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The value of serum uric acid in predicting adverse pregnancy outcomes of women with hypertensive disorders of pregnancy

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ABSTRACT

Objectives: This study aims to investigate the clinical value of uric acid in predicting adverse pregnancy outcomes (APOs) of women with hypertensive disorders of pregnancy.

Material and methods: A total of 180 pregnant women with HDP from September 2015 to January 2017 were selected for this study. These subjects were classified into two groups, according to serum uric acid level: high UA group (n = 137) and normal UA group (n = 43). In addition, 180 healthy pregnant women were selected and assigned as the control group (n = 180). The monitored biochemical indices and APOs in these three groups were analyzed. Furthermore, non-conditional logistic regression analysis was performed to determine influencing factors of APOs in women with HDP and hyperuricemia.

Results: The non-conditional multi-factor logistic regression analysis revealed that HUA (SUA > 357 umol/L) is the risk factor of APOs in women with HDP (OR = 1.258, P < 0.05).

Conclusions: Women with HDP and HUA are often accompanied with a variety of abnormal biochemical indicators, and is correlated with the severity of the disease and APOs.

Key words: hyperuricemia, hypertensive disordersof pregnancy, risk factor, perinatal outcomes

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INTRODUCTION

In China, hypertensive disorders of pregnancy (HDP) still remains as one of the leading causes of maternal and perinatal morbidity and mortality. In the present study, we aimed to provide our expert evidence that hyperuricemia (HUA) in women with HDP may exert an adverse influence on their pregnancy and perinatal outcomes, and this effect is independent of gestational age, preeclampsia and other factors. However, it remains controversial worldwide that uric acid (UA) levels are correlated to HDP. Stander H. F. and Cadden J. F. [1] first discovered the correlationbetween HUA and preeclampsia in pregnant women. Following this discovery, Paula L. G. [2] conducted a large-scale prospective multi-center study in 2008, and pointed out that serum uric acid (SUA) level was correlated to the perinatal prognosis of patients with HDP. In 2011, Bellomo G. et al. [3] considered that UA was a reliable indicator for predicting the development of HDP to preeclampsia and preterm birth, and this played an important role in pathology in preeclampsia. In addition, in 2016, Elmas O. et al. [4] conducted a study to determine the correlation between hypertension and plasma UA, and its predictive capacity in severe preeclampsia. In the same year, Shruti Agrawal [5] also emphasized the value of UA in his risk prediction model for predicting adverse maternal outcomes in women with HDP. However, the importance of monitoring UA levels in pregnant women remains controversial. In 2012, through a retrospective cohort study, Hawkins T. L. et al. [6] found that elevated UA levels in pregnant women with HDP had no obvious effect on maternal outcome. This conclusion was supported by another study published in China in 2016 [7]. The author, Chen Q, suggested that SUA may not be involved in the development of preeclampsia, and thereby could not be a reliable marker to predict the incidence of adverse pregnancy outcomes (APOs). Despite all these

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controversial evidences, our study aims to determine whether careful monitoring of UA levels for pregnancies complicated by HDP could improve long-term maternal, perinatal and pediatric outcomes.

Gestation is a normal physiological process, and HDP, including gestational hypertension, preeclampsia (from mild to severe), chronic hypertension complicated by preeclampsia and chronic hypertension in pregnancy, is a special disease that occurs during pregnancy. This disease is complex and fast-changing, and physiological changes during delivery and after birth, as well as various pessimal stimuli, may exacerbate the disease. HDP is one of the main causes of maternal and neonatal mortality, and it is very important to closely evaluate and monitor this during the antenatal, intrapartum and postnatal periods [8]. In this study, the authors conducted a retrospective analysis on 180 pregnant women with HDP, and investigated the APOs of those women, in order to determine the clinical value of UA for HDP patients.

