

First-Trimester Parameters and Mid-Second-Trimester Uterine Doppler Indices

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ABSTRACT

To evaluate the association linking initial combined screening parameters to middle second-trimester uterine artery Doppler markers in a nulliparous population.

A total of 227 nulliparous pregnancies with complete initial screening profiles and mid-second-trimester uterine artery Doppler metrics (18–24 gestational weeks) were evaluated in this retrospective cohort framework. Serum free β -hCG, PAPP-A, and nuchal translucency (NT) metrics from the first trimester were formulated as multiples of the median (MoM). The average uterine artery pulsatility index (mean UtA-PI) was derived, with values at or above the 90th percentile (1.545) designating elevated resistance. Analytical steps involved correlation coefficients, multivariable logistic regression, and ROC curve tracking.

A significant inverse link was found between PAPP-A MoM and mean UtA-PI ($r = -0.34$, $p < 0.001$). multivariable logistic regression, identified decreased PAPP-A MoM as an independent predictor for elevated uterine artery resistance (OR = 2.61; 95% CI: 1.46–4.67; $p = 0.001$), whereas NT MoM and free β -hCG showed no notable associations. PAPP-A displayed moderate accuracy in predictive ROC assessments (AUC = 0.72), yielding an ideal cut-off threshold of 0.65 MoM (sensitivity: 69.6%, specificity: 70.3%). Furthermore, mean UtA-PI levels were substantially elevated in subjects exhibiting PAPP-A values below 0.65 MoM.

Elevated uterine artery resistance during the mid-second trimester is linked to diminished initial PAPP-A concentrations in nulliparous individuals. Such data imply that early biochemical fluctuations could mirror a disrupted uteroplacental vascular remodeling process. Future prospective trials incorporating clinical pregnancy outcomes remain essential.

Keywords: PAPP-A; uterine artery Doppler; pulsatility index; nulliparous pregnancy; placentation

Introduction

Suboptimal trophoblast invasion during early placentation represents the primary pathophysiological driver behind several gestational complications, such as fetal growth restriction, preeclampsia, and pregnancy-induced hypertensive disorders. Insufficient remodeling of maternal spiral arteries during early pregnancy prevents high-resistance channels from transforming into low-impedance pathways, which ultimately culminates in heightened uteroplacental resistance and compromised blood perfusion (1,2). To address this, uterine artery Doppler analysis has emerged as a reliable, noninvasive approach to indirectly gauge placental vascular impedance, especially in the second trimester when

uteroplacental blood flow achieves functional maturity (3).

An increased mean uterine artery pulsatility index (UtA-PI) has been identified as a significant predictor of preeclampsia and fetal growth restriction (4). In addition, recent evidence suggests that the degree of abnormality in UtA-PI is associated with an increasing risk of adverse perinatal outcomes (5). Furthermore, uterine artery Doppler indices have been shown to reflect underlying placental vascular pathology, particularly maternal vascular malperfusion (6). However, uterine artery Doppler measurements remain subject to technical and operator-dependent variability. Factors such as insonation angle, maternal body habitus, fetal position, and equipment calibration may influence results,

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posing challenges for standardization across different populations and clinical settings. These limitations and biological considerations underscore the need for reproducible biochemical markers that could reflect placental perfusion status earlier and more objectively.

Fetal nuchal translucency (NT) sonography is combined with maternal serum free β -hCG and PAPP-A quantifications during the standard first-trimester screening for aneuploidy. Derived from the syncytiotrophoblast layer, both free β -hCG and PAPP-A serve as key indicators of placental health and functional capacity. Decreased levels of maternal PAPP-A point toward impaired trophoblastic invasion, which elevates the risk for several gestational complications such as preterm delivery, fetal growth restriction, and preeclampsia (7,8). Additionally, multiple investigations have confirmed an inverse relationship linking initial PAPP-A markers to uterine artery Doppler outcomes, indicating common pathophysiological pathways rooted in faulty placentation (8).

