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# Maternal hyperuricemia superimposed on maternal hypertension aggravates the risk of small-for-gestational-age fetus

Luna Liu[a,1], Chunxiao Yu[a,b,1], Feifei Yang[c], Zhongshang Yuan[d], Qian Wang[e], Shuang Liu[a], Changting Zuo[f,*], Qingbo Guan[a,**]

[a] Department of Endocrinology, Shandong Provincial Hospital affiliated to Shandong University, Institute of Endocrinology and Metabolism, Shandong Academy of Clinical Medicine, Shandong Clinical Medical Center of Endocrinology and Metabolism, Jinan, Shandong 250021, China
[b] Department of Biological Sciences, The University of Texas at Dallas, 800 W. Campbell Road, Richardson, TX 75080, USA
[c] Department of Pediatrics, TengZhou Central People's Hospital, Tengzhou, Shandong 277500, China
[d] Department of Biostatistics, School of Public Health, Shandong University, China
[e] Department of Ultrasound, Shandong Provincial Hospital affiliated to Shandong University, China
[f] Department of Obstetrics and Gynecology, Shandong Provincial Hospital affiliated to Shandong University, China

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ABSTRACT

*Aims:* Small-for-gestational-age (SGA) fetus is an important public health issue because of its high mortality and long-term effects on health. Maternal hyperuricemia is associated with diverse adverse pregnant outcomes and neonatal disturbance. We aimed to evaluate whether maternal hyper-uric acid (HUA) is associated with the risk of SGA fetus and to explore whether it can modify the association between maternal hyper-blood pressure (HBP) and SGA fetus.

*Materials and methods:* We performed a population-based cross-section retrospective study, a total of 6715 pregnant females were recruited. Multiple logistic regression analysis was performed to identify risk factors significantly correlated with SGA fetus, and then studied the effect of maternal HUA on the association between maternal HBP and SGA fetus.

*Key findings:* We collected 537 SGA fetuses among 6715 pregnant females. Maternal HUA was an independent risk factor for SGA delivery (odds ratio (OR), 2.737; 95% confidence interval (CI), 2.110–3.551). A dose–response association between maternal uric acid and SGA delivery was found among normotensive and hypertensive group. Compared with those whose uric acid was lower than 270 μmo/L with normal–blood pressure (NBP), the risk for SGA delivery in those whose uric acid was higher than 370 μmo/L with stage 2 or 3 hypertension increased 12.695–fold.

*Significance:* Our results suggest that maternal HUA could increase the risk of neonatal SGA, and maternal HUA could be superimposed upon pre-existing maternal HBP and increase the risk for SGA fetus.

## 1. Introduction

Small for gestational age (SGA) is defined as body weight below the tenth percentile from mean gestational age [1,2]. SGA fetus is an important risk for perinatal, and postnatal morbidity and mortality. They are more likely to have neonatal infections, perinatal respiratory repression, jaundice and hypoglycemia in perinatal period, as well as the development of other diseases in later life, including infectious disease, growth faltering, neurodevelopmental deficits, insulin resistance, obesity and hypertension [3–5]. A recent study indicated that SGA fetus was prevalent in low and middle income countries, especially in southern Asia [6]. The prevalence of SGA fetus in south Asia in 2012 was 34%, and 26% of neonatal deaths were due to SGA fetus birth. Reduction of the prevalence of SGA fetus to 10.0% in low and middle

** Correspondence to: Q. Guan, Department of Endocrinology, Shandong Provincial Hospital affiliated to Shandong University, Institute of Endocrinology and Metabolism, Shandong Academy of Clinical Medicine, Shandong Clinical Medical Center of Endocrinology and Metabolism, 324, Jing 5 Rd., Jinan, Shandong 250021, China.
* Correspondence to: C. Zuo, Department of Obstetrics and Gynecology, Shandong Provincial Hospital affiliated to Shandong University, 324, Jing 5 Rd., Jinan, Shandong, 250021, China.
*E-mail addresses:* doctorguanqingbo@163.com (Q. Guan), ChangtingZuo@163.com (C. Zuo).
[1] These authors contributed equally to this work.

