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Causes and Management of Recurrent Pregnancy Loss, a Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Recurrent Pregnancy Loss (RPL) is defined as two or more consecutive failed clinical pregnancies verified by ultrasound or histopathology. It is an important reproductive health issue, affecting 2%–5% of women. Up to one half of all cases of RPL have no identifiable cause. Etiology of the RPL is linked to several genetic, environmental, endocrinal, and anatomic factors which all will be discussed in this article. Treatment of RPL depends on the underlying cause behind it, and thus diagnosis and identifying of such factors plays major role into treating it. Lifestyle changes also is encouraged. Stress, smoking, drinking cessation, and weight loss can be all helpful. In this article we'll be looking at RPL causes, and management.

Keywords: Recurrent Pregnancy Loss (RPL); lifestyle; Antiphospholipid syndrome; miscarriage.

1. INTRODUCTION

Recurrent Pregnancy Loss (RPL) is defined as two or more consecutive failed clinical pregnancies verified by ultrasound or histopathology. It is an important reproductive health issue, affecting 2%–5% of women. Up to half of all cases of RPL have no identifiable cause [1]. Primary and secondary kinds of RPL can be distinguished. Women who have never given birth to a live baby have primary, recurrent pregnancy loss. Secondary RPL affects women who have already given birth to a healthy baby [1].

Couples might be physically and emotionally exhausted by unexpected pregnancy loss, especially if it occurs frequently. RPL also known as recurrent miscarriage or habitual abortion, is defined as a series of pregnancy loses occurring prior to age of fetal viability. RPL should occur about once per 300 pregnancies, based on the prevalence of spontaneous pregnancy loss [2]. RPL affects 1 percent to 2 percent of women, according to epidemiological research [2]. Approximately 12% to 15% of all pregnancies end in spontaneous miscarriage. Between the time of implantation and the sixth week, 30% of pregnancies are lost [3]. The risk of recurrent miscarriages increases with maternal age and previous miscarriages [3]. The management of recurrent miscarriages is a topic that has yet to be solved; up to 50% of instances of recurrent miscarriages will have no identifiable explanation. One of the most heated debates is the examination and management of recurrent miscarriages [2, 3].

Stress, coffee intake, nicotine and alcohol consumption have all been linked to miscarriage, however due to the limited number of cases due to stress, it is not feasible to assume that stress increases the risk of miscarriage based on the currently available evidence [4]. Nicotine intake is also linked to poor maternal and neonatal outcomes include ectopic pregnancy, stillbirth, placenta previa, early birth, low birthweight, and congenital deformity. As a result, all pregnant women should be advised to quit smoking. however, the effect of smoking and quitting smoking on the risk of RM is unknown [3,4].

2. ETIOLOGY

Genetic: Recurrent pregnancy loss is linked to a paternal balanced structural chromosomal rearrangement, most often balanced reciprocal or Robertsonian translocations, in about 2% to 4% of cases [1]. Chromosomal inversions, insertions, and mosaicism are further structural defects linked to RPL. Recurrent pregnancy loss is seldom linked to single gene abnormalities, such as those linked to cystic fibrosis or sickle cell anaemia [2]. RPL is caused by aneuploidy, which is one of the most prevalent causes. In the foetus, balanced, reciprocal, and Robertsonian translocations can all lead to spontaneous miscarriages [1]. Parental karyotyping should be included in a proper evaluation of RPL. In all cases of RPL linked to chromosomal abnormalities in the parents, genetic counselling is recommended. Directed therapy may include in vitro fertilisation with preimplantation genetic diagnosis, depending on the specific disease. In situations of genetic abnormalities that inevitably result in embryonic aneuploidy, the use of donor gametes may be advised (ie, Robertsonian translocations involving homologous chromosomes) [2].

The majority of parents with balanced translocations are asymptomatic. Their product of conception's (POC) karyotype might be completely normal, or it can have a balanced or

unbalanced translocation. Pregnancies with imbalanced translocations generally result in miscarriage, which is often viewed as a natural selection process, but they can also result in stillbirths or live babies with serious congenital problems [5]. It is impossible to determine the number of each option because karyotypes on miscarried POC are not typically organized. Studies suggest that roughly 25%–39% have imbalanced translocations [5].

One of the most common epigenetic alterations is DNA methylation, which is critical for embryonic implantation and development. Miscarriage, hypertension, improper embryonic development, and birth defects are all linked to aberrant DNA methylation [6]. p53 and SP transcription factors are recruited in the CAMP-responsive element binding protein 5 (CREB5) DMR by CREB5 hypomethylation, which promotes CREB5 expression, which is one of the 539 differential methylation regions (DMRs) discovered in RPL patients [5,6]. IL-6 levels influence CREB5 methylation and expression. CREB5 is also involved in RPL pathogenesis [6].

