

Ectopic Pregnancy: Contemporary Perspectives on Risk Factors, Diagnosis, Management, and Reproductive Outcomes

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Abstract

Background: Ectopic pregnancy occurs when the embryo implants and grows outside the endometrial cavity. If not diagnosed and treated promptly, it can become life-threatening. The majority of ectopic pregnancies occur in the fallopian tube, while advances in diagnostic capabilities have enabled earlier identification and treatment with the aim of reducing serious complications and preserving future fertility.

Aim: This review aims to present the clinical and epidemiological profile of ectopic pregnancy, with emphasis on risk factors, clinical presentation, diagnostic evaluation, management options, prognosis, and reproductive outcomes.

Conclusion: Early diagnosis and appropriate selection of treatment are central to reducing morbidity from ectopic pregnancy. Expectant management, methotrexate therapy, and surgery have distinct roles according to clinical stability, implantation site, β -hCG findings, and evidence of rupture. Management should prioritize maternal safety while preserving reproductive potential whenever appropriate.

Keywords: Ectopic pregnancy; Tubal pregnancy; β -hCG; Transvaginal ultrasonography; Methotrexate; Laparoscopy; Fertility.

Introduction

Ectopic pregnancy occurs when a flaw in human reproductive physiology causes the embryo to implant and grow outside the endometrial cavity (Figure 1). This condition inevitably leads to fetal death. If not diagnosed and treated promptly, ectopic pregnancy can become life-threatening [1].

Ectopic pregnancy results from abnormal implantation caused by defects in the anatomy or function of the reproductive tract. These can involve the fallopian tubes, often affected by surgical or infectious scarring; the ovaries, particularly in women undergoing fertility treatments; or the uterus, in cases such as bicornuate uterus or cesarean delivery scars. The majority of ectopic pregnancies occur in the fallopian tube, with the ampullary segment being the most common site, accounting for more than 80% of cases [2,3].

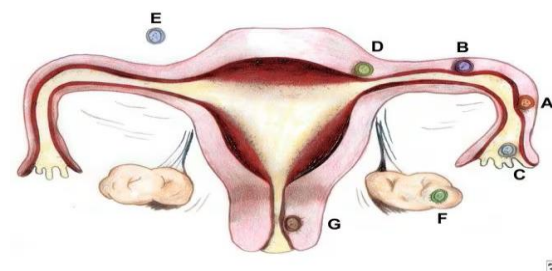


Figure 1: Sites and frequencies of ectopic pregnancy. By Donna M. Peretin, RN. (A) Ampullary, 80%; (B) Isthmic, 12%; (C) Fimbrial, 5%; (D) Cornual/Interstitial, 2%; (E) Abdominal, 1.4%; (F) Ovarian, 0.2%; and (G) Cervical, 0.2% [4].

Nontubal ectopic pregnancies are rare. Abdominal pregnancies represent about 1.4% of cases, while ovarian and cervical implantations each account for approximately 0.2%. Some implantations may occur in the cervix, in cesarean section scars, or in a rudimentary uterine horn; although technically within the uterus, these are not considered normal intrauterine pregnancies [5].

Etiology and Risk Factors

Anything that impedes or delays the migration of the fertilized ovum (blastocyst) into the endometrial cavity may predispose to ectopic pregnancy. Established risk factors include [6,7]:

The most frequent underlying cause of pelvic inflammatory disease (PID) is infection with *Chlamydia trachomatis*. Clinical presentations range from asymptomatic cervicitis to salpingitis and severe PID, and more than half of women with prior chlamydial infection are unaware of having been exposed [8].

Following one ectopic pregnancy, a woman's risk of experiencing another rises significantly, estimated at 7- to 13-fold higher than average. Despite this elevated risk, approximately 50–80% of women with a history of ectopic pregnancy will subsequently achieve an intrauterine pregnancy, while 10–25% may face another tubal pregnancy [9].

Cigarette smoking is a recognized risk factor for the development of ectopic pregnancy, with studies indicating that smokers face a 1.6- to 3.5-fold higher risk compared with nonsmokers. A possible dose-response relationship has also been suggested [7].

