Diagnosis and Management of Ectopic Pregnancy

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Abstract

Ectopic pregnancy is the abnormal location of a pregnancy, outside of the uterus. The most common location of an ectopic pregnancy is the fallopian tube although ectopic pregnancies may also be found in the cervix, interstitial segment of the fallopian tube, ovary, uterine scar from previous cesarean section, or abdominal cavity. The greatest risk to maternal morbidity and mortality associated with ectopic pregnancy is tubal rupture, leading to hemodynamic instability and rapid maternal decompensation. Therefore, early detection and treatment can lead to improved maternal outcomes. Diagnosis of ectopic pregnancy can generally be made using a combination of serial beta HCG monitoring and transvaginal ultrasound. First-line treatment in a stable patient is usually methotrexate. Methotrexate may be administered via a fixed multidose, single-dose, or two-dose regimen in combination with close beta HCG monitoring. For women who fail medical management, in whom medical management is contraindicated, or for whom tubal rupture is suspected, laparoscopic surgery is the treatment of choice. Surgical management may be accomplished by either salpingostomy or salpingectomy, depending on patient characteristics.

Keywords

Ectopic pregnancy • Methotrexate • Discriminatory zone • Pregnancy of unknown location

Contents

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1 Introduction

Ectopic pregnancies represent a significant cause of maternal morbidity and mortality. They remain the leading cause of death in women during the first trimester, accounting for 75% of first-trimester maternal deaths and 9–13% of all pregnancy-related deaths (Guven et al. 2007; Barnhart et al. 2007; Banz et al. 2010). With improvements in diagnostic technologies, including human chorionic gonadotropin (HCG) monoclonal assays and high-resolution transvaginal ultrasound (TVUS), the diagnosis can frequently be made early, allowing for more conservative medical and surgical management and improved fertility outcomes. This has caused a subsequent paradigm shift in treatment, away from emergent life-saving surgery and toward outpatient medical management and minimally invasive surgery techniques that better preserve reproductive anatomy and future fertility. Despite these advances, investigation and diagnosis of early pregnancy of unknown location, and specifically ectopic pregnancy, remains a source of uncertainty and therefore stress for both the patient and the provider. This chapter will discuss the pathogenesis, evaluation, and treatment of ectopic pregnancies.

2 Epidemiology

Due to improvements in early detection and a shift toward outpatient management, the true incidence of ectopic pregnancy has become difficult to accurately measure. It is estimated that ectopic pregnancies account for 2% of all pregnancies with 100,000 cases reported each year (Barnhart et al. 2007). Furthermore, ectopic pregnancies account for approximately 9% of all pregnancy-related deaths (Chang et al. 2003). From 1970 to 1992, the incidence of ectopic pregnancies increased sixfold, while during that same time, the risk of death related to ectopic pregnancy decreased by 90% (Goldner et al. 1993).

Two primary factors have contributed to the increasing difficulty in surveillance of ectopic pregnancy in the United States: inpatient treatment of ectopic pregnancies has decreased, and multiple outpatient healthcare visits per ectopic pregnancy have increased (Zane et al. 2002). Therefore, use of hospital discharge diagnosis codes grossly underestimates new diagnoses, while use of coding data from the ambulatory care setting is likely to lead to overestimation of both the incidence and prevalence. Despite these challenges to contemporary surveillance of disease trends, the estimated incidence of ectopic pregnancies since 2002 has remained stable (Hoover et al. 2010). This trend can likely be attributed to the increase in use of ovulation induction agents and assisted reproductive technologies (ART) and simultaneous improvements in prevention and treatment of sexually transmitted infections (STIs), thus decreasing pelvic inflammatory disease, all of which are risk factors for ectopic pregnancy.

3 Pathogenesis

The term ectopic pregnancy can refer to any pregnancy located outside of the uterine cavity. Ninety-seven percent of ectopic pregnancies are located in the fallopian tube with 80% of these occurring in the ampullary region (ACOG 2008; ASRM 2013). Extrauterine pregnancies can occur in other locations as well, including the cervix, interstitial segment of the fallopian tube, uterine myometrium, uterine scar from previous cesarean section, ovary, and the peritoneal cavity (Fig. 1).

Any abnormal anatomic or physiological process that interferes with normal tubal transport of an oocyte from the ovary to the endometrial cavity can lead to ectopic pregnancy. Histological studies show that the presence of chronic inflammation and postinflammatory changes, characterized by findings of chronic salpingitis and salpingitis isthmica nodosa (SIN) on surgical pathology specimens, are associated with increased rates of ectopic pregnancy (Green and Kott 1989). Furthermore, placentation and growth of the ectopic gestation is usually intraluminal, with tubal rupture more often occurring as the result of progressive tubal distension and focal necrosis than direct invasion of trophoblastic tissue into the tubal muscularis (Stock 1991). The ectopic

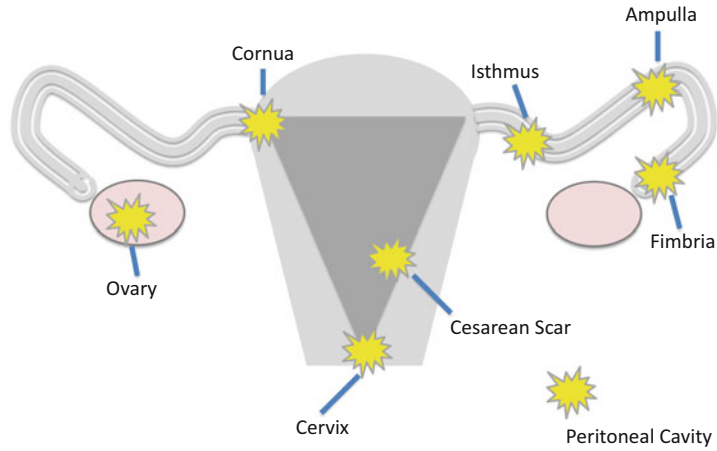

Fig. 1 Sites of ectopic pregnancy

trophoblastic tissue itself may further damage tubal epithelium leading to an increased risk of future, ipsilateral ectopic pregnancy.

