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Research Article

Relationship of serum uric acid, serum creatinine and serum cystatin C with maternal and fetal outcomes in rural Indian pregnant women

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ABSTRACT

Background: Hypertensive disorders are the most common in pregnancy. Several studies showed a positive correlation between elevated maternal serum uric acid (UA), serum creatinine and adverse maternal and fetal outcomes, but only a few studies are available on serum cystatin C and maternal and fetal outcomes. The present study was undertaken to study the association of serum UA, creatinine and cystatin C with maternal and fetal outcomes.

Methods: Out of 116 pregnant women 69 women had no hypertension and 47 had hypertension with or without proteinuria. Serum UA, creatinine and cystatin C was measured by modified Uricase method, modified kinetic Jaffe's reaction and particle-enhanced immunonephelometric assay respectively. Multivariate logistic regression was performed to determine the independent effects of serum UA, creatinine and cystatin C on maternal and fetal outcomes using stata 13.1.

Results: The adjusted odds ratio (OR) was 3.73 (95% CI: 1.18-11.75; P=0.024) for UA; 15.79 (95% CI: 3.04-81.94; P=0.001) for creatinine and 2.03 (95% CI: 0.70-5.87; P=0.192) for cystatin C in hypertensive disorders of pregnancy. All the three renal parameters were not significantly associated with birth weight, gestational age of delivery and mode of delivery after adjusting for the confounding factors.

Conclusions: Serum creatinine and uric acid are independent risk factors for hypertensive disorders of pregnancy. High serum uric acid is associated with low birth weight and delivery by caesarian section whereas high serum creatinine with preterm delivery only before adjustment for confounding factors and not after adjustment. Serum cystatin C was not significantly associated with the maternal and fetal outcomes.

Keywords: Uric acid, Creatinine, Cystatin C, Gestational Hypertension, Preeclampsia, Gestational age, Birth weight, Caesarian section, Logistic regression

INTRODUCTION

Hypertensive disorders account for approximately 2%-10% of all pregnancies.[1,2] Among these pre-eclampsia (PE) is one of the major causes of maternal and perinatal morbidity and mortality worldwide whereas uncomplicated gestational hypertension has a better prognosis. Gestational hypertension is defined as the new onset gestational hypertension after the 20th week of gestation but without proteinuria.[3] PE is characterized by new onset gestational hypertension after the 20th week of gestation, proteinuria and impaired renal function.[3] Due to hormonal and hemodynamic changes of pregnancy, renal function is altered and more so in hypertensive disorders and hence these changes must be considered when assessing renal function in pregnancy. Serum Uric acid (UA), serum creatinine and more recently serum cystatin C levels are the indices of renal function. Several studies have reported a positive correlation between elevated maternal serum UA, serum creatinine and adverse maternal and fetal outcomes.[4-10] We found one study showing an association of high plasma cystatin C levels and PE which reflects the acute kidney dysfunction associated with PE but we did not find studies showing the relationship between serum cystatin C and the fetal outcomes.[11] We hypothesize that elevated levels of serum UA, serum Creatinine and serum cystatin C are associated with adverse maternal and fetal outcomes and hence in our study we would like to evaluate the relationship between the above mentioned parameters and the maternal and fetal outcomes.

METHODS

This pilot study was performed on 116 pregnant women in the Department of obstetrics & gynaecology, Mediciti Institute of Medical Sciences, Ghanpur, Ranga Reddy district, Telangana, India. Written informed consent was taken from all included participants. Among them 69 women did not develop hypertension and 47 developed hypertension with or without proteinuria. All of them had no present or past history of hypertension, diabetes mellitus or renal disease. 5 ml of non-fasting venous blood samples were collected at the time of delivery from all the included participants.[10]