Anatomic: Anatomic anomalies occur for 10% to 15% of RPL instances and are considered to induce miscarriage by disrupting the endometrium's vasculature, resulting in improper and insufficient placentation [3]. As a result, anomalies that disrupt the endometrium's vascular supply are suggested to be possible causes of RPL. Congenital uterine malformations, intrauterine adhesions, and uterine fibroids or polyps are all examples [2]. Recurrent pregnancy loss can be caused by congenital Mullerian tract abnormalities. Septate, unicornuate, bicornuate, didelphic, and arcuate uteri are some of the uterine anomalies that might contribute to RPL. The septate uterus is the most frequent congenital uterine abnormality [1]. Congenital uterine abnormalities were found in roughly 12.6 percent of individuals with recurrent pregnancy loss. Fibroids, polyps, and Asherman syndrome are among acquired uterine defects that might raise a woman's chance of RPL [1].

The higher risk of miscarriage in women who have a subseptate uterus is widely established, but the reason for this is unknown [4]. When compared to hysterosalpingography or hysteroscopy, Ludwin et al. showed much improved diagnostic outcomes when employing sonohysterography to diagnose congenital uterine abnormalities [7,8]. However, comparing diagnostic procedures and evaluating comments is difficult because interobserver agreement was found to be low even when hysteroscopy recordings were provided to experienced international observers [9]. The choice to employ hysteroscopy – maybe in conjunction with laparoscopy or 3D sonography – to diagnose uterine abnormalities in high-risk populations must be taken on an individual basis [10]. In high-risk populations, 3D sonography is indicated for the diagnosis of uterine abnormalities, whereas MRI and endoscopic investigations are advised for diagnostic issues or suspected complicated malformations. [11]

Endocrinal Factors: Endocrinologic problems such as luteal phase defect (LPD), polycystic ovarian syndrome (PCOS), diabetes mellitus, thyroid illness, and hyperprolactinemia have been linked to roughly 17 percent to 20% of RPL cases. Luteal phase defect has long been thought to be caused by insufficient progesterone synthesis by the corpus luteum and insufficient endometrial maturation for appropriate placentation. The exact relevance of LPD in RPL is still debated, and endometrial biopsies for LPD diagnosis are only used in few cases. Some investigations have found abnormally high levels of luteinizing hormone or androgens (both of which are linked with PCOS) in RPL patients, indicating that these abnormalities may lead to premature oocyte ageing and/or dyssynchronous endometrial development [2]. Polycystic ovary syndrome is a disorder characterised by high plasma androgen levels that affects around 5–10 percent of women of reproductive age. High levels of androgen lead to an increase in the number of abortions [6]. Ishikawa cells were given high androgen concentrations as well as normal androgen concentrations. In the high androgen group, eight up-regulated proteins and ten down-regulated proteins were discovered. The cyclin-dependent kinase inhibitor 2a was one of these proteins, and lower levels of protein expression resulted in reduced Ishikawa cell motility, invasion, proliferation, and Jar spheroid attachment. These findings suggest that proteins linked to PCOS may cause RPL. The failure to sustain healthy amounts of progesterone during pregnancy, as well as proper embryo implantation and development, is known as luteal phase deficit (LPD) [6].

Environmental and Psychological factors: Cigarette smoking has been associated to an increased risk of RPL and has been shown to impact trophoblastic function [1]. In women who

conceive spontaneously, obesity is related with an increased chance of recurrent pregnancy loss. Other lifestyle behaviours linked to an increased risk of spontaneous miscarriages include alcohol intake (3 to 5 drinks per week), cocaine usage, and higher caffeine consumption (greater than 3 cups of coffee per day) [1].

Recurrent pregnancy loss may have a substantial psychological impact on a couple's personal and professional lives, and many sentiments have been recorded, including loss and melancholy, hopelessness, guilt, worry, and rage directed towards the spouse, friends, or treating physician. Several studies have looked at a possible psychological aetiology for RPL, but with so many variables and confounding circumstances, such connections are difficult to verify. One research suggested that sadness increased the likelihood of miscarriage in the first trimester, although the evidence is mixed [5,12]. Psychological support, on the other hand, appears to be helpful in couples with RPL, according to some research [13]. Tender loving care entails psychological support in the form of weekly medical and ultrasound checkups, as well as restrictions on strenuous labour, travel, and sexual activity. Couples experiencing RPL should get supportive treatment in specialised clinics, according to international associations [14,15].

