Royal College of Obstetricians and Gynaecologists

Setting standards to improve women's health

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THE INVESTIGATION AND TREATMENT OF COUPLES WITH RECURRENT MISCARRIAGE

1. Purpose and scope

Recurrent miscarriage is defined as the loss of three or more pregnancies. Recurrent miscarriage is a heterogeneous condition that has many possible causes; more than one contributory factor may underlie the recurrent pregnancy losses.

The purpose of this guideline is to review the literature and provide guidance on the investigation and treatment of couples with recurrent miscarriage.

2. 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 2002 was also carried out. The date of the last search was February 2002. In addition, relevant conference proceedings and abstracts were searched.

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

The definitions of the types of evidence used in this guideline originate from the US Agency for Healthcare Research and Quality (Appendix). 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.'

3. Introduction and background

Recurrent miscarriage is a distressing problem that affects 1% of all women.[1] This incidence is greater than that expected by chance alone, since 10–15% of all clinically recognised pregnancies end in a miscarriage[2] and the theoretical risk of three consecutive pregnancy losses is 0.34%.[3] Hence, only a proportion of women presenting with recurrent miscarriage will have a persistent underlying cause for their pregnancy losses.

Maternal age and previous number of miscarriages are two independent risk factors for a further miscarriage.[2,4] Advanced maternal age adversely affects ovarian function, giving rise to a decline in the number of good quality oocytes, resulting in chromosomally abnormal conceptions that rarely develop further.

4. Investigations and treatments

4.1 Genetic factors

C **All couples with a history of recurrent miscarriage should have peripheral blood karyotyping performed. The finding of an abnormal parental karyotype should prompt referral to a clinical geneticist.**

In approximately 3–5% of couples with recurrent miscarriage, one of the partners carries a balanced structural chromosomal anomaly. The most common types of parental chromosomal abnormality are balanced reciprocal or Robertsonian translocations.[5,6] The identification of an abnormal parental karyotype warrants prompt referral to a clinical geneticist. Genetic counselling offers the couple a prognosis for future pregnancy, familial chromosomal studies, counselling and appropriate prenatal diagnosis in future pregnancies where there is a 5–10% chance of a pregnancy with an unbalanced translocation. Recently, preimplantation genetic diagnosis has been explored as a treatment option for translocation carriers.[7,8] However, this is a technically demanding procedure and experience is still limited. Since the technique necessitates that the couple undergo *in vitro* fertilisation (IVF) to produce embryos, couples with proven fertility need to be aware of the low implantation and live birth rates per cycle following IVF. Further, they should be informed that they have a 40–50% chance of a healthy live birth in future untreated pregnancies following natural conception.[9]

Evidence level IV

C **In all couples with a history of recurrent miscarriage cytogenetic analysis of the products of conception should be performed if the next pregnancy fails.**

Recurrent pregnancy loss may be due to an abnormal embryo, which is incompatible with life, e.g. chromosomal abnormalities or structural malformations. As the number of miscarriages increases, the prevalence of chromosomal abnormality decreases[10] and the chance of recurring maternal cause increases.[11] If the karyotype of the miscarried pregnancy is abnormal, there is a better prognosis in the next pregnancy.[10,12] Cytogenetic testing is an expensive tool and may be reserved for patients who have undergone treatment in the index pregnancy or have been participants in a research trial; for them, karyotyping the products of conception provides useful information for counselling and future management.[6,13]

Evidence level IV

4.2 Anatomical factors

It is difficult to assess the exact contribution that congenital uterine anomalies make to recurrent pregnancy loss. The prevalence and reproductive implications of uterine anomalies in the general population have not been clearly established. The reported prevalence of uterine anomalies in recurrent miscarriage populations range between 1.8% and 37.6%.[14] 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 at both early and late stages of pregnancy. The prevalence of uterine malformations appears to be higher in women with late miscarriages compared with women who suffer early miscarriages but this may be related to the cervical weakness that is frequently associated with uterine malformation.[15] A recent retrospective review of reproductive performance in patients with untreated uterine anomalies has suggested that these women experience high rates of miscarriage and preterm delivery and a term delivery rate of only 50%.[14] Open uterine surgery is associated with postoperative infertility and carries a significant risk of uterine scar rupture during pregnancy.[16] These complications are less likely to occur after hysteroscopic surgery[14,17] but no randomised trial assessing the benefits of surgical correction of uterine abnormalities on pregnancy outcome has been performed.

