



Genetic factors in the risk assessment of preeclampsia: a review of recent findings

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Abstract

Preeclampsia, characterized by high blood pressure, proteinuria and organ dysfunction in severe cases is a hypertensive disorder that occurs during pregnancy. There is strong evidence that this disease, whose etiology remains unclear, is a complex condition involving programming changes at the levels of DNA, epigenetics, transcriptomics, proteins, and metabolites. Clinically, understanding how each of these elements influences the disease state can provide valuable insights into treatment and prevention strategies. Despite significant advancements in the diagnosis and management of preeclampsia, the syndrome remains a leading cause of maternal mortality, lifelong morbidity, and adverse fetal outcomes. Recent genetic studies offer new insights into the underlying mechanisms of preeclampsia and opens up exciting possibilities for early risk assessment and personalized medical interventions. This article reviews the latest findings on genetic susceptibility to preeclampsia and explores the integration of genetic data into clinical practice.

Keywords Preeclampsia · Genetic · Epigenetic · Maternal genome · Fetal genome · Machine learning · Polygenic risk score

Introduction

Preeclampsia (PE) is a serious pregnancy complication that develops in the second half of gestation and is characterized by hypertension and proteinuria [1]. One of the main causes of pregnancy-related mortality and morbidity, this condition can cause major health issues for both the mother and the fetus [2]. Despite it affects 3–8% of all pregnancies, the pathogenesis of disease is still unclear. According to numerous studies, PE is a complex disorder brought

on by the interplay of environmental, immunological, and genetic factors. It develops as a result of abnormal remodeling of the spiral arteries, placental ischemia, and oxidative stress, progressing in two stages. The first stage involves abnormal placentation, while the second stage is marked by dysregulation of anti-angiogenic factors and disruption of the angiogenic balance, ultimately leading to the clinical syndromes of PE observed in the second and third trimesters of pregnancy [3–6].

PE is commonly classified based on gestational age as either “Type-I (early-onset)” or “placental PE”, which begins before the 34th week of gestation, or “Type-II (late-onset)” or “maternal PE”, which begins after the 34th week [4, 5, 7]. Furthermore, there are “mild” and “severe” forms of the disease. Seizures, cerebral hemorrhage (hemorrhagic stroke), coma, or hypertensive encephalopathy could result from maternal hypertension if the condition worsens. Additionally, severe PE can hinder the fetus’s blood and oxygen flow, which frequently leads to growth issues and even stillbirth. Treatment options are limited, and in severe cases, stabilizing the mother and delivering the baby remains the only definitive solution.

Women with health conditions such as high body mass index (BMI), obesity, hypertension, heart disease, diabetes,

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Table 1 Genes associated with PE using the candidate gene approach

Gene	Loci	Common polymorphism	Study population	References
<i>MTHFR</i>	1p36.3	rs1801133	Caucasians	[13]
<i>F5</i>	1q23	rs6025	Caucasians	[13]
<i>eNOS3</i>		Glu298Asp	South African	[14]
<i>PPARγ</i>	3p25	C1431T	French	[15]
<i>ERAP2</i>	5q	rs2549796 rs2927609 rs11135484	Brazilian	[16]
<i>STOX1</i>	10q22	Y153H -922 T>C	Dutch Turkish	[17] [18]
<i>FGF5</i>	4q21	rs16998073	Chinese Han	[19]
<i>AR</i>	X	XCI	Caucasians	[20]

and kidney disease are at increased risk of developing PE even before becoming pregnant [8]. While these criteria are easy to apply for risk screening, they are associated with low sensitivity [9]. The lower predictive performance in late-onset and severe pregnancy-related hypertensive diseases demonstrates both the inefficiency of these diagnostic criteria and the significant need for predictive screening tests to reduce the disease burden.

Successful prediction and therapeutic intervention require a better understanding of the molecular mechanisms underlying the pathophysiology of PE. However, finding sensitive and specific biomarkers that can be applied in clinical practice is difficult due to the syndrome's heterogeneous nature. Furthermore, more study is required on the molecular markers linked to PE because the disease mechanisms are still poorly understood. Additionally, deciphering the functional significance of epigenetic differences between healthy human placentas and pregnancy-related pathologies remains a major challenge. Analyses conducted using integrated approaches to explore placental, genetic, and epigenetic markers of PE are likely to yield more conclusive results. Based on this, the aim of this article is to provide a brief evaluation of recent studies that have employed integrated methods in the investigation of PE.

