

Recurrent Miscarriage

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Recurrent miscarriage is defined as the occurrence of three consecutive pregnancy losses during the first trimester. Although it affects only 1% of all couples, it is a most frustrating experience for the patient as well as for the clinician. Frustrating for the couple because they rarely obtain clear-cut reasons for the repeated failure to sustain a pregnancy, nor the prospect of a fail-safe treatment; frustrating for the clinician, too, because it is extremely difficult to disentangle the causes of sporadic and unavoidable miscarriage—most of which have a genetic background—from those of recurrent miscarriage. In the latter case, an underlying defect can potentially be detected and, ideally, should be amenable to treatment. Unfortunately, however, this is rather exceptional. In this paper, literature on genetic, anatomic, endocrine, metabolic, and autoimmune aspects of recurrent miscarriage are reviewed, and a survey of meaningful investigations and treatment is provided.

Introduction

The exact prevalence of recurrent miscarriage is dependent on its definition, but it can be estimated to occur in 1% to 3% of pregnancies. Extending the definition of miscarriage to the period of fetal viability, or including incidences of two consecutive miscarriages without a previous birth or three miscarriages whether or not interspersed with a term delivery of a healthy child, increases the prevalence. This paper is focused on recurrent miscarriage according to the strict definition of the occurrence of three consecutive, first-trimester losses of pregnancy.

Pregnancy loss is very common and, in most cases, it can be considered as nature's method to select for a genetically normal offspring. In fact, since the seminal studies by Boué *et al.* [1] and Hassold *et al.* [2], it has been accepted that at least 50% of clinical abortions result from chromosomal abnormalities. The incidence of fetal chromosomal abnormalities is gradually decreasing with duration of pregnancy to less than 1% among live-born children. By extrapolating this trend toward the time of conception, it can be argued that most pregnancy losses occur at a preclinical stage and that most of

them are due to a genetic abnormality. This hypothesis has, in fact, been corroborated by the data collected by Wilcox *et al.* [3]. They investigated the overall incidence of abortion by measuring daily urinary concentrations of human chorionic gonadotropin (hCG) during menstrual cycles. With an hCG level above 0.025 ng/mL on 3 consecutive days as a criterion of early pregnancy, they found that 22% of pregnancies ended before pregnancy was clinically detected, and the clinically recognized loss rate was 12%. That human reproduction is beset by a high rate of abnormal conceptuses, most of which will be eliminated by the time pregnancy can be clinically recognized, is substantiated by the low fecundity of the human species and the low success rate of in vitro fertilization programs. Cytogenetic analysis of preimplantation embryos has revealed that only 50% of morphologically normal-looking embryos are chromosomally normal [4].

Risk Factors

Age and success of previous pregnancies are two independent risk factors that affect the loss rate. Many authors have observed an increasing risk of fetal death, in particular spontaneous abortion, with increasing maternal age [5,6]. The association of age of the mother and the increased likelihood of chromosomal abnormalities is manifested by the age-related increase of trisomy 21 and cytogenetic studies on preimplantation embryos [7]. Outcome of previous pregnancies is another decisive factor in the risk of pregnancy loss. For young women who have never experienced a loss, the rate of a clinical miscarriage is as low as 5% [8]. The risk increases to approximately 30% for women with three or more losses but with a previous live-born infant [9] and up to 50% for women without a live-born infant [10]. From these data, it is evident that some women are at particular risk for losing their pregnancy and that there must be an underlying cause for it. Before dealing with possible mechanisms of recurrent miscarriage, it should be remembered that investigations are necessarily confounded by the fact that the same mechanisms as those in sporadic miscarriage can be involved. The same uncertainty applies for the evaluation of any treatment. It is estimated that approximately 33% of women with so-called recurrent miscarriage will have had three consecutive sporadic miscarriages by chance [11].

Etiology

The purported causes of recurrent miscarriage are multiple, ranging from genetic, environmental, infectious, meta-

bolic, and endocrine to purely anatomic ones. The best defined causes are parental chromosomal abnormalities, metabolic abnormalities, and anatomic abnormalities.

