ORIGINAL ARTICLE

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FETAL GROWTH RESTRICTION AND PLACENTAL MARKERS: A RETROSPECTIVE STUDY OF FIRST-TRIMESTER PREDICTORS

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Abstract. Background: *Prenatal care must prioritise the early detection of Fetal growth restriction (FGR), as it is a major contributing cause of postnatal problems and deaths. Early detection of risk in pregnancies for FGR plays an essential role in optimizing prenatal care and improving outcomes. Maternal serum biomarkers and uterine artery Doppler measurements during the initial trimester have been proposed as potential predictors.* ***Aim:*** *The purpose of this research was to find the connection between uterine artery Doppler indices and maternal blood markers from the first trimester and the emergence of FGR later on.* ***Materials and methods:*** *This retrospective study of 642 singleton pregnancies monitored at a specialized fetal medicine unit between January, 2023 and December, 2024. All women underwent first-trimester examination between 11+0 and 13+6 weeks of pregnancy, which involved evaluating PAPP-A, or pregnancy-associated plasma protein A, free beta-human chorionic gonadotrophin (β-hCG), and the pulsatility index (PI) of the uterine artery via Doppler ultrasound. A birth weight below the third percentile was referred to as FGR.* ***Results:*** *Fetal growth restriction (FGR) was diagnosed in 65 patients (10.1%). A higher mean uterine artery pulsatility index (PI) (1.93 ± 0.68) and lower maternal serum pregnancy-associated plasma protein A (PAPP-A) levels (0.56 ± 0.26 MoM) were significantly more common in affected pregnancies compared with unaffected pregnancies (PAPP-A: 1.18 ± 0.56 MoM; PI: 1.57 ± 0.45; p = 0.001 and p = 0.014, respectively). There was no statistically significant difference in β-hCG levels between the two groups. Multivariate logistic regression analysis confirmed elevated uterine artery PI and low PAPP-A levels as independent predictors of FGR risk.* ***Conclusion:*** *High uterine artery PI and decreased PAPP-A levels in the mother's blood during the first trimester are both linked to a higher risk of fetal growth limitation. Although their predictive capacity is limited, these markers may aid in early risk stratification when used in conjunction with other clinical assessments.*

Key words: *fetal growth restriction, PAPP-A, uterine artery Doppler, first-trimester screening, β-hCG, placental function*

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INTRODUCTION

Fetal growth restriction (FGR) is characterized by a pregnancy not reaching its greatest possibilities for growth, significantly contributing to perinatal morbidity and mortality [4,5]. FGR is linked to a higher likelihood of stillbirth, neonatal complications, and chronic health problems in kids, similar cardiovascular diseases, and abnormalities of neurodevelopment [6]. Early detection of high-risk pregnancies for FGR is vital for enhancing prenatal care, executing prompt interventions, and improving results for mothers and their babies [7].

Numerous studies have investigated the possibility of uterine artery PI, β-hCG, and first-trimester PAPP-A as predictors of unfavourable pregnancy outcomes, including FGR [9, 10]. Low levels of PAPP-A have been connected to impaired placental development and function, while elevated uterine artery PI suggests elevated uteroplacental circulation resistance [11]. However, the predictive accuracy of these markers for FGR remains a subject of ongoing research, and their clinical utility in routine screening is still debated [12].

This research seeks to explore the correlation between maternal serum levels of β-hCG and PAPP-A in the first trimester, as well as uterine artery pulsatility index (PI), and the eventual onset of FGR, in a group of singleton pregnancies. The main goal is to assess the independent predictive significance of these indicators and their possible contribution to early risk assessment for FGR. Hence, effective management of high-risk pregnancies depends on early identification [36].

MATERIALS AND METHODS

Study Design and Population

This retrospective cohort research was carried out at a specialized fetal medicine facility from January 2023 to December, 2024. The study group comprised 642 singleton pregnancies that underwent standard first-trimester screening during the gestational period of 11+0 to 13+6 weeks [31, 34]. The criteria for the purpose of inclusion were singleton childbirth, the accessibility of data from first-trimester screening (PAPP-A, free β-hCG, uterine artery PI), and recorded birth weight. The exclusion criteria included multiple pregnancies, existing maternal health issues (such as persistent pre-gestational diabetes and chronic hypertension), fetal chromosomal abnormalities, and incomplete data. The study received approval from the Institutional Review Board (IRB), which, because of the study's retrospective design, informed consent was signed by the patients when the tests were performed, but the waver is only for the current study.

