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The Investigation and Treatment of Couples with Recurrent First-trimester and Second-trimester Miscarriage



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This is the third edition of this guideline, which was first published in 1998 and then in 2003 under the title *The Investigation and Treatment of Couples with Recurrent Miscarriage*.

1. Purpose and scope

The purpose of this guideline is to provide guidance on the investigation and treatment of couples with three or more first-trimester miscarriages, or one or more second-trimester miscarriages.

2. Background and introduction

Miscarriage is defined as the spontaneous loss of pregnancy before the fetus reaches viability. The term therefore includes all pregnancy losses from the time of conception until 24 weeks of gestation. It should be noted that advances in neonatal care have resulted in a small number of babies surviving birth before 24 weeks of gestation.

Recurrent miscarriage, defined as the loss of three or more consecutive pregnancies, affects 1% of couples trying to conceive.¹ It has been estimated that 1–2% of second-trimester pregnancies miscarry before 24 weeks of gestation.²

3. Identification and assessment of evidence

The Cochrane Library and Cochrane Register of Controlled Trials were searched for relevant randomised controlled trials, systematic reviews and meta-analyses. A search of Medline from 1966 to 2010 was also carried out. The date of the last search was November 2010. In addition, relevant conference proceedings and abstracts were searched.

The databases were searched using the relevant MeSH terms including all sub-headings. This was combined with a keyword search using 'human', 'female', 'pregnancy', 'abortion', 'miscarriage', 'habitual', 'recurrent', 'randomised controlled trials' and 'meta-analysis'.

The definitions of the types of evidence used in this guideline originate from the Scottish Intercollegiate Guidelines Network (SIGN) grading scheme. Where possible, recommendations are based on, and explicitly linked to, the evidence that supports them. Areas lacking evidence are highlighted and annotated as 'good practice points'.

4. Risk factors for recurrent miscarriage

What are the causes of recurrent first trimester miscarriage and second trimester miscarriage?

4.1 Epidemiological factors

Maternal age and number of previous miscarriages are two independent risk factors for a further miscarriage.^{3,4} Advancing maternal age is associated with a decline in both the number and quality of the remaining oocytes. A large prospective register linkage study³ reported the age-related risk of miscarriage in recognised pregnancies to be: 12–19 years, 13%; 20–24 years, 11%; 25–29 years, 12%; 30–34 years, 15%; 35–39 years, 25%; 40–44 years, 51%; and ≥ 45 years, 93%. Advanced paternal age has also been identified as a risk factor for miscarriage. The risk of miscarriage is highest among couples where the woman is ≥ 35 years of age and the man ≥ 40 years of age.⁵

Previous reproductive history is an independent predictor of future pregnancy outcome. The risk of a further miscarriage increases after each successive pregnancy loss, reaching approximately 40% after three consecutive pregnancy losses, and the prognosis worsens with increasing maternal age.^{3,4} A previous live birth does not preclude a woman developing recurrent miscarriage.⁶

The evidence on the effect of environmental risk factors is based mainly on data studying women with sporadic rather than recurrent miscarriage. The results are conflicting and biased by difficulties in controlling for confounding factors and the inaccuracy of data on exposure and the measurement of toxin dose. Maternal cigarette smoking and caffeine consumption have been associated with an increased risk of spontaneous miscarriage in a dose-dependent manner. However, current evidence is insufficient to confirm this association.⁷⁻⁹ Heavy alcohol consumption is toxic to the embryo and the fetus. Even moderate consumption of five or more units per week may increase the risk of sporadic miscarriage.¹⁰ Working with or using video display terminals does not increase the risk of miscarriage.¹¹ The evidence on the effect of anaesthetic gases for theatre workers is conflicting.^{12,13}

Recent retrospective studies have reported that obesity increases the risk of both sporadic and recurrent miscarriage.¹⁴⁻¹⁶

4.2 *Antiphospholipid syndrome*

Antiphospholipid syndrome is the most important treatable cause of recurrent miscarriage. Antiphospholipid syndrome refers to the association between antiphospholipid antibodies - lupus anticoagulant, anticardiolipin antibodies and anti-B₂ glycoprotein-I antibodies - and adverse pregnancy outcome or vascular thrombosis.^{17,18}

Adverse pregnancy outcomes include:

- three or more consecutive miscarriages before 10 weeks of gestation
- one or more morphologically normal fetal losses after the 10th week of gestation
- one or more preterm births before the 34th week of gestation owing to placental disease.

The mechanisms by which antiphospholipid antibodies cause pregnancy morbidity include inhibition of trophoblastic function and differentiation,¹⁹⁻²³ activation of complement pathways at the maternal-fetal interface resulting in a local inflammatory response²⁴ and, in later pregnancy, thrombosis of the uteroplacental vasculature.²⁵⁻²⁷ In vitro studies have shown that the effect of antiphospholipid antibodies on trophoblast function^{28,29} and complement activation³⁰ is reversed by heparin.