Genetic factors

Recurrent aneuploidy

The major cause of clinically recognized abortions is genetic. In order of frequency, the main chromosomal abnormalities are autosomal trisomies, polyploidy, and monosomy X. Most trisomies show a maternal age effect, with chromosomes 16 and 22 most commonly involved. Triploidy and tetraploidy account for 30% of chromosomally abnormal spontaneous abortions. Triploid fetuses are usually 69,XXY or 69,XXX and result from dispermic fertilization. Some triploid conceptuses present as a partial mole, characterized by a large gestational sac and cystic degeneration of the placenta. Tetraploidy rarely progresses beyond 4 or 5 weeks of gestation. Monosomy X is the single most common chromosomal abnormality among spontaneous abortions, accounting for 15% to 20% of all abortions. Chromosomal abnormalities are less likely to occur in spontaneous abortions for women younger than age 36 with a history of recurrent abortion [12]. Numeric chromosomal abnormalities, however, might be involved in both recurrent and sporadic losses.

Couples who are predisposed toward chromosomal abnormal conceptions will also be at increased risk for aneuploid live-born infants. In fact, women with a previous trisomy 18 or 21 pregnancy have an increased risk for a subsequent affected fetus [13]. Data from preimplantation embryos support the concept of recurrent aneuploidy in women with recurrent abortion [14].

Structural chromosomal abnormalities

Chromosomal translocation is the most common structural rearrangement involved in recurrent miscarriage. Cytogenetic screening of couples with recurrent abortion reveals that the prevalence of translocation in either parent is 3% to 5%, with the wife being affected twice as frequently as the husband [11]. Pregnancy loss and fetal abnormalities depend on the size, location, and type of structural rearrangement.

Mendelian and polygenic factors

Single-gene or polygenic factors, involved in fundamental cellular and reproductive processes, are rarely detected, but could be causing recurrent euploid losses. Skewed X inactivation, defined as 90% inactivation of one specific parental allele, has also been found more frequently in women with recurrent abortion [15•]. This is only one example of how mutant genes could be involved in repetitive losses of pregnancy.

Uterine abnormalities

There is no doubt that uterine defects can predispose women to reproductive difficulties, including first- and second-tri-

mester pregnancy losses, preterm labor and birth, and abnormal fetal presentation. These anatomic abnormalities can be congenital, including diethylstilbestrol-related abnormalities, or acquired, such as intrauterine adhesions or leiomyomata. In women with three or more consecutive spontaneous abortions who have undergone hysterosalpingography or hysteroscopic examination of their uteri, müllerian anomalies have been found in 8% to 10%. Women with müllerian anomalies might be predisposed to recurrent pregnancy loss because of inadequate vascularity to the developing embryo and placenta, reduced intraluminal volume, or cervical incompetence. Recurrent pregnancy losses resulting from a uterine septum, bicornuate uterus, intrauterine adhesions, and fibroids mainly occur in the second trimester of pregnancy. There is little evidence that surgical correction of uterine abnormalities is of any benefit in preventing recurrent first-trimester abortion.

Antiphospholipid antibody syndrome

The antiphospholipid antibody syndrome is a broad and heterogeneous entity encompassing patients with specific antibodies to both lupus anticoagulant and anticardiolipin, as well as nonspecific antinuclear antibodies. An association between second- and third-trimester pregnancy complications and fetal loss is well established. More controversial is the role of this syndrome in first-trimester losses. Many studies have found an increased prevalence of the antiphospholipid antibody syndrome, ranging from 7% to 25% in patients with recurrent, spontaneous abortion. Although a causal relationship between the antiphospholipid antibody syndrome and recurrent abortion is not yet firmly established, several therapeutic trials with low doses of aspirin, heparin, and corticosteroids have been conducted. The effects of these interventions were recently reviewed [16•]. The conclusion from 10 trials ($n = 627$) that fulfilled the inclusion criteria was that a combination therapy with aspirin and heparin might reduce pregnancy loss in women with antiphospholipid antibodies by 54%. The authors, however, wisely add that further large, randomized controlled trials with adequate allocation concealment are still necessary.

