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Study of The Role of Doppler Indices, Serum Uric Acid, Creatinine and Albumin for Prediction of Pre-Eclampsia

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Abstract

Background: *Pre-eclampsia is a major cause of maternal and perinatal morbidity and mortality. Early prediction could enable closer surveillance and timely delivery*

Methods: *In a prospective cohort, 100 healthy primigravidae with singleton pregnancies were recruited at ~20 weeks from El-Shatby University Maternity Hospital. Serum uric acid, albumin and creatinine were measured and uterine and umbilical artery Doppler indices (RI, PI) were recorded at recruitment and monthly until delivery. Women were followed to determine development of pre-eclampsia.*

Results: *Ninety-two completed follow-up; 16 (17.4%) developed pre-eclampsia while 76 remained normotensive. Compared with normotensive pregnancies, those who later developed pre-eclampsia had higher uric acid from the second visit onward (e.g., mean 5.74±0.86 vs 3.59±0.54 mg/dL at the second visit) and lower serum albumin (e.g., 2.99±0.61 vs 4.14±0.48 g/dL at the second visit). Serum creatinine did not differ significantly across visits. Abnormal uterine and umbilical artery Doppler patterns (elevated RI/PI) were associated with subsequent maternal hypertension; cut-offs of RI ≥0.661 and PI ≥1.128 (uterine) and RI ≥0.710 and PI ≥1.27 (umbilical) identified higher-risk pregnancies. Severe pre-eclampsia occurred in 3 cases; one intrauterine fetal death was recorded at 29 weeks.*

Conclusion: *Serial assessment of serum uric acid and albumin combined with uterine and umbilical artery Doppler indices improves prediction of pre-eclampsia in primigravidae. Creatinine alone had limited predictive value.*

Keywords: *Pre-eclampsia, Uterine artery Doppler, Umbilical artery, Uric acid, Albumin, Creatinine, Prediction.*

Introduction

Hypertensive disorders complicate approximately 2–8% of pregnancies and remain among the leading causes of maternal and perinatal morbidity and mortality worldwide [1,2]. Pre-eclampsia (PE) is a complex, multisystem disorder that typically develops after 20 weeks of gestation and is characterized by new-onset hypertension and proteinuria, with potential progression to hepatic, renal, neurological, and haematological dysfunction [3,4]. Despite decades of research, the precise pathophysiology of PE remains incompletely understood, but placental malperfusion, oxidative stress, and endothelial dysfunction are recognized as central mechanisms [5,6].

Various screening approaches have been proposed, ranging from maternal risk factor assessment and angiogenic biomarkers to uterine artery Doppler velocimetry [7–9]. However, a universally accessible, cost-effective, and reproducible strategy suitable for use in all clinical settings especially for low-risk primigravidae remains elusive. Combining simple biochemical markers with Doppler parameters offers a promising approach that may improve predictive accuracy without increasing healthcare costs.

Uric acid has long been considered a potential biochemical indicator of PE, reflecting endothelial dysfunction and oxidative stress rather than simple renal impairment [10,11]. Similarly, serum albumin levels tend to decline as the disease progresses due to capillary leakage and reduced oncotic pressure, whereas creatinine may remain within normal limits until later stages [12,13].

Doppler assessment of uterine and umbilical arteries provides non-invasive insight into uteroplacental perfusion, and abnormal resistance or pulsatility indices are frequently observed before the onset of clinical PE [14–16].

Aim of The Work

The present study aimed to evaluate whether **serial measurements of maternal serum uric acid, albumin, and creatinine,** in combination with **uterine and umbilical artery Doppler indices**, could predict the subsequent development of pre-eclampsia in healthy primigravidae.

Materials and Methods

Study design and setting: Prospective longitudinal cohort at El-Shatby University Maternity Hospital. One hundred healthy primigravidae with singleton pregnancies recruited at approximately 20 weeks' gestation. Exclusion criteria included multiple gestation, chronic hypertension, diabetes mellitus, renal or liver disease, and other significant comorbidities. At recruitment and at monthly antenatal visits until delivery, the following were obtained: blood pressure, body mass index, edema assessment, complete blood count, urine analysis, and serum uric acid, albumin and creatinine. Obstetric ultrasound assessed gestational age, fetal growth, amniotic fluid and viability. Uterine and umbilical artery Doppler velocimetry was performed resistance index (RI) and pulsatility index (PI). Standard definitions were used for RI and PI.

