CHAPTER 18

Ectopic pregnancy

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LEARNING POINTS
- The majority (more than 95%) of cases of ectopic pregnancy occur in the fallopian tube, with most implanting in the ampulla.
- Patient factors conferring the greatest risk of ectopic pregnancy include a history of a previous ectopic pregnancy, known tubal damage or previous tubal surgery, failure of a progestin-only contraceptive, and a history of transabdominal tubal sterilization.
- Patients with an ectopic pregnancy can present in early pregnancy with amenorrhea, abdominal pain, or vaginal bleeding.
- Diagnosis of ectopic pregnancy may require serial high-resolution ultrasounds and serum quantitative human chorionic gonadotropin (hCG) assays.
- Medical treatment of ectopic pregnancy with methotrexate allows properly selected patients to avoid surgery.

Introduction

Ectopic pregnancy occurs when a fertilized ovum implants outside the endometrial cavity, most commonly in the fallopian tube [1]. The exact incidence of ectopic pregnancy is difficult to determine. Traditional methods of measuring rates of ectopic pregnancy, such as the use of hospital records, are no longer accurate due to the increasing numbers of ectopic pregnancies managed in outpatient settings. Using US national survey data on inpatient admissions and visits to hospital emergency and outpatient departments, the Centers for Disease Control and Prevention (CDC) estimated that ectopic pregnancy accounted for 2% of all pregnancies (19.7 per 1,000 reported pregnancies) in the USA in 1992. Because this analysis did not include patients managed exclusively in physicians’ offices, the true incidence of ectopic pregnancy is undoubtedly greater. Although the number of US women hospitalized for ectopic pregnancy has decreased over time, data suggest that the incidence of ectopic pregnancy increased sixfold from 1970 to 1992 [2]. For unclear reasons, studies have consistently reported lower rates of ectopic pregnancy (less than 1%) in women presenting for induced abortion [3,4].

Ectopic pregnancy remains an important cause of mortality and morbidity in women of reproductive age. In the 1990s, ectopic pregnancy accounted for 6% of all pregnancy-related deaths in the USA [5]. Although the mortality rate from ectopic pregnancy declined from 84.2 deaths per 100,000 ectopic pregnancies in 1979 to 1980 to about 32 per 100,000 during 1991 to 1999 [6], ectopic pregnancy remains the leading cause of maternal death in the first trimester. Most deaths occur due to rupture of the fallopian tube and massive hemorrhage. The cost of treating ectopic pregnancy is considerable, totaling approximately 1.1 billion US dollars in 1992 [7]. Based on a systematic review of the distribution of causes of maternal death worldwide, the World Health Organization found that reported deaths from ectopic pregnancy accounted for nearly 5% of maternal mortality in developed countries and less than 1% in developing countries [8]. Although ectopic pregnancy remains an important public health problem in developing countries where limited resources and poor access to care often lead to late diagnosis, the relative contribution of ectopic pregnancy to maternal mortality is low compared to hemorrhage, infection, hypertensive disorders, and unsafe abortion [8].

Because more than 60% of US women seek abortion care during the first 8 weeks of pregnancy [9], abortion providers have an opportunity to decrease morbidity from ectopic pregnancy by diagnosing and treating the condition early. This chapter assists this process by describing risk factors and diagnostic algorithms for ectopic pregnancy, as well as
Figure 18.1 Possible sites of ectopic pregnancy. Although most ectopic pregnancies implant in the fallopian tube, extratubal locations may occur.

approaches to medical and surgical management of the condition. Most of the chapter pertains to ectopic pregnancies located in the fallopian tube because they are the most common type; less frequent types of extrauterine pregnancies are described at the end of the chapter.

Background

Pathogenesis

Most (more than 95%) cases of ectopic pregnancy occur in the fallopian tube. Tubal ectopic pregnancies implant most frequently in the ampulla (70%), followed by the isthmus (12%), the fimbria (11.1%), and the cornua (2.4%) [1]. Rare locations for ectopic pregnancies are the ovary, the abdominal cavity, and the cervix (Fig. 18.1). As cesarean section rates increase, reports of implantation at the site of the scar (cesarean scar ectopic pregnancies) are becoming more frequent.

Ectopic pregnancy occurs in the fallopian tube when proliferating trophoblasts invade the tubal wall. The ampullary portion of the fallopian tube is more distensible than other areas of the tube. Ectopic gestations implanting at this site are often found within the tubal lumen and may result in tubal abortion rather than tubal rupture. In contrast, ectopic pregnancies that implant in the narrow isthmus portion of the fallopian tube are more prone to rupture [10].

The etiology of tubal ectopic pregnancy may be due to slowed migration of the blastocyst as it travels through the fallopian tube, resulting in implantation before it reaches the uterine cavity. Impaired movement in the fallopian tube can be secondary to tubal damage from underlying disease, inflammation, or hormonal factors that affect tubal mobility [11]. Intrinsic factors of the blastocyst do not appear to play a role in the etiology of ectopic implantation. Studies analyzing the karyotypes of ectopic embryos have not found greater than expected rates of chromosomal abnormalities [12,13]. However, abnormalities in molecular signaling surrounding the event of implantation may be important [11].

