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Recurrent pregnancy loss: Evaluation and discussion of the causes and their management

■ ABSTRACT

Women who miscarry two or more consecutive pregnancies deserve an evaluation to look for the cause, which sometimes can be treated. They can also be reassured that approximately 70% of women in this situation ultimately succeed in having a baby, even though the cause of recurrent miscarriage can be determined in only about half of cases.

■ KEY POINTS

Chromosomal abnormalities account for more than 50% of pregnancy losses. Some couples can overcome this problem by in vitro fertilization.

Some uterine anomalies, such as a septate uterus, can be surgically corrected.

Cerclage for cervical incompetence should be performed late in the first trimester.

Luteal phase defect is generally treated with progesterone, although the benefit of this therapy is uncertain and it may cause hypospadias in the infant.

Women with polycystic ovary disease should be treated with metformin until 12 to 20 weeks of gestation.

If pregnancy loss is attributed to antiphospholipid antibodies or systemic lupus erythematosus, in subsequent pregnancies women can be treated with prednisone throughout the first trimester, as well as with aspirin and possibly heparin.

MANY THINGS can go wrong in pregnancy. The cause of a miscarriage can reside in one's genes, anatomy, endocrine system, immune system, blood-clotting system, or environment—but in many cases no cause can be found.

The experience can be painful for the couple, especially if they have lost several pregnancies in a row. Fortunately, most couples ultimately succeed in having a baby, regardless of the cause of their recurrent pregnancy loss or their treatment.

This paper discusses known and suspected causes of recurrent pregnancy loss and how to evaluate and treat the problem.

■ 'RECURRENT' MEANS THREE CONSECUTIVE LOSSES

Recurrent pregnancy loss (also called recurrent abortion, recurrent spontaneous abortion, and recurrent miscarriage) is usually defined as three or more losses in a row.

About 15% of couples lose one recognized pregnancy, and 2% lose two. The theoretical risk of three or more losses is only 0.34%. Only two consecutive losses is cause enough to evaluate some patients, particularly those who are older or who have a history of infertility. Most miscarriages occur within 12 weeks of conception.

The cause of recurrent pregnancy loss is often very difficult to assess. In fact, the cause

The author has indicated that he has served on the speaker's bureaus of the Adeza Biomedical and Aventis corporations.

can be determined in only about half of patients.

■ CHROMOSOMAL ABNORMALITIES

Chromosomal abnormalities account for more than half of recurrent pregnancy losses. Most of the losses are in the first trimester; about 2% to 5% of all fertilized ova contain chromosomal abnormalities at conception, but this number falls to fewer than 1% in fetuses at term.^{1,2}

Aneuploidy

Aneuploidy means having a different number of chromosomes than the 46 found in the normal (euploid) cell.

Trisomy (having one additional whole or partial chromosome) accounts for 52% of all pregnancy losses due to chromosomal abnormalities. About 16% of losses due to chromosomal abnormalities are due to trisomy 16; trisomy 13, 18, and 21 account for 9% and are found in 0.1% of live births, with trisomy 21 being the most common.³

Monosomy (having only one chromosome of a normally diploid pair) accounts for 18% of pregnancy losses due to chromosomal abnormalities; 98% of these losses are in the first trimester.⁴ The 45,X genetic pattern is the most common genetic cause of recurrent pregnancy loss; nevertheless, this pattern is present in up to 7 of 10,000 live births.

Triploidy (having three complete haploid sets of chromosomes instead of two, for a total of 69 chromosomes) accounts for 17% of pregnancy losses due to chromosomal abnormalities.

Mosaicism is more than one chromosomal pattern in a single person. The most common mosaic abnormality is 45,X/46,XX.

