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REVIEW ARTICLE

Early Pregnancy Loss: A Management Guide

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Abstract

One of the most difficult aspects of reproductive medicine is the management of recurrent pregnancy loss. Recurrent pregnancy loss is one of the most emotionally devastating challenges facing couples who want to grow their family. For many couples, risk factors that increase the chances of experiencing a loss can be identified and treated. For other couples, however, a definitive cause is never identified. The aim of this article is to outline the causes for recurrent pregnancy loss and available therapies that optimize pregnancy outcomes.

Keywords

Recurrent pregnancy loss, RPL, Miscarriage, Spontaneous abortion, Embryo, Aneuploid, Antiphospholipid, Lupus anticoagulant, Heparin

Introduction

While spontaneous abortion occurs in approximately 15% of clinically diagnosed pregnancies of reproductive aged women, recurrent pregnancy loss occurs in about 1-2% of this same population [1]. Great strides have been made in characterizing the incidence and diversity of this heterogeneous disorder and a cause of increased propensity to experience pregnancy loss can be established in over half of couples after a thorough evaluation [2,3]. A complete evaluation will include investigations into genetic, endocrinologic, anatomic, immunologic and iatrogenic causes. These causes are then treated, resulting in an increased chance of achieving pregnancy in many patients. However, while all such therapies are aimed at decreasing the chances of recurrent pregnancy loss, no intervention is capable of completely eliminating the chance of miscarriage in the future. The traditional definition of recurrent pregnancy loss (RPL) included those couples with three or more spontaneous, consecutive pregnancy losses. Ectopic and molar pregnancies are not included. More recently, The American Society for Reproductive Medicine (ASRM) has defined RPL as "a distinct disorder defined by 2 or more failed clinical pregnancies [4]". The authors of this paper recommend a RPL evaluation after 2 or more pregnancy losses.

Anatomic Causes of Rpl

Anatomic causes of RPL are typically diagnosed using hysterosalpingography (HSG) or sonohysterography, commonly with three-dimensional ultrasonography. Hysteroscopy, laparoscopy, or magnetic resonance imaging (MRI) can supplement these tests as needed. The treatment of congenital and acquired uterine anomalies often involves corrective surgery.

Congenital malformations

Congenital malformations of the reproductive tract are present at the time of birth. The most common congenital abnormality associated with pregnancy loss is the septate uterus. The spontaneous abortion rate is high, averaging about 65% of pregnancies in some studies [4]. A septum is primarily composed of fibromuscular tissue that is poorly vascularized, making normal growth of the placenta difficult. Other congenital abnormalities, such as uterine didelphys, bicornuate and unicornuate uterus are more frequently associated with later trimester losses or preterm delivery.

Intrauterine adhesions

Intrauterine trauma resulting from a D+C or uterine infection is associated with a risk for the development of scar tissue (adhesions) within the uterus. This scar tissue

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may completely replace normal uterine tissue or make implantation and growth of an embryo more difficulty. Thankfully, in many cases, these adhesions may be treated with surgical resection.

Intrauterine masses

Intrauterine cavity abnormalities, such as fibroids and polyps, can contribute to pregnancy loss. Depending on the size and location, these masses may compromise the ability of an embryo to implant and growth. Thankfully, in most cases, these masses may be treated with surgical resection [5].

Cervical weakness

Cervical weakness is defined as the propensity for the cervix to dilate prematurely without cause. Cervical incompetence commonly causes pregnancy loss in the second, rather than first, trimester. It may be associated with congenital uterine abnormalities such as septate or bicornuate uterus. It is postulated that most cases occur as a result of surgical trauma to the cervix from conization, loop electrosurgical excision procedures, overdilation of the cervix during pregnancy termination, or obstetric lacerations [6].

Endocrinologic Causes of Rpl

Endocrine factors may contribute to 8-12 percent of recurrent pregnancy loss. Therefore, an endocrinologic evaluation is a critical component of the RPL workup.