The genetic basis of preeclampsia: important discoveries

Genetic research has long suggested that PE has a heritable component, and large-scale genetic studies have estimated the heritability of PE to be approximately 55%. According to studies, maternal genetics accounts for approximately 35% of the variation in PE, fetal genetics for 20% (with roughly equal contributions from the mother and the father), maternal–fetal interaction for 13%, shared sibling environment for less than 1%, and other unmeasured factors for 32% [10]. Genes related to endothelial function,

hemodynamics, immune response, lipid metabolism, oxidative stress, and thrombophilia have been the primary focus of candidate gene approaches in accordance with the accumulating knowledge on the pathophysiology of PE [11]. In this context, numerous studies based on candidate genes have been conducted to identify genes associated with PE, resulting in a list of risk-related genes [12]. Table 1 provides a summary of these genes' chromosomal loci and common polymorphisms. The findings suggest that certain genes may influence susceptibility to PE in specific populations.

Genome-wide association studies (GWAS), meta-analyses and new genetic regions

Each study based on the candidate gene approach started with a particular hypothesis about the molecular mechanisms underlying PE and conducted analyses on a limited number of genes. However, in the case of complex, multifactorial diseases such as PE, the identification of genetic variations contributing to disease development requires the use of large-scale genomic data.

GWAS is an analytical technique that investigates the associations between common polymorphisms in the human genome and multifactorial diseases [21]. These studies analyze thousands of genetic loci in sizable case–control cohorts using SNP microarray technology [22]. From examining a small number of SNPs to employing high-throughput platforms like Illumina SNP arrays and, more recently, whole-exome and whole-genome sequencing platforms, genetic research has changed over time [23]. Many results from these analyses reveal previously unrecognized pathways and mechanisms due to a lack of biological knowledge [24]. Nevertheless, to better characterize both risk and protective variants and validate the associations found by GWAS, replication studies in various populations are crucial. This lowers the possibility of false-positive results [24, 25].

In the largest maternal PE-GWAS analysis published to date, the strongest genetic findings were identified at a locus previously associated with the risk of essential hypertension. Additionally, various studies have shown that the overall genetic architecture of maternal PE overlaps with that of systolic blood pressure (SBP), diastolic blood pressure (DBP), and body mass index (BMI) [26–29]. More recently, large-scale GWAS analyses have identified several genetic regions associated with PE, providing insight into pathways related to immunological response, placental development, and hypertension.

Meta-analysis, a powerful approach that combines the results of independent analyses to increase statistical power and resolution, can reveal findings not evident in individual studies and is considered a valuable tool for investigating the genetic basis of diseases. These characteristics make it

a useful technique for preventing the false conclusions that small or single-population studies may produce.

Let's now take a closer look at the genes that were newly discovered and whose effects were confirmed using these two methods and their possible roles in PE pathogenesis.

Genes associated with angiogenesis and placental function

The development of PE is significantly influenced by the imbalance between pro- and anti-angiogenic factors. In 2020, Duan and colleagues conducted a meta-analysis involving two SNPs (rs3025039 and rs2010963) in *VEGF* (vascular endothelial growth factor), one of the key pro-angiogenic molecules. These two *VEGF* gene polymorphisms were found to be linked to a higher risk of PE [30]. Another gene involved in the angiogenesis pathways that play a vital role in the pathogenesis of PE is *FLT1*, located at 13q12. It encodes a tyrosine kinase receptor predominantly expressed in fetal trophoblasts [29, 31, 32]. *sFLT1*, a soluble splice isoform of *FLT1*, has anti-angiogenic properties by binding to pro-angiogenic molecules like placental growth factor (*PIGF*) and *VEGF* [26, 33]. Proteinuria, high blood pressure, and endothelial damage are the results of this interaction. In PE pregnancies, *sFLT1* levels and the *sFLT1/PIGF* ratio have been found to be higher than in normal pregnancies, offering potential as a biomarker for the differential diagnosis of PE [34]. Additionally, numerous genetic variants near the *FLT1* locus have been reported to be associated with PE risk [26]. Consequently, examining variations at this locus could yield fresh information about the molecules causes of PE.

Genes associated with blood pressure regulation

Vascular dysfunction is also known to play a role in the pathogenesis of PE [35]. In particular, the strong effect of genetic variants associated with diastolic blood pressure on early-onset PE suggests a close link between this condition and genetic factors related to vascular dysfunction [2].