Translocation

In 6% to 7% of cases of recurrent pregnancy loss, one or both parents carry a chromosomal translocation. Of these, 35% are robertsonian translocations (the fusing of the two long arms of paired chromosomes into a single chromosome, usually followed by the loss of the short arms), and 65% are reciprocal translocations (reciprocal exchange of segments between nonhomologous chromosomes with no gain or loss of genetic material).⁵

Many translocations involve chromosomes 13, 14, 15, 21, and 22.^{1,2}

More women than men carry translocations, because many affected men are sterile.⁶ If a man carries a translocation, the chance of passing it on to an offspring is 2% to 5%; a woman has a 10% to 20% chance of passing on a translocation she carries.^{5,7} If a parent has a balanced translocation, the risk of an unbalanced translocation occurring in the fetus is about 4%.

Do chromosomal abnormalities recur?

Evidence is mixed as to whether chromosomal abnormalities tend to recur in subsequent pregnancies. Hassold⁸ studied 40 couples and found a 70% recurrence risk with a prior aneuploid pregnancy vs 20% with a prior euploid pregnancy. Warburton et al⁹ found no increased risk of chromosomal abnormalities in subsequent pregnancies after spontaneous abortions if the fetus carried an aneuploidy that is always lethal in utero or if the parents had normal chromosomes.

Carriers of a translocation in chromosome 22 almost always miscarry; a woman with a translocation involving breaks in chromosome 13 or 14 has a 25% risk of spontaneous abortion.

Parity and older maternal age. Rates of pregnancy loss are higher in women who have had more children, possibly because these women tend to be older: the risk rises with maternal age, whether or not the fetus is normal. In older women, oocytes tend to have more chromosomal abnormalities and the endometrium is less receptive.

Treatment of genetic problems

Selected couples who have lost pregnancies because of aneuploidy can undergo in vitro fertilization. The blastocysts are examined, and they are implanted only if they are chromosomally normal.¹⁰

If the mother has poor oocytes, the procedure can be done with donated eggs from a younger woman or a woman with proven fertility; the rate of normal live births is high.¹¹

■ UTERINE ABNORMALITIES

From 10% to 15% of women who have lost multiple pregnancies have uterine anomalies such as a partial or complete septum.¹²⁻¹⁴

Most miscarriages are in the first trimester

These anomalies can cause fetal loss in all trimesters¹⁵ via poor implantation because of abnormal vascularization of the septum,¹⁶ uterine distention (possibly resulting in cervical incompetence), abnormal placentation, an abnormal lower uterine segment and cervix, or an increase in uterine contractility resulting in preterm birth or pregnancy loss.

Congenital müllerian abnormalities

The paired müllerian ducts develop into the fallopian tubes, uterus, cervix, and the upper two thirds of the vagina.

The prevalence of congenital müllerian anomalies used to be estimated as 2% of women, but now that magnetic resonance imaging, ultrasonography, and laparoscopy are being performed more often, it is estimated to be as high as 6%.

Septate uterus, resulting from failure of resorption of the septum between the two uterine horns, is associated with the greatest number of pregnancy losses, particularly if a complete septum remains.^{16,17} Other anomalies include uterus didelphys (a double uterus, resulting from complete nonfusion of the müllerian ducts) and bicornuate uterus (from partial nonfusion of the müllerian ducts), but they are less likely to cause recurrent pregnancy loss.¹⁷

Women who have an untreated uterine septum have a fetal survival rate of only 6% to 28%, and more than 60% have recurrent pregnancy loss.¹⁸ Treatment with transcervical uteroplasty results in a high pregnancy success rate.¹³

Congenital müllerian anomalies are linked to renal anomalies: 67% to 75% of women with a unicornuate uterus also have an absent or a bifid kidney, and 15% to 20% of patients with unilateral renal agenesis have a major genital anomaly.¹⁹

Diethylstilbestrol exposure

Diethylstilbestrol (DES) was used in the United States until 1971, and women exposed to DES in utero have high rates of recurrent pregnancy loss.²⁰ For many, the cause is an abnormal lower uterine segment and cervix, resulting in cervical incompetence and preterm labor and birth. This problem should

become rare as women of the generation exposed to DES reach the end of their child-bearing years.

Asherman syndrome (intrauterine synechiae)

The prevalence of intrauterine synechiae (adhesions) is difficult to determine. In a series of 200 patients with adhesions, 43% were sterile and 14% had recurrent pregnancy loss.²¹

Uterine leiomyomata

Submucous leiomyomata or fibroids can distort the uterine cavity and impede implantation. The association of subserosal and intramural fibroids with recurrent pregnancy loss is less clear.

