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Original Article

The association between non-invasive prenatal testing and first-trimester preeclampsia screening

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ABSTRACT

Objective: The non-invasive prenatal testing (NIPT) and preeclampsia screening test (PES) has been widely used to detect fetal chromosomal abnormalities and maternal preeclampsia during early pregnancy. Our aim was to investigate the correlation between PES parameters and NIPT aneuploidy results.
Materials and methods: We retrospectively analyzed pregnancies that underwent both PES and NIPT. PES included multiples of the median (MoM) of PlGF, PAPP-A, MAP, and calculated risks for preeclampsia, intrauterine growth restriction (IUGR), and preterm delivery, while NIPT assessed risks for common aneuploidies, rare autosomal abnormalities, and fetal fraction. Statistical correlation analyses were conducted to evaluate associations between the parameters of the two tests.
Results: Lower PlGF MoM and PAPP-A MoM were significantly associated with high-risk NIPT for Down and Edwards syndromes. Specific PlGF MoM cut-offs (<0.5315, <0.8515) showed higher probabilities of high-risk NIPT for Down and Edwards syndromes (AUC 0.829 and AUC 0.836, respectively). Similarly, PAPP-A MoM cut-offs (<0.7335, <0.429) indicated higher probabilities of high-risk NIPT for Down and Edwards syndromes (AUC 0.765 and AUC 0.909, respectively). High-risk PES for preeclampsia increased the odds of high-risk NIPT for Down and Edwards syndromes by 3.54 and 2.33 times, respectively; for IUGR, the increases were 8.38 and 12.25 times. High-risk PES for preterm delivery was associated with a 1.09-fold increase in the odds of high-risk NIPT for rare autosomal abnormalities. Fetal fraction was significantly lower in high-risk PES cases, positively correlated with PlGF MoM and PAPP-A MoM, and negatively with MAP MoM.
Conclusion: Fetal chromosomal abnormalities may indicate increased risk for PES parameters and risk assessments. Reduced NIPT fetal fraction in high-risk PES suggests potential placental dysfunction. Combining PES parameters and NIPT fetal fraction may provide reference for prenatal risk assessment.
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Introduction

Preeclampsia, a severe complication in 2–8% of pregnancies globally, causes hypertension, proteinuria, and organ failure, potentially leading to maternal or fetal death [1]. The first trimester PES assesses risks for preeclampsia, IUGR, and preterm birth, enabling preventive measures like aspirin or monitoring. Risk estimates from PES are calculated using the Fetal Medicine Foundation (FMF) algorithm, which incorporates maternal clinical factors such as age, weight, height, medical and pregnancy history, and mean arterial pressure (MAP), as well as biochemical markers from maternal blood including placental growth factor (PlGF) and pregnancy-associated plasma protein A (PAPP-A), and ultrasound-derived uterine artery pulsatility index (UAPI). Among the biochemical factors, the two most commonly used for analysis are PlGF and PAPP-A [2]. Both are produced by the placenta. PlGF helps

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the embryo implant and connect to the maternal blood vessels to provide nutrients to the fetus [3], while PAPP-A is crucial for fetal growth [4].

Chromosomal abnormalities can lead to a range of health conditions. Down syndrome, a common and survivable abnormality, affects approximately 1.52% of live births globally [5]. It is associated with intellectual disabilities, heart problems, and immune issues, often requiring ongoing support and care. First trimester maternal serum screening, which assesses Down syndrome risk via biomarkers and nuchal translucency, is recommended by ACOG [6]. Taiwan has seen a significant decrease in the number of live births with Down syndrome since the introduction of maternal serum screening with subsidies in 1994 [7]. The newer NIPT could assess the risk of fetal chromosomal abnormalities by analyzing cell-free DNA (cffDNA) from the placenta and offers higher accuracy for Down syndrome detection than traditional screening. Advanced NIPT can also assess risks for Edwards syndrome, Patau syndrome, sex chromosome abnormalities, microdeletions, and microduplications, making it an increasingly preferred option over traditional first trimester screening.

Since PES and NIPT are performed at a similar time, pregnant women only need to have a single blood draw. As a result, some pregnant women opt to have both tests in the first trimester to assess the risk of adverse pregnancy outcome and fetal chromosomal abnormalities. Since the analytical parameters of both screening test are closely related to the placenta, previous studies have shown the application of PlGF and PAPP-A to the risk of fetal chromosomal aneuploidy [8,9].

To our knowledge, no studies have examined the correlation between PES and NIPT or the potential applications of combining PlGF and PAPP-A with NIPT. This study investigates this correlation, exploring how the combined parameters and results from both tests may help evaluate the risks of fetal chromosomal abnormalities and pregnancy complications. This could provide additional insights for women and clinicians, enhancing awareness of pregnancy risks and guiding more informed evaluations.

Materials and methods

Study population

Data from 19,558 singleton pregnancies that underwent both PES and NIPT at Genetics Generation Advancement Corp. (GGA) between 2016 and 2021 were retrospectively analyzed. Twin pregnancies and cases with incomplete result were excluded.

First trimester preeclampsia screening test (PES)

Maternal PAPP-A and PlGF were measured using the B·R·A·H·M·S PlGF plus KRYPTOR kit. Risk for gestational preeclampsia ($\geq$1:200), fetal IUGR ($\geq$1:150), and preterm birth ($\geq$1:50) were calculated using FMF software incorporating UAPI and maternal clinical information.

Non-invasive prenatal aneuploidy screening test (NIPT)

cffDNA was extracted from maternal plasma, and libraries were constructed using the Berry and Kang reagent kit. Sequencing was performed on Illumina NexpSeq 500. Z-scores for each chromosome were calculated. Z-score $\geq$3 indicated high-risk trisomy, ≤-3 indicated high-risk monosomy. Specific Z-score thresholds were used for sex chromosome abnormalities.

Statistical analysis

NIPT results were categorized into seven groups: low risk, high risk for trisomy 21 (Down syndrome, T21), trisomy 18 (Edwards syndrome, T18), trisomy 13 (Patau syndrome, T13), monosomy X (Turner syndrome, MX), other sex chromosome aneuploidies (other SCAs), and rare chromosomes aneuploidies (RCAs). Mann–Whitney U test compared PES parameters (height, weight, CRL, PlGF MoM, PAPP-A MoM, MAP MoM, UAPI MoM) between NIPT groups. Additionally, proportions of high-risk NIPT results were compared between high- and low-risk PES groups based on preeclampsia, fetal IUGR, and preterm birth risk estimates. ROC statistics assessed PlGF MoM and PAPP-A MoM for predicting high-risk NIPT, calculating AUC and accuracy after adjusting for maternal factors. Fetal fraction distribution in high and low PES risk groups was analyzed. Extreme outliers in PlGF MoM and PAPP-A MoM values were identified using boxplot visualization and excluded based on the 1.5 $\times$ IQR (interquartile range) criterion. Correlation between $\log_{10}$ fetal fraction and PES biomarkers (PlGF, PAPP-A, MAP, UAPI) was assessed using R^2 analysis. Significance values for multiple pairwise comparisons and correlation analyses were adjusted using the Bonferroni correction to control for Type I error. Significance was set at $p < 0.05$.

