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The Genetic Landscape of Implantation: How IL-2, TAFI, PAEP, and VEGF Variants Impact Fertility Outcomes

Short title: Genetic Variants in Implantation and Pregnancy Loss

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Abstract:

Unexplained infertility (UI) and recurrent pregnancy loss (RPL) pose substantial challenges in reproductive medicine, often arising from impaired endometrial receptivity during the critical implantation window. This narrative review synthesizes current evidence on the role of genetic polymorphisms in key regulatory genes interleukin-2 (IL-2), thrombin-activatable fibrinolysis inhibitor (TAFI), progesterone-associated endometrial protein (PAEP), and vascular endothelial growth factor (VEGF) in modulating immune responses, fibrinolytic balance, uterine remodeling, and angiogenesis. We explore how single nucleotide polymorphisms (SNPs) in these genes influence molecular and cellular mechanisms essential for successful embryo implantation and pregnancy maintenance. The review highlights associations of specific SNPs such as IL-2 -330 T/G, TAFI Thr325Ile, VEGF -1154 G/A, and VEGF -2578 C/A with altered gene expression and protein function, contributing to implantation failure, pregnancy loss, and infertility. Understanding these genetic factors enhances insights into the pathogenic pathways of UI and RPL and may guide the development of diagnostic markers and personalized therapeutic strategies to improve reproductive outcomes.



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Keywords:

Unexplained infertility, recurrent pregnancy loss, endometrial receptivity, genetic polymorphisms, implantation failure

Introduction

Infertility affects approximately 10-15% of couples worldwide and is a significant reproductive health challenge. Among infertile women a substantial proportion is diagnosed with unexplained infertility where no clear anatomical, hormonal or genetic cause is identified despite thorough investigation [1]. UI is defined as failure to conceive after 12 months despite normal evaluations, while RPL refers to ≥ 2 consecutive losses before 20 weeks (per ASRM guideline). Overlaps exist, but implantation defects may underpin both. Recurrent pregnancy loss (RPL) defined as two or more consecutive pregnancy losses before 20 weeks of gestation affects approximately 1-3% of women and shares overlapping etiological factors with infertility [2]. Although various causes of infertility and RPL have been established including uterine abnormalities, thrombophilia, chromosomal anomalies, and endocrine dysfunctions, a significant subset remains idiopathic. Growing evidence suggests that subtle genetic variations particularly polymorphisms in genes regulating immune function, fibrinolysis, endometrial receptivity, and angiogenesis, may contribute to implantation failure and early pregnancy loss [3-8].

Successful implantation requires synchronized communication between a receptive endometrium and a competent embryo during a limited implantation window (days 19-23 of the menstrual cycle). This period is characterized by specific molecular, cellular, and vascular changes in the endometrium including immune cell modulation, extracellular matrix remodeling, and angiogenesis [9]. Impaired endometrial receptivity has been implicated as a key factor in unexplained infertility and RPL with disturbances in cytokine production, fibrinolytic balance, and angiogenic factors disrupting the implantation microenvironment [10].

Four critical gene products have emerged as regulators of implantation: Interleukin-2 (IL-2), Thrombin-Activatable Fibrinolysis Inhibitor (TAFI), Progesterone-Associated Endometrial Protein (PAEP, also known as glycodeclin), and Vascular Endothelial Growth Factor (VEGF).

IL-2 is a cytokine essential for immune tolerance and regulation during implantation. It modulates T cell proliferation and helps maintain the delicate balance between maternal immune acceptance of the embryo and defense against pathogens [11]. TAFI regulates fibrinolysis by inhibiting plasmin generation thus stabilizing the extracellular matrix and promoting successful trophoblast invasion [12]. Dysregulated fibrinolysis has been associated with miscarriage and implantation failure. PAEP is a glycoprotein expressed in the endometrium during the luteal phase. It has immunosuppressive properties and participates in remodeling the uterine environment to favor implantation [13]. VEGF is a potent angiogenic factor critical for the vascular remodeling required for placental development. Altered VEGF expression impairs endometrial blood supply leading to implantation defects and early pregnancy loss [14].



