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GESTATIONAL HYPERTENSION;
MATERNAL AND FETAL OUTCOME IN WOMEN WITH ROLE OF HYPERURECEMIA

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ABSTRACT… Objective: Aim of the study was to ascertain prospectively the prognostic value of serum uric acid for fetal and maternal outcomes in women with gestational hypertension. **Patients and Methods:** This prospective study was conducted at department of Gynae & Obs, Maternal and Child Health Center, PIMS Islamabad, from January to December 2003. A total of 200 women with a gestational age >20 weeks, and blood pressure >130/90 mmHg were inducted in the study. At presentation serum uric acid, creatinine, hemoglobin, and platelets were measured along with blood pressure. All patients were divided into group A (uric acid <4.5 mg/dl) and group B (>4.5 mg/dl) and were followed for one month after the delivery to record pregnancy and neonatal outcome. **Results:** A significant difference ($p<0.05$) in the levels of uric acid, hemoglobin, platelet count, creatinine and blood pressure was noted between patients of group A and B. A significant decrease ($p<0.05$) in preterm delivery, baby birth weight and increase in fetal mortality was noted in patients of group B as compared to those of group A. Regarding maternal outcome preeclampsia ($p=0.005$, CI: 0.143-0.689), deranged liver functions ($p=0.000$, CI: 0.062-0.397), and disseminated intravascular coagulation ($p=0.005$; CI: 0.049-0.626) was noted in patients of group B as compared to group A. The patients of Group B showed a significant low birth weight, increased fetal mortality rate ($p=0.005$, CI: 0.030-0.622) and more chances of shifting neonates to NICU ($p=0.002$, CI: 0.164-0.667) as compared to those of group A. **Conclusions:** Hyperuricaemia in setting of gestational hypertension was associated with adverse fetal and maternal outcome.

Key words: Uric acid, Gestational hypertension, Maternal & Fetal outcome

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INTRODUCTION

Hypertensive disorders complicate 2% to 10% of all pregnancies and are responsible for significant increase in maternal and fetal mortality and morbidity. Pregnancy can induce hypertension in women who were normotensive before pregnancy and aggravate hypertension in those who were hypertensive before pregnancy[1].

Preeclampsia, associated with gestational onset of hypertension and proteinuria, is responsible for 10-15% (50,000) maternal death yearly worldwide[2]. One of the characteristic findings of preeclampsia is the elevated levels of serum uric acid and observations showed the severity of preeclampsia increases with increasing uric acid levels[3,4].

The hyperurecemia that shows a pathogenic role in preeclampsia develops before development of hypertension and proteinuria in pregnancy[5]. During healthy early pregnancies the serum uric acid levels are low (≤ 3 mg/dl) due to the effects of estrogen and increased renal blood flow, while the levels in women who are on the verge of developing preeclampsia are relatively high even during their first trimester[5]. The increased serum uric acid in association with preeclampsia is probably due to decreased maternal renal uric acid excretion, acidosis or placental or peripheral ischemia or necrosis[6,7]. Outside of pregnancy, increased serum uric acid is associated with hypertension, renal disease, diabetes, adverse cardiovascular events, obesity and diabetes mellitus[4,5].

Gestational hypertension without proteinuria has much less adverse effect on maternal or fetal outcome, whereas the major risk from hypertension that antidate's pregnancy is superimposition of

preeclampsia. These differences have classified gestational hypertension into that with proteinuria and without proteinuria.

In Pakistan, gestational hypertension remains a serious complication of pregnancy and resulting high maternal mortality of 1 in 89 women; warns early identification of the disease along its epidemiological and clinical risk factors in order to predict it before it threatens the survival of both mother and fetus.

In our study the pregnant women with hypertension were included to evaluate the prognostic value of serum uric acid for fetal outcome like giving birth to small –for – gestational – age infants, transfer for neonatal ICU and resuscitation at birth, as well as outcomes of pregnancy like – live births and preterm in primi and multigrivada.

