

An evidence-based approach to recurrent pregnancy loss

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Recurrent pregnancy loss (RPL) can be defined as more than two to three consecutive miscarriages before 24 weeks' gestation. A literature review was done to provide an evidence-based approach to RPL, identifying the risk factors and causes and also looking at the various special investigations that form part of the work-up and trying to assess which have been proven to be effective or of negative impact, and which of the management options lead to a better outcome. We concluded that the following special investigations should be part of the work-up for all patients with RPL: (i) genetic counselling and karyotyping of the abortus; (ii) anticardiolipin antibodies and lupus anticoagulant testing must be done on two occasions, 6 - 8 weeks apart; (iii) all patients qualify for a pelvic ultrasound scan and hysteroscopy; (iv) syphilis testing must be done routinely; and (v) testing of thyroid function and glucose monitoring/glycosylated haemoglobin (HbA1c) measurement must be done in all patients with a history of thyroid disease or diabetes mellitus, or clinical manifestations thereof. In approximately 50% of couples the cause of RPL remains unexplained, even after evaluation.

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Recurrent pregnancy loss (RPL), a traumatic experience for the patient, is also one of the most difficult areas in reproductive medicine. Little consensus exists regarding which investigations should be done to identify the cause and which treatments are effective, and very few are evidence-based. This paper aims to provide the reader with a simplified approach in identifying the cause of RPL, to assist with everyday management in hospital clinics as well as private practice.

Definition

According to the Royal College of Obstetricians and Gynaecologists (RCOG) Green-top Guideline No. 17, a miscarriage can be defined as the spontaneous loss of a pregnancy before the fetus has reached viability at 24 weeks.^[1] This includes all pregnancy losses from the time of conception until 23 completed weeks of gestation. RPL is defined as three or more consecutive miscarriages. The World Health Organization recommends that in developing countries, where gestation is often uncertain, a birth weight of 500 g should be used to define viability. The American Society for Reproductive Medicine defines RPL as two or more failed pregnancies, which have been documented by either ultrasound or histopathological examination.^[2] They suggest that some investigation must be done after each miscarriage, with a thorough evaluation after three or more losses.

Incidence

RPL (as per the classic definition of three or more consecutive pregnancy losses) affects 0.4 - 1% of couples.^[3] This is approximately twice the incidence that would have been expected by chance alone, and indicates that an abnormality is likely to be present. The risk of miscarriage is also higher the earlier the gestation, the majority occurring in the first trimester (Table 1).^[4]

Epidemiology

Maternal age

The prevalence of miscarriage increases with advancing maternal age (Table 2).^[5] The increase in the risk of miscarriage in this group is due to an increase in chromosomally abnormal conceptuses, probably as a result of poor oocyte quality, and a decline in uterine and ovarian function. Advanced paternal age is also a risk factor for miscarriage. The risk of miscarriage is highest in couples where the woman is older than 35 years and the man older than 40 years.^[6]

Reproductive history

A woman's obstetric history predicts her future risk of miscarriage. Both retrospective and prospective studies have shown that the risk of another miscarriage increases after each subsequent pregnancy loss (Table 3).^[7] RPL typically occurs at a similar gestational age in consecutive pregnancies.

Risk factors for recurrent pregnancy loss

Genetic factors

Embryonic chromosomal abnormalities (structural and numerical) may account for 30 - 57% of miscarriages.^[1] Research has shown that the risk of aneuploidy increases as the number of previous miscarriages increases. Parental chromosomal rearrangements are the cause of RPL in 3 - 5% of couples. The most common abnormalities are balanced reciprocal or Robertsonian translocations.

Anatomical disorders

Congenital uterine anomalies

Congenital uterine malformations are caused by disturbances in Müllerian duct development, fusion, canalisation, and septal reabsorption.^[8] Congenital uterine anomalies most commonly lead to

second-trimester miscarriages, and in patients with RPL the contribution of congenital uterine anomalies is unclear. The septate uterus is the most common uterine abnormality associated with RPL and is associated with the poorest reproductive outcome, with a miscarriage rate of more than 60%. The longer the septum, the poorer the prognosis.^[9]

Leiomyoma

The most important factor where fibroids and fertility are concerned is the location and not the size of the fibroid. Those that distort the uterine cavity, such as submucosal fibroids and intramural fibroids with an intracavitary component, have been shown to play a role in infertility and are associated with an increased risk of miscarriage. A study by Benecke *et al.*^[10] concluded that intramural fibroids cause a lower implantation rate per cycle. A meta-analysis by Sunkara *et al.*^[11] showed a statistically significant reduction in pregnancy rates following *in vitro* fertilisation (IVF) treatment, even in women with non-cavity-distorting intramural fibroids.

