

Recurrent First Trimester Miscarriage: A Typical Case Presentation and Evidence-Based Management Review

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Abstract

Recurrent miscarriage (RM), also known as recurrent pregnancy loss, is a distressing condition which affects about 1% of couples trying to achieve a pregnancy. It can be challenging for both patients and clinicians as the cause remains unexplained in at least 50% of couples despite multiple investigations. A systematic and evidence-based approach to testing and management is important to avoid tests or treatments which are unnecessary or of unproven benefit. Access to specialist RM clinic services and psychological support forms a key part of the management of couples with RM.

Keywords: Recurrent miscarriage; Treatment; Progesterone

Introduction

It is estimated that up to one in four natural pregnancies end up in a miscarriage which is defined as loss of pregnancy prior to viability (24 weeks' gestation) [1]. Recurrent miscarriage (RM) is traditionally defined in the United Kingdom (UK) as three or more consecutive miscarriages and it can affect about 1% of couples trying for a pregnancy [2]. The definition of RM varies between countries with some clinical guidelines recommending investigations and treatment following two or more miscarriages.

The Royal College of Obstetricians and Gynecologists (RCOG) has issued guidance on management of RM in the UK [2]. An updated version of this guideline is currently under consultation and will be released shortly.

This article describes an illustrative typical clinical scenario related to RM and reviews the current best practice recommendations for management of RM.

Clinical Case

The patient, 37 years old, has attended her general practitioner's clinic following a recent pregnancy loss. She and her partner have been trying for a pregnancy for past 18 months but have suffered from three miscarriages between 6 and 8 weeks' gestation. Her last miscarriage happened 2 months ago, and she has resumed her periods 2 weeks back. All the miscarriages were managed conservatively without any medical or surgical interventions. She has regular menstrual cycles (25 - 26 days long) and does not report any dysmenorrhea or menorrhagia. She is upset about the pregnancy losses, wondering if it was her fault and whether something can be done in the next pregnancy to change the outcome.

History

Consultations referring to RM should be performed in a sensitive manner. When discussing previous miscarriages, it is important to enquire about the gestation at which pregnancy loss occurred. Pregnancy loss before 9 - 10 weeks usually (but not always) indicates a pre-placental cause, which may be either fetal (chromosomal) or endometrial (implantation disorder) in origin while that after this gestation could indicate problems such as thrombophilia, placental disorders, or problems with uterine structure. History of pregnancy loss after 12 weeks associated with painless cervical dilatation and rupture of membranes suggests cervical weakness.

Information should be obtained about how the previous miscarriages were managed: was the miscarriage completed naturally or whether medical or surgical management was required? Any possibility of uterine infection following miscarriage should be explored. Changes in the menstrual flow (hypomenorrhea) following possible infection of retained products of conception or uterine curettage could indicate the possibility of intrauterine adhesions. History of excess alcohol consumption or smoking should be obtained to offer advice on reducing risk of future miscarriage. Medical and relevant family history should be obtained as uncontrolled maternal medical conditions such as diabetes, thyroid or rheumatological disorders can impact the risk of miscarriage in future pregnancies. All miscarriages which the patient suffered from happened before 8 weeks gesta-

Manuscript submitted February 11, 2022, accepted March 29, 2022

Published online April 12, 2022

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doi: <https://doi.org/10.14740/jcgo797>

Table 1. Causes and Relevant Investigations for Recurrent First Trimester Miscarriage

Cause	Test
Genetic-balanced chromosomal translocations	Karyotyping of products of conception (if abnormal result detected - parental karyotyping)
Antiphospholipid syndrome	Blood test for anticardiolipin antibodies and/or lupus anticoagulant (blood tests should be performed at least 6 weeks after any pregnancy loss and a repeat confirmatory test should be arranged at least 12 weeks after an initial positive screen)
Endocrine (if evidence of clinical disorder or risk factors): thyroid, diabetes	Thyroid function test (serum free T4 and thyroid-stimulating hormone levels); thyroid peroxidase antibodies; HbA1c
Uterine abnormalities such as septate uterus or intracavitary lesions	Transvaginal ultrasound scan

tion and she bled naturally on all occasions suggesting a likely pre-placental fetal or endometrial cause for her pregnancy loss.

Examination

On examination, patient's body mass index (BMI) was within a normal range (23). Pelvic or speculum examination, guided by clinical history, can be useful as part of initial assessment especially if the woman has presented with irregular bleeding or abnormal vaginal discharge in which case cervix should be visualized to rule out other gynecological pathology such as ectropion/polyp and triple swabs should be obtained. The patient did not report any changes to her menstrual cycles or abnormal discharge following miscarriage.

Risk factors and investigations

The patient and her partner should be referred to and cared for in a dedicated RM clinic [2]. Psychological support and communication in a sensitive manner are extremely important. A discussion about potential risk factors for future miscarriage and testing should cover the following.