Table 18.1 Risk factors for ectopic pregnancy. (Adapted from Seeber et al [16], Ankum et al [17], and Bouyer et al [18].)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
</tr>
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<tbody>
<tr>
<td><strong>High Risk</strong></td>
<td></td>
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<tr>
<td>Previous tubal surgery</td>
<td>6.0–21.0</td>
</tr>
<tr>
<td>Tubal sterilization</td>
<td>3.0–9.3</td>
</tr>
<tr>
<td>Previous ectopic pregnancy</td>
<td>8.3–47.0</td>
</tr>
<tr>
<td>In utero exposure to DES</td>
<td>2.4–13.0</td>
</tr>
<tr>
<td>Current use of IUD</td>
<td>1.1–45.0</td>
</tr>
<tr>
<td>Tubal pathology</td>
<td>3.5–25.0</td>
</tr>
<tr>
<td><strong>Moderate Risk</strong></td>
<td></td>
</tr>
<tr>
<td>Infertility</td>
<td>1.1–28.0</td>
</tr>
<tr>
<td>Previous genital infections</td>
<td>2.5–3.7</td>
</tr>
<tr>
<td>Multiple sexual partners</td>
<td>1.4–4.8</td>
</tr>
<tr>
<td><strong>Low Risk</strong></td>
<td></td>
</tr>
<tr>
<td>Previous pelvic infection</td>
<td>0.9–3.8</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>2.3–3.9</td>
</tr>
<tr>
<td>Vaginal douching</td>
<td>1.1–3.1</td>
</tr>
<tr>
<td>First intercourse &lt; age 18</td>
<td>1.1–2.5</td>
</tr>
</tbody>
</table>

* Tubal sterilization refers to sterilization procedures performed transabdominally. The risk of ectopic pregnancy after transcervical sterilization is not known.

Risk factors

Many factors have been associated with an increased risk of ectopic pregnancy [14–18] (Table 18.1). Factors conferring the greatest risk include a history of a previous ectopic pregnancy and damage to the fallopian tube, either from prior tubal surgery or from tubal pathology such as salpingitis. Women with ectopic pregnancies are three times more likely to have had one prior ectopic pregnancy, and 16 times more likely to have had two prior ectopic pregnancies compared to those with intrauterine pregnancies [14]. A patient with an ectopic pregnancy has up to a 10 to 15% chance of recurrence; this risk varies by treatment method of the original ectopic pregnancy, with salpingostomy having the greatest risk of recurrence [15]. Women who have had reconstructive tubal surgeries are also at high risk. Most likely, the condition requiring the surgery (e.g., salpingitis, adhesive disease, or ectopic pregnancy) is the causative factor for future ectopic pregnancies rather than the procedure itself.

Salpingitis is another important risk factor for ectopic pregnancy. One study found salpingitis isthmica nodosa, a condition that results in anatomic thickening of the...
proximal portion of the fallopian tubes with multiple luminal diverticula, in approximately 14% of the fallopian tubes containing an ectopic pregnancy versus none of the controls [19]. Genital infections associated with salpingitis, such as chlamydia, gonorrhea, and pelvic inflammatory disease, increase the risk for ectopic pregnancy [17]. One retrospective study found odds ratios for ectopic pregnancy of 2.1 in women who had a history of two prior chlamydial infections and 4.5 in women with three or more prior chlamydial infections [20].

Women exposed to diethylstilbestrol (DES) in utero may develop reproductive tract anomalies, including a T-shaped uterus and foreshortened fallopian tubes with small tubal ostia and minimal fimbrial tissue [21]. In utero DES exposure carries a ninefold increased risk of ectopic pregnancy [22]. Women who become pregnant after tubal sterilization or while using intrauterine contraception or progestin-only methods are at greater risk for ectopic pregnancy. Patients who conceive following transabdominal tubal sterilization have a ninefold increased risk of ectopic pregnancy [23]. The 10-year cumulative probability of ectopic pregnancy after such procedures is approximately 0.07% [24]. Tubal sterilization using bipolar coagulation carries a greater risk than other transabdominal methods, such as postpartum bilateral salpingectomy [25]. Rates of ectopic pregnancy after transcervical sterilization are unknown. As many as half of pregnancies occurring in women with a levonorgestrel intrauterine system in place may be ectopic, whereas the rate is 1 in 16 pregnancies in women using a copper intrauterine device [24]. Women who conceive while using a progestin-only method of contraception, such as oral contraceptives or implants, have a slightly greater risk of ectopic pregnancy compared to those who become pregnant while not using any type of contraception [24]. More importantly, because contraception decreases a woman’s overall chance of becoming pregnant the absolute risk of developing an ectopic pregnancy is still lower.

Assisted reproductive technologies (ART) also increase the risk of ectopic pregnancy. In 2004, the frequency of ectopic pregnancy following in vitro fertilization was 2%, which represents a decrease from the 3% rate reported in 1999. The risk of ectopic pregnancy is greatest in couples with tubal factor infertility [26], most likely due to damaged fallopian tubes in this population. Patients with hydrosalpinges undergoing ART have greater rates of ectopic pregnancy [27,28]. Furthermore, exogenous hormones administered for ovulation induction can alter tubal motility [29–31]. The method of embryo transfer may influence the risk as well, with embryos placed at deep fundal locations having a greater risk for implanting in the fallopian tube than those placed in midfundal locations [32].

