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Current Management of Ectopic Pregnancy

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Ectopic pregnancy, which is any pregnancy implanted outside the uterine cavity, remains the leading cause of pregnancy-related first-trimester death among women in the United States. Fertilization of the ovum occurs in the fallopian tube. As the zygote divides, it becomes first a morula and then a blastocyst, normally arriving in the uterine cavity and beginning implantation on day 6 after fertilization. Anything that delays or impedes tubal transport may allow implantation to begin while the blastocyst is still in the tube; approximately 97% of ectopic pregnancies are tubal in location.

Ectopic pregnancies represent approximately 2% of all pregnancies [1,2]. This estimate is conservative, as the analysis did not include patients whose condition was diagnosed and managed exclusively as outpatients. While the incidence of ectopic pregnancy has continued to increase, the case fatality rate has dropped from 69% in 1876 [3], to 0.35% in 1970, and to 0.05% in 1986. The death rate for African American and other minority women remains over double that for white women, and the highest death rate occurs in the 15- to 19-year-old age group [4].

With documented intrauterine pregnancy, the risk of coexisting ectopic (heterotopic pregnancy) is approximated at 1 case in 10,000 patients to 1 case in 30,000 [5,6]. This risk increases to approximately 1 case in 100 patients if the woman is being treated for infertility [7].

Risk factors

Risk factors for ectopic pregnancy are strongly associated with conditions that cause alterations to the normal mechanism of fallopian tubal

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transport. It is postulated that the more damage that occurs to the fallopian tube, the higher the risk for developing an ectopic pregnancy. This damage may result from a number of factors, such as infection, surgery, congenital anomalies, or tumors. Many potential risk factors have been reported in the literature, some with good evidence and others with less convincing data. There is good evidence to support the following as risk factors for developing an ectopic pregnancy: history of previous ectopic pregnancy, previous tubal surgery, tubal ligation, tubal pathology, in utero diethylstilbestrol exposure, and current use of an intrauterine device (IUD) [8].

In a 1996 meta-analysis, Ankum and colleagues [8] reported an odds ratio of 6.6 (95% CI, 5.2–8.4) with a history of a previous ectopic pregnancy. Barnhart and colleagues [9] in 2006 confirmed previous reports that a history of previous ectopic pregnancy was the strongest risk factor associated with ectopic pregnancy. A history of one previous ectopic pregnancy conferred an odds ratio of 2.98 (95% CI, 1.88–4.73) and a history of two ectopic pregnancies increased the risk to 16% overall (odds ratio 16.04; 95% CI, 5.39–47.72). Table 1 presents a comparison of the odds ratios evaluated in these two studies.

Reconstructive tubal surgery has also been shown to be a high risk factor for ectopic pregnancy with an odds ratio of 4.7 [8]. Reconstructive tubal surgery is closely linked to the underlying tubal damage caused by a previous ectopic pregnancy or pelvic inflammatory disease. The complexity of surgical restoration of the damaged tube correlates with subsequent risks of developing an ectopic pregnancy [10]. The underlying risk factors, and not the surgery itself, are the likely major contributing factors in these cases. Patients who have undergone tubal reanastomosis are also at risk for ectopic pregnancy. In one study, 6.6% of patients were diagnosed with an ectopic pregnancy after undergoing tubal reanastomosis. The same study also found that patients who had a history of tubal occlusion by cautery were at higher risk than those who had reversals after noncautery methods [11].

Tubal ligation failures also confer a high risk for ectopic pregnancy. The US Collaborative Review of Sterilization prospectively followed 10,863 women electing tubal sterilization. Thirty-three percent of post-sterilization pregnancies occurring in this population (47 out of 143 pregnancies) were ectopic; all but 1 were tubal. The risk was highest in patients who had a tubal ligation using bipolar cautery, and in women sterilized under the age of 30. The risk of ectopic pregnancy in these patients was 31.9 per 1000 procedures compared with 1.2 per 1000 procedures in patients who had a postpartum salpingectomy [12]. The increased risk with bipolar cautery is most likely associated with fistula formation of the fallopian tube leading to subsequent failure. There are currently no data on the risk of ectopic pregnancy after hysteroscopic sterilization.

