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CLINICAL DEFINITION AND MODERN VIEWS ON THE ETIOPATHOGENESIS OF RECURRENT PREGNANCY LOSS

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Abstract:

Recurrent pregnancy loss (RPL) is a multifactorial reproductive disorder characterized by repeated pregnancy failure and persistent diagnostic uncertainty. This review summarizes current evidence on the clinical definition and major etiopathogenetic mechanisms of RPL, including chromosomal abnormalities, antiphospholipid syndrome, immune dysfunction, endocrine-metabolic disturbances, and uterine structural abnormalities. The strongest evidence supports embryonic chromosomal errors and antiphospholipid syndrome as major contributors, whereas the roles of inherited thrombophilia, natural killer cells, and some metabolic markers remain less consistent. Overall, RPL requires a multidisciplinary, evidence-based, and patient-centered approach, although a considerable proportion of cases remain unexplained.

Keywords: recurrent pregnancy loss; recurrent miscarriage; etiopathogenesis; thrombophilia; thyroid autoimmunity; uterine anomalies; preconception evaluation

INTRODUCTION

The relevance of the topic is determined by the high medical and social burden of recurrent pregnancy loss in women of reproductive age [1,6]. RPL is associated not only with repeated reproductive failure, but also with persistent psycho-emotional stress, prolonged preconception care, and an increased need for repeated diagnostic interventions [4]. Despite major progress in reproductive genetics, immunology, and imaging, a substantial proportion of patients still complete evaluation without a clearly established cause [16]. This persistent idiopathic fraction keeps RPL at the center of both clinical practice and scientific discussion [6].

Another reason the topic remains highly important is the heterogeneity of pathogenic pathways [6,11,20]. RPL is not a single disease; rather, it is a clinical syndrome in which genetic, thrombophilic, immunologic, endocrine, metabolic, and anatomical mechanisms may act independently or in combination [6,11,20]. Because therapeutic effectiveness depends on correct phenotyping of the patient, clinicians need a structured understanding of which etiological factors are strongly evidence-based, which remain controversial, and which should be investigated only in selected circumstances [6].

OBJECTIVE

To summarize modern views on the clinical definition and principal etiopathogenetic mechanisms of recurrent pregnancy loss and to identify the factors with the greatest diagnostic and practical significance for contemporary preconception evaluation.

DESIGN

This article is a review of contemporary international literature devoted to the causes and clinical interpretation of recurrent pregnancy loss. The review synthesizes international guideline documents, systematic reviews, meta-analyses, and representative clinical studies devoted to the definition, classification, and major etiological pathways of RPL. The material was grouped into the following domains: genetic factors, thrombophilia, immunologic mechanisms, endocrine and metabolic disturbances, and congenital or acquired uterine pathology.

RESULTS

RPL is currently understood as the loss of two or more pregnancies, a definition that allows earlier clinical evaluation than older three-loss thresholds and better reflects the cumulative burden carried by affected couples [6]. In practical terms, the distinction between primary and secondary RPL remains useful because it may point to differences in previous reproductive adaptation and, in some women, to different immunologic backgrounds [18]. Modern guidelines also emphasize that the diagnostic pathway should not be identical for all women; instead, it should be tailored to age, prior live birth, gestational age at the losses, and the presence of associated risk factors [19].

Genetic factors remain central in the pathogenesis of early pregnancy failure [14]. The literature indicates that chromosomal abnormalities

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account for a substantial proportion of sporadic first-trimester losses and remain common in recurrent losses, where the frequency of abnormal embryonic karyotypes is still considerable. Therefore, analysis of products of conception has important explanatory value [6,14]. Contemporary evidence suggests that genetic testing of pregnancy tissue, especially when euploid loss can be distinguished from aneuploid loss, may reduce unnecessary additional testing and can improve etiological counseling, even if it does not always predict the outcome of the next pregnancy [14]. Thus, genetics is essential not only as a causal domain, but also as a triage tool in the broader diagnostic strategy.

