32. REPEATED PREGNANCY LOSS

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I. **Definition.** Repeated pregnancy loss (RPL) is defined as three consecutive spontaneous abortions before 20 weeks' gestation. RPL affects 0.5–1.0% of pregnant women and can be divided into **primary**, in women without a previous liveborn infant, and **secondary**, in those women with at least one prior liveborn infant. It is generally accepted that 15–20% of all clinically documented pregnancies result in spontaneous abortion. Many factors affect the actual risk of miscarriage, including maternal age. For women younger than 20 years, miscarriage occurs in 12% of pregnancies. This number increases to 26% for women older than 40. When unrecognized pregnancies are factored into the equation, the loss rate for women over 40 is 75%. For most women who experience a miscarriage, the recurrence rate is below 30%. In fact, 80–90% of women will have a successful pregnancy after a spontaneous abortion. In cases of RPL, the chance of a live birth after three consecutive losses is 55–60%.

II. **Causes** of RPL include but are not limited to genetic, anatomic, endocrine, immunologic, infectious, and environmental factors.

A. **Genetic**

1. **Chromosomal abnormalities** are a common cause of spontaneous abortion. In up to 70% of first trimester miscarriages, a chromosomal abnormality is shown when fetal tissue is tested. These include aneuploidies, trisomies, monosomies, and so forth. Trisomies are the most common type and are detected in almost 50% of miscarriages. The most common trisomies are 13, 16, 18, 21, and 22. The next most common abnormality is 45X, which accounts for 25% of all chromosomal abnormalities.
2. **Parental chromosomal abnormalities** may play a role in RPL. Studies have shown that the incidence of chromosomal abnormalities in couples experiencing RPL is 3–8%, five to six times higher than the incidence in the general population. Balanced translocation is the most common abnormality found in the karyotypes of parents with RPL. Often, the parent is phenotypically normal. The translocation may be passed on in one of three ways: normal karyotype, balanced translocation, or unbalanced translocation, which may be incompatible with life. Other parental chromosomal abnormalities include inversions and mosaicism.

B. **Anatomic** reasons for RPL can be further divided into congenital and acquired problems.

1. **Congenital problems** encompass a variety of conditions often involving müllerian development. These losses more commonly occur during the second trimester, although losses at earlier stages of gestation can occur. Common uterine abnormalities include septate, bicornuate, didelphic, and, less commonly, unicornuate uteri. Of these uterine abnormalities, septate uterus is the most common. Some studies have shown that 27% of women with a history of losses have some anatomic abnormality.

   A septate uterus results from failure of resorption of the paramesonephric ducts and is often associated with poor obstetric outcomes. Studies have reported 15–28% livebirth rates in women with this type of uterine abnormality. With surgical correction, however, successful pregnancy can occur in up to 80% of cases.
2. **Acquired anatomic abnormalities** associated with RPL include leiomyomata, intrauterine synechiae, and in utero diethylstilbestrol (DES) exposure.
   a. **Fibroids**, particularly submucosal, have been purported to cause RPL. These anatomic lesions may result in unfavorable implantation sites and may jeopardize the vascular supply to the placenta. Intramuscular and subserosal fibroids may also be problematic if they are large enough to distort the uterine cavity (see Chapter 33).
   b. **Intrauterine synechiae** most often form after instrumentation of the uterus, although they may occur in cases in which there is an estrogen deficiency. Adhesions are said to account for 5% of RPL cases. Often, these occur after a dilation and curettage procedure in which there is direct trauma to the endometrial cavity. These adhesions may interfere with implantation and future vascular supply to the fetus.
   c. **DES-exposed women** have been shown to have poor reproductive outcomes. One study reported a 42% livebirth rate for these women, with a majority of losses occurring in the first trimester. In utero exposure has been reported to cause multiple anatomic abnormalities, including a T-shaped uterine cavity, a widened lower uterine segment, midfundal constrictions, filling defects, and irregular margins. These defects can be seen on a hysterosalpingogram in 42–69% of DES-exposed women. It has been proposed that these abnormalities may result from DES binding to estrogen receptors during embryologic development of the müllerian system.
   d. **Cervical incompetence** is another anatomic cause of RPL. This is a condition of painless cervical dilation and may be congenital or acquired. Acquired causes include previous cervical surgery (i.e., conization, traumatic delivery with cervical laceration, aggressive cervical dilation during dilation and curettage).

C. **Endocrine.** A defect with the corpus luteum known as **luteal phase deficiency** is a proposed cause of RPL. In this condition, a deficiency in progesterone causes the endometrial tissue to lag by 2 or more days behind the anticipated histologically determined age of the tissue. Progesterone production by the corpus luteum is needed to support a pregnancy until the eighth week, when the placenta starts to produce the majority of this hormone. Individuals with a luteal phase defect do not produce enough progesterone to support an early pregnancy. Losses tend to occur early, at 4–7 weeks' gestation. Although luteal phase defect is thought to be a cause of RPL, the meta-analysis of randomized trials in which pregnant women were treated with progestational agents failed to find any evidence of a positive effect on the maintenance of pregnancy.

   Studies show that subclinical diabetes and thyroid disease are unlikely causes of RPL, although women with poorly controlled insulin-dependent diabetes are at an increased risk of spontaneous abortion.

D. **Immunologic** disorders associated with RPL can be further divided into those involving autoimmune and alloimmune factors.

