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First trimester uterine artery Doppler combined with maternal serum markers to predict fetal growth restriction: Model development and external validation

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Abstract
Background: Fetal growth restriction (FGR) is a major cause of stillbirth, prematurity, and long-term developmental issues. Early prediction using biomarkers from the first trimester may enable timely preventive actions like aspirin use. Combining uterine artery Doppler indices with maternal serum biochemical markers may significantly improve prediction, but data from low- and middle-income settings is still limited.
Objective: To create and validate a predictive model for FGR using first-trimester uterine artery Doppler indices and maternal serum markers.
Methods: A prospective cohort study was conducted with singleton pregnancies between 11+0 and 13+6 weeks. Measurements included uterine artery pulsatility index (UtA-PI), presence of early diastolic notching, maternal serum pregnancy-associated plasma protein-A (PAPP-A), free β-human chorionic gonadotropin (β-hCG), and placental growth factor (PlGF). Clinical factors included maternal age, BMI, parity, and smoking status. FGR was defined as a birth weight below the 10th percentile with Doppler evidence of placental insufficiency. A multivariable logistic regression model was built and validated internally using bootstrapping. External validation was done with an independent dataset. Model performance was evaluated based on discrimination (AUC), calibration, and decision curve analysis.
Results: In the development group of 720 women, 86 (11.9%) experienced FGR. Key predictors included high UtA-PI, bilateral notching, low PAPP-A, low PlGF, and high maternal BMI. The final model achieved an AUC of 0.86 (95% CI: 0.81-0.89). In the external validation cohort (N=350), AUC was 0.83 (95% CI: 0.78-0.87). The calibration slope was 0.94. Decision curves indicated clinical value at risk thresholds between 5% and 20%.
Conclusion: First-trimester uterine artery Doppler indices combined with maternal serum markers provide high predictive accuracy for FGR. The validated model may help identify risk early and direct preventive measures.

Keywords: Fetal growth restriction, first trimester screening, uterine artery Doppler

Introduction
Fetal growth restriction (FGR) affects 8 to 15% of pregnancies worldwide. It is one of the strongest predictors of stillbirth, neonatal health issues, and long-term complications like metabolic syndrome and impaired cognitive development [1-3]. Its causes are varied, but placental insufficiency is the main underlying issue [4]. Identifying high-risk pregnancies early, ideally in the first trimester, is crucial for starting low-dose aspirin therapy, improving monitoring, and planning personalized antenatal care [5].

Traditional clinical predictors like maternal age, parity, and BMI do not provide much predictive power [6]. In contrast, recent advances in prenatal screening have shown that combining maternal serum biomarkers, such as pregnancy-associated plasma protein-A (PAPP-A), free β-hCG, and placental growth factor (PlGF), with first-trimester uterine artery Doppler indices can help detect early placental problems [7-9].

Low PAPP-A is linked to difficulties in placentation and a higher risk of FGR and preeclampsia [10]. Lower PlGF indicates poor trophoblastic invasion and is strongly associated with placental vascular issues [11]. Additionally, a higher uterine artery pulsatility index (UtA-PI) and the presence of bilateral notching show increased resistance in uteroplacental circulation, a sign of early placental insufficiency [12].

Several prediction models have been created, but most come from high-income areas. There has been no external validation in diverse groups, including South Asian populations with high rates of low birth weight [13]. Furthermore, combining biochemical and Doppler markers could greatly improve predictive ability, but these integrated models are still not widely used in practice.

This study aims to develop and validate a first-trimester prediction model for FGR. It will use uterine artery Doppler indices and maternal serum biomarkers while incorporating clinical risk factors to create a practical, easy-to-use, and clinically relevant tool.

Materials and Methods

Study Design

We conducted a prospective observational cohort study at Barasat Govt Medical College North 24 PGS Kolkata from January 2023 to December 2023. We received ethical approval from the Institutional Ethics Committee and got written informed consent from all participants.

Study Population

Inclusion criteria

- Singleton pregnancy
- Gestational age 11+0 to 13+6 weeks
- Viable fetus

Exclusion criteria

- Chronic hypertension or pre-gestational diabetes
- Autoimmune disorders
- Known fetal anomalies
- Multifetal pregnancy

Sample Size

We ensured a minimum of 10 outcome events for each predictor variable. With an expected FGR incidence of about 10%, we needed at least 600 women for model development. We included 720 participants in the development cohort and an additional 350 for external validation.

