BMJ Best Practice

Assessment of recurrent miscarriage

Straight to the point of care

Last updated: Nov 17, 2023

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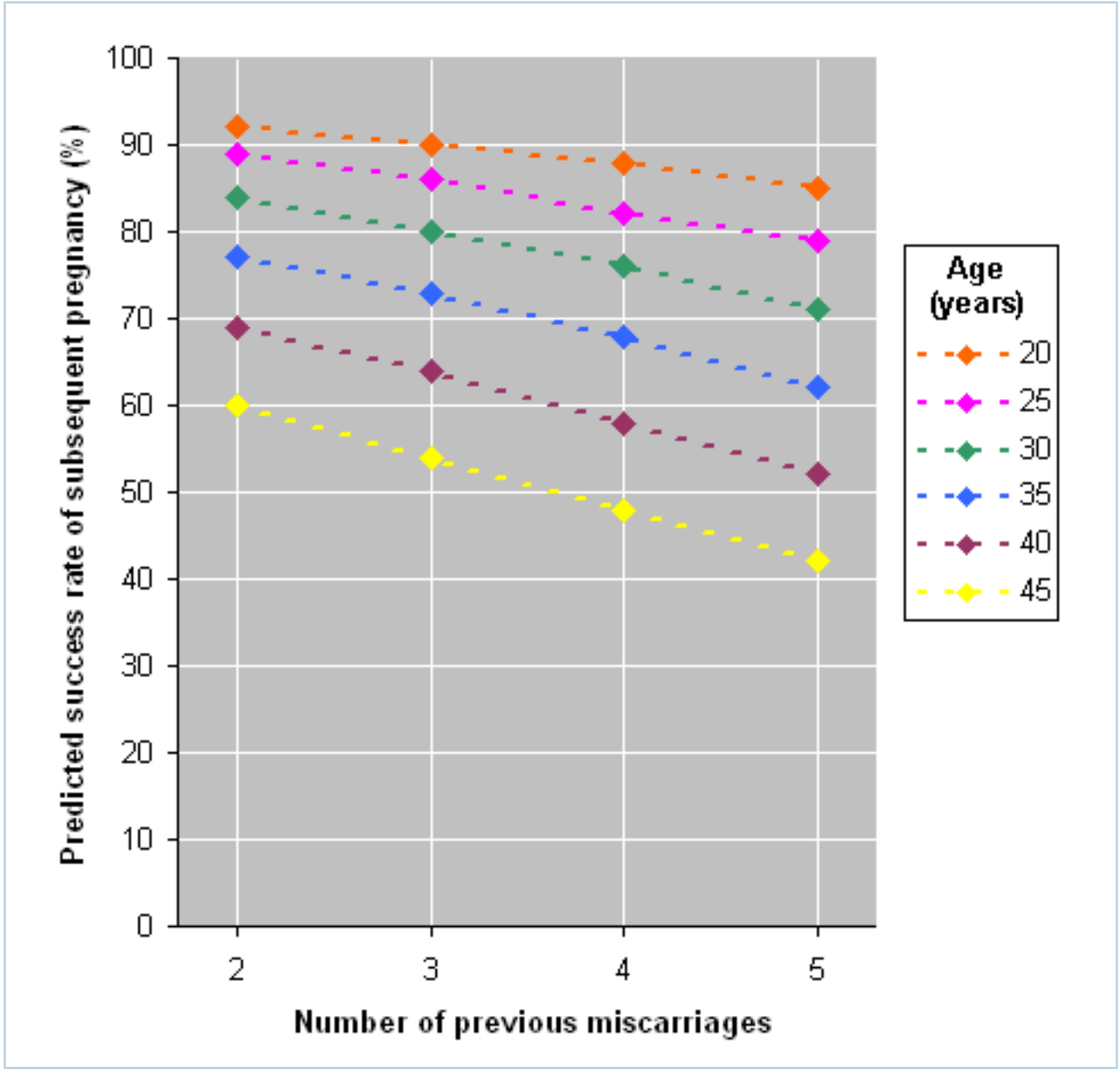
OVERVIEW

Summary

Recurrent miscarriage is defined by the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine as 2 or more failed clinical pregnancies (i.e., documented by ultrasound or histopathology).[1] [2] It affects about 1% of all fertile couples trying to conceive, in comparison with sporadic non-consecutive miscarriages, which occur in about 15% to 20% of all pregnancies.[3] A miscarriage includes any pregnancy that ends before the age of viability, which currently stands at 24 weeks' gestation. A miscarriage that occurs before 12 weeks' gestation is commonly termed an early or first-trimester miscarriage, and one that occurs between 13 and 24 weeks' gestation is known as a late or second-trimester miscarriage.

Evaluation can start after 2 or 3 consecutive miscarriages, as prevalence of causes is similar in those with 2, 3, or more miscarriages.[4] Despite a wide range of investigations, no apparent cause is found in >50% of cases of recurrent miscarriage.[5] About 70% of patients with no cause found will achieve a live birth in the subsequent pregnancy depending on the age of the woman and the number of previous miscarriages.[4] [5]



Predicted percentage success rate of subsequent pregnancy according to age and previous miscarriage history

Created by the BMJ Group; data from Brigham SA, et al. Hum Reprod. 1999;14:2868-2871

Definite associations of recurrent miscarriage include chromosomal abnormalities, antiphospholipid syndrome, certain structural uterine abnormalities such as septate uterus, and certain thrombophilias. However, a reduction in risk of miscarriage in a subsequent pregnancy following treatment has not been proven unequivocally for most of these conditions. Controversy surrounds the possible association of other conditions with recurrent miscarriage, including immunological factors, other uterine abnormalities (e.g., cervical incompetence), infection, and male and endocrinological factors. There is a need for high-quality and methodologically sound research to guide management of these patients.[6]

Risk factors

Increasing maternal age reduces the chance of a successful live birth. Women aged 20 years with 2 previous miscarriages have a 92% chance of success in the next pregnancy compared with only a 60% chance of success in women aged 45 years with 2 previous miscarriages.[7]

Advanced paternal age also appears to be associated with greater risk for spontaneous miscarriage.[8] [9] [10] Increased frequency of chromosomal anomalies in sperm has been implicated.[11] In one systematic review and meta-analysis, risk for pregnancy loss <20 weeks was increased by 23% and 43% among men aged 40-44 and ≥45 years, respectively (compared with men aged 25-29 years).[10]

Primigravidas and patients who consistently have successful pregnancies have only about 5% risk of miscarriage, compared with 24% in patients who have previously miscarried.[12] Other studies similarly show a trend of miscarriage rate increasing with the number of previous miscarriages.[7] [13] Therefore, the risk of miscarriage is directly related to the outcome of previous pregnancies.

Recurrent miscarriage is a stressful condition, so alongside medical investigations and appropriate treatment, patient education, counselling, and support should be provided.

Aetiology

It is common to divide the associations of recurrent miscarriage into the following categories:

- Genetic
- Anatomical
- Immunological
- Thrombophilic
- Endocrinological
- Infective
- Male factor
- Environmental
- Unexplained.