The routine use of hysterosalpingography as a screening test for uterine anomalies in women with recurrent miscarriage is questionable. It is associated with patient discomfort, carries a risk of pelvic infection and radiation exposure and is no more sensitive than the non-invasive two-dimensional pelvic ultrasound assessment of the uterine cavity with (or without) Sonohysterography,[6,18] when performed by skilled and experienced personnel.

The diagnostic value of three-dimensional ultrasound has been explored and appears promising.[19,20] Since three-dimensional ultrasound offer both diagnosis and classification of uterine malformation its use may obviate the need for diagnostic hysteroscopy and laparoscopy.

✓ **All women with recurrent miscarriage should have a pelvic ultrasound to assess uterine anatomy and morphology.**

4.3 cervical weakness

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

Cervical weakness is often over-diagnosed as a cause of mid-trimester miscarriage. 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 late miscarriage, preceded by spontaneous rupture of membranes or painless cervical dilatation. Transvaginal ultrasound assessment of the cervix during pregnancy may be useful in predicting preterm birth in some cases of suspected cervical weakness.[21] However, two randomised controlled trials failed to demonstrate any resulting significant improvement in perinatal survival from ultrasound-indicated cervical cerclage.[22,23] The MRC/RCOG trial of elective cervical cerclage reported a small decrease in preterm birth and delivery of very-low-birthweight babies, but 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.[24]

Evidence level Ib

Transabdominal cerclage has been advocated as a treatment for second-trimester miscarriage and the prevention of early preterm labour in selected women with previous failed transvaginal cerclage and/or a very short and scarred cervix.[25,26] In the absence of any control groups, the reported improvement in pregnancy outcome is difficult to assess. A recent systematic review[27] compared abdominal versus 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, but it may be associated with a higher risk of serious operative complications.

4.4 Endocrine factors

✓ **Routine screening for occult diabetes and thyroid disease with oral glucose tolerance and thyroid function tests in asymptomatic women presenting with recurrent miscarriage is uninformative.**

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.[28] However, well-controlled diabetes mellitus is not a risk factor for recurrent miscarriage, nor is treated thyroid dysfunction.[29,30] The prevalence of diabetes mellitus and thyroid dysfunction in women who suffer recurrent miscarriage is similar to that expected in the general population.[6,31,32]

A **There is insufficient evidence to evaluate the effect of progesterone supplementation in pregnancy to prevent a miscarriage.**

A review of pregnancy rates following hormonal treatments for luteal phase deficiency concluded that the benefits are uncertain.[33] The only meta-analysis to assess progesterone support for pregnancy in recurrent miscarriage found progesterone to have a beneficial effect.[34] However, this meta-analysis was based on three small controlled studies alone, none of which detected significant improvement in pregnancy outcome. Furthermore, the low progesterone levels that have been reported in early pregnancy loss may reflect a pregnancy that has already failed. Exogenous progesterone supplementation should only be used in the context of randomised controlled trials.

Evidence level Ia

A **There is insufficient evidence to evaluate the effect of human chorionic gonadotrophin (hCG) in pregnancy to prevent miscarriage.**

A multi-centre placebo controlled study of early pregnancy hCG supplementation failed to show any benefit in pregnancy outcome.[35] However, another small placebo controlled study cited that the benefit of hCG is confined to a small subgroup (n = 23) of patients with recurrent miscarriage and oligomenorrhoea.[36] HCG supplementation in early pregnancy should only be used in the context of randomised controlled trials.

Evidence level Ib

A **Prepregnancy suppression of high luteinising hormone (LH) concentration among ovulatory women with recurrent miscarriage and polycystic ovaries who hypersecrete LH does not improve the live birth rate.**

Polycystic ovarian syndrome (PCOS) has been linked to miscarriage. LH hypersecretion, a frequent feature of PCOS, has been reported as a risk factor for early pregnancy loss. A randomised controlled trial[37] has shown that prepregnancy pituitary suppression of LH among ovulatory women with recurrent miscarriage and polycystic ovaries who hypersecrete LH does not improve the live birth rate. Furthermore, the outcome of pregnancy without pituitary suppression is similar to that of patients without raised LH.