MATERIAL AND METHODS

Research subject: From September 2015 to January 2017, 180 postpartum women with HDP in the medical intensive care unit (MICU) were studied. All patients were diagnosed through clinical examination according to the Guidelines for Diagnosis and Treatment of Hypertensive Disordersof Pregnancy (2012) [8], and patients with chronic liver and kidney diseases and diabetes were excluded from the study. The age of these patients were between 24 and 39 years old, and the average age was 33.1 ± 2.5 years old. The gestation period was 36–42 weeks, with an average gestation period of 38.1 ± 1.9 weeks. These 180 women were divided into two groups, according to SUA levels: HUA group (n = 137), and normal UA group (n = 43). In addition, another 180 healthy pregnant women were selected and assigned as the control group (n = 180). The age of the women in the control group was between 23 and 40 years old, with an average age of 32.9 ± 2.6 years old. Furthermore, the gestation period of women in the control group was within 35–42 weeks, with an average of 38.3 ± 1.8 weeks. The difference in average age between the study groups (HUA group and normal UA group) and the control group was not statistically significant ($P > 0.05$).

Methods

The SUA levels of pregnant women in the study groups, as well as other indicators such as total protein, albumin, GBT, GOT, LDH, creatinine, BUN, TG, TC, HDL-C and LDL-C, were measured.

HUA diagnostic criteria [9]: HUA was considered when UA > 357 umol/L (6.0 mg/DL). Low birth weight (LBW) infants are newbornswith a weight < 2,500 g, according to *Obstetrics* (8th Edition) [10].

Test method

Three mL of venous blood was drawn from fasted pregnant women early in the morning after theywereadmitted in the ward. Blood biochemistry tests were performed using an Olympus AU 2700 Analyzer (Japan), and SUA was determined according to manufacturer's instructions and protocol using the urate oxidase-peroxidase coupled enzyme system.

Statistical method

SPSS 20.0 was used for the statistical analysis of the data, and the PASS software was used to estimate the minimum sample size. First, normal distributionof all measurement data wasevaluated. If the data were normally distributed, the findings were expressed as $\bar{x} \pm$ standard deviation (SD). For comparing two samples, t-test is adopted for homogeneity of variance, while an improved t-test was adopted for heterogeneity of variance. One-way analysis of variance (ANOVA) was adopted for comparing more than two groups, while the least significant difference (LSD) method was adopted for comparing two groups. Chi-square test was used for counting data, and non-conditioned multi-factor logistic regression analysis was used for correlation analysis. $P < 0.05$ was considered statistically significant.

RESULTS

SUA level and the incidence of HDP was significantly higher in the HUA group than in control group. The average level of SUA was 340.0 ± 119.6 µmol/L and 295.8 ± 81.7 µmol/L in the HUA group and control group, respectively; and the difference was statistically significant ($P < 0.05$, Tab. 1).

The correlation between HDP and HUA, and the patient's condition are presented in Table 2. These results revealed that the difference in total protein, albumin, GBT, GOT, LDH, creatinine, BUN, TG, TC, HDL-C and LDL-C between the HUA group and control group was statistically significant ($P < 0.05$).

Common APOs include preterm birth, LBW, fetal distress, asphyxia, stillbirth, placental abruption, disseminated intravascular coagulation (DIC), liver dysfunction, and serosal fluid and postpartum hemorrhage. The analysis of the maternal and perinatal adverse outcomes in the HUA group in the late trimester is presented in Table 3, and the difference with control group was statistically significant ($P < 0.05$). The

Table 1. Comparison of average blood uric acid level and incidence of HUA between HDP group and control group

Group	Number	SUA ($\bar{x} \pm s$, umol/L)	HUA [(%)]
HDP	180	340. 0 ± 119. 6	69 (76.7)
Control	180	295. 8 ± 81. 7	14 (15.6)
p value		< 0.05	< 0.05

Table 2. Comparison of biochemical test indexes among three groups $\bar{x} \pm S$

Group	Number	Total protein (g/L)	ALB (g/L)	GBT (U/L)	GOT (U/L)	LDH (U/L)
A	137	47.2 ± 4.7[ab]	28.2 ± 3.7[ab]	37.5 ± 14.5[ab]	40.4 ± 12.1[ab]	262.3 ± 100.9[ab]
B	43	53.6 ± 4.9[a]	29.1 ± 4.0[a]	22.7 ± 16.7[a]	29.3 ± 18.3[a]	194.5 ± 98.6[a]
Control	180	62.7 ± 3.2	32.2 ± 3.7	15.6 ± 8.6	20 ± 10.6	135.8 ± 44.9
p value		< 0.05	< 0.05	< 0.05	< 0.05	< 0.05

