Impact of Blood Urea Nitrogen and Creatinine Levels on Maternal and Fetal Outcomes of Pregnancy: a Retrospective Cohort Study

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Research article

Keywords: Urea nitrogen, Creatinine, Adverse pregnancy outcomes, Premature rupture of membranes, Macrosomia, Small for gestational age infants, Large for gestational age infants

Posted Date: April 1st, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-379457/v1>

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Abstract

Background: Blood urea nitrogen (BUN) and creatinine (SCr) are associated with gestational diabetes mellitus (GDM). However, there were limited data in the literature on the influence of BUN and SCr on maternal and fetal outcomes of pregnancy. We aimed to examine the association of BUN and SCr levels during gestation with the risk of selected adverse pregnancy outcomes.

Methods: This retrospective cohort study included 1606 singleton mothers aged 22-44 years. Both BUN and SCr levels were collected and measured during the second (16-18th week), third (28-30th week) trimesters of gestation respectively and followed up pregnancy outcomes. Statistical analysis was used multivariate logistic regression.

Results: In the multivariate adjusted logistic regression model, the highest level of SCr in the second trimester increased the risk of PROM by 45% (95% CI, 1.01-2.09). In the third trimester of gestation, compared with those in the lowest quartile, BUN levels in the highest quartile decreased the risk of macrosomia and LGA by 60%(95% CI, 0.20-0.78), 66%(95% CI, 0.21,0.55) , respectively, and increased the risk of SGA by 137%(1.06, 5.31), 186%(1.29,6.34) in the third and fourth quartiles, respectively. The adjusted OR (95%CI) for macrosomia in the fourth quartile was 0.46 (0.24, 0.87), for SGA in the third quartiles was 2.36 (1.10, 5.10), and for LGA in the fourth quartile was 0.61 (0.41,0.91) compared with those in the first quartile of SCr levels. The elevated changes of BUN (> 0.64mmol/L) was the risk factor of SGA (OR: 2.11, 95%CI: 1.03,4.32).

Conclusion: Higher BUN and SCr levels during the 28-30th week of gestation even those towards the upper limit of the normal range can act as a warning sign of the impending SGA. Elevated changes of BUN and SCr during pregnancy also associated with the lower birth weight.

Background

In the process of pregnancy, the renal workload increases due to rise in maternal and fetus metabolites [1]. These physiological changes may lead to renal pathological damage and renal insufficiency, and the symptoms are relatively insidious [2–4]. A series of studies suggested that significant impairment of kidney function was independently associated with poor obstetric outcomes particularly preterm birth and growth restriction [3, 5–10]. It has been recently reported that pregnancy women in the early stage of chronic kidney disease (CKD) or with a mild decrease in glomerular filtration rate (GFR) were at an increased risk of adverse maternal and fetal events [5]. However, Kidney disease in pregnancy is often under-recognized and under-appreciated owing to the lack of symptoms and routine kidney function testing in pregnancy. Therefore, close monitoring of renal function during pregnancy plays an important role in reducing the risk of adverse maternal and infant events related to renal function.

BUN is the main end product of protein metabolism. The deamination of amino acids produces NH_3 and CO_2 , which are synthesized into urea in the liver and then filter out of the glomeruli and excrete in the

urine eventually [6]. BUN is used as a parameter to evaluate renal function since it will increase when renal efficiency is decompensated. A series of animal and epidemiological researches indicated that elevated BUN levels was a risk factor for insulin sensitivity reduction and increased the risk of diabetes and GDM [7–9]. However, the impact of BUN on fetal and maternal outcomes has not been established. SCr, another indicator to assess renal function, is the product of muscle metabolism. In Muscle cells, creatine slowly forms SCr through irreversible non-enzymatic dehydration reaction, which is released into the blood and excreted by the kidney [6]. A recent large population-based cohort study in non-GDM pregnant women aged 18–45 years showed that higher SCr levels were related to decreased risk of macrosomia [10]. All told, there were limited data in the literature on the association between adverse pregnancy outcomes and maternal BUN and SCr levels. No research has paid attention to the influence of the change values during pregnancy and the combination of the two indicators on the pregnancy outcome as well.

In the present study, we aimed to examine the association of BUN and SCr in the second and third trimesters of pregnancy with adverse pregnancy outcomes including premature rupture of membranes (PROM), macrosomia, small for gestational age infants (SGA), large for gestational age infants (LGA), and to evaluate the influence of the combination of the two indicators and the changes between those two indicators in the second and third trimester of pregnancy on maternal and infant complications in a retrospective cohort study.