4 Risk Factors

While many women presenting with ectopic pregnancy will have a history of one or more well-established risk factors, up to half of affected women will have no such history (ACOG 2008). Risk factors for the development of ectopic pregnancy include (1) history of previous ectopic pregnancy, (2) history of tubal surgery including bilateral tubal ligation (BTL), (3) history of sexually transmitted infection (STI) including tubal infection and pelvic inflammatory disease (PID), (4) history of pelvic surgery and the presence of pelvic adhesions, (5) infertility and use of assisted reproductive technologies (ART), (6) cigarette smoking, (7) current intrauterine device (IUD) use, and (8) in utero exposure to diethylstilbestrol (DES) (ASRM 2013; ACOG 2008).

Recurrent ectopic pregnancy will occur in up to one third of pregnancies following a previous ectopic pregnancy (ACOG 2008). This association is due to a combination of underlying tubal disease leading to the primary event, as well as further tubal damage resulting from its treatment. The number of previous ectopic pregnancies is directly correlated to the risk of recurrence. The odds of developing a subsequent ectopic pregnancy is increased tenfold in women with a history of two previous ectopic pregnancies, compared to women with a history of only one previous event (Skjeldestad et al. 1998). Recurrent ectopic pregnancy is not limited to the ipsilateral fallopian tube. The observation of contralateral recurrence reinforces the theory of chronic inflammation leading to tubal pathology as a primary mechanism of abnormal extrauterine implantation.

An increasingly common source of iatrogenic tubal damage is bilateral tubal ligation (BTL). One third of pregnancies that occur following BTL are ectopic, with post-tubal ligation pregnancies accounting for as many as 10% of all ectopic pregnancies (ACOG 2008). The 10-year cumulative probability of ectopic pregnancy following all methods of tubal sterilization is 7.3 per 1,000 procedures (Peterson et al. 1997). This risk further varies by sterilization method utilized and the woman's age at time of sterilization. Younger age at time of sterilization is associated with an increased risk of lifetime method failure and thus the accompanying risk of ectopic pregnancy. The highest risk of subsequent ectopic pregnancy is associated with sterilization by bipolar tubal coagulation, and the lowest risk is associated with postpartum salpingectomy (31.9 vs. 1.2 ectopic pregnancies per 1,000 procedures, respectively) (Peterson et al. 1997).

Overall, the incidence of ectopic pregnancy is lower for women using any form of contraception compared to women using no contraceptive method at all (Mol et al. 1995). When looking

specifically at ectopic pregnancy risk following contraceptive method failure, concurrent IUD use has the highest association with development of ectopic pregnancy (Furlong 2002). Therefore, any pregnancy in the setting of current IUD use should lead to a high level of clinical suspicion and close surveillance for the presence of an ectopic pregnancy.

Another well-documented cause of anatomic changes to the Mullerian system including tubal pathology is in utero exposure to DES. Associated tubal anomalies include truncated and convoluted fallopian tubes as well as "withered" or constricted fimbriae (DeCherney et al. 1981). These morphologic findings have been associated with up to fivefold increased risk of ectopic pregnancy (Kaufman et al. 2000). Use of DES in pregnancy was banned in 1971 following evidence correlating its use to development of vaginal clear cell adenocarcinoma in exposed offspring. Therefore, potentially affected women are currently reaching the end of their reproductive lifespan; however, this time frame may be extended with increasing availability of ART.

Because early screening and a high level of clinical suspicion can lead to early detection and intervention, counseling of patients with a history of known risk factors for development of ectopic pregnancy is imperative to decreasing associated morbidity and mortality. While in the case of cigarette smoking, lifestyle modification may decrease the risk developing an ectopic pregnancy, for the remainder of patients, presentation early in pregnancy for close monitoring and early documentation of pregnancy location may be beneficial.

5 Diagnosis

Although the incidence of ectopic pregnancies has increased in almost all developed countries, the associated morbidity and mortality have steadily declined due to improvements in early diagnosis (Rabischong et al. 2011). Prompt diagnosis is important for early initiation of appropriate therapy and to reduce the risk of fallopian tube rupture leading to rapid hemodynamic instability. Ectopic pregnancies account for 18% of women presenting to the emergency department with first-trimester bleeding, abdominal pain, or both (ACOG 2008). Because half of women diagnosed with an ectopic pregnancy have no history of associated risk factors, a high level of clinical suspicion should be employed when evaluating any reproductive age woman presenting with vaginal bleeding with or without associated abdominal pain. Although evaluation and diagnosis should be prompt, the finding of an ectopic pregnancy in a hemodynamically stable patient is not always an emergency and can often be treated on an outpatient basis (ASRM 2013).

