Ectopic pregnancy

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Abstract

Ectopic Pregnancy (EP) occurs in around 1–2% of all pregnancies, and is associated with significant morbidity and mortality. Over 98% implant in the Fallopian tube. Women with risk factors, or early pregnancy symptoms of abdominal pain or vaginal bleeding are assessed by Early Pregnancy Assessment Services. The mainstay of diagnosis is by transvaginal ultrasound supported by serial serum human chorionic gonadotrophin (hCG) measurements. Management of tubal EP has moved away from surgery with growing experience with medical (methotrexate) and expectant management for selected women. Surgery will always have a role in the management of women with EP who are acutely unwell, where medical management is not likely to work, and for failed medical management. Ultrasound diagnostic criteria for non-tubal EP have been established and these cases are best managed on an individual basis. Future areas for research are the need to shorten the time to diagnosis an EP and the use of novel combination medical treatments. Future areas of medical education are the critical need to teach healthcare professionals to consider pregnancy related causes of collapse in all women of reproductive age.

Keywords ectopic pregnancy; heterotopic pregnancy; human chorionic gonadotrophin; laparoscopy; methotrexate; salpingectomy; salpingotomy

Background

An ectopic pregnancy (EP) occurs when a fertilized oocyte implants outside the normal uterine cavity, and in the majority of women usually represents the loss of a desired pregnancy. Over 98% implant in the Fallopian tube but non-tubal EP can be found implanted, for example, in the ovary, cervix, interstitium, omentum and caesarean section scars. A heterotopic pregnancy occurs when a pregnancy implants in the uterus with another pregnancy simultaneously implanting outside the uterus. The aetiology of an EP remains uncertain.

Each EP puts the woman at risk of morbidity and mortality, in the short term, from intraperitoneal bleeding or management-related complications, and longer term, from sub-fertility and pain. The most recent MBRRACE report (2016) reveals almost 5% of all maternal deaths in the reporting period are directly related to EP. In five out of the nine women who died from EP the diagnosis was never considered, and death may have been avoided because EP can be treated easily medically or surgically.

The psychological harm from EP in terms of pregnancy loss is apparent but more difficult to research and quantify. Current areas of research includes studies to improve the time to making the diagnosis of an EP, risk stratification of symptomatic women at first presentation, and improving the time to resolution with novel medical management strategies.

Presentation and clinical symptoms

Around 30 women have an EP diagnosed in the UK every day (approximately 12,000 cases each year). EP present with a wide range of clinical presentations, from no symptoms at all to profound circulatory collapse. The presence of unilateral abdominal pain rather than vaginal bleeding tends to suggest EP rather than miscarriage but this is by no means conclusive. A high index of suspicion in all women of reproductive age until an EP is confirmed or excluded is needed. Between 6 and 16% of women who attend emergency departments in the first trimester with pain or vaginal bleeding with have an EP. Non-gynaecological symptoms such as diarrhoea, vomiting or dizziness may predominate, and may not trigger consideration of pregnancy testing at first assessment. For women of reproductive age who present acutely unwell, a pregnancy test is essential to confirm or refute the possibility of pregnancy underlying the symptoms. In such acute cases, catheterisation may be required to obtain urine for human chorionic gonadotrophin (hCG) testing, or serum levels can be checked.

When neither pregnancy nor EP was considered in the differential diagnosis of the collapsed woman of reproductive age, MBRRACE reports attending clinicians have presumed the collapse was due to massive pulmonary embolus, and the ensuing thrombolysis ensured mortality. A 'FAST' (Focused Assessment by Sonography for Trauma) scan to identify intraperitoneal bleeding might have changed the outcome. EP should be considered in women presenting with collapse, dizziness, acute abdominal/pelvic pain or with gastrointestinal symptoms, including diarrhea or vomiting regardless of whether or not she is known to be pregnant (Figure 1).

Repeated presentation in early pregnancy to medical services with abdominal or pelvic pain, or pain that requires opiates, warrants urgent assessment by a gynaecologist and timely ultrasound.

Women with EP often have no identifiable factors. Risk factors for EP include past or present *Chlamydia trachomatis* infection, cigarette smoking, previous EP, pelvic surgery, termination of pregnancy, intrauterine contraceptive use and use of assisted reproductive technology amongst others.

Around 150 Early Pregnancy Assessment (EPA) Units cover the UK to provide a service to women at high risk of EP, such as