For reasons that remain unclear, smoking is also a risk factor for ectopic pregnancy [18,33]. Smoking may lead to impaired immunity, which places women at increased risk for developing genital infections, or smoking may alter fallopian tube mobility, thereby increasing the risk of a tubal implantation.

Clinical assessment

Signs and symptoms
The signs and symptoms of ectopic pregnancy are neither sensitive nor specific. Patients with an ectopic pregnancy may present in the first trimester of pregnancy with amenorrhea, abdominal pain, or vaginal bleeding. However, these symptoms also occur commonly in patients with threatened or spontaneous abortion, making the conditions difficult to differentiate based on clinical assessment alone. In one series, women with ectopic pregnancy presented with complaints of pain in 64 to 80% of cases and with vaginal bleeding in 67 to 83% of cases. In most patients, the vaginal bleeding was mild [34]. Abdominal pain described as moderate to severe or sharp increases the risk of ectopic pregnancy [35]. The minority of patients who present with tubal rupture can exhibit syncope, light-headedness, tachycardia, or hypovolemic shock.

Signs present on physical examination that increase the likelihood of ectopic pregnancy include unilateral or bilateral abdominal tenderness, peritoneal signs such as rebound or guarding, or cervical motion tenderness. A tender adnexal mass is evident in a minority of patients. Women with a uterine size greater than 8 weeks are less likely to have an ectopic pregnancy [35]. The examination in a patient with an ectopic pregnancy also may be nonfocal [36].

Diagnosis
History and physical examination alone will not usually confirm a diagnosis of ectopic pregnancy. Differentiating an ectopic pregnancy from an early intrauterine pregnancy (IUP) or spontaneous abortion usually requires a combination of serum quantitative human chorionic gonadotropin (hCG) measurements, pelvic ultrasound and, in some cases, dilation and curettage [37] (Fig. 18.2). With a normal IUP, specific landmarks using transvaginal ultrasonography typically appear during the following gestational weeks [38]:
- Gestational sac — 4.5 weeks
- Yolk sac — 5 weeks
- Embryonic cardiac activity — 6 weeks

Sometimes ultrasonography allows for an immediate diagnosis of ectopic pregnancy. In units with skilled ultrasonographers, 70 to 90% of women ultimately diagnosed with an ectopic pregnancy had a mass or gestational sac seen in the adnexa by transvaginal ultrasound [39,40]. However, in other settings the majority of initial ultrasounds in women ultimately diagnosed with an ectopic pregnancy are nondiagnostic [41]. The ultrasound finding of an extraovarian, noncystic adnexal mass in a woman with no intrauterine pregnancy and a positive hCG assay has a sensitivity of 84 to
Ectopic pregnancy

Figure 18.2 Diagnostic algorithm for ectopic pregnancy (Adapted with permission from Seeber et al [37].)

90% and a specificity of 94 to 99% for the diagnosis of ectopic pregnancy [40,42,43]. When ectopic pregnancies are visualized on ultrasound, they most frequently appear as a homogeneous mass (58%); less often, they appear as a mass with a hyperechoic ring around a gestational sac (20%) or as a gestational sac with an embryonic pole, with or without gestational cardiac activity (13%) [40].

Other ultrasound findings can be seen in patients with ectopic pregnancies. A pseudogestational sac is a fluid collection in the endometrial cavity that represents bleeding from decidualized endometrial tissue (Fig. 18.3). Unlike a true gestational sac, it is centrally located in the endometrial cavity. Patients with an ectopic pregnancy may also have a corpus luteum cyst that is located on the same side as the ectopic gestation in 70 to 85% of cases [40,44,45]. Blood in the pelvis is evident on ultrasound in 30% of ectopic pregnancy cases and may represent tubal rupture or blood leaking from the fallopian tube [40].

The serum hCG level at which an intrauterine pregnancy should be seen on ultrasound is called the “discriminatory level” (Chapter 6). Depending on the equipment and skills of the personnel at a particular institution, the discriminatory level for transvaginal ultrasonography usually ranges from about 1,500 to 2,500 mIU/ml. A lower discriminatory level is less likely to delay the diagnosis of an ectopic pregnancy, whereas a higher cutoff decreases the risk of missing or dis-

Figure 18.3 Two transvaginal ultrasound images of a pseudogestational sac in a woman with an ectopic pregnancy. The pseudosac is composed of decidualized endometrium (the echogenic rim) and fluid within the endometrial cavity (the anechoic central area outlined by calipers). This fluid is usually either blood or secretions from the hypersecretory endometrium. True early gestational sacs are usually round or elliptical in shape, located eccentrically in the uterine corpus, and surrounded by two bright echogenic rings (so-called choriodecidual reaction or “double-decidual sign”). In contrast, this pseudogestational sac is irregular in shape, centrally located in the uterine cavity, and lacks a double-decidual sign. Often, the pseudogestational sac will come to a point that points toward the cervix, as is the case in this example. (Courtesy of Dr. Matthew Reeves.)
rupting a viable intrauterine pregnancy. If the serum hCG level is above the discriminatory cutoff and transvaginal ultrasonography does not identify an intrauterine pregnancy, then the diagnosis of an abnormal pregnancy is confirmed; however, distinguishing a spontaneous abortion from an ectopic pregnancy remains critical. If the hCG level is below the discriminatory cutoff at the time of presentation, then the patient may have an early intrauterine pregnancy, a failed pregnancy, or an ectopic pregnancy. Serial hCG levels are required to make the diagnosis.

