Ectopic pregnancy - Management

Scenario: Presentation of ectopic pregnancy

What are the clinical features of ectopic pregnancy?

Ectopic pregnancy must be excluded before diagnosing any other cause of pain or bleeding, particularly in the first trimester of pregnancy.

- An ectopic pregnancy typically presents between 5 weeks' and 14 weeks' gestation.
- An ectopic pregnancy may also be asymptomatic and may be found incidentally on an early pregnancy scan.
- The pregnancy test is almost always positive. However, a negative pregnancy test in a woman with clinical features of ectopic pregnancy does not absolutely exclude an ectopic pregnancy; but does make the diagnosis highly unlikely.
- **Typical symptoms** include:
  - Amenorrhoea. However, many women may appear not to have missed a menstrual period, as vaginal bleeding may occur at the time of the expected period.
  - Lower abdominal or pelvic pain, which may vary from mild to severe and is often unilateral.
  - Abnormal vaginal bleeding, which rarely exceeds the normal menstrual flow. It is usually intermittent, and either bright or dark red.
- **Less common symptoms** include:
  - Shoulder tip pain on lying down (referred pain due to peritoneal irritation).
  - An episode of fainting or dizziness.
  - Vomiting or diarrhoea.
- **On examination** there may be:
  - Cardiovascular shock (with low blood pressure, rapid pulse).
  - Abdominal tenderness, rebound tenderness, guarding, rigidity, or abdominal distension.
  - Cervical motion tenderness.
  - Adnexal tenderness.

Basis for recommendation

The clinical features of ectopic pregnancy

- These recommendations are based on expert advice in textbooks [Klentzeris, 2003; Drife and Magowan, 2004a; Seeber and Barnhart, 2008] and non-systematic review articles [Seeber and Barnhart, 2006; Porter et al, 2008; Barnhart, 2009], and the opinion of CKS expert reviewers.
- All the CKS expert reviewers were of the opinion that if a urinary pregnancy test is negative, then an ectopic pregnancy is virtually ruled out. Several pointed out the rare possibility of a false-negative

pregnancy test result and advised a repeat urine pregnancy test or serum beta-human chorionic gonadotropin (beta-hCG) measurement as a possibility. It was emphasized that the result needed to be considered with the clinical findings, and if discordant then an urgent assessment should be arranged.

Physical symptoms and signs are variable

- The classical triad of bleeding, abdominal pain, and amenorrhoea is *not* present in many women, and symptoms and signs are often non-specific. The diagnosis can only be confirmed in secondary care [Seeber and Barnhart, 2008].

Diarrhoea and vomiting

- The report on the confidential enquiry into maternal deaths 2007 emphasized that all clinicians need to be aware of the atypical presentation of some ectopic pregnancies. Ectopic pregnancies are often associated with diarrhoea and vomiting and may mimic gastrointestinal disease [CEMACH, 2007].

What else might cause pain or bleeding in early pregnancy?

Pregnancy-related bleeding in the first and second trimesters may also occur with:

- **Threatened miscarriage**
  - Presents with vaginal bleeding in the first 24 weeks of pregnancy.
  - Bleeding is typically scanty, varying from a brownish discharge to bright red bleeding, and may recur over several days.
  - Midline cramping pain or lower backache, when it occurs, usually develops after the onset of bleeding.
  - Tenderness may be present on abdominal or pelvic examination. If present, ectopic pregnancy must excluded.
  - The internal cervical os is closed.
  - It may be possible to hear a fetal heartbeat if the pregnancy is viable, but this may be difficult to hear with a Sonicaid before 12–14 weeks' gestation. However identifying a fetal heartbeat does not mean that the pregnancy will be viable. Rarely, a fetal heartbeat may be heard in an ectopic pregnancy; a heartbeat may also be present if there is an heterotopic pregnancy, which is a small but real risk after in vitro fertilization.
- **Inevitable miscarriage**
  - Presents with the same symptoms as threatened miscarriage but on examination the cervical os is found to be open or products of conception are found.
- **Completed miscarriage**
  - Presents with resolving symptoms and signs of a threatened miscarriage.
  - The internal cervical os is closed.
- **Molar pregnancy**

- Molar pregnancy commonly presents with bleeding in early pregnancy.
- It is more likely if:
- Bleeding is heavy and prolonged.
- Symptoms of pregnancy are exaggerated.
- The uterus is large for dates.
- Vesicles are passed.