The risk increases further with assisted reproductive technologies (ART) such as in vitro fertilization (IVF) and gamete intrafallopian transfer (GIFT). In a cohort of 3000 clinical IVF pregnancies, the ectopic pregnancy rate was 4.5%, more than double the background rate. Additionally, heterotopic pregnancies—where implantation occurs simultaneously in different sites—occur in up to 1% of ART conceptions compared to 1 in 30,000 spontaneous pregnancies [10].

Clinical Presentation and Diagnostic Evaluation

The classic clinical triad of ectopic pregnancy consists of pain, amenorrhea, and vaginal bleeding, though only about half of patients present with all three. Vaginal bleeding is reported in 40–50% of cases, a palpable adnexal mass in about 50%, and abdominal tenderness in roughly 75%. In a large case series, abdominal pain was present in 98.6% of patients, amenorrhea in 74.1%, and irregular vaginal bleeding in 56.4% [11].

Clinicians should maintain a high index of suspicion when evaluating women with such symptoms, particularly when pelvic tenderness, adnexal masses, or uterine enlargement are identified on examination. About 20% of patients are hemodynamically unstable at presentation, strongly suggesting rupture, but with modern diagnostic tools most ectopic pregnancies can be detected before this occurs [12,13].

Physical examination findings in ectopic pregnancy are highly variable and often nondiagnostic. Many patients present with relatively benign examination results, and adnexal masses are seldom detected. Notably, patients in hemorrhagic shock due to ruptured ectopic pregnancy may not always exhibit tachycardia [14].

Beta–Human Chorionic Gonadotropin Levels

Serum β -HCG levels generally correlate with gestational age and embryonic growth. In normal pregnancies, β -HCG doubles every 48–72 hours until reaching about 10,000–20,000 mIU/mL, whereas in ectopic pregnancies the rise is often slower. In healthy intrauterine pregnancies, doubling occurs every 1.4–2.1 days. Kadar and colleagues determined that the minimum expected increase over two days is 66%. For instance, a level of 100 mIU/mL should rise to at least 166 mIU/mL after two days [15].

Even though ectopic pregnancies typically have lower mean serum β -HCG levels than healthy pregnancies, no single measurement can diagnose ectopic pregnancy. Instead, serial testing is needed to distinguish between normal and abnormal pregnancies and to track resolution after treatment [15].

Ultrasonography

Ultrasonography is one of the most valuable tools for diagnosing extrauterine pregnancy, though it is more commonly used to confirm intrauterine pregnancy. Visualization of an intrauterine sac, with or without fetal cardiac activity, is usually enough to rule out ectopic pregnancy. The exception is heterotopic pregnancy, where both intrauterine and ectopic pregnancies occur simultaneously. This condition is rare in spontaneous pregnancies, occurring between 1 in 4000 and 1 in 30,000 cases, but is more common in patients undergoing ovarian stimulation or assisted reproduction, where the risk is about ten times higher. In such cases, adnexal screening with ultrasound remains essential, even when an intrauterine pregnancy is visible [16].

Transvaginal or endovaginal ultrasound, with its higher resolution, allows for visualization of an intrauterine pregnancy as early as 24 days after ovulation or 38 days after the last menstrual period—about one week earlier than transabdominal ultrasound. It can be performed in outpatient or emergency settings and has a reported sensitivity of 90% and specificity of 99.8%, with predictive values of 93% positive and 99.8% negative. Approximately 75% of tubal pregnancies can be detected using this method [17].

Expectant Management

Expectant management is considered only for asymptomatic patients without signs of rupture or hemodynamic instability. Candidates should also show objective evidence of resolution, such as falling β -hCG levels, and must be fully compliant with close monitoring while accepting the risk of tubal rupture. Approximately 25% of women presenting with ectopic pregnancy demonstrate declining β -hCG levels, and around 70% of this group have successful outcomes with observation, provided the ectopic gestation measures 4 cm or less. Low initial β -hCG titers further increase the likelihood of spontaneous resolution, with levels below 1000 mIU/mL predicting successful outcomes in about 88% of expectantly managed cases [18].