Measuring parameters-mother

The blood pressure was measured using an oscillometric digital sphygmomanometer (Model: Omron HEM-780N3). The international society for the study of hypertension in pregnancy guidelines were followed for the measurement of blood pressure.[3] Two measurements taken 4 hours apart with systolic blood pressure ≥ 140 mm Hg and diastolic blood pressure ≥ 90 mm Hg was used as the diagnostic criteria for the hypertension in pregnancy.Serum uric acid was measured by modified Uricase method in Dade Behring-Dimension Xpand plus system using uric acid flex reagent cartridge according to the manufacturer's instructions.[12] Serum creatinine was measured by modified kinetic Jaffe's reaction in Dade Behring-Dimension Xpand plus system using creatinine flex reagent cartridge according to the manufacturer's instructions.[13] Serum cystatin C was measured by a fully automated particle-enhanced immunonephelometric assay (N Latex cystatin C, Dade-Behring, Inc) in BN Pro-Spec nephelometer (Dade Behring, Inc, Deerfield, IL) according to the manufacturer's instructions.[14] Urinary proteins were measured in random mid-stream urine sample by semi-quantitative dip stick method.[15] Two readings of 1+ (30 mg/dl) were taken as the diagnostic criteria for pre-eclampsia.[3] Further details regarding the methodology were presented previously.[16]

Measuring parameters-new-born

The weight of the new-born was measured by a digital weighing scale (SECA 354/364).

Statistical tools

The data was entered in a MS-Excel database and was analysed using stata 13.1 statistical software (Stata, College Station, Texas USA). We performed multivariate logistic regression to determine the independent effects of serum UA, serum creatinine and serum cystatin C before and after adjusting for the possible confounding factors on maternal and fetal outcomes. The hypertensive disorders of pregnancy, birth weight, gestational age of delivery and mode of delivery were treated as the dependent variables and serum UA, serum creatinine and serum cystatin C as independent variables. Both dependent and independent variables were dichotomized. Hypertension, birth weight and gestational age of delivery were dichotomized using the standard cut-off values.[3,17,18] The cut-offs for dichotomization were taken as 5.88 mg/dl for serum uric acid,[19] 0.8 mg/dl for serum creatinine[16] and 1.3 mg/L for serum cystatin c.[16] Serum uric acid ≥ 5.88 mg/dl, serum creatinine ≥ 0.8 mg/dl and serum cystatin C ≥ 1.3 mg/L were coded as 1 and those less than the cut-offs were coded as 0. For each outcome the first model was unadjusted and the second model was adjusted for the covariates as possible confounders in the analysis. The possible confounders were age, BMI, gestational age, parity and birth weight in the first analysis where hypertensive disorders were taken as the dependent variable (Table 2); age, BMI, gestational age, parity and hypertensive disorders in the second analysis where birth weight was taken as the dependent variable (Table 3); age, BMI, parity, birth weight and hypertensive disorders in the third analysis where the gestational age of delivery is the outcome (Table 4); age, BMI, parity, birth weight, gestational age and hypertensive disorders in the fourth analysis where mode of delivery was taken as the dependent variable (Table 5). A p value of <0.05 was considered as statistically significant.

RESULTS

Table 1: Categorization of included participants.

No.	Dependent variable	N
1	Blood pressure <140/90 mm Hg	69
	Blood pressure ≥140/90 mm Hg with or without proteinuria	47
2	Birth weight (Kg) <2.5	35
	Birth weight (Kg) ≥2.5	81
3	Gestational age of delivery (wks.) <37	17
	Gestational age of delivery (wks.) ≥37	99
4	Mode of delivery: vaginal	87
	Mode of delivery: caesarean section	29
	Independent variable	
1	Serum uric acid ≥ 5.88 mg/dl	26
	Serum uric acid <5.88 mg/dl	90
2	Serum creatinine ≥ 0.8 mg/dl	19
	Serum creatinine < 0.8 mg/dl	97
3	Serum cystatin C ≥ 1.3 mg/L.	25
	Serum cystatin C < 1.3 mg/L.	91

The maternal and child characteristics of the study participants were presented previously in Table 1.[16] The included participants were presently categorized as shown in Table 1.

Table 2: Multivariate logistic regression.