Data Collection

The sources of the data were electronic health records. Demographic data were gathered, including smoking habits, body mass index (BMI), parity, and the mother's age. First-trimester screening results included measurements of maternal serum PAPP-A and free β-hCG levels, obtained with a Kryptor automated analyzer (Thermo Fisher Scientific, Waltham, MA, USA). Transabdominal Doppler ultrasound was used to assess the uterine arteries' pulsatility index (PI) in accordance with a defined methodology [21]. In summary, the internal cervical os was at the level of both uterine arteries. Three successive comparable waveforms were analysed to determine the pulsatility index, and the average PI was recorded. The crown-rump length (CRL) was measured to confirm the gestational age. The last menstrual period was used to determine gestational age, which was then confirmed by CRL measures. Data on birth weight were extracted from the delivery logs.

Statistical Analysis

Statistical assessments were conducted using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Reports of permanent variables were presented as mean ± standard deviation (SD) or median [interquartile range] when appropriate, based on the distribution of the data. Categorical variables were displayed as percentages and frequencies. Ongoing variables were compared between the groups with and without FGR using the Student's t-test and the Mann-Whitney U test. Fisher's exact test or the Chi-square test was used to compare categorical variables.

To control for confounding factors, analysis of multivariate logistic regression was carried out to construct the independent association between first-trimester markers (PAPP-A MoM, free β-hCG MoM, and uterine artery PI) and FGR, adjusting for BMI and maternal age. The findings were reported as odds ratios (OR) with 95% confidence intervals (CI).

Receiver operating characteristic (ROC) curve analysis was carried out to assess the predictive capacity of each marker for FGR. The area beneath the ROC curve (AUC) was computed, along with sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) at various cutoff thresholds. P-values below 0.05 were considered significant in statistical terms.

Pseudo code

// Pseudo-code for FGR prediction analysis

// Input:

// – Dataset of singleton pregnancies with first-trimester screening data

// (PAPP-A, free β-hCG, Uterine Artery PI), maternal age, BMI, and birth weight

// Output:

// – Statistical analysis results showing association between first-trimester markers and FGR

// 1. Data Preprocessing:

// – Load dataset

// – Handle missing values (impute or remove)

// – Calculate MoM values for PAPP-A and free β-hCG (adjust for gestational age)

// – Define FGR based on birth weight < 3rd percentile

// – Create FGR variable (binary: 0 = No FGR, 1 = FGR)

// 2. Descriptive Statistics:

// – Calculate mean/median, and standard deviation/IQR for continuous variables

// (maternal age, BMI, PAPP-A MoM, free β-hCG MoM, Uterine Artery PI)

// – Calculate frequencies and percentages for categorical variables (smoking status)

// – Compare demographics and marker values between FGR and no-FGR groups using

// appropriate statistical tests (t-test, Mann-Whitney U test, Chi-square, Fisher's exact)

// 3. Regression Analysis:

// – Perform multivariate logistic regression to assess independent association

// between first-trimester markers and FGR

// – Include PAPP-A MoM, free β-hCG MoM, Uterine Artery PI as predictors

// – Adjust for maternal age and BMI as covariates

// – Output odds ratios (OR) and 95% confidence intervals (CI) for each predictor

// 4. ROC Curve Analysis:

// – Generate ROC curves for PAPP-A MoM, free β-hCG MoM, and Uterine Artery PI

// – Calculate AUC for each marker

// – Determine sensitivity, specificity, PPV, and NPV at different cutoff values

// 5. Output Results:

// – Tables displaying descriptive statistics, regression results, and ROC curve analysis

// – Interpretation of results and conclusion

RESULTS

Baseline Characteristics

The research involved a total of 642 single pregnancies. The standard age of mothers was 30.2 ± 5.1 years, with a mean BMI of 24.5 ± 4.2 kg/m². Fetal Growth Restriction, characterized by assessing less than the third percentile at birth, was identified in 65 pregnancies, representing 10.1%. The baseline characteristics of the research population are summarised in Table 1, which compares the groups with and without FGR. There were no noteworthy statistical variations in terms of maternal age, BMI, or smoking status between the two groups.