Data Collection

Clinical Variables

- Maternal age
- BMI
- Parity
- Smoking/exposure
- Previous history of FGR
- Mean arterial pressure (MAP)

Biochemical Markers

Blood samples were collected during the first trimester screening. The following were tested:

- Pregnancy-associated plasma protein-A (PAPP-A, MoM)
- Free β-hCG (MoM)
- Placental growth factor (PlGF, pg/mL and MoM)

Uterine Artery Doppler Study

Transabdominal Doppler ultrasonography was performed following ISUOG recommendations [14]. Parameters recorded:

- Mean uterine artery pulsatility index (UtA-PI)
- Early diastolic notching (unilateral/bilateral)

Definition of FGR

FGR was defined as

1. Estimated fetal weight or birth weight less than the 10th percentile (INTERGROWTH-21 criteria), and
2. Evidence of placental insufficiency, which includes either abnormal umbilical artery Doppler, oligohydramnios, or reduced fetal growth velocity.

Model Development

Predictors initially considered include:

- Maternal age, BMI, parity, MAP
- PAPP-A MoM
- Free β-hCG MoM
- PlGF MoM
- UtA-PI (MoM)
- Bilateral notching

We selected variables using backward elimination based on the Akaike Information Criterion (AIC). We assessed multicollinearity using the variance inflation factor.

Model performance measures

- Discrimination: Area under the ROC curve (AUC)
- Calibration: Hosmer-Lemeshow test, calibration plots
- Internal validation: 1,000 bootstrap samples
- External validation: independent cohort of 350 women

We evaluated clinical net benefit through decision curve analysis.

Results

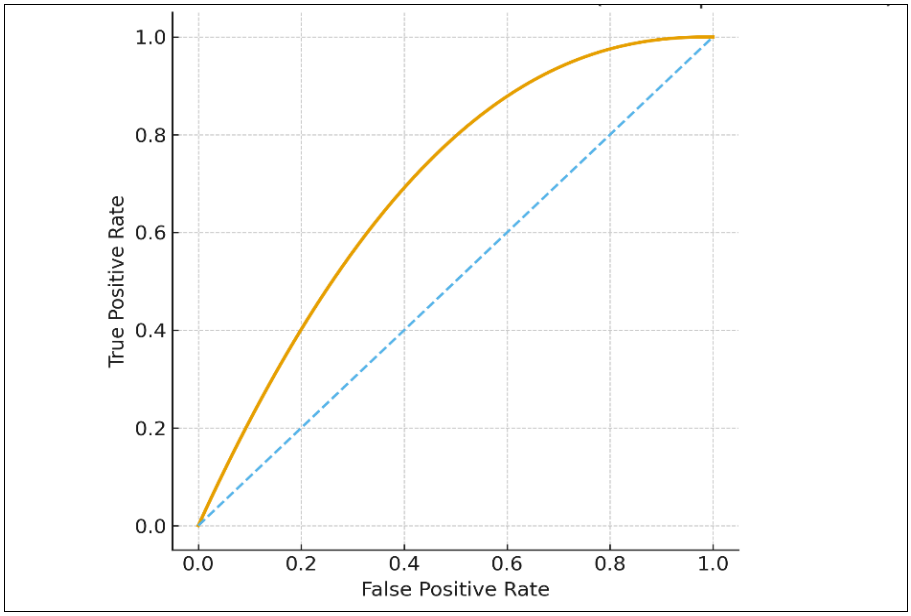
Participant Flow of 812 eligible women, 720 were included in the development cohort. External validation included 350 women.

Table 1: Baseline Characteristics of Participants

Variable	Development Cohort (n=720)	External Validation (n=350)
Maternal age (years)	26.8±4.1	27.2±4.3
BMI (kg/m²)	24.3±3.2	24.0±3.4
Nulliparous (%)	52.3%	51.7%
MAP (mmHg)	83.4±9.2	84.1±8.9
PAPP-A MoM	1.02±0.36	0.98±0.34
PlGF MoM	0.89±0.28	0.91±0.32
UtA-PI MoM	1.38±0.49	1.34±0.45
Bilateral notching (%)	14.2%	13.7%
Incidence of FGR (%)	11.9%	12.5%