The association between maternal serum β -hCG levels and adverse pregnancy outcomes remains controversial, with inconsistent findings across studies (9). Nevertheless, most of these investigations have included mixed-parity populations, which may confound hemodynamic results, as multiparous women exhibit altered uterine vascular resistance due to prior vascular remodeling, and parity itself has been shown to significantly influence uterine artery Doppler parameters (10). In contrast, nulliparous pregnancies offer a more homogeneous physiological model to evaluate placental adaptation, as they eliminate parity-related variability in uterine blood flow and vascular compliance.

Accordingly, the present study aimed to investigate the relationship between first-trimester combined test parameters and mid-second-trimester uterine artery Doppler indices in nulliparous pregnancies. We further aimed to evaluate whether early biochemical markers of impaired placentation correspond with Doppler evidence of increased uterine vascular resistance.

Materials and Methods

This retrospective cohort evaluation was conducted at a tertiary maternal–fetal medicine referral facility [blinded for review] following formal institutional approval on October 14, 2025. Institutional electronic medical records were retrospectively screened to identify nulliparous

individuals who had undergone routine clinical evaluations with uterine artery Doppler measurements during standard mid-second-trimester anatomical scans between April and October 2025, yielding an initial cohort of 330 cases. Complete data regarding first-trimester combined screening were available for 280 of these pregnancies, rendering them suitable for initial screening. To maintain a uniform baseline for biochemical markers, 40 patients who underwent second-trimester quadruple screening rather than the first-trimester combined protocol were excluded from the analysis.

To minimize potential pharmacologic effects on uteroplacental circulation, pregnancies with documented use of antithrombotic agents, including low-dose aspirin and/or enoxaparin at any point before Doppler assessment, were excluded. After application of all exclusion criteria, the final study population consisted of 227 nulliparous pregnancies without exposure to antithrombotic therapy, with complete first-trimester biochemical parameters alongside second-trimester uterine artery Doppler assessments. Furthermore, cases involving multifetal gestations, significant fetal structural defects or chromosomal abnormalities, pre-existing hypertension, pregestational diabetes mellitus, nephropathy, and autoimmune conditions were also excluded from the cohort.

Ultrasound estimation of crown–rump length during the initial trimester was utilized to establish gestational age. At the initial combined screening visit, maternal baseline demographics—comprising maternal age, stature, body weight, smoking status (documented as yes/no), and body mass index (BMI)—were documented. BMI was calculated using maternal weight measured at that visit.

To avoid inter-observer discrepancy, a single experienced perinatologist executed all uterine artery Doppler scans. These evaluations utilized a Philips Affiniti 70G ultrasound platform (Philips Healthcare, Bothell, WA, USA) coupled with a transabdominal C5-1 MHz transducer. Spectral assessments were captured throughout the gestational window spanning 18+0 to 24+0 weeks. Color Doppler modulation guided the localization of both uterine arteries at the site where they visibly cross the external iliac artery, situated laterally to the cervix. Pulsed-wave sampling gates were adjusted to maintain an angle of insonation under 30°, ensuring the acquisition of no fewer than three sequential, identical wave structures for each vessel while the fetus remained motionless.

The presence or absence of unilateral or bilateral uterine artery diastolic notching was qualitatively assessed and documented for each patient.

Automatic computation of the pulsatility index (PI) was achieved through the integrated spectral evaluation software of the ultrasound platform. To determine the mean uterine artery PI (mean UtA-PI), the values obtained from the right and left uterine vessels were averaged. All examinations were performed under standardized machine settings and acquisition parameters.

High uterine artery resistance was defined using a cohort-specific approach. Elevated resistance was defined as a mean UtA-PI value at or above the 90th percentile of the study population distribution ($p_{90} = 1.545$). In the absence of universally validated population-specific reference ranges for our cohort, a percentile-based internal definition was preferred to allow consistent risk stratification. This definition was used consistently for all regression and predictive analyses.

The first-trimester combined test took place between gestational weeks 11+0 and 13+6. A Cobas e601 system (Roche Diagnostics, Mannheim, Germany) utilized electrochemiluminescence immunoassay to evaluate maternal serum free β -hCG and PAPP-A. The resulting values were converted to multiples of the median (MoM) after adjustments for maternal ethnicity, weight, smoking habits, and gestational age. Mid-sagittal sonographic views were used to determine nuchal translucency (NT) according to Fetal Medicine Foundation (FMF) criteria, followed by NT MoM calculations. To assess early placentation and fetoplacental interactions, NT MoM was used only as a correlational indicator and was excluded from the multiple regression analysis.

