

Recurrent miscarriage

Investigating the potential causes

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Ultimately, investigations will find a cause for recurrent miscarriage in fewer than 50% of affected women. Treatment of the underlying conditions provides hope for success in their next pregnancy. Even with multiple losses, the outlook for the next pregnancy should be optimistic even where no cause has been found.

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Miscarriage is the loss of a pregnancy before the 20th gestational week. Recurrent miscarriage is traditionally defined as three such successive losses. Increasingly, couples are carefully planning their families using contraception until they have achieved their social, financial and career goals. Therefore, most pregnancies today are truly planned and very wanted. In this context, pregnancy loss becomes a very significant event, accompanied by feelings of grief and failure. All those involved in the care of couples experiencing a pregnancy loss should be sensitive to the significance of this loss, which is sometimes underestimated due to its common occurrence. Such empathy is even more essential in women experiencing recurrent miscarriage. Two or three miscarriages lead to earlier investigation of the potential causes.

WHAT IS THE RISK OF RECURRENCE?

From the initial positive pregnancy test, at least one in six pregnancies will end in miscarriage. After one or even two miscarriages there is no increased risk of a loss in a subsequent pregnancy (i.e. still about one in six). However, after three miscarriages the chance of future miscarriage increases to one in four due to the increasing likelihood of underlying pathology. Despite this, there is still a 75% chance of a successful live birth. After four or more miscarriages there is a progressively increasing risk of recurrence.

PRESENTATION

Vaginal bleeding and cramping lower abdominal pain are the most common presenting symptoms of a miscarriage. Recurrent miscarriages are more often picked up as a missed miscarriage because of increased ultrasound surveillance in affected women.

CAUSES

Lifestyle factors

There are well-documented relations of increased miscarriage rates with obesity and smoking. These issues should be highlighted as reversible interventions that the couple can make to maximise their chance of success. There are many other lifestyle factors, including use of saunas and hot tubs and occupations involving frequent flying, which are associated with recurrent miscarriage. There is little evidence for any relation with moderate alcohol intake, use of laptops or TV monitors, or sexual intercourse in the first trimester.

Hormone dysfunction

Women experiencing recurrent miscarriage have low progesterone and/or oestrogen levels. However, it is most likely that these levels are a reflection of the pregnancy demise rather than the cause. One of the tragic stories of modern medicine relates to the unscientific use of synthetic oestrogen (diethylstilboestrol) to treat women with threatened and recurrent miscarriages. This agent produced an increased incidence of clear cell carcinoma and genital tract anomalies in the offspring.

Recurrent miscarriage can be a presentation for endocrine disorders such as poorly controlled diabetes and thyroid dysfunction. It has also been associated with polycystic ovary syndrome (PCOS), although when studies correct for obesity, the association is less clear. Other potential hormonal causes include hormonal dysfunction (low progesterone, high luteinising hormone or high insulin levels) or some other factor affecting either egg quality or the endometrium.

Genetic causes

At least 70% of miscarriages are due to aneuploidy, generally trisomy or monosomy. These arise as random aberrations soon after fertilisation. Poor oocyte quality is the predisposing factor usually related to increasing maternal age, explaining the rising risk of miscarriage with age (below 35 years the risk is one in six, at 40 years the risk is one in four and by 45 years the risk is one in two). Therefore, in older women, recurrent miscarriage is increasingly likely to be due to random embryo aneuploidy.

In about 2% of couples experiencing recurrent miscarriage the female or male partner (more common in women) is an otherwise asymptomatic carrier of a balanced translocation. This karyotype abnormality leads to increased chromosomal abnormalities in eggs or sperm, and hence a higher frequency of aneuploid embryos. There are two types, reciprocal and Robertsonian, both of which, if balanced, can be compatible with a normal adult phenotype. Both translocations carry a high rate of miscarriage in the offspring of affected people. Inversions occur when a segment of the chromosome is reinserted 'upside down' after chromosome breakage. The person is phenotypically normal, but when the inversion is paired at fertilisation there is the very high risk of miscarriage (or abnormal live birth).

Anatomical causes

In 5% of couples with recurrent miscarriage there are abnormalities in the female reproductive tract, which lead to poor implantation and miscarriage. These may be congenital (septate uterus, bicornuate uterus) or acquired (fibroids, polyps, adhesions).

Antiphospholipid syndrome

Antiphospholipid syndrome is one of the most common causes and is detected in 15 to 20% of couples experiencing recurrent miscarriage. It may be primary

(recurrent miscarriage in the presence of antiphospholipid antibodies) or secondary (in association with systemic lupus erythematosus). There may be other clinical features present suggestive of antiphospholipid syndrome such as fetal death, venous thrombosis, haemolytic anaemia and autoimmune thrombocytopenia. Untreated women have no better than a 30% chance of carrying a pregnancy into the third trimester. The mechanisms for these adverse effects are thought to relate to coagulation in the small vessels of the placenta, immunological dysfunction and direct toxicity of the cardiolipin antibodies on placental cells.

