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Review Article

Importance of Genetic and Epigenetic Factors in Preeclampsia and their Protentional Translation Improving Antenatal Care

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Abstract:

Preeclampsia is a pregnancy-specific disorder affecting 5-7% of cases, It is a substantial factor in maternal and fetal morbidity and mortality globally. This diverse condition has multiple underlying mechanisms, making its prevention challenging. Although the pathological process has become clearer over the last two decades, the cause of preeclampsia remains unknown. Preeclampsia, characterized by hypertension developing after 20 weeks of gestation, results in high mothers and babies' death rates globally. Crucial barriers to early screening and targeted preventive approaches include gaps in understanding the varied molecular pathways of preeclampsia and the absence of adequate, certain diagnostic ways. Although transcriptional analysis of placentas can categorize patients, incorporating epigenetic data could shed light on the gene regulatory mechanisms underlying different preeclampsia pathologies and identify potential biomarkers with clinical utility.

The potential for early preeclampsia diagnosis using miRNAs as predictors and their clinical application remain uncertain and require further study. It is still unclear whether the likelihood of early-onset preeclampsia correlates with the Intensity of clinical assessments and perhaps histopathology of the placenta. Moreover, the gene regulatory landscape underlying preeclampsia is not well understood. Further research is needed to determine whether preeclampsia can be sufficiently differentiated from other normal and abnormal outcomes.

Research has shown that the scale of placental-derived cell-free DNA increases with preeclampsia; however, the rise in maternal sources of cell-free DNA is also considerable. The exact origin of maternal cell-free DNA and its relationship to the disease phenotype needs further investigation, and there is a lack of consistency among studies identifying altered placental DNA methylation in preeclampsia, with most findings lacking replication. Additionally, there was minimal overlap in the miRNAs identified across different studies. This study aimed to delve into current knowledge regarding the contributions of genetic and epigenetic factors to PE and their implications for antenatal care.

Key words: preeclampsia; genetic; epigenetic; antenatal care

Introduction

Preeclampsia (PE) is considered a gestation-specific syndrome, affecting 5-7% of pregnancies causing maternal and neonatal morbidity and mortality all over the world. The etiology of (PE) still unknown; although research has cast light on its pathological mechanisms [1] (PE) continues to pose significant short-term and long-term health risks for both mothers and their children [1]. This condition places considerable financial stress on the healthcare system. Thus, early prediction and identification are essential for enhancing patient outcomes and treatment strategies.

Regardless of advanced understanding the pathophysiology of (PE), sensitive and specific biomarkers for its early prediction and detection are still deficient, and further researches are necessary to identify the molecular markers linked to (PE) [2]. On top of that, there is a limited overlap in the identified microRNAs (miRNAs) between studies. Moreover, how the mechanisms behind (PE) and genetic variation collaborate with other elements that impact on the rate of this condition remain unclear. [3,4]

Recently, researches has been concerned with identifying novel biomarkers using extracellular RNAs (exRNAs), such as microRNAs (miRNAs) in maternal blood circulation, which could enable noninvasive investigation of placental function. Some studies have explored expression profiles of trimester-specific plasma exosome miRNAs [1] in (Boyano et al. (2023), researchers have developed a novel predictive model using placental DNA methylation patterns to identify early onset preeclampsia (EOPE) [5]

Another promising tool is Genome-wide association studies (GWAS) which have showed liability of genes for (PE) in specific populations also researchers analyze cell-free RNA (cfRNA) transcriptomic patterns in pregnant mothers to identify the genes associated with (PE)[6,7] Furthermore, many investigations have been conducted on the effects of placental long non-coding RNA H19 polymorphisms and promoter methylation on H19 expression in association with (PE) susceptibility [8]also they conduct a comparison of the genomic methylation patterns of fetal endothelial colony-forming cells (ECFC) from uncomplicated and preeclamptic pregnancies have been performed [9]and we have to consider the huge efforts in examination of placental microRNAs (miRNAs) in pregnancies with early onset intrauterine growth restriction and(PE)which have been conducted[3]These studies examine meticulously the current understanding of the genetic and epigenetic contributions to PE and their implications for prenatal care.

