

## Recurrent miscarriage

Management of pregnancy loss includes investigating causes, addressing modifiable risk factors, and providing supportive care in the first trimester of pregnancy.

**ABSTRACT:** Early miscarriages are those occurring within the first 12 completed weeks of gestation. Recurrent miscarriage, defined as two or more consecutive pregnancy losses, affects 3% of couples trying to conceive and can cause considerable distress. The risk of miscarriage increases with maternal age. Genetic abnormalities, uterine anomalies, and endocrine dysfunction can all lead to miscarriage. Other causes of miscarriage are autoimmune disorders such as antiphospholipid syndrome and chronic endometritis. Unfortunately, in nearly 50% of couples no clear cause can be identified. Management includes investigating causes, addressing modifiable risk factors, and providing supportive care in the first trimester of pregnancy. For some couples, in vitro fertilization with embryo screening may be an option.

**E**arly miscarriage has been reported to occur in 17% to 31% of pregnancies,<sup>1,2</sup> and is defined as a nonviable intrauterine pregnancy with either an empty gestational sac or a gestational sac containing an embryo or fetus without fetal heart activity within the first 12 completed weeks of gestation.<sup>3</sup> Recurrent miscarriage occurs in 3% of couples trying to conceive. The American Society for Reproductive Medicine (ASRM) defines recurrent miscarriage as two or more failed clinical pregnancies as documented by ultrasound or histopathologic examination,<sup>3</sup> while the National Institute for Health and Care Excellence (NICE) notes that miscarriages can cause considerable distress.<sup>4</sup>

Although common, recurrent miscarriage is neither well defined nor well understood. Our understanding of recurrent miscarriage has been limited by variable definitions of miscarriage and a lack of standardization in research. Recurrent miscarriage is considered a primary or secondary process, depending on whether the woman has experienced a live birth. Nonconsecutive miscarriages have unclear significance.

### Genetic causes

The risk of miscarriage increases with maternal age. At age 20 to 24 the risk is approximately 10%, with risk increasing to nearly 80% by age 45.<sup>5</sup> The relationship between miscarriage risk and maternal age can be explained by the increasing rate of oocyte aneuploidy that occurs as women grow older. In one study, oocytes examined during in vitro fertilization (IVF) treatment had only a 10% risk of being aneuploid in women younger than age 35, but by age 43 the risk of aneuploidy was 50%, and after age 45 nearly 100%,<sup>6</sup> confirming that the most frequent cause of miscarriage at all ages is aneuploidy.

Genetic factors that contribute to miscarriage include structural and numerical chromosome abnormalities that have arisen de novo in the

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embryo or fetus or have been inherited from the parents. These include trisomy, monosomy, and polyploidy. Trisomy is caused by unequal separation or disjunction of chromosome pairs during meiosis, events that increase with maternal age. Structural chromosome abnormalities include reciprocal translocations, Robertsonian translocations, and pericentric and paracentric inversions. Balanced carriers of these translocations have a complete karyotype and a normal phenotype, but during meiosis unbalanced oocytes or sperm can be produced. Such gametes then result in an embryo with an unbalanced karyotype predisposed to miscarriage. To identify parent-derived chromosome abnormalities, parental karyotyping is recommended. At the time of a miscarriage, genetic testing of the products of conception will help determine whether the miscarriage is the result of a de novo chromosome abnormality of the embryo or fetus, which is unlikely to recur, or whether underlying maternal disease has led to the loss of a chromosomally normal embryo or fetus, which might recur.

### Anatomic causes

Uterine anomalies are observed in 13% of women with recurrent miscarriage, compared with 5.5% of women in the general population.<sup>7</sup> Congenital uterine anomalies result from the abnormal formation, fusion, or resorption of the Müllerian ducts during embryological development. Common congenital uterine anomalies are uterus didelphys, unicornuate uterus, bicornuate uterus, and septate uterus.<sup>8</sup> These anomalies are diagnosed using the following imaging techniques, either alone or in combination: hysterosalpingography, saline infusion sonohysterography, hysteroscopy, 2-D and 3-D ultrasonography, and magnetic resonance imaging.

