Recurrent miscarriage

Siobhan Quenby

Abstract

Missacary is one of the most common complications of pregnancy. Fifteen percent of clinically recognized pregnancies end in miscarriage. The major cause of spontaneous miscarriage is genetic or developmental abnormalities of the foetus. Recurrent miscarriage occurs in 3% of the population and has been associated with thrombophilies, infections and endocrine, anatomical and immune factors. Treatments to prevent miscarriage remain largely untested by randomized controlled trials (RCTs). The results of the limited available evidence indicate that the wide use of empirical treatments has led to minimal benefit for both patients and health care providers. This article is therefore designed to enhance critical thinking and improve clinical skills in an area with extensive and contradictory literature.

Keywords  critical thinking; miscarriage

The topic of recurrent and spontaneous miscarriage will be discussed by looking at two clinical scenarios. These have been chosen to highlight the clinical problems encountered when attempting to apply the current literature on management of miscarriage to patients. The questions are also designed to develop critical thinking framework that is necessary to pass the part 2 MRCOG exam.

Case 1. Outline your management of a 41-year-old distressed woman who has just had an ultrasound scan confirming an 8-week size foetus with no fetal heart beat, her fifth miscarriage.

This initially may seem like a straightforward case. In order to answer this question there is a need for a systematic approach through considering history, examination, investigation and finally treatment. In today’s society, older women with reproductive failure are commonly encountered and need to be sensitively, logically and effectively managed.

History

Firstly, the miscarriages need to be sub-classified into first or second trimester miscarriages, with the former further divided into loss of an empty gestation sac, loss of an embryo or loss of a foetus, in accordance with European Society for Human Reproduction and Embryology Guidelines (see Table 1). Hence, on this occasion the woman has suffered a fetal loss. Most patients describe a pattern of losses such that the majority of losses fit into one of the sub-classifications described in Table 1. Different underlying aetiologies have been associated with different patterns of pregnancy loss. For example, antiphospholipid syndrome has been associated with recurrent and single fetal losses.

A past gynaecological history is important as there may be aetiological differences in women with a history of sub-fertility then miscarriage compared to women who conceive easily and then miscarry. A detailed menstrual history may is important as polycystic ovary disease and oligomenorrhea have been associated with recurrent miscarriage.

A full medical history is necessary, particularly taking account of any personal or family history of thrombosis in order to assess the possibility of inherited thrombophilias being associated with her pregnancy losses. A note of the patient’s body mass index is important as obesity has been linked to all types of reproductive complications.

Most women with a history of four consecutive miscarriages will have taken some treatment to prevent this fifth miscarriage, even in a case of idiopathic recurrent miscarriage, hence it is important to take a detailed drug history. Also antidepressant use and periconceptual non-steroidal anti-inflammatory drugs have been associated with miscarriage. Social history is also important in this case and should be taken in a sensitive manner as caffeine (more than three cups of coffee a day), smoking, alcohol (more than 5 units a week), cocaine and cannabis have all been associated with recurrent miscarriage. Inquiry into life stresses, related to job or family is important; as stress has been associated with miscarriage and this information may help the clinician deal with the patient’s grief in an empathetic manner.

Examination

In this scenario, there is little to be gained from examination.

Investigations

Ultrasound scan: the ultrasound scan that diagnosed the miscarriage could have detected more than the pregnancy loss, particularly if it was a transvaginal scan using a machine with high resolution. Fetal structural abnormalities such as neural tube defects can be detected in the first trimester thus immediately giving the patient and clinician a cause for the pregnancy loss.

Chromosomal abnormalities: at the age of 41, chromosomal abnormalities or structural malformations are the most likely cause of the miscarriage. Cytogenetic analysis of the products of conception should be considered to look for any chromosomal abnormalities. However, culturing and analyzing trophoblast is expensive and this is rarely offered in the National Health Service for women with only one miscarriage. However, considering this scenario of recurrent miscarriage and the woman’s age, it would be important to obtain a cause for her miscarriage. Furthermore, karyotyping the products of conception will provide useful information for counselling and future pregnancy management. Traditionally, cytogenetic analysis of miscarried products was done by culturing trophoblast tissue. This has problems of being a lengthy procedure, with the potential for culture failure and maternal contamination. However, advances in molecular biology mean that cytogenetic analysis can now be done with rapid and more sophisticated techniques such as polymerase chain reaction and genomic hybridization using micro arrays. It is now possible to get rapid, accurate results of the karyotype of miscarriage products in the NHS context.

