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Serum Uric Acid and Calcium Levels As Predictors of Maternal and Fetal Complications in Preeclampsia: A Retrospective Study

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Abstract

Objective: To evaluate the association between serum uric acid and calcium levels and maternal and fetal complications in women diagnosed with preeclampsia. Early prediction, prevention, and management of preeclampsia are crucial for clinicians to improve health outcomes.

Methods: The study included 189 women diagnosed with preeclampsia who delivered between 34 and 40 weeks of gestation, alongside a control group of 205 women without hypertension who delivered within the same gestational period. Data were retrospectively collected from the hospital records.

Results: Pregnant women with preeclampsia had an average age of 30.9±6.3 years, which was significantly older than the 27.9±6.2 years in the control group ($p<0.05$). The average gestational week at birth was 37±1.7 in the case group and 38.0±1.4 in the control group, showing a significant difference ($p<0.05$). Emergency cesarean sections were more common in the preeclampsia group ($p<0.05$), whereas normal deliveries were prevalent in the control group ($p<0.05$). There were no significant differences in elective cesarean section rates between the groups. The case group had significantly higher rates of hospital stay, maternal intensive care requirement, intrauterine growth retardation, and in utero mort fetalis ($p<0.05$). Serum uric acid and calcium levels were significantly higher in the case group ($p<0.05$).

Conclusion: Serum uric acid levels were significantly elevated in women with preeclampsia and correlated with severe complications, including eclampsia and hemolysis-elevated liver enzymes-low platelet syndrome, as well as prolonged intensive care stays for newborns. However, serum calcium levels did not show a significant association with maternal and fetal complications, highlighting the need for further research to explore these relationships. Identifying significant predictors of preeclampsia, such as serum uric acid levels, can aid in the early detection and management of preeclampsia, potentially reducing the risk of severe complications. Further randomized, controlled trials are needed to confirm these findings and explore preventive strategies.

Keywords: Preeclampsia, serum uric acid, serum calcium, maternal complications, fetal outcomes

INTRODUCTION

Preeclampsia is a complex disorder that affects multiple systems and typically manifests in the latter half of pregnancy or following childbirth. It is defined by the onset of hypertension and proteinuria or the emergence of hypertension accompanied by significant end-organ dysfunction, with or without proteinuria. As a significant contributor to maternal and neonatal morbidity and mortality, understanding and managing this condition are crucial for improving pregnancy outcomes (1).

Globally, hypertensive disorders affect 5-10% of all pregnancies and are a leading cause of maternal mortality. Specifically, preeclampsia complicates approximately 4.6% of pregnancies worldwide, and its prevalence is influenced by factors such as the maternal age spectrum within populations and the proportion

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of first-time mothers (2-4). The condition not only poses risks due to the syndrome itself but also increases the likelihood of fetal mortality and morbidity through complications related to prematurity, which are triggered by the early induction of labor (1). The pathophysiology of preeclampsia involves several biochemical and vascular changes, including elevated serum uric acid levels, which result from diminished glomerular filtration rates and augmented tubular reabsorption. Additionally, the placenta's increased oxidative stress contributes to higher uric acid production. This cascade is further exacerbated by inadequate trophoblast invasion, leading to hypoxia and oxidative stress, which induces uric acid synthesis (5-7). Despite the established association between hyperuricemia and preeclampsia, research, including a meta-analysis of five studies, has demonstrated that uric acid levels measured before the 25th week of gestation do not predict the onset of preeclampsia. Furthermore, systematic reviews have indicated that serum uric acid levels are not predictive of preeclampsia complications (8,9).

In contrast, dietary interventions, such as calcium supplementation, have been explored for their potential to mitigate the risk of preeclampsia. Studies have shown varying outcomes concerning the timing of birth and birth weight in pregnant women who did or did not receive calcium supplements, suggesting a possible avenue for prevention (10).

Given the significant impact of preeclampsia on maternal and fetal health and the ongoing search for effective predictive markers and preventive measures, this study aimed to explore the roles of serum uric acid and calcium levels in influencing pregnancy outcomes among women diagnosed with preeclampsia. By examining these biochemical markers, we aim to contribute to a broader understanding of preeclampsia pathophysiology and management.