Methods

Study design and participants

A total of 1,701 pregnant women who registered and attended for their routine first hospital visit in pregnancy at Antenatal Department of Union Shenzhen Hospital of Huazhong University of Science and Technology (Shenzhen, Guangdong) and planned to give birth at this hospital were recruited from January 2015 to December 2018. The following exclusion criteria were included: history of liver disease ($n = 45$), diabetes or hypertension ($n = 13$), kidney disease ($n = 5$), heart disease ($n = 5$), twin or multiple pregnancy ($n = 27$). At last, a total of 1,606 gravidas with singleton pregnancies were included in the present study. The basic information of the participants was collected at the beginning, and serum BUN and SCr were measured in the second (16–18th) and third (28–30th) trimester of gestation respectively. And follow them up until delivery. Participants signed the informed consent at the beginning of the study with all procedures have been approved by the Ethics Committee of the Union Shenzhen Hospital of Huazhong University of Science and Technology.

Collection of baseline information

Age (years), education (primary, secondary, college or above), smoking status (yes or no), alcohol status (yes or no), conception method (natural or artificial), parity (primiparity or multiparity), history of miscarriage (yes or no), embryo number and history of disease (e.g., liver disease, diabetes or

hypertension, kidney disease, heart disease) were obtained through face-to-face interviews by a well-trained investigator and questionnaires were completed simultaneously. Height and weight were measured using a electronic scale with detailed instructions to follow: stands up straight after taking off shoes with shoulder when she taking off shoes, stands up straight, shoulders parallel and the body is naturally relaxed and accurate to 0.1cm and 0.1kg respectively. Pre-pregnancy body mass index, BMI (kg/m^2) was calculated as weight (kg) divided by the square of the height (m^2).

Laboratory assays

At 16-18th weeks and 28-30th weeks of pregnancy, fasting venous blood were collected by professionally trained investigator. The samples were centrifuged at 3,500 rpm for 5 minutes at 4°C within 2 hours of collection. The BUN and SCr level were measured by enzymatic assay. All laboratory measurements were performed using accelerator a3600 automatic analyzer (Abbott, Chicago, USA).

Assessment of pregnancy outcomes

The adverse pregnancy outcomes of this study include: PROM, macrosomia, SGA and LGA. We followed the definition of the International Classification of Diseases, 10th Revision (ICD-10). The diagnostic criteria for PROM was that maternal self-report of vaginal fluid flow, vaginal PH > 6.5 on litmus test paper, and amniotic fluid components on vaginal smear [11-13]. Macrosomia was diagnosed as a newborn with a birthweight greater than 4000g [14]. SGA and LGA were generally defined as below the 10th or above the 90th percentile on the growth chart, respectively [15].

Statistical analyses

Baseline information was presented as means (SD) for continuous variables and proportion (%) for categorical. Statistical difference between second trimester and third trimester were tested using Student's t-test. BUN and SCr were categorized by quartile distribution with the first quartile serving as the reference. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated by using logistic regression models to examine the association of BUN and SCr of gestation with the risk of adverse pregnancy outcomes across each of the quartiles. Then, the differences (d-value) of the levels between BUN and SCr in the third and second trimester was calculated and analyzed in order to illustrate whether the risk of adverse pregnancy outcomes was caused by changing in concentration during pregnancy. Two models were included in the present study: Model 1 was unadjusted; Model 2 was adjusted for age, education, smoking status, alcohol status, conception method, parity and history of miscarriage. Restricted cubic spline(RCS) was used to reflect the nonlinear associations of BUN and SCr and d-value with adverse pregnancy outcomes. The data were regrouped based on the "cut-off value " of BUN and SCr in the RCS, Group1: no indicator exceeded the "cut-off value"; Group2: one of the indicators exceeded the "cut-off value"; Group3: indicators exceeded the "cut-off value", and the above two models were also constructed. Finally, a age-subgroup (< 35 and $\geq$ 35 years) was performed because advanced maternal age is a known risk factor for adverse pregnancy outcomes [16]. All analyses were carried out by using SPSS 24.0 (SPSS Inc., Chicago, IL, USA) and a two-sided P-value < 0.05 was considered statistically

significant. Graphic production was completed by using R version 3.0.3 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

A total of 1606 singleton pregnant women aged 31.59 (3.83) years were included in the study with 308 cases of PROM, 95 cases of macrosomia, 65 cases of SGA, and 237 cases of LGA. As presented in Table 1, 383 cases were elderly pregnant women. The differences of BUN and SCr between the second trimester and third trimester were statistically significant ($P < 0.05$) and the levels of BUN and SCr in the third trimester were higher than those in the second trimester.

