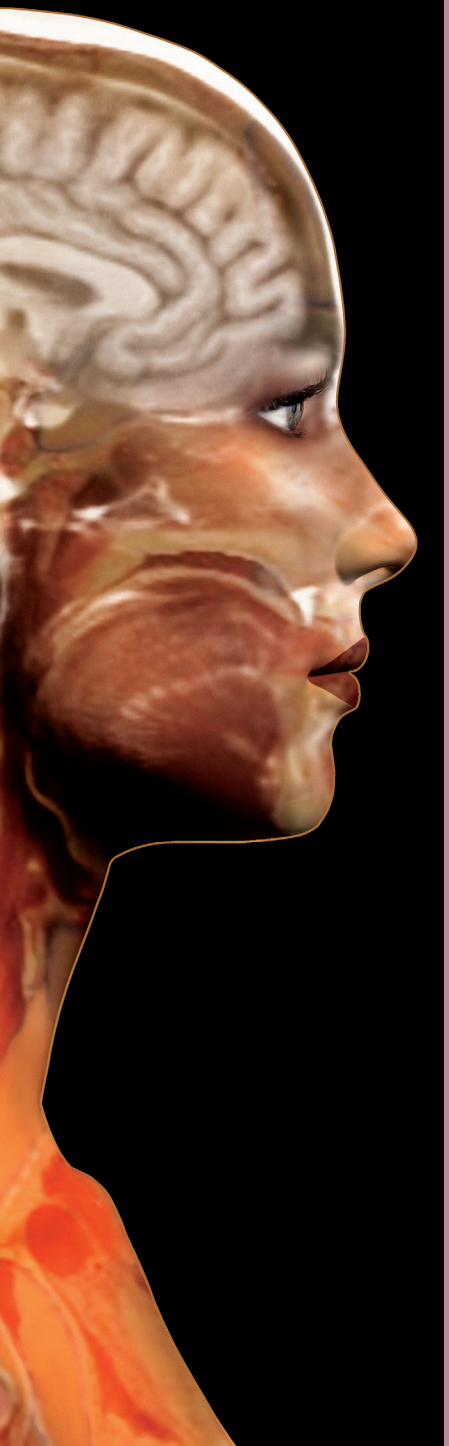
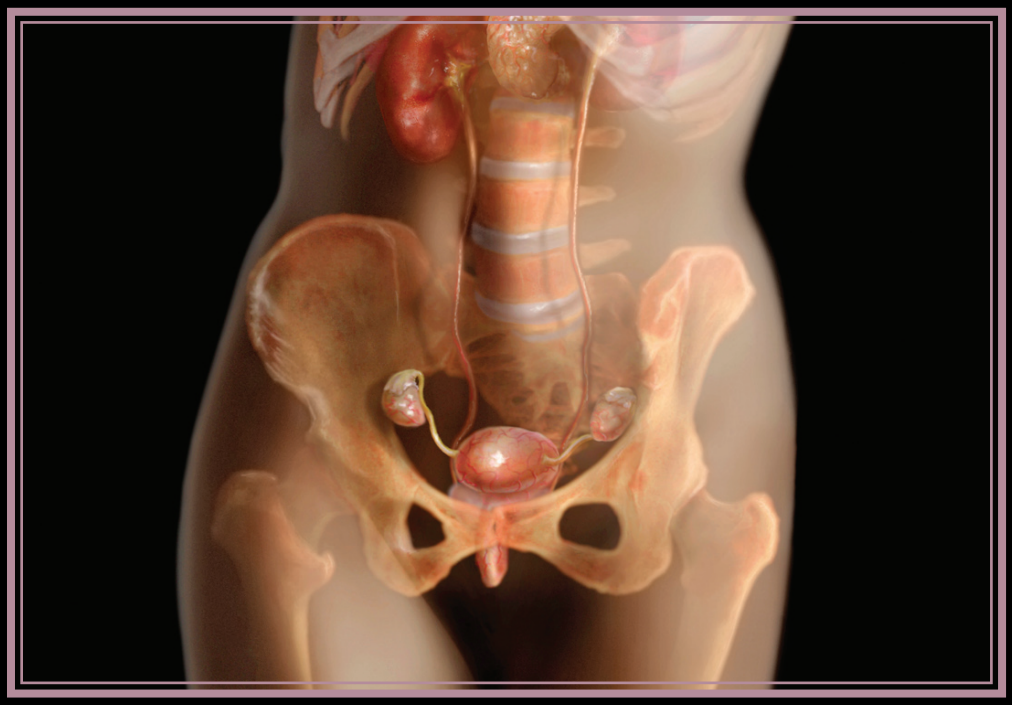
Non-Invasive Management of Gynecologic Disorders





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This book is dedicated to
My wife Meltem and my sons Devin and Deniz
My mentors Aydin Arici, and Joan A. Steitz
And to the loving memory of my father Kemal Seli (1917–2007) whose courage, creativity, and integrity guides me…

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Introduction

Many of us entered the discipline of obstetrics and gynecology because we believed that it uniquely lent itself to a mix of medicine and surgery. This is certainly the most common attraction to the field cited by residency applicants to our institution. But how accurate is that assessment? It certainly applies to obstetrics and maternal fetal medicine where treatment of maternal medical conditions and obstetrical surgical treatments are seamlessly integrated on a daily basis. Moreover, in obstetrics there are many alternative medical and surgical treatments for dysfunctional labor, uterine atony, pregnancy termination, and certain fetal anomalies. But can medical and surgical treatments be viewed pari passu in gynecology? Increasingly the answer is yes. This unique textbook provides ample examples of alternative medical and surgical approaches to a host of common gynecologic conditions including ectopic pregnancy, abnormal uterine bleeding, endometriosis, myomas, and urinary incontinence. Particularly timely are its chapters on uterine artery embolization and fertility preservation in patients with early and reproductive tract malignancies and in women wishing to both delay and preserve fertility for social reasons.

The editors are truly gifted clinicians and scientists. Dr Aydin Arici has authored over 150 peer review publications, has garnered multiple National Institutes of Health (NIH) and sponsored grants, and is internationally recognized as an outstanding reproductive endocrinology and infertility (REI) specialist. He led the REI section at Yale for many years and established it as one of the top divisions in the United States. Having sent scores of patients to him over the years, I can personally attest to his clinical prowess. Dr Emre Seli is a brilliant young reproductive scientist who is conducting landmark research into oocyte biology and maternal age-associated infertility, as well as developing novel technologies for non-invasive assessment of embryo quality. He served his residency and REI fellowship at Yale and subsequently joined the faculty while conducting an NIH sponsored research program. Emre is also a truly gifted clinician. Drs Arici and Seli have assembled an 'All Star' cast of authors, each expert in the topics about which they write. The result is a concise, readable, and highly practicable resource. The goal of the text is to describe available medical treatments for common gynecologic conditions and compare them to surgical options using an 'evidenced-based' approach. This novel and exciting strategy produces a 'must read' for those interested in adding to their therapeutic armamentarium conservative treatments for many gynecologic conditions.