Results

Clinical characteristics

Between 2016 and 2021, 19,558 pregnancies with PES and NIPT from GGA laboratory were categorized into seven NIPT result groups: low-risk, T21, T18, T13, MX, other SCAs, and RCAs. Maternal age and clinical characteristics (weight, height, gestational age, CRL) across different groups are presented in Table 1. Maternal age was significantly higher in the high-risk T21 and T18 syndrome groups than in the low-risk group.

Table 1
Clinical characteristics in cases and low-risk control.

Characteristic	Low-risk (n = 19,178)	T21 (n = 59)	T18 (n = 22)	T13 (n = 6)	MX (n = 61)	Other SCAs (n = 46)	RCAs (n = 186)
Age (years)	31 (15–56)	34 (21–44)[a]	36 (24–41)[a]	33 (24–38)	32 (21–41)	32 (21–45)	31 (19–51)
Maternal weight (kg, PES testing)	56 (32.6–127.8)	57 (40–94.2)	56.3 (41.4–83)	55.2 (50.1–60.6)	56 (42–79)	59 (40.4–85)	57.2 (40–95.3)
Maternal height (cm, PES testing)	160 (139–185.7)	160 (147–173)	160 (150–168)	162 (156–170)	160 (144–173)	161 (152–172)	160 (145–171)
Gestational age (week)	12 (12–13)	12 (12–13)	12 (11–12)	12 (11–12.25)	12 (12–13)	12 (12–12)	12 (12–13)
Fetal crown-rump length (mm)	61 (45–84)	58.9 (46.8–79.1)	56.9 (46.3–74.6)	59.4 (48–68.5)	59.8 (45–83.4)	58.6 (45–79.8)	61.6 (45–84)

Maternal age was significantly higher in the T21 and T18 groups compared to the low-risk group ($p = 0.009$ and $p = 0.005$, respectively).
Values are median (range).
[a] $p < 0.05$ vs Low-risk group (Mann–Whitney U test with Bonferroni's adjusted).

Association between PES parameters and NIPT high-risk results

Differences in PES test parameters across NIPT high-risk groups were compared (Table 2). PlGF MoM values were significantly lower in the high-risk groups for T21 and T18 syndrome compared to the low-risk group (Fig. 1A). A similar trend was observed for PAPP-A MoM values (Fig. 1B).

Association between adverse pregnancy outcome risk scores from PES and NIPT high-risk results

The relationship between the PES risk estimates for adverse pregnancy outcomes and NIPT high-risk results were examined. The probabilities of a high-risk NIPT result for T21 and T18 were 3.54 and 2.33 times higher, respectively, among pregnancies with a high preeclampsia risk score compared to those with a low-risk score (Fig. 2A).

Similarly, the probabilities of a high-risk NIPT result for T21 and T18 was 8.38 and 12.25 times higher, respectively, in pregnancies with high risk PES result for fetal IUGR compared to those with a low-risk result (Fig. 2B).

For pregnancies with a high-risk PES result for preterm birth, the odds of a high-risk NIPT result for RCAs were approximately 1.09 times higher compared to those with a low-risk result (Fig. 2C).

Statistical cut-offs of PlGF MoM/PAPP-A MoM in predicating high-risk NIPT results

ROC analysis identified PlGF MoM thresholds <0.5315 and < 0.8515 for predicting high-risk NIPT results for T21 and T18, with associated probabilities of 88.32% and 59.52%, respectively (Fig. 3A and B). PAPP-A MoM showed a similar trend; values below 0.7335 and 0.429 corresponded to an 88.22% and 98.03% probability of high-risk NIPT results for T21 and T18, respectively (Fig. 3C and D).

Association between NIPT fetal fraction and risk estimates of PES

Fetal fraction distribution was analyzed according to PES risk scores for preeclampsia, fetal IUGR, and preterm birth separately. In all three conditions, the high-risk groups showed significantly lower fetal fractions compared to their respective low-risk group (Fig. 4).

Correlation between NIPT fetal fraction and PES test parameters

Correlation analysis was performed between the $\log_{10}$ value of the PES parameters and the NIPT fetal fraction. PlGF MoM and PAPP-A MoM showed positive correlations with fetal fraction, while MAP MoM was negatively correlated. UAPI MoM showed no significant correlation (Fig. 5).

Discussion

Comparison of PlGF and PAPP-A distributions in NIPT with previous studies

In this study, we aimed to clarify the relationship between NIPT and first-trimester preeclampsia screening parameters, as both tests are influenced by placental function. Prior studies indicated significantly lower maternal serum PlGF and PAPP-A levels in pregnancies at high risk for trisomy 21, 18, or 13 based on first trimester screening [10], consistent with findings from studies with karyotype-confirmed cases showing reduced PlGF MoM and PAPP-A MoM in these trisomies [9].

This study's correlation analysis revealed significantly lower PAPP-A MoM in the high-risk groups for T21 and T18 compared to the low-risk group (Table 2). The median values were consistent with prior karyotype-based studies of high-risk NIPT groups of T18, T13 and MX (Fig. 6). Similarly, PlGF MoM was significantly lower in the high-risk NIPT T21 and T13 groups (Fig. 1, Table 2), aligning with findings from the karyotype-based study (Fig. 7) [9]. Notably, the median of PlGF MoM in the high-risk group of T21 in this study was 0.462, which was the lowest among all NIPT high-risk groups. While this differs from karyotype-based distributions reported in Western populations, it is similar to the data from Chinese studies [11], potentially reflecting ethnic differences in the study populations.

PlGF and PAPP-A as an assessment of high-risk NIPT results

Previous studies linked decreased PlGF MoM to fetal chromosomal abnormalities, attempting its inclusion in first-trimester Down syndrome risk calculation, but this improved detection rate came with a higher false positive rate [12]. In this study, PlGF MoM and PAPP-A MoM values below specific thresholds were linked to a higher likelihood of high-risk NIPT results for T21 and T18 (Fig. 3). Given that pregnancy abnormalities can influence NIPT results [13], and that PlGF and PAPP-A are vital for placental growth, placental dysfunction may lead to abnormal biomarker levels and impact NIPT outcomes.

Association between PES test parameters and fetal fraction in NIPT

Insufficient PlGF post-implantation can lead to abnormal uterine artery blood vessels, increasing risks of preeclampsia, IUGR, and preterm birth. NIPT targets cffDNA in maternal blood.