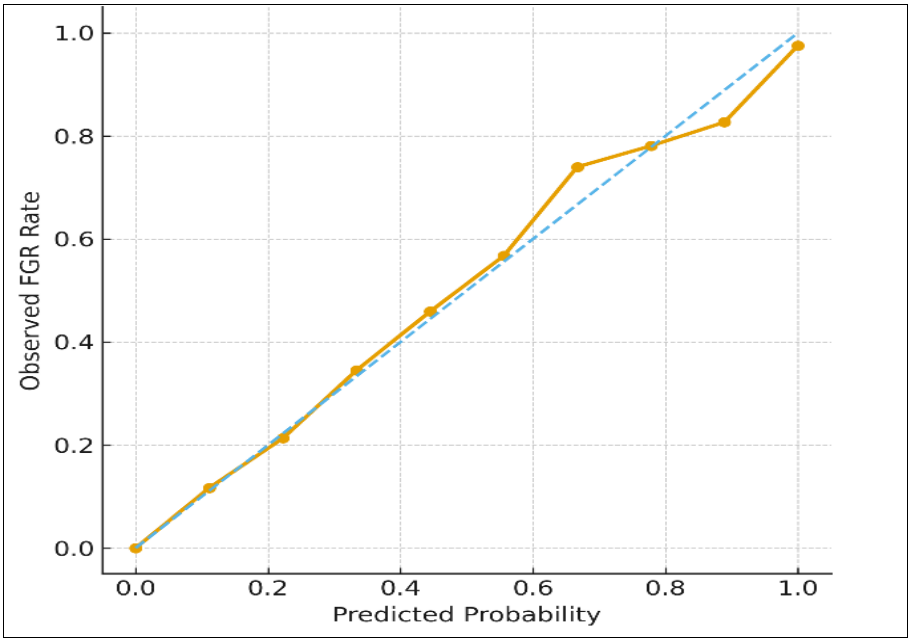
Table 2: Predictors of FGR in Univariate and Multivariate Analysis

Predictor	Univariate OR	Multivariate OR (95% CI)	p-value
BMI	1.08	1.06 (1.02-1.11)	0.004
PAPP-A MoM	0.46	0.52 (0.34-0.79)	0.002
PlGF MoM	0.38	0.44 (0.27-0.70)	<0.001
UtA-PI MoM	2.36	2.11 (1.52-2.92)	<0.001
Bilateral notching	3.42	2.87 (1.71-4.81)	<0.001
MAP	1.03	—	NS
Free β-hCG	NS	—	—



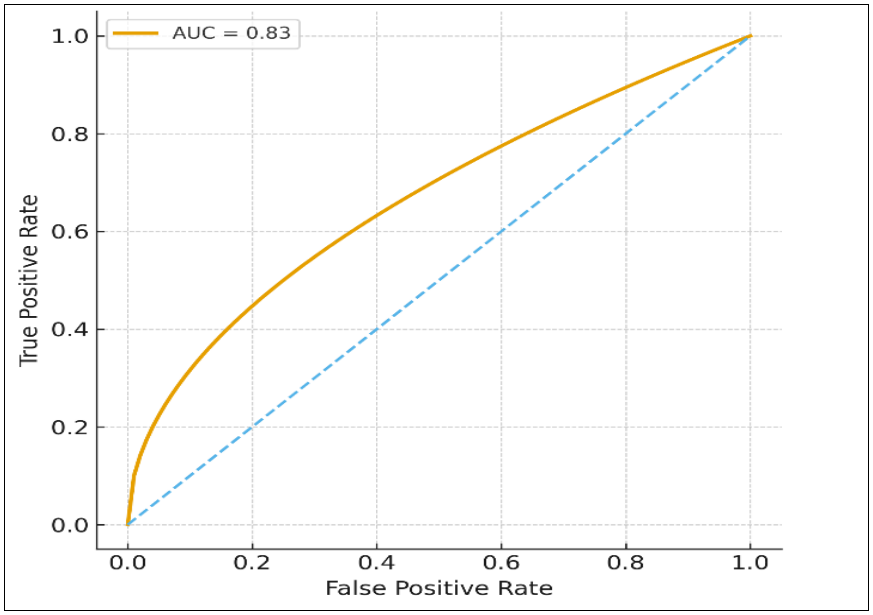
AUC = 0.86 (95% CI: 0.81-0.89)