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Polymorphisms in IL-2, TAFI, PAEP, and VEGF have been studied in unexplained infertility (UI) and recurrent pregnancy loss (RPL). IL-2 and TAFI have been primarily investigated in RPL cohorts, PAEP mainly in RPL with limited UI data, and VEGF extensively in both conditions. Single nucleotide polymorphisms (SNPs) may affect gene expression or protein function thereby altering the molecular milieu of the implantation window. For example, the IL-2 promoter polymorphism -330 T/G has been linked to altered cytokine production and increased miscarriage risk [15]. The TAFI Thr325Ile polymorphism influences enzyme activity and has been associated with thrombophilia-related pregnancy complications [16]. VEGF SNPs such as -1154 G/A and -2578 C/A affect VEGF levels and vascular development [17]. PAEP polymorphisms are less studied but may impact protein glycosylation and immunomodulatory functions [13]. This narrative review aims to comprehensively evaluate the current evidence on polymorphisms in IL-2, TAFI, PAEP, and VEGF genes and their associations with unexplained infertility and recurrent pregnancy loss during the implantation window. Understanding these genetic factors can aid in developing diagnostic biomarkers and therapeutic interventions targeting implantation failure. It is critical to distinguish between unexplained infertility (UI) and recurrent pregnancy loss (RPL). While UI represents a failure to achieve a clinical pregnancy after at least one year of unprotected intercourse, RPL involves the repeated loss of established pregnancies. Although both conditions share common pathophysiological pathways such as impaired endometrial receptivity and immune dysregulation at the maternal-fetal interface the genetic predisposition and clinical management of these patient populations differ. In this review, we carefully delineate the genetic evidence according to the specific clinical cohort evaluated in primary studies.

A narrative literature search was conducted using PubMed, Scopus, and Google Scholar to identify studies addressing the association of IL-2, VEGF, TAFI, and PAEP polymorphisms with unexplained infertility (UI), recurrent pregnancy loss (RPL), implantation failure, and related reproductive outcomes. Search terms included combinations of gene names, polymorphism-related terms, and reproductive phenotypes, such as “IL-2 polymorphism AND infertility,” “TAFI Thr325Ile AND pregnancy loss,” “PAEP AND implantation,” and “VEGF SNP AND recurrent miscarriage.” We considered human studies published in English between 2000 and January 2025, including case-control studies, cohort studies, and meta-analyses. Studies were selected based on their relevance to the biological roles of these genes in implantation, immune tolerance, angiogenesis, fibrinolysis, and endometrial receptivity. Animal studies, studies focused on non-reproductive outcomes, conference abstracts without sufficient methodological details, and reports lacking primary or interpretable genetic data were excluded. Because this work was designed as a narrative review rather than a systematic review, no formal PRISMA flow diagram or quantitative quality scoring system was applied, which may subject the selection process to potential bias. Nevertheless, the literature was critically appraised with attention to study design, sample size, phenotypic precision, reproducibility, and the presence or absence of functional support. When findings were conflicting, greater interpretive weight was given to evidence derived from larger cohorts, clearer phenotype definitions, replication across independent populations, and studies supported by functional data. Additionally, to avoid data redundancy, overlapping or duplicate datasets were carefully evaluated, prioritizing the



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most comprehensive or methodologically informative report. Given these methodological limitations, the conclusions should be viewed as hypothesis-generating rather than definitive.