Non-pregnancy-related causes of bleeding in early pregnancy to consider include:

- Cervicitis, cervical ectropion, or cervical polyps.
- Vaginitis.
- Cancer of the cervix, vagina, or vulva.
- Trauma of the cervix, vagina, or vulva.
- Haemorrhoids.
- Urethral bleeding.

Pregnancy-related causes of abdominal pain in the first and second trimesters may also occur with:

- Miscarriage.
- Ruptured ovarian corpus luteal cyst.
- Pregnancy-related degeneration of a fibroid.

Non-pregnancy-related causes of abdominal pain include:

- Musculoskeletal pain.
- Urinary tract infection.
- Constipation.
- Irritable bowel syndrome.
- Pelvic inflammatory disease.
- Appendicitis.
- Renal colic.
- Bowel obstruction.
- Adhesions.
- Ovarian cyst (due to torsion, rupture, or bleeding).
- Torsion of a fibroid.

- Pelvic vein thrombosis.

Basis for recommendation

- These recommendations are based on the those reported by experts in textbooks [Drife and Magowan, 2004a; Porter et al, 2008] and advice from CKS expert reviewers.

Ectopic pregnancy - Management

Scenario: Suspected ectopic pregnancy

How should I manage someone with suspected ectopic pregnancy?

- **For women with severe pain or bleeding or who are shocked (hypotensive, tachycardic):**
  - Arrange immediate ambulance transfer to hospital without undertaking a pelvic examination.
  - Resuscitate with intravenous fluids if available.
- **For women with a suspected ectopic pregnancy** who are hemodynamically stable, discuss the clinical features, risk factors, pregnancy test result, and the need for urgent assessment with the specialist on call.

Basis for recommendation

Women with severe pain or bleeding or who are shocked

- Immediate admission to hospital is accepted as good clinical practice.

Advice not to perform a pelvic examination if a tubal rupture is suspected

- A pelvic examination may be unnecessary and dangerous because [Klentzeris, 2003]:
  - The examination is usually difficult — the woman is very uncomfortable and so assessment may be inadequate.
  - Information gained is limited because of generalized haemoperitoneum and pain.
  - It could cause total rupture of the ectopic pregnancy.
  - It may delay management.

Suspected ectopic pregnancy when the woman is hemodynamically stable

- Emergency assessment of a woman with suspected ectopic pregnancy is accepted good clinical practice, to reduce the risk of death from a ruptured ectopic pregnancy.
- All the CKS expert reviewers were of the opinion that if a urinary pregnancy test is negative, then an ectopic pregnancy is virtually ruled out. Several pointed out the rare possibility of a false-negative pregnancy test result and advised a repeat urine pregnancy test or serum beta-human chorionic gonadotropin (beta-hCG) measurement as a possibility. It was emphasized that the result needed to

be considered with the clinical findings, and if discordant then an urgent assessment should be arranged.

How is a diagnosis made in secondary care?

- If an ectopic pregnancy is suspected from clinical features, the first step is to carry out a trans-vaginal ultrasound scan which may demonstrate:
  - An intrauterine pregnancy.
  - A definite or probable ectopic pregnancy.
  - No pregnancy (intrauterine or ectopic) visible, (that is, a pregnancy of unknown location).
- If the woman is clinically unstable or symptomatic, or the scan findings strongly suggest ectopic pregnancy, then laparoscopy is indicated.
- A pregnancy of unknown location is diagnosed if the woman is stable and there is no pregnancy (intrauterine or ectopic) visible on the trans-vaginal scan and no other significant pelvic abnormality, and if the serum beta-human chorionic gonadotropin (hCG) level is in the pregnant range (> 5 iU/L). Local protocols/algorithms are followed, using serial serum beta-hCG levels with or without progesterone levels, repeat trans-vaginal scans, and laparoscopy (if indicated) to distinguish between and manage the three possible diagnoses:
  - A miscarriage.
  - An intrauterine pregnancy.
  - An ectopic pregnancy.