Table 2
MoMs for maternal serum placental growth factor (PlGF), pregnancy-associated plasma protein-A (PAPP-A), mean arterial pressure (MAP) and umbilical artery pulsatility index (UAPI).

NIPT result	PlGF MoM	PAPP-A MoM	MAP MoM	UAPI MoM
Low-risk	0.949 (0.698–1.246)	1.364 (0.977–1.846)	0.97 (0.9–1.03)	1.05 (0.85–1.28)
T21	0.462 (0.373–0.711)[a]	0.669 (0.424–1.193)[a]	0.98 (0.925–1.013)	1.04 (0.953–1.273)
T18	0.695 (0.520–0.799)[a]	0.276 (0.163–0.834)[a]	0.93 (0.89–1)	1.14 (1.073–1.173)
T13	0.880 (0.482–1.194)	0.958 (0.485–1.548)	1.045 (0.873–1.158)	0.87 (0.67)
MX	0.891 (0.633–1.200)	1.272 (0.898–1.875)	0.95 (0.905–1.02)	1.03 (0.84–1.335)
Other SCAs	0.934 (0.676–1.207)	1.188 (0.796–1.592)[a]	0.97 (0.88–1.048)	1.14 (0.97–1.475)
RCAs	0.964 (0.693–1.304)	1.167 (0.857–1.752)[a]	0.96 (0.908–1.033)	1.09 (0.835–1.355)

PlGF MoM was significantly lower in the T21 and T18 groups compared to the low-risk group ($p < 0.001$ for both comparisons).
PAPP-A MoM was significantly lower in the T21, T18, other SCAs, and RCAs groups compared to the low-risk group ($p < 0.001$, $p < 0.001$, $p = 0.045$, and $p = 0.026$, respectively).
Values are median (interquartile range).
[a] $p < 0.05$ vs Low-risk group (Mann–Whitney U test with Bonferroni's adjusted).

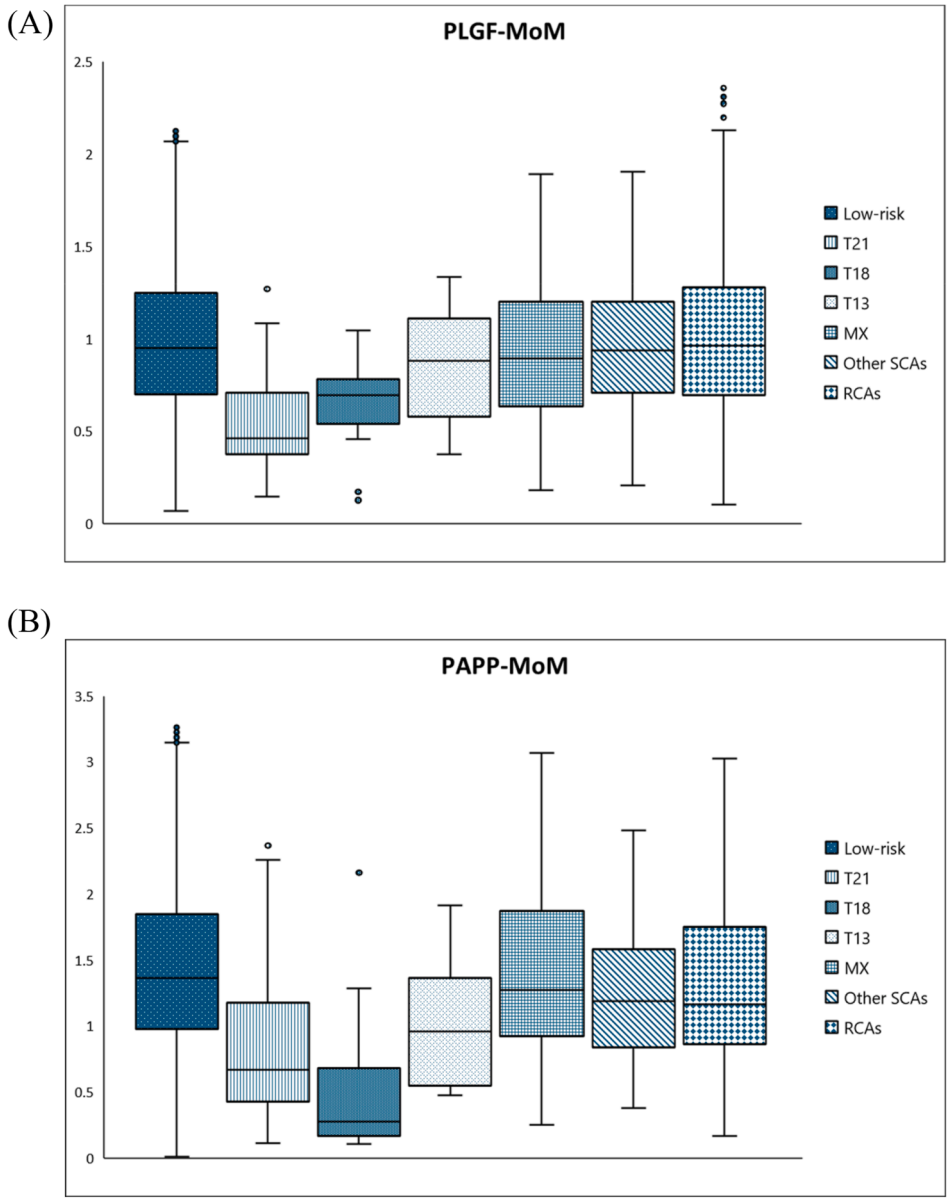


Fig. 1. Distributions of PlGF MoM and PAPP-A MoM in different groups categorized by NIPT screening results. (A) The subjects were divided into seven groups according to the NIPT screening results: low-risk, T21, T18, T13, MX, other SCAs, and RCAs. The distribution of PlGF MoM in each group was observed. The results showed that the PlGF MoM in the T21 and T18 NIPT high-risk groups was significantly lower than that in the NIPT low-risk group ($p < 0.001$ for both comparisons). (B) The distribution of PAPP-A MoM in each NIPT group was observed. The results showed that the PAPP-A MoM in the T21, T18, other SCAs and RCAs NIPT high-risk groups was significantly lower than that in the NIPT low-risk group ($p < 0.001$, $p < 0.001$, $p = 0.045$ and $p = 0.026$, respectively).

Studies have shown that fetal fractions below 4% are associated with higher rates of late-onset preeclampsia, gestational diabetes, and increased risk of fetal chromosomal abnormalities or congenital anomalies [14]. Our data similarly demonstrates that lower fetal fractions are linked to higher risks of preeclampsia, IUGR, and preterm birth (Fig. 4). Furthermore, fetal fraction was positively correlated with PlGF MoM and PAPP-A MoM, and negatively with MAP MoM (Fig. 5), consistent with previous findings in 2018 [15]. A 2023 study also confirmed that lower circulating cffDNA is linked to increased risks of gestational hypertension, small for gestational age, and preterm birth [16].