Table 1
Baseline characteristics of all pregnant women in this study

Characteristics of maternal and neonatal	
No. of maternal	1606
Age(years)	31.59 (3.83)
Age categories	
< 35	1223 (76.2)
≥ 35	383 (23.8)
Pre-pregnancy BMI (kg/m ²)	20.86 (3.34)
Education	
Primary	52 (3.2)
Secondary	226 (14.1)
College or above	1328 (82.7)
Smoking	1 (0.1)
Alcohol	3 (0.2)
Conception method	
Natural	1590 (99.0)
Artificial	12 (0.7)
Parity	
Primiparity	711 (44.3)
Multiparity	867 (55.7)
History of miscarriage	697 (43.4)
BUN (mmol/L)	
Second trimester	2.61 (0.62)^a
Third trimester	2.95 (0.74)^a
D-value	0.34 (0.75)

Data was presented as mean(SD) for continuous variables and n(%) for categorical. Statistical difference between second trimester and third trimester were tested using Student's t-test. Abbreviations: BMI: body mass index; BUN: serum urea nitrogen; SCr: serum creatinine; PROM: premature rupture of membranes; SGA: small for gestational age; LGA: large for gestational age. ^a $p < 0.05$.

Characteristics of maternal and neonatal	
SCr (μmol/L)	
Second trimester	43.47 (6.78)^a
Third trimester	47.54 (7.98) ^a
D-value	4.07 (7.12)
Birth weight (kg)	3323.87 (416.50)
PROM	308 (19.2)
Macrosomia	95 (5.9)
SGA	65 (4.0)
LGA	237 (14.8)
Data was presented as mean(SD) for continuous variables and n(%) for categorical. Statistical difference between second trimester and third trimester were tested using Student's t-test. Abbreviations: BMI: body mass index; BUN: serum urea nitrogen; SCr: serum creatinine; PROM: premature rupture of membranes; SGA: small for gestational age; LGA: large for gestational age. ^a $p < 0.05$.	

Association of BUN and SCr with adverse pregnancy outcomes

The associations of BUN and SCr in the second trimester with adverse pregnancy outcomes were shown in Table 2 and Additional file Fig. 1. The second trimester BUN and SCr levels were not significant associated with PROM, macrosomia, SGA, or LGA. However, maternal with SCr levels in the fourth quartile had a 45% (95% CI, 1.01–2.09) higher risk of PROM than those in the first quartile. And each standard deviation (SD) of SCr levels increased the risk of PROM by 16% (95% CI, 1.02–1.32). Moreover, Additional file Fig. 1 indicated that the BUN level between 26.80 to 43.04 μmol/L was a protective factor to PROM.

Table 2

ORs (95%CI) for the adverse pregnancy outcomes according to the quartiles of urea nitrogen (BUN), creatinine (SCr) in second trimester of pregnant

BUN (mmol/L)						
	Q1 (< 2.23)	Q2 (2.23–2.50)	Q3 (2.55-3.00)	Q4 (> 3.00)	<i>P</i> <i>trend</i>	Per SD
PROM						
Case/N	85/459	76/350	82/449	65/348		
Model 1	1 (reference)	1.22 (0.86,1.73)	0.98 (0.70,1.38)	1.01 (0.71,1.45)	0.796	0.95 (0.84,1.08)
Model 2	1 (reference)	1.25 (0.88,1.79)	1.05 (0.74,1.47)	1.04 (0.72,1.50)	0.977	0.96 (0.85,1.10)
Macrosomia						
Case/N	32/459	23/350	22/449	18/348		
Model 1	1 (reference)	0.94 (0.54,1.64)	0.69 (0.39,1.20)	0.73 (0.40,1.32)	0.169	0.83 (0.67,1.04)
Model 2	1 (reference)	0.89 (0.50,1.56)	0.72 (0.41,1.26)	0.69 (0.38,1.27)	0.163	0.82 (0.66,1.03)
SGA						
Case/N	16/459	11/350	19/449	19/348		
Model 1	1 (reference)	0.90 (0.41,1.96)	1.22 (0.62,2.41)	1.60 (0.81,3.16)	0.135	1.13 (0.89,1.43)
Model 2	1 (reference)	0.93 (0.42,2.04)	1.17 (0.59,2.33)	1.53 (0.76,3.08)	0.207	1.10 (0.86,1.40)
LGA						
Case/N	77/459	57/350	57/449	46/348		
Model 1	1 (reference)	0.97 (0.66,1.40)	0.72 (0.50,1.05)	0.76 (0.51,1.22)	0.066	0.88 (0.77,1.02)
Model 2	1 (reference)	0.89 (0.61,1.32)	0.73 (0.50,1.06)	0.75 (0.50,1.21)	0.082	0.88 (0.76,1.02)
SCr ($\mu\text{mol/L}$)						

Abbreviations: PROM: premature rupture of membranes; SGA: small for gestational age; LGA: large for gestational age. Model 1: without adjustment. Model 2: adjustment for age, pre-pregnancy BMI, education, smoking status, alcohol status, conception method, parity and history of miscarriage.