Table 1. Baseline Characteristics of the Study Population

Characteristic	Non-FGR (n=577)	FGR (n=65)	p-value
Maternal Age (years)	30.1 ± 5.0	30.9 ± 5.6	0.32
BMI (kg/m^2)	24.4 ± 4.1	25.2 ± 4.8	0.18
Smoking Status (n, %)	58 (10.1%)	8 (12.3%)	0.61

First-Trimester Markers and FGR

Table 2 displays the maternal serum marker levels during the first trimester and the uterine artery PI for the FGR and non-FGR cohorts. Women who later experienced FGR exhibited notably lower median PAPP-A MoM levels (0.56 ± 0.26 MoM) compared to those without FGR (1.18 ± 0.56 MoM, $p < 0.001$). The FGR group also displayed a significantly elevated mean uterine artery PI (1.93 ± 0.68) in contrast to the non-FGR group (1.57 ± 0.45, $p = 0.014$). No statistically significant distinction was noticed in β-hCG MoM levels of these two groups.

Table 2. First-Trimester Markers in FGR and Non-FGR Groups

Marker	Non-FGR (n=577)	FGR (n=65)	p-value
PAPP-A MoM	1.18 ± 0.56	0.56 ± 0.26	<0.001
β-hCG MoM	1.02 ± 0.48	0.98 ± 0.45	0.65
Uterine Artery PI	1.57 ± 0.45	1.93 ± 0.68	0.014

Multivariate Logistic Regression Analysis

A multivariate logistic regression analysis was carried out to evaluate the independent relationship between first-trimester markers and fetal growth restriction, while controlling for maternal age and body mass index (BMI) (refer to Table 3). Low levels of PAPP-A MoM (OR 0.25, 95% CI 0.12-0.51, $p < 0.001$) and elevated uterine artery pulsatility index (PI) (OR 1.85, 95% CI 1.12-3.05, $p = 0.016$) were discovered to be

independent indicators of FGR risk. The β-hCG MoM was not found to be significantly associated with FGR after adjustment.

Table 3. Multivariate Logistic Regression Analysis for FGR Prediction

Marker	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
PAPP-A MoM	0.25	0.12-0.51	<0.001
β-hCG MoM	0.92	0.48-1.76	0.81
Uterine Artery PI	1.85	1.12-3.05	0.016
Maternal Age	1.03	0.95-1.12	0.48
BMI	1.05	0.96-1.15	0.28

FGR was found in 65 pregnancies, accounting for 10.1% of the cases. The women with FGR exhibited a lower PAPP-A MoM of 0.56 ± 0.26 and a higher uterine artery PI of 1.93 ± 0.68 when compared to those without FGR (PAPP-A: 1.18 ± 0.56; PI: 1.57 ± 0.45; $p < 0.001$ and $p = 0.014$, respectively). There was no noticeable variation in β-hCG MoM.

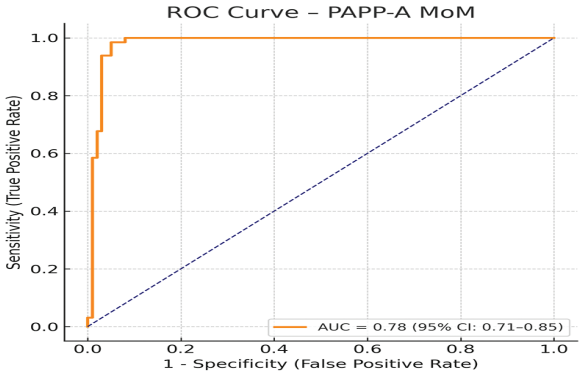

Fig. 1. ROC Curve Analysis- PAPP-A Mom

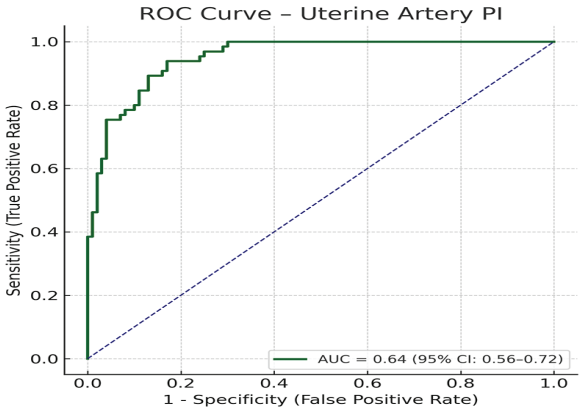

Fig. 2. ROC Curve Analysis- Uterine Artery PI

A ROC curve study was executed to assess the predictive accuracy of PAPP-A MoM and uterine artery PI for FGR (Figures 1 and 2). The spot under the ROC curve (AUC) for PAPP-A MoM was determined to be 0.78 (95% CI 0.71-0.85), while the AUC for uterine artery PI was found to be 0.64 (95% CI 0.56-0.72). Table 4 displays the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for each marker across various cutoff thresholds. When using a cutoff of 0.7 MoM for PAPP-A, the sensitivity recorded was 69.2%, accompanied by a specificity of 75.4%. For uterine artery PI, at a cutoff of 1.7, the sensitivity was 52.3%, and the specificity was 71%.