Clinical manifestations (PE):

The clinical presentation of (PE) varies, reflecting its multisystemic nature. Although hypertension and proteinuria are distinctive features, the absence of one or both does not exclude (PE) [10]. Atypical symptoms, for instance, severe edema, may also occur. All in all, this disorder can affect multiple organ systems and lead to a range of signs and symptoms [11,12].

Hypertension is a key diagnostic criterion typically defined as systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg. Severe (PE) is indicated by a systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 110 mmHg (13–15)

Proteinuria was defined as the presence of ≥ 300 mg of protein in a 24-hour urine sample(16)The International Society for the Study of Hypertension in Pregnancy (ISSHP) defines PE as de novo hypertension accompanied by ≥1 of the new-onset conditions, including proteinuria (≥1+, 30 mg/dL; urine Protein/Creatinine Ratio (PCR) ≥ 30 mg/mmol (0.3 mg/mg))[7]

Although edema has been recognized as a symptom of (PE), it may not always be present [11]

(PE) can lead to dysfunction in various organs and systems. For example, renal disorders, liver function abnormalities, and CNS symptoms are common complications, Neurological complications include persistent headaches and visual disturbances [17]. Thrombocytopenia, which is a reduction in platelet count, may occur. [18]

HELLP Syndrome, which is a complex of hemolysis, increased liver enzymes, and decreased platelet counts, may take place and is considered a severe complication of (PE) [19]

The feared complication is the progression of Eclampsia, which occurs in severe cases and is characterized by seizures. (11)

Diagnostic Criteria

The diagnosis of (PE) connected with an estimation of blood pressure and proteinuria after the 20th week of gestation. According to the American College of Obstetricians and Gynecologists (ACOG), preeclampsia is diagnosed based on the following criteria (14)

Hypertension: Systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm

Proteinuria: Presence of ≥ 300 mg protein in a 24-hour urine sample

However, the current understanding recognizes that (PE) can be also diagnosed in lack the presence of proteinuria. In this circumstance, one or more of the following conditions have to be fulfilled (14)

Kidney disorder

Hepatic dysfunction

CNS disorder

Hemodynamic dysfunctions

Uteroplacental complications

Intrauterine fetal growth restriction

Pathophysiology of (PE)

(PE) It is often described as a disease characterized by abnormal placentation. One of the most relevant theories suggests that PE is a Many-sided disease that involves several genetic and environmental factors despite its clinical manifestation's symptoms appearing later in pregnancy (17,20). The root behind it starts from early placental development.

In normal gestation, the syncytiotrophoblasts invade and remodel the spiral arteries in the myometrium, leading to an elevation in placental blood flow. In contrast, these processes fail and disturb placentation in (PE). Owing to inappropriate blood flow in the placenta, oxygen supply will be affected, resulting in hypoxia and hyperoxia, which activate oxidative stress, inflammation, and necrosis (21)

Importance of placenta

The placenta is one of the major driving forces behind PE pathogenesis. It occurs due to the failure of extravillous trophoblasts to fully invade the maternal decidua and remodel spiral arteries. In a healthy pregnancy, this remodeling is finished by the second trimester, creating decreased resistance. Since an increase in the vessels' blood flow is needed to enhance fetal growth,

defective placentation leads to decreased maternal blood flow to the intervillous zone, compromising the exchange of gases and nutrients. (6,20) This ischemia results in increased placental xanthine oxidase/dehydrogenase system expression and activity, increased generation of reactive oxygen species, impaired antioxidant mechanisms, and increased apoptosis (6,20,21)

Endothelial Dysfunction

The second player in (PE) pathogenesis is endothelial dysfunction. Increased synthesis of vasoactive mediators produces vasoconstriction and insufficient blood circulation in the placental vessels. Prior clinical symptoms appear, uteroplacental blood flow diminishes, and uterine vessel resistance increases, producing placental ischemia (22)

Placental ischemic events give rise to the release of placental factors that contribute to systemic vascular endothelial dysfunction, resulting in increased systemic vascular resistance and high blood pressure. The syndrome is perhaps started by placental elements that enter maternal blood flow and lead to endothelial dysfunction, yielding to high blood pressure and protein in the urine (12)

Risk Factors (PE).