The use of both hormonal and nonhormonal contraceptive methods confers protection against ectopic pregnancy [13]. This includes the use of both hormonal and nonhormonal IUDs. However, should a patient get pregnant

Table 1
Risk factors for ectopic pregnancy

Risk factor	Ankum (odds ratio; 95% CI)	Barnhart (odds ratio; 95% CI)
High risk factor		
Previous ectopic pregnancy	6.6; 5.2–8.4	2.9; 1.9–4.7 (if >2 ectopic pregnancies: 16.0; 5.4–47.7)
Previous tubal surgery	4.7; 2.4–9.5	Not reported
History of tubal ligation	9.3; 4.9–18.0	Not reported
In utero DES exposure	5.6; 2.4–13.0	Not reported
Current use of IUD	4.2–45.0	Not reported
Moderate risk factor		
History of PID	2.5; 2.1–3.0	1.5; 1.1–2.1
History of infertility	2.5–21.0	Not reported
Smoking	2.5; 1.8–3.4	Not reported
History of gonorrhea	2.9; 1.9–4.4	See below
History of chlamydia	2.8; 2.0–4.0	See below
Weak or no association		
Outpatient treatment chlamydia/gonorrhea	Not reported	1.22; 0.6–2.6
Sexual partners >1	2.1; 1.4–4.8	Not reported
Coitarche <18y	1.6; 1.1–2.5	Not reported
Past use of IUD	1.6; 1.4–1.8	1.1; 0.6–1.9
History of TAB	1.6; 1.0–1.6	0.99; 0.6–1.6
Nontubal surgery	1.5; 1.1–2.6	0.95; 0.67–1.4
Prior cesarean section	0.56; 0.3–1.1	Not reported

Abbreviations: DES, diethylstilbestrol; PID, pelvic inflammatory disease; TAB, threatened abortion;

Adapted from Ankum WM, Mol BW, Van der Veen F, et al. Risk factors for ectopic pregnancy: a meta-analysis. Fertil Steril 1996;65(6):1093–9; and Barnhart KT, Sammel MD, Gracia CR, et al. Risk factors for ectopic pregnancy in women with symptomatic first-trimester pregnancies. Fertil Steril 2006;86(1):36–43.

while using an IUD, her risk of an ectopic pregnancy rises dramatically, with reported odds ratios of 4.2 to 45 [13,14]. Some studies have reported a potentially small increased risk of ectopic pregnancy in past users of an IUD, but more current, well-controlled research indicates there is no increased risk with previous IUD use [9,13].

Previous genital tract infection is the major cause of tubal damage and infertility. A history of previous cervical infection with *Neisseria gonorrhea* or *Chlamydia trachomatis* and pelvic inflammatory disease has been linked to increased risk for ectopic pregnancy [8,15]. A recent study found that a previous history of pelvic inflammatory disease had an odds ratio of 1.5 (95% CI, 1.11–2.05) for ectopic pregnancy [9]. This study specifically looked at patients treated for *N gonorrhea* or *C trachomatis* in the outpatient setting versus those requiring inpatient treatment for pelvic inflammatory disease. The investigators found that patients who received outpatient treatment

for *N gonorrhea* and/or *C trachomatis* did not have an increased risk for ectopic pregnancy (odds ratio 1.22; 95% CI, 0.6–2.6). These findings suggest that the insult to the normal tubal transport mechanism may be greater when patients present with symptoms or findings that require inpatient management. Hillis and colleagues [15] reported that repeated chlamydia infections increased the risk for ectopic pregnancy. The odds ratio after two infections was 2.1 and rose to 4.5 after three infections.

A history of nontubal pelvic surgery has been inconsistently reported to confer a potential increased risk for ectopic pregnancy [16–18]. Barnhart and colleagues [9] in 2006 found no strong association for nontubal surgery (including cesarean section) and ectopic pregnancy. In addition, there was also no association between a history of voluntary interruption of pregnancy (therapeutic abortion), regardless of number, and ectopic pregnancy. This study did not mention appendectomy as a risk factor, but in another study, a history of an appendectomy was more commonly reported in cases of ectopic pregnancy [19].

