REVIEW

Recurrent miscarriage

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Abstract

Recurrent miscarriage, the occurrence of three consecutive first-trimester losses of pregnancy, affects 1% of women. The purported causes of recurrent miscarriage include chromosomal abnormalities, thrombophilia, metabolic disorders, anatomical causes and immune factors. At present, the only recommended investigations are testing for lupus anticoagulant and anticardiolipin antibody levels (to diagnose antiphospholipid syndrome, an acquired thrombophilia) and the karyotyping of both parents for chromosomal abnormalities. Women with antiphospholipid syndrome should be offered treatment with aspirin and low molecular weight heparin. Couples with chromosomal abnormalities should be referred to a clinical geneticist with whom the options of prenatal diagnosis, pre-implantation genetic diagnosis, donor gametes and adoption in subsequent pregnancies should be discussed. Couples with unexplained recurrent miscarriage should be offered appropriate emotional support and reassurance that they have a good prognosis for future pregnancies.

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Key message points

- **Couples with recurrent miscarriage should be offered karyotyping and be referred to a clinical geneticist for genetic counselling if they have a chromosomal abnormality.**
- **Screening for antiphospholipid syndrome in women with recurrent miscarriage is recommended and women with antiphospholipid syndrome should be offered treatment with aspirin and low molecular weight heparin.**
- **Supportive care alone is of considerable benefit for cases of unexplained recurrent miscarriage.**

Background

Recurrent miscarriage affects 1% of all women.[1] It is defined as the occurrence of three consecutive first-trimester losses of pregnancy. Although pregnancy loss is common (affecting 10–15% of pregnancies), this incidence is greater than that expected by chance alone (0.34%).[2] It is a very frustrating condition for both the couple and the clinician, because it is rare to find a clear-cut reason for the repeated failure to sustain a pregnancy and, as a consequence, the prospect of a satisfactory treatment. Maternal age and success of previous pregnancies are two independent risk factors for miscarriage. Older mothers have fewer good quality oocytes than younger mothers thus increasing the likelihood of chromosomal abnormalities leading to miscarriage.[3–5] The risk of further miscarriage increases to approximately 50% for women with three or more losses without a liveborn infant.[6,7] The purported causes of recurrent miscarriage include chromosomal anomalies, thrombophilia, metabolic disorders, anatomical causes and immune factors.

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Parental chromosomal anomalies

In approximately 3–5% of couples with recurrent miscarriage one of the partners is affected by a chromosomal translocation (as opposed to 0.2% in the normal population), the wife being affected twice as frequently as the husband.[8] This is usually a balanced reciprocal or Robertsonian translocation[9,10] and results in an unbalanced translocation in the fetus.

Couples should be offered karyotyping and referred to a clinical geneticist for genetic counselling if they have a chromosomal abnormality. The options of prenatal diagnosis, preimplantation genetic diagnosis (PGD), donor gametes, and adoption in subsequent pregnancies should be discussed.

Fetal chromosomal anomalies

Several studies have suggested that fetal chromosomal anomalies account for a large proportion of recurrent miscarriages. Indeed, it has been suggested that recurrent miscarriage is the result of the failure of the prevention of 'poor quality' embryos implanting, allowing embryos that are destined to fail to implant and present clinically as recurrent miscarriage. Thus, recurrent miscarriage could be thought of as a failure of nature's quality control.[11] PGD has shown that women with recurrent miscarriage produce more aneuploid embryos than normal women.[12–15] In one study, when PGD was used to discard karyotypically abnormal embryos, the miscarriage rate after *in vitro* fertilisation (IVF) decreased.[16] Interestingly, the majority of these aneuploid embryos were shown to be as a result of maternal oocyte abnormalities,[17,18] although other studies have also suggested an association between sperm chromosomal anomalies (and sperm DNA damage) and recurrent miscarriage.[19–21] However, the question remains as to why couples who recurrently produce abnormal embryos do not present with infertility because of recurrent subclinical pregnancy loss.