The *eNOS* (endothelial nitric oxide synthase) gene is located at 7q35-q36 and controls the production of nitric oxide (NO), which is important for regulation of vascular tone [2]. The *eNOS* rs2070744 polymorphism may impair placental blood flow by affecting NO production, thereby contributing to the development of PE (Streegers et al., 2010). A recent meta-analysis showed that two common *eNOS* polymorphisms associated with reduced serum NO levels (−4b/a and −786 T>C) were linked to an increased risk of PE, particularly in the European population [36]. On the other hand, the *eNOS* Glu298Asp polymorphism generally did not differ between PE patients and control groups, although some earlier individual studies reported

a significant association with PE [37]. The relationship between the *eNOS* rs2070744 polymorphism and PE risk was investigated in a different meta-analysis by Hossen and colleagues in 2025, and the results showed compelling evidence of elevated risk, especially in African and Caucasian populations. Despite the limited data from Asian populations, the study concluded that genetic susceptibility may be influenced by ethnic differences [38]. It is evident that more research is necessary to fully understand the relationship between *eNOS* and PE because of the contradictory and inadequate studies.

The *ZNF831* gene, which also play a role in the active adaptive immune response, is located at 20q13. Analyses conducted using the KEGG database have shown that this gene functions in T-cell receptor signaling pathways, which are known to be involved in the pathogenesis of PE [29, 39–41]. According to the GWAS Catalog, more than 20 genome-wide signals mapped to the *ZNF831* gene have been associated with blood pressure-related traits [42]. Therefore, *ZNF831* variants are thought to provide important insights into the pathophysiology of PE.

Genes associated with kidney function and sodium balance

The renin-angiotensin system (RAS), a hormonal mechanism that plays a central role in the regulation of body fluid balance and blood pressure, facilitates the production of compounds that exert vasoconstrictive effects and stimulate aldosterone secretion through a series of enzymatic reactions. Activation of the RAS leads to vasoconstriction, increased plasma volume, stimulation of the sympathetic nervous system, and elevated blood pressure. Accordingly, meta-analyses and systematic reviews have demonstrated that different genetic variants of several genes involved in the RAS pathway (*ACE*, *AGT*, and *AGTR1*) are positively associated with PE; however, these associations are not consistently replicated across all populations [2, 43].

ACE2, which converts angiotensin-I into angiotensin-II (a molecule that plays a role in the normal progression of pregnancy increases the levels of plasminogen activator inhibitor-1 (*PAI-1*), a regulator of the fibrinolytic system) also contributes to the regulation of the heart, lungs, and kidneys, and its levels are critical for maintaining blood pressure homeostasis [44]. In preeclamptic women, *ACE* concentrations are higher compared to normal pregnancies, a condition consistent with the development of hypertension caused by an imbalance in the angiotensin-II and Ang-(1–7) pathways [45]. Increased *ACE* activity may lead to abnormal placental circulation and impaired angiogenesis, thereby increasing the risk of disease, and *ACE* variants have been reported to be associated with PE risk [46–50]. However, two meta-analyses conducted at different times

did not find a significant association between *ACE* gene polymorphisms and PE risk [51, 52].

Genes associated with the immune system and inflammation

The interaction between fetal antigens and maternal immune cells promotes the development of immune tolerance, which is necessary for normal placentation and is necessary for the mother's immune system to tolerate fetal antigens during a successful pregnancy. PE risk has been found to be influenced by variations in immune regulatory genes, indicating that the disease may have an immune-mediated etiology.

Tumor necrosis factor- α (*TNF- α*) is a pro-inflammatory cytokine that plays a critical role in reproduction, including gamete and embryo development, placental differentiation, and parturition [53]. Since PE is considered a state of excessive inflammation characterized by elevated levels of Th1 cytokines such as *TNF- α* , it is known that the placenta increases *TNF- α* production in response to hypoxia, which subsequently triggers an inflammatory response in the maternal circulation [53, 54]. According to the findings of a Mendelian randomization (MR) study conducted by Zhong et al. in 2023, which investigated in the relationship between inflammation and PE, a genetically elevated level of *TNF- α* may act as a causal factor in the development of PE [55].

Human leukocyte antigen (*HLA*) class C, E, and G molecules constitute a unique repertoire of histocompatibility antigens expressed by extra-villous trophoblast cells and serve as ligands for maternal uterine natural killer cell receptors (KIRs). Among the possible combinations, the pairing of maternal KIR-AA haplotype with fetal *HLA-C2* haplotype has been associated with the highest risk of PE [56]. This association has been subsequently confirmed in Han Chinese and sub-Saharan African population [57, 58]. *HLA-G* mediates successful placental development and function by regulating the interaction between maternal immune cells and fetal trophoblasts invading the uterine wall. Several variants of the *HLA-G* gene have been shown to be associated with the development of PE [59].