Basis for recommendation

- The basis for these recommendations is expert advice in textbooks [Klentzeris, 2003; Seeber and Barnhart, 2008] and review articles [Seeber and Barnhart, 2006; Barnhart, 2009].

What treatments are available in secondary care?

Ruptured ectopic pregnancy

- Shocked women will receive appropriate resuscitation and immediate surgery (laparotomy or laparoscopy) to prevent further blood loss and worsening symptoms.

Subacute ectopic pregnancy

- Management is individually tailored, based on the woman and the facilities and expertise of the local unit.
- If the woman is haemodynamically stable, the options are surgical, medical, or expectant management. All women (except those who have had a salpingectomy) will be followed up according to local protocols to ensure that serum beta-human chorionic gonadotropin (hCG) levels decrease at an acceptable rate until non-pregnant levels are reached (this may take up to 6 weeks).
- **Surgical management**

- Laparoscopic surgery is usual, either salpingectomy (removal of the Fallopian tube with the ectopic pregnancy) or salpingotomy (incision into the Fallopian tube) if the contralateral tube appears abnormal at laparoscopy. After salpingotomy, serial serum beta-hCG measurements are carried out to identify women who have persistent trophoblastic tissue in the Fallopian tube. Single-dose intramuscular methotrexate is usually used for the treatment of persistent trophoblast, rather than repeat surgery.

- **Medical management**

- Methotrexate is most commonly used. Women most suitable for this treatment are those who have minimal symptoms, an absent fetal heartbeat, and a serum beta-hCG level of less than 3000 iU/L.

- Intramuscular methotrexate is given as a single dose.

- A further dose of methotrexate is given if serum beta-hCG levels have not decreased in the first 4–7 days.

- Following treatment with methotrexate:

- There remains a 7% chance of ruptured ectopic pregnancy with medical treatment, despite decreasing serum beta-hCG levels. Beta-hCG levels are monitored according to local protocols until non-pregnant levels are reached (this may take up to 6 weeks).

- Adverse effects include abdominal pain following treatment and, more rarely, conjunctivitis, stomatitis, and gastrointestinal upset.

- Some women with abdominal pain will need to be admitted for observation and assessment, as it can be impossible to distinguish pain due to tubal abortion from pain due to tubal rupture.

- Sexual intercourse should be avoided until symptoms have resolved.

- Reliable contraception should be used for 6 months post-treatment as there is a possible teratogenic risk to immediate future pregnancies from methotrexate.

- **Expectant management (watchful waiting)**

- Expectant management is an option for women:

- Who have a pregnancy of unknown location, and have minimal or no symptoms, and are clinically stable.

- Who have an ultrasound diagnosis of ectopic pregnancy, are asymptomatic and clinically stable, and have a serum beta-hCG level that is initially less than 1000 iU/L.

- There is still a possibility of ruptured ectopic pregnancy despite declining serum beta-hCG levels.

- Women are given clear instructions about the importance of attending for follow up and of staying within easy access to the hospital which is treating them.

- In women with a pregnancy of unknown location, active intervention will be considered if symptoms of ectopic pregnancy occur or levels of serum beta-hCG fail to decrease at an acceptable rate.

- **All non-sensitized rhesus-negative women should receive anti-D immunoglobulin after an ectopic pregnancy.**

Basis for recommendation

Ruptured ectopic pregnancy

- These recommendations are based on expert advice in a guideline produced by the Royal College of Obstetricians and Gynaecologists [RCOG, 2004].

Surgery

- These recommendations are based on expert advice in a guideline produced by the Royal College of Obstetricians and Gynaecologists [RCOG, 2004].

