

Diagnosis and management of ectopic pregnancy

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The estimated prevalence of ectopic pregnancy is 1-2% worldwide. In the United Kingdom nearly 12 000 ectopic pregnancies are diagnosed each year, which gives a prevalence of 1.1%.¹ Although death after ectopic pregnancy is rare, the burden of disease is high owing to the cost of diagnostic tests and expensive treatment.² Serious adverse outcomes in ectopic pregnancies are typically caused by delayed diagnosis; this highlights the need for primary care and secondary care health professionals to be familiar with the risk factors for ectopic pregnancy, its clinical symptoms, and the local facilities that provide care for women with early pregnancy problems. In recent years it has become more common to treat women with ectopic pregnancy conservatively in the outpatient setting.³ General practitioners increasingly advise women on different management options and support them during follow-up.

What is ectopic pregnancy?

An ectopic pregnancy is any gestation that implants outside the uterine cavity. Most ectopic pregnancies implant within the fallopian tubes, so the terms tubal pregnancy and ectopic pregnancy are often used interchangeably. Between 5% and 7% implant within the uterine wall, but outside the uterine cavity, and these include interstitial, intramural, cervical, and caesarean scar ectopic pregnancies.^{w1} Although rare, “non-tubal ectopic” pregnancies are associated with significantly higher mortality and morbidity than tubal ones because they are often difficult to diagnose and tend to present late with sudden rupture. Pregnancies that implant into

SOURCES AND SELECTION CRITERIA

We searched Embase and Medline for articles with titles that included the keywords “ectopic pregnancy” and “extrauterine pregnancy.” We limited the search to meta-analyses, reviews, and randomised controlled trials published in English in the past 10 years. We consulted a systematic review on ectopic pregnancy in the Cochrane Library and identified articles of interest. We also reviewed published guidelines from national emergency medicine, gynaecological, and radiological societies.

the intramural (‘interstitial’) part of the fallopian tube are particularly dangerous—they represent only 2.5% of all ectopic pregnancies, but the UK’s Confidential Enquiry into Maternal and Child Health 2000-8 found that they account for almost a fifth of all deaths caused by ectopic pregnancies.¹

What causes ectopic pregnancy and who is at risk?

Observational studies have identified several risk factors for ectopic pregnancy, including increased maternal age, history of pelvic infection or surgery, infertility, and smoking. A meta-analysis of studies identified four factors that were strongly associated with ectopic pregnancy: previous ectopic pregnancy, previous tubal surgery, evidence of tubal pathology, and in utero exposure to diethylstilbestrol.⁴ A history of genital infections, infertility, and more than one lifetime sexual partner carried only a moderately increased risk of ectopic pregnancy.⁴ A more recent case-control study from France identified past or current smoking and history of sexually transmitted disease as the most important risk factors for ectopic pregnancy.⁵ Other risk factors were increased maternal age, history of infertility, and tubal surgery.⁵

All methods of contraception protect against ectopic pregnancy because they reduce overall pregnancy rates. In women in whom contraception fails the risk of ectopic pregnancy depends on the method of contraception used. In women who become pregnant after tubal ligation the risk of ectopic pregnancy is particularly high (odds ratio 9.3, 95% confidence interval 4.9 to 18). Having an intrauterine contraceptive device in place also significantly increases risk, whereas rates of ectopic pregnancy in women who use condoms, the combined oral contraceptive pill, or emergency hormonal contraception are similar to those in the general population.⁴

SUMMARY POINTS

The prevalence of ectopic pregnancy is 1-2% and it is an important cause of maternal morbidity and mortality

Consider ectopic pregnancy in all pregnant women presenting with abdominal pain or vaginal bleeding

Women with a history of ectopic pregnancy, tubal surgery, or tubal pathology are at increased risk, as are those who have had tubal ligation or who have an intrauterine contraceptive device in place

A transvaginal ultrasound scan is the best test to diagnose ectopic pregnancy

Laparoscopic surgery is the main treatment; medical and expectant management is used in a select group

Women who are treated for ectopic pregnancy have significantly lower subsequent spontaneous intrauterine pregnancy rates and higher ectopic pregnancy rates than the general population

How is ectopic pregnancy diagnosed?

