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ACOG BULLETIN

Management of recurrent early pregnancy loss

ABSTRACT

Recurrent pregnancy loss is a common clinical problem in reproduction, occurring in approximately 1% of reproductive-aged women[1]. A definite cause is established in no more than 50% of couples, and several alleged causes of recurrent pregnancy loss are controversial. Moreover, in the field of recurrent pregnancy loss, inappropriate emphasis often is given to unproven hypotheses and poorly designed clinical studies. Seeking a solution, some patients and physicians explore less-well-accepted etiologies and empirical or alternative treatments. This bulletin will provide the practitioner with a rational, modern approach to the management of recurrent pregnancy loss. New and controversial etiologies will be presented so that the practitioner can discuss them with couples who have a history of recurrent pregnancy loss.

BACKGROUND

Broadly defined, pregnancy loss includes any type of loss of the conceptus from fertilized ovum to neonate. This bulletin covers the repetitive loss of recognized pregnancies in the first or early second trimester (<15 weeks of gestation). It usually is referred to as recurrent spontaneous abortion, miscarriage, or recurrent early pregnancy loss.

Recurrent abortion must be distinguished from sporadic spontaneous abortions that are nonconsecutive pregnancy losses occurring randomly during a woman's reproductive years. Sporadic pregnancy loss occurs in 10–15% of all clinically recognized pregnancies as first- or early second-trimester spontaneous abortions. Most of these pregnancy losses are clinically evident by the 12th week of gestation and are preembryonic or embryonic losses in which the demise of the conceptus precedes clinical features of pregnancy loss by one or more weeks.

This Practice Bulletin was developed by the ACOG Committee on Practice Bulletins – Obstetrics with the assistance of Sandra A. Carson, MD, and D. Ware Branch, MD. The information is designed to aid practitioners in making decisions about appropriate obstetric and gynecologic care. These guidelines should not be construed as dictating an exclusive course of treatment or procedure. Variations in practice may be warranted based on the needs of the individual patient, resources, and limitations unique to the institution or type of practice.

Recurrent pregnancy loss typically is defined as two or three or more consecutive pregnancy losses. Most women with recurrent pregnancy loss have recurrent pre-embryonic or embryonic losses. Recurrent fetal loss is less common, and recurrent fetal loss at or beyond 14 weeks of gestation is infrequent.

CAUSES OF RECURRENT PREGNANCY LOSS

Genetic Abnormalities

Parental Structural Chromosome Abnormalities

In approximately 2–4% of couples with recurrent pregnancy loss, one partner will have a genetically balanced structural chromosome rearrangement. Balanced translocations account for the largest percentage of these karyotypic abnormalities. They can cause pregnancy loss because segregation during meiosis results in gametes with duplication or deficiency of chromosome segments. Other genetically balanced structural chromosome abnormalities, such as chromosome inversions, account for a small percentage of abnormal parental karyotypes among couples with recurrent pregnancy loss.

Molecular Genetic Abnormalities

In the past decade, the development of techniques for DNA analysis has resulted in identification of molecular genetic abnormalities as causes of various human diseases. One report indicated that highly skewed X-chromosome inactivation is associated with otherwise unexplained recurrent pregnancy loss[2]. As yet, however, commercially available tests for this and other related molecular genetic abnormalities are not widely available.

Recurrent Preembryonic or Embryonic Aneuploidy

Analyses of karyotypes in consecutive abortions suggest that recurrent aneuploidy in the conceptus may be a cause of recurrent pregnancy loss. In one analysis of data, the karyotype of a second successive spontaneous abortion was abnormal in nearly 70% of cases when aneuploidy was found in the first abortus, but in only 20% of cases where the first abortus was chromosomally normal[3]. However, these aneuploid losses may have been a result of the older age of the mothers, rather than a nonrandom event in predisposed couples[4]. More recently, two groups of investigators using different techniques of analysis have shown that the next abortion in women with recurrent pregnancy loss was chromosomally abnormal in 48% or more of cases[5,6], raising the possibility of recurrent aneuploidy despite normal parental karyotypes. Supportive evidence comes from studies of preimplantation genetic studies of women with recurrent pregnancy loss in which more than 50% of embryos were found to have aneuploidy[7,8].

