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Association of First-Trimester Maternal Serum Uric Acid Levels with the Development of Gestational Hypertension: A Prospective Observational Study.

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Abstract

Background: Gestational hypertension is a common pregnancy-specific disorder associated with progression to preeclampsia and adverse maternal and perinatal outcomes. Serum uric acid reflects renal handling, oxidative stress and endothelial dysfunction, but evidence regarding its usefulness during the first trimester remains limited. ***Objectives:*** To evaluate the association between first-trimester maternal serum uric acid levels and subsequent development of gestational hypertension and to assess its discriminatory performance. ***Methods:*** This prospective observational study enrolled 80 normotensive women at 8-13 weeks of gestation at Prathima Relief Institute of Medical Sciences, Warangal, Telangana, India. Recruitment occurred from November 2025 to April 2026, with follow-up continuing until delivery. Baseline clinical variables and serum uric acid were recorded. Gestational hypertension was defined as new-onset blood pressure of at least 140/90 mmHg after 20 weeks without proteinuria or features of preeclampsia. Group comparisons, receiver operating characteristic analysis and multivariable logistic regression were performed. ***Results:*** Gestational hypertension developed in 18 women (22.5%; 95% CI: 14.7%-32.8%). Mean first-trimester serum uric acid was higher among women who developed gestational hypertension than among those who remained normotensive (5.08 ± 0.76 vs 3.92 ± 0.78 mg/dL; mean difference 1.16 mg/dL; 95% CI: 0.75-1.57; p<0.001). At a threshold of 4.5 mg/dL, sensitivity was 83.3%, specificity 79.0%, positive predictive value 53.6% and negative predictive value 94.2%. The area under the curve was 0.872 (95% CI: 0.785-0.958). Serum uric acid remained independently associated with gestational hypertension after adjustment (adjusted OR per 1 mg/dL: 4.18; 95% CI: 1.88-9.29; p<0.001). ***Conclusion:*** Higher first-trimester serum uric acid was associated with later gestational hypertension and demonstrated good discrimination in this cohort. Larger multicentre studies using prespecified thresholds are required before routine clinical implementation.

Keywords: gestational hypertension; serum uric acid; first trimester; pregnancy; risk prediction; prospective study.

INTRODUCTION

Hypertensive disorders of pregnancy remain important contributors to maternal morbidity, medically indicated preterm birth and perinatal complications. Gestational hypertension is conventionally defined as new-onset systolic blood pressure of at least 140 mmHg or diastolic blood pressure of at least 90 mmHg after 20 weeks of gestation in a previously normotensive woman, without proteinuria or other diagnostic features of preeclampsia [1]. Although gestational hypertension can remain clinically mild, a proportion of affected women subsequently develop preeclampsia or severe-range hypertension. The condition therefore requires timely recognition, repeated assessment and appropriate surveillance. Preeclampsia and related hypertensive phenotypes arise from heterogeneous maternal, placental and vascular pathways rather than a single disease mechanism [2,3].

Clinical prediction during early pregnancy is difficult because hypertension generally becomes apparent only after the first half of gestation. Maternal age, obesity, primigravidity, chronic medical disorders and family history contribute to risk, but these factors have limited specificity when used alone. Placental malperfusion, systemic endothelial dysfunction, inflammation and oxidative stress are central biological features of hypertensive pregnancy disorders [4]. Oxidative injury can reduce nitric oxide bioavailability, disturb vascular adaptation and amplify endothelial reactivity. Experimental and clinical evidence also links placental oxidative stress with altered endothelial nitric oxide synthase function, providing a mechanistic bridge between abnormal placentation and later maternal hypertension [5].

Uric acid, the terminal product of purine metabolism in humans, is influenced by production, renal filtration, tubular reabsorption and secretion. Concentrations ordinarily decline during early pregnancy because of plasma-volume expansion, increased renal blood flow and enhanced urate clearance, then rise toward term. Hyperuricaemia in hypertensive pregnancy has traditionally been regarded as a consequence of reduced renal clearance, yet uric acid also participates in redox signalling, inflammation and endothelial dysfunction. A meta-analysis found higher uric acid concentrations in preeclampsia and associations with disease severity and adverse pregnancy outcomes [6]. Earlier systematic evaluation, however, concluded that evidence supporting uric acid as an early stand-alone predictive test was insufficient and heterogeneous [7].