Several preexisting maternal circumstances and pregnancy-specific characteristics have been identified as risk factors for (PE), consisting of:

Maternal Age and BMI: Increasing maternal age and higher BMI places pregnant ladies at higher risk of developing (PE) (23) Preexisting Conditions, i.e. women with preexisting hypertension and diabetes, cardiogenic disease, or renal disease before becoming pregnant have an increased risk of developing (PE) (24,25)

Primiparity: First-time gestation is associated with a higher risk of preeclampsia (21)

Family History: A family history of (PE) and perhaps preeclampsia in a prior pregnancy is a significant risk factor (17)

Multiple gestations and in vitro fertilization Women carrying twins or other multiples are at higher risk (17)

Other Potential Factors

Genetic and Epigenetic Factors

Genetic factors significantly contribute to susceptibility to (PE). (26). Women with an affected first relative are at increased risk, suggesting a genetic component from maternal, fetal, and/or paternal genes. Moreover, polymorphisms in genes that control vascular tone, such as the renin-angiotensin system and endothelial nitric oxide synthetase, can significantly increase the risk of (PE) (22)

Polygenic risk scores (PRSs) exert a significant influence on predicting (PE), with blood pressure being the most significant contributing parameter. one study demonstrated that women with a high blood pressure polygenic risk score (BP-PRS) are more likely to develop (PE) and display higher BP readings throughout pregnancy (27)

Environmental elements can also participate in the risk of PE. External influences affecting pregnancy, like stress and cigarette smoke, are correlated with a higher risk of progressing in to (PE). (5,28)

We have to bear in mind that autoimmune diseases are one of the maternal risk factors for (PE) (29). An exacerbation of inflammatory response related to pregnancy. This results in dysregulation of the immune response in early pregnancy, which might be linked to histone modification. (30)

A genome-wide association study (GWAS) found that (PE) was linked with many autoimmune phenotypes, including celiac disease, type 1 diabetes, and hypothyroidism. The GWAS also showed an association with rheumatoid arthritis in female participants. (29) . Systemic lupus erythematosus is also considered as a risk factor connected with clinical risk factors for (PE) in addition reduced SH2B3 function has been correlated to autoimmune diseases. Lastly, the history of autoimmune disease. (29)

Early diagnosis of (PE) before its clinical manifestation is essential for assessing the risk and practicality of the conservation of the pregnancy. Identifying risk factors before pregnancy allows for timely assessment of the likelihood of developing (PE) and implementation of preventive measures. We have to note that (PE) has a sudden onset, making early predictions very tricky.

Discussion

(PE) is a complex gestation-specific high blood pressure disease, in which several genes associated with angiogenesis, inflammation, oxidative stress, and the renin system exert a significant influence on (PE). In this narrative review article, we assessed the genetic components that are essential for elucidating pathophysiology, identifying potential biomarkers, and developing targeted therapies for (PE) (31).

Genetic factors in PE:

Angiogenesis-Related Genes

Angiogenesis by definition, is the formation of new blood vessels, and it is fundamental for establishing and maintaining a normal placenta. The impairment of angiogenesis is a hallmark of (PE). Several genes and microRNAs (miRNAs) that regulate angiogenesis have been identified in many studies (17)

MicroRNAs (miRNAs): These are involved in regulating trophoblast invasion and immune activation in the placentas. They play numerous fundamental roles in regulating cell growth. Certain miRNAs, such as miR-181a-5p, contribute to trophoblast dysfunction in PE. Also, miR-431 affected trophoblast migration and invasion by targeting ZEB1 (21)

Vascular Endothelial Growth Factor (VEGF) is important for the promotion of angiogenesis. Studies have found that the downregulation of miR-10 causes more expression of both sFlt-1 and Flt-1 and markedly impairs the angiogenic behavior of human endothelial cells. Both sFlt-1 and Flt-1 bind to VEGF, and placental growth factor (PlGF) promotes angiogenesis (17). Ephrin-B2 and EPHB4 genes are targeted by upregulated angiogenesis-associated microRNAs, such as miR-17, -20a, and -20b in preeclamptic placentas (17)

Inflammation-Related Genes

Many studies show the importance of inflammatory-related genes in (PE). An overactivated inflammatory response can generate immune imbalance and vascular endothelial damage, triggering the development of (PE) (31)

miRNA-499 (miR-499) acts as an inflammation suppressor by targeting genes involved in inflammatory responses and regulating hypoxic-ischemic conditions (31)