Sperm DNA fragmentation

Sperm DNA fragmentation can occur as the result of oxidative stress (free radical attack). Factors that can increase sperm DNA fragmentation include smoking, presence of varicocele and diabetes, and paternal ageing. Although it is believed that DNA damage can often be repaired by the egg at fertilisation (and hence maternal age and egg quality are confounding factors), higher miscarriage rates have been reported in cases in which high DNA damage exists.

Other causes

There is a relation between factors predisposing to thrombophilia (e.g. carriers of the factor V Leiden mutation) and recurrent miscarriage. Its significance is not well defined. Severe pyrexia and specific infections (e.g. rubella, varicella, listeriosis, toxoplasmosis) can cause episodes of early pregnancy loss but are unlikely to predispose to recurrent miscarriage.

Abnormal maternal immunological adaptation to pregnancy has been proposed as a cause of miscarriage for more than 50 years. Initial theories likened pregnancy to an allograft, and this led to attempts to suppress the mother's immune system generally. A range of immune-modulating therapies (e.g. prednisolone, intravenous immunoglobulin,

paternal or donor leucocyte infusion) have been tried but none have been proven to be efficacious.¹

INVESTIGATIONS AND MANAGEMENT

There is significant controversy as to the investigations required for recurrent miscarriage (see the box on this page). The tests ordered tend to be dependent on the interests of the clinician, cost and availability. It is important that patients are reassured that all relevant tests have been performed. As there is little strong evidence for most investigations, we recommend a stepwise approach. Interpretation of the test results often requires specialist input as does the formulation of a plan for the couple's next pregnancy attempt. There are an increasing number of subspecialist gynaecologists with reproductive endocrine training who have developed particular expertise in this area.

Ultimately, investigations will find a cause for recurrent miscarriage in fewer than 50% of affected women. Treatment of the underlying conditions provides hope for success in their next pregnancy. However, for the undiagnosed majority, they remain unconvinced that there is not something wrong and will be reluctant and extremely anxious about embarking on a future pregnancy. In all cases a plan should be made to commence as soon as the next positive pregnancy test. Primarily this is based on emotional support and reassurance. Measurements of serial twice-weekly quantitative β human chorionic gonadotropin levels should start from the missed period. Doubling concentrations every two to three days are reassuring. Ultrasound should be undertaken at 5.5 weeks (for checking of sac size and fetal echoes), at seven weeks (for fetal heart action) and at nine and 11 weeks (for continuing viability). Low progesterone levels are an ominous sign. This approach ensures early diagnosis of a failing pregnancy and provides significant reassurance to the woman when

there is an ongoing pregnancy. A well designed and controlled Scandinavian study showed that this management plan in a group of women who repeatedly miscarried increased the ongoing pregnancy rate from 63 to 75%.²

Lifestyle measures

Weight reduction is a first-line measure for women with raised body mass index who are experiencing recurrent miscarriage. There is understandable interest in metformin but its benefit is unproven. Both partners should be encouraged to stop smoking.

Hormonal assessment

Thyroid dysfunction and diabetes should be treated appropriately. Hormonal assessment and an ultrasound scan can help reveal PCOS, although a hormonal basis of miscarriage is not well defined as explained above. There is some preliminary evidence that metformin may reduce the incidence of miscarriage in women with PCOS.³ It appears to be safe but larger trials are awaited.

A review has concluded that progesterone support can improve outcome in women with recurrent miscarriage.⁴ Human chorionic gonadotropin injections on a twice-weekly basis to stimulate progesterone secretion are used by some gynaecologists but without evidence of efficacy. There is no documented harm over more than 30 years of use. Therefore, human chorionic gonadotropin injections can be justified as a placebo in a situation of high stress where to do nothing is regarded by the patient as unacceptable.

Parental karyotypes

Genetic counselling in people who are carriers of translocations is essential. With advances in modern IVF technology, array comparative genomic hybridisation can now screen all embryos in this group to enable replacement of embryo(s) with normal karyotype. Formal fetal karyotyping at chorionic villus sampling or

INVESTIGATIONS FOR RECURRENT MISCARRIAGE

First line

- Pelvic ultrasound scan (to exclude uterine abnormalities)
- Full blood count
- Thyroid-stimulating hormone
- Early follicular phase follicle-stimulating hormone, luteinising hormone, oestradiol (to assess for polycystic ovary syndrome)
- Anticardiolipin antibodies
- Lupus anticoagulant
- Fasting insulin, glucose, homocysteine
- Activated protein C resistance
- Female/male karyotype

Second line

- Hysterosalpingogram, sonohysterogram or hysteroscopy
- *Methylenetetrahydrofolate reductase* mutation
- Factor V Leiden, prothrombin gene mutation, protein C, protein S
- Antithrombin III
- Antithyroid antibodies
- Anti-Müllerian hormone
- Male karyotype deletion
- Sperm DNA fragmentation

Third line

- Peripheral blood natural killer cells
- Uterine natural killer cells
- Embryo quality (IVF)

amniocentesis should also be considered if ongoing spontaneous pregnancy occurs. Donor gametes may be an option in such cases.