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1 Non-invasive management of ectopic pregnancy

Stephan Krotz and John E Buster

INCIDENCE

Over the past 60 years in the United States, the incidence of ectopic pregnancy has increased more than fivefold and now accounts for approximately 2% of all pregnancies.[1,2] Much of this increased incidence can be attributed to the increase in risk factors for ectopic pregnancy such as sexually transmitted infections,[3] surgical sterilization,[4] and the use of fertility enhancing drugs. During the past 30 years maternal mortality has decreased 11-fold, and currently results in one death in every 3135 patients[5] with an ectopic pregnancy. Although maternal mortality rates are significantly decreased and represent improvements in management, ectopic pregnancy is associated with a mortality risk that is four times higher than that of all other causes combined of pregnancy-related deaths.[5] Additionally, ectopic pregnancy remains the leading cause of death in the first trimester.[6]

RISK FACTORS

Despite advances in the diagnosis of ectopic pregnancy and reduced mortality rates, many cases of ectopic pregnancy are either misdiagnosed or missed during initial evaluation. One study of emergency rooms found that 45% of patients eventually diagnosed with an ectopic pregnancy were initially sent home without a correct diagnosis.[7] The old triad of amenorrhea, abdominal pain, and irregular vaginal bleeding occurs in less than half of patients with an ectopic pregnancy and serves more as an indicator for further evaluation than as diagnostic criteria. Therefore, careful consideration of specific risk factors, which are present in about 55% of patients with ectopic pregnancies, may lead to higher clinical suspicion and earlier detection. In general, risk factors can be stratified into three categories for ectopic pregnancy: *highly increased*, *moderately increased*, and *slightly increased* risk (Table 1.1).

Highly increased risk includes etiologies that result in fallopian tube damage including tubal surgery, tubal sterilization, history of previous ectopic pregnancies, and history of surgery for ectopic pregnancies. The risk of recurrence of an ectopic pregnancy ranges 10–27%.[11] Although screening patients with a history of ectopic pregnancy would seem reasonable, the high false-positive rate of screening asymptomatic women leads to higher costs from unnecessary medical intervention.[12] Tubal pathology and infertility also significantly raise the odds of ectopic pregnancy, and may be secondary to impeded tubal motility or otherwise undocumented tubal obstruction leading to ectopic implantation.[8,9]

Moderately increased risk generally relates to tubal blockage via infectious etiologies. A history of pelvic inflammatory disease or gonorrhea or chlamydia infection, or a history of exposure to gonorrhea or chlamydia (as evidenced by circulating antibodies), moderately increases risk, presumably by causing intraluminal adhesions in the fallopian tubes which can prevent fertilized embryos from migrating to the uterus. Having more than one lifetime partner also has been shown to directly increase a patient's risk for ectopic pregnancy.[8] Surveys of US women show that with each additional sexual partner after the first, the risk of sexually transmitted bacterial infections increases, with nine times the risk for patients with more than five lifetime partners.[13] Cigarette smoking is an independent risk factor for ectopic pregnancy, and the risk correlates with the number of cigarettes. The odds ratio of ectopic pregnancy as it relates to smoking can range from 1.6 times the risk for five or fewer cigarettes per day to 3.5 times the risk for patients who smoke one pack or more per day.[14]

Slightly increased risk can be divided into behavioral factors and symptomatic factors. Certain methods of contraception such as birth control pills and the intrauterine device (IUD) are commonly believed to reduce the risk of ectopic pregnancy secondary to an overall reduction in pregnancy rates.[10] Once these methods fail, however, the risk for ectopic pregnancy is increased; in the case of birth control pills the mechanisms are unknown. Early age of intercourse also increases the risk, since younger women are often exposed to ascending infections.[14] Recently, several presenting symptoms and signs have been evaluated and their contribution to risk identified. These include

Table 1.1 Risk factors for ectopic pregnancy compared to all pregnant patients[8–10]

Risk	Odds ratio
Highly increased	
Previous tubal surgery[a]	21
Two prior ectopics[b]	16
Tubal sterilization[c]	9.3
Previous surgery for ectopic[a]	8.3
Tubal pathology[a]	3.5–25
One prior ectopic[b]	3.0
Infertility[a]	2.5–21
Moderately increased	
Chlamydia[a]	2.8–3.7
Gonorrhea[a]	2.9
Pelvic inflammatory disease[a,b]	1.5–2.5
Ever smoking[a]	2.5
Current smoking[a]	2.3
Lifetime sexual partners > 1[a]	2.1
Slightly increased	
Oral contraceptives[c]	1.8
hCG 501–2000 at presenation[b]	1.7
Primigravida[b]	1.6
Age at first intercourse < 18[a]	1.6
IUD in place[c]	1.6
Pain at presentation[b]	1.4
Moderate to severe vaginal bleeding[b]	1.4
Vaginal douching[a]	1.1–3.1

[a]From reference 8
[b]From reference 9
[c]From reference 10

β-human chorionic gonadotropin (hCG) levels between 500 and 2000 mIU/ml, first pregnancy, abdominal or pelvic pain, and moderate to severe bleeding.[9] While several of these may be subjective and consistent with intrauterine pregnancies or abortions, their additive presence may warrant closer patient monitoring.

Factors that have been cited but are not associated with an increased risk include previous non-tubal pelvic surgery, cesarean sections, and assisted reproductive technologies (ART). Previous association of ART procedures with ectopic pregnancy may be related to the initial cause of infertility such as tubal pathology. While zygote intrafallopian transfer (ZIFT) procedures are the only ART procedures associated with an increased risk (3.6%), in vitro fertilization (IVF) with embryo transfer has a significantly decreased risk of ectopic pregnancy (1.4%).[15] The decreased incidence of ectopic pregnancy associated with IVF and embryo transfer may be a result of bypassing the fallopian tubes, and would be consistent with the notion that tubal factor is solely responsible for a higher ectopic pregnancy rate in ART procedures. Other factors such as past IUD use and previous medical or spontaneous abortion remain disputed in the literature[8,9] as to whether they are protective or risk factors.

DIAGNOSIS

Presentation

Generally, any woman of reproductive age who presents with abdominal pain or vaginal bleeding should have a pregnancy test drawn upon initial evaluation, since 79–97% of patients with an ectopic pregnancy have these symptoms.[16] Once pregnancy has been confirmed with a urine or serum pregnancy test, the diagnosis of ectopic pregnancy relies on the combination of radiologic imaging, serum laboratory values, and, when needed, surgical diagnosis. The diagnosis of ectopic pregnancy should always be entertained until intrauterine pregnancy or miscarriage is confirmed. Heterotopic pregnancy is the only exception to this rule, since confirmation of intrauterine pregnancy does not result in proper evaluation or treatment planning for the ectopic portion of the pregnancy. The risk of heterotopic pregnancy is low, reported as 1 in 10 000 to 1 in 50 000 pregnant patients, except in patients who have a history of assisted reproduction for whom the risk has been reported as high, at 1 in 100.[17,18] If patients early in pregnancy present with tachycardia, hypotension, or rebound or cervical motion tenderness, immediate evaluation for ectopic pregnancy should occur, and surgical exploration for tubal or uterine rupture considered.

Confirming the location of an ectopic pregnancy is necessary to determine the course of management. Ninety-seven per cent of ectopic pregnancies are tubal, with 70–80% occurring in the ampullary segment, 12% in the isthmic segment, and 5–11% in the fimbria. The less common sites of ectopic implantation include interstitial or cornual (2%), abdominal (1.4%), ovarian (0.2–3.2%), and cervical (0.2%).[19,20] Rare implantation sites include previous cesarean scars or the abdomen.