Diethylstilbestrol exposure in utero has been shown to confer a ninefold increased risk of ectopic pregnancy [20]. Other potential risk factors include smoking, young age at coitarche, multiple sexual partners, vaginal douching, and infertility [8,21]. Many of these risk factors likely act through a common pathway of tubal damage by infectious or environmental agents.

Location

The most common location for an ectopic pregnancy is in the fallopian tube. Other less common sites include the abdomen, ovary, cervix, and the interstitial portion of the fallopian tube. In one study, over 95% occurred in the fallopian tube in the following locations: ampulla (70%), isthmus (12%), fimbria (11.1%), and interstitium/cornua (2.4%). The remaining sites of ectopic pregnancies were ovarian (3.2%), abdominal (1.3%), and cervical (<1%) [22]. Identifying the location of an ectopic is important for therapy, but may be very challenging. Ultrasound remains the best method to diagnose location. The location of an ectopic pregnancy may alter the approach to treatment and subsequent follow-up. Depending on location, a combination of medical and surgical treatment may need to be employed. This review will focus on the management and treatment of tubal ectopic pregnancy.

Presentation

The classic triad of abdominal pain, amenorrhea, and vaginal bleeding should always alert the clinician to evaluate for an ectopic pregnancy. Unfortunately the diagnosis may be quite challenging because the presentation of an ectopic pregnancy can vary significantly. In one study, the percentage

of patients who presented with ectopic pregnancy with abdominal pain was 98.6%, amenorrhea 74.1%, and irregular vaginal bleeding 56.4%. Abdominal tenderness (97.3%) and adnexal tenderness (98%) were the most common physical findings [23]. Barnhart and colleagues [9] reported an increased odds ratio for ectopic pregnancy in patients presenting with first-trimester symptoms if moderate to severe bleeding (odds ratio 1.42; 95% CI, 1.04–1.93) and pain (odds ratio 1.42; 95% CI, 1.06–1.92) were present.

Although these signs and symptoms are common, the clinical presentation of ectopic pregnancy can vary significantly from the classic presentation. Physical examination findings may also reveal a change in vital signs, such as tachycardia or orthostatic changes; cervical motion tenderness; adnexal/uterine tenderness (from blood irritating the peritoneal surfaces); or a palpable mass. Physical examination findings may also be unremarkable or subtle. Ectopic pregnancy can also mimic other conditions, such as spontaneous abortion, early pregnancy failure, ruptured corpus luteal cyst, and infection. Thus, in the setting of a positive pregnancy test, ectopic pregnancy should always be high on the clinician's differential diagnosis. In clinical scenarios of patients with known high risk factors for ectopic pregnancy, some investigators have advocated early screening for ectopic pregnancy once they have a positive pregnancy test [24].

Diagnosis

Early diagnosis can reduce the mortality and morbidity associated with ectopic pregnancy. Following the history and physical examination, the two most important diagnostic tests in evaluating for an ectopic pregnancy are transvaginal ultrasound (TVUS) and a serum human chorionic gonodatrophin (hCG) level. The sensitivity and specificity of combining these tests has been reported to range from 95% to 100% [25–27].

The first step in the diagnosis of an ectopic pregnancy is to evaluate for an intrauterine pregnancy. Confirmation of an intrauterine pregnancy almost definitively rules out an ectopic pregnancy; the risk of a heterotopic pregnancy is one for every 10,000 to 30,000 spontaneous pregnancies [5,6]. However, in the setting of assisted reproductive technologies the risk can rise to 1% [7].

