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Prediction of preeclampsia incidence by measuring serum uric acid levels in patients with gestational hypertension

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Abstract

Introduction: Some studies have pointed to the predictive role of high uric acid levels and the occurrence of preeclampsia; however, the finding in this field are still controversial and the appropriate level has not been determined.

Objectives: The aim of present study was to investigate the relationship between serum uric acid level and preeclampsia occurrence and also determine the appropriate predictive level in patients with gestational hypertension (GHTN).

Methods: At this prospective cohort study, the serum uric acid levels of 168 singleton pregnant women at the time of diagnosis of GHTN were measured and the patients were followed up until delivery. At the time of delivery, their uric acid levels were re-measured and symptoms of preeclampsia and eclampsia and neonatal outcomes were recorded.

Results: Preeclampsia and eclampsia occurred in 126 (75%) and five of the patients (3%), respectively. Patients with preeclampsia/eclampsia had higher age and body mass index, most of them were primiparous, and had a history of miscarriage. Moreover, their gestational age at the time of diagnosis of GHTN was significantly lower ($P<0.05$). Treatment of hypertension was also significantly more prevalent in the preeclampsia/eclampsia group ($P<0.001$). The level of uric acid at the time of diagnosis of GHTN and at the time of delivery in patients with preeclampsia/eclampsia was significantly higher. In addition, the rate of uric acid elevation during pregnancy in the preeclampsia/eclampsia group was significantly higher (P<0.001). In receiver operating characteristic analysis, the uric acid level of 4.65 mg/dL at the time of diagnosis of GHTN with a sensitivity of 96.9% and a specificity of 81.1%, and a diagnostic accuracy of 93.5% was a predictor of preeclampsia/eclampsia in patients with GHTN.

Conclusion: Our findings showed that 78% of patients with GHTN eventually developed preeclampsia/eclampsia and had significantly higher levels of serum uric acid levels both at the time of diagnosis of GHTN and at delivery. A uric acid level of 4.65 mg/dL at the time of diagnosis of GHTN was considered a predictor of preeclampsia/eclampsia in patients with GHTN.

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Introduction

Preeclampsia is an important complication of pregnancy that is clinically diagnosed after the 20th week of pregnancy or during the first 4-6 weeks after delivery and is associated with high rates of maternal and neonatal morbidity (1). It is estimated that this complication occurs in 5-8% of all pregnancies, although its incidence rate varies in different parts of the world and based on the differences in the definitions of this disorder (2). It should be noted that the pathophysiology of this disorder is not fully understood. Incomplete invasion of trophoblasts and disorder of the spiral arteries appear to lead to ischemic placental injury after which various mediators are released into the maternal circulation. It could lead to a range of disorders, such as diffuse endothelial dysfunction, increased vascular permeability and activation of the coagulation cascade (3).

Although the definitive treatment for preeclampsia is pregnancy termination, most pregnant women are treated as expectant management using monitoring of blood pressure and fetus and also seizure prevention (4). Therefore, prediction of preeclampsia and its complications is important and identify patients at risk of this disorder to prevent maternal and neonatal mortality and morbidity (5).

Some studies have reported biomarkers for the prediction of preeclampsia and the appropriate time to terminate the pregnancy (6). Biomarkers, such as FMS-like tyrosine kinase-1 and placental growth factor, have been suggested for this purpose (7). However, there is a debate about their widespread use for screening (8).

Key point

Preeclampsia, as an important pregnancy complication, is associated with high rates of maternal and neonatal morbidity. Although some studies have suggested a predictive role for serum uric acid, the results of the studies are still controversial and no specific cut off point has been set. We showed that in patients with GHTN, at the time of diagnosis of GHTN, serum uric acid was higher in women who later developed preeclampsia since; a cut-off point of 4.65 mg/dL could distinguish patients at risk for developing preeclampsia.