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income countries could reduce neonatal deaths by 9.2% [7].

Maternal uric acid is final product of purine degradation and can easily pass through placenta via simple diffusion [8]. At physiological concentrations, it exhibits excellent antioxidant activity. However, when it exceeds physiological levels, it can induce oxidative damage and have a proliferative and proinflammatory effect on small blood vessels [9,10]. In addition, mechanisms related to the increase in uric acid have been clarified, such as excess purine intake, obesity, renal dysfunction, and genetic alterations [11,12]. Thus, in mothers with hyper-uric acid (HUA), high uric acid can transfer into fetal circulation via the placenta. And maternal oxidative stress, vascular endothelial excitation of the placenta and upregulation of the inflammatory responses can further induce the formation of a dysfunctional placenta and, ultimately, prevent fetal development [13]. Additionally, serum uric acid levels demonstrated a close correlation with hypertension, and studies have shown that 25%–40% of all patients with hyper-blood pressure (HBP) can have HUA, which could increase to 70% in pre-eclampsia patients [14].

It has been reported that maternal HBP of pregnancy is an important risk factor of SGA fetus [15]. Placental vascular endothelial cell damage and decreased placental perfusion are responsible for gestational hypertension resulting in SGA fetus [16,17]. Although the association between maternal HUA and fetus SGA has been less studied, a Japanese research study has reported that HUA was an independent risk factor for SGA delivery in maternal normal blood pressure (NBP) pregnant females [18]. Nevertheless, studies that explore the association between maternal HUA and SGA fetus usually have a limited sample size, and no studies have evaluated whether the influence of maternal HBP on SGA fetus can be modified by the presence of maternal HUA. Because maternal HBP may influence SGA fetus and maternal HBP demonstrates a correlation with maternal HUA [19], it is unclear whether maternal HUA is a reflection of maternal HBP on the SGA fetus or whether both these conditions are associated with SGA fetus and deterioration of each other.

Thus, we performed this study to evaluate the independent effect of HUA on the risk of SGA fetus in a large-scale Chinese population and to examine whether the influence of maternal HBP on SGA fetus can be modified by the presence of maternal HUA.

## 2. Subjects and methods

### 2.1. Subjects and research design

We retrospectively obtained the medical records of parturient females who were admitted to Shandong Provincial Hospital, Jinan, Shandong, China, and delivered between January 2013 and September 2015. The females were considered eligible for the study if they met the following criteria: (1) singleton pregnancy, (2) blood lipid and blood biochemical levels were tested after overnight fasting within one week preceding delivery, (3) nonsmokers and nonalcoholic, (4) no history of substance abuse in the previous week [20]. After obtaining the informed consent by telephone and excluding 965 pregnant women with large-for-gestational-age fetus (> 90 percentiles), we collected 6715 pregnant females at a gestational week of 28–43 weeks (Fig. 1). This study was approved by the Ethics Committee of Shandong Provincial Hospital, and the records were licensed for research purposes only.

### 2.2. Data and specimen collection

The baseline demographic information of each eligible parturient was collected from their medical records, which was consisted of maternal age, weight, height, blood pressure, gestational weeks, blood lipid level, fasting blood glucose levels, serum uric acid levels and fetus outcomes. Weight and height were measured in kilograms and centimeters, respectively. Blood pressure was measured in the sitting position using an electronic sphygmomanometer after a 5-min rest and

