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Recurrent pregnancy loss - a life changing condition for women

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ABSTRACT

Recurrent pregnancy loss (RPL) is estimated to occur in 2.5% of women trying to conceive. Definition of RPL varies depending on used guideline. In Europe, RPL is defined as two or more lost pregnancies before 24 weeks' gestation. Although many factors have been associated with a higher risk of recurrent miscarriage, the aetiology is unknown in about half of cases. Several factors have been related to recurrent pregnancy loss, such as: environmental, behavioral, genetic, endocrine, metabolic, autoimmune, anatomic, thrombophilia and male factor. Given the multitude of etiopathogenic factors, RPL frequently requires an interdisciplinary approach for diagnosis and treatment. By its repetitive nature, RPL represents a psychological trauma on the couple who wants to conceive a child. Consequently, empathy and support are also necessary to be integrated in the therapeutic approach in the case of couples with recurrent miscarriage.

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Introduction

Pregnancy loss is an important negative life event, with significant impact for the couple experiencing it. The repetitive nature of recurrent pregnancy loss (RPL) accentuates the emotionally traumatic experience and represents a frustrating and challenging area in reproductive medicine as in 50% of cases the aetiology is unclear [1].

The international guidelines did not agree on the definition of RPL. Thus, RPL is defined as the loss of two or more pregnancies before 24 weeks' gestation by The European Society of Human Reproduction and Embryology (ESHRE) guideline [2] and the American Society of Reproductive Medicine (ASRM) [3], whereas the Royal College of Obstetricians and Gynaecologists (RCOG) [4] proposes a different definition of RLP which states that recurrent miscarriage is the loss of three or more consecutive pregnancies before 24 weeks of gestation. A distinction can be made between primary RPL, term that refers to couples that never obtained a live birth and secondary RPL reserved for those who experienced repetitive losses following a successful pregnancy [2].

As there is a variability of definitions and criteria for RPL, it is difficult to evaluate its exact prevalence. It is estimated that RPL is experienced by about 2.5% of women trying to conceive [5].

The purpose of this paper is to provide a summary of the recent literature regarding the risk factors for RPL including environmental and behavioral factors, genetic abnormalities, endocrine and metabolic as well as autoimmune conditions, anatomic variations, thrombophilia and the existing screening methods for each factor.

As the loss of pregnancy is a devastating experience and the couple going through it is in need of a lot of counselling and support, another important focus of this paper is on the psychological impact that RPL has on women as well as their partner.

We performed a review of currently existing literature on the subject of RPL. Eligible studies were found in PubMed, Cochrane library and Medline databases using keywords and Medical Subject Headings terms pertaining to "recurrent pregnancy loss" or "recurrent abortion". An important focus was placed on risk factors for RPL and psychological outcomes.

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The oldest included study was published in 1993 while the latest one was dated with the year 2022. A number of 42 studies were included in total and only 10 were older than 5 years at the time of writing. Among the latter were 2 guidelines published by ESHRE as well as a guideline by the Royal College of Obstetricians & Gynaecologists on RPL.

Discussions

Risk factors for RPL include environmental and behavioral factors, genetic abnormalities, endocrine and metabolic as well as autoimmune conditions, anatomic variations, thrombophilia.

Environment

Recent studies investigate the impact of chemical compounds on RPL. One such study found that exposure to pesticides, namely organophosphates, may affect the levels of steroid hormones in women and the balance between them, leading to increased rates of miscarriage and RPL [6].

A study published by Chang WH and co reinforces the role of phthalates (compounds frequently used in many types of plastics as well as cosmetic products such as hair sprays) and their direct toxicity on reproductive organs [7]. Di-(2-ethyl-hexyl) phthalate (DEHP) which is most commonly found in some types of glue seems particularly potent in this regard.

Another pollutant called benzo[a]pyrene, found most often in tobacco smoke, soot and grilled meats, has been found to inhibit the migration of trophoblast [8], adding to their already known relation with various types of skin cancers.

