

Etiology of recurrent spontaneous abortion

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Abstract

Spontaneous abortion and miscarriage are synonymous terms. In medical literature, spontaneous abortion is most often used, while in clinical practice and among the general population miscarriage is the preferred term. Spontaneous abortion or miscarriage is defined as the involuntary end of pregnancy before 20 weeks of gestation. Recurrent pregnancy loss (RPL), also known as recurrent miscarriages, is defined by the consecutive loss of two or more pregnancies with the same partner and having no more than one living child. The aim of this review is to highlight the most common Etiology of Recurrent spontaneous abortion.

Keywords: Spontaneous abortion; Pregnancy loss; Miscarriage; Gestation

1. Introduction

Historically, recurrent miscarriage has been attributed to either genetic, structural, infective, endocrine, immune, or unexplained causes. Thrombophilic disorders are thought to play a part in the cause of recurrent pregnancy loss, which widens the scope of investigations and management options for recurrent miscarriage. Many syndromes associated with recurrent fetal loss include anatomic anomalies, endocrine/hormonal abnormalities, genetic, chromosomal abnormalities, and blood coagulation protein/platelet defects [1].

The etiology of recurrent pregnancy loss (RPL) remains unclear, but it may be related to a possible genetic predisposition together with involvement of environmental factors. Etiology of recurrent pregnancy loss is among the most studied, yet unresolved issues in modern gynecology. Among the various proposed etiological factors, abnormal parental karyotype, antiphospholipid syndrome and uterine anatomic abnormalities were reported in about 50% of the patients; however, in remaining 50%, the cause is unknown [2].

RSA is a heterogeneous condition, and it is unlikely that only a single pathological factor is attributed to RM. Current literature suggests that the cause of RM is only identifiable in up to 40%-50% of cases. The remaining RM cases are classified as idiopathic. Hence, this merits further research to seek other possible underlying causes of RM. To date the identifiable causes of RM have been categorized as parental, fetal, environmental, and psychological factors. The etiologies of spontaneous miscarriage, as well as of recurrent miscarriage are to some degree the same and to some degree different. Some of the medical causes have a higher incidence in cases of recurrent miscarriage [3].

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2. Parental Factors

2.1. Chromosomal Abnormality

Parental balanced structural chromosomal rearrangement accounts for 2%-4% of RM. There are many factors that come in to play when the egg and sperm unite and form that first cell. Even if both the egg and sperm come with perfect chromosomes, the first few cell divisions can see an abnormality crop up that would certainly be devastating. The main chromosomal abnormalities are autosomal trisomies, polyploidy, and monosomy X. Most trisomies show a maternal age effect, with chromosomes 16 and 22 most involved, triploidy and tetraploidy account for 30% of chromosomal abnormal abortions. [4]. Chromosomal abnormalities are less likely to occur in spontaneous abortions for women younger than age 36 with a history of recurrent abortion. The most common chromosomal rearrangement is balanced reciprocal or Robertsonian translocation which may lead to unbalanced gene translocations in the fetus, resulting in miscarriage. Other chromosomal anomalies associated with RM include chromosomal inversion, insertions, and mosaicism [5].

3. Maternal Factors

3.1. Ages

Paternal age also plays a part. It is well recognized that female fertility declines with advancing age, which manifests in increases in miscarriage and trisomy 21 and monosomy X of the fetus. Frequency of chromosomal anomalies in sperm appears to increase with age. Independent of maternal age, paternal age of more than 40 years carries 1:6 odds of miscarriage compared with paternal age of 25 to 29 years. It is well recognized that female fertility declines with advancing age, which manifests in increases in miscarriage and trisomy 21 and monosomy X of the fetus. RM as part of a range of reproductive failures shares common risk factors. Studies have shown that in women with RM maternal age is positively associated with the numbers of repeated miscarriages and also is an important factor predicting the occurrence of miscarriage. In IVF treatment the pregnancy rate of women with RM declined with advancing maternal age. The value of preimplantation genetic screening (PGS) on the reduction of pregnancy loss in RM women with advanced age is not yet clear. Some studies have shown that PGS significantly reduces the rate of pregnancy loss following IVF treatment in RM patients older than 35 years. Adoption or the use of donor gametes may be recommended to the older couples if IVF has failed. [6].