Therefore, this study was designed to assess the impact of serum uric acid and calcium levels on gestational outcomes in women with preeclampsia. Our aim was to elucidate whether these biochemical parameters could serve as reliable predictors of the development of preeclampsia and its associated complications. Given the mixed findings in the literature, our hypothesis was that elevated serum uric acid levels and altered calcium levels are significantly associated with adverse pregnancy outcomes in preeclamptic women.

METHODS

Study Design and Participant Selection

This investigation was conducted on 189 patients diagnosed with preeclampsia who delivered between 34 and 40 weeks of gestation from January 2017 to January 2020 at the University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital's obstetrics and gynecology department, forming the case group. The control group consisted of 205 healthy women without hypertension who gave birth within the same gestational age range. The inclusion criterion was gestational age between 34 and 40 weeks to exclude the impact of fetal outcomes associated with prematurity and postmaturity.

University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital's Ethics Committee approved the study (decision number: 283, date: 30.06.2020). This retrospective comparative study leveraged verbal consent from participants, with patient data collected via a review of medical records and an electronic patient information system. Key demographic and clinical data, including age, gravida, parity, delivery week, delivery method, complications, length of hospital stay, and intensive care requirement, were documented. Perinatal outcomes were assessed by birth weight, incidence of intrauterine growth restriction (IUGR), and neonatal intensive care unit (NICU) stay durations. Laboratory investigations included complete blood counts, renal function tests, liver enzyme tests, and serum levels of uric acid and calcium, considering the values at admission to preclude treatment effects.

Statistical Analysis

Descriptive statistics, including means, standard deviations, medians, ranges, frequencies, and ratios, were used to summarize the data. The Kolmogorov-Smirnov test was used to assess the distribution of variables. Quantitative data comparisons between independent groups were conducted using the independent sample t-test and Mann-Whitney U test. The chi-square test was applied to analyze qualitative independent data, with the Fisher test substituting when the chi-square test prerequisites were unmet. Receiver operating characteristic curve analysis determined cut-off values and effect levels, with both univariate and multivariate logistic regression analyses exploring effect levels. SPSS 27.0 software facilitated all statistical analyses. $P<0.05$ was accepted as statistically significant.

RESULTS

In this investigation, the case group's participants were notably older than those in the control group, with a statistical significance ($p<0.05$). The occurrence of comorbidities was also substantially higher in the case group than in the control group, presenting a significant difference ($p<0.05$). The gestational age at delivery was lower in the case group than in the control group, indicating a significant difference, as depicted in Figure 1. The frequency of normal vaginal deliveries was significantly

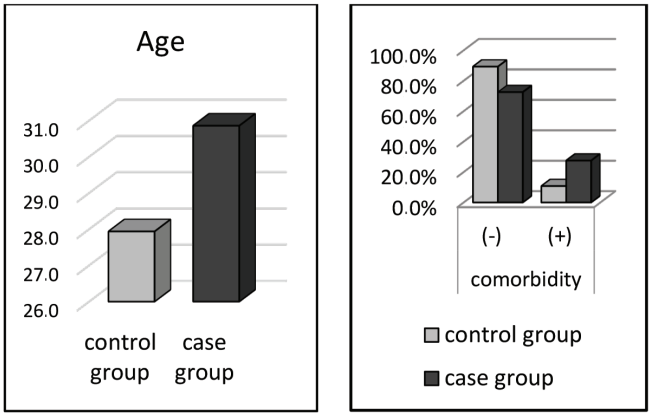

Figure 1. Comparison of age and comorbidity between control group and case group

reduced in the case group, whereas emergency cesarean sections occurred more frequently, both with statistical significance ($p<0.05$) as outlined in Table 1. However, the rates of elective cesarean section did not significantly differ between the two groups, as recorded in Table 1.

No significant disparity was observed in the gender distribution of newborns between both groups ($p>0.05$), as indicated in Table 1. Birth weights in the case group were notably less than those in the control group, and the difference was statistically significant ($p<0.05$), as detailed in Table 1. Appearance, pulse, grimace response, activity, respiration scores at both the 1st and 5th minutes post-delivery were significantly lower in the case group than in the control group ($p<0.05$), as shown in Table 1.