- Persistent trophoblast occurs in about 8% of women after laparoscopic salpingotomy and in about 4% of women after open salpingotomy [RCOG, 2004]. The risk of persistent trophoblast is higher in women who have preoperative serum beta-hCG levels greater than 3000 iU/L, a rapid preoperative increase in serum beta-hCG, or active tubal bleeding. Persistent trophoblast is detected by the failure of serum beta-hCG levels to decrease as expected following initial treatment.

Methotrexate

- These recommendations are based on expert advice in a guideline produced by the Royal College of Obstetricians and Gynaecologists [RCOG, 2004].

- If methotrexate therapy is being considered, laparoscopy is not necessary to make a diagnosis as trans-vaginal ultrasonography combined with serum beta-hCG measurement allows ectopic pregnancy to be diagnosed with confidence.

- Data from large uncontrolled studies show that less that 10% of women who have been given intramuscular methotrexate require surgical intervention.

- Pooled data from uncontrolled studies show that:

- About 15% of women require more than one intramuscular dose of methotrexate.

- 7% experience tubal rupture during follow up.

- 75% experience abdominal pain during treatment.

Expectant management

- These recommendations are based on expert advice in the guidance on the management of tubal pregnancy from the Royal College of Obstetricians and Gynaecologists [RCOG, 2004].

- The Royal College of Obstetricians and Gynaecologists reviewed the available evidence [RCOG, 2004]:

- Pregnancies of unknown location:

- Five observational studies concluded that 44–69% of pregnancies of unknown location resolve spontaneously.
- Intervention was required in 23–29% of women.
- Pregnancies with an ultrasound diagnosis of ectopic pregnancy:
- Seven observational studies concluded that expectant management was successful in 67% of women.
- A favourable outcome was more likely with an initial serum beta-hCG level of less than 1000 iU/L or a rapidly decreasing level, or a reduction in the size of the adnexal mass after 7 days.

Anti-D immunoglobulin

- These recommendations are based on guidelines from the Royal College of Obstetricians and Gynaecologists to reduce the risk of maternal sensitization [RCOG, 2006].

Ectopic pregnancy - Management

Scenario: Review following an ectopic pregnancy

What follow up should I offer following an ectopic pregnancy?

- **Ensure that arrangements for routine antenatal care are cancelled if they have been started.**
- **Give the woman the opportunity to discuss any questions she has about the ectopic pregnancy, the risk of recurrence, and her future fertility.** About 60% of women who have had an ectopic pregnancy are able to have a subsequent spontaneous intrauterine pregnancy.
- **Psychological well-being.** Ensure that following an ectopic pregnancy, the woman is offered follow up to:
  - Assess her psychological well-being and offer counselling, if appropriate. Be aware that:
  - Grief, anxiety, and depression are common following pregnancy loss.
  - Grief following pregnancy loss is comparable in nature, intensity, and duration to grief reactions in people suffering other types of major loss.
  - Distress is commonly at its worst 4–6 weeks after pregnancy loss and may last 6–12 months.
- **Future pregnancies.** Advise the woman that in the future she should inform her GP as soon as she suspects she is pregnant. This is because, even if she is asymptomatic, she will need an early ultrasound scan at 6–7 weeks to establish the location and viability of the pregnancy.
- Inform the woman that advice, information, and support for those who have had an ectopic pregnancy is available through the Ectopic Pregnancy Trust.
- Information leaflets are also available from the Miscarriage Association on:
  - Ectopic Pregnancy (pdf).
  - Pregnancy loss: how you might feel (pdf).

Basis for recommendation

Assessing how the woman is coping with the pregnancy loss

- Recommendations to assess for psychological distress following ectopic pregnancy are based on:
  - Expert opinion that the psychological effect of an ectopic pregnancy is often overlooked, as an ectopic pregnancy may not be viewed in the same way as other pregnancy loss [Tay et al, 2000].
  - Expert opinion that women who have had an ectopic pregnancy may have a similar grief reaction to women experiencing miscarriage, but also have the added stress of a potential reduction in fertility [Tay et al, 2000].
  - Extrapolated evidence on the prevalence and severity of psychological distress following miscarriage [Brier, 1999; Brier, 2004; Brier, 2008].