Intra-uterine adhesions

Asherman's syndrome results from vigorous curettage of the endometrium, the intra-uterine trauma causing adhesions.^[12] This may lead to miscarriage because there is insufficient endometrium to support fetoplacental growth, but no prospective evidence is available to confirm the causal relationship. Genital tuberculosis is a cause of intra-uterine adhesions in the developing world.

Cervical incompetence (insufficiency or dysfunction)

Cervical incompetence leads to recurrent mid-trimester miscarriages.

Thrombophilic factors

It has been hypothesised that thrombophilic disorders cause thrombosis of the utero-placental vasculature (spiral arteries and intervillous space) due to an increased haemostatic response.^[13] The subsequent impaired placental perfusion may lead to recurrent pregnancy loss, fetal death, pre-eclampsia, intra-uterine growth retardation and abruptio placentae.

Inherited thrombophilia is a genetic condition in which there is an increased risk of venous thrombosis. The various types are:

- factor V Leiden (FVL) mutation
- prothrombin G20210A gene mutation (PGM)
- protein S deficiency
- protein C deficiency
- antithrombin deficiency.

Of cases of inherited thrombophilia, 50 - 60% are due to FVL mutation and PGM. The literature on the association between maternal inherited thrombophilia and RPL is mostly contradictory.

Antiphospholipid syndrome

According to the RCOG, antiphospholipid syndrome is the most important treatable cause of RPL.^[1] It is the only autoimmune condition in which pregnancy loss is part of the diagnostic criteria. Antiphospholipid antibodies (APAs), lupus anticoagulant, anticardiolipin antibodies (ACAs) and anti-B₂ glycoprotein-I antibodies are directed against phospholipid-binding plasma proteins. Adverse pregnancy outcomes include:

- three or more consecutive unexplained miscarriages before 10 weeks' gestation
- one or more deaths of morphologically normal fetuses after the 10th week of gestation

Table 1. Risk of miscarriage at specific gestational ages

Gestation	Risk of miscarriage (%)
Before 6 weeks	22 - 57
6 - 10 weeks	15
After 10 weeks	2 - 3

Table 2. Miscarriage rate according to maternal age

Maternal age at conception (years)	Miscarriage rate (%)
20 - 24	9
25 - 29	11
30 - 34	15
35 - 39	25
40 - 44	51
>45	75

Table 3. Risk of miscarriage according to obstetric history

Consecutive pregnancies	Risk of miscarriage (%)
First pregnancy	5 - 13
After 1 miscarriage	14 - 21
After 2 miscarriages	24 - 29
After 3 miscarriages	31 - 45

- one or more preterm births before 34 weeks' gestation due to severe pre-eclampsia, eclampsia or placental insufficiency.

Of patients with RPL, 5 - 15% may have APAs, and the fetal loss rate in untreated future pregnancies may be as high as 90%.^[14]

Immunological factors

The hypothesis that some cases of RPL may be due to failure of maternal allo-immune recognition of the pregnancy has never been proven. There is also no evidence to support the hypothesis that HLA incompatibility between couples may lead to RPL. Testing of these should not be offered to couples.

Uterine natural killer (NK) cells

Some patients with RPL may lack essential components of the networks that provide immunological protection to embryos.^[1] Uterine NK cells appear to regulate placental and trophoblast growth and local immunomodulation, and control trophoblast invasion. The relationship between uterine NK cell numbers and future pregnancy outcome in patients with RPL is still being investigated.