Using quantitative radioimmunoassay, hCG can be detected at levels as low as 1 mIU/ml in the serum and 20 mIU/ml in the urine (Chapter 6). Its appearance in serum and urine coincides with implantation, which occurs approximately 6 to 12 days after ovulation [46]. In viable intrauterine pregnancies with starting hCG levels less than 10,000 mIU/ml, the minimum expected rise in hCG over 48 hours is 53% based on a 99% confidence interval. In rare viable intrauterine pregnancies, the rise in hCG levels may be as low as 35% [47,48]. However, 20% of ectopic gestations can produce an initial hCG pattern identical to that of an intrauterine pregnancy, so an important part of the diagnostic algorithm includes performing an ultrasound once the hCG level reaches the discriminatory cutoff [49]. A decreasing hCG level indicates an abnormal pregnancy. A rapid decline in hCG of 21 to 35% over 48 hours is most indicative of a spontaneous abortion [48], but some ectopic pregnancies have a fast decline in hCG levels as well. Therefore, continuing to obtain serial hCG levels until they fall to undetectable levels is important.

In the majority of cases (70%) of ectopic pregnancy, the rise in hCG levels is slower than that expected for a viable intrauterine pregnancy, or the decline is slower than that expected for a spontaneous abortion [37]. If a woman has a nondiagnostic ultrasound, an initial hCG level above the discriminatory cutoff, and hCG levels that are rising or falling abnormally, performing uterine aspiration can then aid in determining the final diagnosis (Fig. 18.2). Identification of chorionic villi in the tissue aspirate confirms the diagnosis of an abnormal intrauterine pregnancy, and further therapy is necessary. Absence of chorionic villi establishes the diagnosis of ectopic pregnancy, and further treatment is warranted.

Sometimes histological examination is not readily available or accurate. In this situation, a serum quantitative hCG level can be obtained prior to aspiration and 12 to 24 hours later. Data from the medical abortion literature shows that after expulsion of a viable IUP, a drop in the hCG level of at least 50% (average 66%) can be expected at 24 hours [50]. Another study assessing the use of misoprostol for the expulsion of nonviable pregnancies found an expected hCG decline of 80% at approximately 24 hours after misoprostol administration [51]. Within 24 hours after surgical evacuation of an abnormal intrauterine pregnancy, the expected decrease in hCG from preoperative levels is at least 21 to 35%, and is often greater. More information is needed to set a precise minimum expected hCG percent fall after suction curettage. By setting a lower expected minimum decrease in hCG levels postoperatively, fewer patients will be treated incorrectly for an assumed ectopic pregnancy. Performing suction curettage instead of empiric treatment with methotrexate for a presumed ectopic pregnancy does not increase the complication rate [52].

Serum progesterone measurements are not frequently used in diagnostic algorithms for ectopic pregnancy. Serum progesterone levels are greater in viable intrauterine pregnancies than in abnormal pregnancies, and a progesterone level less than 5 ng/ml can accurately rule out a viable IUP. However, a single progesterone level is not useful for diagnosing an ectopic pregnancy, as no definitive value distinguishes an ectopic pregnancy from other abnormal intrauterine pregnancies [53,54].

Up to 50% of women with ectopic pregnancies are asymptomatic and do not have known risk factors [55]. Ideally, screening could allow for early detection of ectopic pregnancy and prevent tubal rupture and the need for surgical management. However, screening for ectopic pregnancy is not recommended due to the low prevalence of the condition and the high false-positive rate of current screening tools [56,57].

### Management of Tubal Pregnancy

#### Medical Management

An ectopic pregnancy can be treated medically with methotrexate, allowing properly selected patients to avoid surgery. Methotrexate is a folic acid antagonist that binds competitively to dihydrofolate reductase and decreases production of folic acid. Because folic acid is needed for DNA synthesis, methotrexate inhibits the synthesis of purines and pyrimidines, and therefore mitosis. Methotrexate affects rapidly dividing cells, and cytotrophoblasts are particularly sensitive to the drug.

Patients eligible for methotrexate treatment of ectopic pregnancy are hemodynamically stable, reliable, and able to return for follow-up monitoring. Traditional relative contraindications to methotrexate treatment include an ectopic gestation greater than 3.5 cm in size as measured by ultrasound or the presence of gestational cardiac activity or an hCG level greater than 5,000 mIU/ml [58]. Although adhering to these guidelines may increase the success rate of methotrexate therapy, other studies suggest that methotrexate is effective in patients who do not fit these criteria [59,60]. Success rates of methotrexate therapy decrease with greater pretreatment hCG levels. In patients treated with the single-dose methotrexate protocol, success rates are significantly lower when pretreatment hCG levels exceed 5,000 mIU/ml [61]. Certain medical conditions are absolute...
contraindications to methotrexate: immunodeficiency, chronic liver disease or alcoholism, preexisting blood dyscrasias, active pulmonary disease, peptic ulcer disease, hematologic or renal dysfunction, breastfeeding, and known sensitivity to methotrexate [62].