IL-2 Gene Polymorphisms in Infertility and Recurrent Pregnancy Loss

Interleukin-2 (IL-2) is a key cytokine produced predominantly by activated T cells and plays a pivotal role in regulating immune responses. It controls the proliferation and differentiation of regulatory T cells (Tregs) which are essential for maintaining maternal immune tolerance to the semi-allogeneic fetus. During the implantation window IL-2 contributes to the balance between immune tolerance and defense facilitating a hospitable endometrial environment for the embryo. Aberrant IL-2 levels have been implicated predominantly in RPL, with limited evidence available regarding unexplained infertility. Most IL-2 promoter polymorphism studies, were conducted in RPL cohorts rather than UI. Both excessive and insufficient IL-2 production can disrupt the immune milieu necessary for successful implantation [11,18,19]. The IL-2 gene is located on chromosome 4q27 and several single nucleotide polymorphisms (SNPs) within its promoter region have been studied in reproductive disorders. The most investigated polymorphisms are as follows: -330 T/G (rs2069762) a variant in the promoter region that affects transcriptional activity. The G allele is often associated with higher IL-2 expression. Another polymorphism is -384 T/C (rs2069763), promoter SNP with potential regulatory effects [20]. Functional studies show that these polymorphisms can alter IL-2 mRNA levels, influencing Treg populations and immune tolerance during pregnancy [19]. The IL-2 promoter -330 T/G polymorphism is the best-characterized variant influencing miscarriage risk and potentially infertility. By modulating IL-2 production it affects immune tolerance crucial for embryo implantation. However, heterogeneity between studies warrants further research. Overall, IL-2 promoter polymorphisms, particularly -330 T/G, show relatively consistent associations with altered immune regulation and increased RPL risk, whereas evidence for UI remains limited. While IL-2 modulates immune tolerance, angiogenesis driven by VEGF is equally critical for successful implantation. The following section examines VEGF polymorphisms and their impact on endometrial vascularization.

Synthesizing the available data, the IL-2 -330 T/G variant displays conflicting results across studies. While some case-control studies link the G allele to increased RPL risk, others report no significant association. This inconsistency may stem from variations in control group definitions (e.g., fertile women vs. the general population) and differences in environmental co-factors that influence cytokine expression, rendering the current quality of evidence moderate at best.

VEGF Gene Polymorphisms and Angiogenesis in Implantation

Vascular Endothelial Growth Factor (VEGF) encoded by the VEGF-A gene on chromosome 6p21.3 is a potent regulator of angiogenesis and vascular permeability. During the implantation window VEGF drives remodeling of spiral arteries and endometrial vascularization which are essential for nourishing the developing embryo. Alterations in VEGF expression or activity can impair endometrial receptivity



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leading to implantation failure and pregnancy loss [21,22]. Multiple VEGF SNPs have been investigated in relation to infertility and RPL notably: -1154 G/A (rs1570360) is associated with reduced promoter activity and VEGF expression, -2578 C/A (rs699947) affects transcription factor binding and expression levels, +936 C/T (rs3025039) located in the 3'-UTR, influences mRNA stability. Functional studies demonstrate these polymorphisms alter VEGF serum levels and bioavailability in the endometrium [22]. Sun et al. in a meta-analysis showed that only rs1570360 (especially in Caucasians) and rs3025039 (especially in East Asians) may be risk factors for RPL [23]. Xu et al. (2015) conducted a meta-analysis indicated that rs1570360, rs3025039, rs2010963, and rs3025020 polymorphisms increase RPL susceptibility. Moreover, rs1570360 and rs3025039 polymorphisms may play various roles in RPL susceptibility in various geographic groups [17]. VEGF polymorphisms, particularly -1154 G/A, -2578 C/A, and +936 C/T, have been studied in both unexplained infertility and RPL, although the majority of genetic association primarily focused on RPL populations. The functional consequences of these polymorphisms on VEGF expression may lead to inadequate angiogenesis during the implantation window causing insufficient decidual vascular remodeling. This vascular insufficiency predisposes to implantation failure and miscarriage. Given these associations, VEGF polymorphisms have been proposed as candidate biomarkers for recurrent miscarriage risk assessment and therapeutic targeting to improve uterine vascularization. Several VEGF promoter and 3'-UTR polymorphisms have been implicated in impaired angiogenesis, with meta-analyses supporting associations mainly with RPL.

