

## CLINICAL REVIEW

## Diagnosis and management of first trimester miscarriage

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Miscarriage is the most common complication of pregnancy. The reported rate of pregnancy loss in women with a missed menstrual period and positive urine pregnancy test is 12-24%.<sup>1</sup> The true rate of miscarriage is probably higher because many losses occur preclinically, before a menstrual period is missed.<sup>2</sup>

About 125 000 miscarriages occur annually in the United Kingdom, resulting in 42 000 hospital admissions.<sup>3</sup> Although miscarriages mostly resolve spontaneously without treatment and rarely cause severe maternal morbidity, the burden of disease is considerable, owing to the high incidence and associated costs of diagnostic investigations, hospital admission, surgical treatment, and follow-up. The loss of a pregnancy is often distressing for women and their partners, with adverse effects on their social and psychological wellbeing.

Reported UK maternal mortality rates after miscarriage in the period 1985 to 2008 range from 0.05 to 0.22 per 100 000 maternities.<sup>4</sup> The most common causes of death were haemorrhage and sepsis, which tended to occur more often after second trimester losses.

Women with miscarriages are often treated conservatively in an outpatient setting, and general practitioners are often asked to advise women on the management options available to them and to provide support during follow-up. The aim of this review is to describe the diagnosis and management of first trimester miscarriage. The causes, pathophysiology, and management of recurrent and second trimester miscarriages differ from earlier losses and will not be covered.

### What is miscarriage?

Miscarriage is defined as a spontaneous loss of an intrauterine pregnancy, which occurs before the fetus can survive outside the uterus. Currently, the limit of viability is set at 24 weeks' gestation, but this will probably change with future improvements in neonatal care.<sup>5</sup> Miscarriages are described as early ( $\leq 12$  weeks' gestation) or late (13-24 weeks' gestation).<sup>6</sup> Recurrent miscarriage is usually defined as the occurrence of three or more consecutive miscarriages, and it affects 1% of women of reproductive age.<sup>7</sup> In some European countries and

in the United States, recurrent miscarriage is defined as two or more miscarriages, either consecutive or non-consecutive.

### What causes miscarriage?

Chromosomal abnormalities are the most common cause of first trimester miscarriage and are detected in 50-85% of pregnancy tissue specimens after spontaneous miscarriage.<sup>8-10</sup> Trisomies account for about two thirds of these, and the risk of trisomy increases with maternal age. Most trisomies involve chromosomes 16, 21, and 22. A large prospective epidemiological study from Denmark found that the risk of miscarriage is 15% or less up to the age of 34 years but increases to 25% at 35-39 years, 51% at 40-44 years, and greater than 90% in women aged 45 years or more.<sup>11</sup> Other less common causes of miscarriage include antiphospholipid syndrome,<sup>12</sup> inherited thrombophilias (antithrombin deficiency, deficiency of protein C and protein S, factor V Leiden mutation, and mild hyperhomocysteinaemia),<sup>13</sup> and congenital structural abnormalities of the uterus.<sup>14</sup> The risk of miscarriage is also increased in women with poorly controlled type 1 diabetes or disease of the thyroid gland.<sup>15 16</sup> Obese women who become pregnant after successful fertility treatment are also more likely to experience miscarriage,<sup>17</sup> but the risk is not increased in those who conceive spontaneously.<sup>18</sup> Studies have shown no clear association of socioeconomic circumstances, caffeine consumption, smoking, or low to moderate alcohol consumption with the risk of miscarriage.<sup>19</sup>

### How is miscarriage diagnosed?

#### Clinical findings

Vaginal bleeding and loss of pregnancy symptoms are suggestive of miscarriage. Miscarriage is traditionally classified as threatened, inevitable, incomplete, or complete on the basis of clinical history and findings on speculum and digital pelvic examination.<sup>20</sup> Information on the diagnostic value of clinical history and examination for the diagnosis of miscarriage is limited. A prospective study of a large number of general

### Summary points

- Miscarriage is the most common complication of pregnancy, affecting 12-24% of all pregnancies
- Most early miscarriages are caused by chromosomal abnormalities, and the risk of miscarriage increases with maternal age
- Transvaginal ultrasound is the best way to diagnose miscarriage
- Most miscarriages resolve spontaneously and expectant management should be offered as the first line management strategy
- Emergency surgery is indicated in women presenting with severe pain or bleeding and in those with signs of infection
- Offer women and their partners access to counselling services, leaflets, web addresses, and helpline numbers for support organisations

### Sources and selection criteria

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

practices in Amsterdam found that a clinical diagnosis of miscarriage based on clinical symptoms and findings on vaginal digital and speculum examinations was inaccurate in more than 50% of cases when compared with ultrasound findings.<sup>21</sup> A retrospective study also reported the presence of products of conception in uterine curettings in 40% of women with a clinical diagnosis of complete miscarriage.<sup>22</sup> These results indicate that clinical diagnosis of miscarriage is unreliable and that pelvic examination, including speculum investigation, may be omitted in clinically stable women who present with a history of mild to moderate vaginal bleeding in early pregnancy. In these cases, ultrasound is more helpful and should be the primary test used to assess the pregnancy viability.