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Parental peripheral blood karyotypes: parental peripheral blood karyotypes are reported in 3–5% of couples suffering recurrent miscarriage and testing of both partners is therefore advocated. The commonest abnormalities appear to be balanced reciprocal and Robertsonian translocations. Liaison with a clinical geneticist for genetic counselling is recommended. However, the need for prenatal diagnosis is subsequent pregnancies is put in perspective by the publication of a series of observational studies of couples with balanced translocations and recurrent miscarriage, which total 800 cases. Of these 800 cases, only five unbalanced translocations were reported in the chronic villous sampling or offspring. Thus, the risk of miscarriage from invasive prenatal diagnosis is at least comparable to the chance of detecting an anomaly.

**Thrombophilia**

**Acquired thrombophilia:** testing for acquired thrombophilias should not be done until 6 weeks after the miscarriage as the pregnancy can affect the results of the tests and all research has been done on non-pregnant samples.

Antiphospholipid syndrome (APS) is an established cause of fetal loss. Explanations for the pathophysiology of APS associated pregnancy loss include defective placentation due to a direct effect of anticardiolipin antibodies on trophoblast, activation of the complement system or thrombosis of the placental vasculature. APS is defined by at least one clinical and one laboratory criterion. The clinical criteria include three or more spontaneous miscarriages or one fetal loss after 10 weeks’ gestation. The laboratory criteria include persistent abnormality of one of the following tests measured at least twice and more than 6 weeks apart; a raised titre of IgG or IgM antibodies to cardiolipin (ACA) and B2 Glycoprotein I antibodies or presence of lupus anticoagulant. Two tests are necessary as mild viral infections can cause falsely positive results. The testing for lupus coagulant can be done using a number of coagulation-based assays, such as the dilute Russell viper venom test. Testing for ACA is done using the enzyme-linked immunosorbent assay technique.

**Inherited thrombophilia:** other thrombophilias such as activated protein C resistance (APCR), Leiden factor V, protein C & S deficiency, prothrombin gene mutation and hyperhomocysteinemia have all been associated with miscarriage. Interestingly, antithrombin III deficiency has not been associated with any type of pregnancy loss despite its strong association with venous and arterial thrombosis. Activated protein C resistance (APCR) is one of the most common genetic causes of thromboembolism. In 95% of the cases, APCR is caused by a point mutation (factor V Leiden). The presence of a family history of Leiden factor V mutation is an indication for thrombophilia screening. The results of these tests can be difficult to interpret, however, most experts agree that the presence of two thrombophilias or homozygosity for the Leiden factor V mutation is likely to contribute to miscarriages such as those in this case scenario. The difficulty arises when the patient is heterozygous for the Leiden factor V mutation due to the fact that 4% of the normal obstetric population are also heterozygous for Leiden factor V. Hence heterozygosity for Leiden factor V may not be necessarily a cause for these pregnancy losses. The most recent publications suggest that it is the fetal genome that determines the miscarriage risk and it is the presence of Leiden factor V on the fetal side that is important. The implication of the fetal genome being the critical one in miscarriage is that paternal thrombophilias may also be important. However, it is not considered cost effective at present to test both parents for thrombophilias as there are no proven treatments for improving pregnancy survival in cases of inherited thrombophilias.

**Treatment of miscarriage**

The RCOG guidelines on management of early pregnancy loss include surgical, medical and expectant management. Patient

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### Table 1: Terminology of miscarriage