Both ruptured and unruptured ectopic pregnancies generally present with the classic triad of symptoms: amenorrhea or delayed menses, abdominal pain, and vaginal bleeding (Alsuleiman and Grimes 1982). Pain associated with ectopic pregnancy is generally moderate to severe, lateral, and sharp. Midline pain is associated with decreased risk of ectopic pregnancy (Dart et al. 1999). Other symptoms commonly associated with presentation for ectopic pregnancy are related to tubal rupture and hemoperitoneum. These symptoms include shoulder pain (caused by peritoneal irritation from hemoperitoneum), dizziness, lightheadedness, and shock. Physical exam findings including the presence of peritoneal signs, cervical motion tenderness, and either lateral or bilateral abdominopelvic tenderness have been found to increase the probability of ectopic pregnancy, while uterine size greater than 8 weeks on bimanual exam is associated with decreased likelihood of ectopic pregnancy (Dart et al. 1999). Unfortunately, no combination of signs and/or symptoms has been found that definitively confirm or exclude the diagnosis of ectopic pregnancy; therefore, further testing is required when clinical suspicion is raised.

5.1 Ultrasound

The value and interpretation of transvaginal ultrasound depends on the gestational age of the pregnancy. Accurate gestational age calculation, not

absolute beta HCG level, is the best determinant for when a normal intrauterine pregnancy should be able to be detected by ultrasound (ACOG 2008).

For women with reliable pregnancy dating including those with regular menstrual cycles, a planned pregnancy, or use of ART such as ovulation induction or embryo transfer to achieve pregnancy, predictable findings on ultrasound can confirm normal location and development of the pregnancy. An intrauterine gestational sac is expected to be visible by transvaginal ultrasound between 5.5 and 6 weeks gestational age or 24 days after conception via ovulation induction or embryo transfer (ASRM 2013). Failure to detect an intrauterine gestational sac in the above scenarios is diagnostic of an abnormal pregnancy. Because pregnancy dating is uncertain for many women, failure to identify an intrauterine pregnancy (IUP) on ultrasound usually requires further evaluation with serial HCG levels before a definitive diagnosis of ectopic pregnancy can be made (ACOG 2008).

> The beta HCG level at which evidence of a normal intrauterine pregnancy, defined as presence of a gestational sac, is expected to be visible on transvaginal ultrasound is termed the discriminatory zone. The discriminatory zone ranges from 1,500 to 2,500 mIU/mL but will differ by institution depending on the serum assay used and the skill of the ultrasonographer performing the exam (ASRM 2013).

The absence of evidence of an IUP on ultrasound with an HCG level above the discriminatory zone implies an abnormal pregnancy although it does not distinguish between abnormal intrauterine and ectopic pregnancies. Proposals have been made regarding standardization of terminology used when discussing early pregnancy ultrasound findings and are listed in Table 1.

Use of a higher, more conservative, discriminatory zone when making management decisions will decrease the chances of terminating a viable pregnancy (ASRM 2013). Furthermore, it is important to keep in mind that multiple gestation pregnancies will have HCG levels that are higher at earlier stages than singleton pregnancies, but the rate of increase should be similar. Given the presence of increased HCG levels earlier in gestation, the standard discriminatory zone will often be inaccurate for multiple gestation pregnancies. Therefore, a normal pregnancy as indicated by a normal rise in serial beta HCG levels should be followed expectantly until a definitive diagnosis of intra- versus extrauterine pregnancy can be made.

Table 1 Standard terminology for ultrasound findings in early pregnancy

Definite ectopic pregnancy – extrauterine gestational sac with yolk sac and/or embryo (+/− cardiac activity)
Probable ectopic pregnancy – inhomogenous adnexal mass or extrauterine sac-like structure
Pregnancy of Unknown Location (PUL) – no signs of either ectopic pregnancy or IUP
Probable IUP – intrauterine echogenic sac-like structure
Definite IUP – intrauterine gestational sac with yolk sac and/or embryo (+/− cardiac activity)

Barnhart et al. (2011)

Finally, the presence of an IUP does not definitively exclude the existence of a concomitant ectopic pregnancy. A heterotopic pregnancy is defined as the presence of intrauterine and extrauterine pregnancies simultaneously (ACOG 2008). While heterotopic pregnancies are rare, making up less than 1% of all pregnancies, the incidence is increasing with increased use of ART (ACOG 2008). Therefore, clinical suspicion should be maintained when the patient's presentation or symptoms are suggestive of ectopic pregnancy even in the presence of a documented IUP.

5.2 Serial Beta HCG

When the initial beta HCG level is below the discriminatory zone, serial HCG measurements are required to differentiate a potentially viable pregnancy versus a nonviable pregnancy (ASRM 2013). The minimum HCG rise of a potentially viable pregnancy is 53% every 2 days (ASRM 2013). This minimum rate of rise is lower than previously suggested and is based on the 99%

confidence interval around the mean of the curve for HCG rise (ASRM 2013). Use of this more conservative value further prevents possible termination of a viable pregnancy, as discussed above.

As long as the minimum rise is achieved, serial HCG monitoring can continue until the discriminatory zone is reached, at which time ultrasound should be performed to confirm pregnancy location. A declining or abnormally rising HCG level indicates an abnormal pregnancy. After a spontaneous abortion, HCG levels are expected to decline at least 21–35% every 2 days, although an appropriately declining HCG does not exclude the possibility of ectopic pregnancy or rupture (ASRM 2013).

5.3 Uterine Curettage

The absence of a gestational sac above the ultrasound discriminatory zone, in association with an abnormally rising or declining HCG level, confirms the diagnosis of abnormal pregnancy of unknown location (PUL) (ASRM 2013). In this situation, it is important to distinguish between ectopic pregnancy and abnormal IUP for the purpose of selecting the appropriate treatment course.