Imaging

Pelvic ultrasound

Pelvic ultrasound should be the first diagnostic test performed after a thorough clinical evaluation (Figure 1.1). A diagnostic sequence beginning with a pelvic ultrasound scan misses the least number of ectopic pregnancies compared to various diagnostic sequences involving ultrasound, β-hCG level, and progesterone level.[21]

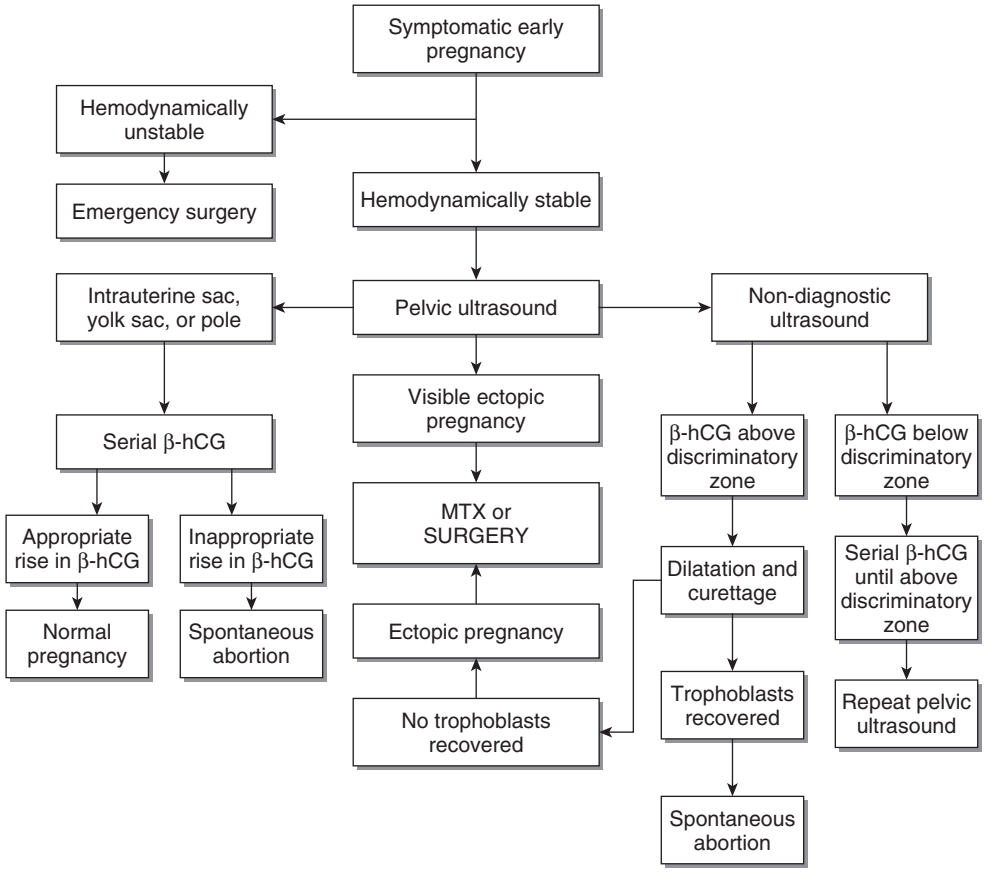

Figure 1.1 Diagnostic and management algorithm for ectopic pregnancies. MTX, methotrexate

Confirmation of an intrauterine pregnancy or miscarriage can occur as early as 4.5 weeks into the pregnancy by the identification of an intradecidual sign ('decidual reaction'), an echogenic rim in the endometrial cavity surrounding a fluid collection.[22] Since this finding can often be confused with a pseudosac in the uterus, which is a collection of blood from either an intrauterine or an ectopic pregnancy, it is advisable to rely on a double decidual sac sign ('double ring sign') or yolk sac, which occurs closer to 5 weeks of gestation.[23] The presence of a fetal pole with or without a heartbeat near 6 weeks confirms the presence of an intrauterine pregnancy.

Scanning the adnexa and pelvis for reliable signs of an ectopic pregnancy can be difficult, since the pathognomonic finding of an extrauterine fetal pole with a heartbeat is present only 8–26% of the time.[24] An extrauterine sac with a yolk sac is the next most reliable sign when imaging the adnexa, but care must be taken not to confuse this with a hemorrhagic cyst.[25] Use of Doppler ultrasound may locate a 'ring of fire' which characterizes the blood flow surrounding an ectopic pregnancy. This sign may be confused with luteal flow, which 90% of the time occurs on the same side as an ectopic pregnancy.[26] The finding of echogenic fluid in the pelvis in the presence of a positive β-hCG has 86–93% positive predictive value for ectopic pregnancy,[25] and may yield information about the urgency of intervention.

Often the pelvic ultrasound scan is non-diagnostic, and a serum β-hCG must be taken to determine whether the ultrasound was performed above, below, or within the discriminatory zone. The discriminatory zone includes β-hCG values between 1500 and 2000 mIU/ml, which was determined by comparing β-hCG levels to ultrasound findings in normal intrauterine pregnancies. Below 1500 mIU/ml, the sensitivity in making the diagnosis of an intrauterine pregnancy is 29%, compared to 92% with values above 1500 mIU/ml. At a β-hCG level of 2000 mIU/ml, which corresponds to a pregnancy at 5.5 weeks' gestation, the sensitivity approaches 100%.[27–29] Failure to diagnose an intrauterine pregnancy with pelvic ultrasound above 2000 mIU/ml indicates an abnormal or non-viable pregnancy. A surgical approach to diagnosis using dilatation and curettage or manual vacuum aspiration should be undertaken to differentiate a spontaneous intrauterine abortion from an ectopic pregnancy. Patients with a β-hCG level below 1500 mIU/ml should be followed with serial

β-hCG levels until it rises above the discriminatory zone, at which time the diagnosis can be confirmed.

The discriminatory zone is traditionally defined as a range of β-hCG values above which an intrauterine pregnancy will always be visualized. A range, instead of a threshold, allows for individual clinicians to determine their own threshold (β-hCG level) above which they expect to see an intrauterine pregnancy. The threshold chosen depends on a clinician's experience with the ultrasound equipment available, the sonographer's experience, and clinical preference. Choosing a threshold close to 1500 mIU/ml would have a high sensitivity and low specificity for an ectopic pregnancy, and risks defining a normal intrauterine pregnancy as abnormal. Choosing a threshold of 2000 mIU/ml or higher reduces the risk of classifying a normal intrauterine pregnancy as abnormal, but lowers the sensitivity for ectopic pregnancy and may delay its diagnosis.[21,30]

Magnetic resonance imaging

Pelvic ultrasound is considered first-line for diagnosis of ectopic pregnancy. When ultrasound is difficult or unclear, magnetic resonance imaging (MRI) can be useful, especially when imaging non-tubal ectopic pregnancies.[31–33] Failure to promptly diagnose an interstitial pregnancy[34] can lead to catastrophic uterine rupture and hemorrhage.

Serum tests

β-hCG

Serum β-hCG is the single most useful analyte used in the diagnosis of ectopic pregnancy. To use β-hCG values to differentiate normal from abnormal pregnancies, the expected rise and decline in both normal and abnormal pregnancies must be defined. Defining the expected rise and fall is especially useful for patients early in pregnancy requiring evaluation for vaginal bleeding or abdominal pain, since 75–80% presenting with these complaints have β-hCG values below the discriminatory zone.

In 1981, the minimum normal rise of serum β-hCG was first described as a 66% increase over 48 hours using the 85% confidence interval surrounding normal intrauterine pregnancies.[35] In 2006, the minimum normal rise for β-hCG was reduced to 35% in 48 hours with a 99.9% confidence interval surrounding normal intrauterine pregnancies.[36] This minimum rise is based on the management of over 1200 normal pregnancies with first trimester bleeding or pain. While this lower threshold may save many intrauterine pregnancies, it may also delay the diagnosis of ectopic pregnancy.