Age

Increasing female age increases the chances of a genetically abnormal pregnancy as the number and quality of oocytes decrease [1]. Women between 20 and 35 years old have the lowest risk of miscarriage while women above the age of 40 years have at least a 50% chance of miscarriage with every pregnancy [3, 4].

BMI

High BMI (> 30) increases the risk of miscarriage [5].

Other risk factors

Other risk factors include previous miscarriages, smoking and

excess alcohol consumption.

The patient is 37 years old and has already had three miscarriages which increase her risk of future miscarriage to about 40% [6].

Causes of RM investigations

The patient should be offered investigations for the causes of RM as listed in Table 1.

Antiphospholipid syndrome (APS)

This is an acquired thrombophilia which affects 15% of women with RM [2] and is diagnosed based on high levels of anticardiolipin antibodies and/or lupus anticoagulant along with evidence of adverse pregnancy outcomes (RM before 10 weeks or loss of one genetically normal pregnancy after 10 weeks or one or more preterm births before 34 weeks due to placental dysfunction) or unprovoked thrombosis. APS causes inhibition of trophoblast function, activation of complement system and thrombosis at the uteroplacental interface and is treated with a combination of aspirin and low molecular weight heparin in pregnancy [1]. Inherited thrombophilias such as factor V Leiden mutation, prothrombin mutation, protein C, protein S and antithrombin III deficiency have an uncertain role in first trimester RM and currently such tests should only be offered in the context of research. The patient had a negative APS screen.

Genetic

Parental balanced structural chromosomal anomalies can cause RM (2-5% of couples with RM). The risk of miscarriage is influenced by the size and the genetic content of the rearranged chromosomal segments. Karyotyping of products of conception should be offered at the time of any future miscarriage and parental karyotyping should follow if analysis of products of conception indicates that a genetic abnormality may have resulted from an unbalanced translocation [2, 3]. Parental karyotyping is not recommended routinely due to low incidence of translocations and relatively high cost associated with testing.

Endocrine

If there is clinical evidence of poorly controlled diabetes or thyroid dysfunction, appropriate blood tests should be performed [2]. The patient did not have any symptoms or signs suggestive of endocrine problems and had had a thyroid hormone profile at the time of her last miscarriage which revealed normal results.

Uterine abnormalities

Uterine abnormalities such as septate uterus or any other uterine cavity pathology such as intrauterine adhesions (especially following an episode of uterine instrumentation and infection), submucous fibroids or polyps should be ruled out by offering a pelvic ultrasound as these may be amenable to treatment by surgery (hysteroscopy +/- laparoscopy) [2, 7].

The patient was offered a transvaginal scan which showed a regular uterine cavity.

The evidence regarding the effects of male partners on RM is weak and no specific testing can be recommended as part of investigations [1].

Advice

Lifestyle advice should always be offered to couples with RM. The patient should be advised to maintain a normal BMI, avoid excess alcohol/smoking, and take pre-conception folic acid [2, 3].

Currently, there is lack of evidence that preimplantation genetic testing for aneuploidy screening (PGT-A) is superior to expectant management in RM patients [3]. If chromosomal translocation was identified at the time of future miscarriage, genetic counselling should be offered to the patient. Reproductive options following genetic counselling would include proceeding to a further natural pregnancy with or without a prenatal diagnosis test, gamete donation and adoption [2].

As in this case, despite thorough investigations, no clear underlying pathology is identifiable in at least 50% of couples with RM (often labelled as “unexplained RM”) [7, 8]. The couple should be reassured about good prognosis for a live birth in future pregnancies and offered supportive care in dedicated early pregnancy unit. Many RM units offer empirical treatment with low dose oral aspirin (75 mg daily) and vaginal natural progesterone (400 mg once/twice daily) from positive pregnancy test until 12 - 14 weeks of pregnancy on a “low harm, possible benefit” basis for unexplained RM. The use of aspirin is not recommended in current clinical guidelines due to debate over its clinical effectiveness.

Based on the evidence so far, it appears that the use of progesterone supplements is beneficial particularly in women with previous miscarriages who bleed in early pregnancy [9, 10]. The patient conceived again 5 months following her third miscarriage and had a successful pregnancy and live birth. She was prescribed vaginal progesterone pessaries from 7 weeks until 14 weeks of pregnancy following one episode of vaginal bleeding.

Conclusions

Couples with RM should be offered psychological support and be referred to a dedicated RM service for investigations. Most couples will have no identifiable pathology, and in such cases, there is good prognosis for future successful pregnancy.

Learning points

RM affects about 1% of couples trying for a pregnancy and no clear underlying pathology is identifiable despite investigations in at least 50% of couples.

Refer couples with RM to a dedicated RM service for investigations and plan for future pregnancies.

Offer psychological support and reassure couples with no identifiable pathology about good prognosis for future pregnancy without pharmacological intervention.

Acknowledgments

None to declare.

Financial Disclosure

No funding was received for preparation of this manuscript.

Conflict of Interest

There is no conflict of interest to declare.

Author Contributions

VT wrote and finalized the manuscript.

Data Availability

The author declares that data supporting the findings of this study are available within the article.

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