Uterine curettage can be used to make this important distinction. The presence of chorionic villi on tissue pathology following uterine curettage simultaneously makes the diagnosis of abnormal intrauterine pregnancy while providing definitive surgical treatment (ACOG 2008). On the other hand, absence of chorionic villi on tissue pathology with a persistent abnormally rising HCG following uterine curettage establishes the diagnosis of ectopic pregnancy (ASRM 2013). Due to the need to await results of tissue pathology, which often takes several days, this course of action is only appropriate for hemodynamically stable patients able to be monitored in an outpatient setting. Endometrial biopsy is insufficient for diagnosis of pregnancy location in the setting of PUL and should not be considered an appropriate alternative for uterine curettage (ASRM 2013).

6 Treatment

6.1 Expectant Management

Women wishing to forgo medical or surgical therapy in favor of expectant management should be appropriately counseled regarding the risks of tubal rupture and hemorrhage, including warning signs requiring further evaluation. Appropriate candidates for expectant management include women who are asymptomatic, have early tubal gestations, and have objective evidence of pregnancy resolution as indicated by low baseline and decreasing HCG levels (ACOG 2008). The likelihood of success of expectant management has been shown to correlate with beta HCG level, with success rates of 98%, 73%, and 25% associated with beta HCG levels of <200, <500, and $>2{,}000$ mUI/mL, respectively (Yao and Tulandi 1997). The US Centers for Disease Control and Prevention (CDC) does not track data regarding rates of treatment with expectant management; therefore, population-based data on its use and efficacy are lacking (CDC 1995). Given the risk associated with method failure, expectant management should not be the preferred method except in asymptomatic patients with a low and already falling beta HCG level.

6.2 Medical Management with Methotrexate

With improved diagnostic modalities leading to earlier diagnosis of ectopic pregnancies prior to tubal rupture, the standard of care for treatment has moved away from surgical interventions toward increased use of conservative medical management. Methotrexate has become widely accepted as the primary treatment for ectopic pregnancy (ASRM 2013). Although methotrexate is not FDA approved for this use, its use is supported by multiple professional organizations including the American College of Obstetricians and Gynecologists (ACOG) and the American Society for Reproductive Medicine (ASRM).

Methotrexate is well studied in pregnancy as the result of its use in the treatment of gestational trophoblastic neoplasia (GTN) since 1956 (ACOG 2008). It was first used to treat ectopic pregnancies in 1982 (ACOG 2008). Long-term data has shown no association with congenital anomalies in future pregnancies (ACOG 2008). In addition, there is currently no evidence to suggest any adverse effect of methotrexate therapy on subsequent fertility or ovarian reserve (ASRM 2013).

Medical management is more cost-effective than surgical management and achieves similar outcomes (Barnhart et al. 2007). Randomized trials comparing the use of methotrexate to fallopian tube-sparing laparoscopic surgery show no difference in overall tubal preservation, tubal patency, repeat ectopic pregnancy, or future fertility (ACOG 2008). Methotrexate, therefore, has the additional benefit of avoiding surgery and its associated complications without compromising efficacy or successive reproductive outcomes. Many advocate evacuation of the endometrium prior to initiating methotrexate therapy since its use may allow a small chance of leaving a damaged but not destroyed intrauterine pregnancy.

6.2.1 Mechanism of Action

Methotrexate is an antimetabolite that works by interrupting DNA synthesis and repair, as well as cell replication (ACOG 2008). Folic acid is normally reduced to tetrahydrofolate by the enzyme dihydrofolate reductase (ASRM 2013). Methotrexate is a folic acid antagonist that acts by binding to the catalytic side of dihydrofolate reductase, interrupting the synthesis of purine nucleotides and the amino acids serine and methionine (ACOG 2008). It affects rapidly proliferating tissues including bone marrow, buccal and intestinal mucosa, respiratory epithelium, malignant cells, and trophoblastic tissue (ACOG 2008). Therefore, the associated side effects are also at the level of rapidly dividing cells and tissues.

6.2.2 Adverse Effects

The most common side effects reported are GI symptoms including nausea, vomiting, and stomatitis (ACOG 2008). Alopecia is associated with higher doses of methotrexate but is uncommon at the treatment doses used in the setting of ectopic pregnancy (ACOG 2008). Methotrexate is known to be directly toxic to hepatocytes and is cleared by the renal system; therefore, women being treated with methotrexate should be advised to abstain from both alcohol and NSAIDs during treatment. Women should also be counseled to avoid prolonged sunlight exposure due to increased skin sensitivity and to refrain from sexual intercourse and vigorous exercise during treatment due to risk of tubal rupture. In addition, women should be instructed to discontinue prenatal vitamins and folic acid supplementation prior to and during methotrexate administration, as these can reduce the effectiveness of treatment (ASRM 2013).

Whenever possible, definitive diagnosis of an ectopic pregnancy should be made prior to initiating medical therapy. In addition to medication side effects, potential consequences of medical management of a presumed ectopic pregnancy include (1) subsequent pregnancies being viewed as high risk for recurrent ectopic pregnancy resulting in repeated, costly, and anxiety-provoking diagnostic evaluation; (2) apparent efficacy of methotrexate to treat ectopic pregnancy will be artificially increased; and (3) risk of exposing an IUP to a known teratogen and abortifacient potentially resulting in embryopathy (ASRM 2013).

6.2.3 Candidates for Medical Therapy

The identification of appropriate candidates for outpatient medical management is imperative to treatment success and risk reduction. Candidates for medical management should demonstrate (1) hemodynamic stability, (2) absence of severe or persistent abdominal pain, (3) commitment to outpatient follow-up until resolution is achieved, (4) normal baseline liver and renal function tests, and (5) an unruptured mass (ASRM 2013; ACOG 2008). Absolute and relative contraindications to medical management are listed in Table 2.