Cervical incompetence

Cervical incompetence classically causes losses in the second trimester (gestational weeks 12 to 28). It is associated with painless cervical dilatation and expulsion of the fetus. The diagnosis requires two consecutive losses.

Cervical incompetence can be caused by congenital factors (eg, DES exposure), trauma (including forceps delivery, especially if performed before dilatation is complete), and surgical procedures (eg, cervical cone biopsies, laser procedures, and loop electrocautery excision procedures).

The chance of carrying the baby to term can be improved by placing a cervical cerclage at 10 to 14 weeks, after fetal viability has been confirmed.

■ HORMONAL CAUSES OF PREGNANCY LOSS

Luteal phase defect

The reported prevalence of luteal phase defect in patients with recurrent pregnancy loss varies from 23% to 60%.²² Whether and how it causes pregnancy loss is unclear.²³

Epidemiologic studies suggest that low progesterone levels, possible due to impaired folliculogenesis,²⁴ play a role in recurrent pregnancy loss. Progesterone is essential for maintaining early pregnancy. Low levels of progesterone-associated endometrial protein have been reported in patients with luteal phase defects, and this abnormality may result

The risk of pregnancy loss increases with parity and maternal age

in recurrent pregnancy loss.²⁵ Progesterone also has an immunosuppressive effect, which may help maintain pregnancy. It also relaxes uterine muscles, possibly by inhibiting prostaglandins, which may help keep the uterus from contracting prematurely.²⁶ On the other hand, serum progesterone levels are not predictive of pregnancy outcome.²⁷

Progesterone supplements are often used to support early pregnancy in patients with recurrent pregnancy loss and luteal phase defect. Generally recommended are vaginal suppositories of progesterone 50 mg twice a day or newer once-a-day formulations such as progesterone gel (Crinone 8%).

But two meta-analyses published simultaneously had conflicting findings on whether progesterone supplementation actually helps.^{28,29} Moreover, it may cause birth defects: Carmichael et al,³⁰ in a case-control study involving 502 babies with severe hypospadias, found that taking progestins during pregnancy was associated with a significantly increased risk of this anomaly.

Clomiphene citrate 50 mg on days 5 through 9 of the menstrual cycle is usually prescribed for either irregular menstrual cycles or luteal phase defect.

Thyroid hormone

Thyroid abnormalities are infrequently diagnosed during pregnancy and are rare in women with recurrent loss. Patients with treated thyroid dysfunction do not have an increased risk of miscarriage.³¹ More women with recurrent pregnancy loss have antithyroid antibodies than in the general population, but evidence that these antibodies actually cause pregnancy loss is lacking.³²

Pregestational diabetes mellitus

Women with poorly controlled diabetes (as reflected by hemoglobin A_{1c} levels greater than 8%) have higher rates of spontaneous abortion in early pregnancy than women without diabetes, and the children they carry to term have more congenital anomalies. However, these risks are not higher in women with subclinical diabetes or well-controlled disease.³³ Miodovnik et al³⁴ did not find an increased risk of recurrent pregnancy loss among diabetic women.

Polycystic ovary disease

From 20% to 40% of patients with recurrent pregnancy loss have polycystic ovary disease, compared with 10% to 20% of women in the general population.³⁵

Abnormalities in polycystic ovary disease can include high levels of luteinizing hormone, glucose, and insulin,³⁶ the latter due to insulin resistance. Patients suspected of having polycystic ovary disease should have fasting insulin levels measured as part of their evaluation.

Metformin 1,000 to 1,500 mg/day seems to reduce the rate of spontaneous abortions in the first trimester in patients with polycystic ovary disease.³⁷ It also improves ovulation cycles and increases the rate of conception. Treatment should be continued until 12 to 20 weeks of gestation.³⁸ Metformin does not cross the placenta, and there is no evidence that it increases the incidence of congenital anomalies when taken throughout the first trimester.