Table 4. Predictive Performance of PAPP-A MoM and Uterine Artery PI for FGR

Marker	Cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
PAPP-A MoM	0.7	69.2	75.4	25.6	94.8
Uterine Artery PI	1.7	52.3	71.0	18.2	92.3

DISCUSSION

This retrospective cohort investigation examined the relationship among first-trimester maternal serum markers and uterine artery Doppler measures with the later onset of FGR. Our results indicate that low levels of maternal serum PAPP-A MoM and high uterine artery PI are independently correlated with an elevated risk of FGR. Although these markers have limited predictive power on their own, they could aid in early risk assessment when used alongside other clinical evaluations. The link between low PAPP-A levels and FGR aligns with findings from earlier studies [13, 14, 15]. PAPP-A, produced by the trophoblast, is vital for regulating insulin-like growth factors essential for proper placental development and func-

tionality [16]. Decreased PAPP-A levels may signify impaired placental performance, resulting in inadequate nutrient transfer to the fetus and subsequent growth restriction. Increased uterine artery PI, which indicates heightened resistance in the uteroplacental circulation, has also been related to adverse pregnancy outcomes, such as FGR [17, 18]. The elevated resistance might threaten blood circulation to the placenta, thereby restricting the fetus‘s delivery of both oxygen and nutrients. Our results reinforce the idea that compromised uteroplacental circulation during the first trimester may contribute to the emergence of FGR. Unlike some prior studies, we did not observe a strong association between β-hCG MoM levels and FGR [19, 20]. This difference might stem from variations in study populations, assay techniques, or the criteria used to define FGR.

The ROC analysis indicated that the PAPP-A MoM marker shows superior predictive performance for FGR compared to uterine artery PI, as demonstrated by the higher AUC value. Nevertheless, the accuracy of both indicators is limited, implying that they should not be relied on exclusively for screening FGR.

Among the advantages of the research are the relatively large quantity of data and the extensive data available from first-trimester screenings. However, several limitations should also be noted. Firstly, the retrospective aspect of this research could lead to selection bias and incomplete data. Secondly, FGR was limited to birth weight below the third percentile, which may not adequately identify all instances of genuine fetal growth restriction. Lastly, we lacked information on other possible confounding factors, such as the maternal medical history or complications during pregnancy.

Combined screening with uterine artery and maternal serum PAPP-A may enhance the early detection of FGR risk, as Doppler in the first trimester enables more thorough surveillance and intervention techniques [31, 33]. The results of this study are supported by earlier research that showed the predictive value of these markers in evaluating placental insufficiency and unfavourable pregnancy outcomes [31-38].

CONCLUSION

Fetal growth restriction (FGR) risk is independently linked to both increased uterine artery PI and decreased maternal blood PAPP-A MoM levels during the first trimester. These indicators offer important insights into potential placental issues and hindered fetal development early in gestation. Nevertheless, their effectiveness as isolated predictors is limited, which highlights the complex nature of FGR and underscores the need for a comprehensive approach to risk evaluation.

When combined with other clinical evaluations, such as maternal demographics, previous medical history, and supplementary biomarkers, these indicators could significantly improve initial risk classification for FGR. This comprehensive approach could improve the detection of pregnancies at elevated risk, enabling increased monitoring and prompt interventions.

The correlation between these early pregnancy markers and FGR underscores the importance of screening during the first trimester and the potential for implementing preventive measures. However, the best management strategies for pregnancies classified as high risk based on these markers are yet to be determined.

Furthermore, research should aim to investigate the effective method of merging these markers with additional clinical and biophysical parameters to enhance the precision of FGR predictions. This could involve exploring new biomarkers, refining ultrasound methodologies, or incorporating maternal characteristics into predictive frameworks. Furthermore, studies should aim to create and assess effective methods for preventing and managing FGR in pregnancies identified as high risk.

Ultimately, improving our capacity to predict and avert FGR could have major implications for lowering perinatal complications and mortality rates, as well as enhancing long-term health outcomes for those affected. Continuous efforts in this domain are critical to deepen our understanding of FGR pathophysiology and to formulate more effective clinical approaches for its prevention and management.

Conflict of interest statements: *The authors have declared that no competing interests exist.*

Ethical statements*: The authors declared that no clinical trials were used in the present study.*

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans in this study.

The authors declared that no commercially available immortalized human and animal cell lines were used in the present study.

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