

Recurrent miscarriage

What is recurrent miscarriage?

Recurrent miscarriage is defined as the loss of three or more consecutive pregnancies.

How common is recurrent miscarriage? (Epidemiology)

Miscarriage, the most common complication of pregnancy, is the spontaneous loss of a pregnancy before the fetus has reached viability at 24 weeks of gestation. (20 weeks of gestation is taken in some parts of the world.)

- Miscarriage occurs in 12–24% of recognised pregnancies.
- 1% of couples trying to conceive have recurrent miscarriages.
- This is much higher than the 0.34% calculated risk of three occurring consecutively by chance alone.
- Following three consecutive miscarriages, the risk of further miscarriage is about 40%.
- A woman may develop recurrent miscarriage after a successful pregnancy.

No underlying cause is found in many women who experience recurrent miscarriage.

Risk factors

- Increasing maternal age affects ovarian function and increases rates of aneuploidy in association with older oocytes. Risk is highest where the woman is over 35 years and the man is over 40 years.^[1]

- As the number of miscarriages increases, the likelihood of chromosomal abnormalities as the cause decreases and the risk of an underlying maternal cause increases.

Causes of recurrent miscarriage (aetiology)^[1]

Genetic abnormalities

- Recurrent miscarriage may be linked to chromosomal abnormality in 2-5% of couples.
- A balanced reciprocal or Robertsonian translocation is the most common type.^[2]

Antiphospholipid syndrome (APS)

- [Antiphospholipid syndrome](#) is the most important treatable cause of recurrent miscarriage.
- The antiphospholipid antibodies, lupus anticoagulant, anticardiolipin antibodies and anti-B2-glycoprotein I antibodies may be associated with recurrent miscarriage before ten weeks.
- Antiphospholipid antibodies are present in 15% of women with recurrent miscarriage.
- APS is the only proven thrombophilia that is associated with adverse pregnancy outcomes.^[3]

Structural^[4]

- Uterine anomalies (arcuate or septate) are seen in between 10-25% of cases of recurrent miscarriage, particularly second-trimester miscarriages. Only 50% of pregnancies where there is a uterine structural abnormality achieve term delivery.
- Multiple intramural and submucosal fibroids are associated with an increased risk of miscarriage but whether myomectomy improves the live birth rate is unclear.
- Cervical incompetence (late miscarriage preceded by spontaneous rupture of membranes or painless cervical dilatation) may often be a cause of mid-trimester recurrent miscarriage.

Endocrine

- Women with polycystic ovary syndrome are at higher risk of miscarriage, which may be related to insulin resistance and hyperinsulinaemia.
 - There is insufficient evidence to support the use of metformin during pregnancy to reduce this risk.
 - Uncontrolled diabetes mellitus is a risk factor for recurrent miscarriage.
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Immune

- Women with recurrent miscarriage have more natural killer cells in their uterine mucosa than controls and those with the highest levels have a correspondingly high rate of miscarriage in subsequent pregnancies.
- However, there is no association between the levels of natural killer cells in peripheral blood and the levels in the uterine mucosa. Levels of natural killer cells in peripheral blood are not predictive of pregnancy outcome in women with unexplained recurrent miscarriage.

Inherited thrombophilia

- Inherited thrombophilia, such as [protein C](#) and [protein S deficiency](#), may have a role in recurrent miscarriage, because of an increased risk of thrombosis in the uteroplacental circulation, although the evidence for a causal effect is weak.^[5] The relationship appears to be strongest for late pregnancy loss as opposed to miscarriage.
- Women with second-trimester miscarriage should be screened for inherited thrombophilia.

Infections

[Bacterial vaginosis](#) in the first trimester is a risk factor for second-trimester miscarriage and preterm delivery.^[6]

Investigations

- Antiphospholipid and B2-glycoprotein I antibodies:
 - The presence of these is associated with early miscarriages and maternal morbidity and is referred to as primary APS. There is requirement for two tests at least six weeks apart showing either lupus anticoagulant or anticardiolipin antibodies at significant levels.
 - Women with recurrent first-trimester miscarriage and all women with one or more second-trimester miscarriages should be screened for antiphospholipid antibodies before pregnancy.
- Women with second-trimester miscarriage should be screened for inherited thrombophilias including [factor V Leiden](#), factor II (prothrombin) gene mutation and protein S.
- All women with recurrent first-trimester miscarriage and all women with one or more second-trimester miscarriages should have pelvic ultrasound to assess uterine anatomy.
- Women who have had one or more second-trimester miscarriages and suspected cervical weakness may be offered serial cervical sonographic surveillance.
- If uterine anomalies are detected then further investigations, such as hysteroscopy and/or laparoscopy, may be required.