■ IMMUNOLOGIC FACTORS

Immunologic factors have long been proposed as causes of recurrent pregnancy loss because the fetus contains paternal antigens, which are immunologically foreign.^{39,40} Evidence suggests that the fetus and placenta are protected by local immunomodulating factors and that pregnancy loss may result from a breakdown of immune homeostasis.

'Blocking-factor deficiency'

One theory of recurrent pregnancy loss is that the mother's immune system mounts a cell-mediated response against the fetus, that antibodies develop in all successful pregnancies to block this response, and that without these blocking antibodies, abortions always occur. However, no direct evidence shows that the conceptus is immunologically attacked in the absence of blocking factors.⁴¹

Dysregulation of a normal immunologic mechanism that operates at the maternal-fetal interface may involve activity of natural killer cells in the endometrium, which appear to regulate effects that support pregnancy, such as promoting placental and trophoblast growth and trophoblast invasion and modulat-

**Septate uterus
can be repaired
transcervically**

ing the immune system at a local level.⁴²

The topic is ripe for investigation, but endometrial factors are impractical to evaluate in vivo. Many immunologic tests can be used only indirectly to try to define an immune dysfunction, especially for very early repeated failures or unsuccessful pregnancies by in vitro fertilization.

Treatment. In the past, patients without blocking antibodies and with antipaternal antibodies were treated by immunization using white blood cells from the spouse, but this treatment is no longer available.

Immunoglobulin G contains antibodies that block T cell receptors, which inhibit natural killer cell activity. Intravenous immunoglobulin infusions are still used in cases in which antibody test results are interpreted as being associated with recurrent pregnancy loss. However, the value of intravenous immunoglobulin G therapy is still controversial, and it should be considered experimental.^{43,44}

Antiphospholipid antibody syndrome

Antiphospholipid antibodies consist of anticardiolipin antibodies and lupus anticoagulant; one or the other is present in 5% to 15% of women with recurrent pregnancy loss.⁴⁵ Recurrent pregnancy loss and late fetal death may occur because of placental infarction or impaired trophoblast function.⁴⁶ Another hypothesis is that complement activation is a central mechanism of pregnancy loss in antiphospholipid antibody syndrome.⁴⁷

The diagnosis of antiphospholipid antibody syndrome requires at least one clinical criterion (arterial, venous, or small-vessel thrombosis in any organ or tissue, or recurrent pregnancy loss) plus at least one laboratory criterion (positive anticardiolipin antibody, lupus anticoagulant, or B2 glycoprotein-1 antibodies on two or more occasions at least 6 weeks apart).

Patients with high levels of anticardiolipin antibodies who have had a fetal death seem to be at high risk of future loss.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is present in 1 in 5,000 pregnancies.⁴⁸ Spontaneous abortions occur in 10% to 40% of women with SLE.⁴⁹ Recurrent losses, particularly

those that occur after 20 weeks of gestation, appear to be associated with a vasculopathy of the decidua (the inner wall of the uterus, which envelops the embryo).⁵⁰

The risk of fetal loss is increased in patients with hypertension, active SLE, lupus nephritis, or abnormally low complement levels.⁵¹ Risk is also increased for patients with antiphospholipid antibodies: from 6% to 24% of patients with SLE are positive for lupus anticoagulant,⁵² and 40% are positive for anticardiolipin antibodies.⁴⁹

Treatment for antiphospholipid antibody syndrome and SLE

Aspirin 80 mg per day can be used for patients with low-level antiphospholipid antibodies, lupus anticoagulant, or anticardiolipin antibodies, although there are no outcome data on this approach.

Low-molecular-weight heparin is recommended for patients with recurrent pregnancy loss or early fetal demise associated with SLE, lupus anticoagulant, or antiphospholipid antibodies. Generally, enoxaparin (Lovenox) 1 mg/kg or dalteparin sodium (Fragmin) 5,000 units daily by subcutaneous injection is recommended. Antifactor Xa should be kept in the range of 0.5 to 1.0 IU/mL. Combined aspirin and heparin is recommended for managing recurrent or late pregnancy loss in patients with SLE or antiphospholipid antibodies.