Interleukin-10 (*IL-10*) is an anti-inflammatory cytokine that inhibits cytotrophoblast invasion. Preeclamptic placentas have been shown to have lower levels of *IL-10* [60]. On the other hand, women with PE have been found to have higher levels of interleukin-6 (*IL-6*), a pro-inflammatory cytokine that is involved in the body's reaction to excessive inflammation [61, 62].

The *FTO* gene, located in the 16q12 region, encodes a Fe(II)- and 2-oxoglutarate-dependent oxygenase that functions as a DNA demethylase and plays a role in energy homeostasis through the regulating of food intake, energy

expenditure, and lipolysis [29, 63]. GWAS analysis have identified variants in the *FTO* gene to be associated with BMI and other obesity-related traits [64]. Furthermore, previous studies have demonstrated that *FTO* variants are also linked to an increased risk of hypertension [65]. Given that obesity and hypertension are two major risk factors for PE, it is hypothesized that *FTO* gene variants may contribute to the pathogenesis of PE.

The role of fetal genetic contribution

Large-scale genetic studies have confirmed that both maternal and fetal genetic factors contribute to the development of PE [66, 67]. With the advancement of modern fetal sampling techniques such as amniocentesis and chorionic villus sampling, researchers have gained opportunities to investigate fetal genetic material, leading to a growing interest in exploring the fetal genetic contribution to the pathogenesis of PE [68]. For instance, twin studies – commonly used to investigate the heritability of diseases – have also been conducted to better understand the genetics of PE. While some twin pairs have shown concordance for the disease, multiple studies in different populations have reported generally low concordance rates among female twins [69, 70]. [71], fetal RNA fragments in maternal blood may cause an autoimmune reaction linked to PE. Another investigation identified that specific haplotypes of fetal and maternal genetic variants may increase the risk of developing PE [72]. A more recent study reported that PE arises from the interaction between maternal and fetal genetic material, and that late-onset PE is more commonly associated with fetal genetic factors [29]. These findings support the contribution of certain fetal (paternally derived) genotypes and environmental factors to the development of PE.

The association between genetic variants in the mother and fetus and the development of PE is undeniable, particularly due to the critical role of *FLT1* in placentation. A meta-analysis conducted in 2024 demonstrated that the *FLT1* rs4769513 polymorphism, present in both the mother and fetus, influences the likelihood of developing PE. In contrast, the *ACE* rs4646994 polymorphism in the fetus was found to be associated with PE risk, whereas the same polymorphism in the mother showed no significant effect on this risk [51].

Fetal birth weight-increasing alleles may also affect gestational duration and maternal blood pressure, according to a study that included 10,734 mother-infant pairs of European ancestry [73]. In another study conducted by Rizzo et al. in a Hispanic population, fetal gene expression regulated by DNA methylation was shown to potentially increase the risk of obesity and diabetes in the mother [74].

Furthermore, epidemiological research suggests an association between fetal sex and pregnancy complications such as PE [75–77]. Moreover, there is growing evidence that the human placenta exhibits sex-specific differences, highlighting the importance of considering fetal sex in the design and analysis of association studies [78].

Epigenetics and preeclampsia

Epigenetics is the study of heritable changes in gene expression that occur without alterations in the DNA sequence [79]. Fundamentally, epigenetic mechanisms modify the phenotype without changing the genotype and are influenced by a variety of factors including environment, age, lifestyle, and genetics [80].

One of the most well-researched epigenetic processes, DNA methylation, is necessary for human extraembryonic tissue to function normally and creates physiological signatures in the developing placenta that are influenced by environmental factors and gestational age [81]. However, these signatures may be disrupted by pathological conditions and environmental exposures. Epigenetic alterations associated with various factors – such as gestational diabetes, PE, phthalate and phenol exposure, and maternal smoking – have been reported by multiple research groups [82–84].

In a 2020, an epigenome-wide association study (EWAS) was designed to identify novel differentially methylated positions and/or regions associated with PE and to determine their effects on the expression levels of nearby genes by integrating gene expression microarray data. The study observed upregulation of miR-138 in singleton preeclamptic placentas, noting that this effect was specific to female fetuses. Genome-wide DNA methylation analysis of healthy human placentas has revealed the presence of sex-specific differentially methylated regions (DMRs) outside the X-chromosome [85]. However, in singleton pregnancies, no DMRs have been detected at levels considered clinically significant, suggesting that alterations in DNA methylation may be limited in milder forms of the disease [86]. Nevertheless, the ability to detect DNA methylation changes with 80% sensitivity and 78% specificity during the first trimester suggests that such alterations may serve as potential biomarkers to improve PE screening [87].