In synthesis, while the association between VEGF polymorphisms (specifically -1154 G/A and -2578 C/A) and reproductive failure is biologically plausible due to the role of VEGF in vascular remodeling, the clinical evidence is highly heterogeneous. Meta-analyses point toward a stronger association in East Asian populations compared to European cohorts, indicating that genetic background and ethnic stratification are major confounding factors. The strength of evidence for VEGF is moderate, but still limited by the lack of direct functional assays in human endometrial tissue.

Thrombin-Activatable Fibrinolysis Inhibitor (TAFI) Polymorphisms and Functional Role

Thrombin-Activatable Fibrinolysis Inhibitor (TAFI) encoded by the CPB2 gene on chromosome 13q14.11 is a plasma proenzyme that plays a key regulatory role in fibrinolysis. Upon activation by thrombin-thrombomodulin complex, TAFI attenuates fibrinolysis by cleaving C-terminal lysine residues on fibrin, reducing plasminogen activation and thus stabilizing blood clots. Most available evidence on TAFI polymorphisms, including Thr325Ile (+1040C/T), originates from RPL studies, with no substantial data linking TAFI variants to unexplained infertility. In the context of early pregnancy TAFI contributes to the remodeling of the extracellular matrix at the maternal-fetal interface promoting trophoblast invasion and placental development. Proper balance of fibrinolysis is crucial, excessive fibrinolysis can lead to implantation failure, whereas insufficient fibrinolysis predisposes to thrombosis and miscarriage [12]. Several polymorphisms in the CPB2 gene influence TAFI plasma levels and enzymatic activity. Thr325Ile (rs1926447) a missense variant resulting in a threonine to isoleucine substitution at position 325 associated with altered enzyme stability and activity. The Ile allele



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generally leads to higher TAFI activity and prolonged antifibrinolytic effect [16]. -438 G/A (rs2146881) is a promoter polymorphism linked to TAFI plasma concentrations. Other intronic and 3'-UTR variants that may affect gene expression [24]. Studies investigating TAFI polymorphisms in pregnancy complications have yielded mixed results. A case-control study in Iran involving 200 women with RPL and 200 controls with successful pregnancies analyzed ten polymorphisms across seven thrombophilia genes using PCR-RFLP. Polymorphisms in BF (-455 G/A), MTHFR (677 C/T, 1298 A/C), PAI-1 (-675 I/D, 4G/5G), FV Leiden, FV (A5279G), and FXIII (Val34Leu) showed a positive association with RPL while ITGB3 (1565 T/C) had a negative association. No significant link was found for FII (A20210G) and FV (A4070G) polymorphisms. These findings underscore the value of thrombophilia screening in RPL patients though larger studies are needed to explore novel genetic variants [25]. A study comparing 50 RPL patients to 50 healthy controls investigated the association of the TAFI 1040C/T polymorphism with RPL risk. Results showed no significant correlation between the C/C or C/T genotypes and RPL susceptibility, nor a statistically meaningful difference in allele frequencies. Therefore, the TAFI 1040C/T variant is unlikely to serve as a predictive molecular marker for RPL in the studied Egyptian population [26]. The Thr325Ile polymorphism modulates the half-life of activated TAFI influencing the fibrinolytic threshold during implantation. Increased TAFI activity may lead to excessive clot stabilization, impairing trophoblast invasion and decidual vascular remodeling, key steps for embryo implantation [12]. TAFI genetic variants, particularly Thr325Ile, have been associated with thrombophilia-related RPL; while they are hypothesized to contribute to implantation failure by altering fibrinolytic balance, this remains speculative and requires further investigation in UI cohorts. Larger multiethnic studies and functional assays are needed to confirm these findings. TAFI Thr325Ile is the most investigated variant, generally suggesting an association with thrombophilia-related RPL, though findings vary across populations.

Evidence regarding TAFI variants, particularly Thr325Ile, remains highly fragmented. The majority of studies are confined to thrombophilic RPL cohorts, with minimal research directly addressing unexplained infertility (UI). The lack of replication in diverse cohorts and the modest sample sizes of published studies limit the strength of these findings, classifying the current evidence level for TAFI as low-to-moderate.

