Recurrent Pregnancy Loss: Genetic Workup

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Key Points

- Recurrent pregnancy loss is usually defined as three or more consecutive losses occurring at less than 20 weeks' gestation of a clinically recognized pregnancy. Recurrent pregnancy loss usually occurs at a similar gestational age in consecutive pregnancies.
- Although genetic conditions are a rare cause of recurrent miscarriage, they should be considered in the workup because identification of a genetic cause may provide information about genetic risk in parents or future children.
- One genetic cause, found in 3-5% of couples with recurrent miscarriages, is a balanced chromosome rearrangement in one member of the couple.
- Other genetic causes of recurrent miscarriage include inherited thrombophilias and X-linked lethal conditions.

Learning Objectives

Participants will be able to:

- Identify the most common genetic causes of recurrent pregnancy loss;
- Explain why individuals with a balanced chromosome rearrangement are at increased risk for pregnancy loss.

Family History Issues

Evaluation of family history may provide indicators of hereditary causes of recurrent pregnancy loss.

- A balanced chromosome rearrangement may be associated with a family history of pregnancy loss and/or children with findings characteristic of chromosomal disorders (cognitive impairment in combination with physical malformations).
- Inherited thrombophilias are associated with an increased risk of pregnancy loss.
- An X-linked lethal condition may result in the loss of male fetuses in

the maternal lineage.



Risk of pregnancy loss increases with two or three consecutive losses:

Pregnancy History	Risk of Pregnancy Loss	From Al- Fozan & Tuland 2004a
First pregnancy	11-13%	
One pregnancy loss	14-21%	
Two consecutive pregnancy losses	24-29%	
Three consecutive pregnancy losses	31-33%	

Case 37. Recurrent Miscarriages after the Birth of a Healthy Child

A 32-year-old patient, Mrs. A, immigrated to the United States several years ago. She and her husband have one six-year-old daughter. Following the birth of their daughter, Mrs. A has had three miscarriages between eight and 12 weeks' gestation, the most recent one being one month ago. She asks you why she is having these miscarriages. On questioning about her family history, Mrs. A reports that her sister and her mother each have had one miscarriage. In addition, her sister reportedly has a child with mental retardation and other medical problems. Mrs. A is not in regular contact with her sister or other members of her family, who still live in her childhood home, so she does not have additional family history information. You wonder about genetic causes of pregnancy loss.

Clinical Care Issues

Recurrent pregnancy loss

An estimated 50% of recurrent pregnancy loss is idiopathic. Specific non-

genetic causes include uncontrolled diabetes, structural abnormalities of the uterus, and acquired anticardiolipin antibodies or lupus anticoagulant. Other endocrine conditions that may be associated with pregnancy loss include polycystic ovary syndrome and luteal phase deficiency. Some studies implicate prolonged exposure to alcohol and heavy smoking. Evaluation of recurrent pregnancy loss usually includes assessment for anatomic or hormonal causes; anticardiolipin antibodies and lupus anticoagulant; and consideration of genetic causes. The specific workup to be undertaken is determined after medical evaluation of the mother and review of family history [ACOG 2002, Al-Fozan & Tulandi 2004b].

Most couples who have had recurrent pregnancy loss are able to have a subsequent successful pregnancy; in a 1983 study the success rate was 77% after a normal diagnostic workup and 71% after a diagnostic workup revealing a specific cause [Harger et al 1983]. A history of a previous successful pregnancy — as in the case of Mr. and Mrs. A — is a positive prognostic factor.

Genetic causes of recurrent miscarriage are rare, but identification of a genetic cause may have important risk implications for future children, parents, and other relatives.

Chromosomal rearrangement as a cause of recurrent miscarriage

In about 3-5% of couples with two or three spontaneous pregnancy losses, a balanced chromosome rearrangement (**translocation** or **inversion**) is found in one member of the couple. A **balanced translocation** is a chromosomal rearrangement in which two chromosomes have exchanged segments without a net gain or loss of genetic material. Balanced translocations are usually not associated with any abnormalities, with the rare exception of a gene disruption occurring at a breakpoint of the rearranged chromosomes. Balanced translocations are present in about 1/500 individuals and may be transmitted through many successive generations.

Although individuals who carry balanced translocations are unlikely to be at risk for health problems, such individuals have a higher risk for conceiving a child with an **unbalanced translocation**. An unbalanced translocation occurs as a result of abnormal segregation of the rearranged chromosomes during egg or sperm formation (meiosis) in the balanced translocation carrier. The resulting egg or sperm have extra or missing chromosomal material from each of the two chromosomes involved. The resulting conceptus has an unbalanced karyotype, which can lead either to a pregnancy loss or a liveborn child with multiple abnormalities due to the unbalanced chromosomal status. The probability of pregnancy loss versus that of the birth of a child with unbalanced chromosomes depends on the breakpoints and size of the translocated material.

An **inversion** is a chromosomal rearrangement in which a segment of a chromosome has inverted from end to end and re-inserted itself into the chromosome. As with translocations, a balanced inversion in which there is no net gain or loss of genetic material is not usually associated with abnormalities. However, individuals with some inversions have an increased risk of pregnancy loss or of having a child with an unbalanced karyotype, similar to people with balanced chromosomal rearrangements.