Genetic

Parental chromosomal abnormalities

These account for about 3% to 5% of patients with recurrent miscarriage and are most commonly balanced reciprocal or Robertsonian translocations.[14] Robertsonian translocation is a common form of chromosomal rearrangement involving chromosomes 13, 14, 15, 21, or 22. It is balanced and results in no excess or deficit of genetic material, thus causing no health difficulties. If these abnormalities are detected, a referral to a clinical geneticist is indicated. Patients with an unbalanced translocation have a 5% to 10% chance of a pregnancy that may result in a child with disabilities, and are therefore entitled to antenatal diagnosis. However, patients with balanced translocation have a 50% to 70% chance of a healthy live birth if they are closely monitored, evaluated for other treatable causes, and offered supportive care.[15] [16]

Chromosomal abnormality of the fetus

- This is the most common cause of miscarriage. It accounts for up to 70% of early miscarriages but only 20% of miscarriages that occur between 13 and 20 weeks' gestation.[17] Therefore, the gestational age at which a miscarriage occurs may help to identify its cause. Defects are commonly trisomy, polyploidy, or monosomy. The risk of having a fetus with chromosomal abnormality is higher in mothers older than age 35 years, confirming the association of advancing maternal age and aneuploidy. However, the underlying mechanism for this is uncertain.[17]
- In the context of recurrent miscarriage, the frequency of fetal chromosomal abnormality significantly decreases with increasing number of previous miscarriages.[13] Thus, an abnormal fetal karyotype in a miscarriage is an important prognostic factor and suggests a successful outcome of about 75% in the next pregnancy.[13] [17]

Other genetic causes

Molecular genetic abnormality such as highly skewed X-chromosome inactivation has been suggested as a potential cause of recurrent miscarriage in some small studies. However, larger studies have failed to confirm this association.[18] [19]

Anatomical or structural

The exact contribution of congenital uterine anomaly in causing recurrent miscarriage is difficult to assess, due to the vast difference in criteria and techniques for diagnosing abnormal uterine morphology. The

prevalence of uterine anomalies such as septate, bicornuate, or arcuate uterus in the general population is 5.5%, and it seems to be higher in patients with a history of miscarriage (13.3%).[20] However, a direct causative link is difficult to establish. Limited evidence from non-randomised trials shows an improvement in pregnancy outcomes if these anomalies are surgically corrected.[21] [22] In the UK, the National Institute for Health and Care Excellence has published guidelines recommending hysteroscopic resection for patients with a uterine septum and history of recurrent pregnancy loss or preterm delivery.[23]

Cervical incompetence is a structural abnormality associated with recurrent miscarriage, more commonly in the second trimester. Unfortunately, there are no objective tests that can consistently identify women with cervical weakness when they are not pregnant. Thus, the diagnosis is often based on a history of painless dilatation of the cervix or spontaneous rupture of membranes, followed by a second-trimester miscarriage. The exact mechanism of how this condition causes second-trimester miscarriage is still uncertain. The cervix probably plays more than just a mechanistic role. Treatment with prophylactic insertion of cervical suture has not been confirmed to improve pregnancy outcomes.[24]

Immunological

Antiphospholipid syndrome (APS) is found in about 15% of patients with recurrent miscarriage.[25] Screening for APS is recommended for all women with recurrent miscarriage, because they may benefit from treatment.[26][27] [28] [1]

APS diagnosis

The presence of at least one clinical and one laboratory component from the following criteria is often used as a guide for APS diagnosis:[29]

Clinical criteria include:

- Vascular (arterial or venous) thrombosis in any tissue or organ
- 3 or more consecutive miscarriages before 10 weeks' gestation
- 1 or more unexplained deaths of a morphologically normal fetus at 10 weeks' gestation or older
- 1 or more premature births of a morphologically normal fetus before 34 weeks' gestation associated with severe pre-eclampsia or placental insufficiency.

Laboratory criteria include:

- Medium or high titres of IgG and/or IgM anticardiolipin (aCL) antibodies in 2 or more tests at least 12 weeks apart
- Presence of lupus anticoagulant (LA) in 2 or more tests at least 12 weeks apart
- High titres of IgG and/or IgM anti-beta-2 glycoprotein-1 antibodies in 2 or more tests at least 12 weeks apart.

The American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR) have produced high-specificity classification criteria intended for APS research.[30]

Other immunological states

Dysregulated natural killer cells (either in the peripheral blood or in the endometrium) have been associated with recurrent miscarriage and recurrent implantation failure.[31] [32] Further research is warranted.

Additional immunological risk factors implicated in recurrent miscarriage include antinuclear antibodies, thyroid antibodies, IgA antibodies against transglutaminase (tTG-IgA), regulatory T-cells (Tregs), HLA-

sharing and HLA associations, and cytokine polymorphisms.[26] [33] [34] There is, however, an absence of high-level evidence to support the association between many of these immunological factors and recurrent miscarriage.[33] One systematic review of 20 trials of various immunotherapies such as paternal cell immunisation, third-party donor cell immunisation, trophoblast membrane infusion, and intravenous immunoglobulin showed no significant beneficial effect over placebo in improving live-birth rates.[35]

Thrombophilia

Women with recurrent miscarriage should be offered testing for acquired thrombophilia, particularly for lupus anticoagulant and anticardiolipin antibodies.[26] [1]

Inherited thrombophilia

Meta-analyses report that FVL mutation (associated with activated protein C resistance) and prothrombin gene mutation are associated with recurrent miscarriage and adverse pregnancy outcomes.[36] [37]

Two systematic reviews have concluded that the prevalence of inherited thrombophilia in women with recurrent miscarriage is similar to that in the general population.[38] [39] The UK and US guidelines recommend against routine heritable thrombophilia screening in women with recurrent miscarriage or a history of fetal loss, respectively.[40] [41] Targeted assessment for inherited thrombophilia may be considered in specific clinical circumstances.[41]

Endocrinological

Polycystic ovarian syndrome

- The prevalence of polycystic ovarian syndrome (PCOS) in recurrent miscarriage ranges from 4.8% to 82% as there was a huge variation in criteria for diagnosing PCOS before the availability of the Rotterdam diagnostic criteria.[42] [43] Thus, reappraisal of the prevalence of PCOS in recurrent miscarriage using the Rotterdam criteria is needed.
- The most likely possible mechanisms by which PCOS could cause recurrent miscarriage are hyperandrogenism, obesity, and insulin resistance, although further work is needed to assess this.[42] [44] Patients with PCOS with abnormal ovarian morphology on ultrasound scan, elevated luteinising hormone (LH), and elevated testosterone have been found to have similar live-birth rates to women without PCOS.[45]

Luteal phase problems

These disorders are diagnosed when there are low progesterone levels and the histological date of the endometrium lags behind menstrual dating for 2 or more days in a minimum of 2 menstrual cycles. Association of luteal phase problems with recurrent miscarriage is controversial, but it is believed to be related to either decreased progesterone production by the corpus luteum, abnormal LH secretion, or poor response of the endometrium to available progesterone.[46] Although a systematic review of progestogen treatment showed no significant difference in the risk of miscarriage, a subgroup analysis of trials involving women who had recurrent miscarriages showed a significant decrease in miscarriage rate.[47] One large RCT found that there was no benefit from giving progesterone supplementation in women with unexplained recurrent pregnancy loss.[48] However, a recent re-evaluation of the results of this trial and another trial involving progesterone supplementation of women with bleeding in pregnancy shows a trend of increasing benefit of progesterone supplementation with increasing number of miscarriages.[49]

Hyperprolactinaemia

The role of hyperprolactinaemia in recurrent miscarriage is debated.[46] Furthermore, a randomised controlled trial that found an improved pregnancy success when recurrent miscarriage patients with hyperprolactinaemia were treated has been criticised for its methodology.[50] Thus, the relationship is still uncertain.

Undiagnosed and untreated thyroid disorders

These disorders are associated with miscarriages, but when women are euthyroid on treatment, thyroid disorders are not risk factors for recurrent miscarriage, and these pregnancies can go to term with minimal complications.[51] The presence of thyroid antibodies has been found to be associated with a higher miscarriage rate.[52] However, the presence of association does not mean causation and could be explained by mechanisms such as an underlying autoimmune state or mild thyroid failure.[52] Although there is no treatment available for autoimmunity against the fetal allograft, screening for subclinical hypothyroidism could be done, as patients may be treated and have better pregnancy outcomes.[51]

Diabetes mellitus

When uncontrolled, diabetes mellitus is known to cause miscarriages and congenital malformations. However, when well managed, diabetes mellitus alone is not a risk factor for miscarriage and thus should not cause recurrent miscarriage.[53]

Infective

Severe infections have been associated with spontaneous miscarriages. However, for infection to be considered a cause for recurrent miscarriage, the bacteria or virus must be capable of persisting in the genital tract (to facilitate an infectious carrier state), or be able to repeatedly cause placental infection.[26][54] The presence of bacterial vaginosis is a recognised risk factor for late miscarriage and preterm birth if found in early pregnancy.[55]

There is no evidence that other bacterial or viral infections such as *Chlamydia*, *Ureaplasma*, *Mycoplasma*, cytomegalovirus, adeno-associated virus, human papillomavirus, toxoplasmosis, rubella, herpes virus, and listeria are associated with recurrent miscarriages in the first trimester.[54] [56] Herpes simplex virus carriers are not known to be more susceptible to recurrent miscarriages.

