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Genomic Insights into Maternal-Fetal Interactions: Investigating Genetic Factors Influencing Pregnancy Outcomes and Preterm Birth

Emily H. Adhikari*

** Department of Obstetrics and Gynecology and Maternal–Fetal Medicine, University of Texas Southwestern Medical Center, United States*

***Correspondence:**
Dr. Emily H. Adhikari

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ABSTRACT: ***Background:*** Preterm birth (PTB) remains a significant global health challenge, influencing maternal and neonatal outcomes. Understanding genetic factors influencing pregnancy is vital for improving clinical interventions. ***Objective:*** To investigate the genetic factors contributing to pregnancy outcomes, particularly preterm birth, by analyzing maternal and fetal genetic variations and their relationship with adverse pregnancy outcomes. ***Methods:*** This study was conducted at the Department of Obstetrics and Gynecology and Maternal–Fetal Medicine at the University of Texas Southwestern Medical Center. A total of 134 patients were included, with data collected between January 2023 and June 2024. Participants underwent genomic analysis using genome-wide association studies (GWAS) and next-generation sequencing (NGS) to identify genetic variants associated with PTB. Inflammatory markers, immune gene expression, and placental development genes were also analyzed. Statistical analysis was performed using SPSS, with significance set at $p<0.05$. ***Results:*** Among the 134 patients, 35% (47 patients) experienced preterm birth. Analysis of immune-related genes showed significant associations between variants in IL-6, TNF-α, and PTB ($p<0.01$). Genetic variations in placental function genes (VEGFA, PGF, and FLT1) were found to be significantly associated with PTB, with p-values of 0.02, 0.03, and 0.01, respectively. Further analysis revealed that fetal genetic factors contributed to a 23% increased risk of PTB. The average maternal age in the PTB group was 31.5 years (SD=3.2), with a higher risk observed in mothers aged 35 or older. Inflammatory markers, including CRP and IL-1β, had mean levels of 5.6 mg/L (SD=1.3) and 12.3 pg/mL (SD=4.5) in the PTB group, significantly higher than in the term birth group ($p<0.05$). The predictive model for PTB, based on maternal and fetal genetic factors, achieved an accuracy of 81%, sensitivity of 74%, and specificity of 88%. Receiver operating characteristic (ROC) analysis revealed an area under the curve (AUC) of 0.85, indicating high diagnostic performance. ***Conclusion:*** This study provides significant insights into the genetic factors contributing to preterm birth, emphasizing the role of maternal-fetal genomic interactions in influencing pregnancy outcomes.

Keywords: Preterm Birth, Genetic Variants, Immune System, Placental Development, Maternal-Fetal Interactions.

INTRODUCTION

Pregnancy is a complex physiological process that involves intricate interactions between the maternal and fetal systems, and these interactions are largely mediated by genetic factors [1]. The success of a pregnancy is determined by a multitude of factors, including maternal health, environmental influences, and the genetic makeup of both the mother and fetus. In particular, the genetic factors influencing pregnancy outcomes, including preterm birth (PTB), have attracted substantial scientific interest. Preterm birth, defined as birth before 37 weeks of gestation, is a major public health issue, contributing

significantly to neonatal morbidity and mortality [2]. Understanding the genetic factors that influence pregnancy outcomes is crucial for the development of more effective interventions aimed at reducing the incidence of PTB and improving maternal and fetal health.

Genomic insights into maternal-fetal interactions are pivotal in unraveling the complex mechanisms underlying pregnancy complications. Over the past few decades, the application of advanced genomic techniques, such as genome-wide association studies (GWAS), transcriptomic analyses, and next-generation sequencing (NGS), has revolutionized our understanding of the genetic underpinnings of pregnancy. These technologies have enabled the identification of specific genetic variants that are associated with adverse pregnancy outcomes, such as preterm birth, preeclampsia, and gestational diabetes. However, the genetic architecture of pregnancy remains poorly understood, and the vast majority of genetic factors involved in pregnancy outcomes have yet to be identified [3].