A study published in 2021 by Caporossi et al. also mentions bisphenol A (an integral part of the production of polycarbonates) as a possible risk factor towards developing RPL [9]. The mechanism through which bisphenol A is linked with diminished ovarian reserves and RPL remains unclear. However, as a component of polycarbonate plastics and epoxy resins, bisphenol A is found in a variety of commonplace products such as thermal paper (most commonly used in the making of receipts), coatings on the inside of food cans as well as textiles. The main way of exposure to bisphenol A has been found to be ingestion closely followed by dermal absorption.

Lifestyle factors

Lifestyle factors that can increase the risk of recurrent miscarriage are smoking, excessive alcohol consumption and body mass index (BMI). A study has shown that obesity can double the risk of miscarriage in patients with RPL, but no significant correlation has been made between being overweight and RPL [10]. Another study that analyzed the risk of miscarriage after oocyte donation discovered that significant differences between obese (38.1%), overweight (15.5%) and normal patients (13.3%) exist [11]. A Mendelian randomization study concluded that smoking significantly increased the risk of pregnancy loss by 30% [12]. Women who were exposed to alcohol during pregnancy have a 20% increased risk of miscarriage compared to abstinence and each additional drink per week up to 5 units increases with 6% the risk [13].

Genetic abnormalities

The embryo's genetic material and embryonic development have also been taken into consideration in regards to both primary and secondary recurrent pregnancy loss. Among the methods used by researchers we find embryoscopy, cytogenetic analysis of chorionic villi, non-invasive methods such as preimplantation genetic diagnosis for aneuploidy screening (PGD-AS) and karyotype evaluation.

As suggested by the aptly-named method, embryonic aneuploidy originates in the preimplantation development period, with origins as far as gametogenesis. Nearly half [14] of early-term miscarriages report abnormal genetic patterns, and de novo anomalies seem to be the most common culprit in spontaneous abortions [15].

When establishing a correlation between aneuploid embryos and primary versus secondary recurrent pregnancy loss, one study concluded that patients with primary RPL had significantly fewer aneuploid embryo anomalies when compared to either the control group of non-RPL patients or secondary RPL patients [16].

Thrombophilia

Thrombophilia, meaning tendency to thrombosis, can be inherited or acquired and has been associated with many pregnancy complications, such as stillbirth, abruption placentae, severe preeclampsia, intrauterine growth restriction and RPL. Most common thrombophilia is antiphospholipid syndrome, an acquired autoimmune condition.

Hereditary thrombophilia associated with RPL are represented by factor V Leiden, prothrombin G20210A, protein S, C and antithrombin deficiencies. Factor V Leiden mutation is characterized by resistance to activated protein C and multiple studies have shown positive correlation between G1691A mutation and RPL [17,18]. In the same manner, prothrombin G20210A mutation leads to a higher prothrombin concentration and is a risk factor for RPL as it has been shown in multiple studies [19,20]. Also, protein S deficiency, a natural anticoagulant, was associated with high risk of recurrent miscarriage [21]. On the other hand, antithrombin and protein C deficiencies have not been significantly associated with a higher risk of recurrent miscarriage [22].

Antiphospholipid syndrome (APS), also known as acquired thrombophilia, is a systemic autoimmune

condition characterized by the persistent presence of antiphospholipid antibodies and vascular thrombosis and/or pregnancy complications [23]. Though Miyakis criteria on diagnostic of APS include as clinical criteria "three or more unexplained consecutive spontaneous miscarriages before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded" [23], studies have proven that there is no difference between women with RPL and APS and women with unexplained RPL in number of preceding miscarriage, sequence of pregnancies or maternal age, so that the ESHRE RPL guideline recommend APS testing to all women with two or more, consecutive or not, pregnancy losses [2].

A 2019 comparison of international RPL guidelines regarding definitions, risk factors, investigations and therapeutic options showed that the guidelines agreed on acquired thrombophilia analysis for couples facing RPL stating its possible role in these cases [24].