IBM SPSS Statistics for Windows (Version 26.0; IBM Corp., Armonk, NY, USA) was utilized to conduct all statistical computations. To evaluate data normality, visual reviews of histograms were combined with the Kolmogorov–Smirnov test. Descriptive statistics for continuous data were formatted as mean $\pm$ standard deviation (SD) or median (interquartile range [IQR]) depending on their distribution characteristics. Initial steps involved univariate testing to examine potential links between uterine artery resistance and both biochemical and maternal parameters.

Spearman's rank correlation coefficient was employed to determine the relationships between mean UtA-PI and first-trimester biochemical factors, including free β -hCG MoM, PAPP-A

MoM, and NT MoM. To isolate independent predictors associated with high uterine artery resistance (defined as a mean UtA-PI $\geq$ 90th percentile), a multiple logistic regression model was established. Gestational age at the time of Doppler measurement, BMI, maternal age, and maternal smoking status served as covariates in this model to account for their established impact on uteroplacental vascular impedance. Before constructing the regression model, collinearity diagnostics were performed using variance inflation factors (VIF). Additionally, standard goodness-of-fit indicators, specifically the Hosmer–Lemeshow test, were utilized to evaluate model calibration and overall fit.

Receiver operating characteristic (ROC) curve analysis was implemented to further assess how accurately first-trimester PAPP-A MoM predicts elevated uterine artery resistance. For this estimation, the area under the curve (AUC) values were detailed alongside their 95% confidence intervals, and the Youden index served to pinpoint the ideal cut-off threshold. Finally, a post-hoc power analysis was performed to evaluate whether the sample size was sufficient to detect significant independent predictors within the multivariable logistic regression model. Statistical significance was established at a p-value of <0.05 . Regarding the core parameters integrated into our logistic regression framework, the dataset contained no missing values.

Formal approval for this research protocol was granted by the Institutional Ethics Committee [blinded for review] (Decision No: 2025/12-31; issued on 14 October 2025). Because of the retrospective design of the investigation, the requirement to obtain informed consent was officially waived by the board. To guarantee rigorous patient anonymity and align with internal institutional policies, all personal information was entirely de-identified. Consequently, participants were tracked exclusively through unique, non-traceable research codes in full agreement with the principles outlined in the Declaration of Helsinki.

Results

The final analytical cohort comprised 227 nulliparous individuals who completed both initial combined screening and mid-second-trimester (18–24 weeks) uterine artery Doppler evaluations. In this study group, the average maternal age stood at 27.9 ± 5.1 years, while the mean gestational age when Doppler scans were done was 20.5 ± 2.5 weeks.

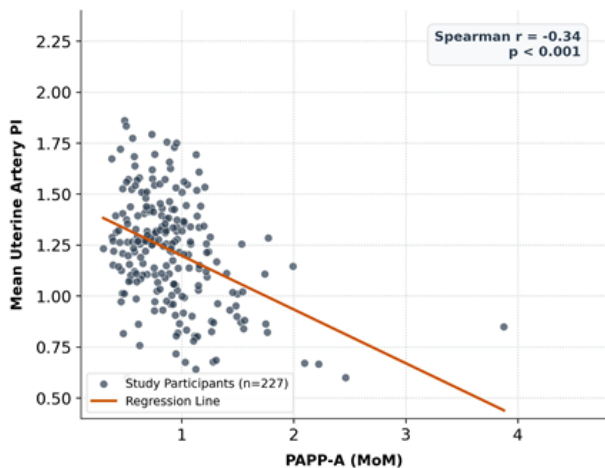
Figure 1A. Correlation Between First-Trimester PAPP-A (MoM) and Mid-Second-Trimester Mean UtA-PI