Future fertility

- Figures regarding future intrauterine pregnancy rate were obtained from a non-systematic review [Barnhart, 2009]. Limited evidence from a Cochrane systematic review (the trials were of poor methodological quality) suggests that the spontaneous intrauterine pregnancy rate is similar following salpingotomy or methotrexate therapy [Hajenius et al, 2007]. For further information on the management of infertility, see the CKS topic on Infertility.

Management in future pregnancies

- All the CKS expert reviewers recommended early assessment in future pregnancies.

The Ectopic Pregnancy Trust

- The Ectopic Pregnancy Trust was established in 1998 and aims to:
  - Raise awareness of ectopic pregnancy amongst women of childbearing age, the medical profession, and the general public.
  - Relieve the emotional and physical distress of women experiencing ectopic pregnancy, and provide ongoing support to them when they are ready to try for another baby, and to those women unable to conceive.

What advice should I give about contraception?

- A history of ectopic pregnancy is not a contraindication to any form of hormonal contraception or intrauterine device.
  - The woman should be informed that the risk of pregnancy is small if using an intrauterine device or levonorgestrel-releasing intrauterine system (LNG-IUS). However, if she does conceive, the risk of ectopic pregnancy is high; particularly if she has an LNG-IUS in situ.
  - Reliable contraception should be used for 6 months post-treatment for an ectopic pregnancy with methotrexate, as there is a possible teratogenic risk due to the prolonged effects of methotrexate.

Basis for recommendation

- These recommendations are based on the UK Medical Eligibility Criteria (UKMEC) for contraceptive use [FFPRHC, 2006] and a guideline from the Faculty of Sexual and Reproductive Healthcare [FSRH, 2007].

Risk of a further ectopic pregnancy with an intrauterine (IUD) device or levonorgestrel-releasing intrauterine system (LNG-IUS) in situ

- A copper IUD reduces the frequency of both extrauterine and intrauterine pregnancies but is more effective at preventing intrauterine compared with extrauterine pregnancies [Guillebaud, 2003].
  - Very few sperm are able to pass through the copper-containing uterine cavity to reach an egg and implant into a damaged tube, but the conceptus has even less chance of implanting in the uterus. Therefore, although the ratio of ectopic pregnancies to uterine pregnancies is increased in women with a copper IUD, the overall incidence of ectopic pregnancy is very low, and is estimated at 0.12 per 100 women-years The risk of ectopic pregnancy for women with an LNG-IUS is estimated to be 0.06 per 100 woman-years [Guillebaud, 2003; ABPI Medicines Compendium, 2009b].

- A meta-analysis of 16 case control studies carried out between 1977 and 1994 investigated the relationship between intrauterine device (IUD) use and ectopic pregnancy [Xiong et al, 1995].

  - After adjusting for confounding factors, women with an ectopic pregnancy were about six times more likely to have an IUD in situ than age-matched pregnant controls (OR 6.29, 95% CI 4.23–9.34). The authors concluded that a pregnancy with an IUD in situ is more often an ectopic pregnancy than a pregnancy without an IUD in situ.

  - Detailed information about the type of IUD was not available in most of the studies. Many of the studies used older types of non-medicated IUDs (such as the Dalkon Shield and the Lippes loop); only six studies looked at copper IUDs. As copper IUDs are more effective in preventing pregnancy, it is likely that the ectopic pregnancy rate associated with IUD use is now less than reported in this study.

- The risk seems to be particularly high if the woman has an LNG-IUS in situ.

  - A questionnaire sent to 17,360 women using the LNG-IUS identified 132 pregnancies [Backman et al, 2004]. Review of the hospital records concerning the pregnancies of 108 of these women found that 40 pregnancies had occurred with an LNG-IUS in situ. Fifteen pregnancies were intrauterine and 25 were ectopic. Therefore if a pregnancy does occur in a woman with an LNG-IUS in situ, it is very likely to be ectopic.

Teratogenic risk with methotrexate

- The manufacturer's summary of product characteristics recommends that conception should be avoided for at least 6 months after methotrexate administration [ABPI Medicines Compendium, 2009a].