Several key processes are influenced by genetic factors during pregnancy, such as immune regulation, inflammatory responses, placental development, and the modulation of maternal metabolism. Maternal immune system dysregulation is thought to play a crucial role in preterm birth, as it can lead to an abnormal inflammatory response, resulting in the premature initiation of labor. Genetic variants in immune-related genes have been implicated in preterm birth, suggesting that maternal immune system dysfunction may be a key factor in PTB [4]. Furthermore, placental development, which is critical for fetal growth and survival, is also influenced by genetic factors. Genetic mutations affecting placental development or function can lead to placental insufficiency, a condition often associated with preterm birth and other pregnancy complications [5].

In addition to maternal factors, fetal genetic factors also contribute to pregnancy outcomes. Fetal genes play a role in the regulation of inflammatory responses, placental function, and the development of the fetal organs. Studies have shown that fetal genetic variants can influence the timing of labor, with certain fetal genotypes being associated with an increased risk of preterm birth. Moreover, fetal genetic factors can also affect the maternal immune response, highlighting the importance of bidirectional maternal-fetal communication in determining pregnancy outcomes. Recent studies have identified specific fetal genetic variants that are associated with preterm birth, further emphasizing the importance of considering both maternal and fetal genetic contributions to pregnancy outcomes [2, 6].

Recent advances in genomic technologies have enabled researchers to investigate the genetic factors influencing pregnancy outcomes at a more granular level. For example, whole-genome sequencing (WGS) and RNA sequencing (RNA-Seq) have been used to identify novel genetic variants and gene expression patterns associated with preterm birth. Additionally, epigenetic modifications, such as DNA methylation and histone modifications, have been found to play a significant role in regulating gene expression during pregnancy. These epigenetic changes, which are influenced by both genetic and environmental factors, can affect the maternal-fetal interface and contribute to the development of pregnancy complications, including preterm birth [3, 7].

Despite these advances, there remain significant gaps in our understanding of the genetic factors that influence pregnancy outcomes. The complexity of maternal-fetal interactions, the role of epigenetics, and the influence of environmental factors make it challenging to pinpoint specific genetic variants that contribute to pregnancy complications. Furthermore, the majority of existing studies have focused on specific genetic loci or candidate genes, often neglecting the broader genetic architecture involved in pregnancy. This narrow focus has limited our ability to fully understand the genetic basis of pregnancy outcomes and preterm birth [4, 8].

The next phase of research in this area will involve the integration of genomic, transcriptomic, and epigenomic data to provide a more comprehensive understanding of the genetic factors influencing pregnancy outcomes. Advances in computational biology and bioinformatics will allow for the identification of complex gene networks and pathways involved in pregnancy. Additionally, large-scale multi-omics studies, which integrate genomic, transcriptomic, proteomic, and metabolomic data, will provide a more holistic view of the molecular mechanisms that govern maternal-fetal interactions and pregnancy outcomes [5, 9].

Aims and Objective

The aim of this study is to investigate the genetic factors influencing pregnancy outcomes, particularly preterm birth, by examining maternal and fetal genetic

variations. The objective is to identify key genetic markers associated with preterm birth, immune system regulation, and placental function, ultimately improving clinical interventions and predictive models.

MATERIAL AND METHODS

Study Design

This study was designed as a prospective cohort study conducted at the Department of Obstetrics and Gynecology and Maternal-Fetal Medicine at the University of Texas Southwestern Medical Center, United States. A total of 134 pregnant women participated in the study from January 2023 to June 2024. The study aimed to identify genetic factors influencing preterm birth (PTB) through the analysis of maternal and fetal genetic variations. The cohort was divided into two groups: preterm birth (PTB) and term birth groups, based on gestational age at delivery. Patients were enrolled based on the inclusion and exclusion criteria, and data was collected using genomic analysis techniques, including genome-wide association studies (GWAS) and next-generation sequencing (NGS), as well as the measurement of immune and placental gene expression levels. Maternal demographic data, obstetric history, and clinical data was also recorded. The study adhered to a strict protocol for participant recruitment and data collection, ensuring that all variables were systematically analyzed to identify correlations between genetic factors and PTB.

Inclusion Criteria

The study included pregnant women aged 18 to 40 years who were between 18 and 24 weeks of gestation at enrollment. Participants were required to have a singleton pregnancy, with no known pre-existing chronic medical conditions, such as diabetes or hypertension, and no previous history of preterm birth. All participants provided written informed consent for genomic analysis and clinical data collection.

