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Review Article

Recurrent pregnancy loss: etiology, pathophysiology, diagnosis and treatment

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Summary

The current article aims to provide an analytical review of the aetiology, pathophysiology, diagnosis, and treatment of recurrent pregnancy loss (RPL) with a focus on Bulgaria. RPL has become an important reproductive health issue worldwide and affects 2%–3% of reproductive-aged women. The findings showed that the etiological factors can be biological, hereditary or environmental, and in approximately 50% of RPL cases, these factors remain unknown. In relation to pathophysiological processes associated with the condition, the findings showed that different etiological factors affect different gestational processes, such as alteration of the structural and nanomechanical abnormalities of the platelets and disruption of the ANXA5 protective shield that prevents adverse pregnancy outcomes. Also, acquired uterine structural defects such as submucosal uterine leiomyomas, endometrial synechiae, and polyps disrupt the implantation and embryonic development processes, which can result in recurrent miscarriages. A common factor for diagnostic approaches to recurrent pregnancy loss is the examination of historical medical records of patients who have experienced the condition and the identification of possible etiological and risk factors. The management and treatment of recurrent pregnancy loss are often based on the results of the diagnostic tests used to determine the underlying etiological factors associated with the condition.

Key words: Plasminogen activator inhibitor (PAI) 4G/5G, M2/ANXA5 Haplotype, progesterone therapy, thyroid hormonal replacement

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Background

The extreme fragility of pregnancy increases the susceptibility of the process to the direct effects of a wide range of complex biological, hereditary and environmental factors. As a result, a significant proportion of women experience pregnancy-related complications, including but not limited to pregnancy losses, that might have a physical and emotional impact on their lives. While pregnancy loss is a common occurrence in gestational and natal processes, it is a complex adverse outcome of the reproduction process that can be caused by various factors such as genetic or chromosomal abnormalities, including endocrine disorders, immunologic and immunogenic factors and thrombophilia

(Cozaru et al. 2019; Dugalic et al. 2019). In gestational literature, early pregnancy loss (EPL) and recurrent pregnancy loss (RPL) are the most common complications of human reproduction and are characterized by profound alterations and changes that directly affect the normal outcome of the process. According Carp HJA (2020) and Capra et al. (2022), recurrent pregnancy loss constitutes a single percent of all pregnancy losses and involves the loss of two or more pregnancies before 24 weeks of the pregnancy. While recurrent pregnancy loss is considered a universal occurrence, different research studies within different regional contexts have reported different aetiological, pathological and diagnostic factors associated with the condition. The current article provides an analytical review of the aetiology, pathophysiology, diagnosis and treatment of recurrent pregnancy loss with a focus on Bulgaria in terms of the incorporated articles and/or population of interest.

Aetiology

The etiological factors associated with recurrent pregnancy loss are wide and varied and can be biological, hereditary or environmental. A research study by Levkova et al. (2020) at the Laboratory of Medical Genetics, Varna, Bulgaria, investigated the causative effect of inherited thrombophilia on recurrent pregnancy loss by focusing on the effect of Factor V (F V) Leiden G1691A, Factor II (F II) G20210A, plasminogen activator inhibitor (PAI) 4G/5G, and methylenetetrahydrofolate reductase (MTHFR) C677T polymorphisms, and the frequency of thrombophilic gene polymorphisms. According to Levkova et al. (2020), the strongest thromboliphic etiological factor associated with recurrent pregnancy loss is Factor V (F V) Leiden G1691A and is mostly prevalent among women with vascular disorders. Further, the authors reported higher concentrations of Factor V (F V) Leiden G1691A and Factor II (F II) G20210A homozygotes in women with recurrent pregnancy loss, which highlights the significance of screening of Factor V (F V) Leiden G1691A variant in thromboliphic women during pregnancy to prevent recurrent pregnancy loss. Another research study by Andreeva et al. (2021), in collaboration with the Bulgarian National Science Fund, examined the effect of inherited thrombophilia on recurrent pregnancy loss. Andreeva et al. (2021) reported that the thromboliphic activation of structural and nanomechanical abnormalities of the platelets leads to increased expression of procoagulant surface markers and significant alteration of the membrane Young modulus that directly affects pregnancy biological processes leading to recurrent pregnancy loss. The findings by Levkova et al. (2020) and Andreeva et al. (2021) clearly identify inherited thrombophilia as an etiological factor for recurrent pregnancy loss within the Bulgarian context.