Hypertensive disorders of pregnancy[€]				
	Model 1		Model 2*	
Parameter	Unadjusted OR (95% CI[β])	P-value	Adjusted OR* (95% CI)	P-value
Serum uric acid (mg/dl)	2.59 (1.06-6.32)	0.036♦	3.73 (1.18-11.75)	0.024♦
Serum creatinine (mg/dl)	19.93 (4.32-91.88)	0♦	15.79 (3.04-81.94)	0.001♦
Serum cystatin C (mg/L)	2.34 (0.95-5.76)	0.063	2.03 (0.70-5.87)	0.192

*model adjusted for age, BMI, gestational age of delivery, parity & birth weight
[€]no hypertension coded as 0 and hypertension with or without proteinuria coded as 1
[β]confidence interval
♦Statistically Significant (P < 0.05)

Table 2 Shows the results of multivariate logistic regression analysis for hypertensive disorders of pregnancy: pregnant women with high serum uric acid (≥5.88 mg/dl) and high serum creatinine (≥0.8 mg/dl) are at over 3.73 times and 15.79 times respectively, the risk of developing hypertensive disorders compared to the pregnant women with low serum uric acid and low serum creatinine after adjusting for the confounding factors. Hence serum uric acid and serum creatinine are independent risk factors for the development of hypertensive disorders of pregnancy. There was no significant association between serum cystatin C and the development of hypertensive disorders.

Table 3: Multivariate logistic regression.

Birth weight[#]				
	Model 1		Model 2*	
Parameter	Unadjusted OR (95% CI[β])	P-value	Adjusted OR* (95% CI)	P-value
Serum uric acid (mg/dl)	2.49 (1.01 - 6.17)	0.047♦	1.53 (0.40-5.79)	0.531
Serum creatinine (mg/dl)	2.45 (0.89 - 6.72)	0.08	1.58 (0.33-7.60)	0.565
Serum cystatin C (mg/L)	1.40 (0.55 - 3.58)	0.475	0.94 (0.25-3.51)	0.937

*model adjusted for age, BMI, gestational age of delivery, parity & blood pressure
[#] birth weight < 2.5 kg coded as 1 and ≥ 2.5 kg coded as 0
[β]confidence interval
♦Statistically Significant (P < 0.05)

Table 4: Multivariate logistic regression.

Gestational age of delivery[δ]				
	Model 1		Model 2*	
Parameter	Unadjusted OR (95% CI[β])	P-value	Adjusted OR* (95% CI)	P-value
Serum uric acid (mg/dl)	1.54 (0.49 - 4.88)	0.456	0.79 (0.13 - 4.66)	0.797
Serum creatinine (mg/dl)	3.60 (1.13 - 11.43)	0.029♦	1.93 (0.35 - 10.51)	0.445
Serum cystatin C (mg/L)	2.29 (0.75 - 6.99)	0.143	1.97 (0.41 - 9.35)	0.391

*model adjusted for age, BMI, birth weight, parity & blood pressure
[δ]gestational age of delivery < 37 wks. coded as 1 and ≥ 37 wks. coded as 0
[β]confidence interval
♦Statistically Significant (P < 0.05)

Table 3 shows the results of multivariate logistic regression analysis for birth weight: pregnant women having high serum uric acid levels (≥5.88 mg/dl) are at over 2.49 times the risk of giving birth to low birth weight babies (<2.5 Kg) compared to the pregnant women with low serum uric acid before adjusting for the confounding factors but not after adjustment. We found no significant association between serum creatinine, serum cystatin C and the birth weight.

Table 4 shows the results of multivariate logistic regression analysis for gestational age of delivery:

pregnant women with high serum creatinine (≥0.8 mg/dl) are at over 3.60 times the risk of having gestational age of delivery < 37 wks. compared to the pregnant women with low serum creatinine before adjusting for the confounding factors but not after adjustment. Serum UA and serum cystatin C were not significantly associated with the gestational age of delivery.

Table 5: Multivariate logistic regression.