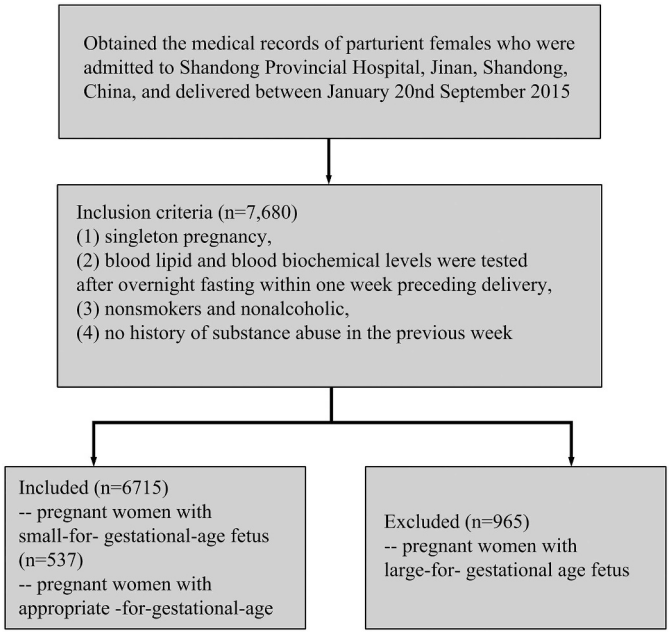


**Fig. 1.** Flow chart of subjects enrollment.

was recorded as the average of three measurements. Gestational age was calculated based on the last menstrual period [21]. Laboratory reports consisted of maternal total cholesterol (TC), triglyceride (TG), fasting blood glucose (FPG), and uric acid (UA) levels. These laboratory indicators were determined using an automatic biochemical analyzer (Olympus AU5400, Tokyo, Japan) in Shandong provincial hospital, and the intra-assay and inter assay coefficients of variation were always below 5% for all of the above parameters. The birth outcomes of fetus, including the neonatal sex, birth weight, the 1–and 5–minutes Apgar scores, the need for neonatal intensive care unit (NICU) admission, and the need for neonatal resuscitation, were recorded [20]. Apgar scores were evaluated from the following five aspects: pulse, breathing, reflex irritability, muscle tone and skin color. Neonatal resuscitation was defined as newborns needed artificial respiration, chest compression or endotracheal intubation after delivery.

### 2.3. Study outcome definition

As recommended by the newest literature related to the diagnostic standard on SGA in China, the newborns were classified into SGA (< 10 percentiles) and appropriate to gestational age (AGA) [21]. Diagnoses of hypertension were made according to the diagnostic criteria of the International Society for the Study of Hypertension in Pregnancy (ISSHP) statement, blood pressure measurements > 140 mmHg systolic and/or 90 mmHg diastolic established the diagnosis of hypertension [22]. We adopted the reference value of pregnant females, as described in the 24th edition of William's obstetrics (> 374.72 μmol/L) to define hyperuricemia [23].

### 2.4. Statistical analysis

All statistical analyses were performed using the SPSS statistical software (version 22.0). Data were presented as the mean ± standard deviations for continuous variables or the percentage for categorical variables. An independent two-sample *t*-test and the Chi-squared test were adopted to compare participants with SGA fetus and fetal AGA. Multiple logistic regression analysis was performed to identify risk factors that were significantly associated with SGA fetus. A *P*-value < 0.05 was considered significant.