Methotrexate is commonly used for the treatment of disorders such as arthritis and malignancies; but it was first used to treat ectopic pregnancies in the 1980s. Stovall et al [63] described the first protocol for outpatient treatment of ectopic pregnancy. In this “multidose” methotrexate protocol (Table 18.2), methotrexate is administered at a dose of 1 mg/kg intramuscularly on days 1, 3, 5, and 7. Leucovorin is given on days 2, 4, 6, and 8 at a dose of 0.1 mg/kg intramuscularly. Leucovorin is a folic acid analog that decreases the side effects resulting from multiple doses of methotrexate, such as mucositis or leukopenia. When leucovorin is used in this manner, it is called leucovorin “rescue.” In this multidose protocol, up to four doses of methotrexate are given in the first week of treatment until serum hCG levels decrease by 15% on two consecutive titers. Weekly hCG levels are checked until the level declines to less than 15 mIU/ml. If hCG levels increase or plateau after the first week of treatment, then a second course of methotrexate can be administered. The multidose methotrexate protocol has a success rate of greater than 90% [63,64].

A “single-dose” methotrexate protocol (Table 18.2) was developed with the goal of enhancing patient compliance without decreasing the efficacy of the treatment. In this protocol, a single dose of methotrexate (50 mg/m² intramuscularly) is administered without leucovorin rescue (day 1). The patient receives a second dose of methotrexate if hCG titers do not decrease by 15% between days 4 and 7. The hCG levels are checked until they are undetectable. In this protocol, up to 20% of patients will require more than one dose of methotrexate [59]. The mean time to resolution of the ectopic pregnancy is 35 days, but it may take as long as 109 days. The success rate of the single-dose protocol ranges from 64 to 89%, making it less effective than the multidose protocol [65–67]. A meta-analysis comparing the two protocols found a 1.96 odds ratio for increased risk of tubal rupture when using the single-dose protocol. After controlling for pretreatment risk factors for treatment failure, including initial hCG level and the presence of gestational cardiac activity, the failure rate for the single-dose regimen was five times greater than that of the multidose protocol [67].

A “two-dose” methotrexate protocol (Table 18.2) has recently been developed with the goal of providing better efficacy than the single-dose protocol without increasing the complexity of the treatment or requiring more patient visits. Using this protocol, the patient receives two doses of methotrexate during the first week of treatment on days 1 and 4. An additional dose can be administered on day 7 or day 11 if hCG titers do not decrease by at least 15% between days 4 and 7. In a trial with 100 patients, the two-dose protocol was found to be safe and well tolerated [68].

When used in the protocols to treat ectopic pregnancy, methotrexate is generally well tolerated. Approximately 30% of patients treated with the single-dose protocol

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**Table 18.2 Methotrexate protocols.**

<table>
<thead>
<tr>
<th>Treatment Day</th>
<th>Single-dose</th>
<th>Two-dose</th>
<th>Multi-dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>T&amp;S, CBC, recent serum hCG, (may need LFTs, Cr)*</td>
<td>T&amp;S, CBC, recent serum hCG, (may need LFTs, Cr)*</td>
<td>T&amp;S, CBC, recent serum hCG, (may need LFTs, Cr)*</td>
</tr>
<tr>
<td>1</td>
<td>Serum hCG</td>
<td>MTX</td>
<td>LEU 0.1 mg/kg</td>
</tr>
<tr>
<td>2</td>
<td>Serum hCG</td>
<td>MTX</td>
<td>LEU</td>
</tr>
<tr>
<td>3</td>
<td>Serum hCG</td>
<td>MTX</td>
<td>LEU</td>
</tr>
<tr>
<td>4</td>
<td>Serum hCG</td>
<td>MTX</td>
<td>LEU</td>
</tr>
<tr>
<td>5</td>
<td>Serum hCG, CBC, LFTs, Cr if &lt;15% decrease in serum hCG from day 4</td>
<td>MTX if &lt;15% decrease in serum hCG from day 4</td>
<td>MTX if &lt;15% decrease in serum hCG from day 4</td>
</tr>
<tr>
<td>6</td>
<td>Serum hCG, CBC, LFTs, Cr if &lt;15% decrease in serum hCG from day 4</td>
<td>MTX if &lt;15% decrease in serum hCG from day 4</td>
<td>MTX if &lt;15% decrease in serum hCG from day 4</td>
</tr>
<tr>
<td>7</td>
<td>Serum hCG, CBC, LFTs, Cr if &lt;15% decrease in serum hCG from day 4</td>
<td>MTX if &lt;15% decrease in serum hCG from day 4</td>
<td>MTX if &lt;15% decrease in serum hCG from day 4</td>
</tr>
<tr>
<td>11</td>
<td>Serum hCG, CBC, LFTs, Cr if &lt;15% decrease in serum hCG from day 4</td>
<td>MTX if &lt;15% decrease in serum hCG from day 4</td>
<td>MTX if &lt;15% decrease in serum hCG from day 4</td>
</tr>
</tbody>
</table>

CBC: complete blood count; LFTs: liver function tests; Cr: serum creatinine; T&S: type and screen; MTX: methotrexate; LEU: leucovorin

*For otherwise healthy patients, the provider may choose not to draw pretreatment LFTs or creatinine.

*Continue methotrexate and leucovorin until 15% decrease in hCG levels between two consecutive titers.