<table>
<thead>
<tr>
<th>First trimester miscarriage</th>
<th>Definition</th>
<th>Gestation in weeks</th>
<th>Ultrasound findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empty gestation sac</td>
<td>Trophoblast development without the development of an embryo</td>
<td>&lt;12</td>
<td>Empty gestation sac (diameter &gt;20 mm, no embryonic pole or yolk sac) or if diameter &lt;20 mm with no change on rescan 7 days later</td>
</tr>
<tr>
<td>Embryonic loss</td>
<td>An early embryo loss before fetal heart activity</td>
<td>&lt;8</td>
<td>An embryo &gt;5 mm size but up to 8 weeks’ size, with no cardiac activity. Or crown rump length &lt;5 mm with no change on rescan 7 days later</td>
</tr>
<tr>
<td>Fetal Loss</td>
<td>Death of a foetus in the first trimester</td>
<td>8–12</td>
<td>Foetus of 8–12 weeks’ size with no fetal heart activity</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Second trimester miscarriage</th>
<th>Definition</th>
<th>Gestation in weeks</th>
<th>Ultrasound findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late fetal loss</td>
<td>Death of a foetus in the second trimester</td>
<td>12–24</td>
<td>Foetus of 12–24 weeks’ size with no fetal heart activity</td>
</tr>
<tr>
<td>Spontaneous second trimester loss</td>
<td>Pregnancy loss associated with SROM or cervical dilation</td>
<td>12–24</td>
<td>Foetus of 12–24 weeks’ size with fetal heart activity</td>
</tr>
</tbody>
</table>
should be offered informed choices. An effective Early Pregnancy Assessment Unit (EPAU) is essential in the medical and expectant management of miscarriages.

**Surgical management:** surgical uterine evacuation still remains the treatment of choice where bleeding is excessive, vital signs are unstable or where infected tissue is present in the uterine cavity. Furthermore, tissues can be obtained for karyotyping in cases where this is important a specific factor in this case. However, surgical management is associated with complications such as, haemorrhage, uterine perforation, cervical tears, intra abdominal trauma, intrauterine adhesions and also complications from anaesthesia. RCOG guidelines recommend that surgical uterine evacuation for miscarriage should be performed using suction curettage as this is safer and easier to perform than the sharp/blunt curettage. The need for cervical ripening should be assessed for all cases of surgical management. In addition, non-sensitized rhesus (Rh) negative women undergoing surgical evacuation should receive anti-D immunoglobulin. In the USA and Europe, surgical evacuation is frequently performed under local anaesthetic with a para-cervical block. This local anaesthetic approach is occurring in some UK units and has the advantages of both cost and convenience.

**Medical management:** the advantage of medical management is that it avoids the risks of surgery and anaesthesia. However, women may experience increased abdominal pain and heavy bleeding. Various medical methods have been described using prostaglandin analogues (germprost or misoprostol) with or without antiprogestrone priming agents (e.g. mifepristone). It is important that the patient should have 24 h direct access to the emergency room for either advice or admission as a third of the patients on medical management will either bleed or miscarry in the priming phase with the antiprogestrone. Mifepristone may cause abdominal pain, nausea, vomiting and diarrhoea. Patient counselling on these common side effects is essential.

**Expectant management:** although expectant management avoids the risks associated with surgery and anaesthesia, it may take several weeks before complete miscarriage. Patients must be counselled appropriately or else more will subsequently request surgical evacuation during the observational period.

**Treatment of recurrent miscarriage**

**Prognosis:** the first problem to tackle with this patient is her poor prognosis because of her age and the high number of miscarriages. It is possible to test the woman’s ovarian reserve, which can be done by measuring early follicular phase follicle stimulating hormone (FSH). A raised, peri-menopausal FSH would indicate that the women’s best hope of successful future pregnancy lies in egg donation.

**Treatment plan:** during the counselling session it is important to formulate a plan for any future pregnancies.

**Chromosomal abnormalities:** if the pregnancy was chromosomally abnormal or if the couple are carriers of a balanced translocation, the only option at present is or them to try again. There was a great hope that pre-implantation genetic diagnosis (PGD) could be employed to discard karyotypically abnormal embryos (known as aneuploidy abnormal) thus reducing the miscarriage rate. However, a randomized controlled trial failed to demonstrate any improvement in the live birth rate using this technology.