Hormonal and Metabolic Disorders

Luteal Phase Defect

The luteal phase defect (LPD) has long been thought to be a cause of spontaneous abortion, but the evidence linking LPD to recurrent abortion is subject to criticism. Investigators initially hypothesized that with LPD, the corpus luteum failed to make enough progesterone to establish a mature endometrial lining suitable for placentation. This theory has evolved to implicate poor follicular-phase oocyte development, which results in disordered estrogen secretion and subsequent dysfunction of either the corpus luteum or progesterone effect. In turn, these effects could result from excess luteinizing hormone or hyperandrogenic states. Some investigators believe that LPD is a common cause of recurrent pregnancy loss, accounting for approximately 25–40% of cases. However, studies of this disorder have not included concurrently tested controls, a serious oversight given that normal women have endometrial histology suggestive of LPD in up to 50% of single menstrual cycles and 25% of sequential cycles[9]. Thus, the association between LPD and recurrent pregnancy loss remains speculative.

Polycystic Ovary Syndrome

Investigators have found that 36–56% of women with recurrent pregnancy loss have polycystic ovary syndrome (PCOS) diagnosed by ultrasound examination of the ovaries[10–12]. One group[11] demonstrated that more than half of women with ultrasonographic evidence of PCOS also had hypersecretion of luteinizing hormone. But ultrasonographic evidence of PCOS in women with recurrent pregnancy loss does not predict worse pregnancy outcome than in women with recurrent pregnancy loss without PCOS[10,12,13]. However, it has been reported that women with PCOS who miscarry have higher levels of circulating androgens[10]. There is no known therapy for reducing the risk of pregnancy loss in women with PCOS.

Other Metabolic Abnormalities

Maternal endocrinologic and metabolic disorders have been implicated as a cause of recurrent pregnancy loss. Women with poorly controlled type 1 (insulin-dependent) diabetes mellitus have an increased rate of abortion[14].

However, there is no evidence that asymptomatic endocrinologic or metabolic disorders, such as mild thyroid disease or glucose intolerance, cause recurrent pregnancy loss.

Uterine Anatomic Abnormalities

Congenital uterine abnormalities have been associated most often with second-trimester pregnancy loss. However, 10–15% of women with recurrent early pregnancy loss have congenital uterine abnormalities. The most common malformations associated with pregnancy loss are variations of the double uterus (bicornuate, septate, or didelphic), with septate uterus predominating. The contribution of arcuate uterus to recurrent pregnancy loss is debated. A recent study using three-dimensional ultrasonography and hysteroscopy found that 15% of 61 women with recurrent pregnancy loss had an arcuate uterus, compared with only 3% of more than 1,000 women attending a gynecology clinic[15,16]. Other investigators doubt an association between an arcuate uterus and recurrent pregnancy loss[17,18]. Severe uterine synechiae (Asherman's syndrome) and uterine abnormalities associated with in utero exposure to diethylstilbestrol also may be associated with pregnancy loss. An association between submucosal leiomyoma and recurrent pregnancy loss is controversial.

Some investigators believe that poor vascularization of the uterine septum is a cause of spontaneous abortion, but studies provide mixed results. In one study of 12 pregnancies, all four successful pregnancies became implanted away from the uterine septum[19]. However, the vascular density in uterine septa removed at the time of metroplasty is similar to that of the normal uterine wall[20].

Infectious Causes

Certain infectius agents, such as *Listeria monocytogenes*, are known to cause sporadic pregnancy loss, but no infectious agent has been

proven to cause recurrent pregnancy loss. In addition, *Toxoplasma gondii* and some viruses (eg, rubella, herpes simplex, and measles viruses; cytomegalovirus; and coxsackieviruses) have been linked to sporadic abortion. However, none has been convincingly associated with recurrent pregnancy loss.

Environmental Factors, Occupational Factors, and Personal Habits

Although a common concern of patients, environmental factors rarely have been linked to sporadic pregnancy loss, and no associations between environmental factors and recurrent pregnancy loss have been established. Likewise, occupational exposures to certain products, such as certain organic solvents, rarely have been linked to sporadic pregnancy loss[21]. However, no associations between occupational exposure or working itself and recurrent pregnancy loss have been established.