The role of thrombophilia in RPL is more nuanced [3,6,7,10,12]. Inherited thrombophilias such as Factor V Leiden mutation, prothrombin G20210A mutation, and deficiencies of protein C, protein S, or antithrombin have been studied extensively [3,7,12]. Some meta-analyses show statistically significant associations, particularly for Factor V Leiden and prothrombin G20210A, but the translation of these associations into clinical benefit from routine screening or universal anticoagulant treatment remains unproven [3,6,7]. In contrast, antiphospholipid syndrome is one of the most robustly confirmed causes of pregnancy loss [13,16]. Persistent lupus anticoagulant, anticardiolipin antibodies, and anti-β2-glycoprotein I antibodies have clear pathogenic relevance because they interfere with placental vascular function and trophoblast biology [13,16]. For that reason, antiphospholipid antibody testing occupies a much stronger place in modern recommendations than inherited thrombophilia panels [6,13,16].

Immunologic mechanisms represent one of the most actively debated areas in RPL research [4-6]. Successful pregnancy requires finely regulated fetomaternal tolerance, and disruption of this balance may impair implantation, placentation, or early embryonic development [5,6]. However, the clinical interpretation of immune findings remains difficult [4-6]. Associations with HLA compatibility patterns have not been reproduced consistently across populations [6]. Antinuclear antibodies and altered natural killer-cell levels are reported in some studies and meta-analyses, but these markers still suffer from heterogeneity of laboratory methodology, uncertain threshold values, and limited predictive specificity [4-6]. Accordingly, immune dysregulation is biologically plausible and likely relevant in a subset of patients, but routine broad immunologic screening remains insufficiently justified in standard practice [6].

Endocrine and metabolic factors also contribute to the contemporary etiopathogenetic model of RPL [2,6,9,11,17,20]. Thyroid hormones are necessary for folliculogenesis, implantation, and early embryonic development, whereas thyroid autoimmunity has shown a more consistent association with miscarriage risk than overt thyroid dysfunction itself [17,20]. Current evidence supports assessment of thyroid-stimulating hormone and thyroid peroxidase antibodies in appropriate clinical settings [2,6,17,20]. Polycystic ovary syndrome and insulin resistance are also important because they are linked with obesity, hyperinsulinemia, chronic low-grade inflammation, and hyperandrogenism, all of which may adversely affect endometrial receptivity and early placentation [9,11]. Yet the available data still do not support indiscriminate laboratory screening for every endocrine or metabolic marker in all patients with RPL [6,11,20]. Hyperprolactinemia and vitamin D deficiency are similarly discussed as potential contributors, but their exact causal and prognostic roles remain incompletely established [1,11].

Anatomical factors retain major practical importance because they are among the few potentially correctable causes of RPL [6,8,19]. Congenital Müllerian anomalies, especially septate and bicornuate uterus, are associated with a higher risk of miscarriage, while acquired intrauterine pathology such as submucosal fibroids, endometrial polyps, intrauterine adhesions, adenomyosis, and chronic endometritis may further worsen reproductive outcomes in selected patients [8,15,19,21]. This explains the continued value of structured imaging of the uterine cavity and morphology [6,8,19]. Modern evidence favors transvaginal three-dimensional ultrasonography as a highly informative first-line modality, with hysteroscopy reserved for clarification or treatment when needed [6,8].

A key integrated conclusion from the reviewed literature is that approximately half of RPL cases remain unexplained despite modern investigation [6]. This idiopathic fraction does not imply absence of pathology; rather, it reflects the interplay of subtle endometrial, vascular, immunologic, genetic, and metabolic abnormalities that are still not fully measurable in routine clinical care [6,11,20]. For this reason, modern concepts increasingly support multidisciplinary phenotyping and preconception optimization instead of indiscriminate testing [6]. In other words, the value of the current etiopathogenetic model lies not in expanding the number of investigations endlessly, but in selecting the most informative tests for each clinical profile [6].

CONCLUSION

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Modern views on RPL confirm that the syndrome is multifactorial and clinically heterogeneous. The strongest evidence supports a meaningful role for embryonic genetic abnormalities, antiphospholipid syndrome, thyroid autoimmunity in selected women, and congenital or acquired uterine pathology. By contrast, inherited thrombophilia, broad immunologic screening, isolated endocrine abnormalities, and vitamin D deficiency remain areas where the evidence is incomplete or context-dependent. Consequently, the most rational contemporary approach to RPL is an individualized and multidisciplinary one that combines targeted diagnostic evaluation with preconception risk modification. The persistence of a large idiopathic subgroup underscores the need for further research into the interaction between classical etiological factors and broader metabolic disturbances, including the potential role of metabolic syndrome.

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