Clinical findings

The clinical presentation of ectopic pregnancy varies. The earliest symptom is usually brown vaginal discharge, which often starts soon after the missed menstrual period. The intensity of bleeding varies, and some women report heavy blood loss, which may lead to an erroneous diagnosis of miscarriage. Between 10% and 20% of women with ectopic pregnancy report no bleeding.^{w2} Abdominal pain is usually a late feature in the clinical presentation and typically follows tubal miscarriage, with bleeding through the fimbrial end of the tube into the peritoneal cavity. The intensity of the pain does not necessarily reflect the volume of blood present in the abdominal cavity. Almost 10% of women diagnosed with ectopic pregnancy do not report abdominal pain.^{6 w3}

Pain that is associated with rupture of the fallopian tube tends to be more intense, and peritonism may be detected on abdominal palpation. Typical signs of haemorrhagic shock—which include pallor, tachycardia, hypotension, and oliguria—should alert the examiner to major intra-abdominal bleeding, regardless of the intensity of abdominal pain. Patients with rupture of the fallopian tube complicated by severe intra-abdominal haemorrhage may present initially with nausea, vomiting, and diarrhoea, which may confusingly suggest a gastrointestinal disorder and delay diagnosis of ectopic pregnancy. More than a third of women who died from ectopic pregnancy in the UK since 1997 were misdiagnosed initially with a gastrointestinal problem.¹ Repeated recommendations from the Confidential Enquiry into Maternal and Child Health are that the diagnosis of ectopic pregnancy should be considered in all women of reproductive age with sudden onset of severe gastrointestinal symptoms.¹

Vaginal examination, including speculum and bimanual palpation of pelvic organs, has traditionally been used in women with suspected complications in early pregnancy. Several observational studies have found that physical examination has limited diagnostic value.^{7 w2 w3} Internal examination is unpleasant for pregnant women and is often uncomfortable, even in those with normal intrauterine pregnancies. Application of pressure on a fallopian tube swollen with an ectopic pregnancy during such an examination could potentially cause tubal rupture, although there is no evidence for this.⁷ In modern clinical practice, where ultrasound diagnostic facilities are usually readily available, experts suggest that generalists consider an early referral for ultrasound examination without performing a vaginal examination first.⁷

Ultrasound

Criteria for the diagnosis of a tubal ectopic pregnancy were first published in 1969.⁸ False negative and false positive findings were common when transabdominal ultrasound examination was used.⁸ A recent meta-analysis of the accuracy of ultrasonography in emergency departments in North America showed a pooled sensitivity estimate of 99.3% (96.6% to 100%), but a specificity of only 71% (60% to 80%).⁹ Transabdominal sonography is still widely used in emergency departments in North America, and the low specificity of the test makes it difficult to exclude an ectopic pregnancy.

Diagnostic accuracy is better if the transvaginal route is used for ultrasound examination.^{10 w4 w5} Several observational studies showed that the presence of an adnexal mass on transvaginal ultrasound is highly specific for tubal pregnancy.^{11 w6 w7} A meta-analysis of findings in 2216 women showed that the presence of an adnexal mass other than a simple cyst separate from the ovary was a highly sensitive (84.4%) and specific (98.9%) test for the diagnosis of ectopic pregnancy.¹² In most cases a skilled operator can determine the location of pregnancy from a single ultrasound examination. The initial test of choice for the assessment of women with suspected ectopic pregnancy is therefore transvaginal ultrasound. Blood tests and laparoscopy are usually used as secondary tests in women with inconclusive findings on ultrasound.

Serum biochemistry

A consensus statement estimated that in 8-31% of women with suspected complications of early pregnancy the initial ultrasound examination fails to establish a conclusive diagnosis of either an intrauterine or ectopic pregnancy,¹³ and that the proportion depends largely on the skill of the ultrasound operators in individual studies, the route used to perform the examination (transvaginal v transabdominal), and the quality of the ultrasound equipment.¹³ In women with non-diagnostic scans, measurement of serum human chorionic gonadotrophin (HCG) and progesterone has been used to aid diagnosis.

Single and serial measurements of serum HCG have been used to try to facilitate non-invasive diagnosis of ectopic pregnancy.^{14 w8-w10} A recent cross sectional study showed that a single reading of serum HCG above a certain value (discriminatory zone) does not help differentiate intrauterine from ectopic pregnancies in symptomatic women.¹⁴ Patterns of HCG secretion in ectopic pregnancies often resemble those found in normal and abnormal intrauterine pregnancies,¹⁵ and it is difficult to determine the location of pregnancy on the basis of changes in maternal HCG concentrations. The measurement of serum progesterone is similarly limited.^{16 w11} Experts agree that studies of hormonal values alone are neither sensitive nor specific enough to be used to diagnose ectopic pregnancy in routine clinical practice.^{w4 w5} A declining serum HCG value on serial measurements,^{w12} or a single low initial reading of serum progesterone,^{w13} can help to identify a woman in whom pregnancy is undergoing spontaneous resolution, regardless of its location. When serum HCG values decline rapidly by more than 13% over 48 hours,¹⁷ or when the initial serum progesterone is 10 nmol/L or less,¹⁸ the risk of a woman requiring any form of medical intervention is low, and further routine follow-up is not needed. This can help to rationalise the workload in early pregnancy units without compromising women's safety. In cases where HCG does not decline appreciably and progesterone remains high, follow-up with ultrasound and blood tests should continue until a final diagnosis is reached.