TVUS can identify intrauterine pregnancy at a gestation of 5.5 menstrual weeks at nearly 100% accuracy [28]. At 4.5 to 5 weeks, the first ultrasound marker of intrauterine pregnancy is a gestational sac with a ''double decidual sign'' (double echogenic rings around the sac) [29]. The yolk sac appears next at 5 to 6 weeks and remains until about 10 weeks. The embryo (fetal pole) and cardiac activity can be first detected at about 5.5 to 6 weeks. A potentially confounding ultrasound finding is a pseudosac. This is described as a collection of fluid within the endometrial cavity that is usually localized centrally within the uterus. This can be potentially mistaken for an intrauterine gestational sac. A pseudosac is the result of endometrial bleeding from decidualized endometrium in the setting of an extrauterine pregnancy

[30]. Unfortunately, identification of a pseudosac is not diagnostic of an ectopic pregnancy, has a high false-positive rate, and thus cannot be relied on to make the diagnosis of an ectopic pregnancy [31].

In the absence of a reliable last menstrual period, the hCG level is instrumental in the evaluation of ectopic pregnancy. The concept of a discriminatory zone should be used to help facilitate ultrasound findings. The discriminatory zone is defined as the level of hCG at which an intrauterine pregnancy should be visualized. With abdominal ultrasound, most radiologists use 6500 mIU/mL, but this has been further refined with the use of TVUS, reducing the discriminatory zone to 1500 to 2500 mIU/mL [30,32]. The exact cutoff to use depends on the success of the institution in diagnosing the discriminatory zone, the quality of the equipment, and the expertise of the sonographer.

When the hCG level has reached the discriminatory zone and an intrauterine pregnancy cannot be diagnosed, an extrauterine pregnancy should be highly suspected. An exception to this would be in cases of multiple gestations. Patients at risk for multiples, such as those using assisted reproductive technologies, can be carefully followed to a higher discriminatory zone [33]. The detection of an abnormally rising or declining hCG has also aided in the diagnosis of an ectopic pregnancy. Kadar and colleagues [34] first reported on the concept of a "doubling" hCG in normal pregnancies every 1.4 to 2.1 days, with a minimum 66% rise in 2 days. More recently the hCG curves have been redefined. The lower limit of a normal rise for a normal pregnancy has been reported to be 53% in 2 days. A rise lower than this is highly suggestive of an abnormal pregnancy [35]. While abnormally rising hCG levels are useful to distinguish an abnormal pregnancy, normally rising hCG levels do not rule out ectopic pregnancy. The same researchers recently reported hCG profiles for women diagnosed with an ectopic pregnancy. They reported that the number of women with ectopic pregnancy who experienced a rise in hCG (60%) was similar to those with a decrease in hCG (40%) and that there was no definitive way to characterize the pattern of hCG for women with an ectopic pregnancy [36].

In situations where there is no definitive ultrasound diagnosis of an intrauterine pregnancy and the hCG level is above the discriminatory zone, uterine evacuation is indicated to differentiate between an early pregnancy failure (miscarriage) and an ectopic pregnancy. In these cases, women have an equal chance of being diagnosed either with a miscarriage or ectopic pregnancy [37]. The same study reported that the presumed diagnosis of ectopic pregnancy was incorrect nearly 40% of the time. The addition of uterine evacuation to the treatment algorithm (Fig. 1) can help minimize the inadvertent administration of methotrexate to patients with early pregnancy failures without a significant difference in complication rates or cost [38]. Uterine evacuation is superior to Pipelle endometrial biopsy in the diagnosis of ectopic pregnancy and should be the method employed [39]. In the absence of chorionic villi, an ectopic pregnancy is likely and medical or surgical treatment is indicated.