Group	Creatinine (umol/L)	BUN (mmol/L)	FBG (mmol/L)	TG (mmol/L)
A	71.9 ± 22.7[ab]	4.9 ± 1.9[ab]	5.1 ± 1.3	4.6 ± 1.8[ab]
B	65.7 ± 31.9[a]	3.8 ± 1.5[a]	5.0 ± 0.9	2.7 ± 1.2
Control	46.9 ± 11.0	2.9 ± 0.9	5.1 ± 0.8	2.6 ± 1.7
p value	< 0.05	< 0.05	>0.05	< 0.05

Group	TC (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)
A	7.6 ± 2.1[ab]	1.7 ± 0.5[a]	3.3 ± 1.4[ab]
B	5.7 ± 1.6[a]	1.6 ± 0.7[a]	2.6 ± 0.7
Control	5.1 ± 1.7	2.2 ± 0.9	2.1 ± 0.8
p value	< 0.05	< 0.05	< 0.05

[a] vs Control Group, P < 0.05; [b] vs Control Group, P < 0.05

correlation analysis shows that SUA is positively correlated with the incidence of APOs, as presented in Table 4. This demonstrates that higher UA is positively correlated with the incidence of APOs. This proves that the clinical evaluation of UA levels in women with HDP and HUA is of high significance for avoiding and reducing the incidence of APOs.

Table 3. Comparison of APOs among three groups [cases (%)]

Group	Number	Preterm birth	Fetal distress	Asphyxia	Stillbirth	LBW
A	137	26 (3 7.7) [a b]	4 (5.8) [a b]	3 (4.3) [a b]	1 (1 .4) [a]	25 (36.2) [a b]
B	43	3 (1 4.3) [a]	1 (4.8) [a]	1 (4.8) [a]	0 (0.0)	3 (14.3) [a]
Control	180	2 (2.2)	1 (1.1)	0 (0.0)	0 (0.0)	2 (2.2)
x^2		32,893	17,285	17,013	14,017	31,567
p value		< 0.05	< 0.05	< 0.05	< 0.05	< 0.05

Group	Number	Placental abruption	DIC	Liver dysfunction	Postpartum hemorrhage	Serosal fluid
A	137	24 (34.8)[a b]	3 (4.3)[a b]	6 (8.7)[a]	18 (26.1)[a b]	8 (11.6)[a b]
B	43	4 (19.0)[a]	0 (0.0)	2 (9.5)[a]	2 (9.5)[a]	3 (14.3)[a]
Control	180	3 (3.3)	0 (0.0)	2 (2.2)	4 (4.4)	1 (1.1)
x^2		36,463	17,693	15,654	31,493	32,893
p value		< 0.05	< 0.05	< 0.05	< 0.05	< 0.05

[a] vs Control, P < 0.05; [b] vs Group B, P < 0.05

Table 4. Non-conditional multi-factor logistic regression analysis of women with HDP

Variables	β	SE	Waldx^2	df	P	OR	95% CI
Constant term	0.497	0.194	27.810	1	0.000	0.441	–
Hyperuricemia	0.228	0.124	4.703	1	0.035	1.258	1.038~1.526
Preeclampsia	0.886	0.328	12.671	1	0.000	2.477	1.657~3.572
Pregnant-duration	0.189	0.079	6.171	1	0.026	1.218	1.069~1.478

"–" refers to the items undetected

DISCUSSION

As a common obstetric complication, HDP is one of the key causes of maternal and perinatal morbidity and mortality. The pathophysiological mechanisms includearterial spasm, blood concentration, microcirculatory impairment and subclinical disseminated intravascular coagulation (DIC). The reduced blood volume and inadequate organ perfusion resulting from blood vessel spasms and the increased permeability of blood vessels may cause maternal and fetal injury, and even death. The clinical syndromes of organ damage include proteinuria, renal insufficiency, hepatic and hematologic diseases and fetal growth restriction [10]. Although the etiology of HDP has not been exactly identified, superficial placental implantation resulting from the release of inflammatory cytokines in maternal blood circulation and other anti-angiogenesis factors is an important cause. In addition, the increased level of UA is one of abnormallaboratory indexes in the treatment of HDP.