It is important to note that no absolute β -hCG threshold guarantees safety for expectant management. Cases of rupture have been reported even with low or declining hormone levels, underscoring the need for strict follow-up and patient reliability [19].

Methotrexate Therapy

Methotrexate is an antimetabolite chemotherapeutic agent that inhibits the enzyme dihydrofolate reductase, disrupting purine synthesis and DNA replication. It has been used widely in oncology and autoimmune diseases, and its effectiveness against trophoblastic tissue was first established in the treatment of molar pregnancies and choriocarcinomas. In the management of ectopic pregnancy, methotrexate is administered via single or multiple intramuscular injections and offers a non-surgical alternative [20].

Indications

Indications for methotrexate therapy include confirmed ectopic pregnancy diagnosed by abnormal β -hCG kinetics and ultrasound, or abnormal β -hCG rise combined with an empty uterus and negative uterine aspiration. Candidates must be hemodynamically stable, compliant with follow-up, and have ectopic masses ≤ 4 cm (≤ 3.5 cm with cardiac activity), absent fetal cardiac activity, no evidence of tubal rupture, and β -hCG levels < 5000 mIU/mL. Predictors of treatment success include initial β -hCG < 1000 IU/L and favorable early decline kinetics, while predictors of failure include hematosalpinx and elevated progesterone levels [21].

Contraindications

Contraindications include high β -hCG levels (> 5000 mIU/mL), fetal cardiac activity, free peritoneal fluid suggestive of rupture, hypersensitivity to methotrexate, breastfeeding, immunodeficiency, liver disease, hematologic dysfunction, renal impairment, peptic ulcer disease, and active pulmonary disease [22].

Adverse effects

Adverse effects may include nausea, vomiting, stomatitis, diarrhea, mild abdominal pain, vaginal bleeding, transient liver enzyme elevation, and rare complications such as bone marrow suppression, pneumonitis, and alopecia. Importantly, many patients experience abdominal pain 2–3 days after treatment due to trophoblastic

separation; this must be differentiated from rupture, which presents with acute abdomen or hemodynamic instability [23].

Single-dose regimen

The most widely used approach is the single-dose regimen, which involves administering methotrexate 50 mg/m² intramuscularly as a single injection. This method has shown comparable efficacy to the multiple-dose regimen, while being simpler, less toxic, and not requiring leucovorin. Stovall and colleagues reported a 96% success rate with this protocol [24].

Monitoring and predictors of success

The initial β -hCG level is the best predictor of outcome. According to Lipscomb's findings, success exceeds 90% when baseline β -hCG is <5000 mIU/mL, drops to ~80% with levels between 5000–10,000 mIU/mL, and falls below 70% when >15,000 mIU/mL. Failure of treatment is defined as plateauing or rising β -hCG, or inadequate decline (<15%) between days 4 and 7 [25].

Surgical Management

Salpingostomy and Salpingectomy

In surgical management, a conservative approach using minimally invasive techniques is preferred when possible to preserve fertility. Procedures include linear salpingostomy, which involves removing the ectopic pregnancy from the ampulla while preserving the tube, and milking the pregnancy from the distal ampulla. More radical interventions, such as segmental resection (with or without reanastomosis) or total salpingectomy, are indicated in cases of severe tubal damage, recurrent ectopic pregnancy in the same tube, or when fertility is no longer desired [26]. Laparoscopy is the standard approach, offering reduced adhesion formation, blood loss, analgesic requirement, cost, and recovery time compared to laparotomy. Laparotomy is reserved for patients with hemodynamic instability, cornual pregnancies, or when dense adhesions, obesity, or massive hemoperitoneum make laparoscopy unfeasible [27].

A systematic review and meta-analysis found no difference in intrauterine pregnancy rates between salpingectomy and salpingostomy in randomized controlled trials. However, cohort studies suggest that salpingectomy may reduce the chance of future intrauterine pregnancy compared to salpingostomy [28].

In unstable patients with uncontrolled bleeding, conservative measures are abandoned in favor of radical surgery to ensure maternal safety [29].

