# Investigation and management of recurrent miscarriage

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## Abstract

Recurrent miscarriage is traditionally defined as three or more consecutive miscarriages and this occurs in approximately 1% of couples trying to conceive. In most couples no pathological cause is identified. The outcome can be improved for women with recurrent miscarriage and antiphospholipid syndrome with treatment with aspirin and/or heparin. Couples with unexplained recurrent miscarriage have an excellent prognosis with supportive care alone and to date no pharmacological intervention has been proven to be beneficial. This review describes the causes of recurrent miscarriage, the clinical work-up and an evidence-based approach to management.

**Keywords** antiphospholipid syndrome; early pregnancy; recurrent miscarriage

## Introduction

Miscarriage is the spontaneous loss of a pregnancy before the fetus reaches viability. This is a common early pregnancy complication with 15% of clinically recognised pregnancies ending in miscarriage. Recurrent miscarriage is traditionally defined as three or more consecutive miscarriages and this occurs in around 1% of couples trying to conceive. Miscarriage is an important cause of morbidity and mortality including significant emotional distress in both partners.

The observed incidence of recurrent miscarriage is much higher than that expected by chance alone (0.34%). This suggests that there are potentially identifiable, and potentially remedial factors, which increase the chance of miscarriage. However the causes and pathophysiology of recurrent miscarriage remain poorly understood. The risk of recurrent miscarriage increases with the maternal age and the number of successive losses. Recurrent miscarriage is associated with parental chromosomal anomalies, maternal thrombophilic disorders, structural or functional uterine or endometrial anomalies, maternal immune dysfunction, and endocrine abnormalities. However in the majority of couples with recurrent miscarriage no cause is found.

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## Risks factors

### Epidemiological

Maternal age at conception is a strong independent risk factor for miscarriage, reflecting a decline in the number and quality of the remaining oocytes. The risk of fetal loss increases steeply after the age of 35 years, rising from 11% at age 20–24 years to 93% at age 45 years and older (Table 1). This means that many cases of recurrent miscarriage will be explained solely by advancing maternal age. Advanced paternal age (age 40 years and older) has also been identified as a risk factor for miscarriage although the association is less marked (OR 1.6 [1.2–2.0]).

Previous reproductive history is an independent predictor of future pregnancy outcome. The risk of a further miscarriage increases after each successive pregnancy loss, from approximately 9% after no losses, 12% after one, 20% after two, reaching 40% after three or more pregnancy losses. Women with a previous live birth are not precluded.

There is little reliable evidence on environmental risk factors and independent variables, causality and association are hard to assess. However maternal cigarette smoking and caffeine consumption (when intake exceeds more than three cups of coffee per day) are likely to be associated with a dose-dependent increased risk of miscarriage. Heavy alcohol consumption has adverse effects on fertility and fetal development, though even moderate alcohol consumption of 5 or more units per week may increase the risk of sporadic miscarriage. Obesity is an increasingly common problem in the UK and is associated with an increase in risk of early miscarriage (OR 1.2 [1.01–1.46]) and recurrent miscarriage (OR 3.5 [1.03–12.01]) as well as other pregnancy complications.

### Genetic factors

Developmental abnormalities are frequently found when miscarried pregnancies undergo detailed examination. Although not all developmental abnormalities are associated with chromosomal disorders, fetal aneuploidy is the most important cause of miscarriage before ten weeks gestation. At least 50–60% of all miscarriages are associated with cytogenetic abnormalities, with trisomy being the most frequent. These mostly arise from errors in the first meiotic division of the oocyte, which is initiated prenatally and is not completed until ovulation and this risk increases with maternal age. It is important to remember however, that as the number of miscarriages increases, the risk of euploid pregnancy loss increases.

In 2–5% of couples with recurrent miscarriage one partner carries a balanced structural chromosomal anomaly. This is

**Miscarriage rates by maternal age at conception**

| Age (years) | Miscarriage rate |
|---|---|
| 20–24 | 11% |
| 25–29 | 12% |
| 30–34 | 15% |
| 35–39 | 25% |
| 40–44 | 51% |
| ≥45 | 93% |

**Table 1**

either a balanced reciprocal translocation in which there is an exchange of two terminal segments from different chromosomes, or a Robertsonian translocation, in which there is centric fusion of two acrocentric chromosomes. Carriers of these translocations are phenotypically normal but 50–70% of their gametes and therefore embryos are unbalanced, because of abnormal segregation at meiosis. The risk of miscarriage is dependent on the type of rearrangement and whether it is carried by the woman or the male partner.

