

# Recurrent Ectopic Pregnancy: Current Perspectives

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**Abstract:** Ectopic pregnancy represents a potentially life-threatening diagnosis. The risk factors for recurrent ectopic pregnancy have been enumerated but are not yet clearly defined. Understanding which risk factors are perhaps more common may allow providers to counsel and manage patients with a higher level of scrutiny.

**Keywords:** ectopic pregnancy, recurrent ectopic pregnancy, management, risk factors

## Background

Ectopic pregnancy represents 2% of pregnancies, according to the Centers for Disease Control and Prevention.<sup>1</sup> In pregnancies achieved via assisted reproductive technologies, ectopic pregnancy incidence was estimated by one study to be about 1.6% in 2011.<sup>2</sup> Ectopic pregnancy represents a potentially life-threatening diagnosis, in the case of tubal rupture. Thus, given the risk of recurrence in those who have had a previous ectopic pregnancy reaches 10–27%,<sup>3,4</sup> it is paramount to attempt to identify those at highest risk of recurrence as well as to attempt interventions in the primary ectopic pregnancy which will mitigate subsequent risk if possible. A lack of uniformity in studies and scarcity of randomized controlled trials on this subject make analysis of the evidence at large difficult, but some trends have emerged that may aid in counseling and management.

## Risk Factors for Recurrent Ectopic Pregnancy

Understanding which risk factors are most prevalent in those with REP will help practitioners maintain a higher index of suspicion and counsel their patients appropriately. If we can identify risk factors for recurrent ectopic pregnancy (REP), then recurrence can potentially be mitigated or prevented. Many studies have evaluated risk factors for REP, and an extensive list has been produced. Risk factors for REP that were identified in common amongst these include factors such as tubal damage, evidence of infectious pelvic pathology, prior pelvic surgery, salpingostomy, salpingitis, infertility, lower annual income, and a lack of contraceptive use.<sup>3–6</sup>

A retrospective cohort of 353 women with 555 pregnancies by natural conception identified factors such as infectious pelvic pathology, first ectopic pregnancy at age 24 or under, initiation of an infertility workup, history of REP, and conception without an IUD in situ at time of first ectopic pregnancy as associated with a higher incidence of REP.<sup>3</sup> Specifically, identification of pelvic pathology consistent with prior infection at the time of surgery for the index ectopic pregnancy, such as tubal adhesions or macroscopic damage such as hydrosalpinx, was associated with an increased risk of REP.<sup>3</sup> In this study, type of surgery at index pregnancy whether salpingectomy or salpingostomy was not found to be correlated with recurrence.<sup>3</sup>

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However, in two other studies, salpingectomy was found to be associated with a lower risk of REP than salpingotomy.<sup>7,8</sup> For instance, in a cohort study which included 143 surgically managed ectopic pregnancies, salpingectomy reduced the risk of REP, with a relative risk of 0.32.<sup>7</sup> In a case-control study, salpingostomy conferred a higher risk of REP with an odds ratio of 7.129.<sup>8</sup> In the same study which evaluated 555 pregnancies, patients who had two previous ectopic pregnancies via natural conception and treated with salpingectomy or salpingostomy were found to have a 10-fold increased risk of further REP as compared to those with one prior. This effectively reduced their ability to achieve a pregnancy naturally and complete it to term to 4%.<sup>3</sup> However, this conclusion was drawn based on only 5 patients who had more than two ectopic pregnancies. In this same study, they noted a higher risk of REP in those whose index ectopic was not associated with an IUD in situ at a rate of 21.2%. In comparison, those whose index ectopic pregnancy was associated with contraception failure with an IUD in situ, had lower rates of REP of 7.2%.<sup>3</sup> In a case-control study including 61 women with REP, the risk of REP was increased with a history of surgery, prior live birth, and history of spontaneous miscarriage.<sup>4</sup> This leads to an association of REP with increasing pregnancy order in general. Notably, many of the prior pelvic surgeries which conferred a risk association in this study were those to treat the index ectopic pregnancy. In the same study, they determined that factors of history of gonorrhea, chlamydia, pelvic inflammatory disease, Caesarean section, or pregnancy termination were not associated with REP.<sup>4</sup>