Surgical correction of most uterine anomalies does not improve pregnancy outcomes. The notable exception is a uterine septum. Several studies have analyzed the reproductive outcome before and after hysteroscopic septum removal. The largest series

showed a significant decrease in the early miscarriage rate from 89.6% to 12.4%, as well as an increase in term delivery rate from 1.4% to 74.4%.<sup>9</sup>

Uterine fibroids and endometrial adhesions may also be associated with recurrent miscarriage. Submucosal fibroids affect implantation by altering vascularization of the endometrium and reducing fluid cytokine concentrations.<sup>10</sup> An association between miscarriage and intramural or subserous fibroids is less clear, having been demonstrated in some, but not all, studies.<sup>10</sup> Recurrent miscarriage may occur in women with intrauterine adhesions as a result of implantation abnormalities in areas of denuded endometrium or insufficient vascularization. The impact varies with the severity of adhesions. Research on the impact and treatment of adhesions is limited.<sup>11</sup>

### Endocrine causes

Endocrine disorders are observed in 10% of women with recurrent miscarriage. The health and receptivity of the endometrium is intimately related to a woman's thyroid, prolactin, androgen, and insulin regulation.<sup>4</sup>

**Recurrent miscarriage—defined as two or more failed clinical pregnancies as documented by ultrasound or histopathologic examination—occurs in 3% of couples trying to conceive.**

### Thyroid dysfunction

The presence of thyroid autoantibodies is associated with an increased risk of both sporadic miscarriage and recurrent miscarriage. A meta-analysis found an increase in the miscarriage rate in the presence of thyroid autoantibodies: OR 3.90 for cohort studies (95% CI, 2.48-6.12); OR 1.80 for case-control studies (95% CI, 1.25-2.60).<sup>12</sup>

Several studies have suggested that levothyroxine treatment of euthyroid women who have thyroid autoantibodies decreases the risk of miscarriage. Two large randomized trials are underway to examine the role of thyroid hormone therapy in women with recurrent miscarriage.<sup>13</sup>

### Hyperprolactinemia

Hyperprolactinemia alters the hypothalamic-pituitary-ovarian axis

leading to impaired folliculogenesis and/or a short luteal phase. One study of women with recurrent miscarriage found a significant decrease in pregnancy loss with suppression of hyperprolactinemia using the dopamine agonist bromocriptine.<sup>14</sup>

### **Polycystic ovary syndrome**

Women with polycystic ovary syndrome (PCOS) have an increased risk of miscarriage, although the incidence rate is uncertain. The underlying mechanism may involve

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elevated levels of luteinizing hormone, insulin, and/or androgens. Further, many women with PCOS have a high BMI, which in itself is a risk factor for miscarriage.<sup>15</sup>

### **Insulin resistance**

Patients with poorly controlled diabetes mellitus have an increased risk of pregnancy loss.<sup>16</sup> When women with a history of recurrent miscarriage and abnormal glucose tolerance test results received metformin therapy, their rate of pregnancy loss was significantly less than that of women in a placebo group (15% versus 55%), suggesting that addressing insulin resistance with metformin may protect against miscarriage.<sup>17</sup>

### **Other causes**

Although early pregnancy loss most commonly has a genetic, anatomic, or endocrine cause, miscarriage may also result from an autoimmune disorder, chronic infection, or a lifestyle factor.

### **Autoimmune disorder**

Antiphospholipid syndrome (APS) is characterized by venous or arterial thrombosis and/or an adverse pregnancy outcome in the presence of persistent laboratory evidence of antiphospholipid antibodies. Commonly

identified antiphospholipid antibodies are lupus anticoagulant, anticardiolipin antibodies, and beta-2 glycoprotein. Between 8% and 42% of women with recurrent miscarriage will test positive for antiphospholipid antibodies.<sup>18,19</sup>

The standard treatment for documented APS consists of low-dose aspirin and heparin (74.3% live birth rate), which has proven superior to treatment with aspirin alone (42.9% live birth rate). The combination of heparin and low-dose aspirin appears to confer a significant benefit when patients have APS and otherwise unexplained recurrent miscarriage.<sup>20</sup>

### **Thrombosis**

Thrombosis of the placental vascu-

lature is associated with fetal growth restriction, fetal death after 20 weeks gestation, and preeclampsia. While there is no association between thrombophilias and recurrent early miscarriage, it may be prudent to screen women at high risk of thrombosis based on their personal or family history.<sup>21</sup>

### **Infection**

Acute infection or asymptomatic colonization of the cervix or vagina with mycoplasma, chlamydia, listeria, ureaplasma, or other pathogens does not increase the risk of miscarriage, and routine screening for such pathogens in women with recurrent miscarriage is not recommended.