**Antiphospholipid syndrome (APS):** patients with APS should be offered low dose aspirin and heparin during pregnancy as this has shown to be effective in randomized controlled trials. Most units use low molecular weight heparin as this only has to be administered once a day. The use of pre-conceptual aspirin is controversial, as recent publications of poorly designed studies have suggested that it causes harm. The treatment plans for a woman with another thrombophilia need to be discussed very carefully with the patient. Firstly, the association between other thrombophilias and pregnancy loss is weak. Recently, two randomized controlled trials have shown that the addition of heparin to low dose aspirin for the prevention of pregnancy loss in women with idiopathic recurrent miscarriage or other thrombophilia is ineffective. The patient should also be counselled that a woman with thrombophilia is also at risk of maternal thrombosis in pregnancy. The risk of thrombosis is 5–10-fold in heterozygous carriers of factor V Leiden and 100-fold in homozygous carriers. Having discussed these issues, most patients and their clinicians assess the available evidence indicating a need for thromboprophylaxis from early pregnancy to prevent miscarriage and until 6 weeks postnatally to prevent thrombosis.

**Polycystic ovarian disease (PCOD):** small studies have suggested that metformin may be beneficial for the prevention of miscarriage in women with PCOD. Metformin corrects the insulin resistance now thought to be the causative factor in the endocrinopathy of PCOD. However, the use of metformin in improving pregnancy survival has not yet been proven in a randomized controlled trial (RCT).

**Immunotherapy:** paternal leukocyte transfusion has been subjected to multiple RCTs and has been definitively shown not to be effective. Human intravenous immunoglobulins are potentially dangerous as they come from pooled serum and have not been shown to be effective. Corticosteroids are currently the subject of RCTs for the prevention of pregnancy loss in recurrent miscarriage.

### Practice points

- Sub-classify the type of pregnancy loss to help with diagnosis.
- Offer choice of treatments for management of miscarriage.
- Attempt to get diagnosis by sending products of conception for karyotyping in view of maternal age and history of recurrent miscarriage.
- Maternal age greater than 40 is a poor prognostic factor in recurrent miscarriage.
- The only proven treatment or recurrent miscarriage is aspirin and heparin for women with antiphospholipid syndrome.
Case 2. A 33-year-old woman presents in labour and rapidly delivers a live 480 g foetus which is resuscitated and dies after a day. One year later she presents to antenatal clinic 12 weeks pregnant. Discuss management options

In this case scenario a detailed history is important to elicit the cause of her preterm delivery in order to manage her appropriately in her current pregnancy.

History
- What was the gestation of the pregnancy loss?
- Was there a history of cervical weakness, unexpected bulging of the membranes before contractions, or of previous history of cervical surgery?
- Was there rupture of membranes before onset of labour?
- Were there any signs and symptoms of infection?
- Was the foetus structurally normal?
- Was a post-mortem performed? If so, were the results normal?

Investigations and treatment
Cervical weakness: cervical weakness is one of the aetiological factors associated with second trimester losses. A history of either mid-trimester miscarriage with painless and progressive dilatation of the cervix followed by bulging of the membranes through the cervix prior to onset of labour, or any previous cervical surgery (e.g. cone biopsy) is highly suggestive of cervical weakness. In the non-pregnant state, the presence of cervical weakness can be investigated using resistance to Hegar dilators under general anaesthetic. Currently, transvaginal ultrasonography (TVS) is used to investigate cervical weakness in the pregnant woman. Cervical length, cervical funnelling and cervical response to abdominal pressure (stress test) can all be measured during pregnancy. Shortening, funnelling and a positive stress test of the cervix have all been shown to be good predictors of late second trimester miscarriage and early preterm labour. However, treating these ultrasound detected findings with cervical cerclage has not been found to be effective in several randomized controlled trials. There are many possible explanations for the fact that an apparent structural weakness in the cervix has not been shown to be effectively treated with a cervical suture.

Gestation: some experts argue that the optimal gestation to scan the cervix is 22 weeks. However, a randomized controlled trial of cervical suture insertion based on these late scans found that sutures failed to prolong pregnancy. Other experts have argued that sutures need to be inserted early and that serial TVS from 16 weeks' gestation can detect cervical shortening. However, a recently presented RCT of this serial TVS approach also failed to demonstrate improved outcomes.

Location of the suture: other experts argue that the location of the suture determines its effectiveness. This means that a transabdominal suture is potentially more effective than a high transvaginal suture, put in after dissection of the bladder, which is more effective than a low cervical suture, put in half way up the cervix without bladder dissection. However, this concept of location of the suture being a determinant of effectiveness is yet to be tested with an RCT.