Surgery and histopathology

In modern practice the diagnostic role of surgery is declining as an increasing proportion of ectopic pregnancies are managed more conservatively. In recent decades laparoscopy has replaced open surgery to diagnose and treat

A PATIENT'S PERSPECTIVE

Seven days after discovering I was pregnant I started to bleed heavily. A scan showed that the pregnancy was located in my right fallopian tube. The doctor suggested expectant management, with a view to avoiding surgical removal of the tube.

We cancelled our holiday and I started the draining process of having blood tests every second day. I was told that my HCG values should start to drop but they kept rising. I was extremely anxious and constantly worried that my tube was about to rupture. I tried to carry on as normal, but life seemed utterly bleak, and I felt so guilty about willing the pregnancy to end.

At week nine of pregnancy I had severe stomach pain and a scan showed some internal bleeding. Because my HCG values had not started to drop, although they were increasing only minimally, I was offered surgical treatment. I decided to stick with the non-surgical option though, to optimise my chances of having a normal pregnancy in the future.

After another six weeks my HCG values had dropped and a pregnancy test was negative. I knew this was good news but I also felt sorry that my pregnancy was over. That same night I had more pain and heavy bleeding. Another scan showed that I had a clot in my fallopian tube—a haematosalpinx. The doctors explained that I was still at risk of rupture (and might still need surgery).

My relationship with my partner was fraught from the worry during this time. A counsellor helped me to process feelings of guilt, disappointment, and worry about the future.

Twelve weeks after diagnosis, things were getting back to normal. A scan showed that the clot in my tube had started to break down and I didn't have to go back to hospital for three months. The haematosalpinx seemed to have resolved at six months. Naturally I'm concerned that any future pregnancy might also be ectopic, but I am trying to concentrate on the positive.

ectopic pregnancy in suspected tubal rupture.¹⁹ Although laparoscopy is still perceived by many as the gold standard for diagnosing ectopic pregnancy, its diagnostic accuracy has never been formally examined. In one observational study, 4.5% of women reported to have no evidence of ectopic pregnancy at the time of initial laparoscopy were subsequently diagnosed with an ectopic pregnancy.²⁰

Histopathology is routinely used to confirm the diagnosis of ectopic pregnancy in a specimen after surgical treatment of ectopic pregnancy. Macroscopically the fallopian tube may be distended with trophoblast and blood clots (haematosalpinx), or there may be signs of rupture. On microscopic examination there should be evidence of chorionic villi within the tube or within the specimen taken at salpingotomy.^{w14} After tubal rupture, and in women with severe haematoperitoneum, it is often not possible to identify chorionic villi in the surgical specimen. In these women, follow-up with serum HCG measurements is advisable in case the surgical diagnosis of ectopic pregnancy was incorrect or the ectopic trophoblast had not been completely removed.

How is ectopic pregnancy treated?

Referral

We recommend early referral of asymptomatic pregnant women with a history of ectopic pregnancy, tubal surgery, and known tubal pathology to dedicated early pregnancy units. Women who become pregnant with an intrauterine contraceptive device in situ or after tubal sterilisation should also be offered early scans. Although there is no robust evidence to support this policy, we consider that the documented high risk of ectopic pregnancy in these women justifies this approach.⁴