The minimum decline of β-hCG for a spontaneous abortion ranges from 21 to 35% at 2 days and 60 to 84% at 7 days for patients with a β-hCG value less than 10 000 mIU/ml.[37] The percentages of minimum decline were derived from the β-hCG levels of 700 patients experiencing spontaneous abortion. The higher is the initial β-hCG, the more rapid is the decline. A decline less than 21% at 2 days or 60% at 7 days suggests an ectopic pregnancy or retained trophoblasts. Seventy-one per cent of ectopic pregnancies exhibit an abnormal rise or fall. This indicates that 29% of ectopic pregnancies exhibit an expected rise or decline in β-hCG levels, which may lead to misdiagnosis of a normal intrauterine pregnancy or spontaneous abortion.[30] If an intrauterine or ectopic pregnancy cannot be identified by an abnormally rising or falling β-hCG above the discriminatory zone, dilatation and curettage or manual vacuum aspiration should be considered to determine whether there is a retained spontaneous abortion instead of an ectopic pregnancy.

Progesterone

Progesterone levels have frequently been incorporated into algorithms for ectopic pregnancy diagnosis.[38,39] More recently, their usefulness has been debated.[40] As progesterone levels rise, the probability of a normal intrauterine pregnancy increases while the probability of an ectopic pregnancy or spontaneous abortion[41] decreases. Unfortunately, only values at the ends of the spectrum yield definitive information. Thus, ectopic pregnancy incidence in patients with progesterone levels above 25 ng/ml is only 3%.[21] In contrast, the probability of a normal intrauterine pregnancy with progesterone below 5 ng/ml is only 0.16% or 1 in 625.[41] No normal intrauterine pregnancies have been documented below a progesterone level of 2.5 ng/ml. Also, low progesterone does not distinguish between ectopic pregnancies and spontaneous abortions,[41] and may only provide additional information in deciding to proceed with dilatation and curettage for an abnormal pregnancy. In one analysis of six approaches to evaluating patients, the use of progesterone prior to ultrasound or β-hCG levels was shown to increase the number of missed ectopic pregnancies,[21] and therefore may be detrimental when evaluating patients for an ectopic pregnancy.

Other serum tests

The use of other serum analytes in the diagnosis of ectopic pregnancy has been decreased. Glycoledin,

human placental lactogen, leukemia inhibiting factor, pregnancy-associated plasma protein A (PAPP-A), and pregnancy specific B1-glycoledin have been looked at independently and are not useful in distinguishing an ectopic pregnancy from an intrauterine pregnancy or spontaneous abortion.[42,43] Vascular endothelial growth factor (VEGF) alone is the only individual marker shown to be significantly elevated in an ectopic pregnancy (median 227.2 pg/ml) versus an intrauterine pregnancy (median 107.2 pg/ml). When using a receiver operating characteristic (ROC) curve to differentiate an ectopic pregnancy from a spontaneous abortion, the use of 174.5 pg/ml as a threshold for diagnosis of an ectopic pregnancy yielded a sensitivity of 78% and a specificity of 100%.[42] When PAPP-A and progesterone levels were combined with VEGF as a 'triple marker analysis' (VEGF/(PAPP-A × progesterone)), it showed a sensitivity of 97.7% and specificity of 92.2%. The discriminatory value of this test decreases below 7 weeks of gestation, a time when most patients with ectopic pregnancies present, as the false-positive rate for ectopic pregnancy increases.[43] When considering the low sensitivity of VEGF individually or in combination with other markers at 7 weeks' gestation or less, and difficulties in attaining prompt results, VEGF has not become a clinically useful marker.

Operative diagnosis

Dilatation and curettage should be performed on patients in whom serial serum β-hCG measurements suggest an abnormal pregnancy, but an ectopic pregnancy cannot be identified on ultrasound. Confirming the presence of chorionic villi with dilatation and curettage is necessary to prevent the administration of methotrexate to patients who may have an abnormal intrauterine pregnancy. Up to 38% of patients with a presumed diagnosis of ectopic pregnancy based on β-hCG values and an empty uterus on pelvic ultrasound may be experiencing a spontaneous abortion.[44] Dilatation and curettage is the definitive treatment for those 38% of patients with a spontaneous abortion, the only exception being a heterotopic pregnancy. Alternatives to dilatation and curettage such as endometrial biopsy have variable sensitivity (30–63%) and specificity (80–100%), making them unreliable for diagnostic purposes.[45,46] Measurement of β-hCG should be performed immediately after dilatation and curettage and repeated 12–24 hours later, since chorionic villi are not identified on pathologic specimens in up to 20% of spontaneous abortions.[47] Expected decreases in β-hCG after dilatation and curettage are consistent with the diagnosis of a spontaneous abortion, while a plateau or rise suggests an ectopic pregnancy. While dilatation and curettage for diagnostic purposes is performed in the United States, the risk of interrupting a normal intrauterine pregnancy is considered too high in many countries, and is not practiced.[48]

EXPECTANT MANAGEMENT

Expectant management is not commonly practiced. Success rates nonetheless have been reported to average 68% in the evaluation of 15 studies.[49] While this number is high, currently there is no standard by which to determine those patients who will successfully experience resolution with expectant management alone. In one report, patients with a serum β-hCG of < 1000 mIU/ml had spontaneous resolution 88% of the time, while patients with a serum β-hCG > 1000 mIU/ml resolved only 48% of the time.[50] In most centers, methotrexate administration or surgery is preferred (Figure 1.2).

MEDICAL TREATMENT

Methotrexate: indications

The use of methotrexate to treat ectopic pregnancy was first described in 1982,[52] and was followed by the first case series in the mid-1980s establishing methotrexate as a viable medical option.[53,54] Methotrexate is a folic acid antagonist[55] that was originally used to treat choriocarcinoma.[56] Methotrexate acts by inhibiting dihydrofolate reductase (DHFR), an enzyme which reduces folate to tetrahydrofolate, a necessary cofactor in the synthesis of DNA and RNA. Methotrexate therefore targets rapidly dividing cells, and is a logical choice in the treatment of ectopic pregnancy, especially since no increased reproductive side-effects have been documented.[57] Leucovorin (folinic acid) is a methotrexate antagonist that is given during the administration of methotrexate, especially with high doses, to reduce some of the prohibitive adverse effects.[55,56] Comparisons between multidose methotrexate and laparoscopic salpingostomy show methotrexate to be equally successful in treating ectopic pregnancies[58] and allow patients a non-surgical, outpatient management option.

Candidates for methotrexate are hemodynamically stable, possess no contraindications to methotrexate,

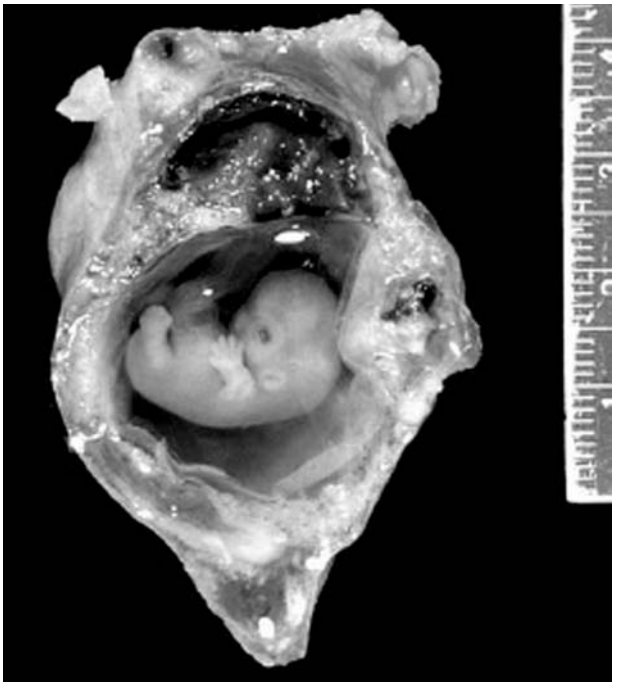

Figure 1.2 Advanced tubal ectopic pregnancy. Advanced ectopic pregnancies (formed limbs) should be treated with surgery. Reproduced with permission from reference 51