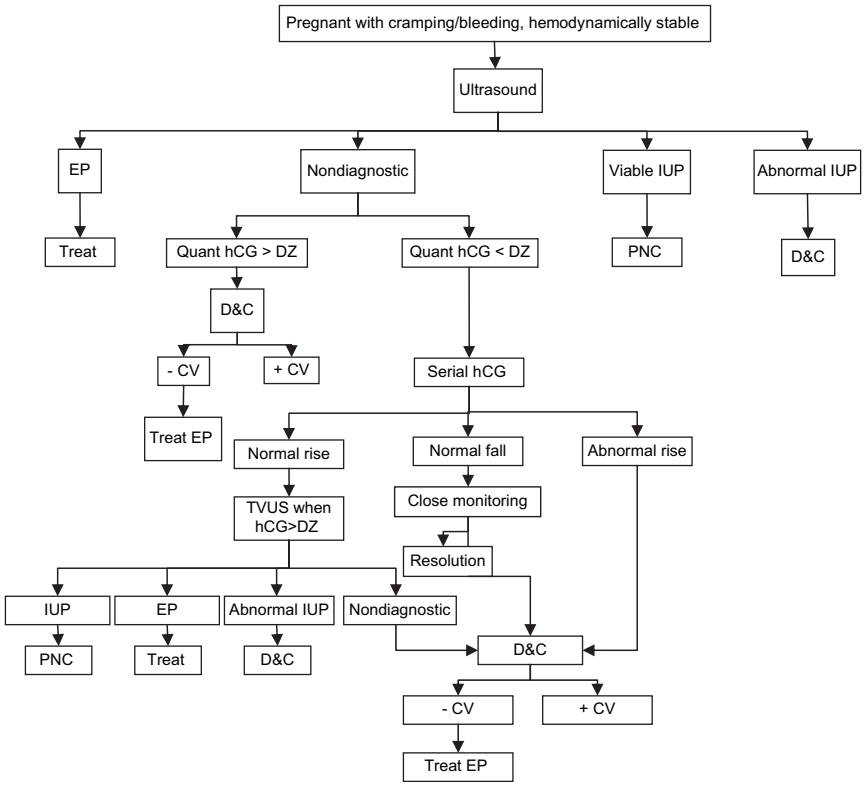

Fig. 1. Evaluation of the symptomatic first-trimester pregnancy. CV, chorionic villi; D&C, dilation and curettage; DZ, discriminatory zone; EP, ectopic pregnancy; IUP, intrauterine pregnancy; PNC, prenatal care.

The usefulness of a single progesterone level to diagnose ectopic pregnancy has been debatable. During the first 8 to 10 weeks, progesterone is produced by the corpus luteum and remains relatively stable. A progesterone level above 25 ng/mL is usually consistent with a normal pregnancy (97% sensitivity), while a progesterone level less than 5 ng/mL has been shown to be 99% specific in confirming an abnormal pregnancy. Unfortunately, the lower limit cannot differentiate between an early pregnancy failure and an ectopic pregnancy [40]. In 1998, a meta-analysis of 26 studies concluded that progesterone alone is not sufficient to diagnose ectopic pregnancy with good reliability [41].

Treatment

After the diagnosis is made, several factors influence the decision to treat an ectopic pregnancy medically or surgically. If the patient is unstable, then immediate surgical treatment via laparotomy or laparoscopy is necessary. In

the past, laparotomy with salpingectomy was considered the gold standard, but with the availability of minimally invasive technology and increasing physician skill, laparoscopy is now the treatment of choice [42]. Laparoscopy is associated with a faster recovery, shorter hospitalization, reduced overall costs, and less pain, bleeding, and adhesion formation. In a hemodynamically stable patient, surgery is still the preferred route for heterotopic pregnancy, tubal rupture, or imminent risk of rupture. Other indications for surgery include no desire for or an inability to comply with medical treatment, contraindication to methotrexate, and failure of medical treatment. Surgery should also be considered for patients with conditions that seem to predispose to failure of medical therapy, such as a tubal pregnancy greater than 5 cm or fetal cardiac activity seen on TVUS [43,44]. These factors are considered in more detail below.

Salpingectomy versus salpingostomy

Once the decision is made to proceed to the operating room, the surgeon must decide on the appropriate surgical technique. Often this decision must be made in the operative suite. Thus, appropriate preoperative counseling is important. Taking into consideration risk factors, patient desire for future fertility, and the condition of the patient also helps guide the intraoperative decision. Salpingectomy is the segmental or entire removal of the fallopian tube. The indications for removing the tube include recurrent ectopic pregnancy in the same tube, a severely damaged tube, uncontrolled bleeding (before or after salpingostomy), heterotopic pregnancy, and lack of desire to bear more children.

