Ectopic pregnancy deaths: what should we be doing?

Emma Kirk, George Condous, Tom Bourne

Ectopic pregnancy is the leading cause of maternal mortality in the first trimester of pregnancy. A greater awareness of risk factors and improved diagnostic techniques now allow ectopic pregnancies to be identified before the development of life-threatening events. Non-surgical management options also decrease maternal morbidity.

An ectopic pregnancy is any pregnancy where the fertilized ovum implants outside of the intrauterine cavity. The majority occur in the fallopian tubes, but other sites include the cornua of the uterus, ovary, cervix, abdominal cavity and caesarean section scars.

Although the incidence of ectopic pregnancy has increased over the last 25 years, concurrently there has been a decrease in associated mortality. In the UK 11.1 per 1000 pregnancies are ectopic pregnancies with almost 32 000 diagnosed annually. It is the fourth leading cause of direct maternal death, accounting for 80% of first trimester deaths according to the 1997–1999 confidential enquiry into maternal deaths (CEMD) (Lewis and Drife, 2001).

PREVENTION

The cause of many ectopic pregnancies is not known, however, in a significant proportion of cases it is thought that chlamydia infection is implicated in the aetiology. A study in Sweden suggested that a greater public awareness of the risk of chlamydia, as well as screening programmes, is associated with a reduction in the incidence of ectopic pregnancy (Egger et al, 1998). The authors would support a similar approach being used in the UK.

DIAGNOSIS

The CEMD report states that most of the women who died from ectopic pregnancy were misdiagnosed in the primary care or accident and emergency (A&E) setting. Its recommendations that all clinicians should be made aware of atypical clinical presentations of ectopic pregnancy are sensible. In the authors' view it is also important to emphasize that women with pelvic pain must have a urinary pregnancy test whether they are seen in the community or hospital setting.

Classically the most common presentation in symptomatic women is unilateral abdominal pain with vaginal spotting, usually occurring after 6–8 weeks of amenorrhoea. Shoulder tip pain, vaginal bleeding, syncope and hypovolaemic shock may also be present. However, it may also mimic gastrointestinal and urinary tract disease. Other women may be completely asymptomatic.

At one time medical students were taught that a young woman with pelvic pain and a positive pregnancy test has an ectopic pregnancy until proved otherwise. This message seems to have been lost. Furthermore the availability of pregnancy testing in primary care would be an advantage in the assessment of these patients. However, it is not possible to exercise clinical judgment in these women in primary care, such women need to have a transvaginal scan (TVS) in order to confirm the location of the pregnancy.

The Royal College of Obstetricians and Gynaecologists (RCOG) has recommended that all maternity units should provide an early pregnancy assessment service with direct access for GPs and patients (RCOG, 2000). The first trimester TVS should be made available to all women. Not only can the pregnancy be accurately dated and viability confirmed, but most importantly the location of the pregnancy can be ascertained. It is clearly advantageous to place facilities for TVS and the rapid immunoassay of serum human chorionic gonadotrophin (hCG) and progesterone at the point of initial contact with the patient. The cost and care benefits of these units have been documented (Bigrigg and Read, 1991). With the advent of these units,

Dr Emma Kirk is Clinical Research Fellow, **Mr George Condous** is Clinical Research Fellow and **Mr Tom Bourne** is Consultant Gynaecologist, Early Pregnancy Unit, St George's Hospital, London SW17 0QT

Correspondence to: Dr E Kirk

more clinically asymptomatic ectopic pregnancies are detected before they have ruptured. This has led to an expansion in the treatment options available. However, the quality of the ultrasonography provided in some units is uncertain and more training is required in this area.

Unfortunately, a significant proportion of hospitals in the UK still perform transabdominal scans (TAS) to assess early first trimester pregnancy. The authors believe that TVS should be the first-line approach. It is acceptable to women and its greater resolution allows the diagnosis of subtle intrauterine gestational sacs and even ectopic pregnancies. An intrauterine gestational sac can be visualized using TAS when the serum hCG level is >6500 U/litre (Romero et al, 1985). In comparison, using TVS an intrauterine gestational sac can be seen at serum hCG levels as low as 1000 U/litre (Cacciatore et al, 1990). TAS is not only outdated, but also potentially harmful because of its low negative predictive value. The use of TAS also creates confusion when assessing for the presence of either a true sac or a pseudosac (a misnomer) which represents a fluid collection or debris in the cavity. Although it is possible to confuse this with an early gestational sac with TAS, misinterpretation is less likely using high-resolution transvaginal probes. Even if one visualizes an intrauterine sac using TAS, with the increasing numbers of assisted conceptions, one cannot confidently rule out heterotopic pregnancy.