Hereditary thrombophilia

Although maternal hypercoagulability is undoubtedly a risk factor in successful reproduction, its role in first-trimester abortion is controversial. An association between recurrent abortion and factor V Leiden, prothrombin G20210A mutation, MTHFR C677T mutation, and other hereditary thrombophilias has been either supported or refuted in numerous studies. Because there is no evidence that antithrombotic therapy effectively prevents abortion, the American College of Obstetricians and Gynecologists' *ACOG Practice Bulletin* from 2001 does not recommend testing for heritable thrombophilias in women with recurrent abortion [17].

Immunologic abnormalities

Alloimmune aspects

For several decades it has been speculated that a defect in the maternal immune response to the semiallogeneic fetal graft could be involved in the mechanism of recurrent abortion. In fact, because the fetus is a semiallograft, some protective immunologic mechanisms should be involved to prevent maternal rejection. Paradoxically, opposing parental histocompatibility seems to be necessary for maintaining pregnancy by induction of protective blocking antibodies. This hypothesis makes sense from a teleologic and evolutionary point of view, because it would guarantee reproductive heterogeneity. Initially, studies showed greater parental sharing in aborters than in controls. Based on this observation, immunization of recurrent aborters with paternal or third-party leukocytes prior to a next pregnancy or repeated boluses of gamma globulins starting before or early in pregnancy have been tried. Although a beneficial effect was observed in some trials, a recent prospective randomized trial involving 183 women with three or more spontaneous abortions failed to show any beneficial effect of immunization [18•]. These negative results do not completely negate the role of parental human leukocyte antigen (HLA)-sharing in the mechanism of abortion in a subset of repetitive aborters. Two recent studies have shown that the sharing of certain HLA-G alleles by both partners was significantly associated with an increased risk for miscarriage [19•,20]. HLA-G and HLA-E are expressed on invasive trophoblast cells. This expression pattern is unique among HLA genes and suggests that HLA-G might be involved in interactions that are critical in establishing or maintaining pregnancy.

Although some studies have shown a beneficial effect of intravenous immune globulin in recurrent aborters, there is, as yet, no convincing evidence to support the systematic use of this treatment in the management of recurrent miscarriage [21•].

Antifetal and other antibodies

Maternal embryotoxic antibodies, induced by fetal or paternal antigens, could interfere with fetal survival. A classic example is the late pregnancy loss caused by anti-D antibodies in Rhesus-negative women. A rare cause of recurrent abortion is the presence of anti-P antibodies in mothers with the P blood group. Successful treatment of repeated pregnancy loss due to blood group P incompatibility by plasmapheresis has been reported.

Several studies have shown an increased frequency of antisperm antibodies among women experiencing repeated abortions. Pregnancy could be endangered by cross-reaction with paternally derived antigens, which might be essential for embryonic survival. In a large, prospective study, however, Simpson *et al.* [22] found no difference in the incidence of antisperm antibodies in women who experienced pregnancy loss and controls.

Endocrine and metabolic disorders

Diabetes, hypothyroidism, polycystic ovary syndrome (PCOS), luteal phase defect, and obesity are classically associated with an increased risk of miscarriage.

To address the effect of diabetes on the risk of spontaneous abortion, Mills *et al.* [23] enrolled 386 women with insulin-dependent diabetes and 432 women without diabetes before or within 21 days after conception and followed both groups prospectively. Incidence of pregnancy loss was the same in both groups (16.1% and 16.2%). Nonetheless, the diabetic women who had spontaneous abortions had higher fasting and postprandial glucose levels in the first trimester than those whose pregnancies continued to delivery.

Thyroid hormones used to be an empirical treatment for recurrent abortion, but clear evidence of an association between thyroid function and pregnancy wastage has never been provided. Antithyroid antibodies, however, are markers for an increased risk for abortion [11].