The final product of purine metabolism is uric acid that is produced by the action of xanthine oxidase. Uric acid plays an important role in the uptake of free radicals (9). Due to increased plasma volume and increased urate clearance, serum urate concentration decreases in normal pregnancy (10). However, in patients with preeclampsia, hyperuricemia occurs due to increased tubular reuptake of urate caused by hypovolemia and the effect of angiotensin II (11). In addition, uric acid production increases due to increased trophoblastic activity and its excretion is impaired due to competition with lactate in the proximal tubules (12).

Moreover, some studies have suggested that uric acid plays a role in the development of preeclampsia by inhibiting the production of nitric oxide, resulting in the insufficient invasion of trophoblasts and endothelial disorders (13). In addition, uric acid can increase the production of pro-inflammatory cytokines, such as interleukin-1β (14). The relationship between uric acid and preeclampsia has long been known and was initially used as a clinical diagnostic criterion for it (15). Serum uric acid levels can be used to diagnose preeclampsia, especially its severe forms, other diagnostic tests, which can also be economical, are able to replace the use of uric acid (16).

In some studies, it has been suggested that uric acid can predict preeclampsia (17), but it has also been mentioned that further studies are required on the inclusion of uric acid in preeclampsia predictive models and its appropriate level.

Objectives

The present study aimed to investigate the relationship between serum uric acid levels and preeclampsia to determine the appropriate predictive level in patients with gestational hypertension (GHTN).

Patients and Methods

Study design

This prospective cohort study was performed on 180 pregnant women referred to Mahdieh and Shohada Tajrish hospitals in Tehran, Iran at the time of diagnosis of GHTN. Inclusion criteria were singleton pregnancy and GHTN (systolic blood pressure [SBP] above 140 mm Hg and diastolic blood pressure [DBP] above 90 mm Hg). Exclusion criteria were history of hyperuricemia, history of heart or liver disorders, twin or more pregnancies, history of preeclampsia in previous pregnancies, and unavailability for follow-up. The patients were selected using the convenience sampling method.

Initially, using a form, patient data were collected, including age, body mass index (BMI) at the beginning of pregnancy, parity, history of abortion, smoking status, gestational age at the time of diagnosis of GHTN, SBP, DBP, and BMI at the time of referral. Next, a 2 cc of blood sample was taken from patients to measure serum uric acid level by enzyme-linked immunosorbent assay. Afterward, patients were followed up until delivery without interfering with their treatment.

At the time of delivery, a blood sample was taken for measurement of the following; hemoglobin, hematocrit, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, creatinine, lactate dehydrogenase, platelet, and uric acid level. Moreover, the usage of medication for GHTN, gestational age at the time of delivery, type of delivery, symptoms of preeclampsia and eclampsia (e.g., seizure, visual disturbances, oliguria, vaginal bleeding, headache, and right upper quadrant pain), and neonatal outcomes [intrauterine fetal death (IUFD), intrauterine growth retardation (IUGR), hospitalization at neonatal intensive care unit, and Apgar score at 5 min] were recorded.

Finally, a total of 12 patients were excluded from the study due to the follow-up loss, and the data of 168 patients were analyzed. Preeclampsia was considered the sudden onset of hypertension (SBP higher than 140 mmHg and DBP higher than 90 mmHg) with proteinuria higher than 300 mg/24 h after the 20th week of gestation. Eclampsia was also considered in case of seizure (18). The incidence of preeclampsia or eclampsia was determined and uric acid levels were compared in individuals with and without preeclampsia.

Statistical analysis

The collected data were analyzed in SPSS statistical software (version 25). Qualitative variables were described using frequency and percentage and quantitative variables were described using mean and standard deviation. Paired t-test was used to compare uric acid levels at the time of delivery and at the time of diagnosis of GHTN. Moreover, the chi-square test and independent *t* test were used to compare the characteristics of patients in the two groups with and without preeclampsia.

Besides, using the receiver operating characteristic analysis and by calculation of area under the curve, the best uric acid level was determined to predict the possibility of preeclampsia and its characteristics were calculated, including sensitivity, specificity, and diagnostic accuracy. A *P* value of less than 0.05 was considered statistically significant.