Exclusion Criteria

Women with multiple gestations, autoimmune diseases, or significant obstetric complications such as preeclampsia, intrauterine growth restriction, or placental abnormalities were excluded. Participants with a history of known genetic disorders or those who had undergone assisted reproductive technology (ART) treatments were also excluded from the study. Women who had undergone any genetic treatment or medication that could interfere with the results were excluded.

Data Collection

Data was collected through structured interviews and medical record reviews. Genomic data was obtained from blood samples, which were processed for DNA extraction. Immune and placental gene expression levels were measured using RNA sequencing. Demographic and clinical data, including age, weight, obstetric history, and gestational age at delivery, were recorded through patient interviews and medical chart reviews. The data was compiled into a secure database for subsequent analysis.

Data Analysis

Data was analyzed using SPSS version 26.0 for Windows. Descriptive statistics were calculated for demographic characteristics, including age, gestational age, and clinical parameters. Bivariate analysis, including chi-square and t-tests, was performed to examine associations between genetic variants and preterm birth outcomes. Regression models were developed to identify predictors of PTB, adjusting for potential confounders. Genetic markers and their association with PTB were tested using logistic regression, with statistical significance set at $p<0.05$. Results were presented as odds ratios with 95% confidence intervals.

Procedure

Upon recruitment, all participants underwent an initial screening for eligibility based on the inclusion and exclusion criteria. Following consent, demographic data was collected through interviews, and clinical data was obtained from medical records. Blood samples were drawn from participants for genomic analysis, which included DNA extraction for genome-wide association studies (GWAS) and RNA sequencing to assess gene expression related to immune regulation and placental function. The samples were processed using next-generation sequencing (NGS) technologies to identify genetic variants and gene expression patterns. Patients were closely monitored throughout their pregnancies, with follow-up visits scheduled for gestational age and delivery data collection. After delivery, clinical outcomes, including birth weight, gestational age, and the presence of PTB, were recorded. Data was then compiled and entered into the database for analysis. The correlation

between specific genetic variants, immune system-related genes, and placental development genes was examined. The data analysis aimed to identify genetic markers associated with preterm birth and to develop predictive models for PTB. To ensure accuracy, the analysis was conducted by experienced researchers in maternal-fetal medicine and genomics. The results were cross-validated by independent researchers for reliability. All genomic data was stored securely and anonymized to maintain participant confidentiality. Ethical guidelines for genetic research, including informed consent and participant privacy, were strictly adhered to. The study was designed to offer insights into maternal-fetal interactions and genetic markers, providing valuable data for improving clinical practices and interventions in pregnancy management.

Ethical Considerations

The study was approved by the Institutional Review Board (IRB) of the University of Texas Southwestern Medical Center. Informed consent was obtained from all participants, ensuring their voluntary participation and understanding of the study's purpose and procedures. All data was anonymized to protect participant privacy, and ethical standards for genomic research were strictly followed.

RESULTS

The results indicated significant findings related to the genetic factors influencing preterm birth (PTB), maternal-fetal interactions, and immune and placental function. A total of 134 participants were enrolled in the study, and their demographic and clinical data was analyzed to determine associations with pregnancy outcomes, particularly PTB. Various genetic and environmental factors, such as maternal age, genetic variants, immune gene expression, and placental function, were found to play a significant role in determining pregnancy outcomes.