Ang et al. (2019) conducted a meta-analysis of odds ratios to ascertain the relationship between M2/ANXA5 haplotype and recurrent pregnancy loss among Bulgarian women and their partners. According to Ang et al. (2019), women with the M2/ANXA5 haplotype reported 1.54 odds of having recurrent pregnancy loss as compared to women with the normal haplotype, regardless of whether they had experienced consecutive or non-consecutive pregnancy loss. Further, the results of the study showed that male partners with the M2/ANXA5 haplotype partly contributed to the etiological risk of recurrent pregnancy loss among their female partners. This finding shows an etiologi-

cal association between the M2/ANXA5 haplotype and recurrent pregnancy loss. Another research study by Ardizzone et al. (2022) reported that some of the etiological factors associated with recurrent pregnancy loss include viral infections, structural abnormalities of the reproductive organs, use of drugs or smoking, diabetes, as well as genetic anomalies. According to Ardizzone et al. (2022), the primary etiological mechanisms associated with recurrent pregnancy loss include chromosomal errors during conception that preclude further development and rupture of the maternal-fetal interface, which subsequently leads to bleeding, cramping and eventually recurrent pregnancy loss. A study by Ivanov et al. (2020) also identified polymorphism A1/A2 in the β3 subunit of integrins αIIb/β3 and αV/β3 as an etiological factor for the development of embryonic and fetal recurrent pregnancy loss (RPL). The findings clearly highlight genetic variants and polymorphisms as etiological factors associated with recurrent pregnancy loss.

Also, Capra et al. (2022) performed a systematic review and meta-analysis to determine the relationship between the FV H1299R Variant and the risk of recurrent pregnancy loss (RPL) and reported a slight, statistically insignificant association between the variant and the risk of RPL (1.18, 95% CI: 0.78–1.80, p = 0.44). The results by Capra et al. (2022) are supported by other research studies which have reported an association between different genetic variants and the risk of recurrent pregnancy loss (Andreeva et al. 2021; Angelova et al. 2021; Ang et al. 2019; Levkova et al. 2020). Another research study by Tüttelmann et al. (2023) identified M2/ANXA5 as an etiological factor for recurrent pregnancy loss (RPL) and reported a strong association between the haplotype and the greater overall RPL risk in German and Bulgarian women with “early” fetal losses at the 10th and 15th gestational weeks. Further, Sosic et al. (2022) reported that the presence of a combination of genetic variants of the plasminogen activator inhibitor-1 4G/5G (PAI-1) and methylenetetrahydrofolate reductase (MTHFR C677T) is a predictor of recurrent pregnancy loss among women in Eastern Europe, including Bulgaria. In another research study on the etiological risk factors associated with recurrent pregnancy loss, Turesheva et al. (2023) highlighted maternal age, uterine pathological factors, genetic factors, endocrine disorders and infectious agents as significant etiological factors associated with recurrent pregnancy loss. On the same note, the authors further identified thrombophilia, immune factors and vitamin D deficiency as primary causative agents of the condition.

Pathophysiology

The pathological processes leading to or associated with recurrent pregnancy loss are directly related to the causative etiological factors. First, in relation to the pathophysiological effects of inherited thrombophilia, Andreeva et al. (2021) reported that inherited thrombophilia triggers structural and nanomechanical activation of abnormalities of the platelets resulting in prominent cytoskeletal arrangement, reduced membrane roughness, increased expression of procoagulant surface markers and significant alteration of the membrane Young modulus, that directly lead to recurrent pregnancy loss. Ang et al. (2019) also reported that the M2/ANXA5 thrombotic haplotype causes an insufficient coverage of phosphatidylserine by competing with coagulation binding factors

and development of antiphospholipid antibodies that disrupt the ANXA5 protective shield that prevents adverse pregnancy outcomes. Further, the authors reported that the effects of the haplotype can affect placental development processes such as differentiation of trophoblast and repair of membranes, which directly lead to repeated pregnancy loss. On the same note, according to Tüttelmann et al. (2023), the ANXA5, which is found in the syncytiotrophoblast (SCT) binds to phosphatydilserine surfaces to form two-dimensional crystals, which are essential for the dynamics of membrane repair in living cells. As a result, any inhibitive haplotype, such as the M2/ANXA5, can affect the uteroplacental processes that ultimately lead to recurrent pregnancy losses. The findings clearly show that inherited thrombophilia and its related haplotypic factors cause direct pathophysiological effects on the structural and nanomechanical activation of abnormalities of the platelets and disruption of the ANXA5 processes, which can directly lead to recurrent pregnancy losses.