Granulocyte-macrophage colony-stimulating factor (G-CSF)

G-CSF is a cytokine with an important regulatory role in embryo implantation and subsequent development. G-CSF deficiency in pregnancy adversely impacts on fetal and placental development.^[15] Recent studies have shown that the best-quality oocytes come from follicles with the highest level of G-CSF. Research has been done to investigate the effectiveness of administering G-CSF in preventing embryo death in women with RPL. Most of the data show that G-CSF may be effective in the treatment of unexplained RPL. However,

further studies are needed to confirm the effectiveness of this treatment.

Endocrine factors

Diabetes mellitus

Several studies have linked high glycosylated haemoglobin (HbA1C) values (>8%) early in pregnancy to an increase in early pregnancy loss and congenital malformations. There is no increased risk of miscarriage in women with well-controlled diabetes mellitus.^[16]

Polycystic ovarian syndrome (PCOS)

Recent studies have shown that reproductive outcome did not differ between patients diagnosed with PCOS and healthy controls. The two groups had similar live birth and miscarriage rates.^[17]

Thyroid antibodies and disease

There are many conflicting reports, and evidence is still lacking with regard to the role of thyroid disease in RPL. Some review articles conclude that increased serum thyroid antibodies (thyroid peroxidase or thyroglobulin) appear to be related to recurrent spontaneous miscarriages, even in euthyroid patients,^[18] but the mechanism is still unclear. Hyperthyroidism (Graves' disease) is associated with spontaneous miscarriage, premature labour, low birth weight and perinatal mortality.^[19] Hypothyroidism is associated with infertility and first-trimester miscarriages, as well as perinatal morbidity and mortality.^[20]

Luteal phase defect and progesterone deficiency

A functional corpus luteum is essential for successful implantation and maintenance of early pregnancy, primarily through progesterone production.^[21] A luteal phase defect (defect in corpus luteum function) with insufficient progesterone production results in endometrial development unsuitable for embryonic implantation and is associated with RPL. The existence of luteal phase defect is controversial, as is whether it is related to RPL, mainly because of inconsistencies in its diagnosis and management. No evidence could be found in the literature regarding a possible association of anti-Müllerian hormone deficiency and RPL.

Environmental factors

There is no high-quality evidence that shows any relationship between RPL and occupational factors, stress, low-level exposure to environmental chemicals, cigarette smoking or caffeine use.^[22] Moderate to heavy alcohol consumption may increase the risk of sporadic miscarriage. Exercise does not appear to increase the rate of sporadic or RPL. Recent retrospective studies have shown evidence that obesity is a risk factor for infertility, sporadic and RPL and late pregnancy complications.

Infection

No infectious agent has been proven to cause RPL. Pregnancies complicated by untreated syphilis may lead to RPL if it remains untreated in the subsequent pregnancy. The typical history is of recurrent mid-trimester miscarriages with macerated fetuses. Genital tuberculosis may cause implantation failure or early embryonic rejection, leading to RPL and ectopic pregnancy.

Candidates for investigation

It is generally accepted that women without any co-morbid medical conditions should not undergo extensive investigations after a single miscarriage, and most experts only start with evaluation and treatment of RPL after either two or three consecutive miscarriages. However, in approximately 50% of these couples the cause of RPL remains unexplained. Women with unexplained RPL (>3 miscarriages) still have an excellent prognosis for future pregnancy outcome, with a live birth rate of over 50%.

History and physical examination

The evaluation of any couple with RPL should include a complete history, including their ages and an obstetric, gynaecological, medical, surgical, genetic, social and family history, as well as a physical examination. A detailed history of the previous miscarriages is essential, including the gestational age. With second-trimester miscarriages, any information that could assist in confirming or excluding cervical incompetence should be reviewed and the medical notes on the previous miscarriages, whether the fetus was macerated or not and whether any uterine abnormalities were seen with evacuation, should be noted. Results from previous laboratory, pathology and imaging studies must also be obtained.

Investigation of recurrent pregnancy loss

Karyotyping

Karyotyping of products of conception

Cytogenic analysis should be performed on the products of conception in all patients with RPL. An abnormal karyotype usually indicates a better prognosis for the next pregnancy.^[1] Structural chromosomal rearrangements in the fetus may be inherited or sporadic, and are an indication for parental karyotyping. The role of pre-implantation genetic diagnosis (PGD) with IVF has been reviewed, and it has been found not to be cost-effective in the management of RPL.^[23] In patients with RPL the spontaneous birth rate is still 50%; with PGD the miscarriage rate may be decreased, but only 33% of women become pregnant after each PGD/ IVF cycle.