BUN (mmol/L)						
	Q1 (< 38.80)	Q2 ($38.80-43.00$)	Q3 ($43.10-47.70$)	Q4 (> 47.70)		
PROM						
Case/N	65/403	68/402	87/406	88/395		
Model 1	1 (reference)	1.06 (0.73,1.54)	1.42 (0.99,2.02)	1.49 (1.04,2.13)	0.009	1.16 (1.03,1.32)
Model 2	1 (reference)	1.06 (0.73,1.56)	1.39 (0.96,2.00)	1.45 (1.01,2.09)	0.019	1.16 (1.02,1.32)
Macrosomia						
Case/N	25/403	25/402	25/406	20/395		
Model 1	1 (reference)	1.01 (0.57,1.78)	0.99 (0.56,1.76)	0.81 (0.44,1.48)	0.513	0.91 (0.73,1.12)
Model 2	1 (reference)	0.91 (0.50,1.64)	0.98 (0.55,1.74)	0.78 (0.43,1.44)	0.505	0.90 (0.73,1.12)
SGA						
Case/N	13/403	21/402	9/406	22/395		
Model 1	1 (reference)	1.65 (0.82,3.35)	0.68 (0.29,1.61)	1.77 (0.88,3.56)	0.370	1.14 (0.90,1.46)
Model 2	1 (reference)	1.76 (0.86,3.59)	0.70 (0.29,1.68)	1.75 (0.86,3.56)	0.423	1.13 (0.88,1.45)
LGA						
Case/N	62/403	70/402	53/406	52/395		
Model 1	1 (reference)	1.16 (0.80,1.69)	0.83 (0.56,1.23)	0.83 (0.56,1.24)	0.165	0.91 (0.79,1.04)
Model 2	1 (reference)	1.08 (0.73,1.59)	0.81 (0.54,1.21)	0.85 (0.57,1.28)	0.238	0.91 (0.79,1.05)
Abbreviations: PROM: premature rupture of membranes; SGA: small for gestational age; LGA: large for gestational age. Model 1: without adjustment. Model 2: adjustment for age, pre-pregnancy BMI, education, smoking status, alcohol status, conception method, parity and history of miscarriage.						

The associations of BUN and SCr in the third trimester with adverse pregnancy outcomes were shown in Table 3 and Additional file Fig. 2. BUN levels were associated with the risk of macrosomia, SGA and LGA. Compared with those in the first quartile of BUN levels, OR 95% CI of macrosomia in the fourth quartile

was 0.40 (0.20–0.78), OR 95% CI of SGA in the third and fourth quartiles were 2.37 (1.06–5.31) and 2.86 (1.29–6.34), OR 95% CI of LGA in the highest quartile was 0.34 (0.21, 0.55). Each SD of BUN levels decreased the risk of macrosomia by 27% (95% CI, 0.57–0.92), increased the risk of SGA by 51% (95% CI, 1.19–1.91), decreased the risk of LGA by 29% (95% CI, 0.61–0.83), respectively. And Additional file Fig. 2 showed that the BUN level between 2.89 to 5.20mmol/L was a protective factor to macrosomia while between 2.91 to 5.20mmol/L was a risk factor to SGA in a non-linear manner. There was no statistically significant correlation between third trimester BUN and PROM. SCr levels were also associated with the risk of macrosomia, SGA and LGA. Compared with those in the first quartile of SCr levels, OR 95% CI of macrosomia in the fourth quartile was 0.46 (0.24–0.87), OR 95% CI of SGA in the third quartiles was 2.36 (1.10–5.10), OR 95% CI of LGA in the fourth quartile was 0.61 (0.41–0.91). And each SD of SCr levels decreased the risk of macrosomia by 26% (95% CI, 0.59–0.93), increased the risk of SGA by 32% (95% CI, 1.04–1.69), decreased the risk of LGA by 17% (95% CI, 0.71–0.96), respectively. And Additional file Fig. 2 showed that when SCr levels between 28.30 to 46.80 μ mol/L, it was a protective factor to SGA, but inversely related with LGA risk in a non-linear manner. Third trimester SCr levels was not statistically significant associated with risk for PROM.