**Table 1**
Baseline characteristics of pregnant women and newborns in SGA group and AGA group.

| Characteristic | SGA(537) | AGA(6178) | *P* |
|---|---|---|---|
| Pregnant women | | | |
| Age(y) | 29.67 ± 4.39 | 30.08 ± 4.26 | 0.034 |
| Gestational weeks(w) | 37.65 ± 2.81 | 38.91 ± 1.96 | 0.000 |
| SBP(mmHg) | 128.71 ± 21.68 | 120.96 ± 14.44 | 0.000 |
| DBP(mmHg) | 84.66 ± 16.80 | 77.60 ± 10.95 | 0.000 |
| Height(cm) | 161.30 ± 4.83 | 162.56 ± 4.66 | 0.000 |
| Weight(kg) | 71.47 ± 11.00 | 74.01 ± 10.01 | 0.000 |
| BMI | 27.43 ± 4.11 | 27.98 ± 3.51 | 0.006 |
| TC(mmol/L) | 6.87 ± 2.34 | 6.69 ± 1.55 | 0.155 |
| TG(mmol/L) | 3.34 ± 1.66 | 3.32 ± 1.38 | 0.828 |
| FPG(mmol/L) | 4.45 ± 0.74 | 4.51 ± 0.70 | 0.096 |
| Hypertension(%) | 32.77% | 13.77% | 0.000 |
| Hyperuricemia(%) | 30.54% | 8.89% | 0.000 |
| Newborns | | | |
| Weight(g) | 2354.92 ± 563.58 | 3306.01 ± 455.10 | 0.000 |
| Gender (male %) | 51.40% | 52.15% | 0.737 |
| Low 1-minute APGAR(%) | 6.89% | 0.94% | 0.000 |
| Low 5-minute APGAR(%) | 3.54% | 0.40% | 0.000 |
| NICU admission(%) | 20.67% | 4.76% | 0.000 |

SGA: small for gestational age, AGA: appropriate for gestational age, SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body mass index, TC: total cholesterol, TG: triglyceride, FPG: fasting plasma glucose, NICU: neonatal intensive care unit.

## 3. Results

### 3.1. Characteristics of the study population

A total of 6715 pregnant females aging from 16 to 48 years at 28 to 43 gestational weeks were selected and enrolled in the final analysis. There were 537 pregnant females giving birth to SGA fetus (7.80%). Mothers who gave birth to the SGA fetus were inclined to have a lower height, weight, BMI, gestational week, and a higher systolic blood pressure, diastolic blood pressure compared with fetal AGA group. The percentage of hypertension and hyperuricemia in pregnant females who gave birth to SGA fetus was 32.77% and 30.54% respectively, however, in pregnant females who gave birth to AGA fetus was 13.77% and 8.89%. It demonstrated that mothers who gave birth to the SGA fetus had higher risk of hypertension and hyperuricemia. SGA newborns had a higher risk of NICU admission, low 1– and 5–minutes Apgar scores (Apgar scores < 7) (Table 1). Newborns were SGA, low birth weight (< 2500 g), premature (gestational week < 37 weeks), low 1– and 5–minutes Apgar scores, NICU admission and newborn resuscitation in a higher proportion when their mothers were hypertension and hyperuricemia (Table 2). The percentage of born SGA fetus in normal–-blood pressure (NBP) and normal–uric acid (NUA), NBP and HUA, HBP and NUA, HBP and HUA group was 5.63%, 15.38%, 10.41% and 33.67% respectively (Table 2).

**Table 3**
Multivariate logistic regression analysis of factors associated with SGA fetus.

| Characteristic | OR | 95%CI | SE | *P* |
|---|---|---|---|---|
| Age (year) | 0.962 | 0.940–0.985 | 0.012 | 0.001 |
| Gestational weeks (w) | 0.872 | 0.836–0.909 | 0.021 | 0.000 |
| BMI | 0.907 | 0.880–0.934 | 0.015 | 0.000 |
| Height (cm) | 0.947 | 0.926–0.968 | 0.011 | 0.000 |
| Hyperuricemia (%) | 2.737 | 2.110–3.551 | 0.133 | 0.000 |
| Hypertension (%) | 2.301 | 1.778–2.977 | 0.131 | 0.000 |

SGA: small for gestational age, OR: odds ratio, 95% CI: 95% confidence interval, BMI: body mass index.

### 3.2. The independence of maternal HUA and HBP for SGA fetus

To evaluate the independent role of maternal HUA and HBP for SGA fetus, after adjusting for confounding factors (pregnant age, BMI, height and gestational weeks), which have been demonstrated in previous studies, we showed that the risk of SGA fetus increased approximately 2.301–fold in maternal HBP compared to maternal NBP, and 2.737–fold in maternal HUA compared to maternal NUA (Table 3).