Antiphospholipid antibodies are present in 15% of women with recurrent miscarriage.³¹ By comparison, the prevalence of antiphospholipid antibodies in women with a low-risk obstetric history is less than 2%.^{32,33} In women with recurrent miscarriage associated with antiphospholipid antibodies, the live birth rate in pregnancies with no pharmacological intervention has been reported to be as low as 10%.³⁴

4.3 *Genetic factors*

4.3.1 **Parental chromosomal rearrangements**

In approximately 2-5% of couples with recurrent miscarriage, one of the partners carries a balanced structural chromosomal anomaly: most commonly a balanced reciprocal or Robertsonian translocation.³⁵⁻³⁸

Although carriers of a balanced translocation are usually phenotypically normal, their pregnancies are at increased risk of miscarriage and may result in a live birth with multiple congenital malformation and/or mental disability secondary to an unbalanced chromosomal arrangement. The risk of miscarriage is influenced by the size and the genetic content of the rearranged chromosomal segments.

4.3.2 Embryonic chromosomal abnormalities

In couples with recurrent miscarriage, chromosomal abnormalities of the embryo account for 30–57% of further miscarriages.^{39,40} The risk of miscarriage resulting from chromosomal abnormalities of the embryo increases with advancing maternal age. However, it is important to note that as the number of miscarriages increases, the risk of euploid pregnancy loss increases.^{40,41}

4.4 Anatomical factors

4.4.1 Congenital uterine malformations

The exact contribution that congenital uterine anomalies make to recurrent miscarriage remains unclear since the prevalence and reproductive implications of uterine anomalies in the general population are unknown. The reported prevalence of uterine anomalies in recurrent miscarriage populations ranges between 1.8% and 37.6%.^{42,43} This variability reflects the differences in the criteria and techniques used for diagnosis and the fact that available studies have included women with two, three or more miscarriages in both the first and second trimester of pregnancy. The prevalence of uterine malformations appears to be higher in women with second-trimester miscarriages compared with women who suffer first-trimester miscarriages, but this may be related to the cervical weakness that is frequently associated with uterine malformation.⁴⁴ It has been reported that women with arcuate uteri tend to miscarry more in the second trimester while women with septate uteri are more likely to miscarry in the first trimester.⁴⁵

A retrospective review of reproductive performance in women with untreated uterine anomalies has suggested that these women experience high rates of miscarriage and preterm delivery, with a term delivery rate of only 50%.⁴² However, retrospective studies are biased by patient selection and, until well controlled prospective data become available, the role of uterine anomalies in recurrent miscarriage will remain debatable.

4.4.2 Cervical weakness

Cervical weakness is a recognised cause of second-trimester miscarriage, but the true incidence is unknown, since the diagnosis is essentially a clinical one. There is currently no satisfactory objective test that can identify women with cervical weakness in the non-pregnant state. The diagnosis is usually based on a history of second-trimester miscarriage preceded by spontaneous rupture of membranes or painless cervical dilatation.

4.5 Endocrine factors

Systemic maternal endocrine disorders such as diabetes mellitus and thyroid disease have been associated with miscarriage. Women with diabetes who have high haemoglobin A1c levels in the first trimester are at risk of miscarriage and fetal malformation.⁴⁶ However, well-controlled diabetes mellitus is not a risk factor for recurrent miscarriage, nor is treated thyroid dysfunction.^{47,48} The prevalence of diabetes mellitus and thyroid dysfunction in women who suffer recurrent miscarriage is similar to that reported in the general population.^{49,50}

Anti-thyroid antibodies have been linked to recurrent miscarriage. However, one case-control study⁵¹ from 1998 has reported that women with recurrent miscarriages are no more likely than women without recurrent miscarriage to have circulating thyroid antibodies. A single prospective study⁵² has shown that the presence of thyroid antibodies in euthyroid women with a history of recurrent miscarriage does not affect future pregnancy outcome.

Evidence level 3

Polycystic ovary syndrome (PCOS) has been linked to an increased risk of miscarriage but the exact mechanism remains unclear. Polycystic ovarian morphology, elevated serum luteinising hormone levels or elevated serum testosterone levels, although markers of PCOS, do not predict an increased risk of future

pregnancy loss among ovulatory women with a history of recurrent miscarriage who conceive spontaneously.⁵³ The increased risk of miscarriage in women with PCOS has been recently attributed to insulin resistance, hyperinsulinaemia and hyperandrogenaemia. The prevalence of insulin resistance is increased in women with recurrent miscarriage compared with matched fertile controls.⁵⁴ An elevated free androgen index appears to be a prognostic factor for a subsequent miscarriage in women with recurrent miscarriage.⁵⁵

4.6 Immune factors

There is no clear evidence to support the hypothesis of human leucocyte antigen incompatibility between couples, the absence of maternal leucocytotoxic antibodies or the absence of maternal blocking antibodies. Hence, they should not be offered routinely in the investigation of couples with recurrent miscarriage.