Table 1.2 Contraindications to methotrexate therapy. Adapted from reference 59

Absolute contraindications

- Intrauterine pregnancy
- Evidence of immunodeficiency
- Moderate to severe anemia, leukopenia, or thrombocytopenia
- Sensitivity to methotrexate
- Active pulmonary disease
- Active peptic ulcer disease
- Clinically important hepatic dysfunction
- Clinically important renal dysfunction
- Breastfeeding

Relative contraindications

- Embryonic cardiac activity detected by transvaginal ultrasonography
- High initial β-hCG concentration (> 5000 mIU/ml)
- Ectopic pregnancy greater than 4 cm on transvaginal ultrasonography
- Refusal to accept blood transfusion
- Inability to participate in follow-up

and are willing to comply with the required follow-up. Relative contraindications for methotrexate include a gestational sac size greater than 4 cm (Figure 1.2), presence of fetal cardiac activity, and β-hCG levels ranging greater than 5000 mIU/ml.[59] Successful treatment of ectopic pregnancy with any of these relative contraindications is possible, but the risk of rupture is elevated. Absolute contraindications to treatment include hemodynamic instability and any of the pre-existing conditions listed in Table 1.2. Therefore, patients should be evaluated for methotrexate contraindications and have the appropriate screening laboratory examinations including complete blood count, liver function tests, an electrolyte panel including creatinine, and blood type including Rh factor. Patients with a history of lung disease should have a chest X-ray prior to methotrexate to evaluate for risk of interstitial pneumonitis.[30]

Methotrexate dosing: multidose or single-dose

Original protocols for methotrexate use were multidose, based on the treatment for gestational trophoblastic disease,[53,54] and are still followed today. Patients using the multidose regimen are given doses alternating every other day starting with methotrexate and followed by leucovorin (Table 1.3). Methotrexate is administered, up to four doses, until the serum β-hCG decreases by a minimum of 15% over 48 hours.[61] Serum β-hCG levels are drawn on day 1 and days 4–8 of the protocol, and are followed weekly until the serum β-hCG levels are negative. Laboratory values (complete blood count (CBC), platelets, liver function tests (LFTs), and creatinine levels) are repeated on day 8 and compared to the original values to evaluate for any adverse effects resulting from methotrexate administration. Additional courses of the multidose regimen can be given if deemed necessary and appropriate.

The individualization of methotrexate protocols[61] during initial studies with the multidose regimen led to development of the single-dose regimen (Table 1.3). Single-dose regimens were developed to increase compliance and lessen side-effects associated with multidose regimens. In single-dose, methotrexate is administered on day 1 of the protocol and again on day 7 if the serum β-hCG has not decreased by at least 15% since day 4. Serum β-hCG levels are drawn on day 1, checked again on days 4 and 7, and followed weekly until they are negative. In 85% of patients undergoing the single-dose regimen the serum β-hCG will rise between days 1 and 4, so following serum β-hCG values during this period will not yield clinically useful information.[62] Laboratory values (CBC, platelets, LFTs, and creatinine levels) are repeated on day 7 and compared to the original values to evaluate for adverse effects from methotrexate administration.

Table 1.3 Single- and multidose methotrexate regimens. Adapted from reference 60

Single dose			Multidose		
	Studies	**Treatment**		**Studies**	**Treatment**
Day 1	β-hCG CBC Platelet count LFTs RFTs	MTX 50 mg/m^2 IM	Day 1	β-hCG CBC Platelet count LFTs RFTs	MTX 1 mg/kg IM
Day 4	β-hCG		Day 2		Folinic acid 0.1 mg/kg IM
Day 7	β-hCG CBC Platelet count LFTs RFTs		Day 3	β-hCG	MTX 1 mg/kg IM
Weekly	β-hCG until negative		Day 4		Folinic acid 0.1 mg/kg IM
			Day 5	β-hCG	MTX 1 mg/kg IM
			Day 6		Folinic acid 0.1 mg/kg IM
			Day 7	β-hCG	MTX 1 mg/kg IM
			Day 8	CBC Platelet count LFTs RFTs	Folinic acid 0.1 mg/kg IM
			Weekly	β-hCG until negative	

hCG, human chorionic gonadotropin; CBC, complete blood count; LFTs, liver function tests; RFTs, renal function tests; MTX, methotrexate; IM, intramuscular

The decision to use single- or multidose is debated. Multiple studies evaluating the overall efficacy of both regimens over the past 20 years have demonstrated a success rate of 75–96%.[63] A recent meta-analysis of 1327 patients showed the success rates of the single-dose regimen and multidose regimen to be 88.1% and 92.7%, respectively.[64] The odds ratio for failure for single-dose compared to the multidose regimen for all data was 1.71. When serum β-hCG and embryonic cardiac activity were controlled for, the odds for failure of the single-dose regimen were 4.74 compared to the multidose regimen. While this meta-analysis represents the largest compiled data comparing the two regimens, it cannot control for all patient characteristics or variation in treatment protocols. When comparing laparoscopic salpingostomy to both regimens, the multidose regimen is equally efficacious[58] to laparoscopic salpingostomy while the single-dose regimen is significantly less efficacious (relative risk (RR) 0.83).[65] More recent data from a retrospective study of 643 patients[66] and a small randomized controlled trial of 108 patients, however, suggest that the single-dose regimen is as effective as the multidose regimen. Future tubal patency using both protocols is comparable to conservative surgical management with laparascopic salpingostomy.[58,65]

The number of methotrexate injections administered for each protocol are also associated with different outcomes. Almost 14% of patients undergoing the single-dose protocol received a second dose of methotrexate, and these demonstrated fewer treatment failures (odds ratio 0.64) compared to their single-dose counterparts.[64] Likewise, slightly fewer than 50% of patients undergoing the multidose regimen received four doses. If more than four doses (6.7% of patients) of methotrexate were required during the multidose regimen, the odds of failure were 4.9 times higher for those patients compared to those who received only four doses. The optimal number of doses remains to be determined, and may lie between one and four doses.

Methotrexate: predictors for success

Determining which patients can be successfully treated with methotrexate traditionally focused on selecting patients with specific criteria such as ectopic size less than 4 cm, no embryonic cardiac activity, no signs of hemoperitoneum, and β-hCG values below a threshold of 5000 mIU/ml.[59] Many of these criteria are based on older and smaller studies; serum β-hCG is the only predictive factor that can be considered reliable across many studies. One large study indicated that hemoperitoneum and size do not correlate with methotrexate success.[67] Data concerning fetal cardiac activity are

conflicting, as some suggest it is a relative contraindication to methotrexate administration while others report success rates approaching 90%.[68] The percentage of ectopic pregnancies with fetal cardiac activity present usually coincides with the level of serum β-hCG.[67] Fetal cardiac activity is another measure of how advanced an ectopic pregnancy is, but is less useful than β-hCG since it cannot be measured on a continuum. Additionally, the presence of fetal cardiac activity also may be suggestive of a more advanced, cytogenetically normal ectopic pregnancy that would be more resistant to medical therapy with methotrexate.[69] In most of the larger studies in which serum β-hCG is identified as a reliable predictor of success, a specific β-hCG value is cited, above which the rate of treatment failure becomes unacceptable. This serum β-hCG level then becomes the chosen threshold above which ectopic pregnancies should be managed surgically, according to the study. In reality, the success of medical management compared to serum β-hCG is most likely a continuum[67] that varies with each physician, institution, patient population, and methotrexate treatment protocol. Increasing efficiency in diagnosis and earlier initiation of medical management may also skew these thresholds towards lower values, since many ectopic pregnancies that are bound to rupture will be detected earlier.[70]

Several additional factors that correspond with the clinical course of the ectopic pregnancy have been suggested as predictive of medical management failure. At presentation, patients with pelvic pain regardless of tenderness elicited on examination experience nine times the risk of methotrexate failure, while patients with vaginal bleeding experience six times the risk of methotrexate failure. The presence of a yolk sac on ultrasound is associated with a 71–88% methotrexate failure rate, with an odds ratio of 19.3 for failure.[71,72] A rise in β-hCG of 66% over 48 hours, prior to confirmation of the diagnosis of ectopic pregnancy, is associated with nine times the risk of tubal rupture.[70] A decline of less than 15% in the serum β-hCG levels between day 4 and day 7 after methotrexate therapy is associated with an odds ratio of 3.8 for medical failure. In summary, when evaluating patients for medical management, the initial β-hCG level should be taken into account with clinical progression and patient suitability for medical management.