There is growing evidence that women with recurrent pregnancy loss have an increased incidence of chronic endometritis (29.67%) as diagnosed by hysteroscopic visualisation, histological assessment, and/or CD138 staining of endometrial biopsy. Chronic endometritis can be treated successfully with antibiotics; however, it is unclear whether this leads to an increase in live birth rate.[57]

Male factor

There has been interest in investigating male factor causes of recurrent pregnancy loss, specifically sperm DNA fragmentation. Meta-analyses have found an association between increased sperm DNA fragmentation in male partners and unexplained recurrent miscarriages.[58] [59] Tests to assess sperm DNA fragmentation measure single and/or double stranded DNA breaks in sperm directly or indirectly.

The European Society of Human Reproduction and Embryology (ESHRE) recommends consideration of sperm DNA fragmentation tests for explanatory purposes in recurrent pregnancy loss, whereas other societies have not endorsed this.[1] [60] At present, there is no general international consensus to offer this testing as a routine diagnostic test.

Environmental

Chemicals

There is a concern that chemicals, either in the surroundings or ingested, can contribute to recurrent miscarriage. However, it is difficult to provide accurate information regarding the reproductive impact of these chemicals, as evidence is not readily available.[61] The potential of an environmental chemical causing miscarriage is also dependent on the type and duration of exposure, the extent to which it enters the fetal circulation, gestational age of the pregnancy at exposure, and other related pregnancy factors, such as presence of any medical disorders. It is clear that heavy metals (e.g., lead and mercury), organic solvents, ionising radiation, and teratogenic drugs are toxins, and exposure could contribute to pregnancy loss.[61] If exposure to these occupational hazards is suspected as the cause of a miscarriage, then it is best to avoid further contact if possible, with the hope of preventing another miscarriage from occurring.

Alcohol and smoking

Alcohol is a teratogen that can lead to fetal alcohol syndrome, with a dose-response relationship.[61] There is no amount of alcohol that is considered safe in pregnancy, and even moderate alcohol consumption can lead to spontaneous miscarriage.[62] Thus, it can be assumed that this risk, if not removed, is also related to recurrent miscarriage. Similarly, many studies have found a dose-dependent association between miscarriage and smoking. Unfortunately, it is difficult to accurately validate the accuracy of reports of smoking with biochemical measurements of tobacco.[61] Evidence concerning lifestyle adaptation and its effect in women with unexplained miscarriage is lacking.

Caffeine

The association is not as evident with caffeine. Numerous studies have observed a positive correlation between maternal caffeine intake and the risk of miscarriage. Unfortunately, most of these studies have methodological problems and have potential bias that does not allow a comparison of results. Hence, evidence for this causal link remains inconclusive.[63] Genetic factors may be involved, demonstrated by a possible increased susceptibility to recurrent miscarriage with increased caffeine intake if genetic polymorphisms are present.[64]

Diagnostic x-rays, radiation, air travel, ultrasound, and cosmetics

Diagnostic x-rays, air travel, ultrasound, and cosmetics such as nail polish and hair dye are not thought to cause recurrent miscarriage.[61] Radiation <5 rad is not teratogenic, and most diagnostic radiological imaging delivers less than this. Additionally, any risk attributed by low radiation is much lower than the background risk of spontaneous miscarriage or congenital abnormality. Ultrasound is also thought to be safe if done for the right indications, and reduces the necessity of exposure to radiation.[65]

Unexplained

No causes or associations are found in >50% of patients with recurrent miscarriage, and these patients fall into the category of unexplained or idiopathic recurrent miscarriage.[4] [5] However, they have an excellent prognosis. Up to 75% achieve a successful live birth in future pregnancies if given only supportive care (with regular ultrasound scans for reassurance) and psychological support in a dedicated early pregnancy assessment unit (EPAU).[7] [26] Thus, empirical treatment in this group of women is unnecessary and not recommended.[26]

Urgent considerations

(See **Differentials** for more details)
The following conditions may occur in people with recurrent miscarriage or present similarly to recurrent miscarriage. They have the potential to be life-threatening, due to severe bleeding and haemodynamic shock.

Ectopic pregnancy

Ruptured ectopic pregnancies are still a cause of maternal mortality. A pregnant patient with vaginal blood loss and pelvic pain should be considered a patient with an ectopic pregnancy until proven otherwise. Severe haemodynamic shock can occur, so patients should be regularly monitored. Resuscitation measures (ABC) should be administered immediately if this occurs. Intravenous access should be secured and intravenous fluids (either Hartmann's solution or normal saline) administered. Blood transfusion will be required if blood loss is excessive. Blood should be sent for urgent investigations including:

- FBC
- Serum electrolytes
- Clotting studies (prothrombin time and activated partial thromboplastin time)
- Blood grouping and cross-matching for at least 4 units of blood.

When a patient is stable, serum hCG should be ordered and an ultrasound (transvaginal or transabdominal if transvaginal is unacceptable to the woman or if the woman has an enlarged uterus or other pelvic pathology) done to verify the location and viability of the pregnancy.[66] In pregnancies of unknown location, there is evidence that shows that a 53% rise in hCG level over 48 hours is associated with an intrauterine pregnancy.[67] Consideration needs to be given to the possibility of a heterotopic pregnancy (an intrauterine pregnancy coexistent with an ectopic pregnancy).

When an ectopic pregnancy is confirmed and the patient remains well, she can be offered either conservative management, medical treatment with methotrexate, or surgical management, depending on the clinical symptoms, serum hCG levels, ultrasound findings, and patient choice.[68] [66] If the patient is unwell, arrangements need to be made for urgent laparotomy and salpingectomy to remove the ectopic pregnancy and stop the bleeding after stabilising the patient.

Incomplete miscarriage

Incomplete miscarriage occurs when the uterus is still not emptied of all products of conception. These patients are at risk of shock if the blood loss is excessive. Quick and efficient management is required, as significant blood loss resulting in circulatory compromise and anaemia can occur in a short period of time. Resuscitation (ABC) measures are needed if there is haemodynamic instability. If bleeding continues, an emergency surgical evacuation of the uterus to remove all retained products of conception needs to be performed.

For patients who can be stabilised, a vaginal examination is performed to assess for the presence of any products of conception at the cervical os. A transvaginal ultrasound should be offered to establish whether there are signs of retained products of conception. However, clinical assessment is most important. If the diagnosis of a miscarriage has not been made previously on ultrasound, fetal viability needs to be checked.

Expectant care or medical management with misoprostol are alternatives to routine surgical evacuation in women who are haemodynamically stable and have a non-viable fetus.[69] [66]

Septic miscarriage

Although more common in countries with poor healthcare resources, women can still die from undiagnosed sepsis secondary to infected retained products of conception. If a patient presents with signs and symptoms of sepsis and is known to have a non-viable fetus, she should be immediately reviewed, treated with antibiotics accordingly, and advised to have a surgical evacuation to remove the infected tissue.

Pregnancy of unknown location (PUL)

Patients who present with a positive pregnancy test and either vaginal spotting or abdominal pain need to have the location of their pregnancy identified with an ultrasound scan (transvaginal or transabdominal if transvaginal is unacceptable to the woman or if the woman has an enlarged uterus or other pelvic pathology). If the ultrasound scan is inconclusive, serial serum hCG measurements are needed. A rise of more than 53% in 48 hours is commonly associated with an intrauterine pregnancy. A follow-up pelvic ultrasound scan can be arranged in one week to confirm the presence of an intrauterine gestational sac. However, if the rise is suboptimal, further investigations such as another serum hCG, repeat pelvic ultrasound scan, or even diagnostic laparoscopy need to be considered to confirm the location of the pregnancy.

Approach

Evaluation for recurrent miscarriages traditionally starts after the third consecutive miscarriage. However, depending on the discretion of the physician and presence of other factors such as maternal age, investigations can start after 2 miscarriages. Prevalence and frequency of causes found after 2 miscarriages are similar to those found after 3 or more miscarriages.[4]

History

A history is needed to confirm the clinical diagnosis of recurrent miscarriage and to attempt to discover any underlying cause for this condition. It is common to start history-taking with basic demographics such as:

- Maternal and paternal age
- Ethnicity
- Occupation
- Consanguinity.