Inflammation: the cervical changes detected on ultrasound scan may not be the result of structural weakness but the result of the start of an inflammatory process. If ultrasound detected cervical changes reflect the start of an inflammatory process then anti-inflammatory agents should be given to women with short cervixes. The accumulating number of RCTs that shows that progesterone (which has anti-inflammatory properties) is an effective treatment in the prolongation of pregnancy in high risk women thus adds credence to this hypothesis. However, to date none of the trials of progesterone has included infant outcomes. These means that there is still a possibility that progesterone may maintain the foetus in an unfavourable environment and therefore increase disability.

In the scenarios under discussion, most experts would follow a management plan of serial TVS of cervix, with cervical suture and progesterone administration should shortening occur.

Infection: bacterial vaginosis (BV) is an imbalance of vaginal flora caused by a reduction of the normal lactobacilli, and a heavy overgrowth of abnormal mixed anaerobic flora of the vagina. Fifty percent of women with BV are asymptomatic. BV is not associated with vaginal mucosal inflammation and rarely causes a vulval itch. The presence of bacteria vaginosis has been associated with second trimester losses and preterm delivery. Tests for BV can either be gram stain of a vaginal swab or by Amsel’s criteria (three out of the four of the following (1) thin white homogenous vaginal discharge (2) vaginal pH of 4.5 or above, (3) release of fishy odour when adding 10% potassium hydroxide (4) clue cells on microscope). Current evidence from randomized controlled trials supports treatment with clindamycin, as this was effective in preventing preterm delivery. Conversely, RCTs of metronidazole to prevent preterm delivery suggest that this antibiotic increases the chance of preterm delivery. Hence metronidazole should be avoided in this scenario.

There are no RCTs to support that treatment of other infections such as ureaplasma or mycoplasma could prevent fetal loss. However, treatment of gonococcal and chlamydia infections offers health benefits to the baby as this prevents neonatal eye infections. The long-term follow-up of the ORACLE trials found an association of cerebral palsy with antibiotic use to prevent preterm labour. Hence empirical antibiotic use is not advised in women with second trimester loss.

Bed rest: there is some suggestion, from the placebo arms of trials of cervical suture, that bed rest is beneficial in prolonging pregnancy in women at high risk of premature delivery. However, bed rest is not without potential side effects; stasis in pregnancy renders the women at increased risk of thrombosis and osteoporosis, and lack of activity can also be psychologically stressful. However, when cervical membranes prolapse into the cervical canal and/or the vagina, it is logical to advise bed rest as an antigravity measure to prolong pregnancy.

Congenital uterine anomalies: recent publications have associated septate and bicornuate uterine abnormalities with second trimester miscarriage. 2D ultrasound can only be considered as a screening tool for uterine abnormalities, which are best detected using 3D ultrasound, combined laparoscopy and hysteroscopy or sonohysterography. No randomized controlled trial of treatment
has been completed, however, there are many case series of hysteroscopic resection of septae with good results.

MCQs

(a) Maternal age is a risk factor for miscarriage
(b) IVF and PGD are effective treatments for recurrent miscarriage
(c) Heparin and aspirin are proven to be effective at preventing recurrent miscarriage in women heterozygous for Leiden factor V
(d) Caffeine consumption has been associated with miscarriage
(e) A common cold virus can give a positive test for anti-phospholipid syndrome

- a, true; b, false; c, false; d, true; e, true

(a) Bicornuate uterus is associated with second trimester miscarriage
(b) Metronidazole is a recommended treatment for bacterial vaginosis to prevent second trimester miscarriage
(c) Progesterone prolongs pregnancy in women with cervical shortening
(d) Cervical sutures have been shown to prolong pregnancy in women with cervical shortening
(e) 2D ultrasound is an adequate investigation for congenital uterine anomalies.

- a, true; b, false; c, true; d, false; e, false

FURTHER READING


Practice points

- Cervical shortening as detected by transvaginal ultrasonography is a good predictor of second trimester miscarriage.
- Bacteria vaginosis is associated with second trimester miscarriage and can be treated with clindamycin.
- Progesterone is effective in prolonging pregnancy in women at high risk of early labour and delivery.