6.2.4 Laboratory Evaluation

Before deciding to proceed with methotrexate therapy, women should undergo appropriate testing including CBC (demonstrating no evidence of

Table 2 Contraindications to methotrexate therapy

Absolute contraindications	Relative contraindications
Blood dyscrasias including leukopenia, thrombocytopenia, or significant anemia	Gestational sac >3.5 cm
Breastfeeding	Embryonic cardiac activity detected by TVUS
Chronic liver disease including alcoholism and alcoholic liver disease	Initial HCG concentration >5,000 mUI/mL
Hemodynamic instability	Refusal to accept blood transfusion
Immunodeficiency	Inability to participate in outpatient follow-up
Intrauterine pregnancy	
Peptic ulcer disease	
Pulmonary disease	
Renal dysfunction	
Rupture ectopic pregnancy	
Sensitivity to methotrexate	

ACOG (2008), ASRM (2013)

bone marrow dysfunction indicated by significant anemia, leukopenia, or thrombocytopenia), LFTs, creatinine, and blood type with Rh status (ASRM 2013; ACOG 2008). Women who are Rh negative necessitate treatment with RHOGAM in the presence of any vaginal bleeding. These blood tests are typically repeated 1 week after treatment to evaluate for any adverse effects of medical therapy on renal, hepatic, or hematologic function (ACOG 2008). Elevation of transaminase levels are most commonly seen with multidose regimens and usually resolve within 1–2 weeks of completion or discontinuation of therapy (ACOG 2008). Women with a history of pulmonary disease should have a chest x-ray prior to treatment due to the risk of interstitial pneumonitis in the setting of underlying lung disease (ASRM 2013). Because of this rare but serious risk, all women should report any fever or respiratory symptoms that develop following treatment (ACOG 2008).

6.2.5 Multidose Regimen

Three separate methotrexate administration regimens have been described in the literature and include fixed multidose, singe-dose, and two-dose options. The fixed multidose regimen has been used for treatment of ectopic pregnancy the longest (Barnhart et al. 2007). This treatment regimen alternates methotrexate 1 mg/kg on treatment days 1, 3, 5, and 7 with leucovorin (folinic acid) 0.1 mg/kg on treatment days 2, 4, 6, and 8 (ACOG 2008). The use of a folinic acid "rescue" on alternating days serves to reverse the effects of methotrexate thereby reducing the side effects associated with large doses (Barnhart et al. 2007). This alternating regimen is continued until the beta HCG level falls by at least 15% from the peak concentration, and as many as 50% of women will not require the full 8 days of treatment (ASRM 2013). Once an initial 15% decline in HCG is obtained, HCG monitoring should be continued weekly until a negative result is achieved. Complete HCG resolution usually takes 2–3 weeks but may take up to 6–8 weeks (ASRM 2013) (Fig. 2).

6.2.6 Single-Dose Regimen

The single-dose regimen is the simplest treatment course available. It was developed in response to pitfalls of the multidose regimen, in order to reduce side effects, increase convenience of administration, and eliminate the need for folinic acid rescue (Barnhart et al. 2007). This regimen consists of administration of methotrexate 50 mg/m^2 on treatment day 1 followed by monitoring of HCG levels on treatment days 4 and 7. If a minimum 15% decrease in HCG is observed between treatment days 4 and 7, no further treatment with methotrexate is required, and HCG levels should be monitored weekly until negative. If a 15% decrease in HCG is not observed, a second dose of MTX 50 mg/m^2 should be administered on treatment day 7 with HCG monitoring repeated on days 4 and 7 after the second dose (ACOG 2008). Up to 20% of women undergoing treatment with this regimen will require a second dose of methotrexate (Barnhart et al. 2007). This can be repeated as necessary; however, failure to obtain a 15% decrease in HCG after two doses should prompt consideration of surgical management (ACOG 2008). An initial rise in HCG may be observed on treatment day 4 in relation to the

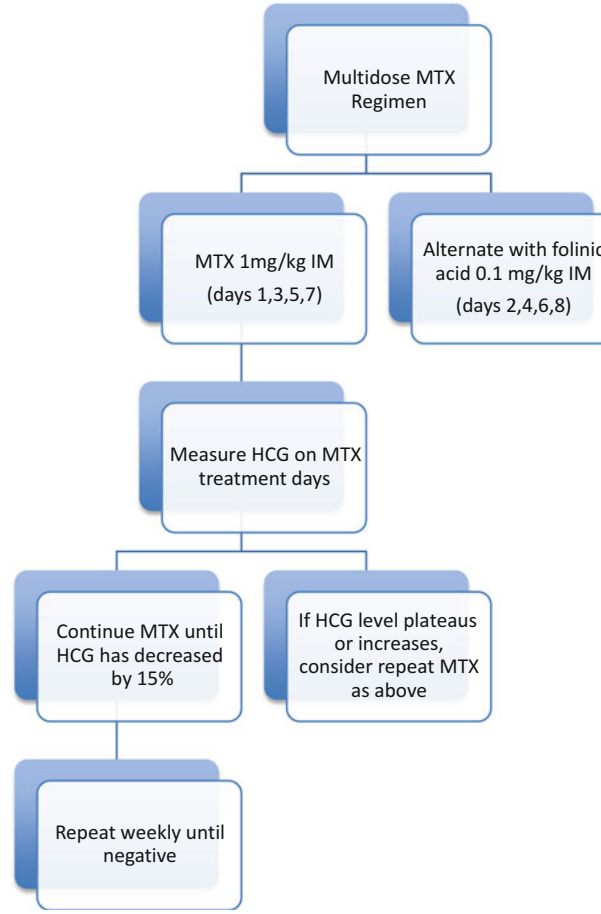

Fig. 2 Multidose methotrexate regimen

pretreatment baseline HCG and should not be a cause for concern (ACOG 2008). If, during the course of follow-up, HCG levels plateau or increase, repeat administration of methotrexate may be warranted (ACOG 2008) (Fig. 3).