Follow-up after methotrexate

After the administration of methotrexate, up to 60% of patients may experience increasing abdominal pain.[62] The pain experienced after methotrexate administration is believed to be secondary to tubal abortion or more commonly hematoma formation in the tube, both of which are a normal part of the resolution process. One study using ultrasound to monitor patient progress showed that 63% of patients who were successfully treated with methotrexate experienced an increase in fallopian tube size with increased vascular flow.[73] Abdominal pain after methotrexate administration is usually self-limited and can be treated with non-steroidal anti-inflammatory drugs (NSAIDs). Approximately 20% of patients treated with methotrexate will experience severe pain and 13% will require hospitalization[74] for pain management. Serial ultrasound monitoring of patient response to methotrexate or for predicting rupture is generally not useful, since hemoperitoneum is present in 30–100% of patients with ectopic pregnancies, regardless of methotrexate success or failure.[67,74]

In the first 1–4 days after methotrexate administration, β-hCG levels will rise in the majority of patients[59,62,75,76] and should peak at the 4th day of injection. A decrease in β-hCG levels of 15% or more from day 4 to day 7 represents an adequate response to methotrexate.[59,62] If there is less than a 15% decline, then a second injection can be given on day 7 or the patient can undergo surgical management. If the levels plateau or increase in 7 days an additional dose may be given. The average time to resolution after methotrexate administration, when β-hCG reaches undetectable levels, is reported as 20–35 days,[62,68,75,76] but can take as long as 109 days.[68] The average time to rupture requiring surgery is reported as 14 days, but can take as long as 32 days.[68] Consideration to surgical management should be given if β-hCG levels plateau or rise after several doses of methotrexate with the single-dose regimen or four doses of methotrexate with the multidose regimen. Patients who experience significant increases in abdominal pain, hemodynamic instability, or decreases in hematocrit should be managed surgically.

Side-effects of methotrexate

In addition to pain, methotrexate has many potential side-effects. Since low doses of methotrexate are used, most patients do not experience severe side-effects. Thirty-six per cent of patients who receive methotrexate, though, will experience some side-effects. Most are minor, self-limited problems such as gastrointestinal upset, mild stomatitis, or mild elevations in liver

transaminases.[66] While patients receiving the single-dose regimen of methotrexate may experience side-effects less frequently (odds risk 0.79), they experience abdominal pain and hospitalizations at roughly the same rates as in patients receiving the multidose regimen.

Since methotrexate is a folic acid antagonist, its greatest effect is on rapidly dividing cells.[55,59] Side-effects that are often cited but less commonly seen include nausea, vomiting, stomatitis, diarrhea, anorexia, hemorrhagic enteritis, and elevated liver enzymes. Methotrexate can also affect bone marrow, resulting in severe neutropenia, thrombocytopenia, granulocytopenia, and lymphopenia, although these side-effects are rare. Finally, methotrexate can cause nephrotoxicity, interstitial pneumonitis, and, rarely, reversible alopecia. Patients with pre-existing hepatic, renal, hematologic, pulmonary, or bone marrow disease, patients who are breastfeeding, and patients who suffer from alcoholism, therefore, should not be given methotrexate (Table 1.2).

SURGICAL MANAGEMENT

In the past, exploratory laparotomy with salpingectomy was the standard. With advances in surgical care and an emphasis on improving future reproductive outcomes and limiting costs, attention has shifted towards laparoscopy with salpingostomy when possible.[65] The decision to perform a salpingostomy versus salpingectomy depends on the patient's desire for future pregnancy and the degree to which the tube has been damaged. Patients who are hemodynamically unstable are preferably managed by laparotomy.

Initial studies done comparing laparoscopic salpingostomy to laparotomy for ectopic pregnancy individually showed no difference.[77–79] Postoperatively the patients managed by both methods demonstrated equivalent tubal patency and fertility rates.[77,80] However, these studies showed a significant decrease in blood loss, hospital stays, and convalescent periods postoperatively in patients undergoing laparoscopy. Additionally, patients who had undergone laparoscopy developed significantly fewer adhesions postoperatively.[80] A more recent meta-analysis[65] of these initial studies showed laparoscopy to be less effective than laparotomy (RR 0.90) due to a 3.6 times higher rate of persistent trophoblastic activity postoperatively. The persistence of trophoblastic tissue can be reduced by the administration of a single prophylactic dose of systemic methotrexate (1 mg/kg) postoperatively.[81,82] Prophylactic methotrexate significantly reduces the percentage of patients who will experience tubal rupture and require reoperation. Side-effects are minimal (5.5%).

Tubal patency and fertility rates in patients who were treated by laparoscopic salpingostomy versus open salpingostomy are equivalent.[77–80,83] Reproductive potential in patients who have a salpingostomy compared to salpingectomy is substantially better regardless of laparoscopy or laparotomy, but carries a higher risk of ectopic recurrence. The rate of intrauterine pregnancy after salpingostomy is 61% vs 38% for salpingectomy, while the risk for recurrent ectopic pregnancy is 15% for salpingostomy vs 10% for salpingectomy.[84]

Economics of management

The opportunity to manage patients medically in an outpatient setting made methotrexate an attractive therapeutic option. Initial studies, though, suggested that methotrexate was more cost-effective than laparoscopy only for lower β-hCG values (<3000 mIU/ml) and more costly for higher values.[85–88] More recent studies show that methotrexate is significantly less expensive than laparoscopic surgery, resulting in an average saving of $3011 in the United States[89] and €1297 in Europe[90] per patient. When methotrexate follow-up was factored into the European study, the overall cost saving was 45%.

NON-TUBAL ECTOPIC PREGNANCIES

Abdominal pregnancies

Abdominal ectopic pregnancies account for 1.4% of ectopic pregnancies.[19,20] Of all ectopic pregnancies, they present the greatest risk for mother and fetus, with maternal mortality ranging between 0.5 and 18% and perinatal mortality ranging between 40 and 95%.[91] Compared to all ectopic pregnancies, the risk of death is 7.7 times higher and 90 times higher than associated with an intrauterine pregnancy.[91] Abdominal pregnancies result from primary implantation in the abdomen, or from secondary implantation in the abdomen as a result of tubal abortion or rupture. Presenting symptoms according to one series include abdominal pain (100%), nausea and vomiting (70%), general malaise (40%), and painful fetal movements (40%).[92] The most common physical examination findings include abdominal tenderness (100%), abnormal fetal lie (70%), and a displaced uterine cervix (40%).[92] The gold standard in diagnosis of abdominal pregnancies is laparoscopy. They can be diagnosed by ultrasound, although a high

rate of error in diagnosis, up to 60%,[92] has led to increased usage of MRI for this purpose. Early abdominal pregnancies can be managed laparoscopically, while more advanced abdominal pregnancies should be managed with laparotomy. There is still much debate regarding placental management postoperatively. Recovery is most rapid if the placenta can be removed without causing injury to surrounding organs or structures. Other options include allowing placental reabsorption after the administration of methotrexate or preoperative embolization of the placenta and fetus[93] if the pregnancy is diagnosed early enough to warrant termination.