Total salpingectomy

Total salpingectomy is performed by sequentially coagulating and excising the mesosalpinx, starting from the fimbrial end toward the isthmus, and detaching the tube from the uterus by division at its proximal insertion. This radical option is often preferred for patients with recurrent ectopic pregnancy in the same tube, severely damaged tubes, or those who no longer desire fertility. It is also indicated in cases of uncontrolled bleeding or hemodynamic instability, where conservative options are unsafe [30].

This balance between conservative and radical techniques is guided by the patient's clinical status, fertility wishes, and intraoperative findings, with the ultimate goal of optimizing safety while preserving future reproductive potential where possible [31,32].

Monitoring After Surgical Treatment of Ectopic Pregnancy

Following surgical excision of an ectopic gestation, weekly monitoring of quantitative β -hCG levels is essential until they return to zero, confirming complete resolution. This is particularly critical after conservative procedures such as salpingostomy, which carry a 5–15% risk of persistent trophoblastic tissue. On average, β -hCG normalizes within 2–3 weeks, but clearance may take up to 6 weeks [33].

Although most patients resolve without additional intervention, persistence of trophoblastic tissue can lead to tubal rupture and hemorrhage, even with declining β -hCG levels. In such cases, further treatment—either with

methotrexate or repeat surgery may be necessary. Some experts advocate for the use of prophylactic methotrexate following conservative surgery to reduce the risk of persistent ectopic pregnancy [34].

Cesarean Scar Pregnancy

The estimated incidence of cesarean scar pregnancy is approximately one in every 1,800 to 2,200 pregnancies. Its overall frequency appears to be increasing, accounting for up to six percent of ectopic pregnancies among individuals with a prior cesarean section [35].

Typical sonographic findings of cesarean scar pregnancy include an empty uterine cavity and cervical canal, with the gestational sac implanted within the anterior lower uterine segment at the level of the previous cesarean scar. Classification based on gestational sac position helps in determining the depth of implantation and risk of uterine rupture. Cases where the sac crosses the uterine cavity line often indicate a type I (endogenic) CSP, while sacs embedded within the myometrium without crossing the cavity line represent type II (exogenic) CSP. A more advanced form involves the gestational sac crossing the serosal line, denoting potential uterine wall dehiscence or rupture risk (Figure 2) [36].

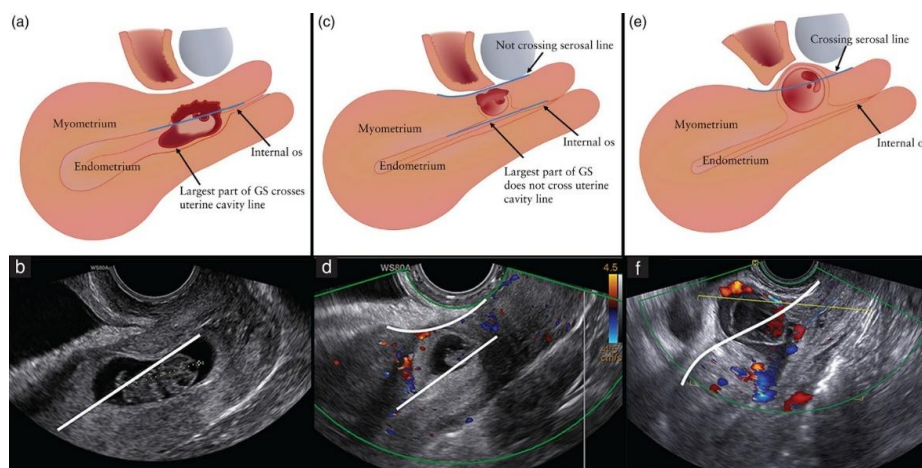


Figure 2: Schematic and ultrasound images illustrating cesarean scar pregnancy types based on gestational sac position relative to the uterine cavity and serosal lines [37].

Management and Prognostic Considerations of Cesarean Scar Pregnancy

Ultrasound-guided methotrexate injection is now recognized as the preferred treatment approach. Surgical or invasive methods, such as dilatation and curettage, are discouraged due to their high risk of complications and unfavorable outcomes. Since future pregnancies carry a risk of uterine rupture, careful assessment of the uterine scar is essential both before conception and throughout subsequent pregnancies [38].