### 3.3. The progressively increased risk for SGA fetus following higher maternal uric acid levels

The maternal uric acid levels were divided into five groups based on quartiles and ninetieth percentile in AGA group. With an increase in maternal uric acid levels, the risk for SGA fetus increased gradually. After adjusting potential confounding factors (pregnant age, BMI, height and gestational weeks), the trend towards increased risk was also clear. The result demonstrated that the maternal uric acid levels were correlated to the risk of SGA fetus in a dose-response manner (Fig. 2). Compared with the lowest percentile group, the risk for SGA fetus increased approximately 3.290–fold in the normal tension group and 8.215–fold in the hypertension group when the maternal uric acid levels were in the highest percentile, after adjusting potential confounding factors (pregnant age, BMI, height and gestational weeks) (Table 4). In the case of normal or high blood pressure, maternal high uric acid increased the risk of SGA, and particularly under the condition of high blood pressure.

### 3.4. Maternal HUA superimposed on maternal HBP aggravates the risk of SGA fetus

Subsequently, we divided the study objects into nine groups according to uric acid level and blood pressure categories. Multivariate-adjusted ORs of SGA fetus in relation to maternal uric acid levels and blood pressure categories are presented in Table 5. With an increase in maternal uric acid levels, the risk for SGA fetus increased gradually after adjusting potential confounding factors (pregnant age, BMI, height and gestational weeks) in maternal normotensive, hypertension (stage 1) and hypertension (stage 2/3) group. Compared with the lowest percentile group, multivariate-adjusted OR of SGA fetus was 3.483,

**Table 2**
different pregnancy outcome characteristics according to serum uric acid and blood pressure among pregnant women.

| Pregnancy outcomes (n/%) | 1NBP + NUA | 2NBP + HUA | 3HBP + NUA | 4HBP + HUA | Total |
|---|---|---|---|---|---|
| SGA | 297/5.63 | 64/15.38 | 76/10.41 | 100/33.67 | 537/7.80 |
| LBW | 208/3.95 | 52/12.50 | 106/14.52 | 187/62.96 | 553/8.24 |
| Preterm delivery | 354/6.71 | 61/14.66 | 132/18.08 | 183/61.62 | 730/10.87 |
| Low 1-minute APGAR | 36/0.68 | 7/1.68 | 21/2.88 | 31/10.44 | 95/1.41 |
| Low 5-minute APGAR | 17/0.32 | 6/1.44 | 5/0.68 | 16/5.39 | 44/0.66 |
| NICU admission | 181/3.43 | 30/7.21 | 64/8.77 | 130/43.77 | 405/6.03 |
| Newborn resuscitation | 56/1.06 | 11/2.64 | 23/3.15 | 29/9.76 | 119/1.77 |

NBP: normal blood-pressure, NUA: normal uric-acid, HUA: high uric-acid, HBP: high blood-pressure, SGA: small for gestational age, LBW: low birth weight, NICU: neonatal intensive care unit.