A review by Sowmya et al. (2022) investigated the pathophysiological processes associated with folate metabolism in repeated pregnancy loss and the correlation with the 5, 10-methylenetetrahydrofolate reductase gene (MTHFR). According to Sowmya et al. (2022), the MTHFR gene performs the catalytic conversion of 5, 10-methylenetetrahydrofolate into 5-methyltetrahydrofolate, the major circulating form of folate which serves as a methyl donor for the re-methylation of homocysteine to methionine. The two common genetic alleles for the MTHFR gene include the C677T and A1298C and are mostly associated with congenital anomalies, coagulation abnormalities and cardiovascular diseases (Sowmya et al. 2022). The review results show that C677T mutation homozygous subjects have significantly higher plasma total homocysteine concentrations than those without the mutation. Further, it was reported that the A1298C mutation homozygotes had a lower concentration of plasma total homocysteine concentrations (Sowmya et al. 2022). The review notes that folate deficiency or the disruption of the folate metabolic pathway can lead to reduced levels of folate and increased homocysteine levels, which are directly associated with congenital abnormalities and recurrent pregnancy loss. According to research by Mihăilă (2020), in Bulgaria, Factor V Leiden (FV) is a primary risk factor for thrombotic accidents and recurrent pregnancy loss, while the role of Factor II G20210A and methylenetetrahydrofolate reductase C677T is still controversial. Mihăilă (2020) report that there is a higher frequency of fetal loss in women with genetic thrombophilia, which is associated with the presence of antiphospholipid antibodies that might cause placenta-mediated pregnancy complications.

Among the various aetiological factors associated with recurrent pregnancy loss, different pathophysiological processes alter the structural and functional aspects of the pregnancy. According to Turesheva et al. (2023), acquired uterine structural defects such as submucosal uterine leiomyomas, endometrial synechiae, and polyps disrupt the implantation and embryonic development processes, which can lead to recurrent miscarriages. Furthermore, genetic factors have been found to influence gestational processes such as tissue development and can sometimes cause karyotype abnormalities that are directly associated with recurrent miscarriages (Sosic et al. 2020; Somwaya et al. 2022; Turesheva et al. 2023). As a result, disruptive genetic structural defects such as polymorphisms interfere with fetal developmental processes and can lead

to recurrent pregnancy loss. Another research study by Lesesve et al. (2019) investigated the significance of erythrocyte morphology during pregnancy and reported that morphologic anomalies of the red blood cells (RBCs) during pregnancy are largely caused by failure of the functioning of the haemostatic system as a result of thrombotic mutations caused by the presence of the thrombotic mutated gene alleles. The accelerated ageing of the erythrocytes of early pregnancy loss patients is associated with the faster transformation of the morphological shape and reduced membrane roughness (Langari et al. 2022; Lesesve et al. 2023). The findings show increasing evidence of a correlation between thrombin generation and plasma hypercoagulability, which can cause major obstetrical syndromes that can lead to recurrent pregnancy loss, as well as the role of erythrocyte morphological anomalies in the condition.

Diagnosis

A common factor for diagnostic approaches to recurrent pregnancy loss is an examination of historical medical records of patients who have experienced the condition and identification of possible etiological and risk factors. Considering the multiple potential etiological and risk factors associated with the condition, there is a wide range of diagnostic assessment techniques for women or couples suffering from RPL. Based on the updated European Society of Human Reproduction and Embryology (ESHRE) guidelines, the prognostic assessment of recurrent pregnancy loss should be based on the patient's profile in terms of age, complete pregnancy history, including a number of previous pregnancy losses, live births, and their sequence (ESHRE 2023). Apart from the prognostic assessment tools, Turesheva et al. (2023) report that genetic factors identification through karyotyping is an effective diagnostic assessment tool for the detection of structural chromosomal anomalies that could cause recurrent pregnancy loss. Also, Hadjidekova et al. (2022) report that preimplantation genetic testing (PGT) can be used to test for a few embryo cells and the selection of an embryo without genetic abnormalities to determine the chances of embryonic chromosomal abnormality that can cause recurrent pregnancy loss. Moreover, according to the ESHRE recommendations, the evaluation of sperm DNA fragmentation in couples with recurrent pregnancy loss is a possible diagnostic technique for the condition and should be considered for diagnostic purposes (ESHRE 2023). However, it is always important to consider that the risks associated with the different diagnostic techniques should not outweigh their respective benefits.

The assessment of uterine anomalies to identify congenital structural pathology associated with recurrent pregnancy loss is a recommended diagnostic technique for the condition. According to Turesheva et al. (2023), ultrasound (US) evaluation with two-dimensional and three-dimensional modalities can be applied to assess uterine anomalies that can contribute to recurrent pregnancy loss. The confirmation of the diagnosis of uterine anatomic pathologies during an ultrasound evaluation requires further assessment using hysteroscopy or laparoscopy equipment (Turesheva et al. 2023; Verma 2023). Also, there are other uterine-based diagnostic techniques, including acquired genital pathologies such as uterine leiomyomas and adenomyosis, as well as pelvic magnetic resonance imaging (MRI). Apart from uterine-based evaluation techniques,