Fig. 1A. Association between first-trimester PAPP-A multiples of the median (MoM) and mean uterine artery pulsatility index (UtA-PI) demonstrated via a scatter plot in 227 medication-free nulliparous gestations. The analysis revealed a statistically significant inverse correlation (Spearman's $r = -0.34$, $p < 0.001$)

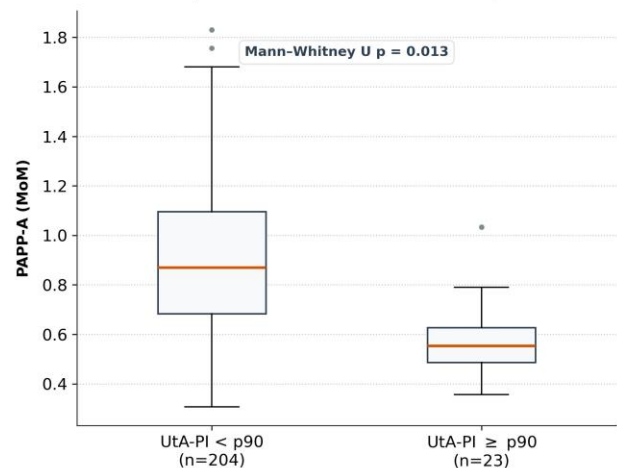
Figure 2A. First-Trimester PAPP-A (MoM) Distribution by Mid-Second-Trimester UtA-PI Groups

Fig. 2A. Box-and-whisker plot displaying PAPP-A MoM levels across cohorts categorized by low (<90th percentile) and high (≥ 90 th percentile; $p_{90} = 1.545$) uterine artery resistance. The high-resistance cohort exhibited a significantly decreased median PAPP-A level (Mann-Whitney U test, $p = 0.013$)

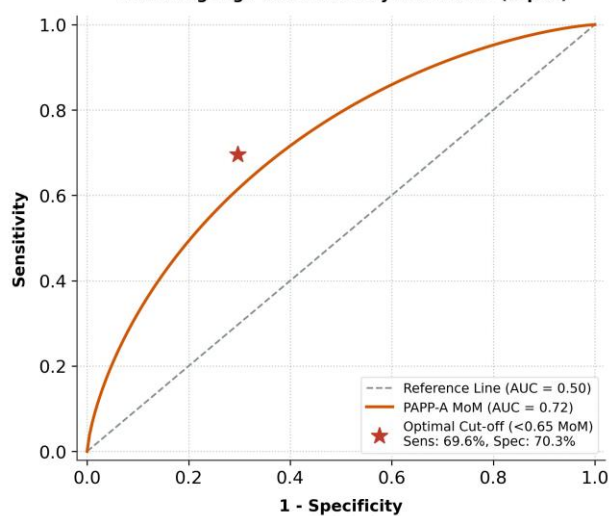
Figure 1B. ROC Curve for PAPP-A (MoM) Predicting High Uterine Artery Resistance ($\geq p_{90}$)

Fig. 1B. Receiver operating characteristic (ROC) analysis evaluating the prognostic capacity of first-trimester PAPP-A (MoM) to detect elevated uterine artery resistance (UtA-PI ≥ 90 th percentile). The area under the curve (AUC) reached 0.72, with the Youden index identifying 0.65 MoM as the ideal threshold value.

was 21.1 ± 1.6 weeks. Median MoM figures for PAPP-A, free β -hCG, and NT were recorded as 0.83 [0.58–1.12], 1.14 [0.77–1.66], and 1.00 [0.88–1.15], respectively. Furthermore, the cohort displayed a mean uterine artery pulsatility index (UtA-PI) of 1.23 ± 0.30 , with the population-specific 90th percentile (p_{90}) calculated at 1.545 (Table 1).