4. Endocrinological Factors

Both estrogen and progesterone play essential roles in pregnancy. During the menstrual cycle the first half is estrogen-dominated while the second half is progesterone dominated. Estrogen and progesterone initially prepare the Endometrium for implantation by initiating a cascade of local morphological and physiological events via their respective receptors. Progesterone acts on the reproductive tract in preparation for the initiation and maintenance of pregnancy by inhibiting contraction of the uterus and the development of new follicles [7]. Following fertilization of the oocyte, the developing embryo secretes human chorionic gonadotropin (HCG) which sustains progesterone levels. During pregnancy, fetoplacental estrogens, progestogens and adrenocorticoids are secreted into both fetal and maternal circulation. Estrogen production is mainly under the control of the fetus and is the primary signaling method by which the fetus directs essential physiologic processes that affect fetal well-being. By the 20th week of pregnancy, approximately 90% of maternal estriol excretion can be accounted for by dehydro epiandrosterone sulfate (DHEA-S) production by the fetal adrenal gland. Estrogens affect progesterone production, uterine blood flow, mammary gland development and fetal adrenal gland function. Many endocrine disturbances have been assumed to be responsible for RSA. Higher rates of spontaneous abortions are observed among women with polycystic ovary syndrome (PCOS). This may be due to hyper androgenemia, hyper secretion of LH, or insulin resistance. High levels of androgens have been shown to interfere with normal endometrial development. They alter the production of certain growth factors and may be responsible for pregnancy failure. LH stimulates ovarian androgen synthesis; therefore, LH hyper secretion is likely to interfere with early pregnancy via hyperandrogenism. [8].

5. Anatomic Factors

Anatomic abnormalities account for 16 - 18% of RM cases. The common anatomic abnormalities include congenital uterine anomalies, uterine adhesions, uterine fibroids and polyps. These abnormalities may cause inadequate vascularity of the Endometrium where the embryos implant, resulting in placental abruption and consequently miscarriage.

Among these anatomic abnormalities, congenital uterine abnormalities such as arcuate, septate or bicornuate uterus may be associated with second trimester miscarriages more than early pregnancy losses. Women with anatomic anomalies may benefit from uterine sonography and HSG in the initial diagnosis. A definitive diagnosis can be obtained by using combined laparoscopy and hysteroscopy as well as 3D sonography. Surgical resection of the uterine septum and adhesions, removal of submucous fibroids and polyps may improve subsequent pregnancy outcomes in these women [9].

6. Immunological Factors

The implanting embryo inherits its antigens from both the mother and the father. The paternal antigens are identified as foreign by the maternal immune system. In order to prevent the rejection of the pregnancy, this immune response needs to be modulated. It has been proposed that in otherwise unexplained pregnancy losses, dysregulation of the immune system could be responsible for the failure [10]. The immunological interaction between the mother and the fetus remains a scientific enigma. In normal pregnancies, the maternal immune system does not react to spermatozoa or the embryo, even though they express antigens that are exogenous to the maternal system. Maternal-fetal tolerance has been compared to that of a semi-allogenic fetal “graft”, and may be the result of a complex array of mechanisms (including HLA-G expression of trophoblast; the leukemia inhibitory factor and its receptor, indoleamine 2,3-dioxygenase; the Th1/Th2 balance; suppressor macrophages; and hormones such as progesterone, or the placental growth hormone, CD95, and its ligand and annexin II) that may be pregnancy-specific and interconnected. Immunological mechanisms are involved in successful implantation. Maternal adaptation of immunological responses to the implanting embryo is a key process in the establishment of the feto-placental unit. Miscarriage may therefore be a consequence of inappropriate humoral or cellular immunological responses towards the embryo. APS belongs to the well-known risk factors of RM and has been reported in 15% of RM patients. Antibodies against anionic phospholipids such as cardiolipins, phosphatidylserine as well as cofactors such as 2-glycoproteins can be found disproportionately more of ten in RM patients as compared to healthy controls. Also, functional tests for lupus anticoagulants frequently show haemostatic changes in APS patients. The diagnosis of APS requires fulfillment of the criteria defined in the international consensus statement. There is evidence that aspirin combined with LMWH significantly increases live birth rate in RM patients with APS. [11].