Table 3

ORs (95%CI) for the adverse pregnancy outcomes according to the quartiles of urea nitrogen (BUN), creatinine (SCr) in third trimester of pregnant

UN (mmol/L)						
	Q1 (< 2.45)	Q2 (2.45–2.90)	Q3 (2.93–3.40)	Q4 (> 3.40)	<i>P</i> <i>trend</i>	Per SD
PROM						
Case/N	85/406	87/442	60/392	76/366		
Model 1	1 (reference)	0.93 (0.66,1.29)	0.68 (0.47,0.98)	0.99 (0.70,1.40)	0.537	0.98 (0.86,1.11)
Model 2	1 (reference)	0.89 (0.63,1.26)	0.65 (0.45,0.95)	0.88 (0.61,1.26)	0.930	0.94 (0.83,1.07)
Macrosomia						
Case/N	33/406	29/442	20/392	13/366		
Model 1	1 (reference)	0.79 (0.47,1.33)	0.61 (0.34,1.08)	0.42 (0.22,0.80)	0.005	0.75 (0.60,0.94)
Model 2	1 (reference)	0.80 (0.48,1.36)	0.58 (0.32,1.04)	0.40 (0.20,0.78)	0.003	0.73 (0.57,0.92)
SGA						
Case/N	9/406	14/442	20/392	22/366		
Model 1	1 (reference)	1.44 (0.62,3.37)	2.37 (1.07,5.27)	2.82 (1.28,6.21)	0.003	1.43 (1.51,1.78)
Model 2	1 (reference)	1.26 (0.53,3.00)	2.37 (1.06,5.31)	2.86 (1.29,6.34)	0.002	1.51 (1.19,1.91)
LGA						
Case/N	81/406	66/442	60/392	30/366		
Model 1	1 (reference)	0.70 (0.49,1.01)	0.73 (0.50,1.05)	0.36 (0.23,0.56)	0.000	0.72 (0.62,0.84)
Model 2	1 (reference)	0.78 (0.54,1.21)	0.79 (0.54,1.15)	0.34 (0.21,0.55)	0.000	0.71 (0.61,0.83)
SCr ($\mu\text{mol/L}$)						

Abbreviations: PROM: premature rupture of membranes; SGA: small for gestational age; LGA: large for gestational age. Model 1: without adjustment. Model 2: adjustment for age, pre-pregnancy BMI, education, smoking status, alcohol status, conception method, parity and history of miscarriage.

UN (mmol/L)						
	Q1 (< 42.05)	Q2 (42.05– 46.80)	Q3 (46.83– 52.25)	Q4 (> 52.25)		
PROM						
Case/N	68/406	73/397	85/402	82/401		
Model 1	1 (reference)	1.12 (0.78,1.61)	1.33 (0.94,1.90)	1.28 (0.90,1.82)	0.114	1.08 (0.95,1.22)
Model 2	1 (reference)	1.08 (0.74,1.57)	1.32 (0.92,1.90)	1.20 (0.83,1.72)	0.209	1.07 (0.94,1.22)
Macrosomia						
Case/N	31/406	23/397	25/402	16/401		
Model 1	1 (reference)	0.74 (0.43,1.30)	0.80 (0.47,1.39)	0.50 (0.27,0.93)	0.045	0.77 (0.62,0.96)
Model 2	1 (reference)	0.75 (0.43,1.31)	0.77 (0.44,1.34)	0.46 (0.24,0.87)	0.024	0.74 (0.59,0.93)
SGA						
Case/N	10/406	13/397	22/402	20/401		
Model 1	1 (reference)	1.34 (0.58,3.09)	2.29 (1.07,4.91)	2.08 (0.96,4.50)	0.027	1.29 (1.04,1.62)
Model 2	1 (reference)	1.34 (0.58,3.12)	2.36 (1.10,5.10)	1.97 (0.90,4.32)	0.040	1.32 (1.04,1.69)
LGA						
Case/N	78/406	54/397	55/402	50/401		
Model 1	1 (reference)	0.66 (0.45,0.97)	0.67 (0.46,0.97)	0.60 (0.41,0.88)	0.011	0.82 (0.72,0.96)
Model 2	1 (reference)	0.75 (0.51,1.10)	0.71 (0.48,1.05)	0.61 (0.41,0.91)	0.016	0.83 (0.71,0.96)
Abbreviations: PROM: premature rupture of membranes; SGA: small for gestational age; LGA: large for gestational age. Model 1: without adjustment. Model 2: adjustment for age, pre-pregnancy BMI, education, smoking status, alcohol status, conception method, parity and history of miscarriage.						

Association of changes for BUN and SCr with adverse pregnancy outcomes

The associations of changes for d-value of BUN and SCr with adverse pregnancy outcomes were shown in Table 4 and Additional file Fig. 3. D-value of BUN levels were associated with the risk of SGA and LGA. Compared with those in the first quartile of d-value for BUN levels, OR 95% CI of SGA in the fourth quartile was 2.11 (1.03–4.32), OR 95% CI of LGA in the fourth quartile was 0.58 (0.34–0.87). And each SD of d-value for BUN levels decreased the risk of SGA by 41% (95% CI, 1.01–1.80), decreased the risk of LGA by 29% (95% CI, 0.70–0.94) respectively. And Additional file Fig. 2 showed that the d-value of BUN Level from 0.31 to 2.45mmol/L was a protective factor for SGA risk, while from 0.29 to 2.45mmol/L was positively associated with risk of LGA in a non-linear manner. The associations of d-value of BUN in the third trimester with the risk of PROM and macrosomia was not statistically significant.