Physiological functions and hypothesized mechanisms of PlGF, PAPP-A, and circulating cffDNA

PAPP-A is a protease that cleaves IGFBP-4, a binding protein that inhibits IGF activity. By degrading IGFBP-4, PAPP-A enhances IGF availability, supporting placental growth. Reduced PAPP-A may lead to impaired placental function and increased risk of fetal growth restriction, potentially affecting placental function and increasing the risk of SGA fetuses [17]. While PAPP-A alone is not highly effective in predicting preeclampsia, the FMF recommends its use with PlGF, UAPI, and MAP to predict early-onset preeclampsia [18]. PlGF aids subsequent

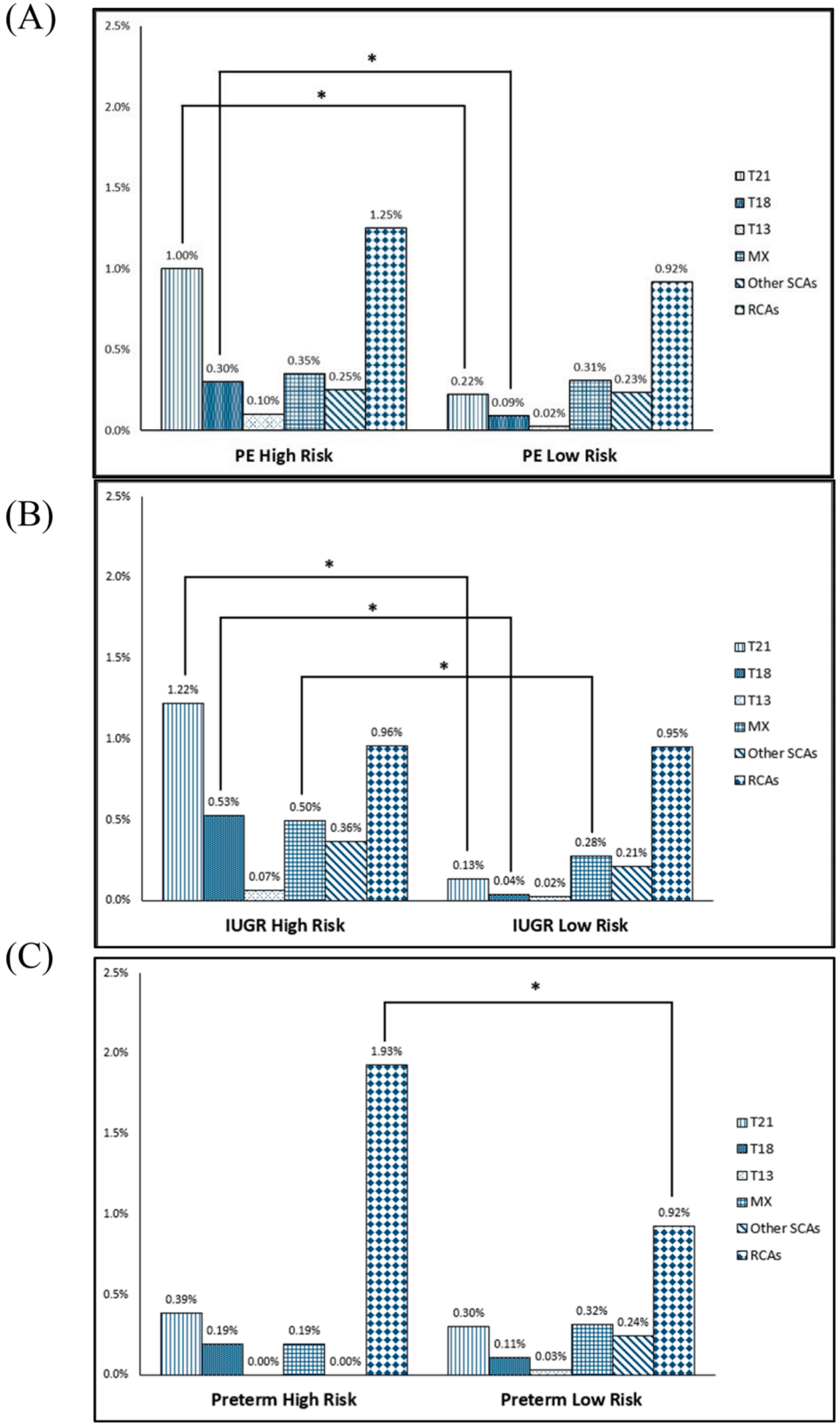


Fig. 2. Differences in proportion of NIPT high-risk results within each risk groups based on PES results. (A) Preeclampsia (PE) risk as calculated within PES test was divided into high-risk (left) and low-risk (right) groups. The proportions of each kind of NIPT high-risk results in the two groups were charted and compared. The results showed that there is a higher proportion of T21 or T18 in the preeclampsia high-risk group ($p < 0.001$ and $p = 0.020$, respectively). (B) The intrauterine fetal growth retardation (IUGR) high-risk group also showed significantly higher NIPT T21, T18 and MX proportions ($p < 0.001$, $p < 0.001$ and $p = 0.048$, respectively). (C) The preterm high-risk group only showed a significantly higher proportion for RCAs ($p = 0.033$).