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experienced side effects compared to 40% of those receiving the multidose protocol [67]. The most common side effects were gastrointestinal symptoms (nausea, vomiting) and stomatitis. Elevated liver transaminases usually occurred only with multidose regimens. Other side effects, such as alopecia or pneumonitis, rarely occurred in women receiving methotrexate for treatment of ectopic pregnancy.

Pretreatment blood work includes a complete blood count (CBC), liver transaminases, serum creatinine, a serum quantitative hCG level, and determination of Rh(D) antigen status. In healthy women, simplifying the required blood work to a pretreatment hemoglobin, Rh status, and a recent hCG level may be appropriate. In patients with a history of pulmonary disease, obtaining a chest x-ray is prudent due to the increased albeit small risk of interstitial pneumonitis.

Once a patient receives methotrexate, hCG levels are repeated according to the protocol being used (Fig. 18.2). Concentrations of hCG may increase between days 1 and 4 due to continuing production of hCG after methotrexate treatment. Serial ultrasound monitoring is unnecessary; the ectopic gestation may actually increase in size due to hematoma formation, and this finding is not predictive of treatment failure [69,70]. Tubal hematoma formation or tubal abortion may cause transient abdominal pain in patients undergoing methotrexate therapy. This pain usually occurs 3 to 7 days after the first dose of methotrexate, lasts 4 to 12 hours, and can often be managed conservatively [71].

A patient who requires surgery for her ectopic pregnancy after methotrexate therapy is considered a treatment failure. Abdominal pain lasting more than 12 hours or orthostatic hypotension may indicate tubal rupture, warranting surgical management. An increase or plateau of hCG levels after the first week of methotrexate therapy may also indicate treatment failure [58].

**Surgical management**

Surgical treatment of ectopic pregnancy is required when methotrexate is contraindicated or has failed and in cases of ruptured ectopic pregnancy or a coexisting wanted intrauterine pregnancy. Some patients choose surgical management over methotrexate therapy; benefits include treatment in one visit and fewer follow-up visits for monitoring. Although standard surgical treatment for ectopic pregnancy originally entailed laparotomy, laparoscopy has become the dominant approach in contemporary medical practice. In a study comparing laparoscopic salpingostomy to salpingectomy performed via laparotomy, the laparoscopic approach was associated with decreases in operating time, blood loss during the procedure, length of hospital stay, cost, and convalescence time [72]. No difference was found in future fertility or repeat ectopic pregnancy between the two approaches, although the rate of persistent ectopic pregnancy was greater after laparoscopy. Ultimately, the preferred approach will depend on several factors, including the surgeon’s skill set and the hemodynamic stability of the patient. Laparotomy may allow for a faster entry into the abdominal cavity and better visualization in a patient with uncontrolled bleeding.

Surgical treatment of ectopic pregnancy includes salpingectomy (excision of the fallopian tube) or salpingostomy (removal of the ectopic pregnancy through an incision in the fallopian tube). Surgical management is often guided by surgeon preference, as available studies do not strongly favor one method over another. Some studies, but not all, have found a greater pregnancy rate after salpingostomy as compared to salpingectomy [15,73–77]. However, salpingostomy may carry a slightly greater risk of repeat ectopic pregnancy compared to salpingectomy [15,73]. The decision to perform a salpingostomy or salpingectomy is often made intraoperatively, and no strict criteria exist for recommending one versus the other. Expert opinion generally favors a salpingectomy in the following situations: uncontrolled bleeding, recurrent ectopic pregnancy in the same tube, ectopic gestation greater than 5 cm in size, or a damaged fallopian tube.

When performing a salpingostomy, injecting a solution of vasopressin (0.2 units/ml) into the fallopian tube at the site of the ectopic pregnancy may help to reduce blood loss. A longitudinal incision should be made using a unipolar needle on the antimesenteric border of the fallopian tube. The surgeon can then flush the products of conception from the fallopian tube using high-pressure irrigation. Any bleeding from the fallopian tube can be controlled with electrosurgical fulguration. The fallopian tube can heal by secondary intention or be sutured. One study found no significant difference in postoperative tubal patency rates, future fertility, or repeat ectopic pregnancy rates in patients who underwent salpingostomy with or without tubal suturing [73].

Persistent ectopic pregnancy occurs in 3 to 20% of patients after salpingostomy [15]. Detection of these cases requires weekly monitoring of serum hCG levels postoperatively. A plateau or rise in hCG levels signals a persistent ectopic pregnancy, which should be treated with a single dose of methotrexate. After treatment with methotrexate, hCG levels are followed until they are no longer detectable. In one study that assessed the predictive value of a postoperative day 1 serum hCG titer, the average decline in hCG level was 60%, and a drop of less than 50% was predictive of a persistent ectopic pregnancy [78]. Preoperative factors that increase the risk of persistent ectopic pregnancy include fewer than 42 days from onset of the patient’s last menstrual period prior to treatment, an ectopic gestation less than 2 cm in diameter, or a rapidly increasing hCG level (greater than 40% per day) [79,80]. Administering prophylactic methotrexate at a dose of 1 mg/kg within 24 hours of surgery may decrease the risk of persistent ectopic pregnancy, but this approach remains controversial [81]. Side effects from this single dose of methotrexate
are mild and occur in 5 to 8% of patients [72]. Some experts advocate prophylactic methotrexate only in certain circumstances, such as in patients at high risk for persistent ectopic pregnancy or when the surgeon is not certain of complete removal of the tubal gestation [82].