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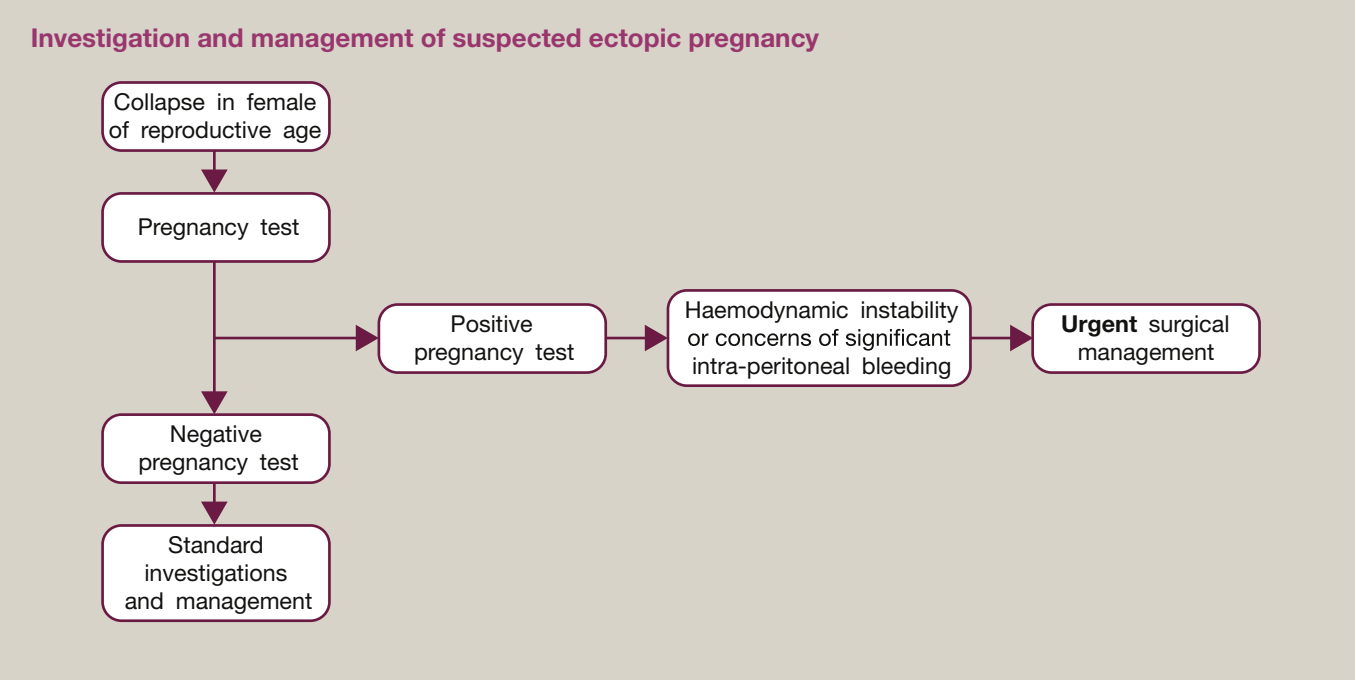

Figure 1

those with symptoms of pain and vaginal bleeding in early pregnancy. EPA services will have different risk assessment and stratification during first contact with the patient, typically by telephone or GP referral. Due to resource availability, the availability and timing of investigations that can be offered may not be ideal. It is recommended that NHS trusts offer a gold-standard 'seven days per week' EPA service, and women outwith hours service are typically assessed by on-call gynaecology medical or nursing staff.

Diagnosis

After EPA risk stratification based on clinical history and current symptoms, the main stay of EP diagnosis is transvaginal ultrasound scan (TVUSS) supported by quantitative serum hCG.

Amongst all women who experience first trimester pain or bleeding and present to an EPA service, around 70% will have an intrauterine pregnancy identified on ultrasound of which approximately 40% will be confirmed as viable at the same examination. These proportions will vary considerably between centres depending on the underlying prevalence and nature of referral i.e. from GP referral to 'Walk-In' centres.

Depending on the population served by the EPA service, around 10% of women will have a diagnosis of miscarriage made on the initial ultrasound. Women with a TV USS diagnosis of intrauterine pregnancy, absent fetal heart activity and a fetal pole under 7 mm, require a follow up ultrasound after a minimum of seven days. Minimal development on interval ultrasound would confidently exclude an ongoing pregnancy. This avoids the false positive diagnosis of miscarriage and is generally required before active management can be started.

Around 10% will be classified as a Pregnancy of Unknown Location (PUL), discussed below, and between 2 and 3% will have an EP. Of those with an EP the majority will have an implantation site within the Fallopian tube, ideally positively identified by visualising an adnexal mass that moves separate to the ovary, with the following scan findings:

- 50–60% will have a heterogeneous non-cystic adnexal mass
- 20–40% will have an empty extra-uterine gestational sac
- 15–20% will have an extra-uterine gestational sac with a fetal pole (with or without visualised fetal heart activity)

TV USS had a sensitivity 87–99% and specificity of 94–99%, with positive predictive value of 96.7% and a negative predictive value of 99.4% for identification of EP.

Correlation of less conclusive scan findings with quantitative measurement of serum hCG can be helpful. The 'discriminatory zone' is the level of serum hCG above which a normally sited and normally developing pregnancy should always be identified on an ultrasound. With the use of TVUSS, this is between 1000 and 1500 IU/L. Serial hCG measurements around 48 hours apart are also helpful in this regard, with both the trend for a >66% increase and the absolute levels guiding timing of imaging. Many EP in modern practice are diagnosed with a hCG under 1000 IU/L and it is important to remember the discriminatory zone is related to the visualization of viable intra-uterine pregnancies. Serum progesterone level is not useful in predicting EP.

EPs are often associated with a below optimal (<66%) rise in hCG over 48 hours, or a largely static hCG. Miscarriage may become clinically apparent due to the amount of vaginal bleeding, and would correspond to a fall in hCG levels, with a 50% decrease over 48 hours meaning a viable pregnancy is very unlikely.

In cases where imaging is technically sub-optimal, caution is needed, with a low threshold for repeating diagnostic testing and a high threshold for intervention until a firm diagnosis is made. This is the case with the presence of uterine fibroids, congenital uterine abnormalities and where only trans-abdominal scans are acceptable to the woman. Where the clinical suspicion of EP is very high,