Results

Preeclampsia and eclampsia occurred in 126 (75%)

and 5 (3%) out of 168 subjects. Table 1 summarizes the characteristics of patients. Patients with preeclampsia/eclampsia were older, had a higher BMI before pregnancy and at the time of referral, mostly were primiparous with a history of miscarriage, and had a significantly lower gestational age at the time of GHTN diagnosis ($P<0.05$). However, history of smoking, SBP, and DBP at baseline were not significantly different between the two groups ($P>0.05$). Furthermore, the use of hypertension medications in the preeclampsia/eclampsia group was significantly higher ($P<0.001$).

Table 2 shows the clinical symptoms, characteristics of labor, and pregnancy outcomes. In terms of clinical symptoms, only vaginal bleeding and right upper quadrant pain were significantly higher in the preeclampsia/eclampsia group ($P<0.05$). The frequency of cesarean section, preterm labor, and neonatal hospitalization in neonatal intensive care units was also significantly higher in this group ($P<0.05$). However, there was no significant difference between the two groups in terms of IUGR and IUFD ($P>0.05$).

Table 3 shows the laboratory tests at the time of delivery, and Table 4 tabulates the serum uric acid level of the patients. Both at the time of diagnosis of GHTN and at delivery, the uric acid level was significantly higher in patients with preeclampsia/eclampsia, compared to those with GHTN ($P<0.001$). In addition, the uric acid levels of all patients and both groups were significantly increased at the time of delivery, compared to the time of diagnosis of GHTN ($P<0.001$). It should be noted that the rate of increase in uric acid during pregnancy in the preeclampsia/eclampsia group was significantly higher ($P<0.001$).

In receiver operating characteristic analysis, the uric acid level of 4.65 mg/dL at the time of diagnosis of GHTN with an area under the curve of 0.892 (95% CI: 0.812-0.972) could predict preeclampsia/eclampsia in patients with GHTN with a sensitivity of 96.9% and a specificity of 81.1%, with the diagnostic accuracy of 93.5% (Figure 1).

Discussion

Our findings showed that 78% of patients with GHTN eventually developed preeclampsia/eclampsia. Moreover, it was found that the preeclampsia/eclampsia group had significantly higher serum uric acid levels both at the time of diagnosis of GHTN and at the time of delivery. The uric acid level of 4.65 mg/dL at the time of diagnosis of GHTN with a sensitivity of 96.9%, specificity of 81.1%, and a diagnostic accuracy of 93.5% was considered a predictor

Table 1. Patients' characteristics

	Total (n=168)	GHTN (n=37)	Preeclampsia/eclampsia (n=131)	*P* value
Age, year	29.7 ± 3.8	28.0 ± 3.8	30.3 ± 3.6	0.001
Pre-pregnancy BMI, kg/m²	29.4 ± 3.0	25.6 ± 2.8	27.9 ± 2.8	<0.001
BMI at beginning of study kg/m²	31.9 ± 3.5	29.7 ± 3.1	32.5 ± 3.3	<0.001
Primiparous	106 (63%)	16 (43%)	90 (69%)	0.005
History of abortion	90 (54%)	5 (14%)	85 (65%)	<0.001
Smoking	29 (17%)	9 (24%)	20 (15%)	0.198
Gestational age at diagnosis of GHTN, weeks	27 ± 3	30 ± 3	27 ± 3	<0.001
SBP, mm Hg	142 ± 6	140 ± 7	143 ± 6	0.055
DBP, mm Hg	92 ± 4	95 ± 5	92 ± 3	0.583
Taking hypertension medication	120 (71%)	17 (46%)	103 (79%)	<0.001

BMI: body mass index, DBP: diastolic blood pressure, SBP: systolic blood pressure, GHTN, Gestational hypertension.
* Independent t test, ** Chi-square test.