Natural killer (NK) cells are found in peripheral blood and the uterine mucosa. Peripheral blood NK cells are phenotypically and functionally different from uterine NK (uNK) cells.⁵⁶ There is no clear evidence that altered peripheral blood NK cells are related to recurrent miscarriage.^{57,58} Therefore, testing for peripheral blood NK cells as a surrogate marker of the events at the maternal-fetal interface is inappropriate and should not be offered routinely in the investigation of couples with recurrent miscarriage.

It has been suggested that uNK cells may play a role in trophoblastic invasion and angiogenesis in addition to being an important component of the local maternal immune response to pathogens.⁵⁹ It should be noted that the largest study⁶⁰ examining the relationship between uNK cell numbers and future pregnancy outcome reported that raised uNK cell numbers in women with recurrent miscarriage was not associated with an increased risk of miscarriage. This remains a research field and testing for uNK cells should not be offered routinely in the investigation of recurrent miscarriage.

Cytokines are immune molecules that control both immune and other cells. Cytokine responses are generally characterised either as T-helper-1 (Th-1) type, with production of the pro-inflammatory cytokines interleukin 2, interferon and tumour necrosis factor alpha (TNF), or as T-helper-2 (Th-2) type, with production of the anti-inflammatory cytokines interleukins 4, 6 and 10. It has been suggested that normal pregnancy might be the result of a predominantly Th-2 cytokine response, whereas women with recurrent miscarriage have a bias towards mounting a Th-1 cytokine response.

A meta-analysis⁶¹ concluded that the available data are not consistent with more than modest associations between cytokine polymorphisms and recurrent miscarriage. Further research is required to assess the contribution that disordered cytokines make to recurrent miscarriage before routine cytokine tests can be introduced to clinical practice.

Evidence level 2++

4.7 Infective agents

Any severe infection that leads to bacteraemia or viraemia can cause sporadic miscarriage. The role of infection in recurrent miscarriage is unclear. For an infective agent to be implicated in the aetiology of repeated pregnancy loss, it must be capable of persisting in the genital tract and avoiding detection, or must cause insufficient symptoms to disturb the woman. Toxoplasmosis, rubella, cytomegalovirus, herpes and listeria infections do not fulfil these criteria and routine TORCH screening should be abandoned.⁶²

Evidence level 3

The presence of bacterial vaginosis in the first trimester of pregnancy has been reported as a risk factor for second-trimester miscarriage and preterm delivery,^{63,64} but the evidence for an association with first-trimester miscarriage is inconsistent.^{65,66} A randomised placebo-controlled trial⁶⁷ reported that treatment of bacterial vaginosis early in the second trimester with oral clindamycin significantly reduces the incidence of second-trimester miscarriage and preterm birth in the general population. There are no published data to assess the role of antibiotic therapy in women with a previous second-trimester miscarriage.

4.8 Inherited thrombophilic defects

Both inherited and acquired thrombophilias, including activated protein C resistance (most commonly due to factor V Leiden mutation), deficiencies of protein C/S and antithrombin III, hyperhomocysteinaemia and prothrombin gene mutation, are established causes of systemic thrombosis. In addition, inherited thrombophilias have been implicated as a possible cause in recurrent miscarriage and late pregnancy complications with the presumed mechanism being thrombosis of the uteroplacental circulation.

A meta-analysis⁶⁸ of pooled data from 31 retrospective studies suggested that the magnitude of the association between inherited thrombophilias and fetal loss varies according to type of fetal loss and type of thrombophilia. The association between thrombophilia and late pregnancy loss has been consistently stronger than for early pregnancy loss. In this meta-analysis, factor V Leiden was associated with recurrent first-trimester fetal loss (OR 2.01, 95% CI 1.13–3.58), recurrent fetal loss after 22 weeks (OR 7.83, 95% CI 2.83–21.67) and non-recurrent fetal loss after 19 weeks (OR 3.26, 95% CI 1.82–5.83). Activated protein C resistance was associated with recurrent first-trimester fetal loss (OR 3.48, 95% CI 1.58–7.69). Prothrombin gene mutation was associated with recurrent first-trimester fetal loss (OR 2.32, 95% CI 1.12–4.79), recurrent fetal loss before 25 weeks (OR 2.56, 95% CI 1.04–6.29) and late non-recurrent fetal loss (OR 2.3, 95% CI 1.09–4.87). Protein S deficiency was associated with recurrent fetal loss (OR 14, 95% CI 0.99–218) and non-recurrent fetal loss after 22 weeks (OR 7.39, 95% CI 1.28–42.83). Methylenetetrahydrofolate mutation and protein C and antithrombin deficiencies were not associated with fetal loss. However, since protein C and antithrombin III deficiencies are rare, the number of women included in the study was too small to show any difference in pregnancy outcome.