Surgery

Surgery remains the principal treatment option for ectopic pregnancy. A recent meta-analysis showed that the lapar-

oscopic approach is associated with significantly shorter operating time, reduced perioperative blood loss, shorter duration of hospital stay, and shorter convalescence times compared with open surgery.³ All these factors result in significant cost savings when laparoscopy is used in preference to laparotomy. Laparotomy, however, may be safer than laparoscopy in women who have had a large intra-abdominal bleed in whom achieving immediate haemostasis is a priority.²¹ Laparotomy may also be indicated for women who have large uterine fibroids, which could make insertion of the laparoscope technically difficult and potentially hazardous. In women who have conservative surgery with tubal preservation (salpingotomy), laparoscopy is associated with a significantly increased risk of residual trophoblast tissue,^{22 23 w15} and postoperative follow-up with serial serum HCG measurement is required to ensure that all active tissue has been removed.²¹ However, if the contralateral tube appears diseased at surgery, guidelines from the Royal College of Obstetricians and Gynaecologists (RCOG) state that salpingotomy should always be attempted to preserve fertility.²¹ Currently, it is not clear whether women with an apparently healthy contralateral tube have better fertility outcomes if the fallopian tube harbouring an ectopic pregnancy is preserved (salpingotomy) rather than removed (salpingectomy).^{w16 w17} A large international trial aimed at answering this question is currently under way.^{w18 w19}

Medical treatment

Medical treatment with systemic methotrexate is considered an acceptable management option for women presenting with few clinical symptoms, a small ectopic pregnancy on ultrasound scan, and low serum HCG values. However, its role is limited in clinical practice because only 25-30% of the total number of ectopic pregnancies satisfy criteria for medical treatment.^{24 25} A randomised trial of clinically stable women with unruptured tubal ectopic pregnancies compared the efficacy of a multiple dose systemic methotrexate regimen to laparoscopic salpingotomy.²⁴ Rates of successful treatment were not significantly different between the medical and surgical groups (relative risk 1.2, 0.93 to 1.4). Women in the medical management group were at increased risk of major haemorrhage from the ruptured tube after administration of methotrexate.²⁴ A study that pooled results from four randomised trials that compared single dose systemic methotrexate to laparoscopic salpingotomy found medical treatment to be significantly less successful than surgery (0.82, 0.72 to 0.94).²³ Concerns remain about side effects and the need for women to delay future pregnancy for a minimum of three months. Medical treatment is, however, more cost effective than surgery, but only in women presenting with very low serum HCG values (<1500 IU/L).^{23 26} Follow-up after medical treatment requires repeated visits and serial measurements of serum HCG until it declines to a very low concentration (usually <20 IU/L). In women with worsening pain, repeated ultrasound scans are also needed to exclude serious intra-abdominal bleeding. Compliance with the follow-up is essential for successful and safe medical treatment of ectopic pregnancy. Women who have difficulty communicating with health professionals because

QUESTIONS FOR FUTURE RESEARCH

- What could be done to decrease the risk of ectopic pregnancy occurring in chlamydia screen positive women and those with previous ectopic pregnancy?
- What is the optimal management of women with positive pregnancy tests and non-diagnostic ultrasound scans?
- What could be done to protect the emotional wellbeing of women undergoing conservative treatment of ectopic pregnancy, which involves prolonged follow-up, serial blood tests, and repeated ultrasound scans?
- How do different management strategies affect future reproductive outcomes?

of a language barrier and those who live far from acute hospital units, alone or unsupported, are less likely to attend for follow-up visits and they should not be routinely offered medical treatment.

Expectant management

Several observational studies suggested that expectant management was highly successful in women with ectopic pregnancy who presented with very low HCG values.^{27 w20} Most clinicians, however, still consider that all ectopic pregnancies need some form of treatment, and few data exist to compare expectant with medical or surgical treatment. Only one randomised trial has been published to date that compared expectant management with systemic oral methotrexate.²⁸ The trial is of limited value because the dose of methotrexate used was much lower than that used in standard clinical practice. Another randomised controlled trial is currently under way to compare expectant management with systemic methotrexate in women with tubal ectopic pregnancies and low serum HCG values.^{w21}

ADDITIONAL EDUCATIONAL RESOURCES

Resources for healthcare professionals

NHS Clinical Knowledge Summaries (www.cks.nhs.uk/ectopic_pregnancy)—Evidence based information and practical “know how” on the common conditions managed in primary care

Early Pregnancy Clinical Study Group (www.earlypregnancy.org.uk/ClinicalStudy.asp)—A part of the National Reproductive Research Network, which brings together scientists, clinicians, healthcare providers, and patient representatives to stimulate development and coordination of research in early pregnancy

Special Interest Group Early Pregnancy (SIGEP) of the European Society for Human Reproduction and Embryology (www.eshre.eu/01/default.aspx?pageid=60)—Aims to provide a clinical and scientific link between the medical fields of infertility, human reproduction, prenatal diagnosis, and fetal medicine

Resources for patients

The Ectopic Pregnancy Trust (www.ectopic.org.uk)—UK charity that provides information about symptoms, diagnosis, and treatment of ectopic pregnancy. Its interactive website also includes a message board

