

RECURRENT PREGNANCY LOSS By Michele Evans, M.D., F.A.C.O.G.

Background

Approximately 15% of all pregnancies between 4 and 20 weeks of gestation will end in a clinically recognized miscarriage (spontaneous abortion). Recurrent pregnancy loss is classically defined as 3 or more consecutive spontaneous miscarriages. This occurs in 0.5-3% of women. Clinical studies indicate that the risk of another miscarriage after 3 consecutive pregnancy losses is 30-45%. Furthermore, without any workup or treatment, the chance of a successful live birth in a couple with a history of recurrent pregnancy loss and no previous live birth is 55-60%. If the couple has a history of recurrent pregnancy loss and has had at least one previous normal pregnancy, the chance of a subsequent live birth is 70%.



These percentages are based on studies of younger women, and it is important to keep in mind that the miscarriage rate increases with age. The causes of recurrent pregnancy loss can be divided into 4 categories: genetic, anatomic, endocrine (related to hormone abnormalities), and prothrombotic. Current medical literature suggests that causes are identified in only 50% of patients.

Genetic Causes

Fetal genetic abnormalities are noted in approximately 70% of early miscarriages. In most cases, the couple has normal chromosomes and the fetal abnormality is a random event. In couples with recurrent pregnancy loss, an initial workup should include a karyotype (chromosome analysis) of the male and female partner. A karyotype will reveal a genetic abnormality in 4% of couples. The most common chromosome abnormality is a translocation (balanced rearrangement of chromosomes). Other chromosome abnormalities include chromosome inversions, X-chromosome inactivation, sex chromosome mosaicism and ring chromosomes. Single gene defects might also be responsible for multiple miscarriages, but will not be detected by a karyotype.

Until recently, the only treatment for known genetic abnormalities was the use of donor gametes (eggs or sperm). Currently, preimplantation genetic diagnosis (PGD) can be utilized to detect certain chromosome abnormalities in an early embryo. PGD is performed in conjunction with in vitro fertilization (IVF). Early embryos are examined in the IVF laboratory, and only those embryos that appear to be genetically normal are transferred into the female patient's uterus in hopes of achieving a successful pregnancy and live birth. It is important to recognize that PGD has its limitations, and therefore

pregnant patients should still undergo routine prenatal testing, including chorionic villus sampling or amniocentesis, if indicated.

Anatomic Causes

Approximately 10-15% of women with recurrent pregnancy loss have a uterine malformation. Uterine malformations include mullerian anomalies (septate uterus, bicornuate uterus, unicornuate uterus), leiomyomata (fibroids) and Asherman's syndrome (intrauterine synechiae/scarring). Many of these conditions can be diagnosed by sonohysterogram (transvaginal ultrasound exam with saline instillation), hysterosalpingogram (HSG) or office hysteroscopy.

Women with congenital or acquired uterine anomalies may be predisposed to recurrent pregnancy loss because of inadequate vascularity to the developing embryo and placenta or reduced intrauterine volume. The septate uterus is the most common congenital uterine abnormality associated with recurrent miscarriages. Hysteroscopic resection of the uterine septum (metroplasty) results in significantly improved reproductive outcome. Surgical treatment is not suggested for bicornuate or unicornuate uteri.

Asherman's syndrome is an acquired condition, which is due to the presence of post-traumatic intrauterine adhesions, often following a dilatation and curettage with postoperative infection. These adhesions can partly or completely obliterate the uterine cavity. The endometrium is less responsive to steroid hormones in the areas affected by adhesions. Successful surgical division of adhesions without extensive fibrosis may restore the endometrial responsiveness. However, dense fibrosis is associated with a poor prognosis.

Uterine fibroids may also affect implantation of an embryo. There are three categories of uterine fibroids: submucosal (distorting the endometrial cavity), intramural (within the muscle layer of the uterus) and subserosal (in the outermost layer of the uterus, away from the cavity). A number of retrospective and cohort studies have indicated that there is good evidence to remove submucous fibroids to reduce miscarriage, and there is some evidence that removal of intramural fibroids also reduces miscarriage.

Endocrine Causes

Many endocrine abnormalities have been cited as causes of recurrent pregnancy loss, including hypersecretion of luteinizing hormone (LH), high androgen levels, hyperprolactinemia, thyroid disease and abnormal glucose metabolism. Current evidence suggests that only thyroid abnormalities, hyperprolactinemia and poorly controlled Type I diabetes are positively associated with recurrent miscarriage. An initial workup for recurrent miscarriage should include a screening test for thyroid disease with the measurement of thyrotropin stimulating hormone (TSH) and a prolactin level. In a healthy patient, laboratory evaluation of carbohydrate metabolism is not suggested.

The presence of a luteal phase defect as a cause for recurrent pregnancy loss is controversial. A luteal phase defect is defined as inadequate secretory transformation of the endometrium (uterine lining) resulting from a deficient ovarian progesterone secretion. A luteal phase defect can be diagnosed by out-of-phase endometrial biopsies in 2 consecutive menstrual cycles. Studies suggest that the majority of cases of luteal

phase defect are associated not with suboptimal progesterone but with an abnormal response of the endometrium to progesterone. Therefore, a recent study indicates that treatment should be targeted at improving the endometrial responsiveness of progesterone by enhancing priming of the endometrium in the follicular phase (first half of the menstrual cycle). In the study cited, this was done by stimulating the ovary with gonadotropins to increase estrogen production in the follicular phase. Estrogen priming is associated with normalization of endometrial development in the luteal phase.

Prothrombotic Causes

Antiphospholipid syndrome is a well-recognized cause of recurrent miscarriage. Antiphospholipid antibodies are directed to the negatively charged phospholipids that are constituents of all cell membranes. Lupus anticoagulant and anticardiolipin antibodies are types of antiphospholipid antibodies. The diagnosis of this syndrome, as related to recurrent pregnancy loss, requires fulfillment of the following criteria: three or more unexplained consecutive spontaneous miscarriages before the 10th week of gestation, with all other causes excluded. In addition, there must be a persistent abnormality of one of the following tests when measured at least twice, greater than 6 weeks apart: lupus anticoagulant and/or anticardiolipin antibodies. The optimal treatment is low dose aspirin and subcutaneous heparin.

Conclusions

Recurrent pregnancy loss is very distressing for patients. A thorough medical evaluation is critical, but often frustrating, because a cause for the repeated pregnancy losses can be identified in only 50% of cases. There are still many unresolved questions about the causes and treatment of recurrent miscarriage. Fortunately, the number of publications on this topic have substantially increased over the past 10 years, reflecting a growing interest among clinicians and scientists.