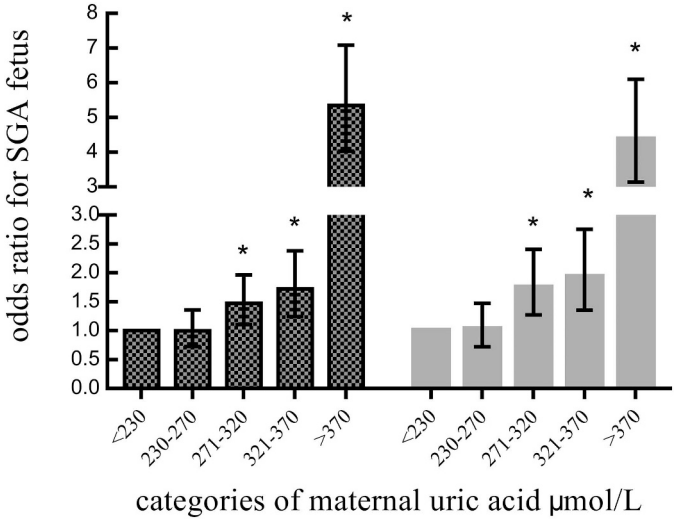


**Fig. 2.** The odds ratio for SGA fetus in different categories of maternal uric acid. The group of uric acid lower than 230 μmol/L was reference standards, the data are expressed as the odds ratio (OR) for fetus SGA. The black column presents unadjusted OR for SGA fetus, gray column present adjusted OR for SGA fetus (adjusting for pregnant age, BMI, height and gestational weeks). *$P < 0.05$ vs. the group of uric acid lower than 230 μmol/L. Abbreviations: SGA, small for gestational age. (Fig. 2s used graph pad prism6 to create the artwork).

2.314, 7.080 in the normotensive, hypertension (stage 1) and hypertension (stage 2/3) group respectively, when the maternal uric acid levels were in the highest percentile (Table 5). Multivariate-adjusted ORs of SGA fetus according to combination of maternal uric acid levels and blood pressure categories are presented in Fig. 3. In fact, maternal high uric acid and high blood pressure can both increase the risk of SGA fetus. Compared to normotensive and the lowest uric acid percentile group, multivariate-adjusted ORs of SGA fetus was 6.172, 6.812 and 12.695 respectively in following three groups, hypertension (stage 1) and the highest uric acid percentile group, hypertension (stage 2/3) and the middle uric acid percentile group, hypertension (stage 2/3) and the highest uric acid percentile group (Fig. 3). It demonstrated that the strengthening effect of maternal HUA on maternal HBP existed with regards to the risk of SGA fetus.

## 4. Discussion

SGA fetus is an important public health issue because of its high mortality and long-term effects on health. Related studies have demonstrated that SGA fetus is associated with poor maternal nutrition, young maternal age, maternal hypertension and maternal infection [24]. We provided precise insight into the association between maternal HUA combined with maternal HBP and SGA fetus in a large-scale population of pregnant females. We demonstrated that either maternal HBP or HUA can increase the risk of SGA fetus and that when maternal HBP combined with maternal HUA, maternal HUA can strengthen maternal HBP with regards to the risk of SGA fetus.

In our study, we demonstrated that SGA fetus was associated with young pregnant age, low height and low BMI. These associations have been verified and explained by other studies [25,26]. The mechanisms of which young pregnant women are likely to have SGA fetus are maternal-fetal incomplete physical maturation, competition for nutrition and immune intolerance for the semi-allogenic nature of fetus [27,28]. Low height and low BMI provide less flexibility to meet the demand of fetal growth during pregnancy [29].

In the present study, we also demonstrated that maternal HBP was independent risk of SGA fetus, which is consistent with the results in previous studies [30]. In the case of normal or high blood pressure, the maternal uric acid levels were correlated to the risk of SGA fetus in a dose-response manner, even adjusting potential-confounding factors (pregnant age, BMI, height and gestational weeks). Multivariate-adjusted OR of SGA fetus showed an obvious increased trend following the increase of maternal uric acid in the normotensive, hypertension (stage 1) and hypertension (stage 2/3) group respectively. These findings demonstrated that maternal HUA increased the risk of SGA fetus, which are consistent with other studies conducted in Japanese and Iranian populations [17,19]. They had demonstrated that there was a strong negative correlation between serum uric acid levels and birth weight.

Naina Kumar et al. also demonstrated that fetus was more likely to have a lower body weight when mother was hypertensive with high serum uric acid levels, but the number of participants was only 110, and not involving the birth weight according to gestational age [31].Hawkins et al. studied 1880 Australian pregnant women and demonstrated that plasma uric acid remained a marker of SGA fetus in hypertensive pregnancy, without adjusting for gestational age, maternal height and other potential risk factors [32]. In our study, we found that maternal HUA not only significantly increased the risk of SGA fetus among hypertensive groups, which is consistent with previous findings, but maternal HUA superimposed on maternal HBP aggravated the risk of SGA fetus.