As an end product of human purine metabolism, UA has two sources in human body: (1) the decomposition and catabolism of nucleic acid in the body (approximately 80%), and (2) the decomposition of food containing purine or nucleoprotein (approximately 20%). UA is excreted in three ways: (1) after four steps including glomerular filtration, proximal renal tubular reabsorption, proximal renal tubular secretion in the distant part, and reabsorption after secretion, and UA is eventually discharged with urine (approximately 70%); (2) entering into the intestinal cavity through the secretion of intestinal mucosal cells, the uricase in intestinal bacteria can transform UA into allantoin, and is discharged with urine (approximately 30%); (3) decomposition in white blood cells (approximately 2%) [11, 12]. UA is one kind of colorless and tasteless water-soluble weak organic acid, which has low solubility in the urinary system with a pH value between 5.0 and 6.0, and lower physical solubility in blood circulation. In early pregnancy, SUA concentration is lower than that of non-pregnant women due to increasedblood volume, renal blood flow and glomerular filtration rate, and the elevatedexcretion of UA stimulated by estrogen caters. However, from the second trimester, SUA begins to increase and eventually reaches normal levels during full-term pregnancy. A low UA concentration has the anti-oxidation effect, but it may cause HUA due to increasing SUA when UA metabolism disorder occurs, increasing UA or decreasing excretion; and this may lead to a series of pathological and physiological changes: (1) UA can separate crystals out and deposit in the blood vessel wall, which may directly damage the intima; (2) UA can promote adhesion and aggregation, as well as the thrombosis of blood platelets; (3) UA can increase oxygen-derived free radicals, and induce functional damage of the mitochondria and lysosomes, which promotes the aggregation of granulocytes in vascular endothelial cells; (4) UA promotes low density lipoprotein cholesterol (LDL-C) oxidation and produces toxicity in endothelial cells, which may cause the apoptosis of vascular smooth muscle cells, and further vascular inflammatory reaction [13, 14]. In conclusion, elevated SUA not only causes vascular endothelial disorder and decreasesthe synthesis of nitric oxide, but also activates the renin-angiotensin system in the body, which can easily result in high blood pressure. Therefore, it can be concluded that SUA is a strong oxidant that can promote the production of oxygen-derived free radicals. However, it is a double-edged sword. Elevated SUA is common in preeclampsia, and it can be detected earlier than the diagnosis of hypertension, proteinuria and preeclampsia. In view of its destructive effect on vascular endothelial cells, this can be used to reveal the significant role of UA in the pathogenesis of HDP [15].

Since the correlation between HUA and preeclampsia in pregnant women was first discovered by Stander J. F. and Cadden H. F. [1], SUA has been considered as an important marker in the early diagnosis of preeclampsia. However, since urinary proteins can better reflect the renal damage of patients with HDP, the diagnostic value of HUA has remained controversial. In a large-scale prospective multi-center study in 2008, Paula L. G. pointed out that SUA level was correlated to the perinatal prognosis of patients with HDP [2]. In 2011, Bellomo G. et al. [3] considered that UA was a reliable indicator for predicting the development of HDP for preeclampsia and preterm birth, and it played an important role in pathology in preeclampsia. Continuous high levels of UA may trigger a series of ischemic injuries, because it may decrease nitric oxide concentration, obstruct placental vascular remodeling and reduce intramuscular perfusion. Hence, UA is of significant clinical value in predicting perinatal outcome. This is consistent with the conclusions in this study. In 2012, Hawkins T. L. et al. [6] found through a retrospective cohort study that increased UA in pregnant women with HDP could lead to higher risk of adverse fetal outcomes such as small-for-gestational age infants and premature birth, but it had no obvious effect on maternal outcome. However, with the increase in UA of women with preeclampsia, the risk of APOs for both mothers and infants would significantly increase. This shows that SUA is a marker of predicting the APOs of patients with HDP. In addition, it was also found that the coincidence of increased incidence of preterm birth and decreased natural childbirth shows that maternal and fetal complications resulting from HUA may accelerate the need for termination of pregnancy. Other studies have also focused on the correlation between UA and fetal birth weight [16]. In a cohort study involving 1,487 cases, Joel R. [17] also confirmed Hawkins' conclusion, wherein he considered that the corrected UA according to gestational age can better predict adverse perinatal outcomes than random