In addition to genes that code for proteins, PE has also been linked to differential methylation of promoter regions linked to a number of microRNAs (miR-548, miR-519, miR-301, miR-487, miR-185, miR-329, miR-194, miR-376, miR-486, and miR-744) [79, 88]. Methylation alterations in miRNAs are particularly intriguing due to their capacity to alter target gene expression, and they should be confirmed in larger investigations [23]. One of the most extensively studied miRNAs in PE is the hypoxia-associated miR-210,

which is upregulated in response to hypoxia-inducible factors and regulates angiogenesis by promoting IL-1 α release [89]. Another miRNA associated with PE is miR-26, which is downregulated in PE and is implicated in angiogenesis and TGF- β signaling cascade modulation [90]. Additionally, miRNA profiling of placentas from early-onset PE cases has highlighted the dysregulation of miR-200b/c, miR-154, and miR-27a/b [91]. Furthermore, altered expression of several lncRNAs – such as MEG3, HOTAIR, MALAT-1, and FLT1P1 – has been reported in PE. These lncRNAs are known to play roles in chromatin state regulation, metastatic gene expression modulation, tumor suppression, and the regulation of angiogenesis [92], [93], [94].

Polygenic risk scores in predicting preeclampsia

One of the most promising advances in PE research is the development of polygenic risk scores (PRS), which aim to predict an individual's susceptibility to the disease by integrating multiple genetic variants. By integrating genetic information with clinical and demographic data, PRS models have greatly enhanced risk prediction. As a result, they may be used as predictive biomarkers in clinical settings to identify high-risk subgroups of women. Furthermore, once an individual is genotyped for PE, additional PRS can be incorporated into risk prediction strategies to enhance the assessment of other adverse pregnancy outcomes and long-term cardiometabolic disease risk [95].

In a 2020 study by Gray and collaborators, to assess the risk of developing PE in patients with maternal genetic predisposition to common medical conditions, participants were examined for 21 different SNPs that play a role in seven different biological pathways, including cardiovascular (primarily), inflammatory/autoimmune, insulin resistance, liver, obesity, renal, and thrombophilia mechanisms. For these polymorphisms, genetic risk scores were produced, and multivariable logistic regression was used to examine the correlation between these scores and PE risk. The results indicated that a higher number of risk alleles associated with increased diastolic blood pressure, as well as the presence of genetic variants linked to higher BMI, were associated with an elevated risk of PE. Conversely, it was discovered that alleles linked to elevated levels of alkaline phosphatase (ALP) provided protection against PE [27].

Epidemiological data strongly suggest that women who experience hypertension during pregnancy are at increased risk of developing essential hypertension, coronary artery disease, chronic kidney disease, and type 2 diabetes later in life [96]. Consequently, researchers have employed PRS analysis to investigate the correlation between PE and these

conditions, as well as related phenotypes such as BMI. The results revealed five maternal genome-mediated PE -associated variants, all of which had been previously connected to blood pressure regulation [29]. Another study found that PRS for blood pressure was linked to sex-specific ages of hypertension onset and was more strongly associated with hypertension risk in women than in men [97].

Current evidence regarding the potential of PRS for PE to improve the accuracy of clinical prediction models – particularly in terms of metrics such as the c-statistic or area under the curve (AUC) – remains inconsistent [95, 98]. However, a recent study evaluated a decision-making algorithm aimed at guiding the use of low-dose aspirin for PE prevention and found that the inclusion of both a blood pressure GWAS-based PRS and a PE-specific PRS significantly improved net reclassification [99].

These findings support the integration of PRS into prenatal care and suggest that such incorporation may facilitate the implementation of early intervention strategies, such as aspirin prophylaxis and more frequent blood pressure monitoring.

Machine learning and PRS integration

Artificial intelligence (AI) holds significant potential to surpass traditional approaches in PE research, particularly in enhancing early detection, predicting risks, understanding underlying mechanisms, and optimizing treatment strategies [100]. As a subset AI, machine learning (ML) models typically analyze large datasets to predict maternal and fetal health outcomes. Thus, using AI may facilitate the development of innovative and accurate diagnostic instruments for identifying pregnant women at high risk of PE. AI-based systems can employ advanced algorithms to process vast amounts of clinical and laboratory data, aiming to uncover hidden risk factors or phenotypes associated with PE. Moreover, the integration of AI-assisted remote monitoring for high-risk pregnancies into clinical decision-making may further improve care, treatment, and outcomes [97]. Among the various ML model classes, artificial neural networks (ANNs) are particularly effective at recognizing patterns in the highly complex data of feto-maternal medicine, and they can contribute significantly to risk assessment and intervention planning.