Considering the pathogenesis of HBP usually involving large blood vessels and microvasculature, studies have shown that HBP correlated with renal arteriolar sclerosis, resulting in decrease of effective renal blood flow and the excretion of uric acid. However, microvascular lesions induce hypoxia, which increase the blood lactic acid level of the kidney and induce the formation of uric acid substrates, such as adenine and hypoxanthine, which can result in HUA [33]. Conversely, HUA can increase the blood pressure levels. It down-regulate nitric oxide (NO) production, which could damage endothelial cells and activate the renin angiotensin system, which could, in turn, deteriorate HBP. It has also been reported that uric acid can induce human vascular smooth muscle cells to proliferate in a dose-dependent manner. At last, uric acid salt will deposit on the small arteries of the damaged artery intima, leading to atherosclerosis and HBP. Thus, HUA and HBP can affect each other and, upon entering a vicious cycle, promote mutually [34–36].

Due to the common pathogenesis of HBP and HUA in pregnancy and the potential interaction [37,38], maternal uric acid can also transfer into the fetal circulation via the placenta. Maternal HUA may be superimposed upon pre-existing maternal HBP and jeopardize the

**Table 4**
Association between maternal uric acid levels and risk for SGA fetus among hypertension and normal tension.

| | Unadjusted OR and 95% CI | | Adjusted OR[a] and 95% CI | |
|---|---|---|---|---|
| Uric acid (μmo/L) | Non-hypertension | Hypertension | Non-hypertension | Hypertension |
| < 230 | 1.000 | 1.705(0.880–3.304) | 1.000 | 1.767(0.809–3.858) |
| 230–270 | 0.934(0.662–1.318) | 2.138(1.227–3.727) | 0.929(0.630–1.370) | 2.784(1.489–5.203) |
| 271–320 | 1.413(1.032–1.934) | 2.667(1.658–4.289) | 1.639(1.161–2.313) | 3.713(2.206–6.248) |
| 321–370 | 1.645(1.143–2.367) | 2.577(1.540–4.311) | 1.887(1.272–2.799) | 2.954(1.673–5.217) |
| > 370 | 3.454(2.423–4.923) | 9.854(7.017–13.836) | 3.290(2.199–4.922) | 8.215(5.354–12.603) |

[a] Adjusted for age, BMI, height and gestational weeks.

**Table 5**
Multivariate-adjusted Odds ratio[a] of SGA fetus according to serum uric acid and blood pressure categories[b] among pregnant women.

| Uric acid (μmo/L) | Non-hypertension | Hypertension (stage 1) | Hypertension (stage 2/3) |
|---|---|---|---|
| < 270 | 1.000 | 1.000 | 1.000 |
| 270–370 | 1.786(1.378–2.315) | 1.061(0.544–2.067) | 3.150(1.003–9.890) |
| > 370 | 3.483(2.437–4.977) | 2.314(1.113–4.811) | 7.080(2.306–21.733) |

SGA: small for gestational age.
[a] Adjusted for age, BMI, height and gestational weeks.
[b] Based on 2010 Chinese Guidelines for the Management of Hypertension.

