

A young woman with early pregnancy loss

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A 27-year-old woman visits her family doctor after having had her third six-week pregnancy loss. She is otherwise well. All pregnancies had been planned, with conception occurring within two to four months for each pregnancy. Her cycles are 28 days long, with 5 days of menses. A dilatation and curettage procedure was not required after any of the losses. The results of her physical examination, including pelvic examination, are normal. She wants to know whether she should be referred to a specialist.

Should this patient undergo investigations for pregnancy loss?

Given that this patient has had three early pregnancy losses, she should undergo investigations for recurrent early pregnancy loss. Pregnancy loss in the first trimester is common, regardless of age. The incidence of a first-trimester loss is estimated at 15%–30%, but it varies substantially according to age, increasing to 51% among women 41–44 years of age.^{1,2} This patient has at least a 15% probability of a first-trimester loss (and it may be as high as 30%).³ After one early loss, the probability of a subsequent successful pregnancy is identical with that of any woman in this age group.⁴

Whether women with two early pregnancy losses should undergo investigation is debatable, because the probability of a successful third pregnancy after two losses is only slightly lower. After three early losses, the probability of a subsequently successful pregnancy is about 73%.² The Royal College of Obstetricians and Gynaecologists in the United Kingdom recommends investigation or referral to a specialist in recurrent early pregnancy loss after three losses occurring before 10 weeks' gestation.⁵ However, the American Society for Reproductive Medicine suggests evaluating after two consecutive clinical pregnancy losses.⁶ Given the societal shift toward delayed child-bearing, some older women may be unhappy about waiting for a third loss before investigating.

What diagnoses should be considered?

Anatomic abnormalities will be identified in 15% of cases of recurrent early pregnancy loss.⁷ These include intrauterine abnormalities, such as septa, polyps and fibroids. Between 3% and 6% of cases with recurrent early pregnancy loss will be due to a karyotype abnormality in one or both partners, usually a translocation.² In a 27-year-old woman, however, aneuploidy would be uncommon.³

As an underlying cause for recurrent early pregnancy loss, hormonal abnormalities such as a luteal-phase deficiency are more

controversial. In patients 35 years of age or older, the quality and quantity of oocytes may contribute to recurrent early pregnancy loss, whereas in a younger population, polycystic ovary syndrome or polycystic ovarian morphology may be an underlying cause in 8%–10% of patients.⁸ Abnormalities in prolactin and thyroid hormone levels are associated with ovulatory disturbances, with the latter also being problematic for fetal development.⁸

No immune abnormalities have been definitively associated with recurrent early pregnancy loss. Investigations have shown an increased incidence of pregnancy loss among those with confirmed antiphospholipid antibodies.^{2,6} These antibodies include immunoglobulin G and immunoglobulin M anticardiolipin, anti- β_2 glycoprotein I and the lupus anticoagulant. However, the presence of these antibodies is not predictive of pregnancy loss or an adverse pregnancy event.^{2,9}

There is no association of recurrent early pregnancy loss with thrombophilias. However, some coagulation abnormalities have been implicated in second- or third-trimester losses.¹⁰

What investigations should be considered for this patient?

Possible investigations include assessment of uterine anatomy, karyotyping of both partners, determination of basal hormone levels (including thyroid hormone and prolactin) and testing for immune and coagulation abnormalities.⁶

The objective of anatomic investigations is to rule out intrauterine anomalies, most commonly with sonohysterography or hysterosalpingography, performed during the follicular phase before ovulation. If an anomaly is found, hysteroscopy is often performed to identify and correct the defect.⁵⁻⁷

Karyotyping of both partners is essential in investigating recurrent early pregnancy loss; genetic counselling should be undertaken if an abnormality is found. Chromosomal analysis of the products of conception should ideally be performed, despite the challenges of procuring such testing, as it will help to determine whether the pregnancy loss is explained by aneuploidy.^{3,5,6}

In older women (especially those 35 years of age or older), evaluation of basal follicle-stimulating hormone levels on day 3 and of anti-müllerian hormone levels may be considered. Elevation of basal follicle-stimulating hormone suggests problems with the quality and quantity of the oocytes. A low quantity of oocytes can be substantiated by a low anti-müllerian hormone level.¹¹ In a younger population, investigations for polycystic ovary syndrome or polycystic ovarian morphology, as well as measurement of prolactin and thyroid-stimulating hormone levels, should be undertaken.⁸

Box 1: Choosing Wisely Canada recommendation for testing in early pregnancy loss¹²

Don't order thrombophilia testing in women with early pregnancy loss.

- Early pregnancy losses are common among healthy women. Current guidelines do not support the routine screening of women with pregnancy loss for inherited thrombophilias. Moreover, there are recommendations against instituting thromboprophylaxis in women with inherited thrombophilias wishing to achieve a successful term pregnancy. By undergoing testing for inherited thrombophilias, patients may be unnecessarily exposed to the harms of thromboprophylaxis, may be inappropriately labelled with a disease-state and may unnecessarily modify future plans for travel, pregnancy or surgery based on detection of an "asymptomatic" thrombophilia. Further, patients with negative testing may receive false reassurance.

Current recommendations are to screen for antiphospholipid antibodies in women with three losses before 10 weeks or two losses after 10 weeks.^{2,6} Although recent evidence now questions the association of antiphospholipid antibodies with recurrent early pregnancy loss,⁹ guidelines still recommend such testing.⁶

Recent evidence has indicated that there is no association of recurrent early pregnancy loss with thrombophilias.¹⁰ Therefore, thrombophilia testing should not be ordered for these women (Box 1).¹²

Should this patient be referred?

For patients with three or more early pregnancy losses, family physicians are faced with the decision to undertake initial investigations or refer immediately. Referral to a specialist should be planned. Before referral, baseline investigations for anatomic, hormonal and genetic abnormalities may be undertaken. Specific immune or coagulation studies might best be left to the specialist. However, if such investigations are initiated before referral, the family physician should be selective, ordering only tests for which there is some evidence associating them with the clinical problem.

The case revisited

The primary care physician undertook investigations for hormonal and uterine anatomic abnormalities; the results were normal. However, karyotype analysis of the patient and her male partner showed a balanced translocation in the woman's partner. The couple was referred for genetic counselling.

The geneticist explained to the couple that the losses were likely due to the occurrence of an unbalanced translocation and informed them that without intervention, a successful pregnancy was possible, but there was an increased risk of early miscarriage. Altern-

tively, the couple could be referred to an in vitro fertilization (IVF) clinic for discussion of IVF with preimplantation genetic diagnosis, whereby an embryo without an unbalanced translocation could be selected for transfer. Although a successful pregnancy with IVF would still be subject to the variables affecting the IVF cycle, the probability of a live birth in such a pregnancy would likely exceed that associated with natural conception without intervention.

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The clinical scenario is fictional.

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