MATERIAL & METHOD

This prospective study was conducted at department of Gynae & Obs, Maternal and Child Health Center, PIMS Islamabad, from January to December 2003. A total of 200 women with a gestational age more than 20 weeks, a blood pressure greater than 130 mmHg systolic and >90 mmHg diastolic were inducted in the study; while the patients with known hypertension, renal failure and endocrine disorders, proteinuria and heart diseases were excluded from the study. The patients who gave birth to congenitally abnormal babies, like anencephaly and gross hydrocephalus were also excluded from the study.

The blood pressure was taken on 2 separate occasions during the day in sitting and relaxed condition. The blood pressure was measured with mercury which was calibrated against electronic pressure generator. The systolic pressure was taken as Krotcoff's phase 2 and diastolic blood pressure as Krotcoff's phase 5 (corresponding with intra-arterial pressure). A total of 3 measurements at 5 minutes interval were taken and average was calculated. While recording blood pressure blood pressure cuff of appropriate sizes were used and applied to left arm.

After overnight fast, 5 ml. venous blood was collected under aseptic technique for measurement of Hb%, platelet count, uric acid, blood urea and serum creatinine. The Hb% and platelet count was done by Sysmex, while blood urea, uric acid and serum creatinine were analyzed by Hitachi 911 auto-analyzer.

On the basis of uric acid levels, patients were divided into group A (uric acid <4.5 mg/dl) and group B (>4.5 mg/dl) at any stage of gestation. All patients were followed up till end of pregnancy and one month after delivery.

The neonatal outcome was assessed with weight of the neonates, APGAR score, and transfer to neonatal intensive care unit and whether resuscitation was required or not; while the pregnancy outcome was assessed by live births, and preterm.

The transient gestational hypertension was defined as presence of persistently greater than 140 mmHg systolic and or greater than 90 mmHg diastolic for the first time after 20 weeks of gestation and 4 weeks after delivery in untreated women who had hypertension without preeclampsia during 3rd trimester of pregnancy. The infant for small-for-gestational-age was defined as those weighing <1.5 Kg.

Data was collected with the help of predesigned proforma including patient's name, age, address, booked or not booked, gravidity and parity status, number of living issues, neonatal deaths or any previous congenital abnormal babies.

STATISTICAL ANALYSIS

The results were analyzed using SPSS version 16. Student's' test was used for continuous variables for comparison between the groups and chi square for percentages. The 'p' value <0.05 was taken as significant.

RESULTS

A total of 200 women were included in the study, while 20 were excluded because they did not meet the inclusion criteria; 10 because of incomplete

data, 5 withdrew their consent, 3 did not meet blood pressure criteria on entry and 2 because of gestational age less than 20 weeks.

In the study group the mean age was 28.5 years (range: 21-37 years). Median gravidity was 2 (range: 1 to 4) and parity was 1 (range: 0 to 4) while median gestational age was 32 weeks and 5 days.

Table-I shows demographic criteria of the patients based on the admission uric acid levels, group A (uric acid levels ≤4.5mg/dl) and group B (uric acid levels >4.5mg/dl). The uric acid levels, hemoglobin, platelet count, serum creatinine levels, systolic and diastolic blood pressure showed significant difference ($p<0.05$) between patients of group A and of group B. A positive family history of hypertension was also significantly higher ($p<0.05$) in group B patients. The blood pressure and other maternal characteristics were found to be within normal limits before 20 weeks. An increased percentage of mild to moderate hypertension (BP=140/90) was noted in patients of group A as compared to those of group B, while severe hypertension was only noted in patients of group B specifically in third trimester ($p<0.05$). A positive family history of hypertension was significantly high ($p<0.05$) in patients of group B as compared to those of group A.

Table-II shows maternal outcomes. The patients of group B were associated with more proportion of women getting complicated. The occurrence of preterm delivery in group A patients was significantly decreased ($p<0.05$) as compared to patients of group B. The percentage of women of group B diagnosed with preeclampsia was significantly higher (26% versus 10%; $p=0.005$, 95% CI 0.143-0.689) than women of group A. A similar trend of significantly increased levels for deranged liver functions (29% versus 6%; $p=0.000$, 95% CI 0.062-0.397), and disseminated intravascular coagulation (15% versus 3%, $p=0.005$; 95% CI0.049-0.626) was also seen in patients of group B as compared to those of group A. However, the chances for acute renal failure (14% versus 7% $p=0.165$), and HELLP (12% versus 10%, $p= 0.822$) were found to be non significant.