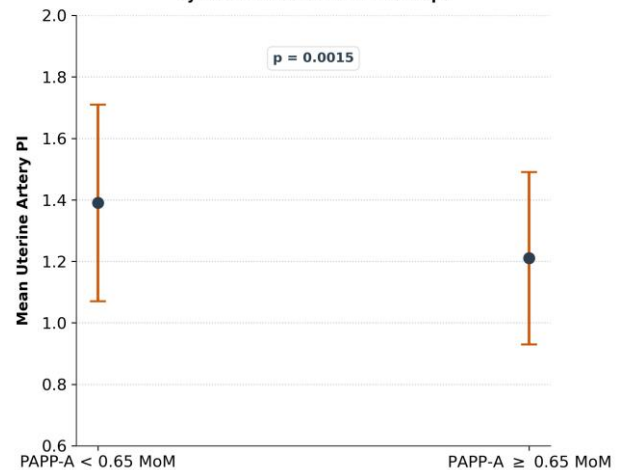
Figure 2B. Mid-Second-Trimester Mean UtA-PI by First-Trimester PAPP-A Groups

Fig. 2B. Mean UtA-PI values compared across low (PAPP-A < 0.65 MoM) and normal (PAPP-A ≥ 0.65 MoM) cohorts using an error bar chart. The mean UtA-PI was substantially higher within the low PAPP-A category (Mann-Whitney U test, $p = 0.0015$)

Looking at the initial screening parameters, a significant inverse link was established between PAPP-A MoM and mean UtA-PI parameters (Spearman $r = -0.34$, $p < 0.001$) (Figure 1A). Conversely, maternal serum free β -hCG MoM exhibited a weak, statistically negligible positive correlation with mean UtA-PI ($r = 0.09$, $p = 0.16$). Similarly, no meaningful association was noted for NT MoM metrics ($r = 0.05$, $p = 0.42$) (Table 2).

When analyzing potential indicators of elevated uterine artery resistance (UtA-PI $\geq p_{90}$) through multivariable logistic regression, low PAPP-A

Table 1: Baseline Demographic and Biochemical Parameters of The Study Cohort

Maternal age (years) (mean $\pm$ SD)	27.9 $\pm$ 5.1
Gestational age at Doppler (weeks)	21.1 $\pm$ 1.6
PAPP-A (MoM), median [IQR]	0.83 [0.54]
Free β -hCG (MoM), median [IQR]	1.14 [0.89]
NT (MoM), median [IQR]	1.00 [0.27]
Mean UtA-PI (mean $\pm$ SD)	1.23 $\pm$ 0.30
UtA-PI $\geq$ p90 (n, %)	23 (10.1%)

Footnote: Values are expressed as mean $\pm$ standard deviation (SD) or median [interquartile range (IQR)], depending on data distribution. MoM, multiples of the median; UtA-PI, uterine artery pulsatility index

Table 2: Spearman's Rank Correlation Analysis Evaluating The Relationship Between First-Trimester Markers and Mean Uterine Artery PI

Parameter	r	p-value
PAPP-A (MoM)	-0.34	<0.001
Free β -hCG (MoM)	0.09	0.16
NT (MoM)	0.05	0.42

Footnote: MoM, multiples of the median; UtA-PI, uterine artery pulsatility index

Table 3: Multiple logistic regression analysis identifying predictors of elevated uterine artery resistance (UtA-PI $\geq$ p90)

Variable	Adjusted OR	95% CI	p-value
PAPP-A (MoM)	2.61	1.46–4.67	0.001
Free β -hCG (MoM)	1.18	0.74–1.89	0.467
NT (MoM)	1.09	0.62–1.92	0.762

Footnote: Adjusted for maternal age, BMI, and gestational age during the Doppler examination. CI, confidence interval; MoM, multiples of the median; UtA-PI, uterine artery pulsatility index

MoM persisted as an independent risk marker (OR = 2.61; 95% CI: 1.46–4.67; $p = 0.001$) even after controlling for gestational age, BMI, maternal age, and smoking status. The multivariable regression model demonstrated excellent calibration and goodness-of-fit (Hosmer–Lemeshow test: $p = 0.68$) with no evidence of multicollinearity among the covariates (maximum Variance Inflation Factor [VIF] = 1.18). On the other hand, no significant relationships linking the clinical outcome to either NT MoM or free β -hCG were detected (Table 3).

According to the ROC curve evaluation, initial PAPP-A readings achieved a moderate capacity for predicting pregnancies characterized by high uterine artery resistance (AUC = 0.72; 95% CI: 0.66–0.82). The Youden index pinpointed the ideal diagnostic cut-off at 0.65 MoM, which yielded a specificity of 70.3% and a sensitivity of 69.6% (Figure 1B).