Table 4

ORs (95%CI) for the adverse pregnancy outcomes according to the quartiles of the d-value between the second and the third trimester

	D-value of BUN(mmol/L)				<i>P</i> <i>trend</i>	Per SD
	Q1 (<-0.20)	Q2 (-0.21-0.20)	Q3 (0.21–0.63)	Q4 (> 0.64)		
PROM						
Case/N	67/374	68/259	73/394	100/511		
Model 1	1 (reference)	1.20 (0.83,1.75)	1.04 (0.72,1.50)	1.12 (0.79,1.57)	0.735	1.02 (0.90,1.15)
Model 2	1 (reference)	0.99 (0.69,1.46)	1.78 (0.81,1.70)	1.42 (0.99,2.04)	0.033	0.97 (0.85,1.11)
Macrosomia						
Case/N	22/374	22/327	28/394	23/511		
Model 1	1 (reference)	1.15 (0.63,2.13)	1.22 (0.69,2.18)	0.75 (0.41,1.38)	0.377	0.89 (0.72,1.10)
Model 2	1 (reference)	1.13 (0.61,2.10)	1.18 (0.66,2.11)	0.68 (0.37,1.27)	0.243	0.87 (0.70,1.09)
SGA						
Case/N	12/374	9/327	15/394	29/511		
Model 1	1 (reference)	0.85 (0.36,2.05)	1.19 (0.55,2.59)	1.82 (0.91,3.61)	0.040	1.33 (1.05,1.67)
Model 2	1 (reference)	0.92 (0.38,2.28)	1.56 (0.70,3.49)	2.11 (1.03,4.32)	0.015	1.41 (1.10,1.80)
LGA						
Case/N	63/374	50/327	69/394	55/511		
Model 1	1 (reference)	0.89 (0.59,1.34)	1.05 (0.72,1.53)	0.60 (0.40,0.88)	0.022	0.82 (0.71,0.94)
Model 2	1 (reference)	0.91 (0.60,1.39)	1.10 (0.74,1.62)	0.58 (0.34,0.87)	0.022	0.81 (0.70,0.94)
D-value of SCr (μmol/L)						

Abbreviations: PROM: premature rupture of membranes; SGA: small for gestational age; LGA: large for gestational age. Model 1: without adjustment. Model 2: adjustment for age, pre-pregnancy BMI, education, smoking status, alcohol status, conception method, parity and history of miscarriage.

	D-value of BUN(mmol/L)				<i>P</i> <i>trend</i>	Per SD
	Q1 (<-0.20)	Q2 (-0.21-0.20)	Q3 (0.21–0.63)	Q4 (> 0.64)		
	Q1 (<-0.5)	Q2 (-0.48-3.70)	Q3 (3.71–8.30)	Q4 (> 8.31)		
PROM						
Case/N	79/406	81/399	73/398	75/403		
Model 1	1 (reference)	1.05 (0.75,1.49)	0.93 (0.65,1.32)	0.95 (0.67,1.35)	0.609	0.94 (0.83,1.06)
Model 2	1 (reference)	0.98 (0.68,1.40)	0.93 (0.65,1.34)	0.91 (0.63,1.30)	0.557	0.93 (0.82,1.06)
Macrosomia						
Case/N	32/406	25/399	15/398	23/403		
Model 1	1 (reference)	0.78 (0.45,1.34)	0.46 (0.24,0.86)	0.71 (0.41,1.23)	0.087	0.83 (0.67,1.03)
Model 2	1 (reference)	0.82 (0.47,1.41)	0.43 (0.22,0.82)	0.18 (0.39,1.20)	0.056	0.81 (0.66,1.01)
SGA						
Case/N	12/406	13/399	21/398	19/403		
Model 1	1 (reference)	1.11 (0.50,2.45)	1.83 (0.89,3.77)	1.63 (0.78,3.39)	0.098	1.20 (0.95,1.53)
Model 2	1 (reference)	1.04 (0.46,2.36)	1.85 (0.89,3.84)	1.62 (0.77,3.41)	0.094	1.23 (0.96,1.58)
LGA						
Case/N	75/406	59/399	40/398	63/403		
Model 1	1 (reference)	0.76 (0.53,1.11)	0.49 (0.33,0.74)	0.82 (0.57,1.18)	0.094	0.90 (0.78,1.04)
Model 2	1 (reference)	0.83 (0.56,1.21)	0.49 (0.32,0.74)	0.82 (0.56,1.20)	0.085	0.89 (0.77,1.03)
Abbreviations: PROM: premature rupture of membranes; SGA: small for gestational age; LGA: large for gestational age. Model 1: without adjustment. Model 2: adjustment for age, pre-pregnancy BMI, education, smoking status, alcohol status, conception method, parity and history of miscarriage.						