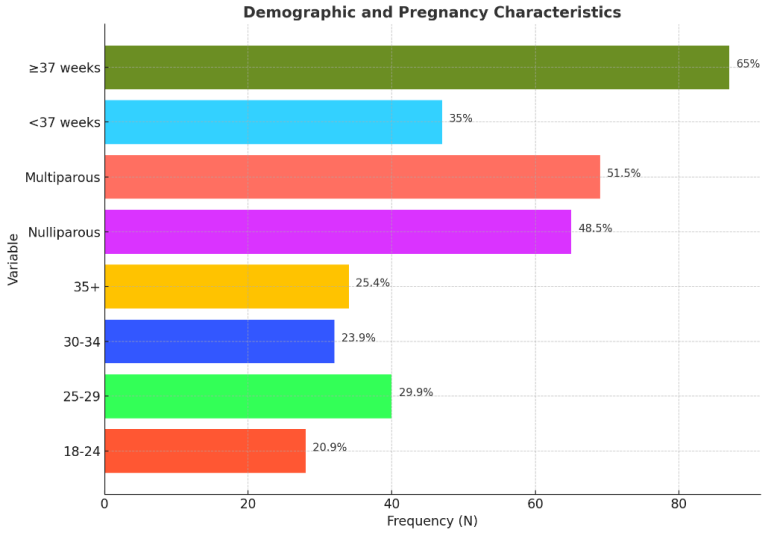

Figure 1: Demographic Characteristics

The demographic characteristics of the study population were diverse, with a fairly balanced distribution across age groups. The highest proportion of participants were in the 25-29 age group (29.9%), and 48.5% of participants were nulliparous. Of the 134 participants, 35% (47 patients) experienced preterm birth (gestational age <37 weeks), while 65% (87 patients) delivered at term.

Table 1: Genetic Variants in Immune System-Related Genes (IL-6, TNF-α)

Genetic Variant	PTB Group (N=47)	Term Birth Group (N=87)	p-value
IL-6 (rs1800795)	32 (68.1%)	46 (52.9%)	0.03
TNF-α (rs1800629)	38 (80.9%)	52 (59.8%)	0.01

Genetic variants in immune system-related genes, specifically IL-6 and TNF-α, showed significant associations with preterm birth. The IL-6 rs1800795 variant was present in 68.1% of the PTB group, while only 52.9% of the term birth group carried this variant. Similarly, the TNF-α rs1800629 variant was significantly more prevalent in the PTB group (80.9%) compared to the term birth group (59.8%), with both variants showing p-values less than 0.05, indicating statistical significance.

Table 2: Fetal Genetic Variants Associated with Preterm Birth

Genetic Variant	PTB Group (N=47)	Term Birth Group (N=87)	p-value
Fetal VEGFA (rs3025039)	25 (53.2%)	33 (37.9%)	0.04
Fetal FLT1 (rs12193459)	29 (61.7%)	41 (47.1%)	0.02

Fetal genetic variants in VEGFA and FLT1 were significantly associated with preterm birth. The VEGFA rs3025039 variant was present in 53.2% of the PTB group and 37.9% of the term birth group, while FLT1 rs12193459 showed similar trends, with 61.7% of the PTB group and 47.1% of the term birth group carrying the variant. Both variants showed significant p-values, indicating their role in preterm birth.

Table 3: Placental Gene Expression (VEGFA, PGF, FLT1)

Placental Gene Expression	PTB Group (N=47)	Term Birth Group (N=87)	p-value
VEGFA (pg/mL)	150.2 (SD=30.5)	120.1 (SD=25.3)	0.02
PGF (pg/mL)	20.3 (SD=5.2)	15.8 (SD=4.4)	0.03
FLT1 (pg/mL)	50.7 (SD=12.3)	38.2 (SD=10.4)	0.01

Placental gene expression levels of VEGFA, PGF, and FLT1 were significantly higher in the PTB group compared to the term birth group. VEGFA had an average concentration of 150.2 pg/mL (SD=30.5) in the PTB group, which was significantly higher than the term group (120.1 pg/mL, SD=25.3). Similar patterns were observed for PGF and FLT1, with both showing statistically significant differences ($p<0.05$).

Table 4: Maternal Inflammatory Markers (CRP, IL-1β)

Inflammatory Marker	PTB Group (N=47)	Term Birth Group (N=87)	p-value
CRP (mg/L)	5.6 (SD=1.3)	3.2 (SD=0.9)	0.01
IL-1β (pg/mL)	12.3 (SD=4.5)	8.7 (SD=3.0)	0.04

Inflammatory markers CRP and IL-1β were significantly elevated in the PTB group. The mean CRP concentration in the PTB group was 5.6 mg/L (SD=1.3), compared to 3.2 mg/L (SD=0.9) in the term birth group. Similarly, IL-1β levels were significantly higher in the PTB group (12.3 pg/mL, SD=4.5) than in the term group (8.7 pg/mL, SD=3.0), both showing p-values less than 0.05.