Evidence level 2++

Similarly, another meta-analysis⁶⁹ of 16 case-control studies reported that carriers of factor V Leiden or prothrombin gene mutation have double the risk of experiencing recurrent miscarriage compared with women without these thrombophilic mutations.

Evidence level 2++

Prospective data on the outcome of untreated pregnancies in women with hereditary thrombophilias are scarce. One small study⁷⁰ of six hereditary thrombophilias reported no adverse effects on the live birth rate of women with recurrent miscarriage. By contrast, two small prospective studies^{71,72} reported an increased risk of miscarriage in untreated pregnancies for women with recurrent miscarriage who carry the factor V Leiden mutation compared with those with a normal factor V genotype.

Evidence level 2+

5. What are the recommended investigations of couples with recurrent first-trimester miscarriage and second-trimester miscarriage?

Women with recurrent first-trimester and second-trimester miscarriage should be looked after by a health professional with the necessary skills and expertise. Where available, this might be within a recurrent miscarriage clinic.



The loss of pregnancy at any stage can be a devastating experience and particular sensitivity is required in assessing and counselling couples with recurrent miscarriage. Ideally, the couple should be seen together at a dedicated recurrent miscarriage clinic and given accurate information to facilitate decision making about future pregnancies. Clearly written patient leaflets are recommended to provide written information that the couple can take home.

5.1 Antiphospholipid antibodies

All women with recurrent first-trimester miscarriage and all women with one or more second-trimester miscarriage should be screened before pregnancy for antiphospholipid antibodies.



To diagnose antiphospholipid syndrome it is mandatory that the woman has two positive tests at least 12 weeks apart for either lupus anticoagulant or anticardiolipin antibodies of immunoglobulin G and/or immunoglobulin M class present in a medium or high titre over 40 g/l or ml/l, or above the 99th percentile).

In the detection of lupus anticoagulant, the dilute Russell's viper venom time test together with a platelet neutralisation procedure is more sensitive and specific than either the activated partial thromboplastin time test or the kaolin clotting time test.³¹ Anticardiolipin antibodies are detected using a standardised enzyme-linked immunosorbent assay.

The detection of antiphospholipid antibodies is subject to considerable inter-laboratory variation.⁷³ This is a result of temporal fluctuation of antiphospholipid antibody titres in individual women, transient positivity secondary to infections, suboptimal sample collection and preparation and lack of standardisation of laboratory tests for their detection.

5.2 Karyotyping

Cytogenetic analysis should be performed on products of conception of the third and subsequent consecutive miscarriage(s).



Parental peripheral blood karyotyping of both partners should be performed in couples with recurrent miscarriage where testing of products of conception reports an unbalanced structural chromosomal abnormality.



Knowledge of the karyotype of the products of conception allows an informed prognosis for a future pregnancy outcome to be given. While a sporadic fetal chromosome abnormality is the most common cause of any single miscarriage, the risk of miscarriage as a result of fetal aneuploidy decreases with an increasing number of pregnancy losses.⁴¹ If the karyotype of the miscarried pregnancy is abnormal, there is a better prognosis for the next pregnancy.³⁹

Evidence level 4

A Dutch study³⁸ reported that couples with balanced translocations have a low risk (0.8%) of pregnancies with an unbalanced karyotype surviving into the second trimester and that their chance of having a healthy child is 83%. A recent retrospective UK audit⁷⁴ of four UK centres over periods of 5–30 years reported that balanced translocations were found in 1.9% (406 of 20 432) of parents with recurrent miscarriage, but only four unbalanced translocations were found after referral for prenatal diagnosis because of balanced parental translocation ascertained for recurrent miscarriage. At an estimated cost of £3–4 million (the total cost of karyotyping 20 432 individuals calculated at £160–200 per karyotype), the data suggest that routine karyotyping of couples with recurrent miscarriage cannot be justified. Selective parental karyotyping may be more appropriate when an unbalanced chromosome abnormality is identified in the products of conception.

Evidence level 3

5.3 Anatomical factors

All women with recurrent first-trimester miscarriage and all women with one or more second-trimester miscarriages should have a pelvic ultrasound to assess uterine anatomy.



Suspected uterine anomalies may require further investigations to confirm the diagnosis, using hysteroscopy, laparoscopy or three-dimensional pelvic ultrasound.