Unlike acute infection, however, chronic endometritis is associated with pregnancy loss. One study identified chronic endometritis in 9% of women with recurrent miscarriage, and found a per-pregnancy live birth rate of 7% before and 56% after treatment with antibiotics.<sup>22</sup>

While the causative organism is rarely identified in cases where endometritis is suspected, the presence of plasma cells on endometrial histopathology is diagnostic and hence endometrial biopsy is recommended.

### **Lifestyle factors**

Cigarette smoking has been shown to increase the risk of sporadic miscarriage, as has obesity. Other lifestyle factors such as cocaine use, alcohol consumption (three to five drinks per week), and increased caffeine consumption (more than three cups of coffee per day) have been associated with risk of miscarriage.<sup>21</sup> Psychological stress has also been shown to affect pregnancy outcomes, with confirmation of this seen in a decreased rate of miscarriage when an intensively supportive care model is used to reduce stress.

**Unexplained**

Unfortunately, no clear causative factor is identified in nearly 50% of couples who experience recurrent miscarriage. Studies are currently examining the role of sperm factors and endometrial and embryonic factors that might improve our understanding of the causes of recurrent miscarriage.

**Management**

The management of couples affected by recurrent miscarriage requires investigating possible causes of pregnancy loss (see **Table**), addressing modifiable risks, and providing supportive care in the first trimester of pregnancy (see **Box**).

Assisted reproductive technology may be a treatment option for patients who are not helped by addressing modifiable risks or who have limited time to conceive because of advancing maternal age. As most miscarriages are caused by de novo structural chromosome abnormalities, IVF with embryo screening by preimplantation genetic diagnosis (PGD) or comprehensive chromosomal screening (CCS) can, theoretically, reduce the risk of miscarriage by selecting euploid embryos for transfer into the uterus.

The presumed advantages of IVF and preimplantation embryo screening over expectant management are a shorter time to pregnancy, a decreased miscarriage rate, and a higher live birth rate, although these advantages have not been demonstrated by the few studies published. There is an advantage to PGD/CSS if a euploid embryo is obtained. However, since many couples who undergo embryo screening do not obtain a euploid embryo for transfer because IVF cycles are cancelled or do not result in a viable embryo, PGD/CSS has not been shown to improve live birth rates when compared with expectant management.<sup>23</sup>

**Management for recurrent miscarriage**

- Investigate genetic, anatomic, and endocrine causes of pregnancy loss:
  - Structural and numerical chromosome abnormalities such as trisomy and polyploidy.
  - Uterine anomalies such as septate uterus.
  - Thyroid dysfunction, hyperprolactinemia, polycystic ovary syndrome, insulin resistance.
- Consider other possible causes of pregnancy loss:
  - Antiphospholipid syndrome.
  - Chronic endometritis.
  - Lifestyle factors such as cigarette smoking.
- Address modifiable risk factors.
- Provide supportive care in the first trimester of pregnancy.

**Summary**

Recurrent miscarriage, defined as two or more consecutive losses of an early pregnancy, occurs in 3% of couples trying to conceive. The risk of miscarriage increases as women age, with the most common cause being chromosome abnormalities that have arisen de novo in the embryo or fetus. Uterine anomalies and endocrine dysfunction can also lead to miscarriage, as can disorders such as antiphospholipid antibody syndrome and chronic endometritis. In nearly 50% of couples, however, no clear cause can be identified. Management includes investigating possible causes,

addressing modifiable risk factors, and providing supportive care in the first trimester of pregnancy. For some couples, in vitro fertilization with embryo screening may be an option. **BCMJ**

**Competing interests**

None declared.

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**Table. Investigating recurrent miscarriage.**

Possible causes	Investigations
Genetic	Parental karyotyping
Anatomic	Imaging: hysterosalpingography, saline infusion sonohysterography, hysteroscopy, ultrasonography, MRI
Endocrine	Laboratory testing: thyroid-stimulating hormone, thyroid antibodies, prolactin, fasting glucose
Autoimmune	Laboratory testing: lupus anticoagulant, anticardiolipin antibodies, beta-2 glycoprotein
Thrombosis	Medical and family history
Infection	Endometrial biopsy

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