The Association of Early Pregnancy Units (www.earlypregnancy.org.uk)—Provides accessible information to help patient choice and facilitate access to their local early pregnancy unit when needed

The Miscarriage Association (www.miscarriageassociation.org.uk)—Provides information on the causes, management, and treatment of miscarriage, ectopic pregnancy, and molar pregnancy. Provides a telephone helpline and network of volunteers who offer support to women who have lost a pregnancy

Royal College of Obstetrician and Gynaecologists (www.rcog.org.uk)—Provides online information for patients covering a wide range of topics in women’s health, including ectopic pregnancy

Clinically stable women with small (<3 cm) ectopic pregnancies and low HCG should be given the choice between expectant, medical, and surgical treatment, depending on their personal preferences, perception of the risks associated with different management options, and their willingness to comply with follow-up visits. Women should be offered patient information leaflets containing details of different management options and long term outcomes to help them make an informed choice about their treatment.

In a recent online survey conducted by the Ectopic Pregnancy Trust, a UK charity, 90% of women ranked the preservation of their future fertility as their primary concern. A woman’s confidence that her carers will do their best to protect her fertility may be crucial for ensuring good emotional and physical recovery after ectopic pregnancy. Some women leave hospital with no information or access to additional support. Health professionals who look after women with ectopic pregnancy should strive to provide them with consistent and evidence based information about the diagnosis and should direct them towards emotional support to help them overcome any physical and emotional trauma posed by ectopic pregnancy.

Does ectopic pregnancy affect future fertility?

The estimation of reproductive outcomes relies mainly on data from observational studies. Reported rates of spontaneous intrauterine pregnancy after salpingectomy range from 38% to 66%.^{23 29 w22} Women who underwent surgery with tubal conservation have a tendency towards higher intrauterine pregnancy rates (62% to 89%).^{29 w22} Reported rates of recurrent ectopic pregnancy after surgery range from 6% to 18%, with a trend towards higher rates after salpingotomy.^{w16 w17 w22-w24} Fertility outcomes after expectant management and medical treatment with methotrexate are not significantly better than after surgery.^{23 29 30 w25}

What are the recommendations from clinical guidelines?

The RCOG has produced a clinical guideline on the management of tubal ectopic pregnancy.²¹ The guideline recommends that laparoscopic surgery should be used in preference to laparotomy in clinically stable patients. Salpingotomy should be used in preference to salpingectomy in women with a damaged or absent contralateral tube. Medical treatment with methotrexate should be offered as an option to suitable women—that is, those with minimal symptoms and serum HCG less than 3000 IU/L.

The American College of Obstetricians and Gynecologists has issued clinical guidance on the medical management of ectopic pregnancy with methotrexate.³¹ The guideline states that comparisons of medical treatment with tube preserving surgery (salpingotomy) showed no differences in overall rates of tubal preservation, tubal patency, repeat ectopic pregnancy, or future pregnancies.

Guidelines from the Faculty of Sexual and Reproductive Healthcare of the RCOG on contraceptive use state that the use of hormonal contraception, intrauterine contraceptive devices, and sterilisation should not be restricted in women with a history of ectopic pregnancy.³² In women using

progesterone only contraceptives methods, inhibition of ovulation may be the preferred choice.

Psychological support

Ectopic pregnancy not only results in the loss of a pregnancy but may also threaten a woman's life. Although the development of more sophisticated diagnostic tools and an increasing choice of treatment options are welcome, they may also cause confusion and anxiety in women. The Ectopic Pregnancy Trust, a UK charity, has found that many women with suspected or diagnosed ectopic pregnancy need additional information about their condition. Individual women respond very differently to ectopic pregnancy, and the response may depend on past health problems, the standard of medical and nursing care received, and the quality of communication with health professionals. Some women ask for emotional support, whereas others seek contact with women who have experienced similar problems themselves. Some women are severely emotionally traumatised and may require dedicated one to one counselling and long term psychological support. Women diagnosed with ectopic pregnancy are particularly anxious to ensure that they are treated in a way that will preserve their future fertility. The Ectopic Pregnancy Trust has found that many women contact its helpline in a state of confusion and emotional turmoil. Many women need reassurance that they will be able to conceive again and have a normal pregnancy. There is often an underlying fear of recurrent ectopic pregnancy, which would involve going through the same traumatic experience again. Some women will not try to become pregnant again because they do not feel emotionally strong enough.

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