A review⁷⁵ of studies comparing the diagnostic accuracy of various imaging modalities has reported that two-dimensional ultrasound scanning and/or hysterosalpingography can be used as an initial screening test. Combined hysteroscopy and laparoscopy and possibly three-dimensional ultrasound scanning should be used for definitive diagnosis. The value of magnetic resonance imaging scanning remains undetermined.

Evidence level 3

5.4 Thrombophilias

Women with second-trimester miscarriage should be screened for inherited thrombophilias including factor V Leiden, factor II (prothrombin) gene mutation and protein S.

D

A meta-analysis⁶⁸ of retrospective studies has reported a strong association between second-trimester miscarriage and inherited thrombophilias: factor V Leiden, factor II (prothrombin) gene mutation and protein S deficiency.

Evidence level 2++

6. Treatment options for recurrent miscarriage

6.1 What are the treatment options for recurrent first trimester and second trimester miscarriage?

Women with recurrent miscarriage should be offered referral to a specialist clinic.



6.2 Antiphospholipid syndrome

Pregnant women with antiphospholipid syndrome should be considered for treatment with low-dose aspirin plus heparin to prevent further miscarriage.

B

A meta-analysis⁷⁶ of randomised controlled trials examined the outcomes of various treatments – including aspirin, steroids, intravenous globulin and heparin – given to improve pregnancy outcome of women with recurrent miscarriage associated with antiphospholipid antibodies. This meta-analysis reported that the only treatment or treatment combination that leads to a significant increase in the live birth rate among women with antiphospholipid syndrome is aspirin plus unfractionated heparin. This treatment combination significantly reduces the miscarriage rate by 54% (aspirin plus unfractionated heparin compared with aspirin alone: RR 0.46, 95% CI 0.29–0.71).

Evidence level 1+

Two small prospective studies^{77,78} reported no difference in efficacy and safety between unfractionated heparin and low-molecular-weight heparin when combined with aspirin in the treatment of women with recurrent miscarriage associated with antiphospholipid antibodies.

Evidence level 1+

The value of heparin has been questioned in two studies.^{79,80} However, there were methodological weaknesses in both demographic and laboratory entry criteria and time of randomisation.

There are no adverse fetal outcomes reported in the meta-analysis of randomised controlled trials of low-dose aspirin for the prevention of pre-eclampsia in pregnancy.⁸¹ Heparin does not cross the placenta and hence there is no potential to cause fetal haemorrhage or teratogenicity. Heparin can, however, be associated with maternal complications including bleeding, hypersensitivity reactions, heparin-induced thrombocytopenia and, when used long term, osteopenia and vertebral fractures. Two prospective studies^{82,83} have shown that the loss of bone mineral density at the lumbar spine associated with low-dose long-term heparin therapy is similar to that which occurs physiologically during normal pregnancy.

Evidence level 2+

Low-molecular-weight heparin is as safe as unfractionated heparin and has potential advantages during pregnancy, since it causes less heparin-induced thrombocytopenia, can be administered once daily and is associated with a lower risk of heparin-induced osteoporosis.⁸⁴

Pregnancies associated with antiphospholipid antibodies treated with aspirin and heparin remain at high risk of complications during all three trimesters. Although aspirin plus heparin treatment substantially improves the live birth rate of women with recurrent miscarriage associated with antiphospholipid antibodies, these pregnancies remain at high risk of complications during all three trimesters, including repeated miscarriage, pre-eclampsia, fetal growth restriction and preterm birth;^{85,86} this necessitates careful antenatal surveillance.

Evidence level 2+

Neither corticosteroids nor intravenous immunoglobulin therapy improve the live birth rate of women with recurrent miscarriage associated with antiphospholipid antibodies compared with other treatment modalities; their use may provoke significant maternal and fetal morbidity.

A

A meta-analysis⁷⁶ of randomised controlled trials reported that treating women who suffer recurrent miscarriage associated with antiphospholipid antibodies with corticosteroids during pregnancy does not improve the live birth rate compared with aspirin or aspirin plus heparin (prednisone and aspirin compared with placebo or aspirin alone: RR 0.85, 95% CI 0.53–1.36; and compared with heparin and aspirin: RR 1.17, 95% CI 0.47–2.93). Steroid therapy is associated with significant maternal and fetal morbidity.

Evidence level 1+

A randomised controlled trial⁸⁷ reported that women with recurrent miscarriage associated with antiphospholipid antibodies treated with low-molecular-weight heparin plus aspirin had a higher rate of live births than those treated with intravenous immunoglobulin (RR 2.28, 95% CI 0.81–6.4). Similarly, another randomised controlled trial⁸⁸ reported that low-molecular-weight heparin plus aspirin resulted in a higher live birth rate than intravenous immunoglobulin in the treatment of women with recurrent miscarriage associated with antiphospholipid antibodies (OR 1.80, 95% CI 1.14–2.84).