Luteal phase deficiency

Maintenance of early pregnancy depends on the production of progesterone by the corpus luteum. Between 7 and 9 weeks of gestation the developing placenta takes over the progesterone production. Luteal phase deficiency (LPD) is defined as an inability of the corpus luteum to secrete progesterone in high enough amounts or for too short a duration. Traditionally, a diagnosis of LPD was diagnosed based on blood progesterone levels [7]. However, progesterone levels are subject to large fluctuations because of pulsatile release of the LH hormone, making blood progesterone levels generally unreliable [8]. While conflicting data exist, a recent Cochrane review evaluating 15 trials concluded that there was a benefit to the routine administration of progesterone to all women with a history of RPL [9,10].

Untreated hypothyroidism

Untreated hypothyroidism may increase the risk of miscarriage. A study of over 700 patients with recurrent pregnancy loss identified 7.6% with hypothyroidism [11]. Hypothyroidism is easily diagnosed with a sensitive TSH test and patients should be treated to become euthyroid (defined for the purposes of RPL as between 1.0 and 2.5 uIU/mL) before and during pregnancy [12].

Abnormal glucose metabolism

Patients with poorly controlled diabetes are known to have an increased risk of spontaneous miscarriage, which is reduced to normal spontaneous loss rates when women are euglycemic preconceptually [13]. Testing for fasting insulin and glucose is simple and treatment with insulin-sensitizing agents can reduce the risk of recurrent miscarriage [14]. 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.

Hyperprolactinemia

Normal circulating levels of prolactin may play an important role in maintaining early pregnancy Data from animal studies suggest that elevated prolactin levels may adversely affect corpus luteal function; however, this concept has not been proven in humans [15]. A recent study of 64 hyperprolactinemic women showed that bromocriptine therapy was associated with a higher rate of successful pregnancy and that prolactin levels were significantly higher in women who miscarried [16,17].

Autoimmune/Thrombotic Factors as the Cause of Rpl

Immunologic disorders

Autoimmune factors: Maternal response to self: In some instances, there is a failure in normal control mechanisms that prevent an immune reaction against self, resulting in an autoimmune response [18]. Autoantibodies to phospholipids, thyroid antigens, nuclear antigens and others have been investigated as possible causes for pregnancy loss [11]. Antiphospholipid antibodies include the lupus anticoagulant, *Anti-beta 2 glycoproteinI*antibodies, and anticardiolipin antibodies. There is still controversy concerning testing for other phospholipids, but an increasing number of studies suggest that antibodies to phosphatidyl serine are also associated with pregnancy loss [19]. Women with systemic lupus erythematosus and aPL have increased risks for miscarriage compared to those with lupus and negative aPL [1].

Microbiologic

Certain infectious agents have been identified more frequently in cultures from women who have had spontaneous pregnancy losses [20]. These include *Ureaplasma urealyticum, Mycoplasma hominis,* and Chlamydia. Other less frequent pathogens include *toxoplasma gondi,* rubella, HSV, measles, CMV, coxsackievirus and listeria monocytogenes. It is important to be aware that none of these pathogens have been causally linked to RPL. Because of the association with sporadic pregnancy losses and the ease of diagnosis, some clinicians will test women with RPL and treat for the appropriate pathogen in both parents.

Thrombotic disorders

Thrombophilias, including factor V Leiden, Antitrombin activity, Protein C+S activation, and MTHFR muta-

tions are now not thought to be associated with RPL. However, these abnormalities are thought to be responsible for more than half of maternal venous thromboembolisms in pregnancy, however ACOG recommends that only patients with a personal or family history of thromboembolic events should be tested [21].

Genetic Factors as the Cause of Rpl

There are a variety of genetic factors that may result in failure of a pregnancy to develop. The overall frequency of chromosome abnormalities in spontaneous abortions exceeds 50% [22-26]. These abnormalities include aneuploidy (the gain or loss of a chromosome), chromosomal imbalances as a result of parentally harbored translocations or inversions, deletions or duplications of genetic information within chromosomes, and single-gene mutations. Broadly, genetic factors may be divided into embryonic errors derived from known parental chromosomal abnormalities and embryonic errors that arise de novo in apparently chromosomally normal parents.