### Antiphospholipid syndrome

Antiphospholipid syndrome (APS) is an important treatable cause of recurrent miscarriage. APS is an acquired autoimmune disorder associated with vascular thrombotic events and pregnancy failure. The disease can occur as a discrete entity (primary APS) or in association with other autoimmune disease, usually systemic lupus erythematosus (SLE). Antiphospholipid antibodies are a family of around 20 antibodies that are directed against phospholipid binding plasma proteins and include lupus anticoagulant, anticardiolipin antibodies, and anti-$\beta_2$ glycoprotein-I antibodies.

Antiphospholipid antibodies are present in 15% of women with recurrent miscarriage. These women have a potential 90% risk of further fetal loss if left untreated. The pathophysiological mechanisms by which antiphospholipid antibodies cause pregnancy morbidity include inhibition of trophoblastic function and differentiation, activation of complement pathways causing inflammation-mediated placental injury, and in later pregnancy thrombosis of the uteroplacental vasculature.

### Inherited thrombophilias

Inherited thrombophilias (factor V Leiden, activated protein C resistance, prothrombin gene mutation, and protein S deficiency) are strongly associated with second-trimester miscarriage and late pregnancy complications and also increase the risk of recurrent miscarriage. The mechanism for these effects is uncertain but is presumed to include thrombosis of the uteroplacental circulation.

### Anatomical factors

Congenital uterine anomalies (uterine septate and bicornuate uterus) are found in between 1.8% and 37.6% of women with recurrent miscarriage and the reproductive implications remain unclear. Women with untreated uterine anomalies are reported to experience high rates of miscarriage and preterm delivery though no reliable data are available.

Uterine fibroids are present in 30% of women, but their impact on reproductive outcome is controversial. It has been postulated that uterine fibroids have a mechanical or space-occupying effect that impedes embryonic implantation though the expression of *HOX10*, a gene that controls differentiation and is involved with implantation has been shown to be lower in uteri with fibroids than in those without.

Cervical weakness is a recognised cause of second-trimester miscarriage but the incidence is unknown as there is no objective test that can identify women with cervical weakness in the non-pregnant situation. The diagnosis is mainly a clinical one based on a history of second-trimester miscarriage preceded by spontaneous rupture of membranes or painless cervical dilatation.

### Endometrial factors

There is an increasing amount of research into the role of the endometrium in recurrent miscarriage. Decidualisation is the changes to the endometrial glands, stroma and cellular composition induced by progesterone that supports implantation of the embryo. It has been suggested that there may be disorders or decidualisation in some women with recurrent miscarriage. The endometrium interacts with the embryo and seems to favour implantation of normally developing embryos. One current theory suggests that in some cases of recurrent miscarriage the endometrium allows abnormally developing embryos, which will ultimately miscarry, to implant. This is supported by the observation that time to conception is markedly reduced in some women with recurrent miscarriage.

Progesterone, secreted mainly by the corpus luteum, induces secretory changes in the endometrium which are essential for implantation of the embryo. It has been suggested that some cases of miscarriage might be due to inadequate secretion of progesterone, either in the luteal phase of the menstrual cycle or the in early pregnancy.

### Immune factors

The physiological mechanisms which allow a mother to tolerate her semi-allogeneic fetus remain unclear and it has been postulated that immunological aberrations may be responsible for cases of otherwise unexplained recurrent miscarriage. There is no clear evidence to support the hypothesis of human leucocyte antigen (HLA) incompatibility between couples, the absence of maternal leucocytotoxic antibodies or the absence of maternal blocking antibodies.

Natural killer (NK) cells are lymphocytes, and are part of the innate immune system. They are thought to contribute to the control of trophoblastic invasion. Peripheral blood NK cells are phenotypically and functionally different from uterine NK cells. In women with recurrent miscarriage high levels of uterine NK cells may be associated with high rates of subsequent miscarriage. Levels of peripheral blood NK cells have not been shown to reflect levels in the uterine mucosa and are not predictive of pregnancy outcome.

NK cells in uterine mucosa contribute to the cytokine response at the maternal–fetal interface. This is generally characterised either as a T-helper-1 (Th-1) type (with production of interleukin 2, interferon, and tumour necrosis factor $\alpha$) or a T-helper-2 (Th-2) type (with interleukins 4, 6 and 10). In a Th-2 type response blocking antibodies mask fetal trophoblast antigens from maternal immunological recognition. Women with recurrent miscarriage tend to produce a predominantly Th-1 type response both during implantation and pregnancy.

### Endocrine factors

Maternal endocrine disturbances such as diabetes mellitus and thyroid disease have been associated with miscarriage. Diabetes that is well controlled is not a risk factor for recurrent miscarriage but women with high haemoglobin A1c levels in the first trimester are at increased risk of miscarriage and fetal malformation. Thyroid autoantibodies have been linked to recurrent miscarriage in the past though their presence in euthyroid women does not seem to affect future pregnancy outcome. There is currently a randomised trial (The TABLET trial) to assess the