7. Infections

Infective causes of recurrent miscarriage remain speculative. For any infective agent to be implicated, it must be capable of persisting in the genital tract undetected and must cause few maternal symptoms. The pathogenetic mechanisms of these infections are unique. Because of their relatively low virulence, the organisms involved seldom lead to fetal death beyond the earliest stages of embryogenesis. Since the fetus is essentially a graft of foreign tissue in the uterus, the placenta constitutes a protective immunologic barrier that shields the fetus from the mother's humoral and cell-mediated immune responses. This makes the fetus especially susceptible to infection during the first trimester [6].

8. The role of Inherited Blood Coagulation Disorders in Recurrent spontaneous abortion

During pregnancy, the pregnant mother undergoes significant anatomical and physiological changes in order to nurture and accommodate the developing fetus. Inherited blood coagulation factors has been shown to be a major cause of recurrent miscarriage syndrome, patients with recurrent miscarriage should be evaluated for clotting disorders, even in the absence of clinical signs because there were some studies concluded that many positive hemophilic causatives finding without any clinical [12-15]. The inherited thrombophilia includes activated protein C resistance 95% due to factor V Leiden (FVL) mutation], protein S deficiency, protein C deficiency, antithrombin III deficiency, FII (prothrombin) mutation and hyperhomocysteinemia. Factor V Leiden (FVL) and prothrombin (G20210A) mutations are the most common causes have been implicated as risk factors of hereditary thrombophilia which in turn can result in placentation [5]. Also, alterations in blood coagulation system have been reported in patients of hypertension and Fibrinogen has been identified as a major independent risk factor for cardiovascular diseases and this also can affect the pregnancy [16]. An association between recurrent pregnancy loss and prothrombotic states rendered by some genetic single nucleotide polymorphisms of factor V Leiden G1691A. Etiology is determined in approximately 50% of couples with RPL. Most of the diagnosed etiologies include endocrine abnormalities, autoimmune disorders, uterine anomalies, and genetic factors. Still, 50% of couples have no known etiology. The aim of the current study was to correlate heterozygosity of maternal factor V G1691A (Leiden) and relationship with times of pregnancy loss among unexplained recurrent pregnancy loss [17].

9. Other factors

Also, there are many causes of pregnancy loss related to environmental factor like cigarette smoking has been suggested to have an adverse effect on trophoblast function and is linked to an increased risk of sporadic pregnancy loss. Also, obesity has been shown to be associated with an increased risk of pregnancy loss[18]. Smoking especially during pregnancy is dangerous. During the first few days after conception, when the fetus is developing rapidly, it's highly susceptible to genetic damage caused by cigarette smoke. And because chromosomal problems are the most common cause of miscarriages, it's possible heavy exposure to cigarette smoke could play a role. Smoking also can affect the lining of the uterus, making it difficult for a fertilized egg to implant [19].

10. Conclusion

Most cases of RPL remain unexplained and inherited coagulation disorders causes account for majority causes among women . Inheritance blood coagulation factors has been shown to be a major cause of recurrent pregnancy loss, patients with RPL should be evaluated for clotting disorders, even in the absence of clinical signs because there were some studies concluded that many positive hemophilic causatives finding without any clinical signs . There are many infections that can negatively affect pregnancy outcomes. To determine if screening newly pregnant women for infections that may be treated might enhance reproductive outcomes, more study is needed.

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