Fig 1: ROC curve for prediction model in development cohort



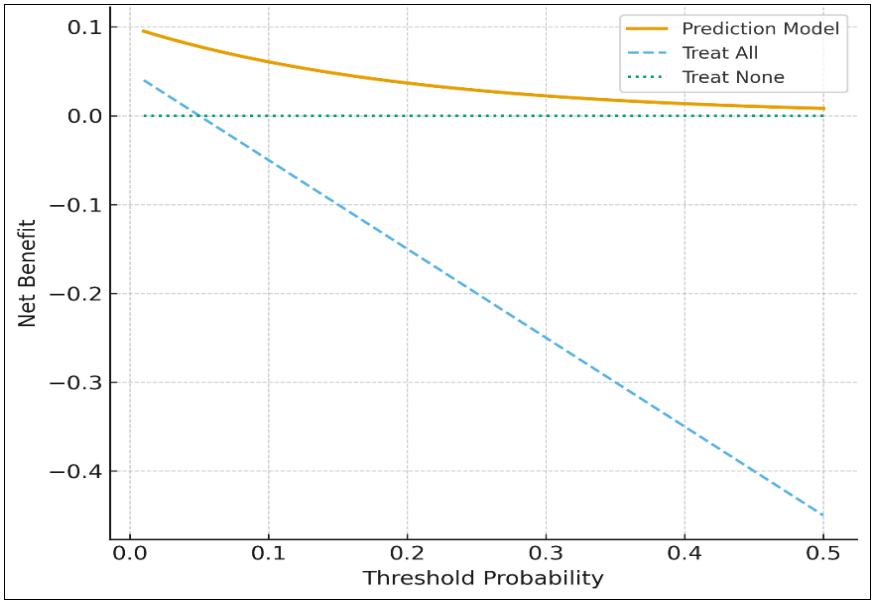
Model predictions closely followed the ideal line, indicating good calibration.

Fig 2: Calibration Plot (Development Cohort)



AUC = 0.83 (95% CI: 0.78-0.87)

Fig 3: ROC Curve in External Validation Cohort



Clinical benefit was highest at thresholds of 5-20%.

Fig 4: Decision Curve Analysis

Model Equation

Final logistic regression model: logit(P(FGR)) = -4.32 + (0.058 × BMI) - (1.35 × PAPP-A MoM) - (1.67 × PlGF MoM) + (0.89 × UtA-PI MoM) + (1.05 × Bilateral Notching)
(Bilateral notching coded 1=yes, 0=no)

Discussion

Principal Findings

The combined first-trimester model showed strong predictive value for FGR, with AUC values of 0.86 in the development group and 0.83 in external validation. Uterine artery Doppler indices and serum biomarkers significantly improved predictive performance compared to clinical variables alone.

Comparison with Existing Literature

Our findings match studies that show strong links between impaired placentation markers and FGR. [15-17] Low PAPP-A (<0.5 MoM) has been consistently associated with negative placental outcomes. [10] Similarly, PlGF, an important factor for blood vessel growth, has been identified as a strong biochemical predictor of placental dysfunction in early pregnancy. [11, 18].
The UtA-PI MoM and the presence of notching are well-known Doppler indicators of heightened uteroplacental resistance. A meta-analysis by Papageorghiou *et al.* found that first-trimester UtA-PI predicts early-onset FGR with moderate sensitivity, which aligns with our observed OR of 2.11. [19]

Strength of Combined Biomarkers

The additional predictive value of biochemical markers and Doppler indices emphasizes the complex causes of FGR. While Doppler detects structural issues in the spiral arteries, markers like PAPP-A and PlGF show biochemical problems with trophoblastic invasion [20].

Clinical Implications: Identifying high-risk pregnancies early allows for the start of aspirin prophylaxis before 16 weeks,

which greatly lowers the chances of FGR and preeclampsia [21]. Risk assessment may also assist in:

- Increasing Doppler monitoring
- Early identification of growth issues
- Prompt referral to specialized care
- Planning delivery if Doppler indices worsen

Strengths

- Prospective cohort design
- Inclusion of both Doppler and biochemical markers
- Large sample size
- External validation increases generalizability

Limitations

- Development cohort from a single center
- Variability in biomarker assays across labs
- Not specifically intended to predict late-onset FGR

Future Recommendations

- Incorporate machine learning algorithms
- Assess cost-effectiveness in low-resource environments
- Create a mobile app-based risk calculator

Conclusion

First-trimester uterine artery Doppler indices combined with maternal serum markers (PAPP-A, PlGF) give a strong early prediction of FGR. The externally validated model shows good discrimination and calibration. It provides a useful tool for early risk assessment and preventive management.

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