At present, karyotyping the products of conception following miscarriage may be viewed in some hospitals as an unnecessary luxury. However, in the absence of karyotyping, it is assumed that women who repeatedly miscarry are losing normal pregnancies. Data detailed above have shown this is unlikely to be the case. Women with recurrent miscarriage are given expensive, intensive treatment (such as heparin) to prevent miscarriage. Such treatment is not appropriate if the losses are due to karyotypic abnormalities. Therefore, obtaining a karyotype after several pregnancy losses is important.

Antiphospholipid syndrome (acquired thrombophilia)

The diagnosis of antiphospholipid syndrome is made when an adverse pregnancy outcome (such as recurrent miscarriage) or vascular thrombosis is associated with the presence of antiphospholipid antibodies (aPL). To diagnose the antiphospholipid syndrome, it is mandatory that the patient should have two positive tests at least 6 weeks apart

for either lupus anticoagulant or anticardiolipin antibodies of immunoglobulin G (IgG) and/or IgM class present in medium or high titre. Antiphospholipid antibodies are present in 15% of women with recurrent miscarriage (compared to 2% in the low-risk population).[22] Although a causal relationship between the antiphospholipid syndrome and recurrent miscarriage has not been identified, several therapeutic trials with low-dose aspirin, heparin and steroids have been conducted.[23–26] A recent review concluded that a combination of aspirin and low molecular weight heparin therapy might reduce pregnancy loss in women with aPL by 54%.[27] There is no evidence that steroids improve the live birth rate of women with recurrent miscarriage.[23,24]

Live birth rate in women with recurrent miscarriage and aPL is significantly improved by treatment with a combination of aspirin and heparin. Screening for antiphospholipid syndrome in women with recurrent miscarriage is recommended.

Hereditary thrombophilia

There have been a number of small studies reporting a positive association between factor V Leiden (FVL) and recurrent miscarriage[28–30] and three uncontrolled studies have suggested that heparin therapy may improve the live birth rate for women with FVL mutation.[29,31,32] Further unpublished, randomised controlled studies have suggested that routine screening for FVL, and offering thromboprophylaxis for those with FVL mutation and recurrent miscarriage, may be justified (L. Regan, personal communication).

Exaggerated haemostatic response

It has been recently proposed that many cases of recurrent miscarriage are due to an exaggerated haemostatic response during pregnancy leading to thrombosis of the uteroplacental vasculature and subsequent fetal loss.[33] In a large study, thromboelastography (a test of whole blood haemostasis) has shown that there is a subgroup of women with recurrent miscarriage who are in a prothrombotic state outside of pregnancy and at risk of future miscarriage.[34]

Metabolic disorders

Elevated levels of luteinising hormone (LH) and polycystic ovarian syndrome (PCOS) have been shown to be associated with miscarriage.[10,35] However, the Cochrane Subfertility Review Group concluded that there was not enough evidence that prepregnancy suppression of high LH, among ovulatory women with recurrent miscarriage and polycystic ovaries who hypersecrete LH, improves live birth rate.[36,37] Furthermore, recent data actually refute the association between elevated LH levels and PCOS with poor pregnancy outcome.[38–40] However, two studies have shown that androgen levels (independent of PCOS) in the follicular phase are higher in women who have recurrent miscarriage than in fertile controls.[41,42] *In vitro* studies have suggested that androgens increase epidermal growth factor receptor concentration that in turn has an adverse effect on endometrial glandular cell function.[43,44] A randomised controlled trial has reported that treatment with bromocriptine increased the percentage of successful pregnancies in women with a history of two or more miscarriages and hyperprolactinaemia.[45] Nevertheless, there is no firm evidence to suggest that hyperprolactinaemia is associated with recurrent miscarriage.[39] Insulin resistance and obesity have both been shown to be associated with recurrent miscarriage,[46,47] and two small studies have also shown that metformin was found to decrease the incidence of spontaneous miscarriage.[48,49] However, there is no strong evidence to support an association between either diabetes or thyroid function and pregnancy loss.[39,42,50,51]

Infective factors

The role of infection in recurrent miscarriage is unclear. Whilst bacterial vaginosis is associated with late pregnancy loss, preterm labour and premature rupture of membranes,[52] its association with recurrent miscarriage is not known. However, a recent study has shown that bacterial vaginosis was associated with an increased risk of early miscarriage in women undergoing IVF treatment.[53] Toxoplasmosis, rubella, cytomegalovirus, herpes (TORCH) and listeria infections are not thought to be infective causes of miscarriage.[54,55]

TORCH and bacterial vaginosis screening are not helpful in the treatment of recurrent miscarriage.