Interleukin-10 (IL-10): This is linked with preeclampsia in a Tunisian population, suggesting its role in the inflammatory pathways of the disorder (31)

INHBA, OPRK1, and TPBG: These elements of inflammation-associated genes can be used as potential genetic biomarkers for (PE) prediction and treatment (31) RELA-miR-548K/miR-1206-TPBG this perhaps a potential RNA controlling course that governs the progression of early (PE) (31)

Oxidative Stress-Related Genes

Oxidative stress, known as the disproportion between the generation of free radicals and antioxidant defenses, gives rise to the development of (PE). For example, Polymorphisms in genes such as GPx-1 (rs1050450) and MnSOD (rs4880) have been studied for their association with (PE) susceptibility (31)

OPRK1, also recognized as KOR, is associated with ROS generation of Reactive Oxygen Species. Animal experiments have shown that a-opioid receptor agonists do not stimulate any generation to mitigate the impact of hyperlipidemic destruction on endothelial function (32)

Renin-Angiotensin System (RAS)-Related Genes

RAS is a fundamental regulator of blood pressure and fluid balance. Dysregulation of the RAS has been implicated in (PE). Components of the renin-angiotensin system pathway, which harbors genes that were previously reported to be protective or disease-causing for (PE) for

example the genetic variations in genes like AGTR1, AGTR2, ERAP1, ERAP2, LNPEP, CYP17A1, and CYP21A2. (26,33)

Variations in these genes can alter receptor function, enzyme activity, and hormone synthesis, affecting blood pressure regulation and potentially leading to (PE) note that Natriuretic peptides work against the RAS, offering potential protective effects (29). eNOSgene regulation of normal blood pressure depends on IP3R1-mediated eNOS (12).

Genome-Wide Association Studies (GWAS)

GWAS generally is scanning the genomes of many individuals to distinguish genetic variants, such as single nucleotide polymorphisms (SNPs) linked to a precise trait or disease. GWAS have been useful tool for identifying the genetic loci associated with (PE) susceptibility; however, it also has limitations. We must recognize the importance of both strengths and limitations of interpreting results and designing future research strategies (2).

A GWAS in the Chinese Han population identified rs13210237 and rs13176432 as potential (PE)-susceptible genetic factors; rs13210237 is linked to HSF2 and GJA1, whereas rs13176432 is linked to TRIM36 (15). Pathway analysis indicated enrichment in the adenylyl cyclase-inhibiting G protein-coupled receptor signaling pathway

Another study, which is a many-ancestry GWAS meta-analysis, distinguished 18 independent genomic locations related to preeclampsia and perhaps gestational hypertension (29), which stresses the roles of angiogenesis, natriuretic peptide signaling, renal glomerular function, and immune dysregulation in the pathogenesis of these conditions. It also demonstrates that the placental genetic variant rs4769613 upstream FLT1 is linked with (PE) development (6). The C allele of rs4769613 is a preeclampsia-specific risk factor participates in the early recognition of high-risk women (34)

Other Specific Genes and SNPs GWAS are as follows:

The C allele of rs2021783 in CYP21A2 indicates an increased risk of preeclampsia

The TT genotype for rs1004467 and GG genotype for rs3824755 were identified as risk Factors for mild (PE) (28)

Genetic variants of ERAP1 and ERAP2 are associated with eclampsia and preeclampsia, respectively (33). The rs1640299 and rs720014 polymorphisms in DGCR8 are associated with an increased risk of late-onset preeclampsia (LOPE) (35)

A genetic likelihood to high blood pressure is linked with (PE) in women who are genetically liable to hypertension and have a high risk of (PE). The blood pressure polygenic risk score (BP-PRS) is strongly associated with (PE) and gestational hypertension (13)

Strengths of GWAS

GWAS offers several advantages for studying genetics (PE). GWAS examines the entire genome, allowing the discovery of novel genes and pathways that may not have been previously suspected (15). Furthermore, it does not require prior knowledge of specific candidate genes, making it possible to uncover unexpected genetic associations.