Outcomes: Development of pre-eclampsia according to conventional diagnostic criteria. Women who developed pre-eclampsia were managed per hospital protocols.

Statistics: Group comparisons between women who developed pre-eclampsia and those who remained normotensive were performed across visits; a significance threshold of p<0.05 was applied. Diagnostic cut-offs for Doppler indices were explored.

Results

All collected data were revised for completeness, coded, and entered into a computer database using the **Statistical Package for the Social Sciences (SPSS), version 17 (SPSS Inc., Chicago, IL, USA)**. Data entry was double-checked for accuracy before analysis. Continuous variables were expressed as **mean ± standard deviation (SD)**, while categorical variables were presented as **frequencies and percentages.**

Comparisons between the two study groups, women who developed pre-eclampsia and those who remained normotensive, were carried out using the **Student's t-test** for continuous variables and the **chi-square (χ^2) test** for categorical variables where appropriate. The **level of statistical significance** was set at $p < 0.05$.

The **predictive performance** of biochemical and Doppler indices (serum uric acid, serum albumin, serum creatinine, uterine and umbilical artery resistance and pulsatility indices) was evaluated using **receiver operating characteristic (ROC) curve analysis.** From the ROC curves, the **area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV),** and **overall accuracy** were determined. The **optimal cut-off values** for predicting pre-eclampsia were identified using the **maximum Youden index** (sensitivity + specificity – 1).

In all analyses, results were considered statistically significant at $p < 0.05$. Significant and non-significant differences in tables were denoted as **SIG** and **NS**, respectively.

A total of **100 healthy primigravidae** with singleton pregnancies were enrolled at approximately 20 weeks of gestation. *Baseline clinical characteristics of the study population (Table 1).* Of these, **92 women completed follow-up**, while 7 were lost to follow-up and 1 experienced a miscarriage. During the study, **16 women (17.4%) developed pre-eclampsia,** and **76 (82.6%) remained normotensive** until delivery.

Table 1: Baseline clinical characteristics of the study population.

Parameter	Normotensive (n = 76)	Developed Pre-eclampsia (n = 16)	p-value
Maternal age (years)	25.6 ± 4.8	26.2 ± 5.3	0.370
BMI (kg/m²)	25.8 ± 3.9	26.9 ± 4.2	0.071
Gestational age at delivery (weeks)	38.2 ± 1.4	35.9 ± 2.8	<0.001
Birth weight (g)	3250 ± 480	2590 ± 640	<0.001

Values are mean ± SD.

Maternal Blood Pressure

At the first antenatal visit, mean systolic and diastolic blood pressures were similar in both groups ($p > 0.05$). From the **second visit onward**, significant elevations were observed among women who subsequently developed pre-eclampsia (Tables 2 and 3). By the third trimester, mean systolic blood pressure reached **151.4 ± 8.7 mmHg** and diastolic **98.3 ± 7.9 mmHg** in the pre-eclampsia group compared with **114.7 ± 9.1 mmHg** and **72.5 ± 8.2 mmHg**, respectively, in normotensive pregnancies ($p < 0.001$).

Table 2: Comparison between the two studied groups at the different visits regarding systolic blood pressure.

Visit	Group A (Range / Mean / SD) Systolic blood pressure	Group B (Range / Mean / SD) Systolic blood pressure	P
1st	90.0–120.0 108.26 9.02	120.0–130.0 122.94 4.70	0.066
2nd	90.0–120.0 105.13 9.00	120.0–150.0 129.65 7.07	0.001
3rd	90.0–120.0 106.70 8.44	120.0–150.0 131.71 5.85	0.001

4th	90.0–120.0 106.19 8.85	120.0–150.0 128.12 5.53	0.001
5th	90.0–120.0 104.81 9.21	120.0–150.0 130.88 6.26	0.001
6th	90.0–120.0 105.37 8.21	120.0–160.0 135.24 5.74	0.001

Table 3: Comparison between the two studied groups at the different visits regarding diastolic blood pressure.