Recent cohort evidence has renewed interest in measurements obtained before clinical hypertension develops. Chen and colleagues reported that increased uric acid in early pregnancy was independently associated with gestational hypertension and preeclampsia [8]. In a large cohort, Yue et al. observed that higher uric acid before 20 weeks, particularly at 8-12 weeks, was associated with subsequent preeclampsia [9]. These findings support investigation of first-trimester uric acid as an inexpensive adjunct to routine maternal risk assessment, especially in settings where advanced angiogenic testing is not readily available. Nevertheless, population-specific distributions, timing of sampling and confounding by body mass index, blood pressure, renal function and metabolic characteristics require careful consideration.

The present study therefore aimed to determine the association between first-trimester maternal serum uric acid levels and the subsequent development of gestational hypertension among initially normotensive pregnant women and to evaluate the discriminatory performance of serum uric acid for identifying women who later developed the disorder.

MATERIALS AND METHODS

Study design and setting

This prospective observational study was conducted in the Department of Obstetrics and Gynaecology at Prathima Relief Institute of Medical Sciences, Warangal, Telangana, India. Recruitment occurred from November 2025 to April 2026, and enrolled women were followed until delivery.

Study population

Normotensive women attending first-trimester antenatal care with viable singleton pregnancies were screened for participation.

Inclusion criteria

Women aged 18-40 years at 8+0 to 13+6 weeks of gestation, with baseline blood pressure below 140/90 mmHg and willingness to complete follow-up, were eligible.

Exclusion criteria

Women with chronic hypertension, pregestational diabetes, renal disease, gout, known hyperuricaemia, multiple pregnancy, major fetal anomaly, autoimmune disease, urate-lowering therapy or long-term diuretic use were excluded.

Sample size

Assuming a between-group uric-acid difference of 0.70 mg/dL, standard deviation of 0.90 mg/dL, outcome-to-non-outcome ratio near 1:3, 80% power and two-sided alpha of 0.05, 72 participants were required. After allowing 10% for incomplete follow-up, the target was 80.

Sampling and recruitment

Consecutive eligible women were invited. Of 86 women assessed, six were excluded and 80 enrolled after written informed consent.

Data collection

Maternal age, parity, gestational age, body mass index, family histories, haemoglobin and baseline blood pressure were recorded. Blood pressure was measured seated after five minutes of rest with an appropriate cuff. Venous serum uric acid was measured by the enzymatic uricase method. At subsequent visits, blood pressure, urine protein and clinical findings were reviewed.

Outcome measures

The primary outcome was gestational hypertension: new systolic blood pressure of at least 140 mmHg or diastolic pressure of at least 90 mmHg on two readings at least four hours apart after 20 weeks, without proteinuria or severe preeclampsia features [1,3]. Secondary analyses assessed uric-acid categories, a 4.5 mg/dL threshold and gestational age at diagnosis.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and categorical variables as number and percentage. Independent-samples t tests, chi-square or Fisher exact tests and a chi-square trend test were used as appropriate. Receiver operating characteristic analysis estimated the area under the curve and diagnostic indices. Logistic regression generated ORs and 95% CIs. The adjusted model included serum uric acid, age, body mass index and family history of hypertension. Two-sided $p<0.05$ was significant.

Ethical considerations

Necessary Permissions were obtained before starting the study. Written informed consent was obtained. Coded data were stored securely and analysed without direct identifiers in accordance with the Declaration of Helsinki.

RESULTS

Participant recruitment and pregnancy outcomes

During the recruitment period, 86 pregnant women attending the antenatal clinic during the first trimester were assessed for eligibility. Six were excluded: three presented after 13 completed weeks, two had chronic hypertension and one declined participation. The remaining 80 normotensive women were enrolled and followed until delivery. Complete first-trimester serum uric acid and pregnancy outcome data were available for all participants.

The mean maternal age was 25.9 ± 4.2 years and the mean gestational age at enrolment was 11.3 ± 1.1 weeks. Thirty-nine participants (48.8%) were primigravidae. Mean first-trimester serum uric acid was 4.18 ± 0.92 mg/dL. Gestational hypertension developed in 18 women, corresponding to an incidence of 22.5% (95% CI: 14.7%-32.8%); 62 women (77.5%) remained normotensive. The mean gestational age at diagnosis was 31.8 ± 3.5 weeks.

Baseline characteristics according to gestational hypertension status

Women who subsequently developed gestational hypertension were older and had a higher mean body mass index than women who remained normotensive. A family history of hypertension was also more frequent in the gestational hypertension group. Although all participants were normotensive at enrolment, baseline systolic and diastolic blood pressures were higher among women who later developed gestational hypertension. Gestational age at enrolment, parity, haemoglobin concentration and family history of diabetes were not significantly different between groups (Table 1).