Study results are conflicting on the association of smoking, use of alcohol, and use of caffeine with sporadic pregnancy loss. They may act in a dose-dependent fashion or synergistically to increase the rate of sporadic pregnancy loss. However, none of these habits has been associated with recurrent pregnancy loss. Exercise does not appear to increase the rate of sporadic pregnancy loss, particularly in women in good physical condition, and there are no studies of exercise effects in women with recurrent pregnancy loss.

Thrombophilia

The most common inherited thrombophilic disorders are factor V Leiden and prothrombin G20210A mutation, found in approximately 8% and 3%, respectively, of Caucasian women in the United States. These mutations are associated with approximately 25% of isolated thrombotic events and approximately 50% of familial thrombosis. Other less common thrombophilias include deficiencies of the anticoagulants protein C, protein S, and antithrombin III. Some investigators have[22–25], and some have not[13,26–29], found that one or more of these thrombophilic mutations are associated with recurrent pregnancy loss. In two studies[22,30], however, these heritable thrombophilias were associated with second- or third-trimester fetal loss, not with first-trimester loss. Also, one group has found that next pregnancy outcomes among women with recurrent pregnancy losses are no different with or without factor V Leiden[13].

Despite the recent interest in this field, no treatment trials have been performed. Thus, which therapy, if any, is effective in promoting successful pregnancy among women with recurrent pregnancy loss and thrombophilia is uncertain.

Autoimmune Disorders

Antiphospholipid Antibodies

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by the presence of significant levels of antiphospholipid antibodies and one or more clinical features, among which are recurrent pregnancy loss, fetal death, and thrombosis[31]. Antiphospholipid syndrome may occur as a primary condition in women with no other recognizable autoimmune disease, or as a secondary condition in patients with underlying autoimmune disease (eg, systemic lupus erythematosus). The diagnosis of APS is made by demonstrating lupus anticoagulant, anticardiolipin antibodies, or both.

Some investigators have found that a small percentage of women with recurrent pregnancy loss who test negative for anticardiolipin antibodies have antibodies to other phospholipids, such as phosphatidylserine or phosphatidylethanolamine[32]. Others have found that no such relationship exists[33] or that testing for antibodies other than lupus anticoagulant and anticardiolipin antibodies does not increase the rate of diagnosis of APS[34]. In addition, assays for phospholipid-binding antibodies other than anticardiolipin are not standardized. Finally, there is no proven treatment for women with recurrent pregnancy loss and phospholipid-binding antibodies other than lupus anticoagulant and anticardiolipin antibodies.

Thyroid Antibodies

Autoantibodies to thyroid antigens (thyroglobulin and thyroid peroxidase) are associated with an increased rate of pregnancy loss if identified in early pregnancy or immediately before pregnancy[35,36]. However, current evidence does not allow a definite conclusion regarding the association of antithyroid antibodies and recurrent pregnancy loss, and no treatment options have been proven beneficial.

Antinuclear Antibodies

A significant percentage (approximately 15%) of women with recurrent pregnancy loss have detectable antinuclear antibodies (ANA)[37,38]. Without treatment, subsequent pregnancy outcomes among women with a positive ANA test result are similar to those among women with a negative ANA test result. More important, a randomized treatment trial of women with recurrent pregnancy loss and a positive autoantibody result, including ANA, found no difference in pregnancy outcomes between women treated with prednisone and low-dose aspirin and women treated with placebo[39]. Thus, currently available data do not support testing women with recurrent pregnancy loss for ANA.

Alloimmune Disorders

Alloimmune traits – immunologic difference between individuals – have been proposed as factors between reproductive partners that cause otherwise unexplained recurrent pregnancy loss. The tendency for 1) partners with recurrent loss to share human leukocyte antigens, 2) the female partner to fail to produce serum "blocking factor," and 3) the female partner to produce antileukocytotoxic antibodies against paternal leukocytes have been described. Others have refuted the significance of each of these factors. In addition, no test for these traits provides results that predict the next pregnancy outcome in patients treated or untreated for recurrent pregnancy loss[40,41]. More recently, some researchers have claimed that flow cytometric assays for maternal antibodies to paternal leukocytes are useful in evaluating couples with recurrent pregnancy loss. However, studies of these assays have lacked appropriate controls and are of unproven value in terms of indicating an efficacious treatment.