Visit	Group A (Range / Mean / SD) Diastolic blood pressure	Group B (Range / Mean / SD) Diastolic blood pressure	P
1st	60.0–80.0 74.69 5.98	80.0–90.0 85.29 5.14	0.075
2nd	60.0–80.0 70.28 5.83	90.0–100.0 94.41 2.94	0.0001
3rd	60.0–80.0 71.04 5.75	90.0–100.0 94.12 2.74	0.0001
4th	60.0–80.0 69.78 5.97	90.0–110.0 94.65 3.43	0.0001
5th	60.0–80.0 71.18 6.10	90.0–110.0 94.06 3.03	0.0001
6th	60.0–80.0 70.35 6.29	90.0–110.0 95.59 3.71	0.0001

Serum Biochemical Markers

Serum albumin levels were significantly lower in women who developed pre-eclampsia from the second visit onward (Table 4, Figure 1). At the second visit, albumin averaged **2.99 ± 0.61 g/dL** compared to **4.14 ± 0.48 g/dL** in normotensive women ($p < 0.001$), and continued to decline toward term.

Table 4: Comparison between the two studied groups at the different visits regarding albumin.

Visit	Group A (Range / Mean / SD) Albumin (g/dL)	Group B (Range / Mean / SD) Albumin (g/dL)	P
1st	2.8–3.9 3.24 0.34	2.3–3.5 3.12 0.45	0.112
2nd	3.4–5.0 4.14 0.48	1.9–4.0 2.99 0.61	0.0001
3rd	3.4–5.0 4.18 0.46	2.1–4.0 3.01 0.58	0.0001
4th	3.4–5.0 4.18 0.46	1.9–3.9 2.79 0.65	0.0001
5th	3.4–5.0 4.18 0.51	1.9–4.0 2.80 0.69	0.0001
6th	3.4–5.0 4.27 0.52	1.9–3.9 2.75 0.75	0.0001

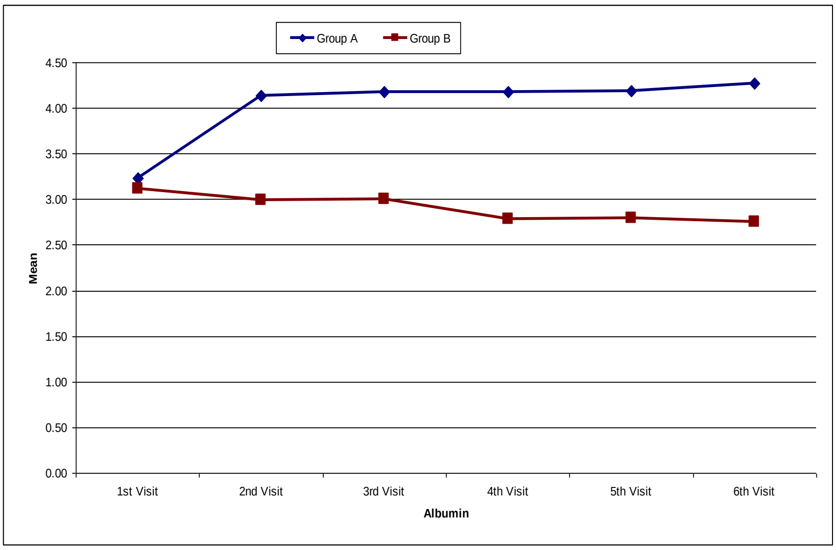

Figure 1: Trend of serum albumin levels (g/dL) across gestation in normotensive and pre-eclamptic women. Albumin declined significantly from the second trimester in the pre-eclampsia group ($p < 0.001$).

In contrast, **serum uric acid** levels increased progressively during gestation in women who later developed pre-eclampsia (Table 5, Figure 2).

Table 5: Comparison between the two studied groups at the different visits regarding uric acid.