Uterine abnormalities

It is difficult to assess the exact contribution that uterine anomalies make to recurrent pregnancy loss. Their reported prevalence and reproductive implications are contested. The most common congenital structural uterine anomaly associated with miscarriage, including diethylstilboestrol-related anomalies, is the septate uterus.[56] It would appear that the septal endometrium shows defective development, indicative of a reduction in sensitivity to steroid hormones.[57] Of the acquired conditions, Asherman's syndrome is the best documented.[58] In this condition, post-traumatic intrauterine adhesions partly, or completely, obliterate the uterine cavity. Successful division of the uterine adhesions is thought to restore the responsiveness of the endometrium to the sex steroid hormones. Pregnancy rates after hysteroscopic treatment of the intrauterine adhesions depend upon the degree of the initial problem,[59] being 93% for mild and 57% for severe disease. The situation with respect to the fibroid uterus is less clear. It is not known whether the endometrium covering a submucous fibroid responds suboptimally to steroid hormones increasing the risk of pregnancy loss. However, there is some evidence that removal of submucous fibroids reduces miscarriage rates.[60,61]

The routine use of the hysterosalpingogram as a screening test for uterine anomalies is questionable.

Endometrial causes

Recurrent miscarriage may be associated with retarded endometrial development in the peri-implantation period or luteal phase defect (LPD).[39] To our knowledge, only two studies have examined endometrial morphology in women with recurrent miscarriage[62,63] by taking precisely timed endometrial biopsy specimens in women in whom comprehensive investigations into the cause of recurrent miscarriage were conducted. The incidence of LPD in these two studies was reported as 17.4%[62] and 29%.[63] It is possible that steroid receptor abnormalities may be an explanation for the observed abnormality. Delayed downregulation of the progesterone receptor (PR) was observed in timed endometrial biopsies from a small group of women with recurrent miscarriage.[39] However, no data so far exist differentiating the two isoforms of PR, or examining the expression pattern of those of the oestrogen receptor. Also, no differences have been observed in androgen receptor expression in women with recurrent miscarriage.[39] Furthermore, a review of

hormonal treatments for LPD concluded that the benefits are uncertain.[64] The measurement of glycodelin A (previously called PP14) in endometrial flushings has been used successfully to identify endometrial defects.[65,66] The concentration of glycodelin A was significantly lower in the flushings from the recurrent miscarriage patients than in those from fertile controls on both day LH+10 and LH+12. MUC1 is an anti-adhesion molecule that is thought to contribute to the barrier function of the endometrial surface, which resists implantation except during a specific time window in the mid-secretory phase.[67,68] Expression of the endometrial protein MUC1 was found to be lower in the endometrium of women suffering from recurrent miscarriage than controls,[69] suggesting that epithelial function may be compromised in some cases of recurrent miscarriage.

The treatment of endometrial defects is controversial. The earlier studies that observed an association between LPD and recurrent miscarriage led to the development of a number of unsuccessful hormonal treatments. In particular, the use of progesterone supplementation has not been shown to be of benefit. More recent studies that have identified specific molecular abnormalities have contributed to our overall understanding of the aetiology of recurrent miscarriage, but not to its management.