More recent investigations of the maternal-fetal immunologic relationship suggest that pregnancy losses may result from dysregulation of normal immune mechanisms, probably operating at the maternal-fetal interface. It has been proposed that a predominance of Th-2 lymphocytic cytokines is crucial for successful pregnancy and that Th-1 lymphocytic cytokines, such as interferon-γ and tumor necrosis factor-α, adversely affect embryo and trophoblast viability[42–44]. The presence of natural killer (NK)-like cells secreting a transforming growth factor at the maternal-fetal interface may be necessary for successful pregnancy[45]. Clinical studies have found decreased[45,46] or increased[47] numbers of these cells in the luteal phase endometria of women with recurrent pregnancy loss. Pregnancy outcomes may be worse in women with recurrent pregnancy loss found to have increased numbers of NK-like cells in the luteal phase endometria[48], but further studies are necessary before valid conclusions can be drawn. One group has found that an embryotoxic factor, similar to interferon-γ, generated by patient leukocytes in vitro predicted pregnancy failure in the next pregnancy attempt[44], but others have not been able to reproduce these findings[49]. Others have found that an increased percentage of circulating NK cells in women with recurrent pregnancy loss predicts a relatively poor next pregnancy outcome[50,51]. There is, however, no proven treatment for women with recurrent pregnancy loss found to have increased percentages of circulating NK cells.

Unexplained Recurrent Pregnancy Loss

In 50% or more of couples with recurrent pregnancy loss, an evaluation, including parental karyotypes, hysterosalpingography or hysteroscopy, and antiphospholipid antibody testing will be negative. Therefore, a majority (approximately 50–75%) of couples with recurrent pregnancy loss will be no certain diagnosis. Informative and sympathetic counseling appears to serve an important role in this situation. Live birth rates between 35% and 85% are commonly reported in couples with unexplained recurrent pregnancy loss who undertake an untreated or placebo-treated subsequent pregnancy[12,52–55]. Meta-analysis of randomized, prospective studies suggests that 60–70% of women with unexplained recurrent pregnancy loss will have a successful next pregnancy[56], figures that many couples will view as optimistic.

CLINICAL CONSIDERATIONS AND RECOMMENDATIONS

- ***When is a diagnosis of recurrent pregnancy loss appropriate?***

  Traditionally, recurrent pregnancy loss has been defined as three consecutive spontaneous abortions. However, the risk of abortion after two successive abortions (30%) is clinically similar to the risk of recurrence among women with three or more consecutive abortions (33%)[37,57–66]. Thus, patients with two or more consecutive spontaneous abortions are candidates for an evaluation to determine the etiology, if any, for their pregnancy losses.

  The number of previous pregnancy losses influences the likelihood of successful pregnancy. One study reported recurrent pregnancy loss rate of 29%, 27% 44%, and 53% after 3,4,5, and 6 or more recurrent pregnancy losses, respectively[67]. In addition, maternal age influences the current pregnancy loss rate[67,68], with a recurrent pregnancy loss rate of approximately 25% in women aged 30 years or younger and a recurrent pregnancy loss rate of 50-60% in those 40 years or older. Some investigators have found the pregnosis for a successful pregnancy is increased by 10–20% in women with at least one previous live birth[58,69], but others did not[67].

- ***Should all couples with recurrent pregnancy loss have chromosomal analysis performed?***

  Parents with recurrent pregnancy loss should be analyzed for balanced chromosome abnormalities because: 1) couples would like to know why they are experiencing repetitive pregnancy loss; 2) a couple in which one partner carries a balanced chrosome abnormality is at increased risk for having a fetus with an unbalanced chromosome

abnormality and may benefit from prenatal genetic testing; and 3) the apparently normal offspring of a couple in which one partner carries a balanced chromosome abnormality is at risk for carrying the same balanced chromosome abnormality and, thus. is at risk for reproductive complications.

Balanced chromosome abnormalities occurring in one partner are relatively infrequent among couples with only recurrent pregnancy loss but no other adverse perinatal outcomes (eg, stillborns, anomalous infants). One study reported that of couples with recurrent loss, only 2.4% of female partners and 1.6% of male partners with a history of stillbirths or anomalous infants had a balanced chromosome abnormality, compared with 4.6% of female partners and 1.7% of male partners with a history of adverse perinatal outcomes[70]. However, no historic factor unequivocally allows the clinician to determine which couples may benefit from karyotype analyses. In addition, phenotypically normal offspring do not exclude the possibility of a balanced abnormality in a couple with recurrent pregnancy loss.