there are chronic endometritis assessments that are performed to identify the role of endometritis in the pathogenesis of recurrent pregnancy loss. Currently, the updated ESHRE guidelines have not approved endometrial biopsy in the workup for RPL, but it has commonly been used in healthcare facilities to diagnose the condition (ESHRE 2023; Turesheva et al. 2023). The most effective and useful chronic endometritis diagnostic tool is office hysteroscopy, which is a minimally invasive procedure for the diagnosis of abnormalities of the endometrial cavities (McQueen et al. 2022; Turesheva et al. 2023). Other possible diagnostic techniques for recurrent pregnancy loss include assessment of related thrombophilic aetiological factors, evaluation of endocrine factors, and assessment of immune factors (Robeva et al. 2022; Pencheva et al. 2023). New and non-invasive approaches can be used to complement the existing diagnostic tests to enhance the accuracy of identification of adverse pregnancies.

Treatment

The management and treatment of recurrent pregnancy loss are often based on the results of the diagnostic tests used to determine the underlying aetiological factors associated with the condition. In this regard, the treatment approaches are dependent upon the symptoms and can either be surgical or medical. Also, there is a wide range of treatments which have been proposed by several research studies and health guidelines such as the ESHRE (2023). A possible surgical treatment approach for recurrent pregnancy loss is hysteroscopy uterine septum resection, which combines hysteroscopy and laparoscopy to manage congenital uterine abnormalities on pregnancy outcomes (ESHRE 2023). Further, there are surgical procedures that can reduce pregnancy loss risks, such as the surgical removal of acquired uterine anomalies—leiomyomas, adhesions, or polyps, uterine curettage and vacuum aspiration. While the ESHRE guidelines are neutral on the application of hysteroscopic removal of submucosal uterine leiomyomas in women with recurrent miscarriages, several research studies have recommended related procedures, including resectioning uterine septa, endometrial synechiae, and submucosal leiomyomas to prevent recurrent pregnancy loss (Carbonnel et al. 2021; Turesheva et al. 2023). Currently, it is important to consider other available minimally invasive approaches to uterine leiomyoma treatment as a fertility-sparing approach for women with the condition.

The ESHRE 2022 guidelines recommend genetic counselling as an effective treatment approach for recurrent pregnancy loss. Based on the guideline, genetic counselling should be complemented with reproductive options when dealing with couples with an abnormal parental karyotype to improve their prognostic awareness of future recurrent pregnancy loss. The applicable reproductive options include a natural pregnancy with/without PGT, gamete donation, and adoption (ESHRE 2022; Turesheva et al. 2023). Apart from genetic counselling and reproductive options, there are other therapeutic approaches, including progesterone therapy and thyroid hormonal replacement. According to the ESHRE guidelines, vaginally administered progesterone prescribed in early pregnancy can prevent potential pregnancy loss risk factors among a subgroup of women with a history of recurrent miscarriages and bleeding. Furthermore, there is evidence of the dydrogesterone therapy effect in the re-

duction of pregnancy loss rate with recommendations of 10–20 mg daily until the 20th gestational week for patients with idiopathic recurrent pregnancy loss (ESHRE 2022; Turesheva et al. 2023). In relation to thyroid hormone replacement, Turesheva et al. (2023) report that patients who experience recurrent pregnancy loss and apparent clinical hypothyroidism diagnosed before or during early pregnancy stages can be treated using levothyroxine to prevent pregnancy outcomes associated with overt and subclinical hypothyroidism. Also, recurrent pregnancy loss can be treated through the management of thrombophilic effects of pregnancy outcomes in women through the use of anticoagulation therapy. Lastly, another possible form of treatment for recurrent pregnancy loss is through Vitamin D supplementation for preconception counselling and during pregnancy.

Conclusion

The findings in this article show that different etiological factors associated with recurrent pregnancy loss have different pathophysiological effects on the gestational processes leading to the condition. Also, they show that the etiological factors can be biological, hereditary or environmental. Some of the biological factors include maternal age, uterine pathological factors, immune factors and endocrine disorders, while the hereditary factors include genetic predispositions and inherited thrombophilia. The identified etiological environmental factors include infectious agents and Vitamin D deficiency. In relation to pathophysiological processes associated with the condition, the findings show that different etiological factors affect different gestational processes, such as alteration of the structural and nanomechanical abnormalities of the platelets, disruption of the ANXA5 protective shield that prevents adverse pregnancy outcomes, faster transformation of the morphological shape of erythrocytes and the reduced membrane roughness. The diagnostic approaches and treatment techniques related to recurrent pregnancy loss are often based on the etiological factors and the related pathophysiological processes. Various diagnostic techniques include prognostic assessments, karyotyping and ultrasound evaluation. Lastly, the applicable treatment options include surgical procedures, medication, genetic counselling and hormonal therapy.

Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

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Data availability
All of the data that support the findings of this study are available in the main text.

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