Although sensitive, information about paternity of all pregnancies, and whether the partner previously fathered any children in previous relationships, should be established. Thereafter, detailed information about every pregnancy, preferably in chronological order, including miscarriages and live births, is obtained. For all miscarriages, history needs to include:

- The gestational age at which the miscarriage occurred
- How the diagnosis of miscarriage was made
- Findings on ultrasound scan, if it was used
- Details regarding how the miscarriage was managed
- Results of any fetal karyotype performed.

Miscarriages can be classified into:

- First-trimester miscarriage (early pregnancy loss of <12 weeks' gestation)
- Second-trimester miscarriage (late pregnancy loss of >12 weeks' gestation).

The gestational threshold for the definition of miscarriage varies between countries and regions: in the US it is usually 20 weeks (but may vary in different states); in the UK and Europe, the gestational threshold for miscarriage is 24 weeks.[26] [1] [70] Pregnancy loss is defined as stillbirth when it occurs after the gestational threshold for miscarriage.

This information may help to define possible aetiology and the type of further evaluation required. It is also important to ask whether the patient has been using any treatment for the prevention of recurrent miscarriage.

Similarly, for live births the following information needs to be documented:

- Gestational age at birth
- Complications during pregnancy and delivery
- Mode of delivery
- Weight of the baby
- Current condition of the baby.

Gynaecology history should include:

- Complete menstrual history, including last menstrual period, cycle length, regularity of cycle, and symptoms of intermenstrual bleeding
- Cervical smear history and any previous treatment for abnormal smears, such as large loop excision of the transformation zone (LLETZ) or cone biopsy
- Contraceptive history, such as the method, duration of use, and adverse effects (if relevant)
- History of previous pelvic inflammatory disease
- History of any infertility treatment (e.g., ovulation induction or assisted conception).

The medical history should particularly include:

- Inquiry about the presence of autoimmune disease, arthritis, diabetes mellitus, thyroid dysfunction, vascular thrombosis, and skin disorders
- A family history regarding the medical conditions mentioned above
- A family history of congenital abnormalities, recurrent miscarriage, or pregnancy complications.

The surgical history should focus on:

- Previous abdominal surgery
- Cervical surgery (e.g., knife cone biopsy) or uterine surgery (e.g., hysteroscopic septal resection or myomectomy)
- The number of surgical uterine evacuations performed as the management option for previous miscarriage.

Information on any regular medicine taken and drug allergy should be attained. It is important to ask regarding the use of folic acid if the patient is trying for a pregnancy. Social history should include the smoking status and number of cigarettes smoked a day, amount of alcohol intake, and amount of caffeine consumed.

Physical examination

A general assessment of the patient should be made, including measurement of the BMI. Particular note should be made of any hirsutism or acne (may be signs of polycystic ovarian syndrome). Abdominal palpation is routine to exclude large masses, such as fibroids. A speculum examination is carried out to exclude obvious cervical structural abnormality. Bimanual examination is performed to assess uterine size and the presence of adnexal masses.

Laboratory investigation

Recurrent idiopathic miscarriage is the most common type of recurrent miscarriage and is a diagnosis of exclusion when all investigations ordered are normal or have returned negative. Laboratory investigations are the most important investigations for recurrent miscarriage. Results of some of these tests may diagnose a cause for recurrent miscarriage. The rationale for choice of investigations should be evidence-based and focused on the possible causative factors and the treatment available that can improve pregnancy outcome.[26]

Initial blood tests for all patients with recurrent miscarriage could include:

- FBC
- Blood group and antibodies

- Antiphospholipid antibodies (ELISA for IgG and IgM anticardiolipin antibodies; lupus anticoagulant using dilute Russell's viper venom time, kaolin clotting time, or activated partial thromboplastin time; and ELISA for IgG and IgM for beta-2 glycoprotein-1 antibodies).[1]

Although some national guidelines do not recommend routinely screening for thyroid disorders, diabetes mellitus, and hyperprolactinaemia in the absence of symptoms, these are easily treatable conditions where there is a potential to improve pregnancy outcome, and thus are commonly requested in many hospitals.

Screening for thrombophilia (factor V Leiden gene mutation, prothrombin G20210A gene mutation, protein S and C assays, activated protein C resistance assay, and antithrombin assay) may identify an associated condition.[26][27] [71] The American Society for Reproductive Medicine recommends screening a patient if there is a personal history of venous thromboembolism or if the patient has a first-degree relative with known or suspected thrombophilia; otherwise screening is not recommended.[2] UK and US guidelines recommend against heritable thrombophilia screening in women with recurrent miscarriage or a history of fetal loss, respectively.[40] [41] Targeted assessment for inherited thrombophilia may be considered in specific clinical circumstances.[41]

There is no evidence for routine screening for various autoantibodies (e.g., antinuclear antibody, mitochondrial and smooth muscle antibody) and thyroid antibodies as they have no clear association with recurrent miscarriage and/or there is no recommended treatment available. Similarly, investigations for natural killer cells should not be done unless in the context of a research setting.[72]

Genetic analyses

It is important to ascertain the karyotype of a miscarried fetus, as the finding of an abnormal karyotype provides for a better prognosis in a future pregnancy and reassures the patient that this is more than likely to be a random event. Cytogenetic analysis of a second miscarriage is often recommended before performing other tests, because if the products of conception are abnormal, further work-up is not required as the miscarriage is due to abnormal karyotype.[60] This strategy is often used in older women as the incidence of aneuploidy is greater in these women.[73] [74] Chromosomal microarray analysis has been found to be associated with an increased rate of detecting chromosomal abnormalities compared with karyotyping; however, some of these abnormalities are variants of uncertain significance.[75]

Karyotype of both partners to exclude balanced Robertsonian translocation may be considered. Although knowledge of this problem may allow for genetic counselling, it does not necessarily change the management plan (because active intervention would involve in-vitro fertilisation (IVF) with or without preimplantation genetic diagnosis to replace only chromosomally normal embryos, which does not improve live-birth rates).[76][77] [78] Furthermore, these couples have encouraging pregnancy outcomes of 70% live-birth rates in the subsequent pregnancy. Thus, routine parental karyotyping for chromosomal abnormalities is not recommended. It should be offered only when karyotype of the products of conception shows an unbalanced structural chromosomal abnormality, or if there is no pregnancy tissue available for testing, or testing of pregnancy tissue is unsuccessful.[26]

Screening for infection

It is not necessary or beneficial to universally perform a high vaginal swab on every patient with recurrent miscarriage to detect vaginal infections, including bacterial vaginosis.[26] Systematic screening and treatment for bacterial vaginosis in low-risk pregnancies does not appear to reduce the risk of late miscarriage or spontaneous preterm birth.[79] [80] Patients with recurrent miscarriage who are screened and treated for bacterial vaginosis in early pregnancy may have a reduced risk for another late miscarriage or

preterm birth.[80] [81] Chronic endometritis can be treated successfully with antibiotics; however, it is unclear whether this leads to an increase in live-birth rate.[57]

Imaging and surgical investigations

Guidelines recommend that a transvaginal or transabdominal ultrasound scan, ideally 3-dimensional, be arranged for all patients as part of the initial investigations, to exclude obvious congenital uterine malformations and for assessing the morphology of both ovaries.[26][82] However, the evidence for treatment and outcome for both uterine malformations and polycystic ovarian syndrome in the next pregnancy remain inconclusive, and patients need to be aware of this before having an ultrasound scan.