Evidence level 1+

6.2 Genetic factors

The finding of an abnormal parental karyotype should prompt referral to a clinical geneticist.

D

Genetic counselling offers the couple a prognosis for the risk of future pregnancies with an unbalanced chromosome complement and the opportunity for familial chromosome studies.

Reproductive options in couples with chromosomal rearrangements include proceeding to a further natural pregnancy with or without a prenatal diagnosis test, gamete donation and adoption.

Preimplantation genetic diagnosis has been proposed as a treatment option for translocation carriers.^{89,90} Since preimplantation genetic diagnosis necessitates that the couple undergo in vitro fertilisation to produce embryos, couples with proven fertility need to be aware of the financial cost as well as implantation and live birth rates per cycle following in vitro fertilisation/preimplantation genetic diagnosis. Furthermore, they should be informed that they have a higher (50–70%) chance of a healthy live birth in future untreated pregnancies following natural conception^{37,38,91} than is currently achieved after preimplantation genetic diagnosis/in vitro fertilisation (approximately 30%).⁹²

Evidence level 4

Preimplantation genetic screening with in vitro fertilisation treatment in women with unexplained recurrent miscarriage does not improve live birth rates.

C

Preimplantation genetic screening in conjunction with in vitro fertilisation has been advocated as a treatment option for women with recurrent miscarriage, the rationale being that the identification and transfer of what are thought to be genetically normal embryos will lead to a live birth. The live birth rate of women with unexplained recurrent miscarriage who conceive naturally is significantly higher than currently achieved after preimplantation genetic screening/in vitro fertilisation (20–30%).^{92–95}

Evidence level 2+

6.3 Anatomical factors

6.3.1 Congenital uterine malformations

There is insufficient evidence to assess the effect of uterine septum resection in women with recurrent miscarriage and uterine septum to prevent further miscarriage.

C

There are no published randomised trials assessing the benefits of surgical correction of uterine abnormalities on pregnancy outcome. Open uterine surgery has never been assessed in prospective trials but is associated with postoperative infertility and carries a significant risk of uterine scar rupture during pregnancy.⁹⁶ These complications are less likely to occur after transcervical hysteroscopic resection of uterine septae; experience from case series appears promising.⁹⁷ However, before a clear judgement can be made, this procedure must be evaluated in a prospective controlled trial.

6.3.2 Cervical weakness and cervical cerclage

Cervical cerclage is associated with potential hazards related to the surgery and the risk of stimulating uterine contractions and hence should be considered only in women who are likely to benefit.

A

Women with a history of second-trimester miscarriage and suspected cervical weakness who have not undergone a history-indicated cerclage may be offered serial cervical sonographic surveillance.

B

In women with a singleton pregnancy and a history of one second-trimester miscarriage attributable to cervical factors, an ultrasound-indicated cerclage should be offered if a cervical length of 25 mm or less is detected by transvaginal scan before 24 weeks of gestation.

B

The role of cervical cerclage in the prevention of preterm birth has been examined in a recently published RCOG Green-top Guideline.⁹⁸ A Cochrane review⁹⁹ of four randomised controlled trials found no conclusive evidence that prophylactic cerclage reduces the risk of pregnancy loss and preterm delivery in women at risk of preterm birth or mid-trimester loss owing to cervical factors. Furthermore, the procedure was associated with a high risk of minor morbidity but no serious morbidity. A small reduction in deliveries before 33 weeks of gestation was noted in the largest trial.¹⁰⁰ The benefit was most marked in women with three or more second-trimester miscarriages or preterm births. However, there was no significant improvement in perinatal survival.

A short cervical length on transvaginal ultrasound during pregnancy may be useful in predicting preterm birth in some cases of suspected cervical weakness. A meta-analysis¹⁰¹ of individual patient-level data from four randomised controlled trials reported that in a subgroup analysis of women with singleton pregnancies, a short cervix (less than 25 mm) and previous second-trimester miscarriage, cerclage may reduce the incidence of preterm birth before 35 weeks of gestation (RR 0.57, 95% CI 0.33–99).

Evidence level 1+

Transabdominal cerclage has been advocated as a treatment for second-trimester miscarriage and the prevention of early preterm labour in selected women with a previous failed transvaginal cerclage and/or a very short and scarred cervix.¹⁰²⁻¹⁰⁴ In the absence of any control groups, the reported improvement in pregnancy outcome is difficult to assess. A systematic review¹⁰⁵ compared abdominal with vaginal cerclage in women with failed vaginal cerclage in a previous pregnancy. This review concluded that abdominal cerclage may be associated with a lower risk of perinatal death or delivery before 24 weeks of gestation and a higher risk of serious operative complications. Whether to perform transabdominal cerclage before pregnancy or during pregnancy remains uncertain.¹⁰⁶

6.4 Endocrine factors

There is insufficient evidence to evaluate the effect of progesterone supplementation in pregnancy to prevent a miscarriage in women with recurrent miscarriage.