Parental chromosomal disorders

Parental chromosome anomalies occur in 3-5% of couples with RPL as opposed to 0.7% in the general population. These include translocations, inversions, and the relatively rare ring chromosomes. Balanced translocations are the most common chromosomal abnormalities contributing to recurrent pregnancy loss [22]. Chromosomal abnormalities in one of the parents can be found in up to 3-5% of couples who experience multiple spontaneous abortions. If no fetal POC are available and the couple has a history of at least 2 consecutive or 3 nonconsecutive fetal losses, we recommend obtaining parental karyotypes.

Genetic causes of RPL may be subdivided into embryo abnormalities that are the result of known parental abnormalities (such as parental balanced translocations or inversions) and embryo aneuploidy in parents believed to be chromosomally normal. Preimplantation genetic testing is a technology that is designed to minimize the effects of these and other embryonic genetic abnormalities. Preimplantation genetic testing is accomplished by performing an *in vitro* fertilization (IVF) cycle, removing a cell(s) from the resultant embryos or oocytes, evaluating this cell for genetic abnormalities, and using the results to determine which embryos are ideal for uterine transfer. Recent data evaluating pregnancy rates in RPL patients using 23 chromosome microarrays are encouraging [27,28].

Lifestyle Issues and Environmental Toxins

Couples experiencing recurrent pregnancy losses are often concerned those toxins within the environment may have contributed to their reproductive difficulty. It is important that health care providers, counseling patients about exposures to substances in the environment, have current and accurate information in order to respond to these concerns.

Cigarette smoking

Cigarette smoking reduces fertility and increases the rate of spontaneous abortion. The data evaluating smoking and miscarriage are extensive and involve approximately 100,000 subjects. The studies suggest a clinically significant detrimental effect of cigarette smoking that is dose dependent, with a relative risk for miscarriage among moderate smokers (10-20 cigarettes a day) being 1.1 to 1.3 [29]. Patients should be aggressively counseled to stop cigarette smoking prior to attempting pregnancy.

Alcohol consumption

Alcohol consumption associated with a risk of spontaneous abortion [30]. The minimum threshold dose for significantly increasing the risk of first trimester miscarriage appears to be 2 or more alcoholic drinks per week [31,32]. When personal habits, cigarette smoking and alcohol are utilized in the same individual, the risk of pregnancy loss may increase 4-fold. Couples should be counseled concerning these habits and strongly encouraged to discontinue these prior to attempting subsequent conception [33].

Obesity

Obesity, defined as a body mass index over 30, has been associated with an increased risk of miscarriage. Obesity (BMI > 30 kg/m^2) has been shown to be an independent risk factor for first trimester miscarriage [34]. The association is strongest in women with BMI > 40. The etiology of this phenomenon is unclear. However, many studies have linked obesity to a generalized increase in systemic inflammatory responses [35].

Caffeine intake

Several studies have shown that caffeine in excess of 300 mg/day (3 cups of coffee per day) is associated with a modest increase in spontaneous abortion, but it is not clear if this relationship is causal [36].

Outcome

Thankfully, the prognosis for women with RPL to eventually deliver with medical therapy is quite good. Women who suffer RPL have already begun to prepare for their baby, both emotionally and physically, as compared to couples with infertility who have never conceived. When a miscarriage occurs, a couple may have great difficulty informing friends or family about the loss. Feelings of hopelessness may continue long after the loss. Patients may continue to grieve and have episodes of depression on the expected due date or the date of the pregnancy loss. Participation in support groups or referral for grief counseling may be beneficial in many cases (SHARE, Pregnancy and Infant Loss Support, Inc., www.nationalshareoffice.com).

Contributors

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Competing Interests

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