Speculum examination is still appropriate in women who present with heavy bleeding and signs of cardiovascular instability. In such instances a speculum examination can detect retained products protruding through the cervix and facilitate their immediate removal.

## How can ultrasound help diagnose miscarriage?

In modern practice, transvaginal ultrasonography has become the accepted standard for examining women with suspected complications of early pregnancy.<sup>23 24</sup> Ultrasound classification of miscarriage is based solely on the morphological appearances of pregnancy and does not take into account the amount of vaginal bleeding or cervical findings.<sup>6</sup>

### Early fetal demise

Early fetal demise (also described as empty sac; blighted ovum; missed, delayed, or silent miscarriage) refers to the early stage in the course of a miscarriage when an intact gestational sac is still present within the uterine cavity (figure 1). The diagnosis of early fetal demise is based either on the absence of an embryo within a gestational sac or on the absence of cardiac activity in a visible embryo. The main difficulty when diagnosing early embryonic demise is to avoid confusing a healthy, early, normal intrauterine pregnancy with a miscarriage. Because the ultrasound diagnosis of early fetal demise is based on negative findings, the risk of diagnostic error is high. This is particularly so in women who are unsure of their dates, have irregular cycles, conceived while taking hormonal contraception, or have had fewer than three menstrual periods since their last pregnancy. The risk of misdiagnosis is also increased in women with a retroverted uterus, congenital uterine anomaly, uterine fibroids, intra-abdominal adhesions after previous caesarean sections, or other pelvic surgery affecting uterine position.

Misdiagnosis of a normal pregnancy as a miscarriage could result in inadvertent termination of a wanted normal pregnancy. This problem has caused wide public concern and has led to several public inquiries that have offered recommendations intended to prevent such diagnostic errors.<sup>25 26</sup> A recent systematic review highlighted the paucity of high quality, prospective data on which to base guidelines for the accurate diagnosis of early fetal demise.<sup>27</sup> A wide range of cut-off points for the size of the gestational sac or embryo above which embryonic cardiac activity should be visible in a normal early intrauterine pregnancy have been proposed.<sup>27</sup> Although they all include a certain margin of safety, the main cause of misdiagnosis is operator error, and this can occur irrespective of a chosen cut-off value. Therefore, recent National Institute for Health and Care Excellence (NICE) guidelines recommend that the diagnosis is confirmed at a follow-up visit seven to 14 days later or by a second observer in all women with suspected early fetal demise on ultrasound.<sup>28</sup>

### Incomplete miscarriage

Incomplete miscarriage is defined by the presence of retained products of conception without a well defined gestation sac. The ultrasound diagnosis of incomplete miscarriage is difficult and no consensus exists regarding the best diagnostic criteria. Endometrial thickness (measured as the anterior-posterior diameter of the uterine cavity) has been used to aid this diagnosis. Several studies have looked at various cut-off levels, ranging from 5 mm to 25 mm.<sup>29 30</sup> A recent prospective observational study, however, showed that none of these criteria are accurate enough to diagnose the presence of chorionic villi within the uterine cavity.<sup>31</sup> Subjective assessment of the morphological characteristics of the tissue within the uterine cavity, combined with colour Doppler assessment of its vascularity, has been proposed to overcome the limitations of using cut-off measurements.<sup>32</sup> However, no good quality prospective studies have determined the accuracy of these diagnostic criteria.

### Complete miscarriage

The diagnosis of complete miscarriage is made in women in whom ultrasound fails to identify any signs of pregnancy tissue within the uterine cavity. This diagnosis can be made with confidence only in women who had clear evidence of intrauterine pregnancy on previous ultrasound examinations. If no scan has previously been done, the pregnancy should be described as a "pregnancy of unknown location" and followed up with biochemical markers.<sup>28</sup>

## What is the role of biochemical markers?

Biochemical markers are not routinely used in the diagnosis of miscarriage. They are useful, however, to confirm the diagnosis of early pregnancy failure in women in whom ultrasound findings are non-diagnostic.