GWAS generally emphasize large sample sizes, increasing the statistical power to detect genetic associations. Meta-analyses generate data from multiple GWAS can further boost statistical power and effectively identify common genetic variants that contribute to disease risk development (15,34)

Many studies have identified common SNPs associated with (PE) susceptibility (6), extracted from GWAS can be used to calculate polygenic risk scores (PRSs) to estimate an individual's risk of (PE). BP-PRSs have shown promise in predicting hypertensive disorders during pregnancy (36)

Limitations of GWAS

Despite their strengths, GWAS have several limitations that need to be considered

GWAS identifies genetic variants associated with a disease but does not prove causation. Further functional studies are needed to determine whether the identified variants directly contribute to PE pathogenesis (34). It primarily focuses on common genetic variants, meaning that rare variants with large effects on (PE) risk may be missed. We have to bear in mind the genetic architecture of preeclampsia may vary across different populations, leading to inconsistent findings across research. Studies on specific populations, such as the Han Chinese population, may identify unique genetic factors (15).

GWAS often demonstrates only a little percentage of the heritability of complex diseases such as (PE). The "missing heritability" may be due to rare variants, gene-environment interactions, epigenetic factors, or other genetic mechanisms not detected by GWAS (34)

Many SNPs recognized by GWAS are in non-coding areas of the DNA, making it challenging to determine their functional importance; hence, further research is required to understand how these SNPs affect gene expression and protein function (6)

The sample sizes in preeclampsia GWAS are often smaller than those in GWAS for other common diseases, limiting the statistical power. Larger multicenter studies and meta-analyses are needed to increase power and identify additional genetic associations (29)

PE is clinically heterogeneous, with different subtypes (e.g., early onset vs. late onset), potentially having distinct genetic bases. GWAS

that do not account for this heterogeneity may miss subtype-specific genetic associations. It is important to mention that the majority of GWAS have been established in populations of European backgrounds, limiting the generalizability of findings to other ethnic groups. In addition, environmental elements such as diet, smoking, and obesity can impact the risk of (PE) and interact with genetic factors. WAS may not fully capture these gene-environment interactions (28). Finally, GTEx samples had a limited database and were segregated from a cohort of male (67.1%) and female (32.9%) tissue donors, none of whom were pregnant (GTEx database, V8 Donor Info) (6)

Familial aggregation and heritability

Familial aggregation and heritability have a major impact on (PE). Studies have suggested that a substantial proportion of the tendency to (PE) can be assigned to maternal genetics. Familial aggregation indicates that (PE) occurs more frequently in some families than in the general population.

Mother and baby genetic factors are worth a large proportion of familial aggregation (PE). Heritability estimates suggest that a considerable percentage of (PE) predispositions are due to maternal genetics.

One study (Honigberg et al., 2023) estimated that 31–35% of (PE) predispositions are attributable to maternal genetics

A family background of chronic hypertension is more frequent in women with eclampsia and HELLP syndrome, indicating having common genetic

components between essential hypertension and hypertensive diseases during gestation (37)

Epigenetics factors in (PE)

Investigations of alterations in the manner of methylated DNA in placental tissues and maternal blood in (PE) have found exactly what genes and pathways are affected in (PE) and many prior studies have demonstrated that PE is linked with alteration in DNA methylation in the placental cytology (10). To explain this more clearly, DNA methylation is an epigenetic modification that regulates various cellular activities and genetic phenotypes (10).PE and PE+IUGR placentas illustrate hypomethylation at L1s (long interspersed element-1) in comparison to control placenta. Moreover, L1s consist of approximately 18% of the human genome. Consequently, the hypomethylation of these elements in PE indicates possible global hypomethylation (2)

Besides, these variants of microRNAs (miRNAs) are connected with (PE). miRNA196a2 rs11614913 CT, TT genotypes and the T allele of placental tissues are with low possibility of (PE) however both placental and maternal miR-499 rs3746444 CC genotypes are related to (PE) (21)

Specific methylation pattern

Note that research found that Early onset (PE) is linked to a specific pattern of hypermethylated locations which are mostly found in promoter regions and introns. Also, methylation haplotypes are enriched in CTCF on the X chromosome (38).

Considerable differential methylation in the CMIP gene has been recognized and validated, putting forward its association with PE pathogenesis and it's found in blood which makes them a potential diagnostic biomarker (39). Moreover, DNA methylation signatures in PE are distinguished from those in uncomplicated pregnancies.