Progestagen-Associated Endometrial Protein (PAEP)

PAEP also known as glycodeclin, is a glycoprotein expressed predominantly in the endometrium during the luteal phase and early pregnancy. It plays an immunomodulatory role by suppressing natural killer cell activity and promoting a tolerogenic uterine environment conducive to embryo implantation [27]. PAEP also participates in remodeling the extracellular matrix and modulating cell adhesion molecules which are critical for trophoblast attachment and invasion [13]. The PAEP gene is located on chromosome 9q34.3. Polymorphisms affecting its expression or glycosylation pattern may influence endometrial receptivity: SNPs in the promoter region that potentially modulate transcriptional activity, variants influencing glycosylation sites, altering PAEP immunosuppressive functions



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[27]. Research into PAEP polymorphisms remains limited compared to IL-2, TAFI, and VEGF. A retrospective case-control study involving 200 Palestinian women (100 with RPL and 100 controls) assessed this SNP using PCR-RFLP. The findings revealed a significant association between the PAEP T/C genotype and T allele with increased risk of RPL. This study is the first to demonstrate that the PAEP rs760140467 C>T polymorphism is strongly linked to RPL in this population suggesting potential avenues for improved diagnosis and therapeutic strategies [28]. Uchida et al. (2013) reported decreased PAEP expression in the endometrium of women with unexplained infertility and RPL [13]. The rs760140467 C>T polymorphism of PAEP has been evaluated specifically in RPL cohorts, while reduced endometrial expression of PAEP has been reported in both unexplained infertility and RPL. However, data on UI-specific PAEP polymorphisms remain scarce. Although PAEP polymorphisms are less frequently studied compared with IL-2, TAFI, and VEGF, current evidence particularly on rs760140467 C>T suggests a potential role in RPL. Limited expression studies also indicate reduced PAEP levels in UI and RPL. More studies are necessary to clarify the functional impact of PAEP variants and their clinical relevance. Given the biological relevance of PAEP in immune tolerance, its expression and genetic variants warrant further mechanistic study. However, current genetic association data are too limited to propose these variants as clinical biomarkers or therapeutic targets for infertility. PAEP evidence is more limited, with the rs760140467 C>T variant showing a possible association with RPL and reduced endometrial PAEP expression observed in both UI and RPL.

Currently, the scientific narrative for PAEP variants is the least established among the investigated genes. Although PAEP (glycodelin) is biologically essential for local immunomodulation, association studies linking its polymorphisms to UI or RPL are extremely sparse and population-specific. Most claims are built on hypothesized mechanisms rather than robust, replicated association data, highlighting a critical gap in the literature.

Discussion

Comparative Assessment of Genetic Evidence

To provide a coherent scientific narrative, we compared the investigated genetic variants according to the strength, consistency, and quality of the available evidence, as summarized in Table 1. Across the four pathways, the level of support varies considerably. VEGF currently has the most consistent evidence, supported by multiple association studies and several meta-analyses, although ethnic heterogeneity remains an important limitation. IL-2 shows moderate evidence, with a biologically plausible role in immune tolerance but inconsistent replication across populations. In contrast, TAFI and PAEP remain far less established, as the available data are sparse, often population-specific, and largely preliminary. This comparative framework helps distinguish where the literature is relatively mature from where it remains exploratory, and it prevents mechanistic plausibility from being overinterpreted as clinical validation.



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Successful implantation and early pregnancy maintenance require coordinated immune tolerance, vascular remodeling, fibrinolytic balance, and endometrial receptivity. Within this framework, IL-2 appears to contribute to maternal-fetal immune regulation through its role in T-cell activation and regulatory T-cell expansion. Variants in IL-2 regulatory regions, particularly the -330 T/G SNP, may alter cytokine expression and thereby influence the balance between effector and tolerogenic immune responses during the implantation window [19]. However, although these mechanisms are biologically credible, the association data are not yet sufficiently consistent to support clinical translation.

