

Recurrent Pregnancy Loss
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Pregnancy Loss

Miscarriage is the loss of a pregnancy before 20 weeks. It occurs in 20 percent of all first pregnancies. When it recurs, it is known as recurrent pregnancy loss (RPL). It is estimated that three to five percent of all couples desiring pregnancy will suffer RPL. The experience of a pregnancy loss is both physically and emotionally draining and often results in feelings of grief. A complete evaluation is needed to identify the causes of RPL. The majority of couples with RPL will eventually have a successful outcome.

Overall, approximately 12–15 percent of clinically recognized pregnancies end in spontaneous miscarriage between four and 20 weeks of gestation. However, the true early pregnancy loss rate, including both clinically recognized and unrecognized occult early miscarriages, is two to four times greater, depending on age. Careful studies in normally cycling healthy young women attempting pregnancy have shown that human chorionic gonadotropin (hCG) can often be detected transiently in the urine of women who are otherwise quite unaware that they had conceived and miscarried.¹²⁻¹⁴ No less than 30 percent and as much as 60 percent of all conceptions abort within the first 12 weeks of gestation, and at least half of all losses go unnoticed. The reproductive loss that occurs even before a first missed menses is substantial.

The Causes of Loss

After a complete evaluation, the cause(s) of RPL can be determined in two-thirds of cases. Identification and treatment of problems significantly increases the successful outcome in most cases. However, a complete evaluation is necessary to identify possible problems. This includes a medical history, history of all prior pregnancies, review of all test results on the couple, evaluation of social and environmental risks, and a complete laboratory evaluation (Table 1).

Genetic Problems

Many couples tend to ascribe RPL to genetic factors, so it is important to emphasize some basic points. There are two broad types of chromosomal (genetic) abnormalities, with the first and most common kind occurring in the baby. This usually involves a problem unique to the particular union of egg and sperm that resulted in a baby that was not capable of survival. This finding has no bearing on future pregnancies in many cases. The second kind of chromosomal abnormality exists in the patient or her partner and may be of concern in all of their future pregnancies. Fortunately, this type of genetic abnormality is discovered in only three to five percent of couples with RPL.

Hormonal Problems

Abnormal ovarian function with decreased progesterone production has been termed a "luteal phase deficiency" and is found in five to eight percent of women with RPL. Other hormonal deficiencies that are infrequently associated with pregnancy loss include hypothyroidism, an excess in the production of a hormone called prolactin, and an imbalance in glucose and insulin. These conditions can be treated medically.

Anatomic Problems

Uterine abnormalities are found in 15 to 20 percent of women with a history of RPL. These abnormalities may be congenital (from birth) or acquired in the course of the woman's lifetime. Many of the congenital and acquired abnormalities can be treated with a surgical procedure called operative hysteroscopy. This day-surgical procedure can be used to treat uterine septa, intrauterine scar tissue (adhesions), and growth of smooth muscle (leiomyomas) or glands (polyps).

Immune Problems

The area of immunology has become one of the most controversial in the assessment of pregnancy loss. The causes include autoimmune factors (immune reaction against another) and alloimmune causes (immune reaction against another). An example of an autoimmune disease is rheumatoid arthritis, and an example of an alloimmune problem would be rejection of a kidney after transplantation. Tests for lupus anticoagulant and antiphospholipid or anticardiolipin antibodies are clinically indicated diagnostic tests and are abnormal in 20 percent of women with RPL. Other tests under investigation include natural killer (NK) cells and embryotoxic factors. Treatment may include the use of a blood thinner, such as heparin with baby aspirin.

Coagulation Problems

Imbalances in the blood clotting system have recently been recognized as an area of importance in RPL. A number of inherited disorders may predispose women to venous and arterial thrombosis and block the blood flow to the developing baby. As many as 15 percent of women with unexplained RPL may have a blood clotting disorder. These include deficiencies of protein C and protein S, antithrombin, genetic mutations in factor V and factor II, and hyperhomocystinemia that is often caused by a B vitamin deficiency. Once identified, these conditions can be treated.