Women with a high risk of ectopic pregnancy should be advised to attend an early pregnancy unit (EPU) as soon as possible in the pregnancy. Risk factors include a history of pelvic infection, previous ectopic pregnancy, a history of tubal surgery, or fertility treatment. Heterotopic pregnancy should also be considered in those who have undergone in vitro fertilization (IVF) or gamete intrafallopian transfer (GIFT).

TVS is the imaging modality of choice for ectopic pregnancy and should be offered to all women with abdominal pain with or without vaginal bleeding in the first trimester. Using this approach 80–90% of ectopic pregnancies can be visualized (Condous et al, 2003). The authors believe that ectopic pregnancy should not be diagnosed on the basis of the absence of an intrauterine pregnancy, but rather by the positive visualization of an adnexal mass using TVS. It is no longer acceptable to read a report that says 'intrauterine pregnancy not visualized, an ectopic pregnancy cannot be excluded'. Such scans are unhelpful for the clinician and worrying for the patient. The authors assert that if an intrauterine pregnancy can be excluded using TVS, so too can ectopic pregnancy. When there is no pregnancy either inside or outside the uterus, these women should be classified as having pregnancies of unknown location (PUL) and not as being possible ectopics, being closely followed up with serum hormone assays and ultrasound.

The appearance of an ectopic pregnancy can be highly variable on TVS. There may be an inhomogeneous non-cystic adnexal mass (blob sign), a gestational sac with a hyperechoic ring (bagel sign) or a gestational sac with visible embryo with or without cardiac activity. Blood or serous fluid may be seen within the pelvic cavity.

In the hospital setting most problems arise when a pregnancy cannot be visualized on TVS. These have been termed PUL. While the majority of these pregnancies resolve spontaneously, 14–25% of them will actually have an ectopic pregnancy (Hajenius et al, 1995; Banerjee et al, 1999). These women should undergo serial hCG and progesterone measurement until a diagnosis can be made and appropriate management instigated. More recently mathematical models have been proposed to improve overall test performance (Condous et al, 2004). Laparoscopy, although still performed in some units as a first-line management option for some PULs, is no longer acceptable practice. It should only be considered in those who are symptomatic. Clear unambiguous protocols for the management of these patients are needed in all units.

MANAGEMENT

Surgical

Historically laparotomy with salpingectomy has been the treatment of choice for ectopic pregnancy. Now with the advances in minimal access surgery, laparoscopy should be first-line surgical management. Laparoscopic procedures have been associated with shorter operating times, less intraoperative blood loss, shorter hospital stays and lower analgesic requirements (Murphy et al, 1992). There is, however, still a role for laparotomy as a first-line management if it is the only way further blood loss can be prevented in an already haemodynamically unstable patient.

There is no clear evidence to suggest that salpingotomy should be performed in preference to salpingectomy in the absence of any other pelvic disease (RCOG, 2004). There are no randomized-controlled trials specifically comparing salpingotomy to salpingectomy. However, a study has showed a higher subsequent pregnancy rate (both intra- and extrauter-

ine) in those undergoing salpingotomy (Bangsgaard et al, 2003). Salpingotomy does, however, expose a woman to an increased risk of tubal bleeding after surgery and the possible development of persistent trophoblastic disease. For those with contralateral tubal disease laparoscopic salpingotomy is considered to be the primary treatment, with higher subsequent intrauterine pregnancy rates compared to salpingectomy (RCOG, 2004). In the authors' unit, if surgery is indicated, 90% of ectopic pregnancies are managed with salpingectomy.

Medical

Medical management has become important for those with asymptomatic tubal ectopic pregnancies and for those with non-tubal ectopic pregnancies for which a surgical approach is more hazardous. In general medical management is under-utilized.

In the UK, systemic methotrexate at a dose of 50 mg/m^2 is the most widely used medical treatment. It has been reported to be successful in almost 90% of cases (Glock et al, 1994). It should only be used in haemodynamically stable women. Women most suitable for methotrexate therapy have a serum hCG <3000 iu/litre and minimal symptoms (RCOG, 2004). Successful outcome is dependent on the initial hCG measurement (less likely with higher levels), the size of the ectopic mass on TVS and the presence or absence of fetal cardiac activity (reduced chance of success if cardiac activity present). The RCOG actually suggest that fetal cardiac activity is a contraindication to the use of methotrexate in tubal ectopic pregnancies.

Women should be given clear written information about the use of methotrexate, its possible adverse effects and need for further treatment. Ideally this should be provided in an EPU to which they have telephone contact. At least 15% of women will need a second dose and up to 7% will experience tubal rupture during follow up. Women should be advised to avoid sexual intercourse during treatment, to maintain ample fluid intake, to avoid folic acid and alcohol, and to not conceive for at least 3 months after one dose of methotrexate, and 6 months after multiple doses, because of the risk of teratogenicity. Women should also be advised that they might have abdominal pain following treatment. This pain, possibly as a result of tubal abortion, may be quite difficult to distinguish from that of tubal rupture so admission for observation and assessment may be necessary. Women will need to have their hCG levels checked on days 4 and 7 post treatment. A further dose of methotrexate will be needed if the hCG does not fall by more than 15% between day 4 and day 7. Follow up should be weekly after this point until the hCG is less than 15 iu/litre as there are case reports of tubal rupture at low levels of hCG (Tulandi et al, 1991).