The antiphospholipid antibodies are lupus anticoagulant (LA), anticardiolipin antibodies (ACA), and anti-B2glycoprotein-I antibodies (B2 GPI) [23]. When it comes to which of these antibodies women should be tested for, the ESHRE guideline recommends screening for LA and ACA (Ig G and Ig M) as there is a body of evidence that proves a significant association of them with RPL [2]. In regards to B2 GPI, there are no studies to prove a statistically significant association with RPL so that the guidelines only recommend screening for these as a means to improve what is known about their role in the pathophysiology of RPL.

To diagnose APS two positive tests are compulsory, in a medium or high titer over 40g/l and taken at least 12 weeks apart for LA or ACA [4]. In regards to when it should be done the first test, ESHRE guidelines recommends is done in an interval of 6 weeks after the pregnancy loss [2].

The mechanism by which APS is involved in RPL implies antiphospholipid antibodies effects on the trophoblast interfering with its differentiation and invasion into the decidua and inducing syncytiotrophoblast apoptosis [3], initiation of complement pathways resulting in inflammation at the trophoblast level and, later in pregnancy, thrombosis of the placental vasculature [25].

The following categories of fertile aged non-pregnant women are eligible for thrombophilia screening:

- History of venous thromboembolism (VTE) associated with a transient risk factor;
- History of unprovoked VTE or recurrent VTE or in association with combined oral contraceptives/ pregnancy;
- First-degree relative with a history of high-risk thrombophilia.

Immunologic factors

Sometimes miscarriages can be caused by immunologic factors as the foetal tissue represents a potential immunologic trigger since it can express paternal antigens or, in the case of assisted reproductive technology, antigens of a gamete donor. Normally, during pregnancy local adaptation of the mother's immune system makes possible the development of the product of conception expressing both maternal (self) and paternal (non self) genes [26]. Any disruption of the maternal-foetal immune homeostasis can contribute to RPL.

It is known that special immune interactions take place at the maternal-foetal interface and that the coexistence between the mother and the fetus and placenta is possible by local adaptation of the maternal immune system through complex mechanisms allowing the development of the pregnancy [26]. It is easy to assume that aberrations in these interactions may lead to RPL but the efforts invested in researching immunological testing has led to controversial results [26].

Regarding immunological testing in the diagnosis of RPL for human leukocyte antigens (HLA), antibodies against male-specific minor histocompatibility (HY) antigens, cytokines, antinuclear antibodies (ANA), natural killer cells (NK cells) and other immunological tests have not been proven to be of value in clinical practice [2].

Endocrine factors

Pregnancy is regulated by a constellation of hormones such as progesterone, oestrogen and thyroid hormones. Progesterone, also known as "the hormone of pregnancy" is one of the widely-known hormones that could be mentioned here. Low level of progesterone seems to be a risk factor for miscarriage. While progesterone supplementation has not been found to add any benefit to women with a history of RPL alone, one study claims that women who suffer from the association of early pregnancy bleeding and a history of miscarriages can benefit from progesterone supplementation [27].

Another factor that has been associated with RPL is hypothyroidism [28] and those patients can clearly benefit from thyroid hormone replacement therapy. Researchers are implying that subclinical hypothyroidism might play a part in recurrent pregnancy loss and while this association remains unclear, a recent study finds that levothyroxine provides no benefit for these patients [29].

Hilali et al. found that metabolic syndrome can lead to a higher frequency of RPL. Of particular significance in relation to a higher rate of miscarriage was a low level of high-density lipoprotein cholesterol (HDL-C). Another important aspect is the elevated risk of coagulation disorders in patients who are at the same time experiencing pregnancy and suffering from metabolic syndrome, both of these being procoagulant state [30].