Salpingostomy is the method of choice in women of reproductive age who wish to preserve their fertility. Salpingostomy is typically performed by making an incision on the antemesenteric border of the fallopian tube at the point of maximal distension. The use of vasopressin before incision has been reported to reduce bleeding and operative time in some studies, but has also been found to not be significant in others [45,46]. Removing the product of conception by hydrodissection is recommended, along with avoiding excessive handling of the tube and excessive cautery to prevent potential further damage to the fallopian tube. The rate of intrauterine pregnancy is improved in patients having linear salpingostomy versus salpingectomy, although the recurrent ectopic pregnancy rate is also higher [47–49].

Persistent ectopic pregnancy

One of the potential hazards of conservative surgical management of ectopic pregnancy with salpingostomy is persistent ectopic pregnancy. The risk of persistent ectopic pregnancy after salpingostomy is reported to be

2% to 11% with laparotomy and 5% to 20% with laparoscopy [32,50]. The increased rate in patients treated by laparoscopy is thought to be associated with the learning curve of laparoscopy. Because of the potential risk of tubal rupture and hemorrhage, some investigators recommend following weekly hCG serum levels to ensure complete resolution [51]. If the hCG level plateaus, methotrexate is usually indicated as the first option, followed by salpingectomy if medical treatment fails. Some investigators have advocated the use of prophylactic methotrexate after salpingostomy to reduce the risk of persistent ectopic pregnancy [52,53]. Risk factors for salpingostomy failure, such as an ectopic pregnancy less than 2 cm, or rapidly rising preoperative hCG levels, may help guide the decision to administer prophylactic methotrexate after salpingostomy [54]. Small masses, by preventing complete evacuation of the ectopic pregnancy, may potentially place patients at higher risk for persistent ectopic pregnancy.

Medical management

Before the mid-1980s treatment for ectopic pregnancy was exclusively surgical. The first case report of methotrexate for the treatment of ectopic pregnancy appeared in 1982 [55]. Many other agents have been used with varying rates of success. Prostaglandins, dactinomycin, etoposide, hyperosmolar glucose, anti-hCG antibodies, potassium chloride, and mifepristone have all been described in the literature [56].

Methotrexate has been the most successful method of medical management for ectopic pregnancy and is currently the medical treatment of choice. Methotrexate for ectopic pregnancy was proposed after the observation that actively replicating trophoblasts in gestational trophoblastic disease were successfully treated with methotrexate [57]. Methotrexate is a folinic acid antagonist that binds to the catalytic site of dihydrofolate reductase inhibiting the synthesis of purines and pyrimidines, thus interfering with the synthesis of DNA and cell replication [58].

Hemodynamically stable patients are eligible for medical management with methotrexate. The inclusion and exclusion criteria for administration of methotrexate are listed in Boxes 1 and 2 [59]. The initial treatment regimens for ectopic pregnancy consisted of multiple doses of methotrexate with citrovorum rescue. Stovall and colleagues [60] in 1989 demonstrated a success rate of 96% with their multiple-dose regimen. Their protocol consisted of intramuscular methotrexate, 1 mg/kg of actual body weight alternating with citrovorum rescue factor 0.1 mg/kg. Methotrexate was continued only until there was a 15% decline in the level of hCG. These investigators then observed that most of their patients treated with the multidose regimen had declining levels of hCG before receiving the second and/or third dose of methotrexate [61]. This led to the publication of the development of the single-dose regimen without citrovorum rescue [62]. Table 2 describes the

Box 1. Criteria for receiving methotrexate

Absolute indications
- Hemodynamically stable without active bleeding or signs of hemoperitoneum
- Patient desires future fertility
- Nonlaparoscopic diagnosis
- Patient able to return for follow-up care
- General anesthesia poses risk
- Patient has no contraindications to methotrexate

Relative indications
- Unruptured mass ≤3.5 cm at greatest dimension
- No fetal cardiac activity
- β-hCG limit does not exceed a predetermined value (6–15 K)

Adapted from American College of Obstetricians and Gynecologists (ACOG). Medical management of tubal pregnancy. Int J Gynaecol Obstet 1999;65:99; with permission.

single-dose methotrexate regimen. The single-dose protocol uses 50 mg/m^2 of patient body surface area, administered intramuscularly. Lipscomb [63] later reported the University of Tennessee's experience with their first 315 patients treated with single-dose methotrexate and reported an overall success rate of 91.1%.