UA value, and its sensitivity and specificity were 93% and 27%, respectively. Through comparing the perinatal period information of women who have normal blood pressure, but respectively deliver small-for-gestational age infants and infants of right age, Akahori Y. et al. [18] found that the levels of hematuria acid, creatinine and blood pressure of the former were obviously higher than those of the latter. Increased SUA is correlated to mild kidney function damage and LBW infants. Multi-factor regression analysis revealed that the level of SUA in pregnant women is an independent risk factor of LBW infants. However, the UA level of pregnant women who deliver very light birth weight infants has no correlation with birth weight, but it has a positive correlation with creatinine. In the meantime, the fluctuation of SUA levels in pregnant women who deliver small-for-gestational age infants and infants of the right age is similar to the difference in the UA level of metabolic syndrome and the normal control group. This shows that the change in UA level may be correlated to fetal growth. In order to timely and effectively cure pregnant women with preeclampsia, Payne B. A. [19] designed an integrated risk prediction scoring system for women with preeclampsia, in which the UA value is included. One shortcoming of Payne's study is that he excluded women with HDP, and only studied pregnant women with preeclampsia [20]. Different from Payne's study, this study includes pregnant women with preeclampsia, chronic hypertension and HDP, and draws the basic consistent conclusion with Paula L. G., Hawkins J. and Joel R.

Although hyperuricemia is commonly seen in women with preeclampsia, a systematic review of five studies concluded that measurement of SUA concentration before 25 weeks of gestation was not useful for predicting which women would develop preeclampsia. One study [21] used a rise in SUAconcentration above baseline level as the criterion for a positive test result, while the other four studies used threshold values above 3.5 to 4 mg/dL (0.21 to 0.24 mmol/L) as the cut-off for a positive test result. Sensitivities ranged from 0 to 56 percent and specificities ranged from 77 to 95 percent.

Similarly, a second systematic review [22] concluded that SUA measurement was not useful for predicting development of complications in women with preeclampsia.

However, SUA may be useful in predicting the length of the latency period from diagnosis to delivery. The author of another article [23] showed that admission uric acid levels correlate with the length of expectant management in preterm patients with preeclampsia. Pregnancy prolongation for > 1 week is significantly more likely in patients with low and medium uric acid levels at the time of admission. Uric acid levels may be helpful in assessing disease severity and counseling preeclamptic patients regarding likelihood of extended expectant management.

In conclusion, this study argues that increased UA levels would represent a higher incidence of women's perinatal adverse outcomes, fetal preterm birth, fetal distress, LBW infants and perinatal mortality. Although due to limited articles to give more evidence to verify the importance of SUA test in pregnant women with hypertension, many professional bodies such as the American College of O&G do not advocate laboratory and imaging screening tests but rather a detailed medical history to assess a patient's risks of developing pre-eclampsia. However, we believe for the patients with increased SUA, when UA > 357 mmol/L, maternal and fetal health should be closely monitored. In addition, through an unconditional multi-factor logistic regression analysis and after the correction of confounding factors, it was shown that HUA is a high risk factor for women with HDP (OR = 1.258), and this further proves that HUA in the women with HDP may exert an adverse influence on their pregnancy and perinatal outcomes, and this effect is independent of gestational age, preeclampsia and other factors.

No evidence can prove that APOs of women with HDP can be reduced through lowering SUA. However, given the close link between HUA and the adverse prognosis of vascular, heart, kidney and other systematic organs, and the possible result of adverse maternal outcome, it may be one effective measure for high-risk pregnant women to publicize health education, advocate low-purine and low-fat diet, and control SUA levels.

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Competing interests

The authors declare that they have no competing interests.

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