There were 21 women who showed more than one complication having a uric acid levels >4.5 mg/dl. Comparing pregnancies the patients of group B delivered an average of 0.5 weeks earlier than those of group A.

The patients with hyperurecemia (Group B) showed a significant ($p<0.05$) low birth weight of their babies as compared to those with uric acid of ≤4.5 mg/dl.

The patients of group B showed significant ($p<0.05$) increased risk of fetal outcome regarding APGOR score in 1 minute ($p=0.042$, 95% CI 0.328-1.028); more chances of shifting neonates to NICU ($p=0.002$, 95% CI 0.164-0.667) as compared to those of group ma. A same trend of mortality rate ($p=0.005$, 95% CI 0.030-0.622) was noted in patients of group B as compared to those of group A, however, APGOR Score for 5 minutes ($p=0.408$) and resuscitation required at time of delivery ($p=0.312$) were found to be non significant.

DISCUSSION

Our results indicates that maternal hyperuricaemia measured near delivery is associated with an increased prevalence of fetal and maternal outcomes, specifically maternal preeclampsia, liver disease, renal dysfunction, disseminated intravascular coagulation, and preterm birth. These results are in consistence with a number of studies[1,5,8] who showed a relationship between hyperuricaemia and adverse maternal and fetal outcomes in hypertensive pregnancy[1,8,9]. Studies also showed a relationship between serum uric acid and serum creatinine; however, most of the women in our population had a serum creatinine within what is considered a normal range for pregnancy, suggesting that serum creatinine is not a sensitive marker of progressive hypertensive disease in pregnancy.

Uric acid is the end product of purine catabolism catalyzed by the enzyme xanthine oxidase/ dehydrogenase. This bifunctional enzyme in its dehydrogenase form produces uric acid and

	Uric acid ≤4.5 mg/dl (n=100)	Uric acid >4.5 mg/dl (n=100)	p value
Mean age (years)	25.05±3.22	32.02±3.29	0.000
Hb g/L	111.24±8.53	117.16±7.47	0.000
Platelet x 1000/mm^3	220.32±4.96	190.40±24.55	0.000
Creatinine umol/L	62.1±12.1	78.4±9.2	0.000
Uric acid	3.72±0.50	5.09±0.49	0.000
Gravidity 1 2 3 4	 28% (28) 28% (28) 18% (18) 26% (26)	 45% (45) 46% (46) 9% (9) 0% (0)	0.000
Systolic pressure	114.90±9.38	147.44±9.99	0.000
Diastolic pressure	75.03 ±11.19	92.32 ±7.90	0.000
Hypertension Mild Moderate Severe	 73% (73) 17% (7) 10% (10)	 17% (17) 52% (52) 31% (31)	0.000
F/H of Hypertension	% (15) 15	44% (44)	0.000
Gestational age 1st Trimester 2nd Trimester 3rd Trimester	 13% (13) 42% (42) 45% (45)	 1% (1) 22% (22) 77% (77)	0.000
Mean baby weight (Kg)	2.153	1.731	0.010

Table-I. Demographic characteristics of the patients

Variable			p value	Pearson's Chi Square	95% CI
ARF	7%	14%	0.165	2.607	.178 - 1.20
LFT	6%	29%	0.000	18.32	.062 - .397
HELLP	10%	12%	0.822	0.204	.335 – 1.98
DIC	3%	15%	0.005	8.791	.049 - .626
Severe maternal HTN	6%	13%	0.146	2.850	.156 – 1.173
Pre-eclampsia	10%	26%	0.005	8.672	.143 - .689
Ventilator support	1%	12%	0.003	9.955	.009 - .581
Preterm delivery mean (months)	8.5	8.0	0.047		