Stratification of the cohort based on the 90th percentile of mean UtA-PI revealed that median

PAPP-A MoM levels were down-regulated in the high-resistance category relative to the cohort under the 90th percentile (0.61 [0.48–0.79] vs. 0.84 [0.61–1.15]; Mann–Whitney U $p = 0.013$) (Figure 2A). In a similar manner, individuals presenting with PAPP-A < 0.65 MoM exhibited markedly increased mean UtA-PI entries compared to those with PAPP-A $\geq$ 0.65 MoM (1.39 $\pm$ 0.32 vs. 1.21 $\pm$ 0.28; $p = 0.0015$) (Figure 2B).

Pulsatility index metrics did not differ substantially between the left and right uterine arteries (right = 1.25 $\pm$ 0.34 vs. left = 1.23 $\pm$ 0.33; $p = 0.41$). Additionally, bilateral uterine artery diastolic notching was significantly more prevalent in the high-resistance cohort (mean UtA-PI $\geq$ p90) compared to the normal-resistance group (43.5% vs. 4.2%; Chi-square $p < 0.001$). Combined mean PI values were utilized across all regression models and correlation tests. Finally, based on the sample size of 227 patients and the 10% prevalence of the primary outcome (mean

UtA-PI $\geq$ p90, $n = 23$), a post-hoc power analysis indicated that the study achieved a statistical power of 81.4% to detect the reported odds ratio of 2.61 for PAPP-A MoM at a significance level of 0.05. The main parameters evaluated within the regression framework demonstrated no missing observations.

Discussion

This investigation evaluated how early combined screening markers correlate with uterine artery Doppler metrics during the mid-second trimester within a nulliparous cohort. Our data revealed a notable inverse link connecting PAPP-A MoM to average uterine artery pulsatility index (UtA-PI) outcomes. On the contrary, neither mid-gestational uterine hemodynamics nor Doppler values showed significant links with nuchal translucency (NT) MoM or free β -hCG levels. Women presenting with lower PAPP-A readings consistently demonstrated elevated uterine vascular resistance. Additionally, diminished initial biochemical metrics correlated directly with a higher probability of presenting with elevated mean UtA-PI parameters, a pattern that appeared consistent within the high-resistance subgroup of the population. Taken together, these results imply that decreased initial PAPP-A values might point toward suboptimal trophoblastic performance and strongly correlate with sustained second-trimester uterine artery impedance.

Our findings are consistent with previous investigations demonstrating that low PAPP-A is associated with impaired placentation and subsequent elevations in uterine artery resistance (7,8). Depressed first-trimester PAPP-A levels have been linked to placenta-mediated complications such as preeclampsia and fetal growth restriction, reinforcing its clinical role as an early serum marker of abnormal placentation (7,8). Additionally, previous evidence indicates that combining first-trimester biochemical markers with uterine artery Doppler substantially improves the identification of severe placental dysfunction and adverse pregnancy outcomes (3). These observations are also in line with data showing a strong association between low first-trimester PAPP-A levels and the presence of uterine artery diastolic notching (11). In that context, early vascular anomalies—particularly when bilateral—were significantly associated with suboptimal obstetric outcomes. Physiologically, PAPP-A is synthesized and secreted by the syncytiotrophoblast, and low maternal serum

concentrations have been closely correlated with histopathological features of impaired placental function, providing a plausible biological explanation for our observations (12).

Physiologically, uterine artery resistance progressively declines with advancing gestation as a result of physiological trophoblastic invasion and spiral artery remodeling. Consequently, persistently elevated pulsatility index values beyond 18 weeks of gestation indicate incomplete spiral artery transformation, which characterizes the high-resistance subgroup identified in our sample. Histopathological analyses further support that inadequate trophoblastic invasion leads to downstream restriction of uteroplacental perfusion (1). Furthermore, uterine artery Doppler findings—particularly the persistence of diastolic notching between 16 and 22 weeks of gestation—directly reflect this increased vascular resistance and signify impaired uteroplacental blood flow (13).