Table 2. Clinical symptoms, characteristics of labor and pregnancy outcomes

	Total (n = 168)	GHTN (n = 37)	Preeclampsia/eclampsia (n=131)	*P* value
Seizure	5 (3%)	0 (0%)	5 (4%)	0.587*
Visual disorders	6 (4%)	0 (0%)	6 (5%)	0.341*
Oliguria	17 (10%)	1 (3%)	16 (12%)	0.124*
Vaginal bleeding	28 (17%)	2 (5%)	26 (20%)	0.037**
Headache	47 (28%)	6 (16%)	41 (31%)	0.071**
RUQ Pain	16 (10%)	0 (0%)	16 (12%)	0.024*
Cesarean section	111 (66%)	15 (41%)	96 (73%)	<0.001**
Preterm labor (less than 37 weeks)	97 (58%)	3 (8%)	94 (72%)	<0.001**
Hospitalization in NICU	103 (61%)	6 (16%)	97 (74%)	<0.001**
IUGR	28 (17%)	3 (8%)	25 (19%)	0.114**
IUFD	5 (3%)	1 (3%)	4 (3%)	1.000*

IUFD: Intrauterine fetal death , IUGR: intrauterine growth retardation, NICU: neonatal intensive care unit, RUQ: right upper quadrant.
*Fisher's exact test, ** Chi-square test.

Table 3. Laboratory tests at delivery time

	Total (n=168)	Gestational hypertension (n=37)	Preeclampsia/eclampsia (n=131)	*P* value*
Hct, %	34 ± 3	34 ± 3	34 ± 3	0.152
Hb, g/dL	10.9 ± 1	11.3 ± 0.9	10.8 ± 1.1	0.010
PLT, ×1000/mm^3	181 ± 45	198 ± 24	176 ± 48	<0.001
BUN, mg/dL	20 ± 5	14 ± 2	21 ± 5	<0.001
Cr, mg/dL	0.8 ± 0.2	0.7 ± 0.1	0.8 ± 0.2	<0.001
LDH, U/L	493 ± 96	444 ± 74	507 ± 97	<0.001
AST, U/L	45 ± 33	20 ± 8	52 ± 34	<0.001
ALT, U/L	43 ± 30	20 ± 6	50 ± 31	<0.001

AST: aspartate aminotransferase, ALT: alanine aminotransferase, BUN: Blood Urea Nitrogen, Cr: Creatinine, Hb: hemoglobin, Hct: hematocrit, LDH: Lactate Dehydrogenase, PLT: platelets.
* Independent sample *t* test.

Table 4. Uric acid levels

	Total (n=168)	Gestational hypertension (n=37)	Preeclampsia/eclampsia (n=131)	*P* value*
At the time of diagnosis of GHTN, mg/dL	4.7 ± 0.6	4.1 ± 0.6	5.1 ± 0.4	<0.001
At the time of delivery, mg/dL	6.1 ± 1.0	4.6 ± 0.6	6.5 ± 0.6	<0.001
Change rate, mg/dL	1.2 ± 0.7	0.5 ± 0.5	1.4 ± 0.6	<0.001

* Independent sample *t* test.

of preeclampsia/eclampsia in patients with GHTN.

Uric acid is a known biomarker for oxidative stress, placental ischemia, and kidney damage. Preeclampsia can lead to hyperuricemia by increasing the production of uric acid by activating xanthine oxidase (19). Studies have reported higher serum uric acid levels in women with preeclampsia, compared to women with normal blood pressure. Wu et al reported that among women with GHTN, in those who later developed preeclampsia, mean uric acid levels were significantly higher than in those who did not develop it (5.06 mg/dL and 4.59 mg/dL, respectively) (20).

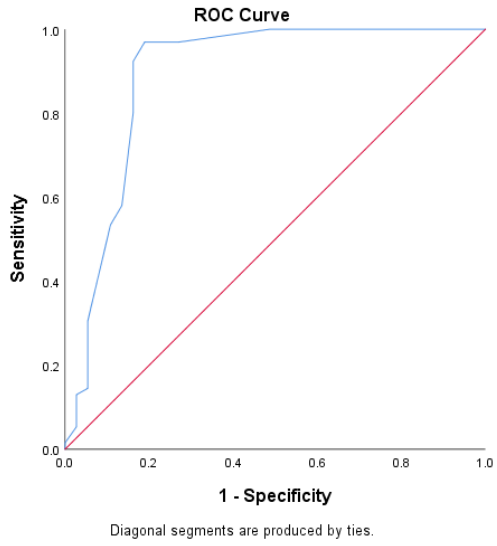

Figure 1. Receiver operating characteristic curve of serum uric acid level at time of gestational hypertension diagnosis predicting preeclampsia/eclampsia

Bellomo et al also reported that in pregnant women with GHTN, the high uric acid level was associated with a 9-fold increase in the risk of preeclampsia. Moreover, they found that uric acid sensitivity in the initial assay is acceptable in predicting progression to preeclampsia (21). Results of the present study also showed that higher levels of serum uric acid at the time of diagnosis of GHTN in women with GHTN can lead to preeclampsia.