Prednisone. Patients with SLE with or without lupus anticoagulant and anticardiolipin antibody have been treated with prednisone and aspirin or heparin, or all three. Aspirin plus heparin appears to be the better approach for the management of both recurrent pregnancy loss and late pregnancy loss.

Patients with active lupus should ideally be treated before the onset of pregnancy and should be in remission preferably for about 6 months before attempting pregnancy. It should be noted that prednisone is used for treatment of the disease and not simply for patients with recurrent pregnancy loss with a positive antinuclear antibody titer.

Patients with SLE in remission who are taking prednisone in a low dose at the onset of pregnancy should continue taking it at the same dose. Prednisone is often started in patients who are in a lupus flare at the onset of

Data are mixed on whether progesterone supplements improve pregnancy outcomes

pregnancy to control lupus activity and maximize the chance of a successful pregnancy. For patients with recurrent pregnancy loss, the dose should be maintained throughout the first trimester and then tapered. Often, patients with active SLE or with multiorgan involvement are co-managed by a rheumatologist.

Prednisone has not been shown to be associated with congenital anomalies in humans, but intrauterine growth retardation and gestational diabetes may develop in patients who are maintained on prednisone throughout pregnancy. However, active SLE is also associated with poor fetal outcome.

■ THROMBOPHILIAS

Patients with an inherited thrombophilia may have recurrent pregnancy loss due to coagulopathy, especially in the second or third trimester. Thrombosis of the spiral arterioles in the intervillous space may impair placental perfusion and lead to abnormal uteroplacental circulation, causing late fetal loss, intrauterine growth retardation, and placental abruption. Whether pregnancy loss in the first trimester also occurs by this mechanism is uncertain.⁵³

The most common inherited thrombophilic disorders are the factor V Leiden mutation and the prothrombin G20210A mutation. Factor V Leiden, an autosomal-dominant mutation, is present in 5% of white people. Dizon-Townson et al,⁵⁴ in a case-control study, found that the prevalence of the factor V Leiden mutation was twice as high among the mothers of 139 spontaneously aborted fetuses compared with unselected pregnant women. On the other hand, Lockwood⁵⁵ states that whether this mutation is a factor in first-trimester pregnancy loss is uncertain.

Other inherited thrombophilias include deficiencies of protein S, protein C, and antithrombin, which produce a hypercoagulable state that is associated with thromboembolic and other obstetrical complications during pregnancy. Whether they cause recurrent pregnancy loss is unclear.

Low-molecular-weight heparin is recommended for patients with recurrent pregnancy loss or early fetal demise associated with thrombophilia.

■ INFECTION

No evidence suggests that infection causes recurrent pregnancy loss, although infections with *Listeria monocytogenes*, cytomegalovirus, and *Toxoplasma gondii* may cause sporadic losses. To plausibly cause repeated loss, an organism must persist in the genital tract, but possible culprits, including toxoplasmosis, rubella, cytomegalovirus, and herpes infections, do not fulfill the criteria for recurrent loss, ie, persistence or spontaneous recurrence of infection involving maternal, fetal, or placental tissues.⁵⁶

■ ENVIRONMENTAL AGENTS

Data are limited linking recurrent pregnancy loss with environmental agents, occupational factors, or stress. Sporadic losses have been associated with anesthetic agents,⁵⁷ smoking, alcohol, and caffeine.⁵⁸

■ CLINICAL EVALUATION

Evaluation of a patient with recurrent pregnancy loss should include a detailed medical, surgical, family, genetic, and menstrual history. Patients should be questioned about their use of drugs, tobacco, alcohol, and caffeine, and whether they have been exposed to occupational hazards.

All prior pregnancies should be examined in detail, with attention to gestational age at time of loss, complications, ultrasonography findings, pathology reports, and chromosomal analyses.

Physical examination

The physical examination should include evaluation of the thyroid for enlargement or goiter, evaluation of the breasts for galactorrhea, and examination for hirsutism, which could indicate the patient has thyroid dysfunction or hyperprolactinemia.