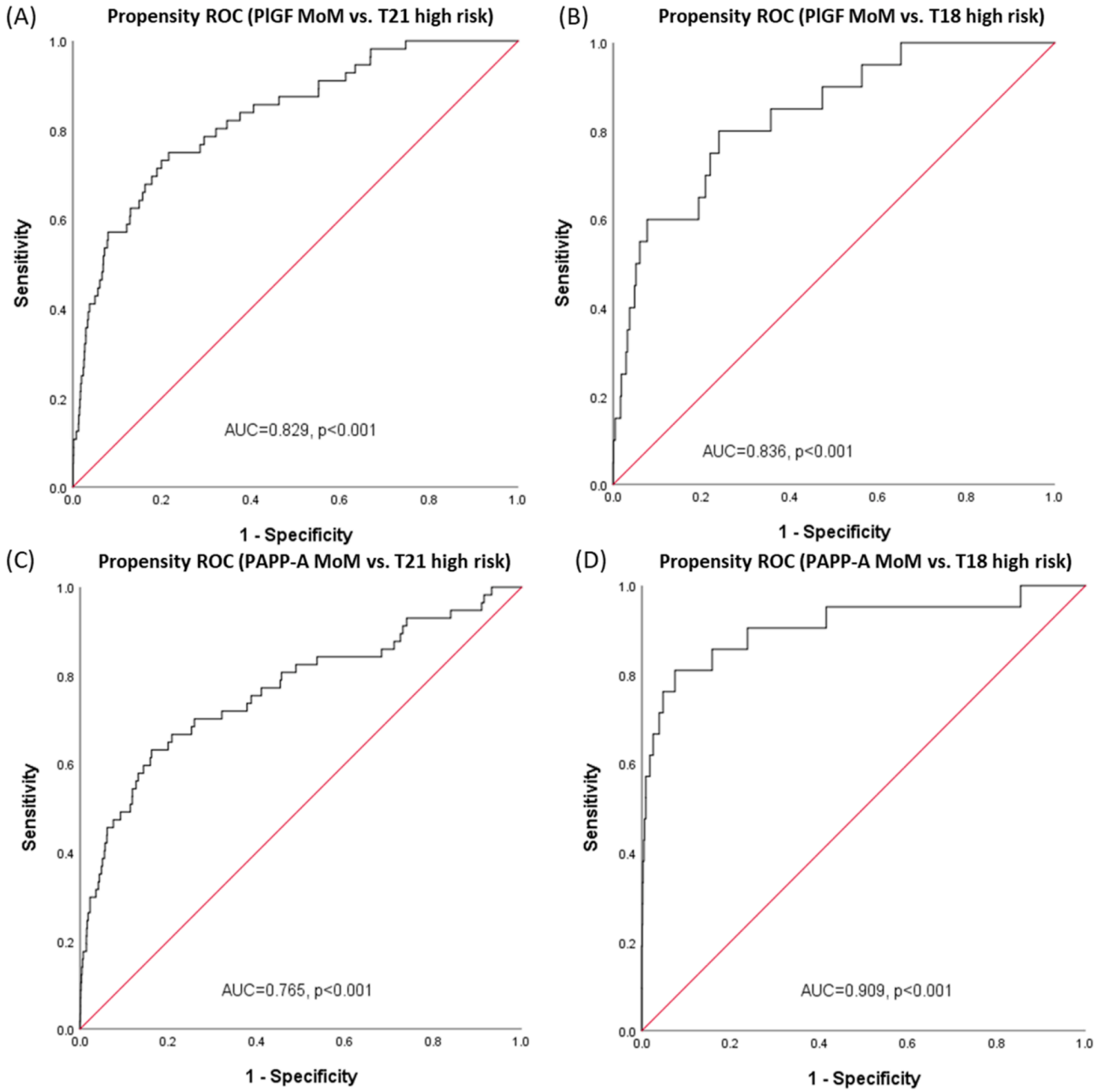


Fig. 3. ROC curves of PlGF MoM and PAPP-A MoM for NIPT high-risk. (A) ROC analysis was performed for the combined PlGF MoM and NIPT high-risk. The results showed that when PlGF MoM <0.5315, there was a higher chance of NIPT screening high-risk for T21, with an AUC of 0.829 and an accuracy of 88.32%. (B) ROC analysis was performed for PlGF MoM and NIPT high-risk. The results showed that when PlGF MoM <0.8515, there was a higher chance of NIPT screening high-risk for T18, with an AUC of 0.836 and an accuracy of 59.52%. (C) When PAPP-A MoM <0.7335, there was a higher chance of NIPT screening high-risk for T21, with an AUC of 0.765 and an accuracy of 88.22%. (D) When PAPP-A MoM <0.429, there was a higher chance of NIPT screening high-risk for T18, with an AUC of 0.909 and an accuracy of 98.03%.

angiogenesis and promotes placental growth post-implantation. Studies indicate that lower PlGF MoM distribution is associated with a higher risk of adverse pregnancy outcomes [19].

The placenta's physiological state is considered crucial in preeclampsia [20]. Prior research noted higher cffDNA and lower PAPP-A levels in pregnant women with preeclampsia and hypertensive disorders of pregnancy (HDP). Consequently, combining cffDNA and PAPP-A in first-trimester screening may enhance the prediction of preeclampsia and HDP [21].

cffDNA is released from trophoblasts in the placenta. The amount of cffDNA released is related to the rate of trophoblast apoptosis [22]. Studies show significantly higher free placental DNA levels in Down syndrome fetuses and pregnancies with preeclampsia [23,24]. Even within low-risk preeclampsia screening groups, cffDNA can indicate potential preeclampsia risk [25].

Previous studies have shown that fetal fraction are positively correlated with placental factors such as PAPP-A and PlGF [26], with another study confirming negative correlations with UAPI and MAP, and positive correlations with PAPP-A and PlGF, consistent with this study's findings [15]. Speculation suggests cffDNA positively correlates with trophoblast apoptosis, and low cffDNA may indicate early placental dysfunction [22]. Combined with Fig. 4 of this study, it is speculated that pregnant women with high-risk tendencies for adverse pregnancy outcomes such as

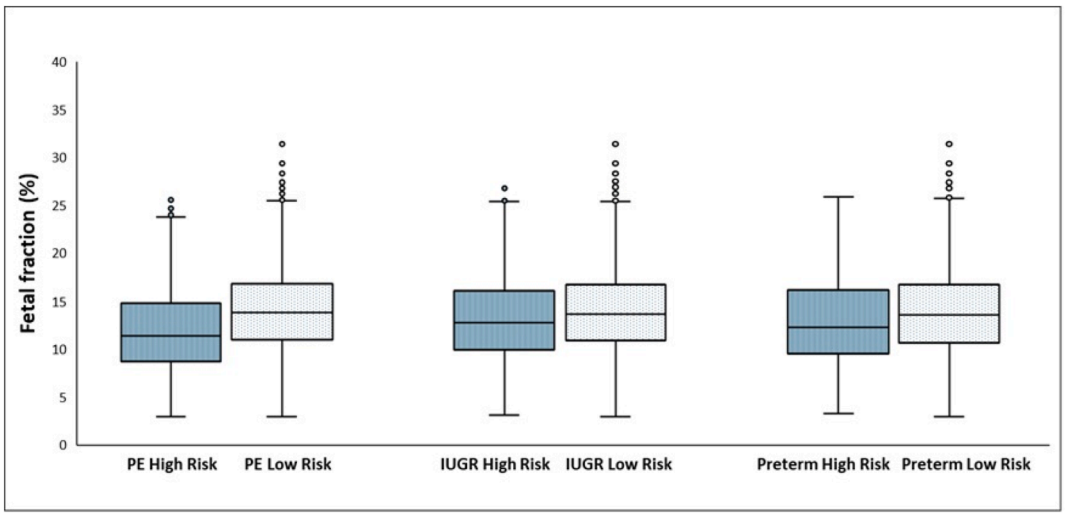


Fig. 4. Proportion of NIPT cffDNA (fetal fraction) and adverse pregnancy outcome risk values from PES. The risk values for preeclampsia (PE), intrauterine fetal growth retardation (IUGR), and preterm birth (Preterm) from the PES test were divided into high-risk (dark bars) and low-risk (light bars) groups. The differences in the distribution of NIPT fetal fraction between the two groups were observed. The results showed that the fetal fraction in the high-risk groups of all three categories were all significantly lower ($p < 0.001$, respectively).