Many studies have shown that uric acid plays an important role in the prognosis of preeclampsia (22); however, a specific level is not mentioned for it. In some studies, levels of 5.6 mg/dl and 6 mg/dL were reported at week 38 (23), but lower levels were also reported in some other studies (24). Uric acid levels of 4.65 mg/dL at the time of diagnosis of GHTN in the present study were predictive for preeclampsia in women with singleton pregnancies. Nevertheless, most studies consider uric acid to be a useful predictor of hypertensive disorders during pregnancy (23). Some other studies have reported that uric acid levels are a poor predictor of maternal and fetal outcomes (25). Therefore, the use of uric acid for the prediction of preeclampsia in various studies has not been confirmed. Moreover, the results of some studies have not shown a significant difference in serum uric acid levels in pregnant women with preeclampsia, compared to women with normal pregnancies (26).

In a meta-analysis of the predictive role of uric acid for preeclampsia performed in 2020, Bellos et al reported that preeclampsia was associated with increased uric acid levels in the first to third trimesters. They also found that laboratory conditions, such as hemolysis, high liver enzymes, and low-platelet syndrome are associated with higher levels of uric acid. Uric acid sensitivity for predicting adverse perinatal outcomes ranged from 67.3%

to 82.7% and its specificity ranged from 70.7% to 47.7%. Finally, it was concluded that uric acid can be used to predict preeclampsia and its severity, but more studies are needed (17). However, Chescheir et al
that while serum uric acid levels can be used to diagnose preeclampsia, especially its severe forms, other diagnostic tests, which can be economical, are able to replace uric acid (16).

The relationship between biomarkers, such as uric acid, and adverse pregnancy outcomes in preeclampsia patients has also been discussed in the guidelines of the American College of Obstetricians and Gynecologists (27), however its use as a diagnostic marker is still under debate and not yet confirmed (17). Nevertheless, the results of the present study showed that uric acid levels greater than 4.65 mg/dL at the time of diagnosis of GHTN can be used to predict the next incidence of preeclampsia.

Conclusion

Findings of this study showed that 78% of patients with GHTN eventually developed preeclampsia/eclampsia. In addition, it was revealed that uric acid levels both at the time of diagnosis of GHTN and at delivery were significantly higher in the preeclampsia/eclampsia group. The uric acid level of 4.65 mg/dL at the time of diagnosis of GHTN with a sensitivity of 96.9%, specificity of 81.1%, and a diagnostic accuracy of 93.5% was considered as a predictor of preeclampsia/eclampsia in patients with GHTN. Therefore, the use of uric acid to predict the occurrence of preeclampsia can be recommended, however larger studies in multiple centers, recommends

Limitations of the study

The small sample size of this study may prevent the results from being generalizable to larger communities. Therefore, it is recommended to conduct multi-center studies with larger sample sizes.

Authors' contribution

All authors passed four criteria for authorship contribution based on recommendations of the International Committee of Medical Journal Editors. PP, MM, MA, ZD and ND designed the protocol of study. PP and MM developed the protocol and performed it. Critical revision of the manuscript for important intellectual content was performed by all. Analysis of data performed by MM. All authors read and approved the final paper.

Ethical issues

This study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran with a code of IR.SBMU.MSP.REC.1398.484. In addition, after explaining the objectives of the study to the patients, written consent was obtained from all of them to participate in the study. This study was extracted from residency thesis of Maryam Mohammadi at this university (Thesis #18665). Accordingly, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Conflicts of interest

There is no conflict of interest among authors.

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