Studies comparing laparoscopic salpingostomy to multidose methotrexate therapy found no difference in treatment success rates. Patients receiving methotrexate had more side effects and a lower health-related quality of life compared to those treated surgically. Research also demonstrates similar success rates in women treated with single-dose methotrexate therapy or laparoscopic salpingostomy, although approximately 20% of medically treated patients received more than one dose of methotrexate. Rates of post-treatment tubal patency, future fertility, and repeat ectopic pregnancies did not significantly differ between the two groups [72].

Reproductive outcome

Although multiple studies have examined fertility after ectopic pregnancy, varying treatment modalities and rates of follow-up make this outcome difficult to measure. In one review, 57% of patients treated with conservative laparoscopic surgery for ectopic pregnancy had a subsequent intrauterine pregnancy, similar to 58 to 61% of patients treated with methotrexate [83]. Preexisting fallopian tube damage is likely a major factor in future reproductive success after an ectopic pregnancy. One study found that at 1 year posttreatment, 75% of women without tubal damage were pregnant compared to 55% of women with prior tubal damage [75]. Women with an ectopic pregnancy are at risk for recurrence; approximately 10% (range 5 to 28%) will have another ectopic pregnancy [75,83,84].

Rare types of ectopic pregnancy

Heterotopic pregnancy

A heterotopic pregnancy is the coexistence of an intrauterine and an ectopic gestation. In the majority of cases of heterotopic pregnancy, the ectopic gestation is found in the fallopian tube. Traditionally, heterotopic pregnancies occurred at a rate of 1 in 30,000 pregnancies but they are now more frequent, occurring in 1 of 3,900 pregnancies overall and 1.5 of 1,000 pregnancies conceived through assisted reproductive technologies [85–87]. The reassuring presence of an intrauterine pregnancy on ultrasound may delay the diagnosis of the ectopic gestation. Treatment of heterotopic pregnancies usually involves salpingectomy: methotrexate is contraindicated in a patient with a desired intrauterine pregnancy. In cases of undesired pregnancy, a possible treatment option could include uterine aspiration of the intrauterine pregnancy, followed by methotrexate treatment of the ectopic gestation in those patients meeting the criteria for medical management. Case reports describe successful treatment with local injection of potassium chloride [88–90]. In heterotopic pregnancies, the intrauterine pregnancy is more likely to end in a spontaneous or induced abortion when compared to singleton ART pregnancies. Perinatal outcomes are similar between the two groups [87].

Interstitial (cornual) pregnancy

Located at the junction of the fallopian tube and uterine cavity, interstitial (cornual) pregnancies comprise less than 3% of all ectopic gestations [1] (see Plate 18.1). Risk factors for interstitial ectopic pregnancies include a history of ipsilateral salpingectomy, previous ectopic pregnancy, and in vitro fertilization [91]. Interstitial ectopic pregnancies can be difficult to differentiate from intrauterine pregnancies and require an experienced ultrasonographer to make the diagnosis. Interstitial pregnancies are eccentrically located in the endometrial cavity with extremely thin surrounding myometrium, typically less than 5 mm. Their similarity to intrauterine pregnancies may delay the diagnosis. In one series, 14 of 32 interstitial pregnancies presented after rupture through the uterine wall [91]. Treatment traditionally consists of laparotomy with a cornual resection or a hysterectomy. Case reports describe treatment of these pregnancies with laparoscopic resection or a combined laparoscopic and hysteroscopic approach [92–95]. Treatment of nonruptured interstitial pregnancies with methotrexate also has been described [93,96].

Abdominal pregnancy

Abdominal pregnancies are rare types of ectopic pregnancies [1]. They occur in the peritoneal cavity and can be found on the omentum, pelvic sidewall, or abdominal organs. The etiology of abdominal ectopic pregnancies remains unclear. They may result from primary peritoneal implantation or secondary implantation of an aborted tubal pregnancy. Patients with abdominal ectopic pregnancies can present with a variety of signs and symptoms. Ultrasound is useful for initial diagnosis, but CT scan or MRI may be necessary for confirmation. Although diagnosis can occur at any gestational age, some abdominal ectopic pregnancies progress to the third trimester. Late diagnosis places patients at risk for life-threatening hemorrhage or hypovolemic shock if the placenta invades a large vessel [97].

The optimum management for abdominal ectopic pregnancy is not clear. Treatment in the first trimester usually consists of laparoscopic removal of the pregnancy [98]; methotrexate may not be efficacious [99]. Management of pregnancies that have progressed to the second and third trimesters is determined on a case-by-case basis but usually entails laparotomy. Prompt intervention is indicated due to the life-threatening risk of continuing to carry these pregnancies. A few case reports have described delivery of viable fetuses after diagnosis in the third trimester, but fetal morbidity is high [100,101]. Disposition of the placenta remains
controversial; the surgeon may choose to leave it in situ if the placenta is attached to large blood vessels or organs. Patients with placentas left in situ warrant close monitoring, as they are at risk for sepsis, secondary hemorrhage, and other complications [97,102].