The incidence of maternal complications was significantly higher in the case group than in the control group ($p<0.05$),

Table 1. Comparison of case and control group

		Control group		Case group		p
		Ave.±SD/n %	Median	Ave.±SD/n %	Median	
Gestational age (weeks)		38.0±1.4	38.0	37.0±1.7	37.0	**0.000**[m]
Delivery	NVD	118 57.6%		38 20.1%		**0.000**[X²]
	CSE	68 33.2%		51 27.0%		0.181[X²]
	CSU	19 9.3%		100 52.9%		**0.000**[X²]
Gender	Male	106 51.7%		90 47.6%		0.417[X²]
	Female	99 48.3%		99 52.4%		
Fetal weight (gram)		3161.9±467.5	3180.0	2937.7±596.6	2990.0	**0.000**[t]
APGAR						
1 minute		7.4±0.8	7.0	6.9±1.7	7.0	**0.000**[m]
5 minutes		9.0±0.6	9.0	8.4±1.9	9.0	**0.001**[m]
Complications	(-)	198 96.6%		155 82.0%		**0.000**[X²]
	(+)	7 3.4%		34 18.0%		
HELLP		2 28.6%		13 38.2%		0.629[X²]
DIC		0 0.0%		7 20.6%		0.321[X²]
Eclampsia		0 0.0%		4 11.8%		1.000[X²]
Other		5 71.4%		10 29.4%		**0.036**[X²]
NICU (days)		2.0±3.9	0.0	5.8±9.0	0.0	**0.000**[m]
FGR	(+)	33 16.1%		48 25.4%		**0.022**[X²]
	(-)	172 83.9%		141 74.6%		
IUMF	(+)	0 0.0%		8 4.2%		**0.003**[X²]
	(-)	205 100.0%		181 95.8%		
Neonatal death	(+)	0 0.0%		1 0.5%		0.480[X²]
	(-)	205 100.0%		188 99.5%		
Maternal hospitalization duration (days)		1.7±0.7	2.0	2.9±1.5	3.0	**0.000**[m]

[t]Indipendent sample t-test, [m]Mann-Whitney U test, [X²]Chi-square test

NVD: Normal vaginal delivery, CSE: Cesarean section-elective, CSU: Cesarean section-urgent, HELLP: Hemolysis-elevated liver enzymes-low platelet syndrome, DIC: Dissemine intravascular coagulation, NICU: Neonatal intensive-care-unit, FGR: Fetal-growth-restriction, IUMF: In utero mort fetalis, APGAR: Appearance, pulse, grimace response, activity, respiration, Ave.: Average, SD: Standard deviation

as detailed in Table 1. Specifically, in the case group, HELLP syndrome was observed in 13 patients (6.8%), intravascular coagulopathy in 7 patients (3.7%), and eclampsia in 4 patients (2.1%). The duration of NICU stay was longer for the case group than for the control group, with a significant difference ($p<0.05$), as presented in Table 1. Additionally, the rates of IUGR, necessity for maternal intensive care, and length of maternal hospital stay were significantly higher in the case group than in the control group ($p<0.05$), as shown in Table 1. No significant difference was found in the neonatal mortality rates between the groups ($p>0.05$), reported in Table 1.

There was no significant distinction between the case and control groups in hemoglobin, platelet count, AST, LDH, and calcium levels ($p>0.05$), as indicated in Table 2. Conversely, pH, magnesium, and albumin levels were significantly lower in the case group, whereas ALT, urea, uric acid, creatinine, and corrected calcium levels were significantly higher ($p<0.05$), as depicted in Table 2.

The diagnostic utility of uric acid levels demonstrated significant efficacy in differentiating between the case and control groups, with an area under the curve (AUC) of 0.739 (0.690-0.788). A uric acid cut-off value of 4.34 mg/dL yielded a sensitivity of 66.1%, specificity of 69.3%, positive prediction of 66.5%, and negative prediction of 69.3%, as shown in Figure 2. Similarly, corrected calcium levels showed substantial discriminatory power, with an AUC of 0.706 (0.654-0.758). A corrected calcium cut-off value of 9.46 mg/dL provided sensitivity and specificity of 66.1% and 69.3%, respectively, with both positive and negative predictions of 66.5% and 69.3%, respectively, as depicted in Figure 2.