Protective factors include increasing number of normal pregnancies from the index or first ectopic pregnancy.<sup>3</sup> Therefore, with each subsequent pregnancy remote from the index ectopic, women are less likely to have a REP. This was substantiated in another study which found multiparity to be a protective factor for REP.<sup>6</sup>

From a counseling perspective, all aforementioned risk factors should be considered, and discussion should be highly individualized. Notably, in one study, while evidence of pelvic infection on laparoscopy for treatment of ectopic pregnancy was associated with an increased risk of REP, the findings of pelvic adhesive or tubal disease did not correlate with patients' previous diagnosis and treatment of pelvic inflammatory disease (PID).<sup>3</sup> The history of treatment for PID in this study was based on medical record review or a questionnaire response when the medical record was incomplete. In another study, this finding

was echoed and again; no correlation of REP with a historical diagnosis of PID was noted.<sup>4</sup> In this second study, the history of PID was recorded for those who had a hospitalization with the diagnosis of PID. Likely, these findings represent the heterogeneity in clinical features associated with a diagnosis of PID, the lack of concordance of severity of PID with resultant pelvic pathology, the possible under-reporting of PID due to its silent nature or patient reporting error.

In one study, investigators addressed the specific pelvic infectious pathology of salpingitis and its role in REP.<sup>5</sup> Patients who underwent laparoscopy for symptoms of acute PID were given grades for severity of tubal pathology. Information on pregnancies prior to laparoscopy was collected, and patients were followed for subsequent pregnancy. They determined that while salpingitis increases the risk of initial ectopic pregnancy, that additional episodes of salpingitis do not add any incremental risk for REP.<sup>5</sup> In another study, patients with REP had a higher incidence of chlamydial infection as determined by cervical antigen or serum antibody than those who achieved intrauterine pregnancies after an index ectopic pregnancy.<sup>9</sup>

Other risk factors have been cited that are unique to singular studies. For instance, in one study of over 100,000 women, the prior diagnosis of psychiatric illness conferred a higher risk of REP with an adjusted odds ratio of 1.8 ( $p < 0.001$ ).<sup>10</sup> In another study, a lower education level was a significant risk factor for REP.<sup>8</sup>

Alternative locations of ectopic pregnancy also warrant discussion as they have been found to confer risk of REP with a slightly different profile than that of a traditional tubal ectopic pregnancy. In a retrospective cohort study of patients with a cesarean scar pregnancy (CSP) treated with high-intensity focused ultrasound and uterine artery embolization (UAE), treatment with UAE was associated with a higher risk of recurrent CSP. In addition, patient characteristics of greater than or equal to four prior abortions or being asymptomatic with the index CSP were risk factors for recurrent CSP.<sup>11</sup>

## Diagnosis

There is some evidence to suggest that those with REP may actually present in a slightly different manner than a primary ectopic pregnancy. For instance, in one study, the investigators looked at characteristics at first presentation and found that among pain symptoms, bleeding, initial HCG level, ultrasonographic findings, and positive cervical cultures for gonorrhea or chlamydia, those with REP

were less likely to have bleeding at initial presentation with an odds ratio of 0.4.<sup>4</sup> The other factors evaluated were not found to be significantly correlated.