**Ovarian pregnancy**

Ovarian pregnancies account for approximately 3% of all ectopic pregnancies [1,103]. Patients may present with signs and symptoms similar to those seen in fallopian tube ectopic pregnancies, such as amenorrhea, abdominal pain, and vaginal bleeding. A large percentage of patients with ovarian pregnancies present after rupture has occurred [103]. On ultrasound examination, ovarian pregnancies can be difficult to distinguish from fallopian tube pregnancies. Intraoperatively, ovarian pregnancies are frequently mistaken for ruptured ovarian cysts or other ovarian pathologies [104], and the diagnosis is made at the time of histologic examination. Treatment of ovarian pregnancies consists of cystectomy, ovarian wedge resection, or oophorectomy, all of which may be accomplished laparoscopically [105].

**Cervical pregnancy**

A cervical pregnancy occurs when a fertilized oocyte implants within the endocervical canal. Cervical pregnancies account for less than 1% of ectopic pregnancies [1]. Risk factors for cervical pregnancies include prior dilation and sharp curettage (D&C), which may be reported in 50 to 68% of patients [106,107], prior cesarean delivery, or in-vitro fertilization treatment [106,108]. The main symptom of cervical pregnancy is painless vaginal bleeding.

Most case reports of cervical ectopic pregnancies have used ultrasound for diagnosis. Ultrasound criteria used to diagnose a cervical pregnancy include the following:

- A gestational sac in the cervix with peritrophoblastic flow (with or without an embryonic or fetal pole)
- An enlarged cervix with hourglass uterine shape
- Multiple echogenic areas within the cervix.

A closed internal cervical os or a pregnancy below the level of the uterine arteries helps to differentiate a cervical pregnancy from an isthmo-cervical pregnancy [106,109,110]. A cervical pregnancy can be mistaken for an intratubal pregnancy implanted in the lower uterine segment or an early spontaneous abortion with the gestational sac located in the cervix. Serial ultrasound examinations are useful for diagnosis. The gestational sac in spontaneous abortions tends to change position in the cervix and become increasingly irregular. In cervical ectopic pregnancies, the gestational sac remains in the same position and retains its shape or grows larger. Moreover, gestational cardiac motion may be seen in cervical ectopic pregnancies, unlike in spontaneous abortions. MRI is another useful diagnostic modality [111]. Although more expensive and not as readily available as ultrasound, MRI may be helpful when ultrasound evaluation is indeterminate.

Historically, cervical ectopic pregnancies were diagnosed at the time of dilation and curettage, when massive hemorrhage occurred, often requiring hysterectomy. In contemporary practice, diagnosis of cervical pregnancy more commonly occurs before surgical intervention. In an attempt to preserve fertility, numerous treatment modalities have been used as adjuncts to suction curettage, including intracervical Foley catheter tamponade, uterine artery embolization, internal iliac artery ligation, cervical packing, cervical cerclage, and cervical amputation [112–114]. Case reports suggest that treatment with methotrexate, either systemically or via direct injection with or without potassium chloride, may have success rates exceeding 80% [106,112,114–117].

**Cesarean section scar pregnancy**

Cesarean section scar pregnancies are a rare type of ectopic gestation in which the pregnancy implants into a uterine scar from a prior cesarean section. The pregnancy is implanted in the muscle (intramural) and not connected to the endometrial cavity. Cesarean scar pregnancies occur in up to 1 in 1,800 pregnancies [118], and the incidence may be increasing due to heightened awareness by sonographers. Current data are limited to case reports, and diagnosis and treatment are not standardized. The most common symptom may be painless vaginal bleeding [118]. Ultrasound (transvaginal and Doppler) is useful in making the diagnosis. The sonographer may see a mass or gestational sac anterior to a previous cesarean section scar that appears to bulge outward toward the bladder. Abnormal vascularity in this area of the lower uterine segment may be visualized with the use of Doppler and helps differentiate a cesarean ectopic pregnancy from a spontaneous abortion.

Various treatments for cesarean scar ectopic pregnancy have been described, and include surgery via an abdominal approach or dilation and curettage, systemic or direct injection of methotrexate or direct injection of potassium chloride into the ectopic gestation, and expectant management [118–120]. In the first trimester, laparotomy or laparoscopy with local wedge resection or hysterectomy provides definitive management [119,120]. Dilation and curettage for cesarean scar pregnancy may result in excessive blood loss and the need for uterine tamponade with a Foley catheter [121]. One case series reported an approximate 70% success rate with local injection of methotrexate [121]. However, the risks with this type of management include uterine rupture or significant hemorrhage. Because the risk of hemorrhage or uterine rupture with expectant management of a cesarean scar pregnancy appears to be high, this approach is not recommended [118,121]. A second-trimester cesarean scar pregnancy requires surgical management. One small series reported a 5% risk of recurrent cesarean scar pregnancy.
in future pregnancies [122]. Viable full-term gestations following cesarean scar pregnancies have been reported [122].

**Conclusion**

Despite advances in diagnosis and management, ectopic pregnancy remains an important public health problem worldwide. In the USA, ectopic pregnancy is still the leading cause of maternal death in the first trimester. Ectopic pregnancies occur most frequently in the fallopian tube. Abortion providers can play an important role in decreasing morbidity from ectopic pregnancy by remaining vigilant for the diagnosis. Algorithms using ultrasonography and serum hCG assays facilitate early diagnosis. Many unruptured tubal pregnancies can be treated medically using methotrexate regimens.

**References**