Parental cytogenetic analysis should be offered to all couples with recurrent pregnancy loss. In addition, all couples in which one partner has been found to have a balanced translocation or inversion should be offered prenatal genetic diagnosis because of the increased risk of a karyotypic abnormality in the conceptus.

In addition, many experts obtain a karyotype of the abortus tissue when a couple with recurrent pregnancy loss experience a subsequent spontaneous abortion. The rationale is that if the abortus is aneuploid, the physician and patent may conclude that a maternal cause of pregnancy loss is excluded. Also, an abnormal abortus karyotype is a legitime explanation for the loss that may provide a source of comfort to the couple. However, no published evidence supports these hypotheses, and definite recommendations for routinely obtaining abortus karyotypes cannot be made.

- ***How should the uterine cavity be evaluated in a woman with recurrent pregnancy loss, and how should abnormal findings be treated?***

  Uterine anatomic abnormalities are diagnosed by hysterosalpingography, hysteroscopy, or sonohysteroscopy. Three-dimensional ultrasonography, although not routinely available in the United States, also has been shown to be useful in the diagnosis of uterine abnormalities. Suspicious or confusing cases can be evaluated further by magnetic resonance imaging. However, the relationship between uterine abnormalities and recurrent pregnancy loss is uncertain, and some authorities do not recommend routinely evaluating the uterine cavity by hysterosalpingography, hysteroscopy, or sonohysteroscopy[71].

  No prospective, controlled trials have proved that the correction of uterine anatomic abnormalities benefits the next pregnancy outcome. Retrospectively analyzed case series suggest that 70–85% of women with recurrent pregnancy loss with bicornuate and septate uteri who undergo surgical correction will deliver viable live born infants in their next pregnancies[72], but these seemingly excellent results are subject to criticism because of the methods of patient selection and the lack of controls.

  Hysteroscopic resection has been used successfully for treatment of the uterine septum, and subsequent pregnancy results are comparable to those for metroplasty[72]. It is preferable to abdominal surgery because it is an outpatient procedure with low morbidity and allows for labor with expected vaginal delivery. Uterine synechiae also may be treated hysteroscopically.

- ***Should women with recurrent pregnancy loss be evaluated for luteal phase defect?***

  Although assessment of luteal phase progesterone production or effect is firmly entrenched in the traditional evaluation of women with recurrent pregnancy loss, the evidence supporting this practice is scant. The endometrium is considered out of phase when the histologic dating lags behind the menstrual dating by 2 days or more. However, interobserver variation in the interpretation of the biopsies is considerable[73], and modest intra-observer variation occurs[74]. Because of 1) such variation, 2) the frequent finding of out-of-phase endometrial histology in normal women, and 3) the consistent expression of luteal phase defect in affected women, luteal phase defect is diagnosed only when two consecutive biopsies are out of phase. The measurement of luteal phase progesterone concentrations is not an adequate method for diagnosing or excluding luteal phase defect.

  No property designed studies have evaluated the role of progesterone treatment in women with recurrent pregnancy loss with luteal phase defect. Two meta-analyses of studies from the 1950s and 1960s reached conflicting conclusions regarding the efficacy of progesterone treatment in variously selected women with recurrent abortion[75,76]. The

studies included in these meta-analyses are difficult to interpret because they 1) did not assess patients for luteal phase defect using currently accepted criteria, 2) employed 17-OH progesterone caproate or medroxyprogesterone as treatment, 3) used various inclusion criteria, and 4) entered patients after pregnancy had progressed to at least 8 weeks of gestation. Also, these studies totaled only 130 patients, and one of them[77] was not randomized. In addition, in a more recent randomized trial, a subgroup of women with PCOS and three or more miscarriages were randomized to treatment with either progesterone or placebo pessaries[78]. There was no difference in the pregnancy outcomes.

Human chorionic gonadotropin has been used in an attempt to stimulate the corpus luteum support of pregnancy in women with recurrent abortion. One international multicentered trial randomized 75 women to receive either placebo or 10,000 IU of human chorionic gonadotropin at the first diagnosis of pregnancy and 5,000 IU weekly, thereafter[79]. No significant difference in the successful pregnancy rates (83% versus 79%) between the groups was found.