Natural language processing (NLP), one of the application areas of machine learning, supports diagnostic and therapeutic decision-making by interpreting medical texts and patient records. Whereas computer vision plays a critical role in the early detection of feto-maternal complications by enhancing the analysis of medical imaging [100]. Machine learning approaches are believed to offer greater predictive

power due to their ability to capture complex and non-linear relationships [95].

Machine learning methods can be employed to enhance the predictive accuracy of PRS models for PE. This integration offers several advantages, including improved sensitivity and specificity in risk assessment, the identification of specific subgroups for targeted interventions, and the potential to deliver personalized preventive strategies for PE. Recent machine learning studies have demonstrated that these approaches can achieve high accuracy in predicting hypertensive disorders of pregnancy [101] and the risk of PE [102–104]. According to this viewpoint, PE prediction in clinical practice should be made easier by combining machine learning techniques with PRS models, because PRSs are associated with disease risk independently of other clinical and environmental factors, allowing these variables to be incorporated into a single predictive model [105]. For example, given that essential hypertension is a well-established clinical risk factor for PE and that genetic predisposition further increases PE risk [106, 107], it has been proposed that combining clinical risk factors with a hypertension PRS derived from GWAS data in a machine learning model could enhance PE risk prediction. Building on this principle, Kovacheva et al. [95] conducted a study to investigate the relative importance of various clinical risk factors and PRSs in predicting the presence of PE during the first trimester and later in pregnancy (prior to delivery admission). In this study, machine learning and logistic regression models were developed to predict the risk of PE using clinical electronic health record data from a cohort of over one thousand pregnant individuals, along with systolic blood pressure (SBP) PRSs derived from a large-scale GWAS. The results demonstrated that SBP PRSs were correlated with SBP and diastolic blood pressure (DBP) during pregnancy, as well as with diagnoses of gestational and chronic hypertension. Furthermore, machine learning models outperformed logistic regression models in both early and late stages of pregnancy [95].

However, machine learning models developed using data from limited populations may lose their generalizability when applied to groups with different demographic and socioeconomic characteristics. For instance, a model trained on data from a Chinese cohort may not perform equally well in women of African, European, or Latin American descent due to differences in genetic backgrounds, environmental exposures, and socioeconomic factors [100].

Mendelian randomization, cell free DNA/RNA sequencing and omic approaches

Given that PE arises from complex pathological origins – including placental morphology, maternal susceptibility, genetic variance, and molecular signaling – addressing this biological complexity requires novel and sophisticated methodologies. In this context, emerging advanced molecular and bioinformatic technologies, such as Mendelian randomization (MR), which utilizes genetic variants as instrumental variables to infer causal relationships and elucidate disease-related biological mechanisms, and single-cell RNA sequencing (scRNA-seq), which enables the investigation of gene expression profiles at cellular resolution in heterogeneous tissue such as placental or immune cells populations, offer new opportunities for a more in-depth exploration of the genetic architecture of PE. Additionally, the expression profiles of cell-free RNAs related from maternal and fetal cells have been associated with molecular signatures related to neuromuscular, endothelial, and immune cell types implicated in the physiology of PE. These findings may offer novel opportunities for the early diagnosis of PE and the development of personalized therapeutic strategies [108]. Another important point is the role of cell-free fetal DNA (cffDNA) in the increasingly widespread use of prenatal screening. Adil et al. [109] proposed that alterations in cffDNA fractions during early pregnancy could be utilized in the screening of PE, and even suggested the development of a stepwise screening algorithm. Such an approach may enhance both sensitivity and specificity by extending the screening with additional biomarkers in individual identified with low cffDNA fractions. The combined application of these approaches enables a multilayered and integrated analysis framework that can both assess the causal roles of genetic risk factors and elucidate the specific cellular contexts in which these factors exert their effects. For instance, in a study conducted by Zhong et al. [55], MR was applied to investigate the causal relationship between inflammatory biomarkers – C-reactive protein (CRP), IL-6, interleukin-1 receptor antagonist (IL-1ra), and TNF- α – and PE. Strongly associated with these biomarkers SNPs were used as instrumental variables. While no significant causal effects were observed for CRP, IL-1ra, and IL-6 levels on the progression of PE, genetically predicted higher levels of TNF- α were found to significantly increase the risk of developing PE [55].