Evidence level Ib

B **Polycystic ovary morphology itself does not predict an increased risk of future pregnancy loss among ovulatory women with a history of recurrent miscarriage who conceive spontaneously.**

Polycystic ovary morphology is a classical feature of PCOS. The prevalence of polycystic ovaries, identified using pelvic ultrasound criteria, is significantly higher among women with recurrent miscarriage (41%) when compared with the general population (22%).[38] However, despite this high prevalence, polycystic ovary morphology itself does not predict an increased risk of future pregnancy loss among ovulatory women with a history of recurrent miscarriage who conceive spontaneously.[38] Future research should be directed at identifying alternative endocrine features that are predictive of miscarriage in women with PCOS.

Evidence level III

A history of subfertility (conception delay greater than 12 months) is present in 25–30% of women with recurrent miscarriage. It is most frequently due to ovulatory disorders and confers a poor prognosis for future pregnancy outcome.[6] Persistently raised follicle-stimulating hormone levels are found in a small percentage of these women and this should prompt further investigation and counselling for the implications of premature ovarian failure.[6]

A **There is insufficient evidence to assess the effect of hyperprolactinaemia as a risk factor for recurrent miscarriage.**

The role of hyperprolactinaemia as a risk factor for recurrent miscarriage is debatable and the evidence is conflicting.[31,32] A randomised controlled trial[39] involving 64 women with a history of two or more miscarriages and hyperprolactinaemia not associated with any ovarian or endocrine abnormality has reported that the percentage of successful pregnancies was significantly higher in the bromocriptine-treated group (85.7%) compared with those receiving no treatment (52.4%). However, this study is open to criticism due to the definitions used for hyperprolactinaemia and recurrent miscarriage.[40]

Evidence level Ib

4.5. Immune factors

4.5.1. Antithyroid antibodies

B **Routine screening for thyroid antibodies in women with recurrent miscarriage is not recommended.**

A case–control study[41] has shown that women with recurrent miscarriages are no more likely than fertile controls to have circulating thyroid antibodies. A prospective study[42] 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 III

4.5.2. Antiphospholipid syndrome

Primary antiphospholipid syndrome (APS) refers to the association between antiphospholipid antibodies (aPL) and adverse pregnancy outcome or vascular thrombosis.[43] Adverse pregnancy outcomes include (a) three or more consecutive miscarriages before ten weeks of gestation, (b) one or more morphologically normal fetal deaths after the tenth week of gestation and (c) one or more preterm births before the 34th week of gestation due to severe pre-eclampsia, eclampsia or placental insufficiency. Where APS exists in chronic inflammatory disorders, such as systemic lupus erythematosus, it is referred as secondary APS.

The mechanisms by which aPL causes pregnancy morbidity include inhibition of trophoblastic function and differentiation[44–47] and, in later pregnancy, thrombosis of the uteroplacental vasculature.[48–50]

C **To diagnose APS it is mandatory that the patient should have two positive tests at least six weeks apart for either lupus anticoagulant or anticardiolipin (aCL) antibodies of IgG and/or IgM class present in medium or high titre.**

In detection of lupus anticoagulant, the dilute Russell's viper venom time (dRVVT) test is more sensitive and specific than either the activated partial thromboplastin time (aPTT) or the kaolin clotting time (KCL) tests.[51] Anticardiolipin antibodies are detected using a standardised enzyme-linked immunosorbent assay (ELISA). The detection of aPL is subject to considerable inter-laboratory variation.[52] This is due to temporal fluctuation of aPL titres in individual patients, transient positivity secondary to infections, suboptimal sample collection and preparation and lack of standardisation of laboratory tests for their detection.