In summary, the relationship between the luteal phase defect and recurrent pregnancy loss remains a subject of controversy. It has not been shown conclusively that progesterone treatment or corpus luteum support influences pregnancy outcome in women with recurrent pregnancy loss.

- ***Should thyroid tests and tests for glucose intolerance be performed in women with recurrent pregnancy loss?***

  An association between recurrent pregnancy loss and asymptomatic endocrinologic or metabolic disorders such as mild thyroid disease or glucose intolerance has not been established. Thus, tests for thyroid dysfunction or glucose intolerance are not required in the evaluation are not required in the evaluation of otherwise normal women with recurrent pregnancy loss.

  An association between antithyroid antibodies and recurrent pregnancy loss has been reported by some investigators[31,80–83]. Very few patients identified in these studies are clinically hypothyroid, and less than 20% have abnormal thyroid-stimulating hormone test results[80]. In addition, no treatments have proved to benefit next pregnancy outcome in women found to have antithyroid antibodies. Thus, tests for antithyroid antibodies are not required in the evaluation of women with recurrent pregnancy loss.

- ***Should women with recurrent pregnancy loss be evaluated for possible infectious causes, and should they be treated?***

  Endocervical *Chlamydia* and *Mycoplasma* have been implicated as causes of recurrent pregnancy loss, but study results are conflicting. Bacterial vaginosis may be associated with midtrimester pregnancy loss[84,85] and one study found an increased rate pregnancy loss in women with bacterial vaginosis undergoing in vitro fertilization[86]. However, there is no direct evidence(confirmed by cultures) of *Chlamydia*, *Mycoplasma*, and organisms causing bacterial vaginosis in systematically analyzed recurrent abortus specimens. These infectious agents are very common. *Mycoplasma* may be recovered from the endocervix of one third of sexually active adults. One group of investigators found that women with recurrent pregnancy loss have a significantly higher rate of endometrial colonization with Ureaplasma urealyticum compared with controls, raising the speculation that endometrial (but not endocervical) colonization with *Mycoplasma* may play a role in recurrent pregnancy loss. Existing nonrandomized studies of the effects of antibiotic treatment on subsequent pregnancy outcome in women with endocervical *Mycoplasma* colonization have yielded conflicting results.

  Currently routine serologic or endocervical cultures for *Chlamydia* or *Mycoplasma* and vaginal evaluation for bacterial vaginosis are not useful in evaluating otherwise healthy women presenting with recurrent abortion. In addition empiric treatment with antibiotics in the absence of documented infection is not warranted.

- ***Should women with recurrent pregnancy loss be evaluated for antiphospholipid syndrome?***

  Antiphospholipid syndrome is associated with pregnancy loss in 3–15% of women with recurrent pregnancy loss[33,87–90]. Some investigators have emphasized the relationship between APS and second- or early third- trimester fetal death[91], whereas others have found that a small percentage of women with recurrent first-trimester pregnancy loss have antiphospholipid antibodies[90]. Women with previous fetal death[33,92] and high levels of anticardiolipin immunoglobulin G (IgG) antibodies[92] are at the greater risk of fetal loss in subsequent pregnancies. Therefore, women with recurrent pregnancy loss should be tested for antiphospholipid syndrome using standard assays for anticardiolipin antibodies and lupus anticoagulant.

Antihosopholipid syndrome is identified in a woman with recurrent pregnancy loss by the detection of lupus anticoagulant, β_2-glycoprotein, I-dependent anticardiolipin antibodies, or both on two occasions at least 6 weeks apart[31]. The IgG isotype if anticardiolipin is most relevant clinically, but tests repeatedly positive for IgM anticardiolipin may be used to make the diagnosis. In individuals demonstrating only anticardiolipin antibodies, definite APS is diagnosed when the antibody levels are repeatedly 20 units or greater. Repeatedly positive test results for anticardiolipins antibodies with levels of less than 20 units are of uncertain significance.

Women with APS benefit from treatment with heparin and low-dose aspirin during pregnancy. Two studies have shown that women with recurrent early pregnancy loss and positive test results for antiphospholipid antibodies benefit from treatment with low-dose aspirin and heparin. Successful pregnancy rates for these women are 70–75%, compared with less than 50% for the untreated patients[93,94]. These studies used heparin dosages in the range of 10,000–25,000 U/d, and neither study included women with a history of thrombosis or systemic lupus erythematosus.