Cervical pregnancies

Cervical ectopic pregnancies are rare, and account for 0.2% of all ectopic pregnancies. After a cervical pregnancy is diagnosed, first-line treatment is systemic single- or multidose methotrexate with an overall success rate of 62%.[94] The success rate of primary methotrexate treatment can be as high as 92% if no fetal cardiac activity is present, or as low as 40% if fetal cardiac activity exists. Factors predisposing patients to an unsatisfactory result with primary methotrexate treatment alone include a gestational age ≥9 weeks, a serum β-hCG ≥10 000 mIU/ml, the presence of fetal cardiac activity, or a crown–rump length greater than 10 mm.[94] In patients in whom one of the above factors is present, localized treatment such as intra-amniotic injection of methotrexate, hyperosmolar glucose, or potassium chloride can reduce treatment failure with methotrexate.[94] Approximately 11% of patients treated with methotrexate may suffer from sudden massive bleeding,[4–28] days after methotrexate administration, secondary to failure of cervical involution after pregnancy termination or tissue necrosis from local methotrexate administration.[94] As a result, the need for surgical intervention including dilatation and curettage or hysterectomy after the administration of methotrexate can be as high as 43% in viable cervical pregnancies and 13% in non-viable cervical pregnancies.[95] Therefore, in patients who fail primary methotrexate treatment or a combination of primary systemic methotrexate and local medical treatment, prophylactic embolization of hypogastric arteries, vaginal ligation of cervical branches, or laparoscopy-assisted ligation of the uterine arteries may reduce the occurrence of massive bleeding.[96] If embolization or any other surgical intervention is the primary intervention, methotrexate should be given to eradicate any residual trophoblasts.[96]

Heterotopic pregnancies

The risk of heterotopic pregnancy is reported as 1 in 10 000 to 1 in 50 000, but can reach as high as 1 in 100 for patients undergoing in vitro fertilization.[18] Diagnosis is complicated by the coexistence of an intrauterine pregnancy, to which symptoms are often attributed;[97] β-hCG values are confounded by the intrauterine pregnancy. Pelvic ultrasound is the most sensitive diagnostic tool for indentifying heterotopic pregnancies.[98] Laparoscopy is the gold standard for heterotopic pregnancies;[99] otherwise, methotrexate can be a first-line agent. Treatment with ultrasound-guided transvaginal injection of KCl or hyperosmolar glucose has been described, but the risk of rupture in tubal heterotopic pregnancies and need for salpingectomy may be as high as 55%.[100] However, success rates in ultrasound-guided transvaginal injection of KCl or hyperosmolar glucose for unusual ectopic pregnancies such as cervical and cornual pregnancies have been described as high as 92%.[101] Injection of KCl or hyperosmolar glucose may be especially useful in interstitial (corneal) or cervical pregnancies when surgical management options could threaten to disrupt the intrauterine pregnancy.

Interstitial pregnancies

Interstitial (cornual) ectopic pregnancies represent 2% of all ectopic pregnancies[19,20] and exhibit a maternal mortality risk of 2–2.5%,[102] which is much higher than the 0.14% mortality rate for ectopic pregnancies overall. They result from implantation of the fertilized ovum in the proximal segment of the fallopian tube that is surrounded by the myometrium of the uterus. As a result of their location and the pliability of the myometrium, interstitial pregnancies can reach a greater gestational age and size before rupture compared to tubal ectopic pregnancies, and the related blood loss can be 2–2.5 times as much.[103] Risk factors are similar to those for any ectopic pregnancy, and include a history of ectopic pregnancy, salpingectomy, in vitro fertilization or ovulation induction, and sexually transmitted infections.[104] Pelvic ultrasound is the main diagnostic tool, and the following criteria on ultrasound can assist in making the diagnosis: an empty uterine cavity, a chorionic sac seen separately and located >1 cm from the most lateral edge of the uterine cavity, and a thin myometrial layer less than 5 mm surrounding the chorionic sac.[105] In 1993, Ackerman and the other radiologists described the 'interstitial line sign' (an echogenic line extending into

the cornual region and abutting the mid-portion of the interstitial mass), which is reported to be 80% sensitive and 98% specific in the diagnosis of interstitial pregnancy.[106] MRI can be used when the diagnosis is not clear from pelvic ultrasound. If neither modality provides a definite diagnosis, laparoscopy or hysteroscopy can be used. Medical management of interstitial pregnancies is possible, with local methotrexate injection exhibiting a higher success rate than systemic methotrexate (91% vs 79%).[107] Additionally, resolution of the β-hCG levels with local injection is three times faster (22 ± 8 days vs 65 ± 52 days).[107] Predicting who may be successfully treated with methotrexate prior to administration is difficult, since patients who are successfully treated and those who fail have similar β-hCG levels and ectopic gestational sac sizes.[107] Traditionally, cornual pregnancies were treated with laparotomy followed by cornual resection or hysterectomy. Now more conservative approaches such as laparoscopy and hysteroscopy have become the primary surgical approach in hemodynamically stable patients.[107] To date, no clear information exists as to the risk of uterine rupture in subsequent pregnancies after medical or surgical treatment of interstitial (cornual) pregnancies.[107]

Ovarian pregnancies

Ovarian pregnancies are uncommon, accounting for 0.2–3.2% of ectopic pregnancies.[19,20] In 1878, Spiegelberg established four pathologic criteria for the diagnosis of ovarian pregnancy: an intact ipsilateral tube separate from the ovary, a gestational sac occupying the position of the ovary, an ovary and gestational sac connected to the uterus by the utero-ovarian ligament, and histological presence of ovarian tissue in the gestational sac wall.[108] Risk factors for ovarian pregnancy include pelvic inflammatory disease, tubal surgery, and oophoritis. Most patients with ovarian pregnancies are younger and of higher parity than their counterparts with non-ovarian ectopic pregnancies, and the use of intrauterine devices is disproportionately high in patients who develop ovarian pregnancies.[109] Pelvic ultrasound is first-line in the diagnosis of ovarian pregnancy, although 75% of early ovarian pregnancies are misdiagnosed as a ruptured corpus luteum cyst.[110] More advanced ovarian pregnancies may present similarly to abdominal pregnancies. Primary treatment consists of laparoscopic ovarian wedge-resection or oophorectomy; an open approach may be used when surgically or clinically indicated. Successful treatment of ovarian pregnancies with systemic methotrexate has been reported in several cases[111] but is not yet widespread.

Cesarean scar pregnancies

Cesarean scar pregnancies, once considered the rarest form of ectopic pregnancy, are becoming increasingly common (1 in 2000 pregnancies).[112] Two out of three patients present with symptoms: most commonly painless vaginal bleeding, then painful vaginal bleeding, and least commonly abdominal pain alone. The sensitivity in diagnosis of cesarean scar pregnancy with pelvic ultrasound is 84.6%, with remaining cases incorrectly diagnosed as cervical pregnancies or spontaneous abortions. In 2000, Vial et al proposed the following ultrasound criteria for diagnosis of cesarean scar pregnancy: (1) the trophoblast is located between the bladder and the anterior uterine wall; (2) fetal parts are not present in the uterine cavity; and (3) on a sagittal uterine view that runs through the amniotic sac, no myometrium is seen between the gestational sac and the urinary bladder (lack of continuity of the anterior uterine wall).[113] Doppler ultrasound and MRI can be used adjunctively to clarify the diagnosis. Given that cesarean scar pregnancy is a relatively new entity in the literature, no standard of treatment has been defined. Expectant management is generally not recommended because of uterine rupture risk.[112] Systemic methotrexate has been successful in 50% of patients with cesarean scar pregnancy in whom it was attempted, and 100% successful in patients with an initial β-hCG less than 5000 mIU/ml.[112] Other medical options include local administration of methotrexate, KCl, or hyperosmolar glucose, and fine needle aspiration of the sac.[112] Laparotomy or laparoscopy with wedge resection, and hysteroscopic resection are all surgical approaches that have reasonable success rates.[112] Dilatation and curettage is often complicated by severe hemorrhage[112] and sequelae.