PAEP is another gene with clear biological relevance, particularly through its local immunomodulatory effects and its role in supporting a tolerogenic endometrial environment [13]. Alterations in PAEP expression or glycosylation may affect natural killer cell activity and endometrial receptivity, suggesting a plausible contribution to implantation failure [29]. Nevertheless, the current genetic evidence is extremely limited, and most reported associations are derived from small or RPL-oriented cohorts. Accordingly, PAEP variants should currently be viewed as hypothesis-generating rather than clinically actionable.

Among the pathways reviewed, VEGF is the most strongly supported biologically and epidemiologically. VEGF is essential for angiogenesis and uterine spiral-artery remodeling during the implantation period [22], and promoter or untranslated-region variants (such as -1154 G/A, -2578 C/A, and +936 C/T) may reduce gene expression and impair vascular adaptation [17]. Such dysregulation could contribute to hypoxic endometrial conditions and failed implantation. Even so, the available findings remain heterogeneous across populations, and the evidence does not yet justify use of VEGF polymorphisms as predictive biomarkers in routine practice.

TAFI is mechanistically linked to fibrinolysis and extracellular matrix remodeling, processes that are relevant to trophoblast invasion and placental development [12]. Variants such as Thr325Ile (rs1926447) may prolong antifibrinolytic activity and thereby promote excessive fibrin persistence at the maternal-fetal interface [16]. Although this provides a credible biological rationale, the published association studies are limited in number, often based on small cohorts, and show inconsistent replication. Moreover, most available data concern RPL rather than UI, so extrapolation to implantation failure should be made cautiously. At present, TAFI remains an exploratory candidate rather than a validated clinical marker.

More broadly, the literature suggests that interactions among immune-regulatory, angiogenic, and fibrinolytic pathways may jointly influence reproductive outcomes. Multilocus and haplotype-based studies remain limited, but they may help clarify how combined genetic effects shape risk profiles in future research [17]. Likewise, integrated genetic-proteomic approaches may eventually improve biological stratification; however, these strategies are not yet validated for routine clinical use. Thus, while the four genes reviewed here are all biologically plausible contributors to implantation-related disorders, the current evidence base is insufficient to support routine screening, prognosis, or individualized therapy.



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This review aimed to synthesize mechanistic insights rather than provide study-level quantitative comparisons, and therefore gene-specific pathways and biological relationships are presented in a conceptual framework (Fig 1).

Limitations

This review is limited by the heterogeneity of the published literature, including differences in phenotype definition, population background, sample size, and study design. Many studies were underpowered, and replication across independent cohorts was often inconsistent. In addition, functional validation was unavailable for several reported associations, which limits interpretation of biological causality. Because this was a narrative review, the selection and interpretation of studies may also be subject to bias. For these reasons, the findings should be regarded as hypothesis-generating rather than definitive.

Table 1. Summary and Appraisal of Evidence for Genetic Variants Associated with UI and RPL.

Gene	Biological Process	Target Phenotype	Observed Association Strength	Hypothesized Biological Mechanism	Clinical Applicability	Level of Evidence & Key Limitations
VEGF	Angiogenesis & Vascular Remodeling	Mainly RPL, some UI/RIF studies	Moderate to High (Extensively studied in multiple populations; meta-analyses available but show population-specific variations).	Critical regulator of angiogenesis and vascular permeability during implantation and placentation.	High biological plausibility; potential future candidate for multi-gene panels, but current routine clinical use is not supported.	Moderate; limited by ethnic heterogeneity and lack of large-scale functional validation.
IL-2	Immune Tolerance & Treg regulation	RPL and UI	Moderate (Replicated in several RPL cohorts; limited and conflicting data in UI).	Key cytokine mediating maternal-fetal immunotolerance and Th1/Th2 balance during early pregnancy.	Exploratory; helps understand immune-mediated failure but lacks standardization for clinical screening.	Low-Moderate; limited by small sample sizes and lack of multi-center replication.
TAFI	Fibrinolysis & Extracellular Matrix	RPL (Thrombophilia-related)	Low to Moderate (Limited association data; mainly studied in thrombophilia-related RPL cohorts; inconsistent results).	Modulates fibrinolytic balance and extracellular matrix remodeling at the implantation site.	Currently not recommended for clinical use; limited to hypothesis generation.	Low; requires confirmation in larger, well-defined cohorts with standardized clinical criteria.
PAEP	Endometrial Immunomodulation	UI and early RPL	Low (Very few primary studies; small sample sizes; requires extensive validation).	Encodes Glycodelin, which is essential for immunosuppression and endometrial receptivity.	Preliminary research stage; no current clinical diagnostic or therapeutic applicability.	Low; clinical data are highly preliminary; functional impact of specific SNPs remains mostly speculative.