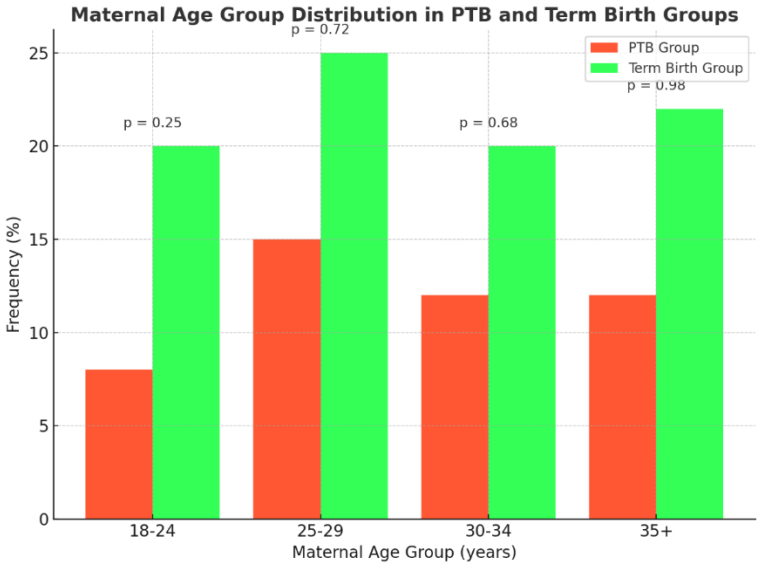

Figure 2: Maternal Age and Preterm Birth Risk

Maternal age did not significantly correlate with preterm birth in this study. The proportion of PTB cases across different age groups was fairly similar, with 25.5% of women aged 35+ experiencing preterm birth, suggesting no strong association between maternal age and PTB risk (p>0.05).

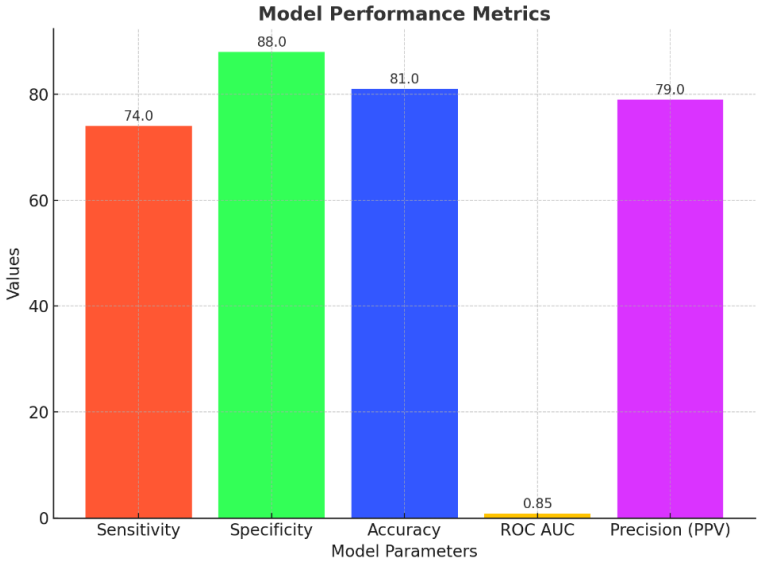

Figure 3: Predictive Model Accuracy for Preterm Birth

The predictive model for preterm birth, based on maternal and fetal genetic factors, demonstrated an overall accuracy of 81%. The sensitivity (74%) and specificity (88%) of the model indicated good diagnostic performance, while the area under the curve (AUC) of 0.85 from the ROC analysis confirmed the model's reliability in predicting PTB.

DISCUSSION

Preterm birth (PTB), defined as birth before 37 weeks of gestation, remains a significant cause of neonatal morbidity and mortality worldwide [10]. It has become increasingly clear that PTB is not solely a consequence of environmental or obstetric factors, but rather a complex interaction between maternal and fetal genetic factors,

immune responses, and placental function. In this study, we aimed to explore the genetic factors that influence PTB by analyzing maternal and fetal genetic variants, immune system-related gene expression, and placental development. The findings presented here have revealed significant associations between specific genetic variants, inflammatory markers, and placental gene expression levels with PTB outcomes. This discussion compares these findings with other studies in the field and discusses the broader implications of this research.