REPRODUCTION AFTER ECTOPIC PREGNANCY

In women with an unruptured ectopic pregnancy, future reproduction is a concern. Many papers have been published on the issue, but the data are contained only within small case series over the past 30 years; therefore, deriving any meaningful conclusion on the subject has been difficult. The effect of therapeutic

Table 1.4 Reproductive performance following four treatments for ectopic pregnancy: no difference in future reproductive outcome has been shown based on treatment regimen. Adapted from reference 49

Method	Number of Studies	Number of patients	Number with successful resolution	Tubal patency rate	Subsequent intrauterine pregnancy rate	Subsequent ectopic pregnancy rate
Laparoscopic salpingostomy	36	1750	1636 (93%)	170/233 (73%)	477/826 (58%)	105/866 (12%)
Variable-dose methotrexate	12	338	314 (93%)	136/182 (75%)	67/129 (52%)	10/129 (8%)
Single-dose methotrexate	7	393	340 (87%)	61/75 (81%)	39/64 (61%)	5/64 (8%)
Expectant management	15	717	488 (68%)	60/79 (75%)	388/681 (57%)	90/681 (13%)

approach, whether medical, surgical, or expectant, on future reproduction remains unknown. Patients undergoing emergency surgery for ruptured ectopic pregnancy cannot be included in these studies since their treatment options are limited by their clinical circumstance.

Comparison of the success rates of the four most common methods of treatment, laparoscopic salpingostomy (93%), multidose methotrexate (93%), single-dose methotrexate (87%), and expectant management (68%), demonstrates that resolution rates are all relatively equal except for expectant management in the studies containing information on reproductive performance (Table 1.4).[49] When comparing reproductive performance after ectopic pregnancy for the four management methods, all appear comparable. While selection criteria for medical and expectant management in these studies is comparable to those for laparoscopic salpingostomy (the gold standard), patients have never been randomized. Additionally, life-table analyses of pregnancy rates, birth rates, miscarriages, and repeated ectopic pregnancies following any of the four common treatments are not controlled for time, making comparison of these statistics difficult. Future reproductive performance should not factor in treatment selection.

CONCLUSION

The incidence of ectopic pregnancies has significantly increased over the past 60 years and now accounts for 2% of pregnancies. A history of previous ectopic pregnancies, tubal surgery, or infections in symptomatic patients in the first trimester should raise suspicion for ectopic pregnancy. Diagnosis should be performed with pelvic ultrasound first and then comparison to serum β-hCG levels should be undertaken. Patients with serum β-hCG less than 2000 mIU/ml should be followed until their levels exceed 2000 mIU/ml. Determination should then be made that the pregnancy is intrauterine or ectopic. It is suggested that patients with an abnormal rise in β-hCG levels should have a dilatation and curettage if an intrauterine gestation cannot be identified on ultrasound. Multidose intramuscular injection of methotrexate is the first-line treatment in patients who are hemodynamically stable and who have no medical contraindications. Surgical management should be reserved for patients who are hemodynamically unstable, refractory to methotrexate treatment, or unable to follow up appropriately for medical management. Unusual ectopic pregnancies are increasingly documented and their management remains controversial. No one method of management has been shown to enhance reproductive performance after an ectopic pregnancy better than another. Future reproductive performance should not be factored into management decisions.

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2 Pregnancy loss and termination

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INTRODUCTION

The approach to management of abnormal pregnancies is important to master. The techniques of medical or surgical uterine evacuation are similar regardless of the indication for the procedure. The indications for uterine evacuation or pregnancy termination can be divided into four categories: elective/therapeutic, fetal indications (diagnosis of genetic/structural abnormalities), fetal demise (failure of development), maternal indications (e.g. Eisenmenger syndrome), or ectopic location of pregnancy.

This chapter aims to outline the management of abnormal pregnancies and methods of pregnancy termination. Management of ectopic pregnancy is reviewed in Chapter 1.

PREGNANCY LOSS

Spontaneous abortion (SAB), also known as miscarriage, refers to a pregnancy that ends spontaneously before the 20th week of gestation.[1] The World Health Organization defines it as expulsion or extraction of an embryo or fetus weighing 500 g or less from its mother. The frequency of non-viable or non-continuous intrauterine pregnancies is higher than initially estimated, with reported rates ranging from 20 to 62%.[2]

Epidemiology

SAB is the most common complication of early pregnancy.[1] Eight to 20% of clinically recognized pregnancies less than 20 weeks' gestation will result in a spontaneous abortion; 80% of these occur in the first trimester.[3,4] The risk of SAB after 15 weeks is approximately 0.6% for chromosomally and structurally normal fetuses.[5] These statistics vary according to maternal age and ethnicity.

Numerous factors are associated with an increased risk of pregnancy loss: age, previous spontaneous abortion, smoking, alcohol, gravidity, cocaine, non-steroidal anti-inflammatory drugs, fever, caffeine, prolonged ovulation to implantation interval, prolonged time to pregnancy, and low folate level.

Two per cent of pregnant women lose two consecutive pregnancies. Only 0.4–1% of women have three consecutive losses.[6] The recurrence rate of miscarriage is about 20% after one miscarriage, 28% after two miscarriages, and 43% after three or more.[7] When a woman has repeated miscarriages of three or more clinically recognized pregnancies (or two or more in some instances such as advanced maternal age) a workup is warranted. Recurrent pregnancy loss is an important condition; however, the cause of it can only be determined in about 50% of patients.[8] Chromosomal anomalies are the most common reason for recurrent pregnancy loss. Other etiologies of recurrent pregnancy loss include genetic, uterine, endocrine, immunologic, thrombophilic, and environmental factors. Further in depth discussion is outside the scope of this chapter.

Etiology of spontaneous abortion

One-third of the products of conception from spontaneous abortions occurring at or before 8 weeks are 'blighted' or anembryonic. When an embryo is found, about one-half are abnormal, dysmorphic, stunted, or too macerated for examination.[9]

Chromosomal abnormalities account for about one-half of miscarriages (Table 2.1) Most of these are aneuploidies, and arise de novo. Structural abnormalities, mosaicism, and single gene defects are responsible for relatively few abortions. Cytogenetic defects are more common in earlier-age abortions. Abnormal fetal karyotype is 50% at 8–11 weeks' gestation and is 30% at 16–19 weeks.[10] The most frequent types of abnormalities are: autosomal trisomies (52%); monosomy X (19%); polyploides (22%); other (7%).

Spontaneous abortion may also be caused by host factors such as congenital or acquired uterine abnormalities (septum, submucosal leiomyoma, intrauterine adhesions) that interfere with optimal implantation and growth of the embryo. Maternal infection such as with *Listeria monocytogenes*, *Toxoplasma gondii*, parvovirus B19, rubella, herpes simplex, cytomegalovirus, or lymphocytic chroriomeningitis virus can also lead to abortion. Maternal endocrinopathies (thyroid dysfunction, Cushing's syndrome, polycystic ovarian syndrome) can also contribute to suboptimal host environment.