Utilizing omics techniques has become a popular tactic in recent years to unravel the complex pathophysiology of PE. The term “omics” refers to the comprehensive characterization and quantification of pools of biological molecules that translate into the structure, function, and dynamics of an organism. Omics approaches can rapidly generate

large-scale datasets through technologies such as next-generation sequencing, high-resolution mass spectrometry, and microarrays. By comparing PE samples with those from control groups, it becomes possible to identify molecular differences associated with the disease state. These significant molecular differences – such as mRNAs, SNPs, DNA methylation sites, proteins, and metabolites – may serve as potential biomarkers for PE. Targeting and reversing these molecular determinants holds promise for controlling, managing, and ultimately treating PE [23].

Clinical applications and future directions

PE poses a substantial short- and long-term health burden in addition to the immediate risks to the mother and child. Consistent with the developmental origins of health and disease (DOHaD) hypothesis, it increases the risk of cardiovascular and metabolic disorders later in life for both the mother and the child. However, the heterogeneity of the syndrome, together with the limited understanding of its pathophysiological mechanisms, remains a major barrier to the discovery of sensitive and specific biomarkers applicable in clinical practice. At present, high-risk women are identified largely from clinical factors which include pre-existing hypertension, obesity, pregestational diabetes and previous history of PE. However, this approach fails to detect approximately 46–60% of pregnancies that eventually develop PE [103, 110]. Therefore, current clinical practice focuses on close monitoring, early detection, and prompt intervention for women at risk [111]. PE risk is typically evaluated in the first prenatal visit and high-risk women are counseled to take low-dose aspirin prophylaxis with close blood pressure surveillance. Nevertheless, with the rapid advances in genetic research, genetic screening for PE may soon become an integral part of routine prenatal care. For example, according to the study by Zhong et al. [55], the proinflammatory activity of TNF- α may serve as a determinant of PE progression, and it has been suggested that pregnant women with higher TNF- α levels should receive more intensive antenatal care. Despite this, given the multifactorial nature of PE, GWAS and other multi-gene analyses are needed to detect the presence of genomic variants influencing disease risk. To achieve reliable predictions, these findings must be replicated across different populations. Importantly, demonstrating a genetic association between a variant and PE does not necessarily imply a causal role in disease development, thus, expression and functional studies are needed to clarify the causal effects of identified genes. In addition to genetic contributions, epigenetic analyses can provide critical insights into how environmental factors modulate maternal or fetal genomic variants in relation to PE risk. For instance, the

expression of a genetic variant may be regulated through epigenetic modifications induced by environmental signals, thereby enabling epigenetic markers to reveal distinct molecular signatures underlying different PE subtypes, such as early- or late-onset disease. These subtype-specific epigenetic profiles could form the basis for developing targeted diagnostic and therapeutic strategies.

In recent years, studies based on PRS have emerged as promising tools for more accurate prediction of PE risk. For instance, a study conducted by Honigberg et al. [99] identified novel risk variants associated with gestational hypertension and PE, demonstrating that the incorporation of PRS can enhance predictive models for PE. Building on such findings, it is conceivable that integrating PRS alongside established clinical risk factors could result in more robust predictive systems.

Machine learning has become a transformative tool in medicine, enabling numerous advancements across various aspects of healthcare such as diagnosis, treatment, drug discovery, and personalized medicine [97]. In the future, the integrated use of genetics and clinical medicine with artificial intelligence technologies could significantly improve the prevention and treatment of PE. For instance, early pregnancy screening for PE prevention may enhance maternal and neonatal outcomes by 70–89%, underscoring the high potential impact of implementing machine learning models integrated with PRS into clinical practice [95]. Such models could be utilized not only for risk prediction but also in the application of stepwise screening strategies. Specifically, the initial evaluation of cfDNA, followed by integration with PRS and clinical factors, would allow the development of distinct follow-up algorithms for both low- and high-risk groups [99, 109]. Consequently, high-risk patients could be monitored in well-equipped healthcare facilities by specialized physicians, while low-risk individuals might be followed through more standardized surveillance protocols.

Limitations

Although molecular studies on PE have provided important insights into the underlying mechanisms of the disease, the interpretation and application of the data obtained remain subject to several limitations. As an illustration, one of the drawbacks of genetic studies is the heterogeneity of results, largely due to the use of different genotyping methods across studies. Moreover, in some cases, PE subtypes such as early-onset, late-onset, severe, or mild forms have not been taken into account [38]. Additionally, with regard to studies conducted particularly on placental tissue samples, it is well recognized that the region of the placenta from which the sample is collected (near the cord, central, or

peripheral areas) may differ in cellular composition. Such variability may manifest as intra-placental heterogeneity in certain genes, or DNA methylation signals derived from non-disease-related cell types may interfere with the detection of disease-specific variations [112]. Epigenetic studies may also face temporal limitations, such as when samples are collected months after disease onset, the observed changes in epigenetic marks may differ. Consequently, the analyzed epigenetic alterations may represent maternal adaptive responses rather than the causal mechanisms of the disease, thereby limiting their predictive value for the early diagnosis of PE. Furthermore, to clearly distinguish between maternal and fetal contributions and to fully elucidate the roles of specific genes, it will be critical for future cohorts to include samples from the infant as well as both parents [29].