Karyotyping

- Karyotyping of products of conception should be undertaken on the products of conception from the third (and any subsequent) miscarriages. If an unbalanced structural chromosomal abnormality is found, referral to genetics is indicated.^[7]
- 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.

NB: the Royal College of Obstetricians and Gynaecologists (RCOG) does **not** recommend routine screening for diabetes, inherited coagulopathies, thyroid disease, serum prolactin, or TORCH syndrome (toxoplasmosis, other, rubella, cytomegalovirus, herpes simplex).^[7]

Recurrent miscarriage treatment and management

General advice^[4]

Reassurance should be given about the high probability of a successful outcome. In a large trial that included women with 4.2 consecutive miscarriages and an average age of 32.7 years, the placebo group was shown to have a live birth rate of 65%. There is a suggestion that the reassurance gained from frequent antenatal visits and ultrasound examinations may improve outcomes.

Pharmacological treatment

Heparin

- In primary APS patients, heparin combined with low-dose aspirin improves live birth rate to 70% from reported rates in untreated women with APS of as low as 10%.^[8]
- A systematic review and meta-analysis has shown no reduction in the risk of miscarriage in women with inherited thrombophilia treated with low molecular weight heparin (LMWH).^[5]

Metformin

- There is some evidence suggesting that use of metformin during pregnancy is associated with a reduction in the miscarriage rate in women with polycystic ovary syndrome.^[9] However, the data are contradictory and a systematic review and meta-analysis found no effect on the miscarriage risk.^[10]
- The RCOG **does not** recommend its use in pregnancy at present, until further randomised prospective study results are available to provide adequate evidence of safety and efficacy of its use.

Progesterone

- The progesterone in recurrent miscarriage (PROMISE) study, a large randomised, double-blind, placebo-controlled multicentre trial, has shown: ^[11]
 - No sign that progesterone delays the time of miscarriage.
 - Over 60% of the women who conceived within a year of inclusion in the study, all of whom had a history of recurrent miscarriage, had a live birth, whether they had progesterone treatment or placebo.
- A 2019 Cochrane review found there may be some benefit from progesterone supplementation for future pregnancies in women with unexplained recurrent miscarriages. ^[12]

Human chorionic gonadotrophin (hCG) hormone

The evidence supporting hCG supplementation to prevent recurrent miscarriage is equivocal; higher-quality evidence shows no benefit. ^[13]

Immunotherapy

Paternal cell immunisation, third-party donor leukocytes, trophoblast membranes, and intravenous immunoglobulin have all been used to treat women with otherwise unexplained miscarriage. None has shown any significant benefit over placebo in improving the live birth rate. ^[14] .

Surgical treatment ^[15]

- Cervical cerclage (a Shirodkar or McDonald suture) is a prophylactic measure inserted around 12-14 weeks, when cervical incompetence is suspected. However, cervical incompetence may be overdiagnosed as a cause of second-trimester miscarriage. The cerclage procedure also carries a risk of stimulating uterine contractions.
- In women with a history of one or more second-trimester miscarriages attributable to cervical factors and a singleton pregnancy, a cerclage should be offered if a cervical length of ≤ 25 mm is detected by transvaginal scan before 24 weeks of gestation. ^[16]
- In the USA, 1 in 300 women receive a cerclage but the rate is over 1% in many other populations.

- Preconceptual abdominal cerclage is increasingly used; there is no evidence that it has any detrimental effects but evidence of benefit is still lacking.

Further reading

- [Jeve YB, Davies W](#); Evidence-based management of recurrent miscarriages. *J Hum Reprod Sci.* 2014 Jul;7(3):159–69. doi: 10.4103/0974-1208.142475.
- [Coomarasamy A, Dhillon-Smith RK, Papadopoulou A, et al](#); Recurrent miscarriage: evidence to accelerate action. *Lancet.* 2021 May 1;397(10285):1675–1682. doi: 10.1016/S0140-6736(21)00681-4. Epub 2021 Apr 27.

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