Single-dose versus multidose protocol

There is currently no consensus as to which methotrexate protocol should be used [59]. The overall success rate reported in the literature for both protocols is approximately 90% [64]. In a recent randomized trial of 108 patients, the success rate with a single dose was 88.9% compared with 92.6% for multidose patients [65]. This was not considered statistically significant (odds ratio 0.64; 95% CI, 0.17–2.1) and no differences in side effect profiles were reported. In a systematic review, women treated with the single-dose regimen were reported to have a higher failure rate (odds ratio 4.74; 95% CI, 1.77–12.62) [66]. The data obtained for this review were from case series and not randomized controlled studies. In addition, it is difficult to ascertain whether there may have been selection bias between patients receiving single- versus multidose regimens. The review did confirm that success was inversely associated with hCG levels for both protocols. Given the current available data, the single-dose methotrexate protocol appears to have similar efficacy and side effect profile while making the least impact on resources of patients and providers.

Box 2. Contraindications to medical therapy

Absolute
- Breastfeeding
- Immunodeficiency
- Abnormal creatinine (>1.3 mg/dL), aspartate aminotransferase (twice the normal value)
- Alcoholism or liver disease
- Preexisting blood dyscrasias
- Peptic ulcer disease
- Active pulmonary disease
- Known sensitivity to methotrexate

Relative
- Gestational sac >3.5 cm
- Cardiac activity

Adapted from American College of Obstetricians and Gynecologists (ACOG). Medical management of tubal pregnancy. Int J Gynaecol Obstet 1999;65:99; with permission.

Predictors of success

Various predictors of success with methotrexate have been reported in the literature. Limited and anecdotal evidence has attributed success partially or entirely to such factors as hCG levels, ectopic size, fetal cardiac activity, progesterone levels, and free peritoneal blood in the cul-de-sac. Lipscomb and colleagues [44] reviewed their experience and reported that high hCG and progesterone levels and, the presence of fetal cardiac activity, were associated with higher failure rates. They further concluded that the single best predictor for success with methotrexate was the initial hCG level. In counseling patients who receive a single-dose methotrexate regimen, it is important to consider the available data on failure rates (Table 3). Patients with an hCG below 5000 mIU/mL had the best success with methotrexate.

Table 2
Single-dose methotrexate protocol

Day	Therapy
0	hCG ± dilation and curettage
1	hCG, aspartate aminotransferase, serum urea nitrogen/creatinine, complete blood cell count, Rh, methotrexate (50 mg/m^2)
4	hCG
7	hCG

Data from Stovall TG, Ling FW, Gray LA. Single-dose methotrexate for treatment of ectopic pregnancy. Obstet Gynecol 1991;77(5):754–7.

Table 3
Success rates by hCG

Serum β-hCG	Success rate
<1000	98% (118/120)
1000–1999	93% (40/43)
2000–4999	92% (90/98)
5000–9999	87% (39/45)
10,000–14,999	82% (18/22)
>15,000	68% (15/22)

Data from Lipscomb GH, McCord ML, Stovall TG, et al. Predictors of success of methotrexate treatment in women with tubal ectopic pregnancies. N Engl J Med 1999;341(26): 1974–8.

Patients with hCG levels between 5000 mIU/mL and 9999 mIU/mL had failure rates of 13%, increasing to 18% with an hCG between 10,000 mIU/mL and less than 14,999 mIU/mL. Above 15,000 mIU/mL, the failure rates rose to 32%. This study also concluded that a large ectopic and the presence of free peritoneal blood were not associated with higher failure rates. There is currently no set defined limit above which methotrexate should not be administered, but based on available data, the higher failure rates with hCG levels above 5000 mIU/mL need to be taken into consideration.

Surveillance

Once the decision is made to proceed with medical management, it is important to counsel patients about potential side effects (Box 3) and the need for close follow-up. The day of methotrexate administration is considered day 1 (see Table 2). Patients receiving the single-dose protocol then need to follow up on day 4 and 7 for additional laboratory draws and reevaluation. The day-4 hCG level can plateau or rise before a decrease begins. It is not uncommon to see a rise in the day-4 hCG level because of the continued production of hCG from syncytiotrophoblasts, despite cessation of hormone in the cytotrophoblast [67]. A study looking at the predictability of day-4 hCG on success of methotrexate found no association with success of treatment or the need for potential surgical intervention [68].