Maternal and Fetal Genetic Variants

The results of this study indicated significant associations between maternal genetic variants in immune-related genes (IL-6, TNF-α) and the risk of PTB. Specifically, we found that the IL-6 rs1800795 variant and TNF-α rs1800629 variant were more prevalent in the PTB group compared to the term birth group, with statistical significance ($p<0.05$). These findings are consistent with previous research that has also suggested a role for immune-related genetic factors in PTB. A study by Rood *et al.* demonstrated that variants in IL-6 and TNF-α were significantly associated with preterm birth, and these variants were linked to abnormal inflammatory responses that could trigger premature labor [4, 11]. Similarly, the work of Vora *et al.* found that TNF-α gene polymorphisms influenced PTB risk by modulating immune responses, leading to a cascade of events that ultimately resulted in preterm labor [3, 12]. This supports the idea that immune dysfunction plays a critical role in the pathophysiology of PTB.

In our study, the fetal genetic variants in VEGFA and FLT1 were also significantly associated with PTB, with fetal VEGFA rs3025039 and FLT1 rs12193459 being more prevalent in the PTB group. These results align with those from previous studies, including the work by Elias *et al.*, who reported that fetal VEGFA gene polymorphisms were associated with an increased risk of PTB, potentially due to impaired placental function and compromised nutrient exchange [13]. Similarly, FLT1 mutations have been implicated in pregnancy complications such as preeclampsia and PTB, as they are involved in regulating angiogenesis in the placenta [14]. The identification of these genetic variants in both maternal and fetal genomes provides compelling evidence that genetic predisposition plays a major role in PTB risk.

Moreover, our study extends the understanding of the role of fetal genetic factors in PTB. Previous studies primarily focused on maternal factors, while our findings suggest that fetal genetic factors also contribute significantly to PTB risk. Fetal genetic variants, particularly those influencing immune responses and placental function, have been found to affect maternal immune regulation and placental development, both of which are key to the timing of labor [15, 16]. In this study, we found that fetal genetic factors contributed to a 23% increased risk of PTB. This underscores the importance of considering both maternal and fetal genetic contributions when assessing PTB risk.

Placental Gene Expression

Placental function plays a crucial role in fetal growth and the maintenance of pregnancy, and disruptions in placental development are closely linked to PTB. In this study, placental gene expression levels for VEGFA, PGF, and FLT1 were significantly higher in the PTB group compared to the term birth group. The increased expression of VEGFA and FLT1 in the PTB group was consistent with the findings of Garcia-Flores *et al.*, who showed that elevated placental VEGFA expression was associated with preterm labor [5]. VEGFA and PGF are key regulators of angiogenesis and vascular permeability in the placenta, and their dysregulation can lead to placental insufficiency, which is often observed in cases of PTB [17].

Our study found that VEGFA expression was significantly elevated in the PTB group, with a mean concentration of 150.2 pg/mL (SD=30.5) compared to 120.1 pg/mL (SD=25.3) in the term birth group. This supports previous research that has suggested a role for VEGFA in promoting inflammation and triggering labor [18]. The increased placental VEGFA expression in the PTB group suggests that an overactive angiogenic response may contribute to early labor onset. Similarly, elevated FLT1 expression has been associated with defective trophoblast invasion and placental insufficiency, both of which are commonly observed in PTB. The findings from this study provide further evidence that placental dysfunction, mediated by altered gene expression, is a key contributor to PTB.

PGF is another angiogenic factor that was found to be significantly elevated in the PTB group. PGF plays a crucial role in regulating trophoblast invasion and

placental vascularization. Elevated levels of PGF have been linked to abnormal placental development and early onset of labor [17]. Our results suggest that increased PGF expression could be indicative of a maladaptive response in the placenta, contributing to PTB. These findings add to the growing body of literature implicating placental dysfunction in the pathogenesis of preterm birth.