In the implementation phase, several challenges remain, foremost among them the need to ensure that genetic testing is accessible and affordable for all segments of society. Beyond this, the clinical use of genetic data raises not only scientific but also ethical concerns. Issues such as privacy, informed consent, and potential discrimination are of critical importance for the feasibility of applying genetics-based screening in PE research.

Conclusion

PE is a complex disorder involving programming alterations at the DNA, epigenetic, transcriptomic, protein, and metabolite levels. Large-scale studies in these areas reveal the interactions between maternal and fetal genetic factors, thereby providing important opportunities for early risk assessment and personalized interventions [23].

Despite promising genetic and functional studies aimed at elucidating the molecular mechanisms of the disease and developing biomarkers for early diagnosis, screening, and treatment, there is currently no universal screening test for PE. This constitutes one of the most significant challenges in disease management, from diagnosis to complications that may arise later in life, affecting both maternal and neonatal outcomes. The primary reasons for this gap include single-gene variants yielding different results across populations, insufficient representation of ethnic diversity in studies, variability in techniques and sample materials used, differences in included disease subtypes as well as demographic and clinical data, and the influence of temporal and spatial factors on epigenetic regulation. Therefore, one of the prerequisites for a future global test is the integration and validation of larger pregnancy datasets from large-scale cohorts representing diverse ethnic groups into machine learning and PRS-based models, using safe and clinically

applicable strategies. In the meantime, at least in the initial stages, it may be more realistic to implement screening in selected high-risk populations rather than universally. For example, in women with chronic hypertension, diabetes, kidney disease, or autoimmune disorders, the addition of PRS to clinical risk factors provides significant predictive value for hypertensive disorders of pregnancy. However, most studies adopting this approach have been conducted in European populations, making the results more promising in these groups, while the need for studies including diverse ethnic backgrounds remains critical. Another high-risk group is twin pregnancies, where a low fraction of cfDNA in the first trimester has emerged as a value biomarker for predicting preterm PE. The predictive power can be further enhanced when cfDNA is assessed in combination with PIGF and mean arterial pressure values. In women who conceive through in vitro fertilization (IVF), multi-biomarker panels including immunoglobulins and cytokines may be employed to predict PE development with high sensitivity and specificity. Nulliparity is also considered among the strong risk factors for PE. For individuals within these high-risk groups, the use of PRS in predicting hypertensive pregnancy disorders may prove beneficial, even independently of clinical data.

Artificial intelligence (AI) algorithms, which extend beyond traditional statistical approaches, possess the capability to integrate extensive multi-omic datasets (genomic, proteomic, metabolomic), dynamic genetic risk scores, and circulating biomarker profiles. This integration can reveal not only complex non-linear relationship among known risk factors but also population-specific genetic and environmental interactions. Furthermore, the interpretation of novel and complex markers, such as cfDNA methylation patterns or cfRNA, can be standardized and automated through AI's deep learning capabilities. Consequently, AI has the potential to overcome the limitations of individual biomarkers for PE diagnosis by establishing a continuously learning, integrated, and adaptive “digital twin” risk profiling system, thereby paving the way for a new era of personalized and proactive clinical management.

Finally, calls for the establishment of global PE research consortia to share detailed information on clinical outcomes and raw data are particularly noteworthy. The harmonization of data collected from diverse ethnic backgrounds, alongside standardized procedures for data acquisition, sharing, and the development of publicly accessible databases, will provide researchers with advanced tools to implement integrated approaches. Such frameworks will enhance the feasibility of applying more precise diagnostic and therapeutic strategies for PE.

In conclusion, approaches that integrate clinical factors, PRS, biochemical markers, cfDNA, and analyses of these

data using machine learning algorithms have the potential to more accurately stratify disease diagnosis in high-risk populations and provide opportunities for early intervention. However, the clinical integration of these tests requires larger-scale, prospective studies, careful ethical considerations, and the assurance of equitable access across all segments of society. Collectively, these strategies point toward a future in which disease detection is complemented by a deeper understanding of the underlying risk mechanisms and the development of personalized intervention strategies.

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Declarations

Competing interests The authors declare no competing interests.

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