Scientists noticed a low expression level of DNMT3A (DNA methyltransferase 3A) implicated in immunological-associated diseases and abnormal placentation in (PE) (39). ZNF417 hypomethylation in PE with severe features compared with PE without severe features. The total cell-free DNA concentration is higher in (PE) patients than in healthy control women (27)

Histone modifications

Many studies Suggests a great reaching importance of Histone modifications in (PE) the concept behind histone modification is they can alter gene production without modification the DNA pattern. Studies reveal that the expression of placental histone proteins H3K4me3 (trimethylated lysine 4 of histone H3) and H3K9ac (acetylated lysine 9 of histone H3) are reduced in PE. one study demonstrated decreased levels of H3K4me3 in PE-affected placentas compared to controlled ones, with similar findings for H3K9ac (30) Immunohistochemical staining illustrated that H3K4me3 and H3K9ac reduction occurs in the syncytium and decidua. Positivity of cells to these histone changes have been recognized as extra villous trophoblasts (EVTs) (30). A notable reduction in H3K4me3 and H3K9ac levels suggests a loss of accessibility for gene transcription. Since H3K4me3 and H3K9ac typically show active locations at gene promoters and enhancers, their reduction points to low gene activation in PE. Furthermore, the expression of methylated histone H3K4me3 demonstrates a positive correlation with higher maternal age in PE placentas (30)

Also, we have to consider that many studies highlighted the power of H3K9ac in the production of vascular endothelial cadherin, which is fundamental for angiogenesis. Defective remodeling of spiral arteries and vascular dilation are key elements in the pathological mechanisms of PE, resulting in dysfunctional uteroplacental perfusion and systemic inflammation.

Histone modifications are associated with macrophage activation and polarization during mucosal inflammation, leading to derangement of the immune response, which is a distinguished component of PE pathophysiology. (30).

An abnormality of H3K9 trimethylation is observed in the promoter region of vascular endothelial growth factor (VEGF) in PE. modified histone acetylation of H3 and H4 in the promoter region caused by hypoxia affecting the placental growth factor (PlGF). In essence, these changes suggest that histone modifications contribute to PE pathogenesis (30)

MicroRNAs (miRNAs)

MicroRNAs (miRNAs) are small, non-coding RNAs that have a consequential role in multiple biological processes, including those which are connected to (PE) miRNAs are classified as epigenetic regulators because they control gene production without changing the DNA sequence. They govern gene expression post-transcriptionally by attaching to the 3 untranslated regions (UTRs) of target messenger RNAs (mRNAs), leading to mRNA degradation or translational inhibition (40)

There are several biological processes linked to (miRNAs) including cell growth, proliferation, invasion, apoptosis, autophagy, stress response, death, angiogenesis, and differentiation. The most important point is that miRNA) regulate trophoblast invasion and immune activation in the placenta (20).

Specific miRNAs, such as miR-195, are hinting to control PE via their target genes and manipulate processes, for example, placental proliferation, apoptosis, and angiogenesis (14).

In many research studies there are growing suggestions that miRNAs are potential biomarkers for (PE), owing to their stability and presence in tissues and fluids (35). Single nucleotide polymorphisms (SNPs) within miRNA biosynthesis genes can alter miRNA expression and are linked with the risk of some diseases (8)

Long non-coding RNAs (lncRNAs) These are RNA molecules that are larger than 200 nucleotides and do not code for protein and have been involved in the pathogenesis of (PE) and have important participation in genome formation and expression through various mechanisms (8).

H19 lncRNA:H19 polymorphisms are linked to PE susceptibility, and their production governs certain mRNAs via post-transcription modifications and function as a primary microRNA precursor. Moreover, H19 methylation patterns are closely related to (PE) and trophoblast abnormalities (8)

H19 long non-coding RNA modifies trophoblast cell migration and invasion by controlling TβR3 in placenta with intrauterine fetal growth restriction (8).

LINC-HELLP lncRNA: LINC-HELLP is hyper-expressed in PE

It is a specific type of lncRNA found in early pregnancy extra villous trophoblasts and negatively affects their differentiation of the extra villous trophoblasts. It is important to mention that

Mutations in LINC-HELLP recognized in HELLP families negatively influence trophoblast differentiation (8).