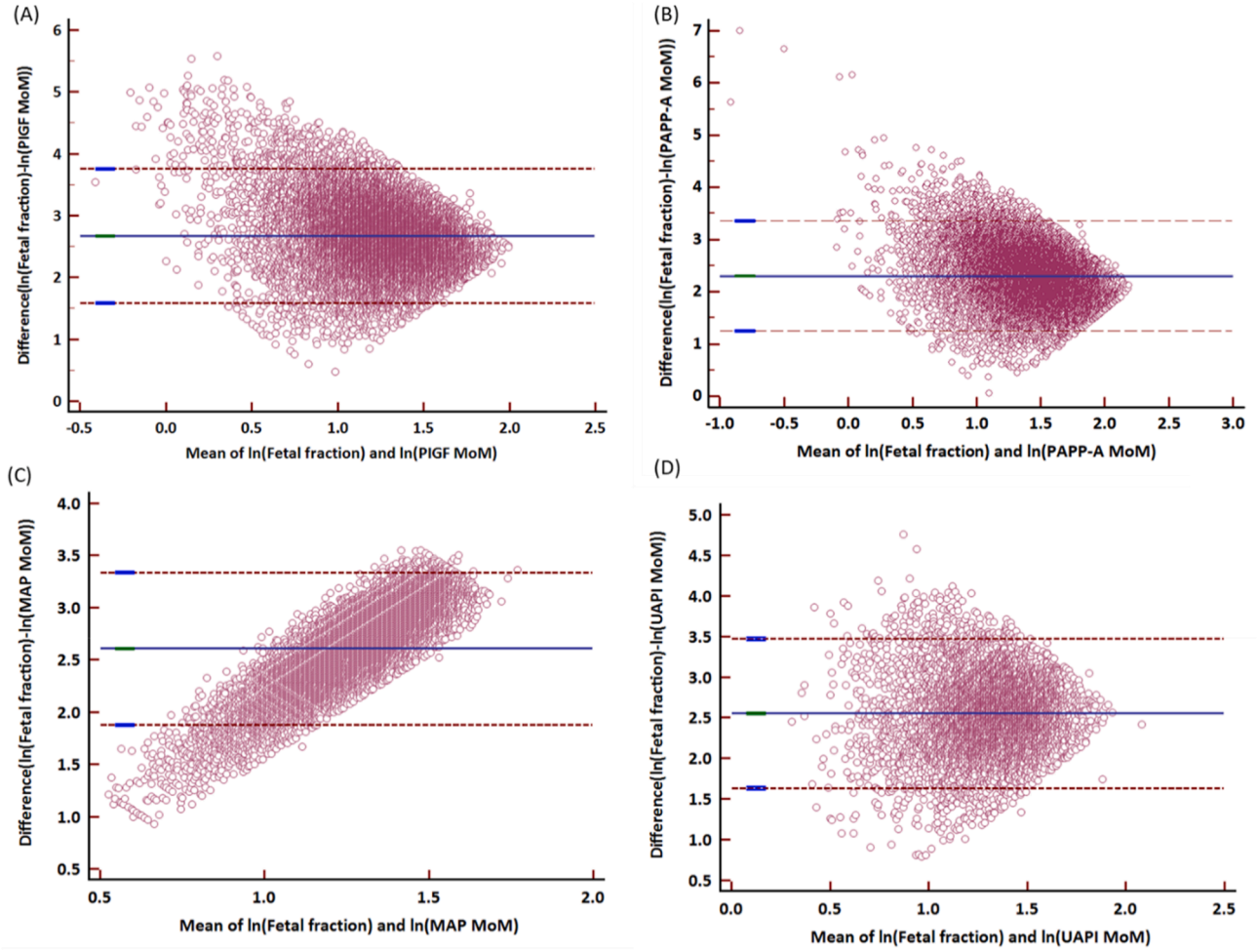


Fig. 5. Correlation between PES test parameters and NIPT fetal fraction. (A) Fetal fraction (vertical axis) and PlGF MoM (horizontal axis) are significantly positively correlated, with a correlation coefficient of 0.081. (B) Fetal fraction (vertical axis) and PAPP-A MoM (horizontal axis) are significantly positively correlated, with a correlation coefficient of 0.177. (C) Fetal fraction (vertical axis) and MAP MoM (horizontal axis) are significantly negatively correlated, with a correlation coefficient of −0.177. (D) Fetal fraction (vertical axis) and UAPI MoM (horizontal axis) are not significantly correlated (correlation coefficient of −0.015).

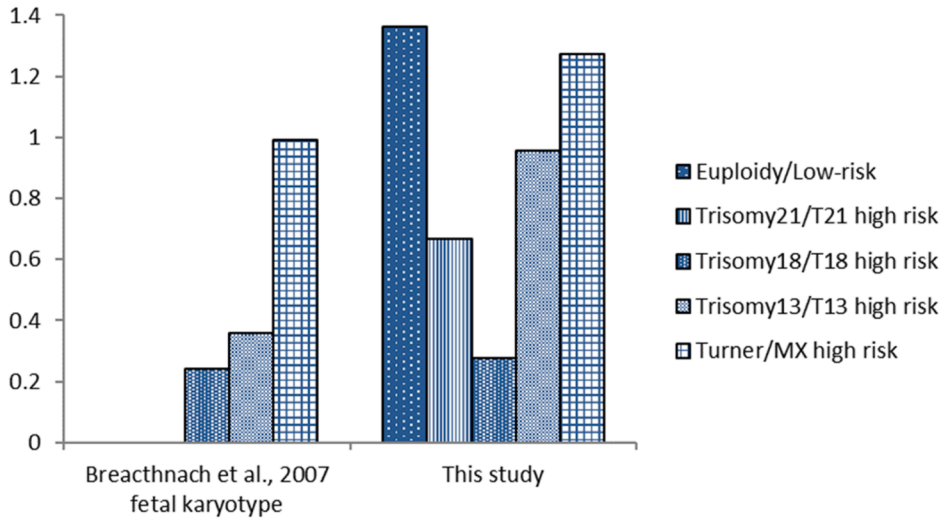


Fig. 6. Comparison of PAPP-A MoM in this study and the literature. This study shows that the median PAPP-A MoM in this study and the previous study showed similar trends for trisomy 18, trisomy 13, and Turner syndrome. This suggests that PAPP-A MoM can be used for initial screening of these three chromosomal abnormalities in NIPT testing.