Human chorionic gonadotrophin concentrations in maternal serum double over 1.4-1.6 days from the time of first detection to the 35th day of pregnancy and then double every 2.0-2.7 days from the 35th day to 42nd day.<sup>33</sup> It has been well documented that slower doubling times are associated with miscarriage.<sup>34</sup> However, absolute concentrations of the hormone cannot be used to discriminate between viable and non-viable pregnancies.<sup>35</sup> In women with non-diagnostic ultrasound scan findings, declining chorionic gonadotrophin values can diagnose a complete miscarriage with a sensitivity of 93-97%.<sup>36 37</sup>

A recent meta-analysis showed that low serum progesterone (<16 nmol/L; 1 nmol=0.31 ng/mL) is strongly associated with a failing pregnancy and can be used to rule out the possibility of a viable pregnancy.<sup>38</sup> However, occasional cases of normal viable pregnancies have been reported in women with very low serum progesterone. Therefore, serum progesterone should not be used in isolation as the definitive test to diagnose miscarriage.<sup>39</sup>

## What is the role of surgery and histology?

In the UK surgery is not routinely used to diagnose miscarriage. However, in women who opt for surgical treatment of miscarriage, uterine curettings are routinely sent for histological examination to confirm the diagnosis of intrauterine pregnancy and to exclude a molar pregnancy.<sup>6</sup> Uterine curettage is used more liberally in the US, mainly to help to confirm the diagnosis of miscarriage and to exclude an ectopic pregnancy in women with non-diagnostic ultrasound findings.<sup>40</sup> Chromosome testing should be performed on products of conception of the third and subsequent consecutive miscarriage only and not after sporadic pregnancy loss.<sup>7</sup>

## Is it possible to prevent miscarriage?

There is no evidence that miscarriage can be prevented by bed rest or by administration of vitamin supplements.<sup>41 42</sup> A meta-analysis of four trials showed that treatment with progesterone in women with threatened miscarriage was associated with significantly lower risk of miscarriage compared with placebo.<sup>28</sup> The quality of evidence, however, was poor, the dose and route of administration of progesterone varied between the studies, and the final outcome measures varied. Routine progesterone supplements should not be offered to women with threatened miscarriage until the results of a well conducted prospective multicentre randomised trial are available.<sup>28</sup>

## How is miscarriage managed?

Emergency surgery under general anaesthesia used to be the standard—often the only—treatment option offered to women diagnosed with miscarriage. The management of miscarriage has radically changed over the past 20 years. The emphasis on urgent surgical management has moved towards individualised treatment and patient choice between expectant, medical, and semi-elective surgical treatment.

## When to refer?

We recommend early referral of all women with pain and bleeding in early pregnancy to a local early pregnancy unit. Immediately refer women presenting with severe symptoms or

signs of cardiovascular instability and infection to the nearest emergency department because some may have an undiagnosed, ruptured ectopic pregnancy. Asymptomatic women with a history of early pregnancy losses may be referred for an ultrasound scan at seven or eight weeks' gestation to help alleviate anxiety and to provide reassurance that the pregnancy is progressing normally.<sup>18</sup>

## Expectant management

Expectant management is often chosen by women because of a desire for a natural approach. It is becoming an increasingly popular option, and in one observational study, 70% of women opted to wait for the pregnancy to resolve spontaneously.<sup>32</sup> In controlled trials, placebo treatment (expectant management) was successful in 29-42% of women with early fetal demise and 55% to 86% of women with incomplete miscarriage.<sup>43-47</sup> A meta-analysis of published studies comparing expectant management with active management (medical or surgical) showed a higher rate of unplanned emergency interventions (35% v 18%; relative risk 2.28, 95% confidence interval 1.93 to 2.7).<sup>28</sup> It also found higher rates of blood transfusions (1.6% v 0.4%; 3.39, 1.08 to 10.61) in women randomised to expectant management, but no significant difference in infection rates.<sup>28</sup> The chance of successful spontaneous completion of miscarriage increases with the length of follow-up.<sup>48</sup> Women are usually advised to wait for two weeks for miscarriage to complete, but it is safe to continue with expectant management for longer if there are no signs of infection.