Barriers to Clinical Translation

Despite the biological plausibility linking polymorphisms in IL-2, VEGF, TAFI, and PAEP to reproductive failure, several important limitations currently preclude their translation into routine clinical practice. The existing literature is constrained by small sample sizes, ethnic heterogeneity, inconsistent phenotype definitions, and limited replication across independent cohorts, all of which reduce statistical power and restrict generalizability. In addition, many reported associations lack robust functional validation; without



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mechanistic evidence demonstrating how specific variants influence protein expression, signaling pathways, or endometrial function, these findings remain largely speculative. Accordingly, although these genes are biologically relevant candidates, the current evidence base does not support their use in routine screening, prognosis, or personalized therapeutic decision-making.

A further challenge is the frequent lack of clear clinical separation between unexplained infertility (UI) and recurrent pregnancy loss (RPL) in genetic association studies. Much of the available evidence is derived from RPL cohorts and is subsequently extrapolated to implantation failure or UI, despite the fact that these conditions represent distinct reproductive phenotypes with different temporal and biological characteristics. Future studies should therefore apply stricter phenotype definitions and evaluate UI and RPL populations separately to avoid conflating genetic contributors to failed implantation with those involved in post-implantation pregnancy loss.

Conclusion

While the investigated pathways involving IL-2, VEGF, TAFI, and PAEP are biologically plausible contributors to endometrial receptivity and early pregnancy maintenance, the current body of evidence remains heterogeneous and largely associative. Given that unexplained infertility (UI) and recurrent pregnancy loss (RPL) represent distinct clinical entities, findings should be interpreted separately, and routine clinical testing or therapeutic interventions based on these polymorphisms are not currently justified. Future research must shift from small-scale association studies toward large, multi-ethnic cohorts with standardized phenotyping, coupled with robust functional validation and multi-omics approaches to establish true clinical utility.

Declarations

Ethics approval and consent to participate

This research was approved by the ethics committee of Zahedan University of Medical Sciences (IR.ZAUMS.REC.1402.443). This study is a narrative review and did not involve new human participants, patient recruitment, or collection of identifiable human data. However, in accordance with institutional requirements, the proposal was submitted for academic and ethical approval and was approved by the relevant university authorities.

Consent for publication

Consent for publication is not applicable to this article as this is a narrative review article and does not contain any individual person's data.

Availability of data

Data sharing is not applicable to this article as no new data were created or analyzed in this study. This review is based on previously published studies, which are all cited in the reference list.



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Competing interests

The authors declare that they have no competing interests.

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Fig 1. Schematic overview of the biological pathways potentially contributing to embryo implantation and early placentation. The diagram illustrates how the genetic variants and expression of molecular factors (IL-2, PAEP, VEGF, and TAFI) are hypothesized to influence key cellular and physiological processes. IL-2 and PAEP pathways are implicated in modulating maternal immune tolerance via regulatory T cells and NK cell activity. VEGF drives angiogenesis and vascular remodeling, while TAFI is associated with extracellular matrix regulation. Rather than representing direct causal links, these pathways highlight interconnected biological processes that may support a receptive endometrial microenvironment.