3-dimensional (3D) ultrasonography is non-invasive and offers both accurate diagnosis and classification of congenital uterine anomalies. Furthermore, it is highly reproducible and not operator-dependent, as volume is generated by automatic sweep of the mechanical transducer. This may remove the consideration for any surgical investigations such as hysteroscopy or diagnostic laparoscopy.[83] Sonohysterography or saline-infused sonography can be considered if 3-dimensional ultrasound is not available.[84] MRI can be used for diagnosing complex mullerian anomalies or if the findings from other imaging is inconclusive.[85]

In a patient with second-trimester miscarriages, or a history suggestive of cervical incompetence, transvaginal ultrasound scan can be performed in the second trimester and serially thereafter to measure the cervical length, as this predicts risk of preterm birth.[86] In a non-pregnant state, measurement of the cervical length has not been proven useful for predicting outcome in a subsequent pregnancy. A cervical length of >25 mm in second trimester of pregnancy is associated with a reduced risk of preterm delivery.[86]

Surgical investigations (hysteroscopy or diagnostic laparoscopy) are usually considered only if previously mentioned investigations are normal. Even so, they are not commonly carried out unless there is a specific indication. Hysteroscopy is now performed only when there is uncertainty about the diagnosis of a uterine anomaly. Therapeutic measures may be carried out simultaneously, such as removal of endometrial polyps, endometrial adhesiolysis, and correction of uterine anomalies.[21] [22] Similarly, diagnostic laparoscopy was traditionally used to diagnose bicornuate uterus, but with advancements in ultrasonography, it is rarely carried out now for this indication.

Common pregnancy loss events and ultrasound findings[87]

Biochemical pregnancy loss:

- Typical gestation <6 weeks
- No fetal activity ever detected
- Pregnancy not located on ultrasound
- Beta hCG levels are low and then fall.

Early pregnancy loss:

- Gestation typically 6 to 8 weeks
- No fetal activity ever detected
- Empty sac or large sac with minimal structures without fetal heart activity
- Beta hCG levels show an initial rise and then fall.

Late pregnancy loss:

- Typical gestation >12 weeks

- Loss of fetal heart activity
- Crown to rump length and fetal heart activity previously identified
- Beta hCG rises, then remains static or falls.

Differentials overview

Common
Idiopathic recurrent miscarriage
Fetal chromosomal abnormality
Chronic endometritis
Uncommon
Parental chromosomal abnormality
Antiphospholipid syndrome
Cervical incompetence
Uncontrolled diabetes mellitus
Uncontrolled thyroid dysfunction
Thrombophilias
Uterine abnormalities (e.g., bicornuate, septate, or arcuate uterus)
Bacterial vaginosis
Polycystic ovarian syndrome (PCOS)
Smoking, caffeine intake

Differentials

Common

◊ Idiopathic recurrent miscarriage

History	Exam	1st Test	Other tests
3 or more consecutive miscarriages where no cause is found	no specific abnormalities	»**FBC:** normal »**blood group and antibodies:** no antibodies »**antiphospholipid antibody screen:** normal The exact tests may vary between laboratories but the screen generally includes testing for anticardiolipin antibodies, lupus anticoagulants, and anti-beta-2 glycoprotein-1 antibodies. »**cytogenetic analysis for the karyotype of products of conception:** normal »**pelvic ultrasound scan (transabdominal or transvaginal, ideally 3-dimensional):** normal Excludes obvious congenital uterine malformations.[26] Useful for assessing the morphology of both ovaries.	»**sperm DNA fragmentation:** increased Assessing sperm DNA fragmentation in couples with recurrent pregnancy loss can be considered for explanatory purposes.[1] »**thrombophilia screen:** normal This screen involves a combination of tests, which may vary slightly between different laboratories. It generally includes protein S and protein C assay, activated protein C resistance assay, antithrombin III activity, and tests for factor V Leiden gene mutation and prothrombin G20210A gene mutation. UK and US guidelines recommend against heritable thrombophilia screening in women with recurrent miscarriage or a history of fetal loss, respectively.[40] [41] Targeted assessment for inherited thrombophilia

Common

◊ Idiopathic recurrent miscarriage

History	Exam	1st Test	Other tests
			may be considered in specific clinical circumstances (e.g., personal history of VTE).[41] Consult local guidance.

◊ Fetal chromosomal abnormality

History	Exam	1st Test	Other tests
no specific features	no specific abnormalities	»**cytogenetic analysis for the karyotype of products of conception:** chromosomal abnormalities detected Most commonly trisomy, polyploidy, or monosomy. »**FBC:** normal »**blood group and antibodies:** no antibodies »**antiphospholipid antibody screen:** normal The exact tests may vary between laboratories but the screen generally includes testing for anticardiolipin antibodies, lupus anticoagulants, and anti-beta-2 glycoprotein-1 antibodies. »**cytogenetic analysis of blood for the karyotype of both partners:** normal	»**thrombophilia screen:** normal This screen involves a combination of tests, which may vary slightly between different laboratories. It generally includes protein S and protein C assay, activated protein C resistance assay, antithrombin III activity, and tests for factor V Leiden gene mutation and prothrombin G20210A gene mutation. UK and US guidelines recommend against heritable thrombophilia screening in women with recurrent miscarriage or a history of fetal loss, respectively.[40] [41] Targeted assessment for inherited thrombophilia may be considered in specific clinical

Common

◊ Fetal chromosomal abnormality

History	Exam	1st Test	Other tests
		»**pelvic ultrasound scan (transabdominal or transvaginal, ideally 3-dimensional):** normal Excludes obvious congenital uterine malformations.[26] Useful for assessing the morphology of both ovaries.	circumstances (e.g., personal history of VTE).[41] Consult local guidance.

◊ Chronic endometritis

History	Exam	1st Test	Other tests
often asymptomatic; non-specific symptoms include pelvic pain, vaginal discharge, dyspareunia and abnormal vaginal bleeding	suprapubic and uterine tenderness	»**endometrial biopsy:** histologic appearance of endometritis with or without CD138 staining	

Uncommon

◊ Parental chromosomal abnormality

History	Exam	1st Test	Other tests
may be a family history of recurrent miscarriage or congenital abnormalities	no specific abnormalities	»**cytogenetic analysis of blood for the karyotype of both partners:** chromosomal abnormality detected Commonly Robertsonian translocation. Genetic counselling indicated. »**FBC:** normal »**blood group and antibodies:** no antibodies	»**thrombophilia screen:** normal This screen involves a combination of tests, which may vary slightly between different laboratories. It generally includes protein S and protein C assay, activated protein C resistance assay, antithrombin III activity, and tests

Uncommon

◊ Parental chromosomal abnormality

History	Exam	1st Test	Other tests
		»**antiphospholipid antibody screen:** normal The exact tests may vary between laboratories but the screen generally includes testing for anticardiolipin antibodies, lupus anticoagulants, and anti-beta-2 glycoprotein-1 antibodies. »**cytogenetic analysis for the karyotype of products of conception:** occasionally normal »**pelvic ultrasound scan (transabdominal or transvaginal, ideally 3-dimensional):** normal Excludes obvious congenital uterine malformations.[26] Is useful for assessing the morphology of both ovaries.	for factor V Leiden gene mutation and prothrombin G20210A gene mutation. UK and US guidelines recommend against heritable thrombophilia screening in women with recurrent miscarriage or a history of fetal loss, respectively.[40] [41] Targeted assessment for inherited thrombophilia may be considered in specific clinical circumstances (e.g., personal history of VTE).[41] Consult local guidance.

◊ Antiphospholipid syndrome

History	Exam	1st Test	Other tests
previous history of thrombotic event, thrombotic event in family member, autoimmune disease	no specific abnormalities	»**antiphospholipid antibody screen:** ELISA for IgG and/or IgM anticardiolipin (aCL) antibodies: medium or high titres (>99th percentile) in 2 or more tests	»**thrombophilia screen:** normal This screen involves a combination of tests, which may vary slightly between

Uncommon

◊ Antiphospholipid syndrome

History	Exam	1st Test	Other tests
		at least 12 weeks apart; activated partial thromboplastin time (lupus APTT): prolonged in 2 or more tests at least 12 weeks apart if lupus anticoagulant present; dilute Russell viper venom time (DRVVT): increased in 2 or more tests at least 12 weeks apart if lupus anticoagulant present; kaolin clotting time (KCT): increased test-control ratio in 2 or more tests at least 12 weeks apart if lupus anticoagulant present; ELISA for IgG and/or IgM anti-beta-2 glycoprotein-1 antibodies: medium or high titres (>99th percentile) in 2 or more tests at least 12 weeks apart The test for lupus anticoagulants is done by either APTT, KCT, or DRVVT, or sometimes 2 of these tests. It is unlikely all 3 tests are used in all laboratories. »**FBC:** normal »**blood group and antibodies:** no antibodies »**cytogenetic analysis for the karyotype of products of conception:** normal »**pelvic ultrasound scan (transabdominal or transvaginal, ideally**	different laboratories. It generally includes protein S and protein C assay, activated protein C resistance assay, antithrombin III activity, and tests for factor V Leiden gene mutation and prothrombin G20210A gene mutation. UK and US guidelines recommend against heritable thrombophilia screening in women with recurrent miscarriage or a history of fetal loss, respectively.[40] [41] Targeted assessment for inherited thrombophilia may be considered in specific clinical circumstances (e.g., personal history of VTE).[41] Consult local guidance.