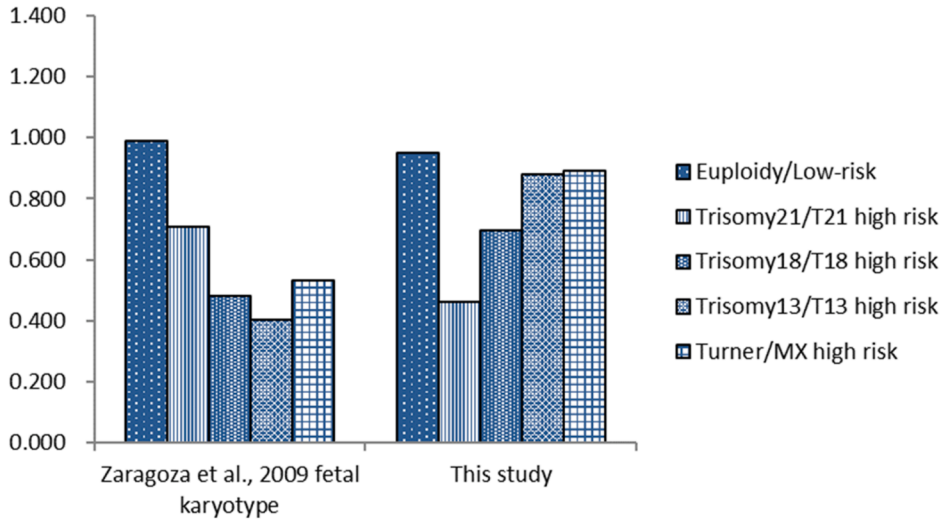


Fig. 7. Comparison of PlGF MoM in this study and the literature. This study shows that the median PlGF MoM in this study and the previous study showed different trends.

preeclampsia, IUGR, and preterm birth will have lower levels of fetal fraction.

Previous research has shown that pregnant women with preeclampsia exhibit higher cffDNA levels than those without [24], with more significant differences in severe cases [27]. This is speculated to occur when placental stress (e.g., oxidation) causes syncytiotrophoblasts to release pro-inflammatory cytokines, anti-angiogenic agents, and free placental DNA via necrosis or apoptosis [28]. Preeclampsia might also affect cffDNA metabolism by the liver and kidneys, leading to accumulation [29]. The seemingly contradictory results (increased absolute cffDNA but decreased fetal fraction) may arise because the increase in cffDNA is relatively small compared to the overall maternal circulating DNA.

Prior studies link abnormal cffDNA and PlGF levels to adverse pregnancy outcomes. Our data also show a correlation between fetal fraction and PlGF MoM (Fig. 5). We observed significantly lower fetal fraction in high-risk PES groups (preeclampsia, IUGR, preterm birth) (Fig. 4), while lower PlGF MoM correlated with higher risks of T21 and T18 (Fig. 3A and B). This correlation may serve as an additional warning: low NIPT fetal fraction suggests increased risk for adverse pregnancy outcomes, and lower PES PlGF MoM suggests increased risk for fetal chromosomal abnormalities. These data highlight the importance of careful interpretation of prenatal tests. Increased risk of third-trimester adverse outcomes may warrant close monitoring, and increased risk of fetal abnormalities may prompt appropriate chromosomal testing. Proper prenatal management can reduce maternal distress and costs, avoid unnecessary hospitalization, monitor disease progression, optimize delivery timing, and minimize premature births. Further research is needed to confirm these findings and their clinical utility.

Although some of the observed correlation coefficients between fetal fraction and PES markers (e.g., PlGF, PAPP-A) were modest in magnitude, they reached statistical significance after Bonferroni correction and are consistent with known biological mechanisms. Therefore, these associations warrant further exploration but should be interpreted with caution regarding their clinical relevance.

Nevertheless, it is important to recognize certain limitations regarding the clinical application of these findings. The cut-off values for PlGF MoM and PAPP-A MoM identified in this study were derived from retrospective analysis without external validation or linkage to actual pregnancy outcomes. As such, these thresholds are preliminary and should not be directly applied in clinical practice. Prospective studies including follow-up of pregnancy outcomes and independent validation cohorts are required to assess their predictive value and clinical utility.

Limitations

In this study, preeclampsia risk was calculated using FMF software, incorporating maternal serum PAPP-A and PlGF, UAPI, MAP, and maternal clinical characteristics. However, some participants had incomplete data (e.g., missing MAP or UAPI) due to variations in clinical practice, which may have affected the accuracy of PES risk assessment. Missing data could not be retrieved due to the study's retrospective design.

The study was conducted in a single laboratory within a specific population and included only pregnancies that underwent both PES and NIPT. This design may exclude certain high-risk cases who were referred directly for invasive diagnostic testing, introducing selection bias. While a subset of cases in our dataset did undergo follow-up diagnostic procedures, we were unable to consistently obtain or verify their final diagnostic outcomes. Therefore, the analysis focused solely on screening-level data. These factors may contribute to underrepresentation of specific high-risk populations and limit the generalizability of our findings. Furthermore, despite a large sample size, the relatively small number of high-risk cases for Down syndrome ($n = 59$) and Edwards syndrome ($n = 22$) may affect the robustness of ROC analyses and the reliability of derived cut-off values. These results should be interpreted with caution and validated through larger, multi-center, or population-based studies with more high-risk cases.

Lastly, this study was based on screening results from PES and NIPT without diagnostic confirmation, so false positive or false negative results may have occurred and could influence the observed associations. NIPT, in particular, can be affected by placental or maternal chromosomal content. Comprehensive follow-up of high-risk cases is necessary to determine the true origin of abnormal chromosomal fragments. These findings should be regarded as exploratory, and future studies incorporating diagnostic confirmation and clinical follow-up are required to validate these associations.

Conclusion

This study shows that low levels of fetal fraction on NIPT may be associated with high-risk for poor placental development and dysfunction. Studies have also confirmed that fetal fractions are significantly correlated with first-trimester serum markers used in first trimester preeclampsia screening test, as well as preeclampsia and fetal growth restriction risk score provided on the PES. Present study also showed that low PlGF MoM and low PAPP-A MoM values maybe a predictor of high-risk NIPT for Down syndrome and Edwards syndrome. PES and NIPT both analyze important placental factors. If either screening is abnormal, it may be a sign of placental abnormalities which could lead to abnormal pregnancy or fetal chromosomal abnormalities. Further studies are needed to validate the findings of this study and to investigate the clinical utility of combining PES and NIPT for the early detection and management of placental disorders.

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Conflict of interest

The authors have no conflicts of interest relevant to this article.