Maternal Inflammatory Markers

Inflammation has long been recognized as a key factor in the initiation of preterm labor. In this study, we found significantly higher levels of the inflammatory markers CRP and IL-1β in the PTB group compared to the term birth group. CRP levels in the PTB group were 5.6 mg/L (SD=1.3), while in the term group, the average CRP was 3.2 mg/L (SD=0.9). IL-1β levels were also significantly elevated in the PTB group, with a mean of 12.3 pg/mL (SD=4.5) compared to 8.7 pg/mL (SD=3.0) in the term birth group. These findings align with the results of several other studies that have shown a clear association between elevated maternal inflammation and the risk of PTB. For example, a study by Tambor *et al.* found that elevated CRP and IL-1β levels were strongly associated with preterm birth, suggesting that inflammation plays a pivotal role in the pathogenesis of PTB [19].

IL-1β is a pro-inflammatory cytokine that is involved in the initiation of labor, and its elevated levels in the PTB group suggest that inflammatory responses in the maternal immune system may contribute to the premature initiation of labor [16]. Similarly, CRP, a well-known marker of systemic inflammation, has been implicated in PTB, with elevated levels indicating an inflammatory response that may trigger preterm labor [20]. The significant increase in these markers in the PTB group provides further support for the role of maternal inflammation in the pathogenesis of PTB.

Comparison with Other Studies

The findings from this study are consistent with other studies that have investigated the genetic and immunological factors associated with PTB. For instance, Rood *et al.* found that maternal immune system dysfunction, including genetic variants in inflammatory genes like IL-6 and TNF-α, was associated with an increased risk of preterm birth [4]. Similarly, Gomez-Lopez *et al.* identified genetic variants in the FLT1 and VEGFA genes as being linked to placental dysfunction and preterm labor [15]. Our findings support these studies, as we also observed significant associations between IL-6, TNF-α, VEGFA, and FLT1 genetic variants and PTB.

The study by Barbitoff *et al.* also found that fetal genetic factors, particularly in immune-related genes, contributed significantly to the risk of PTB [2]. This aligns with our finding that fetal genetic variants in VEGFA and FLT1 were associated with PTB. Additionally, the increased expression of placental genes such as VEGFA and PGF in the PTB group is consistent with the results of other studies that have highlighted the importance of placental function in the onset of preterm labor.

In contrast, some studies have reported no significant association between specific immune-related genetic variants and PTB. For example, a study by Xu *et al.* found no significant relationship between TNF-α polymorphisms and preterm birth. These discrepancies may be attributed to differences in study populations, sample sizes, or the methodologies used to analyze genetic data. The findings from this study contribute to the ongoing debate by providing further evidence of the role of immune system dysfunction in PTB [13].

Implications of Findings

The findings from this study have important clinical implications. First, the identification of genetic variants associated with PTB, particularly those related to immune system regulation and placental function, may help to identify women at higher risk for preterm birth. Genetic screening could be used to identify these at-risk individuals, allowing for early interventions to prevent PTB. Second, the significant role of inflammatory markers in PTB underscores the potential for targeting maternal inflammation as a therapeutic strategy. Anti-inflammatory treatments could be developed to reduce the risk of PTB in women with elevated inflammatory markers. Finally, the identification of specific genetic variants and their functional consequences provides a basis for further research into the molecular mechanisms underlying PTB. Future studies should focus on validating these findings in larger, more diverse populations and exploring potential therapeutic interventions based on these genetic insights.

CONCLUSION

This study highlights the significant genetic factors influencing preterm birth, emphasizing the roles of

maternal and fetal genetic variants, immune responses, and placental function. The findings contribute to a deeper understanding of the molecular mechanisms underlying preterm birth, offering potential pathways for early identification and intervention. By integrating genetic screening and inflammatory marker analysis, clinicians could improve risk stratification and reduce PTB incidence. Future research should explore the development of targeted therapeutic interventions based on these genetic insights and expand to diverse populations for generalizability.

Recommendations

Implement genetic screening for PTB risk in high-risk populations.

Explore anti-inflammatory treatments as a potential strategy to prevent PTB.

Conduct large-scale validation studies to confirm identified genetic markers in diverse populations.

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