## Medical management

Medical management is chosen as the primary treatment option in 20-30% of women.<sup>49 50</sup> The drug most commonly used is a prostaglandin analogue misoprostol, which can be given in single or divided doses. It is licensed for oral use only, but can also be given vaginally, sublingually, or rectally.<sup>51 52</sup>

Mifepristone, an oral anti-progesterone drug, is thought to potentiate the effects of prostaglandins.<sup>53</sup> It is sometimes used before administration of misoprostol for miscarriage. However, a recent randomised trial showed that the addition of mifepristone does not significantly increase the success rate compared with misoprostol alone.<sup>54</sup>

The success of medical management depends on the type of miscarriage, the drug dosage, the route of administration, and the time allowed for products to be passed. Data from randomised trials show that medical management avoids the need for surgical intervention in over 70% of women with early fetal demise.<sup>43-47</sup> Medical management was highly effective in women with incomplete miscarriage, but the success rates were not significantly better than with expectant management.<sup>45</sup>

Medical treatment may be arranged on an outpatient or inpatient basis. Side effects include nausea in 22-35% of women, fever in 15%, diarrhoea in 6-21.2%, and vomiting in 7%.<sup>44-46</sup> Bleeding usually starts within hours of administration of the drug and may continue for up to three weeks. Heavy bleeding requiring emergency surgery occurs in 1% of women treated with misoprostol.<sup>55</sup> Review women who do not start bleeding within 24 hours after initiation of treatment to decide on further management. Women who bleed for longer than three weeks should also attend for clinical review to rule out persistent retained products of conception or molar pregnancy.<sup>28</sup>

## Surgical treatment

Emergency surgery remains the primary treatment of choice for women who present with excessive bleeding, are

haemodynamically unstable, have signs of infected retained products of conception, or have a provisional diagnosis of gestational trophoblastic disease.<sup>6</sup> In clinically stable women, surgery can be offered as a semi-elective procedure for those who prefer surgical intervention and for those in whom conservative management has been unsuccessful.

A meta-analysis of clinical trials found that surgical management is more successful than medical treatment of miscarriage.<sup>28</sup> Women randomised to medical management had higher unplanned intervention rates (21.3% v 2.5%; 8.13, 6.26 to 10.55) and were more likely to experience gastrointestinal side effects (22.8% v 7.8%; 2.36, 1.39 to 4.0). Women also reported a significantly longer duration of bleeding after medical versus surgical treatment (median 11 v 8 days).<sup>56</sup> No significant differences were seen in infection rates (1.6% v 2.2%) or the need for blood transfusion (1.1% v 0.8%).<sup>28</sup>

Five trials have reported rates of surgical complications, including uterine perforation, cervical laceration, haemorrhage, and intrauterine synechiae. The rate of complications was relatively high (2-8%) in women randomised to surgery.<sup>56-60</sup> Mental health and social functioning at two weeks did not differ between women who had medical or surgical management.<sup>59 61 62</sup>

In recent years, surgery has also been carried out using manual vacuum aspiration under systemic analgesia (including patient controlled analgesia) in operating theatres.<sup>63</sup> This procedure can also be carried out in the outpatient setting, under local anaesthetic.<sup>64</sup> The benefits of outpatient procedures are increased safety due to reduced anaesthetic risks, minimal social disruption, and reduced costs.

## Choice of treatment

Provide women experiencing miscarriage who present with minimal or mild symptoms the opportunity to make an informed choice between different management options. Most are likely to opt for expectant management, but some will prefer medical or surgical treatment. Recently published NICE guidelines recommend the use of expectant management for seven to 14 days as the first line management strategy.<sup>28</sup> Offer women in whom expectant management is unsuccessful medical treatment (single dose misoprostol 800 µg transvaginally) or surgery. Emergency surgical treatment should be offered to all women with severe bleeding or pain, those with signs of infection, and when conservative management has failed. Antibiotic prophylaxis and anti-D for Rhesus negative women are not needed with expectant or medical treatment but should be offered to women undergoing surgical treatment.<sup>6</sup>

## What to expect during the recovery period?

Normal menstrual periods usually resume within a month or two after miscarriage. It is safe for women to resume sexual activity once the bleeding has stopped. Women need not delay trying for a new pregnancy for medical reasons. Because most miscarriages are caused by chromosomal abnormalities, women need not be routinely investigated for other less common causes of miscarriage unless they experience recurrent losses. A large retrospective study from Scotland showed that women who conceive within six months of the initial miscarriage are less likely to have another miscarriage or other pregnancy complications than women in whom the interpregnancy interval is longer than six months.<sup>65</sup>

## What are the psychological needs of women who miscarry?

Miscarriage is often an unhappy and stressful event for women and their partners. For many, it represents the loss of a baby, even in early gestations, and this can be exacerbated by previous fertility or pregnancy problems. Feelings of loss and grief are common but generally self limiting. Treat all women who miscarry with respect and sensitivity; give them clear explanations of processes, procedures, and options; and give them time to make decisions, where clinically possible. Provide women with leaflets, web addresses, and helpline numbers for support organisations. Some women may develop anxiety and depression after a pregnancy loss and they may benefit from receiving additional counselling and psychological support.<sup>28</sup>