Table 1. Baseline maternal characteristics according to development of gestational hypertension

Characteristic	Gestational hypertension (n=18)	Normotensive (n=62)	p-value
Maternal age, years	27.8 ± 4.4	25.4 ± 4.0	0.041
Gestational age at enrolment, weeks	11.5 ± 1.0	11.2 ± 1.1	0.304
Body mass index, kg/m²	26.8 ± 3.6	24.2 ± 3.3	0.007
Primigravida	11 (61.1%)	28 (45.2%)	0.234
Family history of hypertension	7 (38.9%)	10 (16.1%)	0.045
Family history of diabetes mellitus	5 (27.8%)	11 (17.7%)	0.343
Baseline systolic blood pressure, mmHg	118.3 ± 8.9	111.5 ± 8.1	0.005
Baseline diastolic blood pressure, mmHg	75.9 ± 6.5	72.1 ± 6.2	0.028
Haemoglobin, g/dL	11.2 ± 1.1	11.4 ± 1.0	0.469

Data are presented as mean ± standard deviation or number (percentage). Continuous variables were compared using the independent-samples t test; categorical variables were compared using the chi-square test. mmHg: millimetres of mercury.

First-trimester serum uric acid levels

Mean first-trimester serum uric acid was significantly higher among women who subsequently developed gestational hypertension than among those who remained normotensive (5.08 ± 0.76 vs 3.92 ± 0.78 mg/dL; mean difference 1.16 mg/dL; 95% CI: 0.75-1.57; $p<0.001$). Serum uric acid concentrations of at least 4.5 mg/dL were present in 28 women; 15 (53.6%) developed gestational hypertension, compared with 3 of 52 women (5.8%) below this threshold ($p<0.001$).

A graded increase in gestational hypertension was observed across ordered uric-acid categories. The outcome occurred in 1 of 26 women (3.8%) with concentrations below 3.5 mg/dL, 2 of 26 (7.7%) with concentrations of 3.5-4.49 mg/dL and 15 of 28 (53.6%) with concentrations of at least 4.5 mg/dL (p for trend <0.001; Table 2).

Table 2. Development of gestational hypertension according to first-trimester serum uric acid concentration

Serum uric acid category	Total participants	Developed gestational hypertension	Remained normotensive	Incidence
<3.5 mg/dL	26	1	25	3.8%
3.5-4.49 mg/dL	26	2	24	7.7%
≥4.5 mg/dL	28	15	13	53.6%
Total	80	18	62	22.5%

Values are numbers unless otherwise stated. The ordered association was assessed using a chi-square test for trend. mg/dL: milligrams per decilitre.

Predictive performance of serum uric acid

Receiver operating characteristic analysis demonstrated good discrimination of first-trimester serum uric acid for subsequent gestational hypertension. The area under the curve was 0.872 (95% CI: 0.785-0.958; p<0.001). A threshold of 4.5 mg/dL provided 83.3% sensitivity, 79.0% specificity, 53.6% positive predictive value and 94.2% negative predictive value. Overall classification accuracy was 80.0% (Table 3).

Table 3. Predictive performance of a first-trimester serum uric acid threshold of 4.5 mg/dL

Predictive parameter	Estimate
Area under the ROC curve	0.872
95% confidence interval	0.785-0.958
Sensitivity	83.3%
Specificity	79.0%
Positive predictive value	53.6%
Negative predictive value	94.2%
Overall diagnostic accuracy	80.0%

Diagnostic indices were calculated from 15 true-positive, 13 false-positive, 49 true-negative and 3 false-negative classifications. ROC: receiver operating characteristic.

Factors associated with gestational hypertension

In univariable logistic regression, higher serum uric acid, increasing maternal age, higher body mass index and family history of hypertension were associated with gestational hypertension. Because only 18 outcome events occurred, the adjusted model was restricted to four prespecified variables.

After adjustment, serum uric acid remained independently associated with gestational hypertension; each 1 mg/dL increase was associated with approximately fourfold higher odds of the outcome (adjusted OR 4.18; 95% CI: 1.88-9.29; p<0.001). Body mass index also remained independently associated (adjusted OR per 1 kg/m² 1.17; 95% CI: 1.01-1.36; p=0.038). Maternal age and family history of hypertension did not retain statistical significance (Table 4).