TRAF3IP2-AS1 lncRNA: TRAF3IP2-AS1 long non-coding RNA a key controller of IL-17 signaling through the SRSF10-IRF1-Act1 axis in autoimmune diseases. Hence, from all the above we can come to the idea

that aberrant lncRNA expression contributes to PE pathogenesis and may act as important biomarkers and influence gene expression in pregnancy complications (8)

Implications for Antenatal Care

The integration of genetic and epigenetic markers into risk prediction models for PE could empower early detection and management by markedly reducing maternal and fetal morbidity and mortality. Markers can be incorporated into predictive models. Here, we delve into some of these promising markers and how they influence antenatal care, highlighting the advantages and obstacles facing such strategies.

Genetic and Epigenetic Markers in Risk Prediction (PE)

Genetic Markers

Genetic studies have identified several susceptibility genes associated with PE, such as COL4A1, SLC2A4, and FLT1, which can be used in risk-prediction models. (37)

The identification of novel candidate genes, such as SORD, DGKI, and ICA1, through whole-genome bisulfite sequencing (WGBS) suggests that genetic markers can provide insights into the heritable components of PE risk (37)

Epigenetic Markers

Epigenetic modifications, particularly DNA methylation, have been linked to PE. Differentially methylated regions (DMRs) associated with genes involved in PE pathogenesis can serve as biomarkers for risk prediction (41)

Studies have shown that epigenetic changes in placental tissues, such as those affecting the TGF-β signaling pathway, are associated with different PE subtypes, indicating their potential utility in personalized risk assessment (42)

The benefits of incorporating markers improved prediction accuracy to illustrate this the

Combining genetic and epigenetic data with traditional clinical factors could enhance the sensitivity and specificity of PE risk prediction models, allowing for more accurate identification of high-risk pregnancies. (43)

The use of machine learning models, such as neural networks, that integrate these markers can improve predictive performance compared to models based solely on clinical data (44)

Personalized Medicine

Genetic and epigenetic markers can facilitate personalized interventions for instances targeted aspirin therapy by recognizing individuals who would benefit the most from preventive measures (40) to clarify more using biomarkers can promote early risk assessment and prediction, leading to individualized preventive therapies. Established biomarkers like PlGF are useful for screening the "placental" subclass. (45)

Challenges in Implementation

Technical and Logistical Barriers

Collaboration of genetic and epigenetic data into clinical practice requires robust and standardized methodologies for data collection and analysis, which can be resource intensive. For example, the 6PLEX assay requires standardization for widespread use (43).

Variability in epigenetic markers owing to environmental factors and differences in laboratory techniques can complicate the interpretation and application of these markers in diverse populations (42).

Several studies have restrictions owing to small sample sizes that may not include variability of gestational plots. Comprehensive follow-up researches in independent pregnancy cohorts are required to verify the development of PE in prediction models. (46)

In some research articles, the placental cell-type heterogeneity when analyzing bulk tissue specimens is mandatory to clarify molecular mechanisms of PE and strengthen the accuracy of prediction models. (47)

Ethical and Social Considerations

Genetic information use raises ethical alerts regarding privacy and potential for discrimination, necessitating careful consideration of data handling and patient consent. (40,48)

To avoid discrimination and guarantee equitable access, each research study must emphasize the need for the development and use of multiethnic PRSs (49)

In conclusion, incorporating genetic and epigenetic markers into PE risk prediction models holds promise in improving early detection and personalized care. However, addressing technical, logistical, and ethical challenges is crucial for the successful implementation of these strategies in healthcare facilities (50). Further researches have to concentrate on validating these markers throughout populations and enhance cost-effective standardized guidelines and recommendations for their use. (48)

Conclusion

Recent studies on preeclampsia have used innovative approaches such as multi-omics analysis, DNA methylation patterns, and machine learning. These have helped identify biomarkers, understand the disease, and develop risk-prediction models. This has led to the subclassification of preeclampsia and the creation of noninvasive screening methods.

For future research, it is important to validate findings across diverse populations, conduct long-term studies, perform functional studies, integrate multiple data types, and develop diagnostic tools to apply these discoveries clinically

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