1. In a compilation of studies on women with RPL, 15% were found to have recognizable **autoimmune factors**. The most common antibodies include anticardiolipin and lupus anticoagulant. In vitro, these factors cause thrombosis. In vivo, they may cause thrombosis and placental infarctions that in turn result in spontaneous abortion. The majority of these losses occur during the second trimester.
2. **Alloimmune factors**, meaning immunity against a foreign entity, are another possible cause of RPL. Some couples experiencing RPL share human leukocyte antigens. These antigens are thought to interfere with formation of maternal antibodies that coat fetal antigens and thus prevent rejection. The role of this mechanism is controversial, because the sharing of human leukocyte antigens does not always result in poor pregnancy outcome.

E. **Infectious.** Only a few microbiological agents have been related to RPL, but none have been demonstrated to have an effect in randomized trials. Women experiencing RPL have been shown to be infected with *Ureaplasma urealyticum*. Other organisms that have been implicated but whose role has not been substantiated include *Toxoplasma gondii, Listeria monocytogenes*, and *Mycoplasma hominis*. Overall, infection as a cause of RPL is controversial.

F. **Environmental.** It has been shown that use of tobacco, alcohol, and some drugs is related to RPL. Some chemotherapeutic agents are also a proven cause of pregnancy loss. Ionizing radiation, anesthetic gases, and some heavy metals are other possible causes of spontaneous abortion in women exposed to these agents. Many dermatologic preparations, especially those containing vitamin A derivatives, cause spontaneous abortions.

G. **Unknown.** In as many as 50–60% of women experiencing RPL, there is no identified cause.

III. **Diagnosis.** Although RPL is defined as three consecutive pregnancy losses, a physician need not wait for three losses to begin a diagnostic workup. In particular, for older couples without children, it may be wise to start a workup after two losses. Also, it is important to perform a complete workup, as in some couples there are multiple reasons for RPL.

A complete history and physical examination is the first step. A detailed family history should be taken, including reproductive outcomes and medical illnesses. An occupational history should also be elicited to determine exposure to various chemicals. This should be followed by a thorough examination, including cultures for *Chlamydia*, *Neisseria gonorrhoeae*, *Mycoplasma*, and *Ureaplasma*. Specific blood studies, including thyroid function tests, random or fasting

glucose level, lupus anticoagulant level, and anticardiolipin antibody level should be ordered. A karyotype of each partner is helpful in locating translocations, inversions, and mosaicisms. Karyotypes of fetal tissue obtained from aborted material may also be obtained but may be of limited value.

To diagnose a luteal phase defect, a timed endometrial biopsy should be obtained in two consecutive cycles. A histologically determined lag of 2 or more days is considered significant. Some practitioners obtain a midluteal serum progesterone level, although the sensitivity is considered low by many. A serum progesterone level above 10 ng/dL points to a low probability of an out-of-phase endometrial biopsy. These results should be read carefully, as different pathologists may record varying results for biopsy dating. In addition, several studies have reported a histologically identified lag in endometrial tissue in women with no history of pregnancy loss.

To exclude anatomic abnormalities, several studies may be performed. Evaluation begins with a good physical examination and imaging studies, including hysterosalpingogram, sonohysterography, CT scan, or MRI. In the operating room, an examination under anesthesia, hysteroscopy, and a diagnostic laparoscopy may be performed.

IV. **Treatment.** As mentioned earlier, in as many as 50% of women, no cause is found for the RPL. For these patients, supportive measures are the best treatment.
   A. When **genetic causes** of RPL are diagnosed, it is important to include genetic counseling as part of any treatment plan. The rate of recurrence of miscarriage often depends on the actual genetic abnormality discovered. Some couples with a known translocation or inversion can have a good pregnancy outcome. Others may need to turn to sperm or oocyte donation to avoid lethal abnormalities in their offspring.
   B. Treatment for **anatomic abnormalities** often involves surgery. Hysteroscopic removal of uterine septa and synechiae has resulted in good pregnancy outcomes for many couples. Some physicians also insert an intrauterine device after resection of synechiae and place the patient on oral estrogen therapy to help prevent reformation of adhesions. If surgery is selected for uterine abnormalities, such as fibroids and unicornuate uterus, it should be clearly discussed with the couple that some studies have shown no difference in pregnancy outcome for patients treated surgically versus those not treated. Some women with anatomic abnormalities who are not treated have a fair to good rate of pregnancy success.
   C. **Endocrine abnormalities** can often be treated with replacement therapy. Researchers are currently undecided as to whether luteal phase deficiency affects pregnancy outcome. Many studies have shown no benefit from treating luteal phase defects. Some physicians, however, administer progesterone either as intravaginal suppositories (25 mg twice daily starting the third day after ovulation and continuing for 8–10 weeks), as intramuscular injections, or as orally administered micronized progesterone. It should be mentioned that as many as 60–70% of women diagnosed with a luteal phase deficiency will carry a viable infant with the next pregnancy. Other endocrine abnormalities, such as thyroid disorders and diabetes, should be corrected.
   D. When an **infection** is diagnosed, the appropriate antibiotic therapy should be instituted. Infections with *Mycoplasma* and *Ureaplasma* are treated with doxycycline, 100 mg twice daily by mouth for 10 days. Clindamycin 300 mg three times daily by mouth for 7–10 days can be used for patients who are pregnant or allergic to doxycycline. Both partners should be treated to prevent reinfection.
   E. **Environmental factors.** Women who smoke or drink alcoholic beverages should be encouraged to abstain from these activities. If exposed to environmental toxins, individuals should try to eliminate or reduce exposure.