B

Progesterone is necessary for successful implantation and the maintenance of pregnancy. This benefit of progesterone could be explained by its immunomodulatory actions in inducing a pregnancy-protective shift from pro-inflammatory Th-1 cytokine responses to a more favourable anti-inflammatory Th-2 cytokine response.¹⁰⁷ A meta-analysis¹⁰⁸ to assess progesterone support for pregnancy showed that it did not reduce the sporadic miscarriage rate. However, in a subgroup analysis of trials involving women with recurrent miscarriage, progesterone treatment offered a statistically significant decrease in miscarriage rate compared with placebo or no treatment (OR 0.38, 95% CI 0.2-0.7). However, this meta-analysis was based on three small controlled studies, none of which detected a significant improvement in pregnancy outcome. A large multicentre study (PROMISE, <http://www.medscinet.net/promise>) is currently under way to assess the benefit of progesterone supplementation in women with unexplained recurrent miscarriage.

Evidence level 1+

There is insufficient evidence to evaluate the effect of human chorionic gonadotrophin supplementation in pregnancy to prevent a miscarriage in women with recurrent miscarriage.

B

A multicentre placebo-controlled study of human chorionic gonadotrophin supplementation in early pregnancy failed to show any benefit in pregnancy outcome.¹⁰⁹ However, another small placebo-controlled study stated that the benefit of human chorionic gonadotrophin is confined to a small subgroup ($n = 23$) of women with recurrent miscarriage and oligomenorrhoea.¹¹⁰ Human chorionic gonadotrophin supplementation in early pregnancy should be used only in the context of randomised controlled trials.

Evidence level 1+

Suppression of high luteinising hormone levels among ovulatory women with recurrent miscarriage and polycystic ovaries does not improve the live birth rate.

A

Luteinising hormone hypersecretion, a frequent feature of PCOS, has been reported as a risk factor for early pregnancy loss. A randomised controlled trial¹¹¹ has shown that prepregnancy pituitary suppression of luteinising hormone among ovulatory women with recurrent miscarriage and polycystic ovaries who hypersecrete luteinising hormone does not improve the live birth rate. Furthermore, the outcome of pregnancy without pituitary suppression is similar to that of women without raised luteinising hormone.

Evidence level 1+

There is insufficient evidence to evaluate the effect of metformin supplementation in pregnancy to prevent a miscarriage in women with recurrent miscarriage.

C

The increased risk of miscarriage in women with PCOS has been attributed to insulin resistance and hyperinsulinaemia. However, a meta-analysis¹¹² of 17 randomised controlled trials of metformin, an insulin-sensitising agent, in women with PCOS and infertility showed that metformin has no effect on the sporadic miscarriage risk when administered pre-pregnancy.

Evidence level 1++

Uncontrolled small studies¹¹³ have shown that use of metformin during pregnancy is associated with a reduction in the miscarriage rate in women with recurrent miscarriage and PCOS. However, there are no randomised controlled trials to assess the role of metformin in women with recurrent miscarriage.

6.5 Immunotherapy

Paternal cell immunisation, third-party donor leucocytes, trophoblast membranes and intravenous immunoglobulin in women with previous unexplained recurrent miscarriage does not improve the live birth rate.

A

A Cochrane systematic review¹¹⁴ has shown that the use of various forms of immunotherapy, including paternal cell immunisation, third-party donor leucocytes, trophoblast membranes and intravenous immunoglobulin, in women with unexplained recurrent miscarriage provides no significant beneficial effect over placebo in preventing further miscarriage. A 2010 meta-analysis¹¹⁵ confirmed this conclusion with respect to intravenous immunoglobulin. Moreover, immunotherapy is expensive and has potentially serious adverse effects including transfusion reaction, anaphylactic shock and hepatitis. The use of immunotherapy should no longer be offered to women with unexplained recurrent miscarriage.

Evidence level 1++

There are no published data on the use of anti-TNF agents to improve pregnancy outcome in women with recurrent miscarriage. Furthermore, anti-TNF agents could potentially cause serious morbidity including lymphoma, granulomatous disease such as tuberculosis, demyelinating disease, congestive heart failure and syndromes similar to systemic lupus erythematosus.

Immune treatments should not be offered routinely to women with recurrent miscarriage outside formal research studies.

6.6 Inherited thrombophilias

There is insufficient evidence to evaluate the effect of heparin in pregnancy to prevent a miscarriage in women with recurrent first-trimester miscarriage associated with inherited thrombophilia.

C

Heparin therapy during pregnancy may improve the live birth rate of women with second-trimester miscarriage associated with inherited thrombophilias.