Table-II. Maternal outcome

reduced nicotinamide-adenine dinucleotide and, in the oxidase form, produces uric acid and superoxide. The enzyme is upregulated, and the expression of the oxidase form increased proportionally with hypoxia[2]. Although the cause of hyperuricemia has not definitively been known, however, recent studies suggest that decreased renal clearance is probably the most important mechanism. Though the increase in uric acid levels is not only due to the reduction of glomerular filtration rate; but also there is associated decreased secretion or increased reabsorption characterized by glomerular endothelial injuries that result in a reduction in ultra filtration capacity. Moreover, Angiotensin II stimulates renal urate reabsorption resulting in less urate excretion[5,10]. This phenomenon appears to be analogous to the decrease in urate clearance produced by the infusion of vasoconstrictors, such as nor epinephrine, and to the increase of blood uric acid level and diminution in its clearance observed in glomerulonephritis[11]. According to

Variables	Uric acid <4.5 mg/dl	Uric acid >4.5 mg/dl	p value	Pearson's Chi Square	95% CI
APGOR Score 1 minute 0-5 5-10	 53% 47%	 66% 34%	0.042	3.507	.328 - 1.028
APGOR Score 5 minutes 0-5 5-10	 16% 84%	 11% 89%	0.408	1.070	.676 - 3.512
NICU	14%	33%	0.002	10.04	.164 - .667
Resuscitation	16%	19%	0.710	0.312	.319 - 1.688
Mortality	2%	13%	0.005	8.721	.030 - .622
Weight (Kg) ≤ 1.5 1.6 – 2.5 > 2.5	 20% 26% 54%	 3% 86% 11%	0.000	119.11	--
Prenatal mortality	2%	13%	0.005	8.651 .029 - .592	.009 - .581

Table-III shows fetal outcome

these considerations, uric acid could be an early marker of preeclampsia. Other than reduced renal clearance, there may occur increased placental production of uric acid secondary to placental ischemia and increased trophoblast shedding, leading to further purine availability for breakdown. Fetuses exposed to hypoxia (eg, secondary to decreased placental perfusion) have been shown to have increased serum levels of purine metabolites[3]. In preeclampsia, therefore, it is conceivable that these metabolites can cross into the maternal circulation to be degraded by maternal xanthine oxidase. These latter mechanisms might explain the relationship between raised uric acid levels and fetal growth retardation. Studies on animals have suggested that uric acid may play a more active part in the development of hypertension in preeclampsia and perhaps later in life[12]. Uric acid has been shown to induce endothelial dysfunction in humans[13] and to induce human trophoblast production of interleukin 1ß by activating the Nod-like receptor Nalp 3, stimulating the expression of inflammasome components[14]. In animal experiments, rats rendered minimally hyperuricemic by inhibiting uricase had increased blood pressure that could be reversed by lowering uric acid[2,15]. It has been suggested that, in humans, uric acid might increase hypertension by increasing salt sensitivity and vascular smooth muscle proliferation[15].

Our results are in consistence with Homers et al[16] who showed that women with hyperuricaemia were associated with shorter gestation and reduced birth weight even in the absence of proteinuria. The proteinuric pre-eclamptic women with hyperuricaemia at the time of delivery were more likely to have preterm birth than other women with clinical features of pre-eclampsia who did not have proteinuria.

Our results showed an elevation in hemoglobin may be the result of a combination of reduced plasma circulating volume and enhanced erythropoiesis because of underlying placental hypoxia. Erythrocyte parameters in normal and hyperuricemic pregnancies have been shown to differ[1,17].

CONCLUSIONS

The presence of hyperuricaemia, identifies a population of hypertensive pregnant women at increased risk of adverse maternal and fetal outcome. Hyperuricaemia in the setting of gestational hypertension was associated with adverse fetal outcome, specifically prematurity, suggesting that this subpopulation of gestational hypertensive women cannot be considered to have a benign hypertensive disease. Calculating

the serum uric acid rise (? uric acid) may be useful in predicting which women will go on to develop pre-eclampsia, and is associated with an increased likelihood of developing maternal and fetal complications.

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