Although luteal phase defects have long been a paradigm of an endocrine cause of infertility and early pregnancy wastage, the definition, diagnosis, and, hence, the relation to infertility in general are still very confusing. Initially, a distinction was made between a short luteal phase and a deficient luteal phase. Particularly the latter was deemed to be associated with early pregnancy wastage. In principle, a deficient luteal phase can be diagnosed either by a timed endometrium biopsy or by one or more progesterone determinations in the luteal phase. The diagnostic criteria are, however, moot, and, moreover, owing to biologic cycle variations, it is extremely difficult to ascertain whether a deficient corpus luteum function will also occur in the actual cycle of conception. There is no solid evidence for a beneficial effect of supplementation of the luteal phase with either progesterone or hCG. This is not surprising, because the origin of luteal-phase deficiency could as well originate in the preceding follicular phase, making the endometrium unresponsive to an extraprogestational or a luteotrophic stimulus.

Both elevated luteinizing hormone (LH) levels and PCOS are associated with an increased incidence of abortion [24,25]. By inducing premature oocyte maturation and luteinization, high tonic serum concentrations of LH could have a deleterious effect on oocyte and embryo quality, and perhaps the endometrium. Gonadotropin-releasing hormone analog (GnRHa) used prior to human menopausal gonadotropin (hMG) administration might, therefore, improve the outcome of ovulation induction. The Cochrane Subfertility Review Group, after analyzing all randomized, controlled trials, concluded that there was no sufficient evidence that the combined use of GnRHa and hMG would increase the live-birth rate in these incidences [26]. More recent data refute the association between elevated LH levels or PCOS with the outcome of pregnancy [27,28]. Differences in diagnostic criteria

for PCOS and patient-selection bias could be at the origin of these conflicting opinions. More recently, the focus has been shifted to insulin resistance as a possible explanation for the increased incidence of abortion in patients with PCOS and/or obesity. Wang *et al.* [29] found a positive relationship between body mass index and the risk of spontaneous abortion in 2349 women who became pregnant after assisted reproductive technology treatment. The prevalence of insulin resistance, determined by elevated fasting insulin levels, was higher in women ($n = 74$) with recurrent abortion (27%) compared with controls (9.5%) [30•]. In two small, retrospective studies, metformin, an insulin sensitizer, was found to decrease the risk of spontaneous abortion [31,32].

Lifestyle and environmental factors

This is a very sensitive but also complicated issue. Couples experiencing recurrent pregnancy loss are often concerned that toxins within the environment contributed to their reproductive difficulty, but hard evidence on the impact of potential environmental toxins and other teratogens is not readily available. Heavy metals (such as lead and mercury), organic solvents, alcohol, and ionizing radiation are confirmed environmental teratogens, and exposure could contribute to pregnancy loss. Caffeine, cigarette smoking, and hyperthermia are suspected teratogens, and the teratogenic impact of pesticides remains unknown. As is everybody, pregnant women are exposed to many exogenous agents, some of which have been associated with the risk of fetal loss. Due to many confounding factors and recall bias, all case-controlled studies on this topic are susceptible to uncertainty. For repetitive losses to occur, some chronic exposure to toxic agents should be assumed. Consumption of five or more units of alcohol per week and 375 mg or more caffeine per day during pregnancy were found to increase the risk of spontaneous abortion [33,34], but some authors doubt the validity of most studies on caffeine intake and the risk of abortion [35]. An association between smoking and spontaneous abortion is accepted, but its effect presumably is small and could be totally explained by confounding factors.

Diagnosis and Management

Evaluation

According to the definition of recurrent abortion, investigation should only start after three losses. Indeed, most of the time, spontaneous abortion is a random event and represents the natural selection process, but the odds of losing a next pregnancy increases with each previous spontaneous abortion [36]. Additionally, the patient will insist on explanation for the previous loss, prognosis for the next pregnancy, and, most importantly, advice with regard to prevention. Clinical care of patients who have had one or more abortions should, therefore, be graduated, starting from the first abortion, with a careful history, physical and gynecologic examinations, and investigation of uterine and endocrine factors, particularly insulin resistance. After two or three losses, lupus anticoag-

ulant and anticardiolipin antibody should be determined, and a karyotyping from both parents should be obtained. Because there is no evidence that antithrombotic therapy prevents abortion, the expensive testing for thrombophilia factors cannot be recommended.