The pelvic examination should include evaluation of the cervix if the patient may have been exposed to DES or has had cervical surgery. An enlarged uterus may be associated with fibroids, and enlarged ovaries may indicate polycystic ovary disease.

The most common inherited thrombophilic disorders are factor V Leiden and prothrombin G20210A mutations

Laboratory tests

Laboratory tests should be selected on the basis of findings in each patient's history and examination.

Blood tests may include a complete blood cell count, antinuclear antibodies, anticardiolipin antibodies, lupus anticoagulant, prolactin levels, and thyrotropin levels. Chromosomes of both parents should be evaluated.

Evaluation for thrombophilia includes testing for protein C, activated protein C, the factor V Leiden and prothrombin mutations, protein S, antithrombin, and the fasting homocysteine level.

Timed endometrial biopsy can help confirm ovulation or evaluate a luteal phase defect. Although this procedure is controversial, it remains the best test for evaluating endometrial abnormalities.

Testing for cytomegalovirus, *Listeria*, and toxoplasmosis is possible but is not generally recommended because these agents are associated with sporadic rather than recurrent pregnancy loss.

Imaging tests

Hysterosalpingography, three-dimensional saline ultrasonography,⁵⁹ and magnetic resonance imaging can help detect uterine abnormalities.

Hysteroscopy and laparoscopy are useful if other tests have indicated abnormalities that should be confirmed, such as a uterine septum. In the future, these procedures are likely to be replaced by three-dimensional ultrasonography or magnetic resonance imaging.

Review of pathology

If possible, pathology slides from the aborted pregnancy should be reviewed by a placental pathologist, especially in cases in which no specific abnormalities were found during the evaluation or in the initial pathology report.

Additional tests

The usefulness of additional testing for natural killer cells, antipaternal antibodies, blocking antibodies, cytotoxic antibodies, and HLA antibody typing is questionable: whether these antibodies relate to pregnancy loss is doubtful.

■ MONITORING THE PREGNANCY

Human chorionic gonadotropin beta should be measured quantitatively starting at the patient's missed period and be repeated 2 or 3 times per week until fetal viability is established.

Ultrasonography should be done at 6 to 6-1/2 weeks and repeated every 10 to 14 days until approximately 12 weeks of gestation. Frequent and early ultrasonography has several advantages: a viable fetus is a good indicator that the pregnancy will be successful, seeing a viable fetus offers the mother significant psychological benefit, and an unsuccessful pregnancy can be detected quickly, increasing the chance that placental tissue can be obtained for chromosomal analysis.

Genetic testing with chorionic villous sampling or amniocentesis should be offered.

■ PSYCHOLOGICAL SUPPORT SHOULD BEGIN EARLY

Psychological support and counseling should start before conception and continue throughout the first trimester and beyond. Patients should attend a reproductive loss clinic if available.

Loss of a pregnancy at any gestational age can trigger a significant grief reaction. Early loss was once considered less traumatic than stillbirth or neonatal death, but a better predictor of the severity of a grief reaction may be the degree of attachment to the pregnancy.⁶⁰

Women who suffer recurrent pregnancy loss may experience cumulative grief and increasing ambivalence during subsequent pregnancies. Patients may develop a protective emotional shield during pregnancy in an attempt to reduce the pain of impending loss.

Seeing a healthy fetus with early ultrasonography may help a woman who has suffered recurrent pregnancy loss form an attachment during pregnancy. On the other hand, facilitating early bonding can backfire if the pregnancy is again unsuccessful.⁶¹

■ PROGNOSIS IS GOOD

Various factors influence the risk of a recurrent loss, which increases from 14% to 21% after

For couples with recurrent pregnancy loss, counseling should start before conception

one miscarriage, to 24% to 29% after two losses, to 31% to 33% after three losses. The risk of miscarriage decreases after a pregnancy that results in a live birth.

A positive attitude when managing cou-

ples with recurrent pregnancy loss is important and statistically justified: the chance of eventually having a successful pregnancy is about 70% regardless of evaluation findings and treatments.¹⁸



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