Review of several observational studies show a failure rate of 14.3% or higher with the single-dose regimen when pretreatment HCG levels exceed 5,000 mIU/mL, compared to a failure rate of only 3.7% when the starting HCG level is below 5,000 mIU/mL (ACOG 2008). Other studies have suggested an increased failure rate of the single-dose regimen at even lower HCG levels, above 1,300 mIU/mL (Rabischong et al. 2011). Therefore, patients with higher initial HCG levels should be appropriately counseled regarding the potential need for more than one dose of methotrexate and possible treatment failure.

6.2.7 Two-Dose Regimen

The two-dose regimen was developed to serve as a compromise between the previous regimens detailed above. The goal of this regimen is to maximize the number of doses administered without the need for folinic acid rescue while minimizing the number of medical visits required and optimizing patient convenience and treatment efficacy (Barnhart et al. 2007). This regimen consists of the administration of methotrexate 50 mg/m^2, on each of treatment days 0 and 4, for a total of two doses. An HCG level is then obtained on treatment day 7. If a decline in HCG of at least 15% compared to the pretreatment value is achieved, no further methotrexate administration is required, and HCG levels are monitored weekly until negative. If the decline in HCG on treatment day 7 is less than 15% of the pretreatment level, a

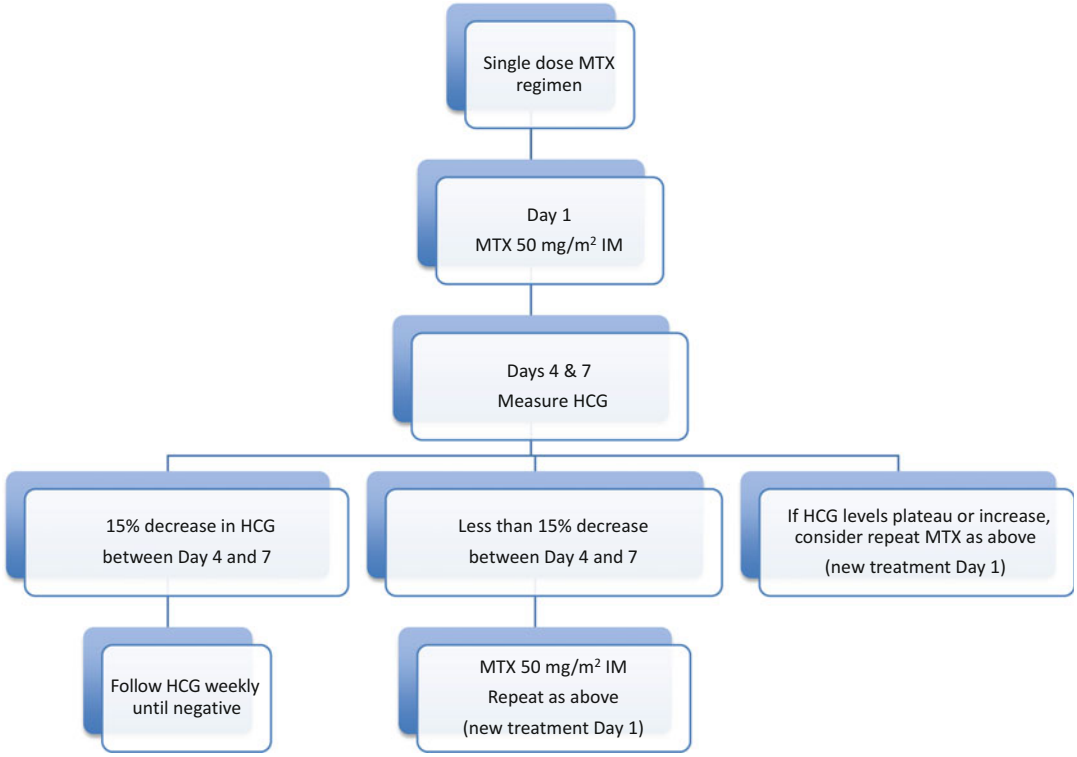

Fig. 3 Single dose methotrexate regimen

third dose of methotrexate is administered on treatment day 7 and the HCG level reevaluated on treatment day 11. If a 15% decline in HCG is still not achieved, a fourth dose is administered on treatment day 11 and the HCG level repeated on treatment day 14. Failure to obtain at least a 15% decline in HCG by treatment day 14 warrants discontinuation of medical therapy and consideration of surgical management (Fig. 4).

Laboratory evaluation including CBC, LFTs, and creatinine should be performed on treatment day 7, at the time of administration of the third and fourth doses of methotrexate if required, and 2 weeks posttreatment (Barnhart et al. 2007). Methotrexate administration should be discontinued if at any point in the treatment process the patient is found to have LFTs greater than 50% above the upper limit of normal, white blood cell count $<3 \times 10^9$/L, or platelet count $<100{,}000$.