Mode of delivery[£]				
	Model 1		Model 2[*]	
Parameter	Unadjusted OR (95% CI[β])	P-value	Adjusted OR[*] (95% CI)	P-value
Serum uric acid (mg/dl)	2.93 (1.15-7.46)	0.024[♦]	2.99 (0.97-9.17)	0.054
Serum creatinine (mg/dl)	1.98 (0.69-5.66)	0.198	1.13 (0.30-4.18)	0.849
Serum cystatin C (mg/L)	2.52 (0.98-6.50)	0.055	2.46 (0.82-7.42)	0.108

*model adjusted for age, BMI, birth weight, parity, blood pressure , gestational age of delivery
[£]caesarean section coded as 1 and vaginal delivery coded as 0
[β]confidence interval
[♦]Statistically Significant (P < 0.05)

Table 5 shows the results of multivariate logistic regression analysis for mode of delivery: pregnant women with high serum uric acid (≥ 5.88 mg/dl) are at over 2.93 times the risk of undergoing cesarean section compared to the pregnant women with low serum uric acid before adjusting for the confounding factors but not after adjustment. Serum creatinine and serum cystatin C were not significantly associated with the mode of delivery.

DISCUSSION

The association between raised serum uric acid and pre-eclampsia was first reported in 1917.[20] The elevation in serum uric acid and serum creatinine may be attributed to reduced uric acid and creatinine clearance secondary to reduced glomerular filtration rate, increased reabsorption and decreased secretion in women with pre-eclampsia.[21-23] The pathophysiologic mechanisms of pre-eclampsia comprising increased trophoblastic tissue shedding, endothelial dysfunction, and reduced blood flow in the fetomaternal unit have also been hypothesized as the underlying cause of hyperuricemia in this condition.[24] The elevation in serum cystatin C in pregnancy might be due to increased production due to increase in the number of nucleated cells.[16]

Several studies have reported a positive correlation between elevated maternal serum uric acid levels and adverse maternal and fetal outcomes.[4-8,25-27] There was disagreement in serum uric acid and serum creatinine as predictors of hypertensive disorders. Studies done by weerasekara D.S et al, Manjareeka M et al concluded that serum uric acid and serum creatinine are not predictive of pre-eclampsia and Thangaratinam S et al concluded that serum uric acid is not predictive of preeclampsia.[19,23,28] However, Studies done by Roberts et al and Bellomo et al found uric acid to be predictive of gestational hypertension.[6,29] Our findings of serum uric acid as an independent risk factor for hypertensive disorders of pregnancy agree with the study done by Gianni Bellomo et al and Roberts et al.[6,29] We did not observe any significant association between serum cystatin C and the development of hypertensive disorders in contrast to the study done by Franceschini et al.[11] There are studies to show the association of high serum uric acid levels with the preterm delivery and small for gestational age but in our study we found an association between high serum creatinine (≥ 0.8 mg/dl) and preterm delivery but not with high serum uric acid and serum cystatin C.[6,30] Also we found in our study that pregnant women with high uric acid levels (≥ 5.88 mg/dl) are associated with low birth weight (<2.5 kg) similar to the studies done by Akahori et al, Sagen et al and Schuster et al but serum creatinine and serum cystatin C were not found to be associated with low birth weight.[31-33] Our findings of high uric acid levels associated with caesarian section agree with the study done by Patel et al.[30] The variability in the findings can be explained by the differences in the population, definitions of hypertensive disorders of pregnancy and test cut-off values. Our study is limited by the small sample size for each hypertensive disorder group of pregnant women. Also the associations of the three renal parameters with maternal outcomes like the complications of PE and fetal outcomes like Intra Uterine Growth Retardation (IUGR), still births, neonatal deaths, small for gestational age (SGA) and Apgar score have not been studied.

CONCLUSIONS

We have observed that serum creatinine and serum uric acid is independent risk factors for developing hypertensive disorders in pregnant women. High serum uric acid levels are associated with low birth weight and delivery by caesarian section whereas high serum creatinine levels are associated with preterm delivery in pregnant women only before adjustment for confounding factors and not after adjustment. Serum cystatin C was not found to be significantly associated with the studied maternal and fetal outcomes. Further large scale cohort studies are required to study the association between the three renal parameters and all the maternal and fetal outcomes.

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