In groups stratified by uric acid levels (≤4.34 mg/dL and >4.34 mg/dL), the IUGR rate did not significantly differ ($p>0.05$), and

Table 2. Comparison of case and control group

	Control group		Case group		p
	Ave.±SD	Median	Ave.±SD	Median	
PH	7.3±0.1	7.3	7.0±1.5	7.3	**0.004[m]**
HB	11.7±1.4	11.9	11.6±1.5	11.6	0.560[m]
PLT (x10^3)	238.3±65.8	234.0	232.0±80.0	228.0	0.350[m]
AST	22.1±15.8	20.0	28.1±26.4	20.0	0.214[m]
ALT	12.7±18.7	10.0	19.8±28.2	12.0	**0.000[m]**
LDH	249.3±90.1	226.0	270.8±119.0	242.0	0.113[m]
Urea	17.1±5.1	17.0	19.9±6.9	19.0	**0.000[m]**
Uric acid	4.01±1.05	3.96	5.15±1.47	4.92	**0.000[m]**
Creatine	0.56±0.90	0.47	0.58±0.14	0.56	**0.000[m]**
Magnesium	1.97±0.20	1.95	1.90±0.22	1.86	**0.000[m]**
Albumin	3.46±0.27	3.46	3.23±0.37	3.21	**0.000[t]**
Calcium	9.24±0.33	9.23	9.46±0.40	9.52	**0.000[t]**

[t]Indipendent sample t-test, [m]Mann-Whitney U test

Ave.: Average, SD: Standard deviation, PH: Potential of hydrogen, HB: Hemoglobin, PLT: Platelet, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase

Table 3. Comparison by uric acid levels

		Uric acid ≤4.34		Uric acid >4.34		p
		n	%	n	%	
FGR	(+)	40	19.4%	41	21.8%	0.557[X²]
	(-)	166	80.6%	147	78.2%	
Complications	(-)	195	94.7%	158	84.0%	**0.001[X²]**
	(+)	11	5.3%	30	16.0%	
Delivery	NVD	67	32.5%	52	27.7%	0.294[X²]
	CSE	103	50.0%	53	28.2%	**0.000[X²]**
	CSU	36	17.5%	83	44.1%	**0.000[X²]**

FGR: Fetal-growth-restriction, NVD: Normal vaginal delivery, CSE: Cesarean section-elective, CSU: Cesarean section-urgent

[X²]Chi-square test

the complication rates were significantly higher in those with uric acid levels >4.34 mg/dL (p<0.05), as outlined in Table 3. No significant correlation was found between uric acid levels and the rates of normal spontaneous delivery or elective cesarean section; however, the emergency cesarean section rate was significantly higher in individuals with uric acid levels >4.34 mg/dL (p<0.05), as shown in Table 3.

For groups categorized by corrected calcium levels (≤9.46 mg/dL and >9.46 mg/dL), no significant difference was observed in the rates of spontaneous delivery and elective cesarean section (p>0.05), as detailed in Table 4. Nonetheless, the rate of emergency cesarean section was significantly increased in those with a calcium level >9.46 mg/dL (p<0.05), as indicated in Table 4.

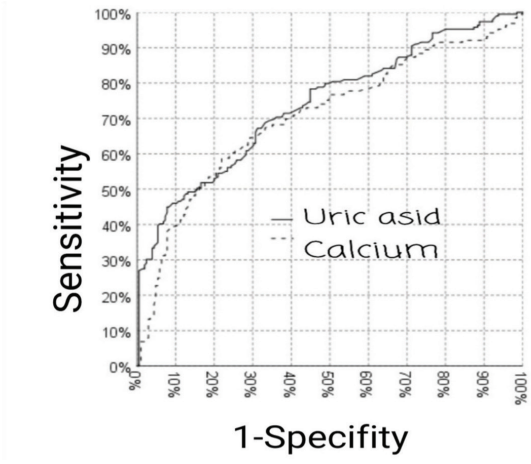

Figure 2. Receiver operating characteristic curves for uric asid and calcium

DISCUSSION

Preeclampsia remains a principal cause of maternal and neonatal morbidity and mortality worldwide. Despite extensive research, the exact etiology and pathogenesis of preeclampsia remain elusive, with prevailing theories suggesting endothelial damage and disrupted placental blood flow as key factors. Elevated serum uric acid levels resulting from compromised placental blood flow and oxygenation have been proposed as indicators of maternal and fetal distress. Given the life-threatening complications associated with preeclampsia for both mother and fetus, there is a continuous search for accessible and practical methods for its prediction and management. During the study period, our hospital recorded 8,927 deliveries, with 244 women diagnosed with preeclampsia, indicating a prevalence rate of 2.7%.