D-value of SCr levels were associated with the risk of macrosomia and LGA. Compared with those in the first quartile of d-value for SCr levels, OR 95% CI of macrosomia in the third quartile was 0.43 (0.22–0.82), OR 95% CI of LGA in the third quartile was 0.49 (0.32–0.74). Additional file Fig. 3 showed that the d-value of SCr level from – 13.40 to 3.65mmol/L was inversely associated with the risk of both macrosomia and LGA in a non-linear manner. The associations of d-value of SCr in the third trimester with PROM and SGA were not statistically significant.

Association of combined classification of BUN and SCr with adverse pregnancy outcomes

The associations of combined classification of BUN and SCr with adverse pregnancy outcomes were shown in Table 5. The associations of combined classification of BUN and SCr in the third trimester with PROM were not statistically significant. However, compared with maternal in the G1, the ORs 95% CI of macrosomia in G2 and G3 were 0.59 (0.37–0.94), 0.46 (0.26–0.82), OR 95% CI of SGA in G3 were 3.34 (1.61–6.94), OR 95% CI of LGA in G2 and G3 were 0.71 (0.51–0.98), 0.54 (0.37–0.79).

Table 5

ORs (95%CI) for the adverse pregnancy outcomes according to the group of the combination of urea nitrogen (BUN) and creatinine (SCr) in the third trimester

Groups of BUN and SCr				<i>P_{trend}</i>
G1	G2	G3		
PROM				
Case/N	92/495	129/661	87/450	
Model 1	1 (reference)	1.06 (0.79,1.43)	1.05 (0.76,1.45)	0.764
Model 2	1 (reference)	1.10 (0.81,1.49)	0.98 (0.70,1.37)	0.913
Macrosomia				
Case/N	41/495	34/661	20/450	
Model 1	1 (reference)	0.60 (0.38,0.96)	0.52 (0.30,0.89)	0.012
Model 2	1 (reference)	0.59 (0.37,0.94)	0.46 (0.26,0.82)	0.005
SGA				
Case/N	10/495	26/661	29/450	
Model 1	1 (reference)	1.99 (0.95,4.16)	3.34 (1.61,6.94)	0.001
Model 2	1 (reference)	1.93 (0.91,4.08)	3.49 (1.67,7.31)	0.001
LGA				
Case/N	93/495	93/661	51/450	
Model 1	1 (reference)	0.71 (0.52,0.97)	0.55 (0.38,0.80)	0.001
Model 2	1 (reference)	0.71 (0.51,0.98)	0.54 (0.37,0.79)	0.001
PROM: premature rupture of membranes; SGA: small for gestational age; LGA: large for gestational age. Model 1: without adjustment. Model 2: adjustment for age, pre-pregnancy BMI, education, smoking status, alcohol status, conception method, parity and history of miscarriage.				

Subgroups younger than 35 years old had the same associations as above, but most subgroups older than 35 years old were not statistically significant (Additional file Table 1, 2). And statistical tests for interactions between BUN/SCr and age on outcome were not significant (all $P > 0.05$).

Discussion

In this retrospective cohort study, we observed an increased risk of PROM in pregnant women with high or even those towards the upper limit of the normal range of SCr levels during 16-18th weeks of gestation.

During 28-30th weeks of gestation, pregnant women with higher or even those towards the upper limit of the normal range of BUN and SCr exhibited an increased risk of SGA. The elevated changes of BUN during pregnancy influenced the birth weight of newborn. In addition, the risk of SGA increased substantially if BUN and SCr levels high or even those towards the upper limit of the normal range simultaneously.

Mild renal function damage would lead to improper regulation of gestational adaptation to volume and vascular pressure change, resulting in obstetric complications [17]. And as kidney function declines, the chance of a women having adverse maternal outcomes increased [18]. A retrospective study conducted by Jessica Kendrick et al. found that women with kidney disease increased the incidence of low birth weight by 138% (95% CI, 1.64–3.44), increased incidence of SGA by 37% (95% CI, 0.94-2.00) [19]. In addition, a recently systematic review and meta-analysis showed that pregnancy with CKD had greater odds of premature delivery (OR, 5.72; 95% CI, 3.26–10.03), small for gestational age/low birth weight (OR, 4.85; 95% CI, 3.03–7.76) [17].