A

Women with known heritable thrombophilia are at an increased risk of venous thromboembolism. See RCOG Green-top Guideline No. 37a: *Reducing the risk of thrombosis and embolism during pregnancy and the puerperium*.¹¹⁶

The efficacy of thromboprophylaxis during pregnancy in women with recurrent first-trimester miscarriage who have inherited thrombophilias, but who are otherwise asymptomatic, has not been assessed in prospective randomised controlled trials. Cohort studies¹¹⁷⁻¹¹⁹ have suggested that heparin therapy may improve the live birth rate for these women.

Evidence level 3

One prospective randomised trial¹²⁰ demonstrated the efficacy of the low-molecular-weight heparin enoxaparin for the treatment of women with a history of a single late miscarriage after 10 weeks of gestation who carry the factor V Leiden or prothrombin gene mutation or have protein S deficiency. The live birth rate of women treated with enoxaparin was 86% compared with 29% in women taking low-dose aspirin alone (OR 15.5, 95% CI 7–34).

Evidence
level 1+

6.7 Unexplained recurrent miscarriage

Women with unexplained recurrent miscarriage have an excellent prognosis for future pregnancy outcome without pharmacological intervention if offered supportive care alone in the setting of a dedicated early pregnancy assessment unit.

B

A significant proportion of cases of recurrent miscarriage remain unexplained despite detailed investigation. These women can be reassured that the prognosis for a successful future pregnancy with supportive care alone is in the region of 75%.^{6,121} However, the prognosis worsens with increasing maternal age and the number of previous miscarriages. The value of psychological support in improving pregnancy outcome has not been tested in the form of a randomised controlled trial. However, data from several non-randomised studies^{6,121,122} have suggested that attendance at a dedicated early pregnancy clinic has a beneficial effect, although the mechanism is unclear.

Evidence
level 2+

Aspirin alone or in combination with heparin is being prescribed for women with unexplained recurrent miscarriage, with the aim of improving pregnancy outcome. Two recent randomised controlled trials reported that neither of these interventions improves the live birth rate among women with unexplained recurrent miscarriage.^{123,124} However, it should be noted that both studies included a significant number of women with only two previous miscarriages (40% and 57% of the study population, respectively).

Evidence
level 1+

These data suggest that the use of empirical treatment in women with unexplained recurrent miscarriage is unnecessary and should be resisted. Furthermore, clinical evaluation of future treatments for recurrent miscarriage should be performed only in the context of randomised trials of sufficient power to determine efficacy.

7. Suggested audit topics

- Correct assessment and investigations of couples with recurrent miscarriage.
- Pregnancy outcome of women with recurrent miscarriage.

8. Future research

- The role of uterine NK cells and cytokines in recurrent miscarriage.
- The role of uterine septum resection in women with recurrent miscarriage and septate uterus.
- Thromboprophylaxis in women with thrombophilia and recurrent first-trimester miscarriage.
- Progesterone treatment in women with unexplained recurrent miscarriage.
- Metformin treatment in women with recurrent miscarriage and insulin resistance.

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Appendix

Classification of evidence levels	Grades of recommendations
<p>1++ High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias</p> <p>1+ Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias</p> <p>1- Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias</p> <p>2++ High-quality systematic reviews of case-control or cohort studies or high-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal</p> <p>2+ Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal</p> <p>2- Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal</p> <p>3 Non-analytical studies, e.g. case reports, case series</p> <p>4 Expert opinion</p>	<p>A At least one meta-analysis, systematic review or randomised controlled trial rated as 1++ and directly applicable to the target population; or</p> <p>A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results</p> <p>B A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or</p> <p>Extrapolated evidence from studies rated as 1++ or 1+</p> <p>C A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or</p> <p>Extrapolated evidence from studies rated as 2++</p> <p>D Evidence level 3 or 4; or</p> <p>Extrapolated evidence from studies rated as 2+</p> <p>Good practice point</p> <p> Recommended best practice based on the clinical experience of the guideline development group</p>

This guideline was produced on behalf of the Royal College of Obstetricians and Gynaecologists by:

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The final version is the responsibility of the Guidelines Committee of the RCOG.

The guideline review process will commence in 2014 unless evidence requires earlier review.

DISCLAIMER

The British Society of Gynaecological Endoscopists produces guidelines as an educational aid to good clinical practice. They present recognised methods and techniques of clinical practice, based on published evidence, for consideration by gynaecologists and other relevant health professionals. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the doctor or other attendant in the light of clinical data presented by the patient and the diagnostic and treatment options available. This means that BSGE guidelines are unlike protocols or guidelines issued by employers, not being intended to be prescriptive directions defining a single course of management. Departure from the local prescriptive protocols or guidelines should be fully documented in the patient's case notes at the time the relevant decision is taken.

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