## Management and the Risk of Recurrence

Management options for recurrent ectopic pregnancy include options available to those with a first ectopic pregnancy – salpingostomy, salpingectomy, medical, and expectant management. Understanding which management options for an index pregnancy may lead to a higher risk of recurrence may also be important in preventing a subsequent occurrence. Several studies have evaluated the differences between the surgical management options of salpingostomy versus salpingectomy. Interestingly, it is unclear whether the method of surgery affects the risk of REP, with some studies suggesting no difference,<sup>3</sup> and some studies suggesting increased risk of REP with salpingostomy from a referent group of expectant management while salpingectomy did not.<sup>6</sup> Whether the contralateral tube at the time of the first ectopic pregnancy is noted to be damaged or abnormal may also affect the risk of recurrence.<sup>3</sup>

In a case–control study, which provided an updated assessment on risk factors given changes in contraceptive practices and assisted reproductive technology, they assessed the risk associated with various approaches to management. When methotrexate, salpingostomy, salpingectomy, and other surgical procedures such as fimbrial milking were compared to a referent group of expectant management, the only group found to have an increased risk of REP was the salpingostomy group with an adjusted odds ratio of 4.59 for those who had a REP versus did not become pregnant and 2.23 for those who had a REP versus an intrauterine pregnancy.<sup>6</sup>

In another study, the investigators looked at the contribution of tubal adhesive disease noted at the time of either salpingostomy or salpingectomy for ectopic pregnancy.<sup>9</sup> They employed mean adhesion scores by revised American Fertility Society stage points (re-AFS). They determined that the surgical approach did not have an effect on the incidence of REP. However, those with higher adhesion scores were more likely to have a REP than intrauterine pregnancy regardless of surgical approach.

In a systematic review using intrauterine pregnancy through natural conception as a primary outcome looking at salpingectomy versus salpingostomy for ectopic pregnancy, investigators evaluated two RCTs and eight cohort studies.

The cohort study evaluation revealed that REP was more prevalent in the salpingostomy group than the salpingectomy group as was the rate of persistent ectopic pregnancy (PEP). However, the rate of intrauterine pregnancy was also higher in the salpingostomy group. Overall, salpingostomy was shown to simply result in more subsequent pregnancies overall, including the number of REPs. In the RCT analysis of this cohort study, no association with the type of pelvic surgery was found with the risk of REP or rate of intrauterine pregnancy.<sup>12</sup> Given the discrepancies between findings based on analysis of RCTs versus cohort studies, it may be that selection bias in the type of surgery carried out is at play in these divergent conclusions.

Medical management with systemic methotrexate represents an option for recurrent ectopic pregnancy. However, in a logistic regression analysis from a study of 262 patients with ectopic pregnancies treated with single dose methotrexate, REP was the only independent variable found to be associated with treatment failure. The authors concluded that other options than single dose methotrexate should be considered for management of REP.<sup>13</sup>

When considering management options for ectopic pregnancy with the aim of reducing the risk of REP, a well-defined standard of practice has not been delineated. As with ectopic pregnancies in general, where the American College of Gynecologists supports either salpingostomy or salpingectomy,<sup>1</sup> either management option with REP is reasonable. Individual patient characteristics, risk factors for REP, and clinical scenario must be assessed.

## Conclusions

There remains to be a consensus on risk factors associated with as well as management of recurrent ectopic pregnancy. Overall, some risk factors that seem to be consistently associated with REP include pelvic adhesions noted at the time of index pregnancy and prior pelvic surgery. Some authors propose that it is not feasible to prevent secondary recurrence in patients with prior ectopic pregnancy.<sup>4</sup> However, with a 10–20% recurrence rate once a patient has a history of ectopic pregnancy,<sup>9</sup> it is worthy to further investigate with if there is a management option that will reduce this risk as much as possible. Two RCTs on this topic have concluded no difference in fertility rates following either salpingostomy or salpingectomy.<sup>14,15</sup> However, given the heterogeneity of clinical presentations and patient as well as provider decision-making, it remains difficult to truly evaluate all

management options of an index ectopic pregnancy and the subsequent risk of recurrence on a level playing field. Although this is not definitive, understanding the risk factors that may put patients at higher risk can give providers the opportunity to counsel and evaluate patients with more precision when a higher index of suspicion exists.

## Disclosure

The authors report no conflicts of interest in this work.

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