Antiphospholipid antibodies are present in 15% of women with recurrent miscarriage.[51] By comparison, the prevalence of aPL in women with a low risk obstetric history is less than 2%.[53,54] In women with recurrent miscarriage associated with aPL, the live birth rate in pregnancies with no pharmacological intervention may be as low as 10%.[55]

A **Currently there is no reliable evidence to show that steroids improve the live birth rate of women with recurrent miscarriage associated with aPL when compared with other treatment modalities; their use may provoke significant maternal and fetal morbidity.**

Two small randomised controlled trials have reported that treating women who suffer recurrent miscarriage associated with aPL with steroid therapy during pregnancy does not improve the live birth rate when compared with aspirin or aspirin plus heparin. Steroid therapy is associated with significant maternal and fetal morbidity.[56,57]

Evidence level Ib

A **In women with a history of recurrent miscarriage and aPL, future live birth rate is significantly improved when a combination therapy of aspirin plus heparin is prescribed.**

A randomised controlled trial[58] showed that the live birth rate of women with recurrent miscarriage associated with aPL treated with low-dose aspirin only is 40% and this is significantly improved to 70% when they are treated with low-dose aspirin in combination with low-dose heparin.

Evidence level Ib

A meta-analysis[59] of two controlled trials concluded that, in women with a history of recurrent miscarriage associated with aPL, treatment with low-dose heparin plus low-dose aspirin significantly reduced the pregnancy losses by 54% when compared with aspirin alone. However, these trials do not exclude the possibility of placebo effect from heparin treatment.

Evidence level Ia

The same meta-analysis[59] examined the role of aspirin alone compared with placebo or supportive care and found no significant benefit (three trials).

A recent randomised controlled trial[60] reported a high success rate with aspirin alone and no significant benefit in live birth rate with the addition of heparin. However, this study included women with low titres of aPL, some of whom were randomised at up to 12 weeks of gestation, by which time most of aPL-related pregnancy losses would have already occurred.

Evidence level Ib

B **Pregnancies associated with aPL 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 aPL, these pregnancies remain at high risk of complications during the three trimesters including repeated miscarriage, pre-eclampsia, fetal growth restriction and preterm birth,[58,61,62] necessitating careful antenatal surveillance.

Evidence level III

Osteopenia and vertebral bone fracture are the major concern of long-term heparin therapy. Two prospective studies[63,64] have shown that the loss in bone mineral density at the lumbar spine associated with low-dose long-term heparin therapy is similar to that which occurs physiologically during pregnancy.

4.5.3. Alloimmune factors

A **Immunotherapy, including paternal cell immunisation, third-party donor leucocytes, trophoblast membranes and intravenous immunoglobulin (IVIG), in women with previous unexplained recurrent miscarriage does not improve the live birth rate.**

There is no clear evidence to support the hypothesis that HLA incompatibility between couples, the absence of maternal leucocytotoxic antibodies or the absence of

Evidence level Ia

maternal blocking antibodies are related to recurrent miscarriage. The role of endometrial immunity in recurrent early pregnancy loss is currently under investigation. It has been suggested that immune effector cell dysfunction (defects in the immunosuppressive factors, cytokines and growth factors at the local maternofetal interface) may be implicated in the pathogenesis of implantation failure and recurrent early pregnancy loss.[65,66] However, this is a research field and the association and methods of treatment require further clarification.

A Cochrane systematic review[67] of 18 randomised controlled trials has shown that the use of various forms of immunotherapy, including paternal cell immunisation, third-party donor leucocytes, trophoblast membranes and IVIG, in women with unexplained recurrent miscarriage provides no significant beneficial effect over placebo in preventing further miscarriage. Another meta-analysis[68] indicated that IVIG treatment does not improve the live birth rate in women with unexplained recurrent miscarriage. 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 and routine tests for HLA type and anti-paternal cytotoxic antibody should be abandoned.