Inherited thrombophilias resulting from genetic mutations in clotting factors have emerged as a potentially important cause of recurrent pregnancy loss, but a great many women with these mutations have completely normal reproductive performance. Why some with thrombophilias miscarry and others do not is unknown; women with more than one type of mutation or whose fetus inherits the mutation may be at greater risk. At present, which women with recurrent pregnancy loss should be screened for thrombophilias and how they should be evaluated remain unanswered questions. Selected screening for the most common abnormalities in women with otherwise unexplained recurrent pregnancy loss with a suspicious loss after eight weeks' gestation or after detection of fetal heart activity is reasonable, but routine screening of all **women** with recurrent pregnancy loss cannot be justified. Whereas preliminary data suggest that combined treatment with aspirin and heparin may improve pregnancy outcomes in women with recurrent pregnancy loss who carry a thrombophilia, empiric aspirin treatment in untested women has no proven benefit.

Infectious Problems

Infection of the uterine lining or endometrium with slow growing bacteria has also been associated with pregnancy loss in five to 10 percent of women with RPL. Certain infectious agents have been identified more frequently in cultures from women who have had a spontaneous pregnancy loss. These include *Ureaplasma urealyticum*, *Mycoplasma hominis*, and *Chlamydia*. Other less frequent pathogens include *Toxoplasma gondii*, rubella, HSV, measles, CMV, coxsackie virus and *Listeria monocytogenes*, though none have convincingly

been shown to be associated with ARPL. Because of the clear association with sporadic pregnancy losses and the ease and low cost of diagnosis, women with RPL should be cultured for the three most frequent organisms (mycoplasma, ureaplasma, and Chlamydia) and both partners should be treated with antibiotics if positive. Some clinicians believe that empiric antibiotic treatment in women suspected of harboring a genital mycoplasma infection is less costly and less complicated than serial cultures.

Environmental Problems

Certain habits and occupations may be related to pregnancy loss. It is known that tobacco use of greater than 15 cigarettes per day or alcohol use of greater than four drinks per week will increase the chance of pregnancy loss up to two-fold. Also, some studies have suggested that airline attendants, women who are exposed to chemicals in their work environment (such as hair stylists), and women with physically strenuous work may have an increased risk of miscarriage. Non-traumatic exercise, intercourse, and normal daily activity do not cause miscarriage.

During the Evaluation

The couple is counseled not to become pregnant while the reason for their past pregnancy losses is being investigated. The couple is advised to use barrier contraception until all test results are back and any necessary treatment plans are made. The entire process requires about six weeks, which approximates the time of physical healing after a loss. The emotional healing may take considerably longer.

Dealing with Pregnancy Loss

The loss of a pregnancy at any stage can result in feelings of grief. Some patients decide they do not want to conceive again, most commonly because they feel that they cannot deal with another loss. Some couples may want to take a few months to sort out their feelings. Couples with recurrent pregnancy loss usually have a greater sense of fear anticipating what might occur in a subsequent pregnancy. Other couples often feel a lack of control over their lives.

It is important to emphasize that the couple's relationship with each other is just as important as the bond either or both may feel with their unborn child. In many cases, the stresses associated with pregnancy loss may serve to strengthen the bond of marriage. In other couples, there may be the false hope that a child will help to save a failing marriage. One partner may place blame on the other, or one partner might believe the other is placing the blame on him or her. Some individuals feel profound guilt and blame themselves for past indiscretions. These couples may be directed to appropriate bereavement resources for support and counseling.

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DIAGNOSIS AND MANAGEMENT OF RECURRENT PREGNANCY LOSS

Etiology	Diagnostic Evaluation	Abnormal Result	Therapy
Genetic	Karyotype partners	3-5%	Genetic counseling Donor gametes
Anatomic	Hysterosalpingogram Hysteroscopy Sonohysterography	15-20%	Septum transection Myomectomy Lysis of Adhesions
Endocrinologic	Midluteal progesterone TSH Prolactin Fasting insulin : glucose Day 3 FSH, estradiol	8-12%	Progesterone Levothyroxine Bromocriptine, Dostinex Metformin Counseling
Immunologic	Lupus anticoagulant Antiphospholipid Antibodies (? Embryotoxicity assay) (? Immunophenotypes)	15-25%	Aspirin Heparin + Aspirin (? IV Gamma globulin)
Thrombophilic	Antithrombin deficiency Protein C deficiency Protein S deficiency Factor V Leiden mutation Factor II (prothrombin) Hyperhomocysteinemia	10-15%	Heparin + Aspirin (? low molecular weight heparin) Folic acid
Microbiologic	Cervical cultures	5-10%	Antibiotics
Psychologic	Interview Questionnaire	Varies	Support Groups Counseling
Iatrogenic	Tobacco, alcohol use Exposure to toxins, chemicals	5%	Eliminate consumption Eliminate exposure

? = current research data inconclusive