexate</th>
<th>Continued rapid rise in β-hCG concentrations during methotrexate</th>
</tr>
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</table>

when rate of βhCG increase exceeded 68%) or if the serum βhCG continued to rise after methotrexate.

Patients with a ruptured ectopic pregnancy often present with signs of hypovolemic shock, including hypotension, tachycardia, and abdominal distention.86 Bedside ultrasonography frequently reveals an adnexal mass and/or free fluid in the pelvis indicative of hemorrhage. While laparoscopy may be performed even in the case of tubal rupture, laparotomy with salpingectomy may be preferable to expedite control of life-threatening bleeding. Although most laparotomies are easily performed via Pfannenstiel incision, consideration should be given to the use of a low vertical incision for optimal surgical exposure. Wide-bore intravenous (IV) access should be obtained and hematologic products made readily available.

• What is the approach to treating ectopic pregnancies that are not tubal in location?

Treating Ectopic Pregnanacies of Unusual Location

Much of the data regarding diagnosis and treatment of these pregnancies is based on anecdotal evidence and case series. Risk factors for ovarian pregnancy are similar to those predisposing to tubal pregnancy, including previous PID, IUD use, endometriosis, and ART. In one case series, ovarian pregnancies had a characteristic ultrasonographic appearance of a wide echogenic ring on the surface or within the substance of the ovary; a yolk sac or fetal heart motion could be seen in some cases. Ovarian pregnancies are often confused with corpus luteum cysts on ultrasonography. The diagnosis and treatment of ovarian pregnancies often require laparoscopic evaluation and resection of the pregnancy and/or ovary and may benefit from intraoperative ultrasonography. Methotrexate may be an option if there is persistent trophoblastic tissue after surgery. In many case reports, subsequent pregnancies have been uncomplicated.

Cervical pregnancies remain the most difficult ectopic pregnancies to treat because of the potential for catastrophic hemorrhage; previous treatments have involved hysterectomy. Risk factors for cervical pregnancy are similar to those for tubal pregnancy, although DES exposure seems to be a major risk factor. Diagnosis is frequently made by ultrasound visualization of an intracervical gestational sac resulting in an “hourglass” or dilated cervix. Recently, several authors have described techniques of managing cervical ectopic pregnancies through a combination of systemic or local methotrexate or prostaglandin injection, surgical resection, and/or physical tamponade via balloon or cervical packing. Uterine artery embolization has been employed as an adjunctive measure to control potential hemorrhage. Early diagnosis and intervention is key in the management of cervical pregnancies, as conservative treatment is more successful before 12 weeks gestation and the onset of fetal cardiac activity and with lower serum βhCG levels. Finally, there are several reports of successful live births in women with previous conservative management of cervical pregnancies.

Interstitial pregnancy is defined as pregnancy within the portion of the fallopian tube that lies within the muscle of the uterus. The term cornual pregnancy is used interchangeably in the United States as a synonym for interstitial pregnancy. These pregnancies may progress asymptptomatically into the second trimester, at which point point rupture may have catastrophic consequences of hemorrhage and death. Diagnosis usually is made by ultrasound, but detection may be better with magnetic resonance imaging or laparoscopy. Conventional treatment is wedge resection performed via laparotomy. Some authors have attempted conservative management with methotrexate with some success. There are also case reports of successful laparoscopic resection of interstitial pregnancies. Future fertility is possible after conservative treatment of interstitial pregnancy, although uterine rupture secondary to the weakened myometrial wall is a concern after surgical or medical therapy.

Abdominal pregnancy refers to implantation in abdominal organs or the peritoneum. These pregnancies can go undetected until an advanced gestational age and often result in severe hemorrhage. Rates of maternal mortality as high as 20% have been reported. Patients with abdominal pregnancies often present with abdominal pain, nausea, and vomiting; vaginal bleeding occurs less frequently. Diagnosis is often made via ultrasonography, which may reveal a viable fetus. Most knowledge regarding optimal treatment of abdominal pregnancy comes from anecdotal case reports. Treatment has been performed laparoscopically for early gestations, but laparotomy is necessary for advanced gestations. When possible, the pregnancy should be removed; however, when the placenta is implanted in a vascular organ, it may be left in situ and systemic methotrexate administered, with patients observed closely for infection and hemorrhage. Hemodynamic instability may necessitate wide-bore IV access, transfusion, and arterial embolization.

CASE CONCLUSION

After a discussion of the risks and benefits of various treatment options, the patient requests an attempt at medical therapy. Manual vacuum aspiration

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is performed and the tissue sent for frozen pathology, which reveals no products of conception. The next day, the patient returns for a repeat serum \( \beta \)-hCG level, which has increased by 75%. The patient receives a single IM injection of 50 mg/m\(^2\) of methotrexate. Two days after the injection, she presents to the fertility clinic complaining of right-sided abdominal pain and dizziness with standing. She is immediately sent to the emergency department, where bedside ultrasonography reveals a large amount of complex free fluid and a complex right adnexal mass consistent with a ruptured ectopic pregnancy. Her vital signs are stable, without evidence of tachycardia or hypotension.

The patient undergoes an emergency laparoscopy. Survey of the pelvis reveals a ruptured ampullary pregnancy in the right fallopian tube. There is approximately 500 mL of active bleeding in the pelvis. A right salpingectomy is performed without difficulty. The patient does well postoperatively, without further complications or need for blood transfusion.

• Is follow-up with serial \( \beta \)-hCG levels required for this patient?
• How should she be counseled regarding her risk for future fertility and repeat ectopic pregnancy?

Since a complete salpingectomy was performed, there is no need for repeat serum \( \beta \)-hCG measurement in this patient. Given the patient’s history of infertility, her future fertility might be somewhat lower than in other women without infertility or in whom a salpingostomy was performed. Her risk of future ectopic pregnancy is difficult to quantify. However, she should be advised to seek medical care as soon as a pregnancy test is positive so she can undergo ultrasonography and/or serial \( \beta \)-hCG measurements to locate the pregnancy as early as possible.

More advanced ectopic pregnancies, particularly those in which tubal rupture has begun, should be treated with surgical salpingostomy or salpingectomy.

REFERENCES