Evidence level Ia

The USA Food and Drug Administration has recently issued a statement to clinicians that administration of such cells or cellular products in humans can only be performed by a licensed clinical researcher holding a currently approved Investigational New Drug application.[69]

4.6 Infective agents

C **TORCH (toxoplasmosis, other [congenital syphilis and viruses], rubella, cytomegalovirus and herpes simplex virus) screening is unhelpful in the investigation of recurrent miscarriage.**

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 women. Toxoplasmosis, rubella, cytomegalovirus, herpes and listeria infections do not fulfil these criteria and routine TORCH screening should be abandoned.[70,71]

Evidence level III

A **Screening for and treatment of bacterial vaginosis in early pregnancy among high risk women with a previous history of second-trimester miscarriage or spontaneous preterm labour may reduce the risk of recurrent late loss and preterm birth.**

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[72] but the evidence for an association with first-trimester miscarriage is inconsistent.[73,74] A Cochrane systematic review[75] of five randomised controlled trials and a further three randomised placebo-controlled trials[76–78] have all shown that there is no benefit in screening and treating all pregnant women for bacterial vaginosis in order to prevent preterm birth and its consequences. However, the Cochrane review[75] has shown that for women with a history of previous preterm birth, detection and treatment of bacterial vaginosis early in pregnancy may prevent a further preterm birth. Whether this treatment improves neonatal outcome is unclear at present.

Evidence level Ia

4.7 Inherited thrombophilic defects

Inherited thrombophilic defects, including activated protein C resistance (most commonly due to factor V Leiden gene mutation), deficiencies of protein C/S and antithrombin III, hyperhomocysteinaemia and prothrombin gene mutation, are established causes of systemic thrombosis.

Retrospective studies[79] have suggested an association between inherited thrombophilic defects and fetal loss and late pregnancy complications, with a presumed mechanism being thrombosis of uteroplacental circulation. However, prospective data are scarce. One small study[80] found that the six hereditary thrombophilias have no effects on the live birth rate of women with recurrent miscarriage. By contrast, another small prospective study[81] has demonstrated that women with recurrent miscarriage who carry the factor V Leiden (FVL) mutation are at significantly increased risk of miscarriage, compared to those with a normal factor V genotype. However, carriage of the FVL mutation did not preclude an uncomplicated pregnancy delivered at term. Currently there is no test that can reliably discriminate those women with recurrent miscarriage and FVL mutation who are destined to miscarry from those who are destined to have a successful pregnancy.

The efficacy of thromboprophylaxis during pregnancy in women with recurrent miscarriage who have inherited thrombophilic defects, but who are otherwise asymptomatic, has not been assessed in prospective randomised controlled trials. Three uncontrolled studies[82–84] have suggested that heparin therapy may improve the live birth rate for these women. Recruitment to a randomised controlled trial of thromboprophylaxis has so far proven to be difficult, owing to the low prevalence[85] of FVL mutation in women with recurrent miscarriage. In the absence of a randomised trial, the poor pregnancy outcome associated with FVL mutation, coupled with the maternal risks during pregnancy, may justify routine screening for FVL and offering thromboprophylaxis for those with FVL mutation and evidence of placental thrombosis.

4.8 Unexplained recurrent miscarriage

C **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.**

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%.[86,87] 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[86–88] have suggested that attendance at a dedicated early pregnancy clinic has a beneficial effect, although the mechanism is unclear. These data suggest that the use of empirical treatment in women with unexplained recurrent miscarriage is unnecessary and should be resisted. Further, clinical evaluation of future treatments for recurrent miscarriage should only be performed in the context of randomised trials that are suitably matched and corrected to exclude fetal chromosomal aberrations.

Evidence level IV

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Clinical guidelines are: 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'. Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in Clinical Governance Advice No. 1: Guidance for the Development of RCOG Green-top Guidelines (available on the RCOG website at www.rcog.org.uk/clingov1). These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research may be indicated.

The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme.

Classification of evidence levels

Ia Evidence obtained from meta-analysis of randomised controlled trials.
Ib Evidence obtained from at least one randomised controlled trial.
IIa Evidence obtained from at least one well-designed controlled study without randomisation.
IIb Evidence obtained from at least one other type of well-designed quasi-experimental study.
III Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
IV Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.

Grades of recommendations

A Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation. (Evidence levels Ia, Ib)

B Requires the availability of well controlled clinical studies but no randomised clinical trials on the topic of recommendations. (Evidence levels IIa, IIb, III)

C Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (Evidence level IV)

Good practice point

✓ Recommended best practice based on the clinical experience of the guideline development group.

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The final version is the responsibility of the Guidelines and Audit Committee of the RCOG

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