Antiphospholipid syndrome

Randomised controlled trials have shown that treatment of women with antiphospholipid syndrome with aspirin (75 to 150 mg) and subcutaneous heparin returns the chance of an ongoing pregnancy to normal (i.e. 80%).⁵ There is

no known risk of such therapy to the fetus. For the mother, however, there is the risk of osteopenia with case reports of vertebral collapse. Therefore, such treatment should only be used in specific proven cases.

Thrombophilia screen

Recent randomised trials have failed to show benefit of treatment with either aspirin or heparin in women with unexplained recurrent miscarriage.⁶ However, many studies have demonstrated associations between thrombophilia factors (e.g. fasting homocysteine, methylenetetrahydrofolate reductase [*MTHFR*] mutation, activated protein C resistance, factor V Leiden, protein C, protein S, anti-thrombin III) and recurrent miscarriage.⁷ Therapy with aspirin or low molecular

weight heparin have been suggested (with heparin probably superior) but no randomised controlled trials have been performed to demonstrate efficacy.

Other immunological abnormalities

The diagnosis of 'subclinical autoimmunity' in which mildly positive autoantibody tests results are found in women experiencing recurrent miscarriages is controversial. Antinuclear antibody, thyroid autoantibody and natural killer estimations should be limited to research programmes.⁸ It is possible that these tests do not in themselves signify an abnormality, but are markers for abnormal maternal immune adaptation to pregnancy. Currently, proponents of natural killer cell testing

claim that excess activated natural killer cells can result in miscarriage.⁹ Thus, the role of natural killer cell testing is to provide a possible means of diagnosing a subgroup who may benefit from immune therapy (e.g. prednisolone). This highly controversial subject is fascinating because patients are clearly keen to pursue the tests and undergo treatment even though current evidence for their effectiveness is poor.

Anatomical problems

Minimal access surgery (hysteroscopy) can significantly improve outcome in women with uterine polyps, septum or adhesions. Myomectomy is indicated for women with submucosal fibroids. Women with large intramural fibroids (>5 cm in

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diameter) require specialist assessment by laparoscopy and possible excision by laparoscopy or laparotomy.

Infective screening

Tests for toxoplasmosis, chlamydia and cytomegalovirus, and possibly listeriosis and urealyticum, are rarely helpful when investigating women experiencing recurrent miscarriage. However, if endometrial curettage reveals inflammation, a course of doxycycline is appropriate to prescribe.

Sperm DNA fragmentation

Measurements of sperm DNA fragmentation are laboratory dependent due to variation in methodologies. Elevated levels of sperm fragmentation must be interpreted with caution. Current treatment recommendations include antioxidant vitamins (C and E) and more frequent ejaculation.

Random aneuploidy

With increasing use of comparative genomic hybridisation in IVF, it is clear that the major reason for failure of IVF is aneuploidy, with more than 50% of embryos biopsied showing abnormalities even with morphologically normal appearing embryos. Selection of euploid embryos appears to increase IVF success rates. More importantly in recurrent miscarriage of undefined cause, comparative genomic hybridisation substantially reduces repeat miscarriage rate by excluding aneuploid pregnancies from the outset. In a recent study of women experiencing recurrent miscarriage, the aneuploidy rate was 60% and replacement with normal embryos resulted in a miscarriage rate of 6.9%.¹⁰ Although, expensive and highly sophisticated technology was used to approach the problem, many couples seem prepared to go to this degree.

Ovarian reserve tests

It is well established that the incidence of miscarriage due to aneuploidy (poor egg quality) increases with age. Ovarian

reserve tests by measuring serum hormones (anti-Müllerian hormone or early follicular phase follicle-stimulating hormone) are used increasingly to individualise a woman's reproductive potential. Although studies have significant methodological difficulties, it has not yet been shown that poor ovarian reserve is associated with poor egg quality. Hence such testing is useful for counselling and decision making (e.g. how long to wait before trying to conceive) rather than identifying a specific cause for recurrent miscarriage. Nevertheless, there is recent interest in the use of dehydroepiandrosterone (DHEA) supplementation to improve ovarian function, and there are claims (currently unsubstantiated) that it may reduce miscarriage rate.¹¹

CONCLUSION

Recurrent miscarriage is a traumatic experience for women and their partners. Exclusion of treatable causes is essential. For the vast majority, a detailed explanation, emotional support and close monitoring of the next pregnancy will provide the basis for a successful outcome. The statistics are clear that even after multiple losses the odds are still in favour of a live birth whatever we do.

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