When choosing which of the above treatment regimens to use, treatment efficacy should be weighed against potential morbidity of repeat methotrexate dosing. A meta-analysis comparing the efficacy of the multidose versus single-dose regimens demonstrated that the single-dose regimen was less effective (88.1%) than the multidose regimen (92.7%) (ACOG 2008). The failure rate for the single-dose regimen remained statistically significantly higher even after controlling for initial HCG level and the presence of embryonic cardiac activity (Barnhart et al. 2007). However, subsequent papers have shown no difference in failure rates between these two treatment regimens (Rabischong et al. 2011). Furthermore, a prospective study evaluating the efficacy of the two-dose regimen demonstrated high patient satisfaction and few side effects (Barnhart et al. 2007). This study demonstrated an overall success rate of 87.1% with 72% of patients requiring a single two-dose course and only 5% requiring a total of four doses. Therefore, the risk of treatment failure should be balanced with the ease of medication administration and improved medication adherence with fewer doses when choosing a treatment regimen.

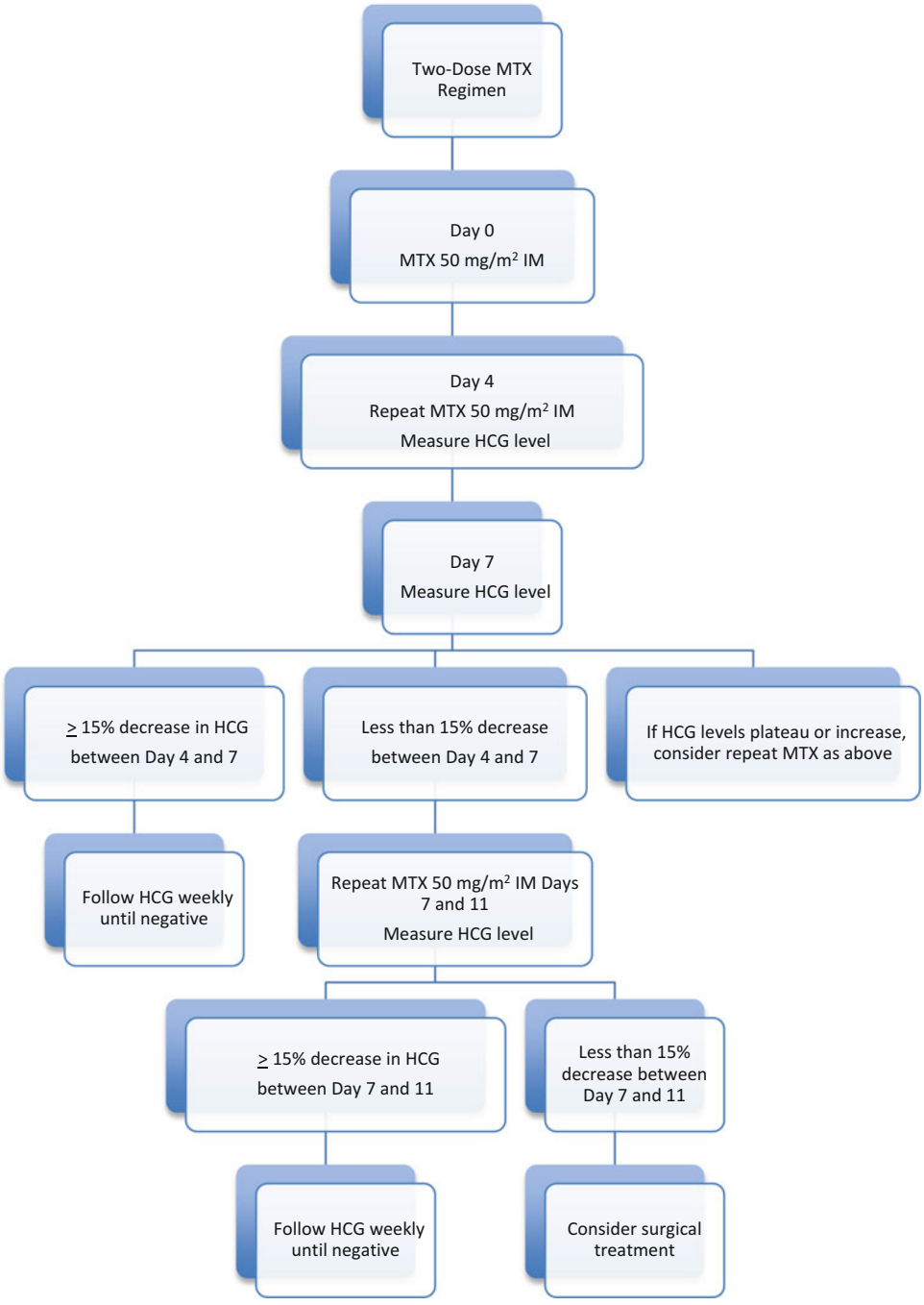

Fig. 4 Two-dose methotrexate regimen

6.2.8 Posttreatment Monitoring

With any of the above treatment regimens, once the initial HCG decline of 15% is achieved, serial HCG levels should be monitored weekly until negative. If at any time in the monitoring process the HCG level is found to increase or plateau, the diagnosis of persistent ectopic pregnancy should be made (ACOG 2008). Tubal rupture can still occur despite declining HCG levels; therefore, clinical suspicion should remain high until a

negative HCG level is obtained. Signs of treatment failure or suspected rupture that are indications to proceed with surgical management (ASRM 2013) include hemodynamic instability, increasing pain regardless of HCG level, and rapidly increasing HCG level >53% in 2 days after four doses of the multidose or two doses of the single-dose regimen (ASRM 2013). Serial ultrasound exams are not necessary nor are they recommended during posttreatment monitoring. Ultrasound findings cannot predict or prove treatment failure unless evidence of tubal rupture is noted (ASRM 2013).