Parental peripheral blood karyotyping

Selective parental karyotyping is appropriate in cases where chromosomal abnormalities were identified in products of conception.^[1] It must be noted that these investigations are expensive and have limited prognostic value and a low yield for abnormality, and it is not cost-effective routinely to do karyotyping of all couples with RPL. The purpose is to detect balanced reciprocal or Robertsonian translocations, or mosaicism that could be inherited unbalanced by the fetus. However, chromosomal abnormalities detected in parental peripheral blood samples are an indirect and limited indicator of fetal karyotype.

Uterine assessment

According to the RCOG, all women with recurrent first-trimester miscarriages or with one or more second-trimester miscarriages should have a pelvic ultrasound scan to assess the uterine anatomy.^[1] Thereafter, if uterine anomalies are suspected, further investigations can be done to confirm the diagnosis, using hysteroscopy, laparoscopy or three-dimensional pelvic ultrasound. Other diagnostic modalities are sonohysterography, hysterosalpingography and magnetic resonance imaging (MRI). MRI is seldom indicated because it is rarely cost-effective.

Hysteroscopy is seen as the gold standard for the diagnosis of intra-uterine anomalies, and most abnormalities can also be treated during the procedure.^[24] Sonohysterography provides information on the internal contour of the uterus, as well as the outer surface and uterine wall. In comparative studies it was found to be more accurate and to provide more information than hysterosalpingography.^[25]

Inherited thrombophilias

Testing for inherited thrombophilia in women with a history of unexplained RPL is controversial. There are no high-quality, placebo-controlled, randomised clinical trials to establish the efficacy of anticoagulation therapy in preventing RPL. There is also limited evidence to help guide the screening process for these conditions.

According to American College of Obstetricians and Gynecologists Practice Bulletin No. 124, inherited thrombophilia testing is not recommended for women who have had RPL or placental abruption, since it is unclear whether anticoagulation reduces recurrence (level B recommendation).^[13] Screening with fasting homocysteine levels

or methylenetetrahydrofolate reductase mutation analyses is not recommended (level B recommendation). Screening should be done for FVL and PGM, as well as antithrombin, protein C and protein S deficiency (level C recommendation). Screening is controversial and only useful if the results will affect management decisions, and not where treatment is indicated for other risk factors.

The RCOG recommends that women with recurrent second-trimester miscarriages should be screened for inherited thrombophilia. This includes testing for FVL, PGM and protein S deficiency (grade D recommendation).^[1] This was based on a meta-analysis of retrospective studies that showed a strong relationship between second-trimester miscarriage and the inherited thrombophilias, as mentioned above.

Antiphospholipid syndrome

All women with RPL should be screened for antiphospholipid syndrome before the next pregnancy.^[26] The work-up includes testing for ACA IgG and IgM, and lupus anticoagulant (LA); it

Table 4. Evidence-based approach to the work-up of couples with recurrent pregnancy loss, to identify a possible underlying cause

Genetic counselling and screening
<ul style="list-style-type: none"> Genetic counselling: All patients Amniocentesis: All women of advanced maternal age Karyotyping of products of conception: All patients Parental karyotyping: Only patients with a personal or family history of genetic abnormalities or when the results of karyotyping of the abortus are abnormal
ACAs (IgG and IgM) and lupus anticoagulant
<ul style="list-style-type: none"> All patients, before the next pregnancy On 2 separate occasions, 6 - 8 weeks apart
Imaging
<ul style="list-style-type: none"> Pelvic ultrasound: All patients Hysteroscopy: All patients Depending on anomalies detected, sonohysterography, a hysterosalpingogram or laparoscopy can be considered
Screening for infection
<ul style="list-style-type: none"> Syphilis testing: All patients
TSH, fasting glucose/HbA1c
<ul style="list-style-type: none"> If clinical manifestations of either disease is present or if the patient is known to have the disease

ACAs = anticardiolipin antibodies; TSH = thyroid-stimulating hormone; HbA1c = glycosylated haemoglobin.