Uncommon

◊ Antiphospholipid syndrome

History	Exam	1st Test	Other tests
		3-dimensional): normal Excludes obvious congenital uterine malformations.[26] Is useful for assessing the morphology of both ovaries.	

◊ Cervical incompetence

History	Exam	1st Test	Other tests
history of painless dilatation of the cervix or spontaneous rupture of membranes followed by a second-trimester miscarriage	no specific abnormalities	»**pelvic ultrasound scan (transabdominal or transvaginal, ideally 3-dimensional):** normal; measurement of cervix may be performed but is not diagnostic In a non-pregnant state, measurement of the cervical length has not been proven useful for predicting outcome in a subsequent pregnancy. A cervical length, measured by transvaginal ultrasound scan, of >25 mm in second trimester of pregnancy is associated with a reduced risk of preterm delivery.[86] »**FBC:** normal »**blood group and antibodies:** no antibodies »**serum antiphospholipid**	»**thrombophilia screen:** normal This screen involves a combination of tests, which may vary slightly between different laboratories. It generally includes protein S and protein C assay, activated protein C resistance assay, antithrombin III activity, and tests for factor V Leiden gene mutation and prothrombin G20210A gene mutation. UK and US guidelines recommend against heritable thrombophilia screening in women with recurrent miscarriage or a history of fetal loss, respectively.[40] [41] Targeted assessment for inherited thrombophilia

Uncommon

◊ Cervical incompetence

History	Exam	1st Test	Other tests
		antibody screen: normal The exact tests may vary between laboratories but the screen generally includes testing for anticardiolipin antibodies, lupus anticoagulants, and anti-beta-2 glycoprotein-1 antibodies. »**cytogenetic analysis for the karyotype of products of conception:** normal	may be considered in specific clinical circumstances (e.g., personal history of VTE).[41] Consult local guidance.

◊ Uncontrolled diabetes mellitus

History	Exam	1st Test	Other tests
polyuria, polydipsia, blurred vision, paraesthesia, fatigue or lethargy, weight loss; may be a family history of diabetes mellitus; diabetic ketoacidosis (nausea, vomiting, abdominal pain); prior history of type 1 or type 2 diabetes mellitus	tachypnoea, signs of skin infection	»**random blood glucose:** ≥11.1 mmol/L (≥200 mg/dL) Diagnostic in presence of typical symptoms. »**FBC:** normal »**blood group and antibodies:** no antibodies »**serum antiphospholipid antibody screen:** normal The exact tests may vary between laboratories but the screen generally includes testing for anticardiolipin antibodies, lupus	»**fasting blood glucose:** >6.94 mmol/L (125 mg/dL) Confirms diagnosis of diabetes mellitus. »**75 g oral glucose tolerance test:** 2-hour postload glucose 11.1 mmol/L or greater (≥200 mg/dL) May be used in addition to confirm diagnosis of diabetes mellitus. »**thrombophilia screen:** normal This screen involves a combination of tests, which may vary slightly between different laboratories.

Uncommon

◊ Uncontrolled diabetes mellitus

History	Exam	1st Test	Other tests
		anticoagulants, and anti-beta-2 glycoprotein-1 antibodies. »**cytogenetic analysis for the karyotype of products of conception:** normal »**pelvic ultrasound scan (transabdominal or transvaginal, ideally 3-dimensional):** normal Excludes obvious congenital uterine malformations.[26] Is useful for assessing the morphology of both ovaries.	It generally includes protein S and protein C assay, activated protein C resistance assay, antithrombin III activity, and tests for factor V Leiden gene mutation and prothrombin G20210A gene mutation. UK and US guidelines recommend against heritable thrombophilia screening in women with recurrent miscarriage or a history of fetal loss, respectively.[40] [41] Targeted assessment for inherited thrombophilia may be considered in specific clinical circumstances (e.g., personal history of VTE).[41] Consult local guidance.

◊ Uncontrolled thyroid dysfunction

History	Exam	1st Test	Other tests
hypothyroidism: cold sensitivity, dry skin, fatigue, weight gain, constipation, menstrual irregularity; hyperthyroidism: heat intolerance, palpitations, sweating, weight loss, tremor,	hypothyroidism: dry skin, bradycardia, facial oedema, goitre; hyperthyroidism: tachycardia, chemosis, proptosis, lid retraction, tremor, goitre	»**serum thyroid-stimulating hormone (TSH):** primary hypothyroidism: elevated; hyperthyroidism: suppressed Rarely, TSH is low in hypothyroidism or high in hyperthyroidism	»**thrombophilia screen:** normal This screen involves a combination of tests, which may vary slightly between different laboratories. It generally includes protein S and protein

DIAGNOSIS

Uncommon

◊ Uncontrolled thyroid dysfunction

History	Exam	1st Test	Other tests
irritability, menstrual irregularity		when they are central in origin. »**serum free thyroxine:** hypothyroidism: below normal range; hyperthyroidism: above normal range Often normal in subclinical hypothyroidism. »**FBC:** normal »**blood group and antibodies:** no antibodies »**serum antiphospholipid antibody screen:** normal The exact tests may vary between laboratories but the screen generally includes testing for anticardiolipin antibodies, lupus anticoagulants, and anti-beta-2 glycoprotein-1 antibodies. »**cytogenetic analysis for the karyotype of products of conception:** normal »**pelvic ultrasound scan (transabdominal or transvaginal, ideally 3-dimensional):** normal Excludes obvious congenital uterine	C assay, activated protein C resistance assay, antithrombin III activity, and tests for factor V Leiden gene mutation and prothrombin G20210A gene mutation. UK and US guidelines recommend against heritable thrombophilia screening in women with recurrent miscarriage or a history of fetal loss, respectively.[40] [41] Targeted assessment for inherited thrombophilia may be considered in specific clinical circumstances (e.g., personal history of VTE).[41] Consult local guidance.

Uncommon

◊ Uncontrolled thyroid dysfunction

History	Exam	1st Test	Other tests
		malformations.[26] Is useful for assessing the morphology of both ovaries.	

◊ Thrombophilias

History	Exam	1st Test	Other tests
previous history of thrombosis; thrombotic event in first- or second-degree relatives	no specific abnormalities	»**thrombophilia screen:** factor V Leiden (FVL) gene mutation: heterozygous or homozygous; activated protein C (APC) resistance assay: resistance ratio >1.2; prothrombin G20210A gene mutation: present; protein S assay: <70%; protein C assay: <50%; antithrombin III activity: <80% This screen involves a combination of tests, which may vary slightly between different laboratories. It generally includes protein S and protein C assay, activated protein C resistance assay, antithrombin III activity, and tests for factor V Leiden gene mutation and prothrombin G20210A gene mutation. If tests are abnormal, they need to be repeated to confirm the diagnosis. »**FBC:** normal	

Uncommon

◊ Thrombophilias

History	Exam	1st Test	Other tests
		»**blood group and antibodies:** no antibodies »**serum antiphospholipid antibody screen: ELISA for IgG and/or IgM anticardiolipin (aCL) antibodies:** normal range »**serum antiphospholipid antibody screen:** normal The exact tests may vary between laboratories but the screen generally includes testing for anticardiolipin antibodies, lupus anticoagulants, and anti-beta-2 glycoprotein-1 antibodies. »**cytogenetic analysis for the karyotype of products of conception:** normal »**pelvic ultrasound scan (transabdominal or transvaginal, ideally 3-dimensional):** normal Excludes obvious congenital uterine malformations.[26] Is useful for assessing the morphology of both ovaries.	