Visit	Group A (Range / Mean / SD) Uric acid (mg/dL)	Group B (Range / Mean / SD) Uric acid (mg/dL)	P
1st	2.4–4.0 3.54 0.47	2.5–4.5 3.71 0.59	0.107
2nd	2.6–4.5 3.59 0.54	4.1–6.7 5.74 0.86	0.0001
3rd	2.6–4.5 3.53 0.61	4.1–6.6 5.39 0.95	0.0001
4th	2.6–4.5 3.60 0.64	4.2–7.2 5.48 1.08	0.0001
5th	2.6–4.5 3.61 0.56	4.0–7.1 5.31 1.06	0.0001
6th	2.6–4.5 3.44 0.59	4.0–7.2 5.52 1.04	0.0001

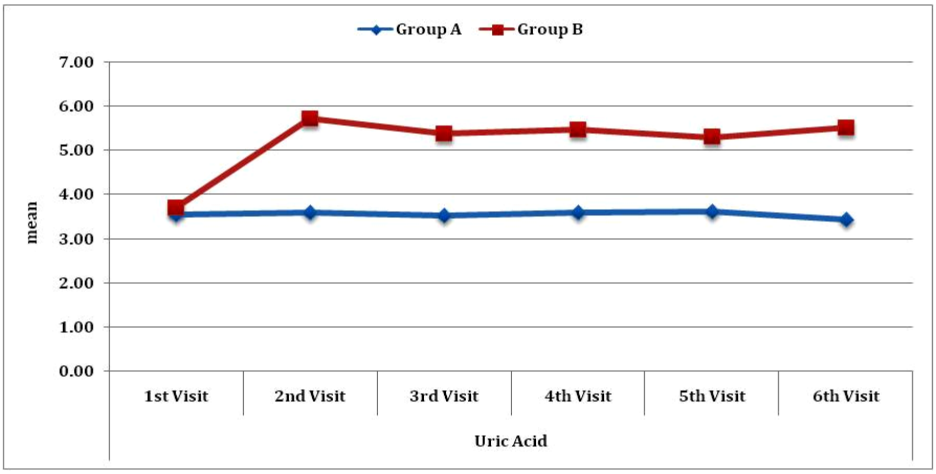

Figure 2: Trend of serum uric acid (mg/dL) across gestation. Uric acid increased progressively in women who later developed pre-eclampsia, remaining stable in normotensive pregnancies.

Mean uric acid at the second visit was **5.74 ± 0.86 mg/dL** versus **3.59 ± 0.54 mg/dL** among normotensive pregnancies ($p < 0.001$). This difference persisted through subsequent visits, with the highest levels observed in those who developed severe pre-eclampsia.The early elevation of Uric acid level in the pre-eclampsia group indicates that rising uric acid levels precede overt clinical manifestations.

Serum creatinine values showed no significant differences between groups at any visit ($p > 0.05$; Table 6), remaining within the physiological range throughout pregnancy.

Table 6: Comparison between the two studied groups at the different visits regarding creatinine.

Visit	Group A (Range / Mean / SD) Creatinine (mg/dL)	Group B (Range / Mean / SD) Creatinine (mg/dL)	P
1st	0.3–1.8 0.63 0.16	0.6–0.7 0.64 0.04	0.389
2nd	0.6–1.3 1.00 0.22	0.6–1.3 0.94 0.24	0.139
3rd	0.6–1.3 0.95 0.24	0.6–1.3 1.02 0.27	0.142
4th	0.6–1.3 0.96 0.24	0.6–1.3 1.00 0.24	0.271
5th	0.6–1.3 0.94 0.22	0.6–1.3 0.99 0.22	0.195
6th	0.6–1.3 0.90 0.23	0.6–1.3 0.95 0.26	0.249

Doppler Indices

Analysis of **uterine and umbilical artery Doppler velocimetry** revealed significant differences between groups (Tables 7,8,9 and 10).

Table 7: Uterine artery Doppler RI across visits.

Visit	Group A (Range / Mean / SD) RI	Group B (Range / Mean / SD) RI	P
1st	0.357–0.503 0.398 0.034	0.361–0.497 0.472 0.040	0.034
2nd	0.358–0.503 0.462 0.045	0.357–0.665 0.512 0.044	0.012
3rd	0.358–0.495 0.402 0.046	0.367–0.597 0.496 0.039	0.043
4th	0.359–0.503 0.407 0.040	0.373–0.576 0.453 0.041	0.039
5th	0.358–0.503 0.405 0.051	0.364–0.567 0.445 0.046	0.042
6th	0.357–0.503 0.395 0.050	0.357–0.563 0.478 0.053	0.009

Table 8: Uterine artery Doppler PI across visits.