## What do clinical guidelines recommend?

NICE has produced a guideline on diagnosis and initial management of ectopic pregnancy and miscarriage.<sup>28</sup> The guideline emphasises the need to provide women and their partners with evidence based information on the diagnosis and management of miscarriage, as well as access to support and counselling services. Early pregnancy assessment services—where ultrasound scanning can be carried out and decisions about management made—should be available seven days a week. Offer expectant management as the primary treatment option to all clinically stable women with a confirmed diagnosis of miscarriage.

The Royal College of Obstetricians and Gynaecologists has produced a clinical guideline on the management of early pregnancy loss that recommends use of the term miscarriage for pregnancy losses before 24 weeks' gestation.<sup>6</sup> It recommends offering surgical management of miscarriage to women who prefer that option and to those with persistent excessive bleeding, haemodynamic instability, evidence of infected retained tissue, and suspected gestational trophoblastic disease.

The American College of Radiology has produced a guideline recommending ultrasonography as the primary imaging modality in the evaluation of patients presenting with bleeding in the first trimester of pregnancy, with magnetic resonance imaging and computed tomography playing a relatively minor role. Because of concerns about temperature increases in tissues in the path of a pulsed Doppler beam, only M mode ultrasound should be used to document fetal cardiac activity and measure the heart rate.<sup>66</sup>

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### Questions for future research

- What could be done to protect the emotional wellbeing of women undergoing conservative treatment of miscarriage, which involves prolonged follow-up and repeated ultrasound scans?
- Does progesterone improve outcomes in women with threatened miscarriage?
- What is the impact of different management strategies on future reproductive outcomes?
- What are the best diagnostic criteria to diagnose incomplete miscarriage?

### Additional educational resources

#### Resources for healthcare professionals

- NHS Clinical Knowledge Summaries (<http://www.cks.nhs.uk/miscarriage>)—Evidence based information and practical “know how” on common conditions managed in primary care
- Association of Early Pregnancy Units ([www.earlypregnancy.org.uk](http://www.earlypregnancy.org.uk))—Support and resources to assist patient choice and maintain standards in early pregnancy care. Your nearest unit can be found at: [www.earlypregnancy.org.uk/FindUsMap.asp](http://www.earlypregnancy.org.uk/FindUsMap.asp)
- Special Interest Group Early Pregnancy (SIGEP) of the European Society for Human Reproduction and Embryology ([www.eshre.eu/01/default.aspx?pageid=60](http://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

- Miscarriage Association ([www.miscarriageassociation.org.uk](http://www.miscarriageassociation.org.uk))—Information on the causes, management, and treatment of miscarriage, ectopic, and molar pregnancy. Telephone helpline and network of volunteers offering support to women who have lost a pregnancy
- Association of Early Pregnancy Units ([www.earlypregnancy.org.uk](http://www.earlypregnancy.org.uk))—Accessible information to help patient choice and facilitate access to the local early pregnancy unit when needed
- Royal College of Obstetricians and Gynaecologists ([www.rcog.org.uk](http://www.rcog.org.uk))—Online information for patients covering a wide range of topics in women's health, including miscarriage
- American Congress of Obstetricians and Gynecologists ([www.acog.org/Search?Keyword=miscarriage](http://www.acog.org/Search?Keyword=miscarriage))—Information leaflets that provide useful information about the effect of tobacco, alcohol, and illicit drug use on early pregnancy

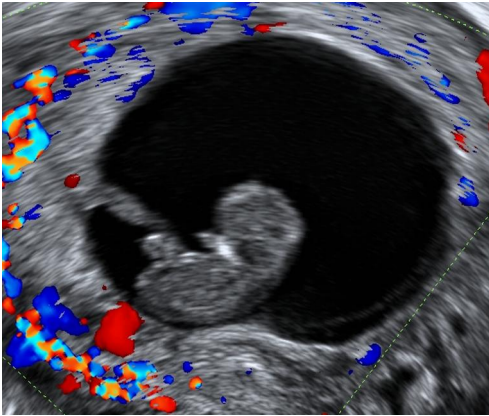
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## Figure



Ultrasound image showing a fetus of 8 weeks' size within a gestational sac. Colour Doppler signals show abundant blood supply to the gestational sac, but there is no evidence of fetal cardiac activity. These findings conclusively demonstrate early fetal demise