Table 5. Controversial factors in the work-up and management of recurrent pregnancy loss

Screening for inherited thrombophilia
<ul style="list-style-type: none"> Association with RPL is controversial Depends on whether RCOG^[1] or ACOG^[13] guidelines are followed RCOG: Test all women with a history of thromboembolism planning pregnancy. Test for factor V Leiden mutation, PGM and protein S deficiency when indicated ACOG: Testing only useful if results will affect management plan, not useful in situations where treatment is indicated for other risk factors. Test for FVL mutation, PGM, antithrombin, protein C and protein S deficiency when indicated
Immunological testing and therapy (uterine NK cells and G-CSF)
<ul style="list-style-type: none"> Currently not indicated, still in research phase
Luteal phase defect
<ul style="list-style-type: none"> No standardised diagnostic method available If progesterone is supplemented, it should be done from ovulation until 7 - 9 weeks' gestation
Thyroid function
<ul style="list-style-type: none"> Controversial whether patients asymptomatic for thyroid disease must be screened routinely for thyroid dysfunction Some authors recommend screening all patients with RPL for thyroid peroxidase antibodies, some limit it to cases where all other causes have been excluded Not recommended by RCOG guidelines

RCOG = Royal College of Obstetricians and Gynaecologists; ACOG = American College of Obstetricians and Gynecologists; FVL = factor V Leiden; PGM = prothrombin gene mutation; NK cells = natural killer cells; G-CSF = granulocyte-macrophage colony-stimulating factor.

should be done twice, 6 - 8 weeks apart, to rule out a false-positive result. The diagnosis of antiphospholipid syndrome requires at least two positive results for either LA or ACA IgG or IgM. Women with one positive test result and a second negative test result should have a third test to confirm the diagnosis. False-positive results may be due to infection, suboptimal methods of sample collection and preparation, and lack of standardisation of laboratory testing.

Infectious causes

A recent review article concluded that most patients with a history of RPL do not benefit from an extensive infection work-up.^[27] The exception is untreated syphilis.

Thyroid function

Thyroid function should be assessed in women known to have a history of thyroid disease or with the clinical manifestations thereof. The American Thyroid Association recommends measuring serum thyroid-stimulating hormone in pregnant women in the following cases:^[28]

- symptomatic for thyroid disease
- from an area known with iodine insufficiency
- family or personal history of thyroid disease
- thyroid peroxidase antibodies present
- type 1 diabetes
- history of preterm delivery or miscarriage
- history of head or neck radiation
- morbid obesity
- infertility
- older than 30 years.

Screening of asymptomatic women for subclinical thyroid disease is controversial. Currently screening for thyroid disease of all women who wish to fall pregnant is not recommended, since there are no data to confirm that such a screening mandate has any meaningful outcome. However, certain authors recommend measurement of thyroid peroxidase antibodies in patients with RPL or preterm birth, where no other cause could be identified.^[29]

Evaluation of ovarian reserve

Taking blood for follicle-stimulating hormone (FSH) concentrations on day 3 of the menstrual cycle can be considered in the evaluation of RPL in women of any age group. In a retrospective comparative analysis, day 3 serum FSH or oestradiol levels, or both, were elevated in 58% of women with unexplained RPL.^[30]

Luteal phase defect

There is no standardised diagnostic method available to assess the true incidence and effect of luteal phase defect. Endometrial biopsy is not recommended, since studies have shown that it does not predict fertility status. Serum progesterone measurement is unreliable, and it is not predictive of pregnancy outcome.^[22]

Medical work-up

Laboratory testing may be indicated in women with clinical manifestations or a history suggestive of a medical disorder.

Treatment options

The management of RPL should be guided by the underlying cause. However, all couples should be treated sensitively, sympathetically,

and with appropriate emotional support. Best practice is to refer couples to a specialist clinic.

Conclusion

The evidence-based recommendations for investigating couples with RPL in order to identify an underlying cause are summarised in Table 4. However, some aspects (including causes, investigations and management) are still surrounded by some controversy (Table 5), and further studies are needed in order to confirm or exclude their role in the approach to a couple with RPL.

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