Immune factors

For many years it has been speculated that a defect in the maternal immune response to the semi-allogenic fetal graft could be involved in the mechanism of recurrent miscarriage. Immunisation of women with recurrent miscarriage with paternal or third-party leukocytes, or with repeated boluses of gammaglobulins, prior to a next pregnancy has been tried in an attempt to replicate the paradoxical opposing parental histocompatibility that seems to be necessary for maintaining pregnancy. However, a Cochrane systematic review has shown that the use of immunotherapy in women with recurrent miscarriage provides no significant benefit.[70] Nevertheless, in the research field a number of observations have been made suggesting other immunological factors may be important in the aetiology of the condition. Autoantibodies are more common in patients with recurrent miscarriage. The most common are antiphospholipid (14%) and antinuclear antibodies (7%), although the significance of the latter is uncertain.[71,72] Thyroid antibodies have also been shown to be increased in women with recurrent miscarriage in a number of studies.[73,74] Their prognostic value is, however, doubtful.[75] Several studies have reported alterations in the cellular immune response. The peripheral blood of women with recurrent miscarriage has been shown to have a higher proportion of activated natural killer cells *in vivo* than control subjects.[76] Women with recurrent miscarriage whose subsequent pregnancies progressed to term delivery have been shown to have a lower natural killer cell number and Th1:Th2 cytokine ratio (Th = T helper cell) than women whose pregnancies miscarried again.[77,78] Endometrial leukaemia inhibitory factor (LIF) is known to be essential for implantation in the mouse.[79] Decreased expression of LIF and interleukin 6 (IL-6), a related T helper cell cytokine, has also been demonstrated in some women who suffer recurrent miscarriage.[80,81] Endometrial leukocyte populations such as stromal CD56+ uterine natural killer cells, and various other stromal leukocyte populations, have been examined in recurrent miscarriage, and found to be of prognostic value. It has been demonstrated that the endometrium of non-pregnant women with a history of recurrent miscarriage contains an increased proportion of CD16+ CD56dim uterine natural killer cells compared with normal fertile women in whom CD16– CD56bright uterine natural killer cells predominate.[82] Increased numbers of CD56+ uterine natural killer cells were also found in the preimplantation endometrium of recurrent miscarriage patients compared with controls.[11,83] Furthermore, there were more CD56+ leukocytes in the endometrium of patients who subsequently miscarried than in those who had live births.[83] There is no general agreement as to the function of uterine CD56+ uterine natural killer cells in relation to pregnancy, however these observations suggest that they might facilitate embryo implantation, including those embryos with abnormal karyotypes, leading to the clinical presentation of recurrent miscarriage.

At present, the administration of cells or cellular products in humans for the treatment of recurrent miscarriage should only be performed in the context of research.

Cervical weakness

Cervical weakness can cause pregnancy loss in the second trimester but there is no single truly diagnostic test for cervical weakness.[84,85] The Medical Research Council/ Royal College of Obstetricians and Gynaecologists 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.[86]

Due to the risks of surgery, cervical cerclage should only be offered to carefully selected women with previous second-trimester pregnancy loss.

Lifestyle factors

Smoking and alcohol consumption are both associated with miscarriage.[87,88] Excessive coffee consumption may also increase the risk of miscarriage.[89,90] It seems sensible to strongly recommend a healthy lifestyle and give advice regarding smoking, alcohol and caffeine consumption to couples with recurrent miscarriage.

Unexplained factors

In up to 50% of cases of recurrent miscarriage no causative factor is found.[10,91] Fortunately, these women have an excellent prognosis for future pregnancy outcome if offered supportive care alone from a dedicated early pregnancy support clinic.[92–94]

Conclusions

According to the definition of recurrent miscarriage, investigation and treatment (if appropriate) should only start after three consecutive losses. Currently, the only recommended investigations are testing for lupus anticoagulant and anticardiolipin antibody levels and karyotyping both parents. Women with antiphospholipid syndrome should be offered treatment with aspirin and low molecular weight heparin. Couples with chromosomal anomalies should be referred to a clinical geneticist with whom the options of prenatal diagnosis, PGD, donor gametes and adoption in subsequent pregnancies should be discussed. Couples with unexplained recurrent miscarriage should be offered appropriate emotional support and reassurance that they have a good prognosis for future pregnancies. Hopefully, continued investigation to further our understanding of the pathophysiology of recurrent miscarriage will lead to more successful treatment and improved outcome in women with recurrent miscarriage.

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