Uncommon

◊ Uterine abnormalities (e.g., bicornuate, septate, or arcuate uterus)

History	Exam	1st Test	Other tests
no specific features	no specific abnormalities	»**pelvic ultrasound scan (transabdominal or transvaginal, ideally 3-dimensional):** structural abnormality seen »**FBC:** normal »**blood group and antibodies:** no antibodies »**serum antiphospholipid antibody screen:** normal The exact tests may vary between laboratories but the screen generally includes testing for anticardiolipin antibodies, lupus anticoagulants, and anti-beta-2 glycoprotein-1 antibodies. »**cytogenetic analysis for the karyotype of products of conception:** normal	»**hysteroscopy:** structural abnormality seen May be performed to confirm structural abnormality. »**thrombophilia screen:** normal This screen involves a combination of tests, which may vary slightly between different laboratories. It generally includes protein S and protein C assay, activated protein C resistance assay, antithrombin III activity, and tests for factor V Leiden gene mutation and prothrombin G20210A gene mutation. UK and US guidelines recommend against heritable thrombophilia screening in women with recurrent miscarriage or a history of fetal loss, respectively.[40] [41] Targeted assessment for inherited thrombophilia may be considered in specific clinical circumstances (e.g., personal history of

Uncommon

◊ Uterine abnormalities (e.g., bicornuate, septate, or arcuate uterus)

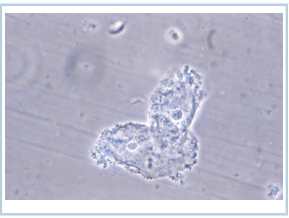
History	Exam	1st Test	Other tests
			VTE).[41] Consult local guidance.

◊ Bacterial vaginosis

History	Exam	1st Test	Other tests
history of previous second-trimester miscarriage	fishy-smelling vaginal discharge	»**FBC:** normal »**blood group and antibodies:** no antibodies »**serum antiphospholipid antibody screen:** normal The exact tests may vary between laboratories but the screen generally includes testing for anticardiolipin antibodies, lupus anticoagulants, and anti-beta-2 glycoprotein-1 antibodies. »**cytogenetic analysis for the karyotype of products of conception:** normal »**pelvic ultrasound scan (transabdominal or transvaginal, ideally 3-dimensional):** normal	»**high vaginal swab for wet mount microscopy, pH, Gram stain, and culture:** wet mount microscopy: clue cells present, the numbers of lactobacilli are decreased, and WBCs are absent; vaginal pH: increased (usually >4.5); Gram stain: reduced or absent lactobacilli; culture: increased *Gardnerella vaginalis* , *Mycoplasma hominis* , and gram-negative anaerobes A diagnosis commonly only involves microscopy for clue cells, clinical symptoms, and an increased vaginal pH. Culture is not always done as is not needed for diagnosis.

Uncommon

◊ Bacterial vaginosis

History	Exam	1st Test	Other tests
			 *Photomicrograph of clue cells: vaginal epithelial cells with a stippled appearance and obscured borders, due to bacteria adhering to their surface* *Adapted from the Public Health Image Library, CDC* »**thrombophilia screen:** normal This screen involves a combination of tests, which may vary slightly between different laboratories. It generally includes protein S and protein C assay, activated protein C resistance assay, antithrombin III activity, and tests for factor V Leiden gene mutation and prothrombin G20210A gene mutation. UK and US guidelines recommend against heritable thrombophilia screening in women with recurrent miscarriage or a

DIAGNOSIS

Uncommon

◊ Bacterial vaginosis

History	Exam	1st Test	Other tests
			history of fetal loss, respectively.[40] [41] Targeted assessment for inherited thrombophilia may be considered in specific clinical circumstances (e.g., personal history of VTE).[41] Consult local guidance.

◊ Polycystic ovarian syndrome (PCOS)

History	Exam	1st Test	Other tests
menstrual irregularities, acne, hirsutism, subfertility	commonly, elevated BMI	»**serum testosterone:** elevated »**pelvic ultrasound scan:** enlarged ovaries with at least 20 follicles in each ovary measuring 2-9 mm in diameter and/or increased ovarian volume (>10 mL) »**FBC:** normal »**blood group and antibodies:** no antibodies »**random blood glucose:** may be elevated Women with PCOS are at risk for abnormal glucose. »**serum antiphospholipid antibody screen:** normal The exact tests may vary between laboratories but the	»**day 1-3 follicle-stimulating hormone:** normal To exclude premature menopause or hypogonadotrophic hypogonadism. »**serum estradiol:** normal To exclude premature menopause or hypogonadotrophic hypogonadism. »**serum LH:** elevated »**thrombophilia screen:** normal This screen involves a combination of tests, which may vary slightly between different laboratories. It generally includes protein S and protein C assay, activated protein C resistance

Uncommon

◊ Polycystic ovarian syndrome (PCOS)

History	Exam	1st Test	Other tests
		screen generally includes testing for anticardiolipin antibodies, lupus anticoagulants, and anti-beta-2 glycoprotein-1 antibodies. »**cytogenetic analysis for the karyotype of products of conception:** normal	assay, antithrombin III activity, and tests for factor V Leiden gene mutation and prothrombin G20210A gene mutation. UK and US guidelines recommend against heritable thrombophilia screening in women with recurrent miscarriage or a history of fetal loss, respectively.[40] [41] Targeted assessment for inherited thrombophilia may be considered in specific clinical circumstances (e.g., personal history of VTE).[41] Consult local guidance.

◊ Smoking, caffeine intake

History	Exam	1st Test	Other tests
history of smoking and caffeine ingestion	no specific abnormalities	»**FBC:** normal »**blood group and antibodies:** no antibodies »**serum antiphospholipid antibody screen:** normal The exact tests may vary between laboratories but the screen generally includes testing	»**thrombophilia screen:** normal This screen involves a combination of tests, which may vary slightly between different laboratories. It generally includes protein S and protein C assay, activated protein C resistance assay, antithrombin III activity, and tests

Uncommon

◊ Smoking, caffeine intake

History	Exam	1st Test	Other tests
		for anticardiolipin antibodies, lupus anticoagulants, and anti-beta-2 glycoprotein-1 antibodies. »**cytogenetic analysis for the karyotype of products of conception:** normal »**pelvic ultrasound scan (transabdominal or transvaginal, ideally 3-dimensional):** normal Excludes obvious congenital uterine malformations.[26] Is useful for assessing the morphology of both ovaries.	for factor V Leiden gene mutation and prothrombin G20210A gene mutation. UK and US guidelines recommend against heritable thrombophilia screening in women with recurrent miscarriage or a history of fetal loss, respectively.[40] [41] Targeted assessment for inherited thrombophilia may be considered in specific clinical circumstances (e.g., personal history of VTE).[41] Consult local guidance.

Guidelines

United Kingdom

Ectopic pregnancy and miscarriage: diagnosis and initial management (https://www.nice.org.uk/guidance/ng126)

Published by: National Institute for Health and Care Excellence
Last published: 2023

Thrombophilia testing: a British Society for Haematology guideline (https://b-s-h.org.uk/guidelines)

Published by: British Society for Haematology
Last published: 2022

Recurrent miscarriage: green-top guideline no. 17 (https://www.rcog.org.uk/guidance/browse-all-guidance/green-top-guidelines)

Published by: Royal College of Obstetricians and Gynaecologists
Last published: 2023

Europe

Recurrent pregnancy loss (https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Recurrent-pregnancy-loss.aspx)

Published by: European Society of Human Reproduction and Embryology (ESHRE)
Last published: 2023

North America

Inherited thrombophilias in pregnancy (https://www.acog.org/clinical/clinical-guidance/practice-bulletin)

Published by: American College of Obstetricians and Gynecologists
Last published: 2018

Oceania

Early pregnancy loss (https://www.health.qld.gov.au/qcg/publications)

Published by: Queensland Health
Last published: 2022

Key articles

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- Practice Committee of the American Society for Reproductive Medicine. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. Fertil Steril. 2012 Nov;98(5):1103-11. Abstract
- Royal College of Obstetricians and Gynaecologists. Recurrent miscarriage: green-top guideline no. 17. Jun 2023 [internet publication]. Full text (https://www.rcog.org.uk/guidance/browse-all-guidance/green-top-guidelines/recurrent-miscarriage-green-top-guideline-no-17) Abstract
- Jauniaux E, Farquharson RG, Christiansen OB, et al. Evidence-based guidelines for the investigation and medical treatment of recurrent miscarriage. Hum Reprod. 2006 Sep;21(9):2216-22. Full text (https://humrep.oxfordjournals.org/content/21/9/2216.full) Abstract