Infection factor: Listeria monocytogenes, Toxoplasma gondii, rubella, herpes simplex virus, measles, cytomegalovirus, and coxsackieviruses are all recognised or suspected diseases that can cause sporadic spontaneous pregnancy loss. Infectious agents, on the other hand, have a less apparent role in recurrent loss [2,16]. 8 Direct infection of the uterus, foetus, or placenta, (2) placental insufficiency, (3) chronic endometritis or endocervicitis, (4) amnionitis, or (5) an infected intrauterine device are all postulated explanations for infectious causes of pregnancy loss. Because the majority of these cases are isolated, infections appear to have a little role in the development of RPL [17]. Mycoplasma, ureaplasma, Chlamydia trachomatis, L monocytogenes, and HSV are among the diseases thought to play a role in RPL. Chronic infection in an immunocompromised patient is the most important risk factor for RPL related to infection [18,19].

Antiphospholipid syndrome (APS): It has long been linked to RPL and is defined by the presence of antiphospholipid antibodies (aPL). Indeed, one of the two clinical criteria necessary to validate the diagnosis of APS is pregnancy morbidity, the other being vascular thrombosis [5,19]. According to research, the prevalence of APS in women with RPL varies from as low as 6% to as high as 42 percent, although it is widely recognised to be between 5% and 20% [20,21]. This is most likely due to the use of nonstandard laboratory-specific tests as well as the many types of antibodies examined throughout time. However, lupus anticoagulant, anticardiolipin antibody, and anti-2 glycoprotein I are the only tests now utilised to diagnose APS. When there is no underlying disease, APS is referred to as primary, and when it is coupled with other disorders, it is referred to as secondary [22].

3. TREATMENT

Recurrent pregnancy loss should be treated by addressing the underlying, curable cause. The dangers, alternatives, and success rates of each possible treatment option should be explained to patients and their families. By offering emotional support to these nervous couples, treatment outcomes can be improved. When feasible, reproductive endocrinologists and obstetricians should work together as a team and communicate clearly.

Thyroid disorders, diabetes, obesity, and other medical diseases should be addressed as medically necessary. For the treatment of uncontrolled thyroid disorders and diabetes, consulting with an endocrinologist is also a viable option. Patients with increased thyroid peroxidase antibodies are more likely to develop RPL and should be treated accordingly.

TNF- controls placentation and subsequent implantation in pregnancy outcomes by acting as an inflammatory mediator. The innate immune cells and placental cells both release TNF-. A proper balance of Th1 (primarily TNF- and Th17) and Th2 (including IL-10) cytokines is critical for a successful obstetric result [6]. In contrast, an increase in Th1-dependent cytokines, particularly TNF-, can cause a variety of obstetric problems, including RPL. TNF-targeted treatments are thus a viable method for treating or curing these conditions. As a result, TNF-blockers have emerged as a viable therapy option for pregnant women with inflammatory and immune-mediated disorders [6].

The first step in treating couples with chromosomal disorders is to send them to

genetic counselling. Couples should be informed about the possibility of foetal chromosomal disorders in subsequent pregnancies. Prenatal genetic testing, such as preimplantation genetic diagnosis, chorionic villus sampling, or amniocentesis, may be used to discover genetic defects in the foetus and determine treatment choices. Although uneven chromosomal configurations may potentially be screened out, PGT (preimplantation genetic testing) is not commonly recommended since the chances of a pregnancy with an unbalanced karyotype surviving into the second trimester are low [1].

Surgery in the uterus can treat extra tissue that splits the uterus (septum), certain fibroids (benign tumours), and scar tissue (womb). Correcting the internal shape of the uterus can significantly reduce the risk of miscarriage [20]. To repair the interior of the uterus, the surgeon utilises an instrument with a camera (hysteroscope) that is passed through the vagina. This is normally a one-day operation with a few days to a week of recovery time [1].

In general, whatever is good for a woman's health increases her chances of having a healthy pregnancy. Stopping smoking and abstaining from illegal drugs (such as cocaine) reduces the chance of miscarriage. Limiting intake of alcohol and caffeine may also assist. Being overweight has been related to an increased chance of miscarriage, thus maintaining a healthy weight can aid with pregnancy outcomes. stress, worry, or moderate depression, these are significant issues that come with RPL. Couples might benefit from psychological therapy and counselling to cope with the emotional sorrow of loss and to build a healthy environment for a pregnancy.

4. CONCLUSION

RPL (RPL) is without doubt one of the challenging conditions that faces medical system. Treatment of RPL depends on the underlying cause behind it, and thus diagnosis and identifying of such factors plays major role into treating it. And yet Up to half of all cases of RPL have no identifiable cause. Lifestyle changes is encouraged for women who trying to give birth. Stress, smoking, drinking cessation, and weight loss can be all helpful. Genetic counselling is also encouraged.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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