Treatment

Given the good outcome for most couples with unexplained recurrent abortion in the absence of treatment, it is difficult to recommend unproven therapies, especially if they are invasive and expensive. Explanation and the appropriate emotional support are the first and perhaps two most important ingredients of therapy. In fact, antenatal counseling and psychological support in pregnancy for couples with recurrent abortion and no abnormal findings resulted in a pregnancy success rate of 86%, compared with a success rate of 33% observed in women who were given no specific antenatal care [37].

Metabolic factors

Because there is strong evidence that obesity and/or insulin resistance are associated with an increased risk of miscarriage, weight reduction in obese women is a first step in the treatment. Metformin seems to improve pregnancy outcome, but this treatment cannot yet be recommended because the evidence is limited to a few cohort studies, and the safety of metformin in the first trimester of pregnancy is not yet established.

Environmental factors

Although the effect of environmental factors on the risk of abortion is not uniformly convincing, it makes sense to strongly recommend a healthy lifestyle, and give explicit advice concerning caffeine (from none to a maximum of two cups of caffeine-containing beverage a day) and alcohol (preferably none, to a maximum of one unit a day) consumption. This is also an ideal time to motivate the patient to completely abandon smoking. The only medication that can be advised to all women intending to get pregnant is folic acid, with no pretense that this will prevent a subsequent miscarriage.

Uterine malformations

There are no randomized trials to prove the value of surgical correction of uterine malformations for the prevention of first-trimester, recurrent abortion, but common sense and observational studies allow the formulation of advice. Because hysteroscopic resection of a uterine septum is a simple procedure, it can be recommended for all patients, even for those without a history of recurrent abortion. The same applies to the hysteroscopic lysis of intrauterine adhesions and the hysteroscopic removal of endometrial polyps and submucous myomata. More caution should be exerted in case of intramural myomata. If large myomata that distort the uterine cavity are the only abnormality found in a woman with recurrent abortion, a myomectomy can be justified. Unification procedures in cases of uterus didelphia or bicornuate

uterus are pointless, particularly when the reproductive failure is limited to the first trimester of pregnancy.

Autoimmune factors

Two studies have shown that treatment with aspirin (75 mg/d) and heparin (5000 U sc bid) result in a higher live-birth rate (71%–80%) than treatment with aspirin alone (42%–44%) [38,39]. In a recent trial, aspirin alone was found to be as effective as the combined treatment with heparin [40•].

Genetic factors

Oocyte or sperm donation is the only etiologic treatment when a recurrent genetic factor is involved. A recent development is preimplantation genetic diagnosis (PGD) for aneuploidy and translocations [41]. Several studies have shown that the incidence of abortion can be reduced by aneuploidy screening. Whether a sizeable proportion of women with recurrent abortion will ultimately benefit from this invasive and expensive treatment remains as yet unanswered.

Conclusions

Recently, the spectrum of etiologies for recurrent miscarriage has been changing. Some causes, such as luteal insufficiency and infectious diseases, have lost much of their previous importance, but some new, exciting findings have enriched our understanding of possible mechanisms of recurrent pregnancy loss. The sharing of parental antigens has become a hot topic again with the finding of specific HLA alleles that seem to be associated with recurrent miscarriage. Although genetic abnormalities have been implicated in recurrent loss of pregnancy for some time, skewed X-inactivation was recently found to be an additional genetic factor.

As in many other areas of medicine, however, increased knowledge of physiopathology does not necessarily lead to advances in treatment. There are several interesting therapeutic issues that remain to be fully explored by randomized trials. The role of low-dose aspirin, whether or not associated with heparin, requires further confirmation. The safety and efficacy of metformin in the treatment of insulin resistance in the first trimester of pregnancy remains to be established, and the place of preimplantation genetic screening is yet to be determined. In spite of all efforts, however, we will be confronted for many years to come with some inherent defects of human reproduction that are not amenable to treatment.

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