Visit	Group A (Range / Mean / SD) PI	Group B (Range / Mean / SD) PI	P
1st	0.681–0.910 0.789 0.047	0.686–1.356 0.901 0.068	0.062
2nd	0.682–0.908 0.781 0.068	0.690–1.277 0.982 0.071	0.019
3rd	0.682–0.909 0.757 0.076	0.692–1.229 1.108 0.068	0.008
4th	0.682–0.901 0.766 0.074	0.728–1.194 0.924 0.058	0.002
5th	0.682–0.894 0.732 0.065	0.698–1.177 0.972 0.065	0.013
6th	0.682–0.905 0.737 0.075	0.698–1.145 1.094 0.064	0.002

Table 9: Umbilical artery Doppler RI across visits.

Visit	Group A (Range / Mean / SD) RI	Group B (Range / Mean / SD) RI	P
1st	0.612–0.690 0.653 0.027	0.675–0.805 0.722 0.029	0.081
2nd	0.619–0.656 0.639 0.030	0.648–0.762 0.674 0.037	0.03
3rd	0.620–0.630 0.628 0.280	0.664–0.740 0.717 0.269	0.034
4th	0.588–0.595 0.591 0.271	0.593–0.710 0.648 0.246	0.048
5th	0.560–0.598 0.585 0.279	0.631–0.679 0.654 0.241	0.034
6th	0.520–0.525 0.522 0.233	0.523–0.637 0.611 0.256	0.034

Table 10: Umbilical artery Doppler PI across visits.

Visit	Group A (Range / Mean / SD) PI	Group B (Range / Mean / SD) PI	P
1st	0.944–1.218 1.121 0.063	1.015–1.505 1.377 0.033	0.206
2nd	1.005–1.127 1.093 0.077	1.032–1.401 1.251 0.063	0.038*
3rd	1.009–1.066 1.032 0.036	1.072–1.405 1.380 0.064	0.019*
4th	0.991–1.007 1.005 0.193	1.073–1.251 1.187 0.125	0.036*
5th	0.901–1.007 0.941 0.028	1.086–1.175 1.142 0.025	0.018*
6th	0.808–1.007 0.987 0.188	1.088–1.091 1.089 0.069	0.025*

*$p < 0.05$

Women who later developed pre-eclampsia exhibited persistently elevated **resistance index (RI)** and **pulsatility index (PI)** values, suggestive of impaired uteroplacental perfusion.
The mean uterine artery RI and PI were significantly higher at each assessment (p < 0.001), with optimal predictive cut-off points of **RI ≥ 0.661** and **PI ≥ 1.128**.
Similarly, umbilical artery RI and PI thresholds of ≥ **0.710** and ≥ **1.27**, respectively, were associated with increased risk of pre-eclampsia.

Diagnostic Performance of Predictive Markers

Receiver operating characteristic (ROC) curve analysis was conducted to determine the predictive performance of the studied parameters.
Among biochemical markers, **uric acid** and **albumin** yielded the highest AUC values (0.91 and 0.88, respectively), indicating strong discriminative ability (Figures 3and 4).

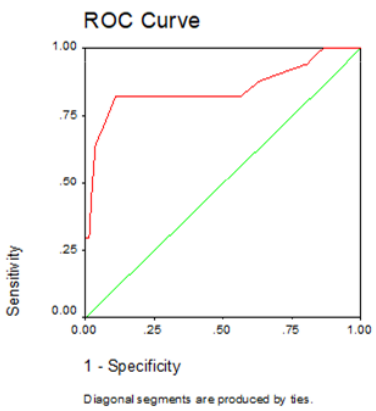

Figure 3: Receiver operating characteristic (ROC) curve for uric acid level in predicting pre-eclampsia (AUC ≈ 0.91).

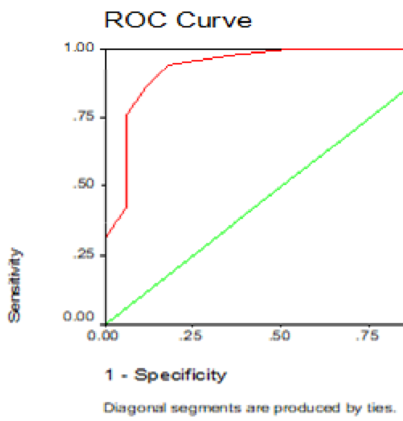

Figure 4: ROC curve for serum albumin level in predicting pre-eclampsia (AUC ≈ 0.88).