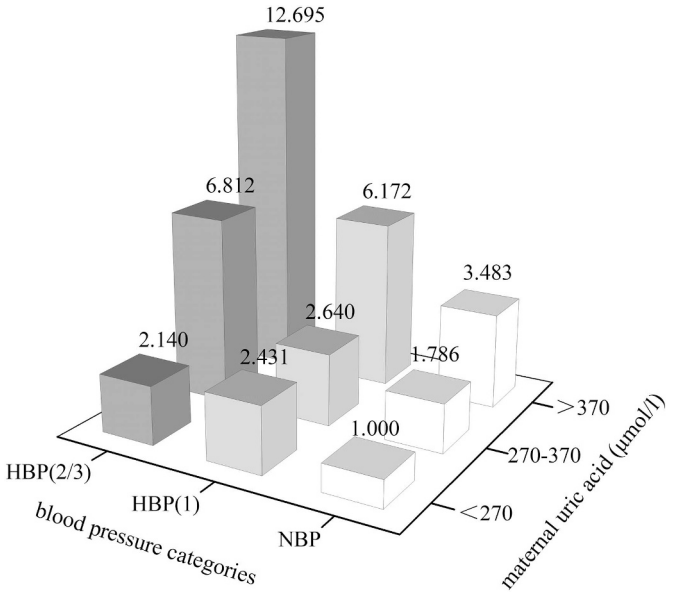


**Fig. 3.** The odds ratio for SGA fetus according to maternal blood pressure and uric acid. The group of normal blood pressure combined with uric acid lower than 270 μmol/L was reference standards, the data are expressed as the odds ratio (OR) for SGA fetus, adjusting for pregnant age, BMI, height and gestational weeks. Abbreviations: NBP, normal blood pressure; HS (1), stage 1 hypertension; HS (2, 3), stage 2 or stage 3 hypertension. (Fig. 3s used origin 8 to create the artwork).

function of the vasculature and placenta, jointly promoting the occurrence of SGA. Another report demonstrated that a HBP patient with HUA was at a 3–5 times risk than pure HBP patients for development of coronary heart disease or cardiovascular disease [39]. This study indicated that hyperuricemia could superimpose upon hypertension and damage the blood vessels.

Related studies have also explored other mechanisms of uric acid leading to SGA fetus. Uric acid could directly inhibit amino acid transfer in the placenta and suppress fetal growth [40]. Several studies have also demonstrated that uric acid was able to stimulate nuclear factor-κB, mitogen-activated protein kinase and increased expression of cyclooxygenase 2, which indicated that inflammatory mechanisms may be involved in the process of fetal growth restriction [41,42]. A Chinese study has demonstrated that increased serum uric acid levels were associated with increased risk of hypoglycemia in type 2 diabetes mellitus [43]. Therefore, increased maternal serum uric acid may result in hypoglycemia leading to fetal developmental restriction. Uric acid is freely transferred via the placenta, however, the effect of fetal hyper-uric acid on the prenatal development remains obscure. Researchers have put forward the hypothesis that in utero exposure to hyper-uric acid might lead to a decreased number of nephrons and a predisposition to insulin resistance [44,45]. Our designed study restricted exploring the effect of fetal hyper-uric acid on SGA fetus. The related mechanism deserves further exploration.

This is the first relatively large sample size study to investigate the risk factor of SGA fetus considering maternal blood pressure and the maternal uric acid levels. The findings attracted our attention to the independence of HUA in the risk of SGA, and we found that HBP combined with HUA can play important roles in SGA. However, several limitations also exist. We didn't have information to evaluate or control other risk factors for SGA fetus including pre-pregnancy BMI, weight gain during pregnancy, nutritional status and previous history of SGA. And laboratory values were available when close to delivery, therefore we were unable to evaluate the temporal effect of maternal high uric acid on fetal development. In addition, as economic level, it is not a regular check when pregnant woman delivery in the hospital, and we failed to have access to the relevant information, non-data are reported on the Doppler evaluation of the fetuses linked with or not linked with the hyperuricemia.

## 5. Conclusion

In conclusion, pregnant females with HUA had a higher risk for SGA fetus, and HUA can be superimposed on pre-existing maternal HBP and increased the risk of a SGA fetus. Thus, the clinical prevention of SGA might be enhanced by paying more attention to the HUA and HBP. Individualized blood pressure management and adequate purine control during pregnancy might be useful for the primary prevention of hyperuricemia of pregnancy and the delivery of a SGA fetus. When maternal uric acid is higher than 370 μmmol/L, clinicians should pay attention to screening for SGA fetus, especially for pregnant women with hypertension.

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## Disclosure statement

The authors have nothing to disclose.

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