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Images

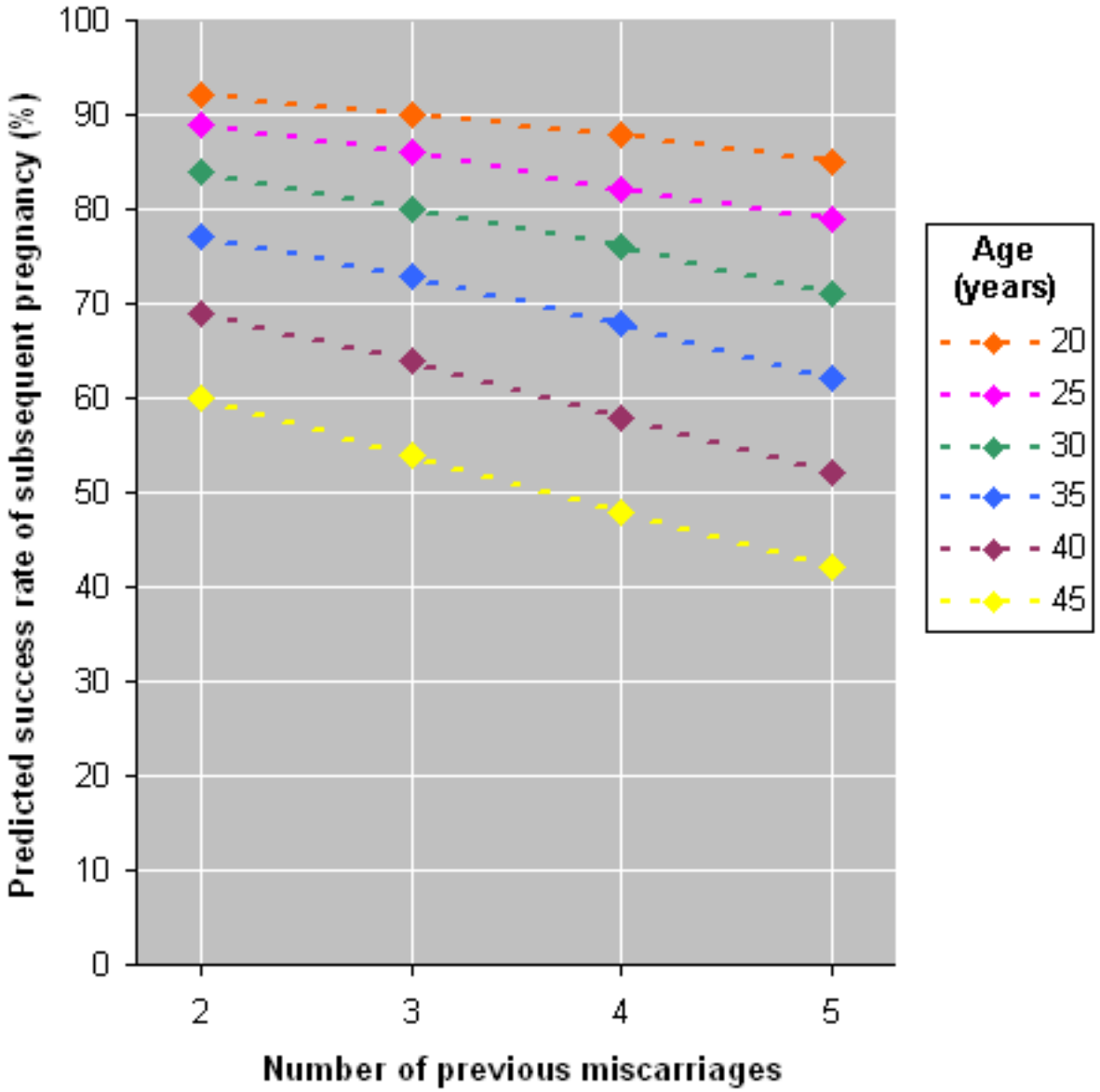

Figure 1: Predicted percentage success rate of subsequent pregnancy according to age and previous miscarriage history

Created by the BMJ Group; data from Brigham SA, et al. Hum Reprod. 1999;14:2868-2871

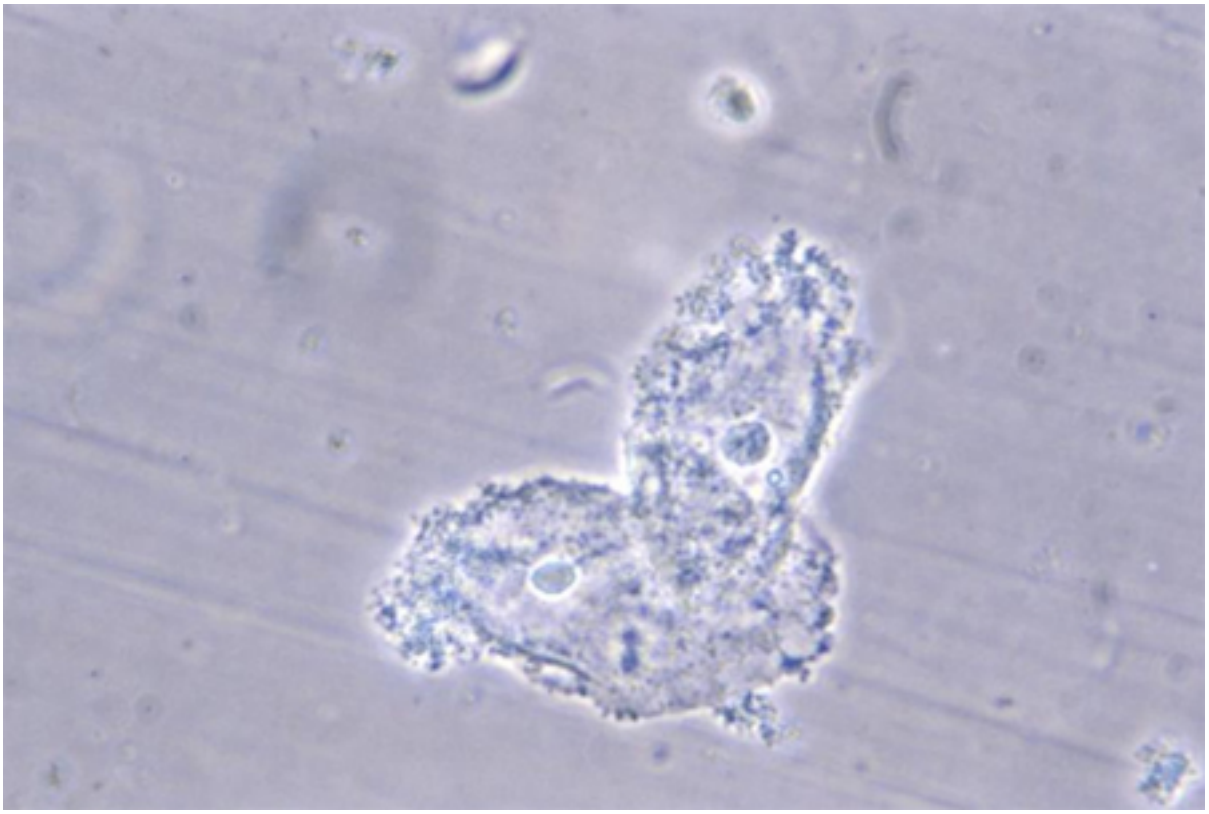

Figure 2: Photomicrograph of clue cells: vaginal epithelial cells with a stippled appearance and obscured borders, due to bacteria adhering to their surface

Adapted from the Public Health Image Library, CDC

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Figure 1 – BMJ Best Practice Numeral Style

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// Acknowledgements:

Dr Winifred Mak would like to gratefully acknowledge Dr Ai-Wei Tang and Dr Siobhan Quenby, the previous contributors to this topic. AT declares that she has no competing interests. SQ is an author of a reference cited in this topic. SQ declares that she has no competing interests.
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