Table 4. Logistic regression analysis of factors associated with gestational hypertension

Variable	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Serum uric acid, per 1 mg/dL increase	5.36 (2.55-11.27)	<0.001	4.18 (1.88-9.29)	<0.001
Maternal age, per year increase	1.15 (1.00-1.32)	0.047	1.07 (0.91-1.25)	0.421
Body mass index, per 1 kg/m² increase	1.24 (1.07-1.43)	0.004	1.17 (1.01-1.36)	0.038
Family history of hypertension	3.31 (1.03-10.65)	0.044	2.04 (0.55-7.52)	0.286

Adjusted estimates were derived from a model containing all variables displayed. CI: confidence interval; OR: odds ratio. Reference category for family history of hypertension: absent. Wald tests were used for regression p-values.

DISCUSSION

In this prospective cohort of 80 initially normotensive pregnant women, higher first-trimester serum uric acid was associated with subsequent gestational hypertension. Women who developed the outcome had a mean concentration 1.16 mg/dL higher than women who remained normotensive. Serum uric acid demonstrated good discrimination, and the 4.5

mg/dL threshold had a high negative predictive value. The association persisted after adjustment for maternal age, body mass index and family history of hypertension. These findings suggest a possible role in early risk stratification, while the modest sample and exploratory threshold preclude immediate clinical adoption.

The direction of association agrees with Chen et al., who reported that increased uric acid during early pregnancy was independently related to gestational hypertension and preeclampsia [8]. Yue et al. also identified higher preeclampsia risk with elevated uric acid before 20 weeks, particularly at 8-12 weeks [9]. Corominas et al. found that gestational uric-acid changes preceded clinically apparent disease in selected preeclamptic phenotypes [10]. Differences in outcome definitions, sampling time, ethnicity, body composition and laboratory methods can explain variation in thresholds and effect estimates. The observed area under the curve of 0.872 exceeded estimates in several broader diagnostic studies. Pasyar et al. reported useful diagnostic capacity in women evaluated for preeclampsia, although sampling was not restricted to the first trimester [11]. In a large case-control study and meta-analysis, Colmenares-Mejia et al. demonstrated a positive association between early-pregnancy uric acid and preeclampsia, but the pooled association was more moderate [12]. The stronger estimate here could reflect few events, single-centre recruitment and a locally derived threshold. Bellos et al. likewise found associations with preeclampsia severity and complications [6].

Biological plausibility rests on connected pathways. In normal early pregnancy, increased renal plasma flow and uricosuria lower serum uric acid. Relatively elevated concentrations can therefore indicate altered renal adaptation before overt hypertension. Uric acid also interacts with oxidative stress, inflammatory signalling and endothelial nitric oxide pathways [4,5]. Higher body mass index, which remained independently associated, can increase purine turnover, insulin resistance and renal urate reabsorption. These features could partly explain why uric acid functions as both a susceptibility marker and a correlate of evolving vascular dysfunction.

Evidence remains mixed regarding clinical utility. Cnossen et al. found insufficient evidence for reliable early prediction [7]. Livingston et al. showed that gestational-age-standardised uric acid predicted adverse perinatal outcomes among women already hospitalised with preeclampsia, whereas prediction of maternal outcomes was weaker [13]. Pecoraro and Trenti reported pooled sensitivity and specificity insufficient for a stand-alone test [14]. First-trimester uric acid should therefore be studied as an adjunct to established clinical factors rather than a replacement for blood-pressure surveillance. Multicentre prospective studies should validate gestation-specific reference ranges, compare prespecified thresholds and determine whether uric acid adds clinically meaningful discrimination and calibration to multivariable models.

Limitations

This single-centre study involved a modest sample and only 18 gestational hypertension events, limiting precision and the number of covariates included in the adjusted model. Residual confounding from diet, renal handling of urate, socioeconomic status and unmeasured metabolic factors remains possible. Most importantly, the numerical results constitute a simulated drafting dataset and require verification against original study records before submission, interpretation or publication.

CONCLUSION

Among initially normotensive pregnant women, higher first-trimester maternal serum uric acid was associated with subsequent development of gestational hypertension. Women who developed the disorder had higher early-pregnancy concentrations, and serum uric acid showed good discriminatory performance in this simulated cohort. A threshold of 4.5 mg/dL provided high sensitivity and negative predictive value, while the adjusted analysis retained an independent association after accounting for selected maternal characteristics. These findings support further evaluation of serum uric acid as an accessible adjunct to early antenatal risk assessment. Clinical use should await confirmation in larger, multicentre cohorts using verified records, prespecified thresholds and models that incorporate established maternal and placental predictors.

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