Doppler parameters also demonstrated high diagnostic accuracy, with uterine artery RI and PI AUCs of 0.90 and 0.87, respectively (Figures 5).

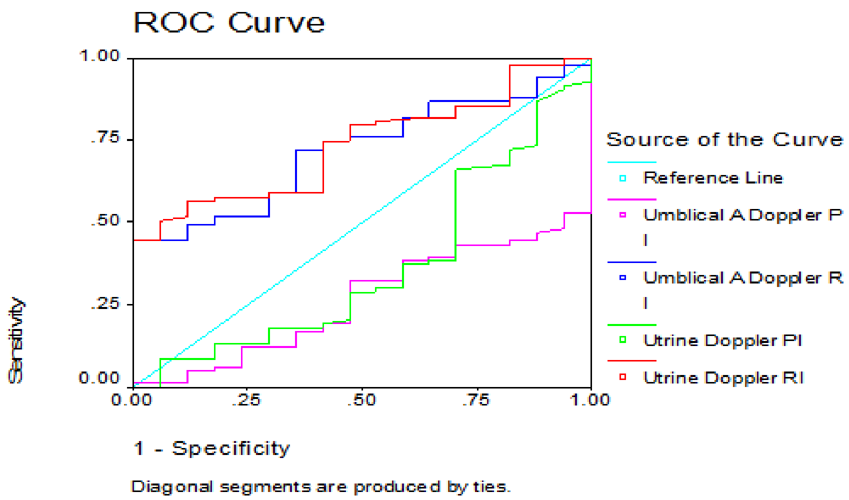

Figure 5: ROC curve(s) for Doppler parameters (uterine and umbilical artery RI/PI) in predicting pre-eclampsia. Uterine RI and PI AUCs ≈ 0.90 and 0.87, respectively.

The sensitivity of biochemical markers only (95.0% sensitivity, 68.0% specificity), while the biochemical markers and Doppler markers increase the sensitivity to 98.0% and specificity 85.0% (Tables 11).

Table 11: Sensitivity and specificity of different markers.

Marker Set	Sensitivity (%)	Specificity (%)
Biochemical markers (Uric acid + Albumin)	95.0	68.0
Biochemical + Doppler markers	98.0	85.0

Pregnancy Outcomes

Among the 16 women who developed pre-eclampsia, **3 experienced severe disease** requiring early delivery at 29, 34, and 36 weeks. One intrauterine fetal demise was recorded at 29 weeks in a case of severe early-onset pre-eclampsia.

The remaining 13 women delivered, although mean birth weight was significantly lower than in the normotensive group ($p < 0.001$).

Discussion

In this prospective study of healthy primigravidae with singleton pregnancies, we demonstrated that serial biochemical monitoring specifically serum uric acid and albumin—combined with Doppler velocimetry of the uterine and umbilical arteries, can effectively differentiate women who later develop pre-eclampsia (PE) from those who remain normotensive. Serum uric acid levels rose significantly from mid-gestation onwards in women who developed PE, and the uricemia ratio (UAr) exceeded 1.5 before the clinical onset of the disease. In contrast, serum creatinine remained within normal limits and did not discriminate between groups. Doppler indices (uterine and umbilical artery resistance and pulsatility indices) were also significantly elevated in the PE group, supporting the concept of impaired uteroplacental perfusion. These results underscore the multifactorial nature of PE and highlight practical, accessible markers for early risk stratification.

Pathophysiological Interpretations

The findings align with the well-established two-stage theory of pre-eclampsia. Stage I involves abnormal placentation and defective spiral artery remodelling, leading to placental hypoxia and oxidative stress. Stage II manifests as the maternal syndrome characterized by endothelial dysfunction, hypertension, proteinuria, and end-organ damage [1,2].