Prognosis and Reproductive Outcomes

Most data on treatment outcomes and future fertility are derived from observational studies and a limited number of randomized trials. Comparisons between treatment modalities are often affected by selection bias, as patients differ in severity and clinical presentation [39].

Evidence in the literature has not shown a consistent or substantial advantage of salpingostomy over salpingectomy in terms of improving reproductive outcomes. Some studies, however, suggest that salpingostomy may offer benefit in women with contralateral tubal damage, although this comes with a higher risk of persistent ectopic pregnancy and slightly greater recurrence rates [40].

Fertility Following Surgery

Parker and Bistis reported that when the contralateral fallopian tube is normal, future fertility rates are not influenced by the choice of surgical procedure. Similarly, Ory and colleagues, in a prospective study of 88 patients, found no effect of surgical technique on fertility when the opposite tube was intact [41].

Future fertility outcomes appear comparable between laparoscopic and open surgery. Reported intrauterine pregnancy rates range from 25–70% after laparotomy salpingectomy and 50–60% after laparoscopic salpingectomy, with similar results for salpingostomy. Persistent ectopic pregnancy rates are also comparable across approaches, typically 5–20% [39].

Methotrexate Versus Surgery

When strict selection criteria are applied, methotrexate therapy achieves success rates comparable to laparoscopic salpingostomy. Multiple-dose methotrexate protocols report success rates between 91–95%. In one study of 77 women planning future pregnancies, intrauterine pregnancies were achieved in 64% and recurrent ectopic pregnancies occurred in 11%, findings echoed by other studies reporting intrauterine pregnancy rates ranging from 20–80% [42].

Single-dose methotrexate regimens demonstrate average success rates of 88–94%. In the series by Stovall and Ling, 94% of patients were treated successfully, with 3.3% requiring a second dose. No adverse effects were observed, and among those followed, 87.2% achieved intrauterine pregnancies while 12.8% experienced recurrent ectopic pregnancies. Other studies have confirmed these outcomes, though some noted mild side effects and slightly lower reproductive success [43,44]. A meta-analysis of 26 trials found a success rate of 88.1% with the single-dose regimen compared with 92.7% for the multiple-dose regimen. A smaller randomized clinical trial reported a marginally higher failure rate with the single-dose approach. Additionally, a two-dose “hybrid” protocol, with methotrexate administered on days 1 and 4 without leucovorin rescue, has been shown to be both effective and convenient, providing an alternative to standard regimens [45].

Complications

Complications of ectopic pregnancy often arise from delayed or incorrect diagnosis, or from the chosen treatment strategy. If diagnosis is missed or late, tubal or uterine rupture can occur, depending on the implantation site. This may lead to massive intra-abdominal hemorrhage, hemodynamic shock, disseminated intravascular coagulation (DIC), and potentially maternal death. Ectopic pregnancy remains the leading cause of maternal death during the first trimester, accounting for 9–13% of pregnancy-related deaths. In the United States, it is estimated that 30–40 women die annually from ectopic pregnancy [46].

Although ectopic pregnancies are nonviable and carry the risk of rupture and hemorrhage, early diagnosis before rupture significantly reduces mortality and preserves fertility potential [47].

Conclusion

Ectopic pregnancy remains a significant health challenge because delayed recognition may result in rupture, hemorrhage, and loss of reproductive potential. Risk is influenced by tubal damage, previous ectopic pregnancy or tubal surgery, pelvic infection, smoking, assisted reproduction, and other reproductive factors. Clinical findings alone are frequently nondiagnostic, making combined assessment with serial β -hCG measurements and ultrasonography essential. Expectant management and methotrexate provide effective nonsurgical options in carefully selected stable patients, whereas surgery remains necessary for rupture, hemodynamic instability, treatment failure, or other high-risk presentations. The choice between conservative and radical surgery should be guided by clinical status, tubal condition, and reproductive goals, with careful follow-up to confirm complete resolution and support future fertility.

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