Other genetic causes of recurrent miscarriage

Inherited thrombophilia. Several gene variants are associated with an increased risk of venous thrombosis; these are designated as genetic thrombophilias. The two most common inherited thrombophilias, factor V Leiden and prothombin G20210A, are associated with an increased risk of first-trimester and later pregnancy loss [Kovalevsky et al 2004, Rey et al 2003]. Another rare thrombophilia, protein S deficiency, is also associated with recurrent pregnancy loss, but other thrombophilic conditions have not been shown to be associated [Rey et al 2003] (see Case 39 and *GeneReview*: Factor V Leiden Thrombophilia for more information about inherited thrombophilias).

The lifetime risk for venous thrombosis is estimated at 10-20% for factor V Leiden, and is probably lower for prothrombin G20210A. Therefore, pregnancy loss in association with these conditions could occur without any prior history of thrombotic events.

Other inherited syndromes. X-linked disorders that are lethal in males may cause recurrent pregnancy loss. When a disorder of this kind is present, the family history shows a pattern of pregnancy loss and female births in the maternal line.

Recurrent pregnancy loss later in the pregnancy may be due to alpha thalassemia. In this circumstance, non-immune hydrops fetalis is present. Typically, this situation occurs when both parents have lost two of four alpha hemoglobin genes and, as a result, have mild anemia; the affected fetus is missing all four alpha hemoglobin genes, a condition not compatible with life (see Thalassemia).

Risk Assessment

A complete family history should be taken as part of the workup of recurrent pregnancy loss, with particular attention to pregnancy or infant losses (including gender), infants with birth defects or failure to thrive, mental retardation, thrombophilic disorders, hemoglobinopathy, or consanguinity.

Testing for factor V Leiden, prothrombin variant G20210A, and protein S deficiency is usually recommended as part of the workup of routine pregnancy loss, even in the absence of specific family history. Some experts recommend routine measurement of peripheral blood karyotypes on both parents; others recommend karyotype studies if no other identifiable cause of recurrent pregnancy loss has been identified [ACOG 2002, AI-Fozan & Tulandi 2004b].

Genetic Counseling and Testing

Genetic counseling is recommended if a genetic cause of recurrent pregnancy loss is found.

If a chromosomal rearrangement is identified, genetic counseling can be helpful in providing information about the risk of future miscarriage or liveborn offspring with an unbalanced karyotype. The risk of pregnancy loss, versus birth of a child with health problems due to chromosomal abnormalities, varies with the size and location of the chromosomal rearrangement and with the gender of the parent with the balanced chromosomal rearrangement: males transmit the unbalanced chromosomal state less often than females. Genetic counseling includes discussion of these risks and also of the option for prenatal diagnosis in future pregnancies. In addition, risk to other family members is considered.

After the diagnosis of a balanced chromosomal rearrangement, testing is recommended for siblings and parents to determine whether other family members are at risk for pregnancy loss and/or affected children. For example, the finding of a chromosomal rearrangement in Mrs. A would raise the possibility that her mother's and sister's pregnancy losses, as well as the health problems of her sister's child, could be the result of unbalanced chromosomes. Further evaluation (ideally, chromosomal testing of Mrs. A's sister and child) would be needed, given that pregnancy loss is common and only limited information is available about the child's health problems. Similarly, the diagnosis of an inherited thrombophilia would prompt consideration of further evaluation in relatives of the affected person (see Case 39).

Interventions

Balanced chromosomal rearrangement. Prenatal diagnosis can be offered to couples in which one partner has a balanced chromosomal rearrangement. Testing can determine the chromosomal status of the fetus; ultrasound may also provide information regarding the presence of malformations. Some couples may choose to terminate a pregnancy when an unbalanced chromosomal status is identified.

Thrombophilia. Some experts recommend prophylactic low molecular weight heparin when recurrent pregnancy loss is associated with an inherited thrombophilia [Lockwood 2005], based on observational data and one randomized trial [Gris et al 2004].

Ethical/Legal/Social/Cultural Issues

Psychological considerations. Some couples feel an increased sense of frustration and despair with each subsequent pregnancy loss. If Mrs. A and her husband are experiencing these feelings, they may benefit from a referral to counseling or other support services. They can also be reassured that the majority of couples who have experienced recurrent pregnancy loss are able to have a subsequent successful pregnancy, and that their previous successful pregnancy is a good prognostic factor.

Use of health care resources. Recommendations differ on the initiation of a workup for recurrent pregnancy loss after two, versus three, pregnancy losses, and on the value of such a workup relative to other health care services. Overall, the likelihood of finding a specific, treatable cause is small. It can be argued that spending health care dollars on expensive testing (for example, chromosomal studies) with little likelihood of obtaining information to guide clinical management is an ethical concern. It is appropriate to consider these resource issues, as well as individual risk factors, in determining the point at which a workup is worth pursuing. In this case, the family history of pregnancy loss and a child with mental retardation and other medical problems is suggestive of a possible genetic cause; if it were possible to gather more medical information on Mrs. A's sister's pregnancy

experience and on the health problems of her child, this information would be helpful in determining how aggressively to pursue workup.

Resources

- Genetics and Public Policy Center: Translocations
- Support for Pregnancy Loss
- Centre for Genetics Education: Changes to Chromosome
 Structure Translocations
- UpToDate Online

Incidence and etiology of recurrent pregnancy loss

Evaluation and management of couples with recurrent pregnancy loss

Inherited thrombophilias in pregnancy

- The National Alliance for Thrombosis and Thrombophilia (NATT)
- Information Center for Sickle Cell and Thalassemic Disorders: Thalassemia

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