Some patients will develop transient pain following administration of methotrexate regardless of the treatment regimen used. This pain, often referred to as "separation pain," generally occurs 2–7 days following methotrexate administration (ASRM 2013; ACOG 2008). The pain is likely caused by the cytotoxic effect of the medication on trophoblastic tissue causing tubal abortion and generally resolves within 4–12 h after its onset (ACOG 2008; ASRM 2013). In the absence of other signs and symptoms of overt tubal rupture, such as hemodynamic instability or significant hemoperitoneum on ultrasound, this pain can be managed expectantly and does not necessarily indicate a surgical emergency. For pain that is severe and/or persistent, evaluation of serial vital signs and hematocrit levels is warranted. Exploratory surgery should be undertaken if at any time tubal rupture is suspected or the patient becomes hemodynamically unstable.

6.3 Surgical Management

Due to rapid advances in minimally invasive surgical technologies, laparoscopic surgery is currently the gold standard for surgical management of ectopic pregnancy over open laparotomy (Rabischong 2010). The two existing techniques of tubal surgery for removal of ectopic pregnancies are tubal-sparing salpingostomy or complete salpingectomy. The decision of which technique to employ depends both on surgeon preference and patient characteristics.

6.3.1 Salpingectomy

Salpingectomy is the complete surgical removal of the affected fallopian tube. This technique allows for nearly certain removal of the abnormal pregnancy in its entirety. It also removes the damaged fallopian tube, excluding the possibility of a repeat ectopic pregnancy in that same fallopian tube in the future. If the woman retains a normally functioning fallopian tube on the contralateral side, she remains capable of achieving spontaneous pregnancy in the future. It is important to note that a normal appearance of the unaffected fallopian tube at the time of surgery does not guarantee normal function. Therefore, even with a history of treatment with salpingectomy, women with a previous ectopic pregnancy should still be treated as high risk for recurrent ectopic pregnancy in the contralateral tube in future pregnancies.

6.3.2 Salpingostomy

Salpingostomy consists of making a single 10–15 mm incision along the antimesenteric portion of the fallopian tube at the point of maximal bulge from the ectopic pregnancy. The pregnancy tissue is then removed using a combination of aspiration, irrigation, and traction. The tubal incision is subsequently left open to heal by secondary intention in lieu of suturing. This technique may be more cost-effective and result in improved future fertility rates compared to salpingectomy (Rabischong et al. 2010). The primary risk associated with salpingostomy is the incomplete removal of all trophoblastic tissue. It has been estimated that 5–20% of women will experience a persistent ectopic pregnancy following laparoscopic salpingostomy (ACOG 2008). A population-based study looking at 3,196 ectopic pregnancies diagnosed from 1992 to 2008 found that 6.6% of women undergoing laparoscopic salpingostomy required subsequent treatment for persistent ectopic pregnancy; however, that rate increased to 8.6% when the preoperative HCG level was greater than 1,960 IU/L (Rabischong et al. 2010). A prospective study following 289 patients 9 years after treatment of ectopic pregnancy found that, of those that underwent laparoscopic salpingostomy, 18.9% experienced

a repeat ectopic pregnancy in a subsequent pregnancy with 42.9% occurring on the side of previous salpingostomy (Banz et al. 2010).

6.4 Adjunctive Use of Methotrexate

The presence of persistent ectopic pregnancy following surgical treatment with laparoscopic salpingostomy can be treated with a single-dose of adjunctive methotrexate (ASRM 2013). One randomized trial of 129 women demonstrated that empiric administration of a single-dose of methotrexate immediately following laparoscopic salpingectomy essentially eliminated the risk of subsequent persistent ectopic pregnancy (Graczykowski and Mishell 1997). However, due to the relatively low incidence of persistent ectopic pregnancy following salpingostomy, many women would need to be treated to prevent one persistent ectopic pregnancy. Therefore, use of HCG monitoring postoperatively in order to identify those who would benefit most from subsequent methotrexate administration is the preferred strategy (ACOG 2008).

7 Conclusions

Ectopic pregnancy remains a significant cause of maternal morbidity and mortality in the first trimester. Therefore, all reproductive age women presenting for vaginal bleeding with or without abdominal pain should be tested for pregnancy, and ectopic pregnancy should be included in the differential diagnosis. Advances in serum beta HCG assays and high-resolution transvaginal ultrasonography allow for earlier diagnosis of ectopic pregnancy, leading to improvements in management options. When initial ultrasound fails to provide a definitive diagnosis regarding pregnancy location, serial beta HCG levels may be followed until the ultrasound discriminatory zone is reached. Uterine curettage may also be utilized to provide a definitive diagnosis in cases of abnormal pregnancy of unknown location. Whereas surgery has historically been the primary treatment for ectopic pregnancy, earlier detection prior to tubal rupture now allows for more conservative medical management with methotrexate in the outpatient setting as the first-line therapy when appropriate. Although multiple treatment regimens exist, close follow-up is warranted to ensure adequate treatment regardless of which regimen is utilized. For those patients in whom medical management fails or is contraindicated, laparoscopic surgery with either salpingostomy or salpingectomy is recommended for definitive treatment.

8 Cross-References

- ▶ Abnormal Vaginal Bleeding During the Early Reproductive Years
- ▶ Anatomy of the Female Genital System
- ▶ Contraception and Family Planning
- ▶ Diagnosis and Management of Gestational Trophoblastic Disease
- ▶ Diagnosis and Management of Pregnancy Loss
- ▶ Management of Acute Pelvic Pain: Torsion, Infection, and Rupture of Tubal or Ovarian Mass
- ▶ Pelvic Inflammatory Disease and Other Upper Genital Infections

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