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References

[1] Karrar SA, Hong PL. Preeclampsia. StatPearls [internet]. StatPearls Publishing; 2023.
[2] Chen Y, Wang X, Hu W, Chen Y, Ning W, Lu S, et al. A risk model that combines MAP, PlGF, and PAPP-A in the first trimester of pregnancy to predict hypertensive disorders of pregnancy. J Hum Hypertens 2022;36(2):184–91.
[3] Murray MJ, Lessey BA. editors. Embryo implantation and tumor metastasis: common pathways of invasion and angiogenesis. Seminars in reproductive endocrinology; Copyright© 1999 by Thieme Medical Publishers, Inc. 1999.
[4] Kalousova M, Muravska A, Zima T. Pregnancy-associated plasma protein A (PAPP-A) and preeclampsia. Adv Clin Chem 2014;63:169–209.
[5] Moorthie S, Blencowe H, Darlison MW, Gibbons S, Lawn JE, Mastroiacovo P, et al. Chromosomal disorders: estimating baseline birth prevalence and pregnancy outcomes worldwide. J Community Genet 2018;9:377–86.
[6] Bulletins ACoP. Practice bulletin no. 163: screening for fetal aneuploidy. Obstet Gynecol 2016;127(5):e123–37.
[7] Shaw SS, Chen C-P, Cheng P-J. From Down syndrome screening to noninvasive prenatal testing: 20 years' experience in Taiwan. Taiwan J Obstet Gynecol 2013;52(4):470–4.
[8] Karl O, Dave W, Caalina V, Nerea M, Nicolaides K. Screening for trisomy 21, 18 and 13 by maternal age, fetal NT, fetal heart rate, free beta hCG and PAPP-A. Hum Reprod 2008;23(9):1968–75.
[9] Zaragoza E, Akolekar R, Poon L, Pepes S, Nicolaides K. Maternal serum placental growth factor at 11–13 weeks in chromosomally abnormal pregnancies. Ultrasound Obstet Gynecol: Off J Int Society Ultrasound Obstet Gynecol 2009;33(4):382–6.
[10] Elbaz ZM, Magdy M, Manjunath N, Menon P, El-Sayed EM, Osamma K. Combination of PLGF and PAPPA as a biochemical markers to the first trimester maternal screening. J Clin Images Med Case Rep 2022;3(11):2176.
[11] Han J, Liu H, Xu Z-P, Cuckle H, Sahota D, Li D-Z, et al. Maternal serum PlGF (placental growth factor) in Chinese women in the first trimester undergoing screening for Down syndrome. Eur J Obstet Gynecol Reprod Biol 2016;201:166–70.
[12] Mazer Zumaeta A, Wright A, Syngelaki A, Maritsa V, Bardani E, Nicolaides K. Screening for trisomy at 11–13 weeks' gestation: use of pregnancy-associated plasma protein-A, placental growth factor or both. Ultrasound Obstet Gynecol 2020;56(3):408–15.
[13] Schuring-Blom H, Lichtenbelt K, van Galen K, Elferink M, Weiss M, Vermeesch JR, et al. Maternal vitamin B12 deficiency and abnormal cell-free DNA results in pregnancy. Prenat Diagn 2016;36(8):790–3.
[14] Becking EC, Wirjosoekarto SA, Scheffer PG, Huiskes JV, Remmelink MJ, Sistermans EA, et al. Low fetal fraction in cell-free DNA testing is associated with adverse pregnancy outcome: analysis of a subcohort of the TRIDENT-2 study. Prenat Diagn 2021;41(10):1296–304.
[15] Rolnik DL, da Silva Costa F, Lee TJ, Schmid M, McLennan AC. Association between fetal fraction on cell-free DNA testing and first-trimester markers for pre-eclampsia. Ultrasound Obstet Gynecol 2018;52(6):722–7.
[16] Becking EC, Scheffer PG, Henrichs J, Crombag NM, Weiss MM, Macville MV, et al. Fetal fraction of cell-free DNA in non-invasive prenatal testing and adverse pregnancy outcomes: a nationwide retrospective cohort study of 56,110 pregnant women. Am J Obstet Gynecol 2023.
[17] Peterson SE, Simhan HN. First-trimester pregnancy-associated plasma protein A and subsequent abnormalities of fetal growth. Am J Obstet Gynecol 2008;198(5):e43–5.
[18] Akolekar R, Syngelaki A, Poon L, Wright D, Nicolaides KH. Competing risks model in early screening for preeclampsia by biophysical and biochemical markers. Fetal Diagn Ther 2013;33(1):8–15.
[19] Ekelund CK, Rode L, Tabor A, Hyett J, McLennan A. Placental growth factor and adverse obstetric outcomes in a mixed-risk cohort of women screened for preeclampsia in the first trimester of pregnancy. Fetal Diagn Ther 2021;48(4):304–12.

[20] Redman C, Sargent I. Placental debris, oxidative stress and pre-eclampsia. Placenta 2000;21(7).
[21] Kim SY, Kim HJ, Park SY, Han YJ, Choi JS, Ryu HM. Early prediction of hypertensive disorders of pregnancy using cell-free fetal DNA, cell-free total DNA, and biochemical markers. Fetal Diagn Ther 2016;40(4):255–62.
[22] Wataganara T, Metzenbauer M, Peter I, Johnson KL, Bianchi DW. Placental volume, as measured by 3-dimensional sonography and levels of maternal plasma cell-free fetal DNA. Am J Obstet Gynecol 2005;193(2):496–500.
[23] Lo YD, Lau TK, Zhang J, Leung TN, Chang AM, Hjelm NM, et al. Increased fetal DNA concentrations in the plasma of pregnant women carrying fetuses with trisomy 21. Clin chem 1999;45(10):1747–51.
[24] Lo YD, Leung TN, Tein MS, Sargent IL, Zhang J, Lau TK, et al. Quantitative abnormalities of fetal DNA in maternal serum in preeclampsia. Clin chem 1999;45(2):184–8.
[25] Farina A, Sekizawa A, Sugito Y, Iwasaki M, Jimbo M, Saito H, et al. Fetal DNA in maternal plasma as a screening variable for preeclampsia. A preliminary nonparametric analysis of detection rate in low-risk nonsymptomatic patients. Prenat Diagn: Published Affil Int Society Prenat Diagn 2004;24(2):83–6.
[26] Scott FP, Menezes M, Palma-Dias R, Nisbet D, Schluter P, da Silva Costa F, et al. Factors affecting cell-free DNA fetal fraction and the consequences for test accuracy. J Matern Fetal Neonatal Med 2018;31(14):1865–72.
[27] Miranda ML, Macher HC, Muñoz-Hernández R, Vallejo-Vaz A, Moreno-Luna R, Villar J, et al. Role of circulating cell-free DNA levels in patients with severe preeclampsia and HELLP syndrome. Am J Hypertens 2013;26(12):1377–80.
[28] Burton GJ, Redman CW, Roberts JM, Moffett A. Pre-eclampsia: pathophysiology and clinical implications. Br Med J 2019:366.
[29] Lau T-W, Leung TN, Chan LY, Lau TK, Chan KA, Tam WH, et al. Fetal DNA clearance from maternal plasma is impaired in preeclampsia. Clin chem 2002;48(12):2141–6.