At present, the reference for biochemical indexes of pregnant women was no unified.[20–22] A recent cross-sectional study of 13656 healthy pregnant women and 2634 non-pregnant women pointed out that the median of BUN at 28–35 weeks of gestation was 2.7mmol/L (95% CI 1.6–4.3), and the median of SCr at 13–20 and 28–35 weeks of gestation was 43.27 μ mol/L (95% CI 31.3–57.6), 40.27 μ mol/L (95% CI 30.3–53.1) [22]. It is worth noting that our study showed that the critical value of increased risk of PROM caused by SCr levels in the second trimester was 47.70 μ mol/L, while the critical value of increased risk of SGA caused by BUN and SCr levels in the third trimester was 2.9 mmol/ L and 46.80 μ mol/ L, respectively. Hence,higher BUN and SCr levels or even close to the upper limit of the normal range, could give an early warning of occurrence for SGA. Renal disease is often clinically silent in the early and middle stage of renal injury. Bun and SCr may change only slightly until GFR drops by more than 50%. However, these pathological changes affect the regulation of blood pressure and blood volume, which can easily lead to insufficient uterine placental perfusion and affect fetal development. The exact mechanism associated with this issue was not well understood and requires further studies.

The increase of an index may be greatly influenced by external factors, thus we combine the BUN and SCr measurements and regroup them for analysis. The risk of SGA increased by 249% in pregnant women whose two indicators exceeded the cut-off value, compared with those whose two indicators did not exceed the cut-off value. We also analyzed the relative BUN and SCr change from the second trimester to the third trimester of gestation age. According to the Table 5 and Supplementary Fig. 3, the risk of SGA was higher with a elevated meteral BUN level of > 0.64mmol/L. Therefore, not only the real-time level of renal function indicators must be paid attention to, but also the dynamic monitoring of renal function. A interaction and subgroup analysis by age (< 35 and $\geq$ 35 years) was also performed to verify whether age would affect the risk of adverse pregnancy outcomes in association with maternal BUN and SCr levels. We found a significant correlation between BUN and SCr levels and adverse pregnancy outcomes in women aged < 35 years, but not in women aged $\geq$ 35 years. There was no significant interaction between maternal age and the level of BUN and SCr (all *P*-interaction > 0.05). Further studies with larger sample

sizes are required to clarify the risk of adverse pregnancy outcomes in relation to BUN and Scr levels and age dependent effects.

Although our study comprehensively explored the association between maternal renal function using two parameters and the risk of adverse pregnancy outcomes in a relatively large sample size, some limitations in this study remain. Firstly, the analytic cohort were from China, which may limit the generalizability of the study results. Secondly, although we accounted for known confounders, some unmeasured or unknown residual confounders remained (either unmeasured or unknown). Finally, the concentrations of BUN and SCr were greatly influenced by other factors, and did not change significantly when GFR was slightly decreased, so they were not sensitive indicators of renal damage. However, the chosen biochemical parameters of BUN and SCr to assess maternal renal function are simple, inexpensive and readily available tests thus should be additionally evaluated [23].

Conclusions

Higher BUN and SCr levels during the 28-30th week of gestation even those towards the upper limit of the normal range can act as a warning sign of the impending SGA. Elevated changes of BUN and SCr during pregnancy also associated with the lower birth weight. Combined analysis of the two indicators is more conducive to evaluate renal function and prevent the occurrence of SGA. More attention should be paid to the dynamic monitoring of renal function during pregnancy.

Abbreviations

BMI: body mass index; BUN: Blood urea nitrogen; CKD: Chronic kidney disease; GDM: Gestational diabetes mellitus; GFR: Glomerular filtration rate; LGA: Large for gestational age infants; SCr: Serum creatinine; SD: standard deviation; SGA: Small for gestational age infants; ORs: Odds ratios 95%; CIs: 95% confidence intervals; PROM: Premature rupture of membranes; RCS: Restricted cubic spline

Declarations

Ethics approval and consent to participate

The protocol for this study was approved by the Ethics Committee of the Union Shenzhen Hospital of Huazhong University of Science and Technology (No. 2019072644).

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

Funding

This work was supported by Shenzhen Nanshan District Science and Technology Project [grant number 2019007]. The funding sources had no involvement in the study design; collection, analysis, or interpretation of data; the writing of the report, nor the decision to submit the article for publication.

Authors' contributions

GD, ZL and LW conceived and designed the study. YW and RS assisted with study design. LW contributed to statistical analysis and wrote the manuscript. YL and HC provided statistical advice and assisted with data analysis. GD and SS reviewed and edited the manuscript. All authors read and approved the final manuscript.

Acknowledgments

We thank the mothers and children who participated in this study and all the clinical staff at Union Shenzhen Hospital of Huazhong University of Science and Technology for their support and contribution.

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