Single dose systemic methotrexate may also be the treatment of choice for non-tubal ectopic pregnancies such as cornual ectopic pregnancies. Alternatively, a multi-dose regimen, which is commonly used in the USA, may be used. This involves giving methotrexate at a dose of 1 mg/kg on days 1, 3, and 5, with folinic acid rescue on days 2, 4, and 6.

Injection of methotrexate into the gestational sac of cervical pregnancies and caesarean section scar ectopic pregnancies is also performed with good results, therefore avoiding surgery, which could result in torrential haemorrhage. Where there is visible cardiac activity intra-amniotic potassium chloride injection may be more appropriate.

Expectant

Expectant management of ectopic pregnancy is appropriate for a select group of women with decreasing hCG levels. Success rates as high as 88% have been reported (Trio et al, 1995). Women should be asymptomatic, with no signs of haemoperitoneum on TVS or other signs of tubal rupture. They must also be compliant and able to attend frequent follow-up appointments as initially hCG levels may need to be checked every 48 hours.

Anti-D immunoglobulin

Irrespective of the type of management, all rhesus negative women diagnosed with an ectopic pregnancy should receive anti-D immunoglobulin.

PSYCHOLOGICAL IMPACT

Ectopic pregnancy can have a huge impact on a woman's psychological health. Not only does she have to cope with the loss of a pregnancy, but also possible emergency surgery and the knowledge that future fertility may be reduced. Symptoms of depression and posttraumatic stress disorder have been reported in women previously diagnosed with ectopic pregnancy. The diagnosis can also lead to relationship problems and may have a substantial effect on future pregnancies. Therefore, it is important that any unit treating women with ectopic pregnancies has access to counselling services and is able to put women in contact with support associations such as the Ectopic Pregnancy Trust (www.ectopic.org).

CONCLUSIONS

The incidence of ectopic pregnancy is increasing in the UK, which is in contrast to Sweden and other countries. More effort needs to be put into prevention of this condition. A more widespread appreciation of the risks of chlamydia infections and the implementation of screening strategies for this disease are likely to form an important part of any overall management strategy.

Errors and delay in diagnosis and treatment start with a lack of patient awareness, continue into primary care and do not stop in hospital. Women must be made more aware of the condition. Pregnancy testing must be made routinely available in primary care, and we must return to basic principles when managing women with pelvic pain and a positive pregnancy test.

Hospitals should provide dedicated EPUs that function every day. Not all hospitals have to provide this level of care and joint units within a district would make sense in many cases. Careful attention must be paid to the competency of those scanning in such units and there must be an understanding of the behaviour of hCG in different clinical settings.

Earlier diagnosis leads to more treatment options. Many ectopic pregnancies do not require intervention and others resolve with medical therapy. However, using these approaches requires well-informed patients and open access to return to hospital if there are problems.

If surgery is required then a laparoscopic approach can be used in nearly all cases. Units should try to organize these cases to be carried out during the day and with appropriate supervision. In 2004 a laparotomy for a simple stable ectopic pregnancy should not be an acceptable standard of care. There will be departments where there is no expertise in operative laparoscopy, but this should be a rare event.

Following treatment women who have had an ectopic pregnancy should be seen after a week or so to discuss their treatment and may need more extensive counselling. Making contact with organizations such as the Ectopic Pregnancy Trust may be helpful. In general the authors' view is that the provision of emergency gynaecology services in the UK is not taken as seriously as other areas of the specialty. In future the authors anticipate EPUs merging with stand-alone emergency gynaecology units to provide ultrasound-based assessment and medical or minimal access treatments for women with acute gynaecological problems. **HM**

KEY POINTS

- Screening and treatment for sexually transmitted infections should be of prime importance and recognized as a risk factor for ectopic pregnancy.
- Pregnancy testing should be available in the primary care setting.
- Clinicians should be aware of the different clinical presentations of ectopic pregnancy.
- All women should have access to an early pregnancy unit which has clear guidelines and protocols for the management of ectopic pregnancy and pregnancies of unknown location.
- The majority of ectopic pregnancies should be diagnosed on transvaginal scan.
- Medical management should be offered to all suitable women.
- In those needing surgery, laparoscopy is preferable to laparotomy.
- Expectant management is an option for asymptomatic women with decreasing human chorionic gonadotrophin levels.
- All rhesus negative women diagnosed with an ectopic pregnancy should receive anti-D immunoglobulin.

Conflict of interest: none.

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