Earlier studies, such as those by Nair and Savitha (7), Shakarami et al. (11), Zhao et al. (12), and Vyakaranam et al. (13), demonstrated a correlation between elevated serum uric acid levels and preeclampsia, underscoring its potential role in disease progression and associated outcomes. Our findings resonate with these observations, revealing significantly higher serum uric acid levels in preeclamptic women than in their normotensive counterparts (p<0.05). Moreover, our analysis identified a significant increase in emergency cesarean sections among women with elevated uric acid levels (p<0.05), which is consistent with the association between high serum uric acid levels and the necessity for emergency deliveries demonstrated by Liu et al. (14).

The determination of the uric acid cut-off values in our study mirrors that of previous research (15,16), thereby indicating predictive sensitivity and specificity for preeclampsia. This finding reinforces the argument that serum uric acid is a valuable

Table 4. Comparison by calcium levels

		Calcium ≤9.46		Calcium >9.46		p
		n	%	n	%	
FGR	(+)	46	19.1%	35	22.9%	0.364$^{X^2}$
	(-)	195	80.9%	118	77.1%	
Complications	(-)	221	91.7%	132	86.3%	0.086$^{X^2}$
	(+)	20	8.3%	21	13.7%	
Delivery	VD	77	32.0%	42	27.5%	0.343$^{X^2}$
	CSE	104	43.2%	52	34.0%	0.070$^{X^2}$
	CSU	60	24.9%	59	38.6%	**0.004**$^{X^2}$

FGR: Fetal-growth-restriction, CSE: Cesarean section-elective, CSU: Cesarean section-urgent, VD: Vaginal delivery
X^2Chi-square test

marker for managing preeclampsia. However, contrasting findings from recent reviews and systematic analyses suggest a more nuanced relationship between serum uric acid levels and severe maternal and fetal outcomes, indicating the need for further investigation.

The role of serum calcium levels in preeclampsia has been debated, with studies by Sukonpan and Phupong (17), Kim et al. (18), and Jain et al. (19) suggesting lower serum calcium levels in preeclamptic women. Our study differed because it showed higher corrected calcium levels in preeclamptic patients, possibly attributed to adjustments for decreased serum protein levels in preeclampsia, which can affect calcium measurement. This discrepancy highlights the complexity of calcium's role in preeclampsia and underscores the importance of accurate calcium measurement in clinical assessment.

Study Limitations

This study's limitation lies in its focus on a population with generally low dietary calcium intake, potentially limiting the generalizability of findings related to calcium supplementation's impact on preeclampsia prevention. This finding underscores the necessity for larger-scale studies to comprehensively evaluate the effects of uric acid and calcium on preeclampsia in diverse populations.

CONCLUSION

Preeclampsia significantly affects maternal and neonatal health, emphasizing the importance of enhanced antenatal care, early detection, and effective management. The present study corroborates the association between increased maternal serum uric acid levels and a higher risk of complications in preeclampsia. Conversely, the association between serum calcium levels and preeclampsia remains ambiguous, suggesting the potential value of early pregnancy assessments of these markers. Elevated uric acid levels in patients with preeclamptic syndrome warrant caution, advocating for simple yet informative tests to mitigate the syndrome's complications. Further randomized controlled trials are necessary to confirm these findings and refine preeclampsia management strategies.

Ethics

Ethics Committee Approval: University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital's Ethics Committee approved the study (decision number: 283, date: 30.06.2020).

Informed Consent: This retrospective comparative study leveraged verbal consent from participants, with patient data collected via a review of medical records and an electronic patient information system.

Authorship Contributions

Surgical and Medical Practices: Y.A., Concept: Y.A., V.M., Design: Y.A., V.M., Data Collection or Processing: Y.A., Analysis or Interpretation: Y.A., Literature Search: Y.A., M.Ş., Writing: Y.A., M.Ş.

Conflict of Interest: Veli Mihmanlı is Associate Editor in European Archives of Medical Research. He had no involvement in the peer-review of this article and had no access to information regarding its peer-review. Other authors have nothing to disclose.

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