Many patients (33%–60%) also experience abdominal pain (''separation pain'') 3 to 7 days after administration of methotrexate [48,69,70]. Separation pain is thought to be secondary to tubal abortion or an expanding hematoma within the fallopian tube [71]. This is usually self-limited and most patients can be managed conservatively with nonsteroidal anti-inflammatory agents. Patients who report no relief with supportive measures should be immediately evaluated to rule out tubal rupture. The majority of methotrexate-treated ectopic pregnancies can be associated with an increase in size by TVUS, likely representing hematoma formation within the tube. This finding does not reliably predict treatment failure unless other signs of rupture are present [72,73].

Box 3. Side effects associated with methotrexate

Drug related
- Nausea
- Vomiting stomatitis
- Gastric distress
- Dizziness
- Reversible alopecia (rare)
- Severe neutropenia (rare)
- Pneumonitis
- Vaginal bleeding
- Increase in abdominal pain
- Increase in hCG levels from day 1 to day 4

Data from American College of Obstetricians and Gynecologists (ACOG). Medical management of tubal pregnancy. Int J Gynaecol Obstet 1999;65:97–103.

Signs of treatment failure include significantly worsening abdominal pain (despite change in hCG levels), signs of hemodynamic instability, less than a 15% decline between day-4 and day-7 hCG levels, and increasing or plateauing hCG levels after the first week of treatment [59]. In a study of ruptured ectopic pregnancies, tubal rupture was encountered more frequently in women with no previous history of ectopic pregnancies [74], suggesting that surveillance of patients at presumed lower risk should be just as diligent as for patients with known risk factors. The same study also reported a rupture rate of greater than 11% in patients with hCG levels less than 100 mIU/mL.

If no signs of treatment failure are present by day 7 and there is a decline of 15% between day 4 and day 7, weekly hCG levels are recommended until complete resolution (hCG <15 mIU/mL) is seen [61,63]. If on day 7 the drop in hCG is not greater than 15% from day 4, and if the patient is clinically stable, a second dose of methotrexate with weekly follow-up is suggested. In general, a second dose is needed in 15% to 20% of patients, with less than 1% requiring more than two doses [63,66]. The average time to resolution (hCG <15 mIU/mL) for patients successfully treated with single-dose methotrexate was 33.6 days [63].

Expectant management

Expectant management of ectopic pregnancy has been employed with rates of reported in the range of 48% to 100%. That large gap in rates is in part due to the differences in inclusion criteria [48,75]. In one study, expectant management was most successful (32 of 33) in women with hCG

levels less than 175 mIU/mL [76]. In subjects with hCG greater than 175 mIU/mL, only 41 out of 74 were managed successfully. In a situation of a clinically stable patient with hCG less than 175 mIU/mL, indeterminate TVUS, and declining hCG levels, it may be reasonable to employ expectant management. On the other hand, given the low complication rate of methotrexate, many clinicians opt for medical treatment over expectant management.

Summary

While mortality from ectopic pregnancy has dropped precipitously because of improved diagnostic and management techniques, it remains a significant gynecologic emergency, and delay in diagnosis or treatment can be catastrophic. Diagnosis rests on maintaining a high index of suspicion for women with symptomatic complaints in the first trimester, or women without complaints but with risk factors, such as a prior ectopic pregnancy, an IUD in situ, or pregnancy following assisted reproductive technology. Algorithms, such as that shown in Fig. 1, identify how combined use of hCG measurement, TVUS, and examination of uterine contents after confirming nonviability may be used to efficiently prevent under- or over-treatment. Choice of the best management technique, ranging from expectant, to outpatient medication, to conservative versus radical surgery, is based on the patient's clinical condition; factors related to the ectopic, such as size, evidence of rupture, or rate of hCG rise; and the patient's wishes.

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