Previous literature has demonstrated that parity can significantly influence uterine artery Doppler parameters, with prior successful deliveries being associated with permanent beneficial alterations in uterine vascular indices (10). Furthermore, uterine artery Doppler has frequently been assessed in the earlier phases of the second trimester, a period during which transient diastolic notching is more prevalent due to ongoing vascular adaptation (13). In contrast, our analysis was restricted to a true mid-second-trimester window, representing a more stable phase of uteroplacental hemodynamics during which physiological vascular resistance is expected to have reached a nadir. Consequently, elevated uterine artery resistance detected at this specific stage is more likely to reflect definitive defective placentation rather than transient early physiological variation. Our findings not only corroborate previous observations but also extend the association between low PAPP-A levels and increased uterine vascular impedance to a later, hemodynamically stable gestational window in a highly homogeneous nulliparous population.

Uterine artery Doppler assessment remains a valuable but highly operator-dependent diagnostic tool that requires specialized technical expertise and standardized measurement protocols. In contrast, maternal serum biochemical parameters such as PAPP-A and free β -hCG are highly reproducible, completely operator-independent, and directly reflect the global functional status of the placenta. In this context, identifying low first-trimester PAPP-A levels may help clinicians risk-

stratify nulliparous pregnancies, isolating a high-risk subset in which targeted mid-trimester uterine artery Doppler assessment would be particularly informative. This approach could optimize resources, especially in clinical settings where advanced Doppler expertise is limited. While the combined interpretation of biochemical and Doppler findings provides a more comprehensive assessment of uteroplacental vascular adaptation, the definitive clinical utility of this strategy requires further prospective validation in trials incorporating longitudinal pregnancy outcomes.

The main strengths of this study include the evaluation of a strictly homogeneous nulliparous population, the implementation of a single-operator standardized ultrasound protocol using high-resolution machinery, and the utilization of population-specific MoM standardization for biochemical parameters. Furthermore, all Doppler examinations were tightly restricted to a defined mid-second-trimester window, effectively minimizing temporal and gestational variability.

On the other hand, certain constraints of our research should be addressed. Due to the retrospective nature of the study, precise data oversight is restricted, which prevents us from confirming direct cause-and-effect relationships. Furthermore, information regarding postpartum maternal-fetal outcomes (such as preeclampsia, fetal growth restriction, or gestational hypertension) and extended longitudinal follow-up is missing from the current dataset. Consequently, our findings describe an association with an intermediate subclinical vascular phenotype rather than the direct prediction of ultimate clinical syndromes. Nonetheless, characterizing this early biochemical-hemodynamic link provides a valuable physiological blueprint of defective placentation before clinical symptom onset. This should be addressed in future prospective trials. Additionally, a limited number of participants in the elevated-resistance cohort represents a further limitation. Lastly, because this research was conducted at a single institution and relied on an internal, cohort-specific 90th percentile threshold for elevated vascular resistance, applying the exact diagnostic cut-off values (e.g., PAPP-A of 0.65 MoM) directly to broader, more diverse cohorts may be constrained. International reference ranges (such as the Fetal Medicine Foundation charts) may yield different diagnostic thresholds. Consequently, these findings ought to be viewed as indicative of a biological relationship unique to this study sample, instead of establishing definitive clinical diagnostic standards.

In conclusion, low first-trimester PAPP-A levels are significantly associated with increased uterine artery resistance in mid-second-trimester nulliparous pregnancies. This finding indicates that early biochemical variation closely corresponds to later Doppler evidence of altered uteroplacental vascular adaptation. Because this study did not assess final pregnancy outcomes, these results should be interpreted as evidence of an association with an intermediate vascular phenotype rather than direct prediction of clinical complications. From a practical perspective, first-trimester PAPP-A may serve as an effective screening filter to identify nulliparous women who would benefit most from advanced uterine artery Doppler assessment. Further prospective, multi-center studies encompassing definitive clinical outcomes are warranted to clarify the absolute utility of this relationship.

Conflict of Interest: The authors declare no conflict of interest.

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