- ***Should women with recurrent pregnancy loss be evaluated for thrombophilias?***

  The role of thrombophilia in recurrent pregnancy loss is a controversial subject of current research interest. Tests for factor V Leiden, the prothrombin G20210A mutation, or deficiencies of protein C, protein S, or antithrombin III should be considered in cases of otherwise unexplained fetal death in the second or third trimester. However, the role of these heritable thrombophilias in recurrent early pregnancy loss is uncertain at present, and tests for these thrombophilias are not required as part of the evaluation. Whether antithrombotic treatment improves subsequent pregnancy outcomes in women with evidence thrombophilia is uncertain.

- ***Should women with recurrent pregnancy loss be evaluated for possible alloimmune causes?***

  Results of tests for human leukocyte antigen types, maternal serum blocking factors, or maternal antileukocytic antibodies directed against the male partner's leukocytes have not been shown to predict subsequent pregnancy outcome. Therefore, testing is not recommended, and treatment is not warranted. Luteal phase biopsy to determined the status of NK-like cells is not recommended because of mixed results in the literature, the uncertainty of prognostic implications, and the lack of an effective treatment. Finally, in the absence of a proven effective treatment, tests for embryotoxic factor determination of the presence of circulating NK cells in women with recurrent pregnancy loss is not beneficial.

- ***Is paternal lymphocyte immunization or intravenous immune globulin (IVIG) an effective treatment for recurring pregnancy loss.***

  The most widely used immunotherapeutic treatment regimen for women with unexplained recurrent loss involves immunizing the female partner with the male partner's leukocytes. Of several randomized, prospective studies[53,54,95], only one found out a benefit to leukocytes immunization[96]. The largest trial, and the only multicenter effort, found that women undergoing leukocyte immunization actually had a higher rate of pregnancy loss than placebo controls[55], suggesting that the treatment may be harmful. In addition, there is no consensus regarding patient selection or the dose, route, or timing of leukocyte immunization, and immunization using viable leukocytes carries risks similar to those of blood transfusion, including the transmission of viral diseases.

  The second immunomodulatory therapy used as a treatment for recurrent pregnancy loss is IVIG[97]. Initial interest in this therapy derives from the observation that IVIG contains antibodies that block antibody-mediated immune damage[98]. Other known immunomodulating effects of IVIG include T cell receptor blockade, inhibition of NK-cell activity, inhibition of Th-1 cytokine secretion. Fc receptor blockade, complement inactivation, down-regulation of B cell responsiveness, and enhanced T cell suppressor cell function[99]. However, only one of five randomized trials using IVIG treatment in women with recurrent pregnancy loss demonstrated a benefit[52]; results of the other were negative[100–103]. In addition, the results of two metaanalyses also were negative[104–105].

SUMMARY

The following recommendations are based on good consistent scientific evidence (Level A):

- Women with recurrent pregnant loss should be tested for lupus anticoagulant and anticardiolipin antibodies using standard assays. If tests results are positive for the same antibody on two consecutive occasions 6–8 weeks apart, the patient should be treated with heparin and low-dose aspirin during her next pregnancy attempt.

- Mononuclear cell (leukocyte) immunization and IVIG are not effective in preventing pregnancy loss.

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- An association between the luteal phase defect and recurrent pregnancy loss is controversial. If a diagnosis of luteal phase defect is sought in a women with recurrent pregnancy loss, it should be confirmed by endometrial biopsy.

- Luteal phase support with progesterone is of unproven efficacy.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- Couples with recurrent pregnancy loss should be tested for parental balanced chromosome abnormalities.

- Women with recurrent pregnancy loss and a uterine septum should undergo hysteroscopic evaluation and resection.

- Cultures for bacteria or viruses and tests for glucose intolerance, thyroid abnormalities, antibodies to infectious agents, antinuclear antibodies, antithyroid antibodies, paternal human leukocyte antigen status, or maternal antipaternal antibodies are not beneficial and, therefore, are not recommended in the evaluation of otherwise normal women with recurrent pregnancy loss.

- Couples with otherwise unexplained recurrent pregnancy loss should be counseled regarding the potential for successful pregnancy without treatment.

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