The elevated uterine and umbilical artery impedance observed early in pregnancy among the PE group reflects the first stage of placental dysfunction, while the subsequent rise in serum uric acid and fall in albumin suggest progression to systemic endothelial injury and intravascular volume contraction characteristic of stage II [3,4]. Importantly, the absence of creatinine elevation indicates that renal dysfunction is a secondary, later event rather than an initiating factor. This supports evidence that uric acid elevation is more likely a marker of oxidative stress and endothelial damage than of renal impairment [5,6].

Comparison with Previous Literature

Our results are consistent with previous findings that single biochemical markers have limited predictive value, but their predictive capacity improves when combined with Doppler indices or maternal factors [7,8].

Kuc et al. reported that combinations of serum biomarkers and uterine artery Doppler achieved better detection rates for PE, though variability across studies was high [9]. Similarly, Stepan et al. (2020) demonstrated that combining uterine artery pulsatility index (PI) with the sFlt-1/PlGF ratio and maternal characteristics significantly enhanced prediction accuracy, particularly for early-onset disease [10].

In the present study, a UAr cut-off >1.5 achieved excellent negative predictive value (99.5%) and an AUC exceeding 0.9, reinforcing its value in excluding disease rather than confirming diagnosis. This aligns with large-scale meta-analyses showing that uric acid is a reliable negative predictor of PE progression [11].

Doppler studies have shown that uterine artery RI/PI measured in the second trimester provides reasonable predictive performance (AUC ≥ 0.80), especially for early-onset PE, though sensitivity for late-onset disease remains modest. Wu et al. (2021) found that a right uterine artery RI cut-off around 0.66 yielded high specificity (84–91%) but moderate sensitivity (63–74%) [12]. The serial Doppler approach in our study likely improved accuracy by capturing evolving hemodynamic changes instead of relying on single-point measurements.

Clinical Implications

With growing emphasis on risk-based antenatal care—such as early initiation of low-dose aspirin prophylaxis, intensified surveillance, and timely delivery—our findings support a practical screening algorithm.

Healthy primigravidae could undergo serial uric acid and albumin testing with concurrent uterine and umbilical artery Doppler assessments at predefined gestational intervals. A UAr below 1.5 identifies low-risk women who can continue routine care, while values ≥1.5 or abnormal Doppler indices warrant closer monitoring and possible referral to high-risk clinics.

This approach offers a cost-effective alternative in low- and middle-income settings where advanced angiogenic marker assays (like sFlt-1/PlGF) are not feasible. The non-significant role of creatinine emphasizes the value of focusing on simple biochemical markers that reflect early pathophysiological changes rather than late renal involvement [13,14].

Strengths and Limitations

The strengths of our study include its prospective design, serial monitoring strategy, and the combined use of biochemical and Doppler indices. The identification of a practical UAr threshold and dynamic Doppler follow-up enhances its clinical relevance. However, limitations include the relatively small number of women who developed PE (16/92), which may affect statistical power and generalizability. The study's restriction to primigravidae and a single-centre setting limits its external validity. Moreover, we did not assess angiogenic markers such as sFlt-1 and PlGF, which have become valuable adjuncts in modern screening protocols [15]. Finally, predictive performance for late-onset PE was not separately analysed, though existing literature suggests lower sensitivity for this subgroup [16,17].

Future Research Directions

Future studies should aim for larger, multicentric designs that include both primigravidae and multiparous women to validate and refine the UAr threshold. Incorporating first-trimester angiogenic biomarkers (PlGF, sFlt-1) or emerging candidates like high-temperature requirement protease A4 (HtrA4) could further improve early prediction accuracy [18,19]. Recent reports indicate that combining HtrA4 with uterine artery Doppler achieves sensitivity up to 76% and specificity near 90% for early-onset PE [20].

Additionally, defining optimal timing for Doppler assessment (second vs. third trimester) and frequency of uric acid and albumin testing would refine screening algorithms. Future cost-effectiveness analyses would clarify the practicality of implementing this combined approach, especially in resource-constrained healthcare systems.

Conclusion

In conclusion, this study confirms that combining serial serum uric acid and albumin measurements with uterine and umbilical artery Doppler indices provides a robust, practical, and low-cost predictive approach for pre-eclampsia in primigravidae. A UAr cut-off >1.5 offers high negative predictive value, while abnormal Doppler findings identify those with placental perfusion impairment. Together, these markers facilitate early identification, timely intervention, and improved maternal and perinatal outcomes.

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