Diabetes mellitus has long been associated with high-risk pregnancies both in women who develop gestational diabetes and women who had diabetes mellitus before the pregnancy. It is also known that the onset of diabetes mellitus does not coincide with the onset of beta-cell dysfunction. Edugbe et al. mention that normoglycemic women with abnormal beta-cell function can have a higher risk of miscarriage and RPL [31]. A higher triglyceride level has been linked to the onset of insulin resistance and since diabetes mellitus is a risk factor for RPL, Liu et al. have investigated the existence of a direct correlation between high triglyceride level, insulin resistance and RPL. It has been found that women with RPL are at a higher risk of developing hyperinsulinemia and the ratio of CD3+CD4+/CD3+CD8+ could potentially be used a marker for this risk but no direct link has been demonstrated between elevated triglyceride levels and RPL [32].

Uterine factors

Uterine conditions that influence the frequency of RPL are congenital or acquired. The most common uterine abnormality is septate uterus, which even after surgical correction does not lead to improved reproductive outcomes considering the pregnancy loss [33,34]. Adenomyosis is positively correlated with recurrent miscarriage [35]. Intrauterine adhesions form when the basalis layer of the endometrium is affected, such as postpartum or postabortum curettage and is associated with 4.9% miscarriage rate [36].

Male factors

Among the factors that lead to RPL, male factors are often overlooked but should be taken into account. One important factor of male fertility is sperm DNA quality and its effect in early abortions [37]. Most often, subfertility is an issue that belongs to the couple as a whole. To that end, one study found that HLA-C incompatibilities could also be the cause of recurrent early miscarriages [38].

Psychological impact of RPL on the couple

While many clinical trials focus on the medical side of recurrent pregnancy loss (RPL), the psychological impact is often overlooked, although many couples are affected. In a prospective cohort study from Denmark, it was shown that women who had RPL experienced feelings of low energy, loss of interest, sadness and guilt. Also 8.6% women had moderate to severe depression and more frequently, those with primary RPL experienced more frequently than those with secondary RPL the feeling that the life is not worth living and had less self-confidence [39]. Another cross-sectional Danish study, discovered that stress and depression were significantly increased among women with RPL, but male partners had the same prevalence of those emotional disorders as in the general population [40]. A different Danish study in which 13 couples with at least 3 consecutive pregnancy losses were interviewed showed that men had their own feelings of loss but had to support their partners, hence not acknowledging their suffering. The couples wished the medical community to be more open to the psychological impact of the RLP and that more support in that direction should be provided [41].

A study focusing on the improvement of the psychosocial health in women with RPL who received empathic caring via nursing counselling sessions shown that depression and stress have significantly decreased in the experimental group [42].

Conclusions

Chemical compounds commonly found in food, drugs, cosmetics, household items, have been associated with an elevated risk of recurrent pregnancy loss (RPL), such as organophosphate pesticides and bisphenol A that results in the production of polycarbonates [43].

Being obese, tobacco user and excessive alcohol consumption can increase the risk of RPL and so does aneuploidy [44].

Hereditary thrombophilia that can significantly increase the risk of RPL are factor V Leiden mutation, prothrombin G20210A mutation and protein S deficiency [45].

Antiphospholipid syndrome antibodies that have a significantly association with RPL are lupus anticoagulant and anticardiolipin antibodies. Guidelines recommend screening of these antibodies for women with two or more miscarriages [46].

Endocrine factors associated with RPL are low progesterone levels, hypothyroidism, metabolic syndrome (especially low levels of HDL cholesterol) and abnormal beta-cell function [47].

Congenital malformations (such as septate uterus, acquired uterine factors like adenomyosis and uterine synechiae) and infectious factors can increase the risk of recurrent miscarriage [48].

Male factors that have been associated with recurrent early abortions are sperm DNA quality and HLA-C incompatibilities [49].

While many studies have been made about the risk factors, screening methods and medical treatment, the psychosocial impact of RPL is not a frequent topic in the literature, although empathy and support are needed for the couple as a whole in order to withstand the challenge of recurrent miscarriage [50].

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

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