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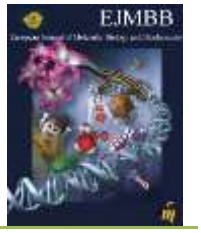

SERUM URIC ACID AND FOETAL OUTCOME IN PREGNANCY INDUCED HYPERTENSION (PIH)

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ABSTRACT
To estimate the serum uric acid levels in pregnancy induced hypertensive (PIH) patients and in normal pregnant women and also to establish a possible association between serum uric acid and foetal outcome in these patients. Case-control study conducted in Department of Biochemistry in collaboration with Department of Obstetrics &Gynaecology, Regional Institute of Medical Sciences (RIMS); Imphal, Manipur. Data collected from 100 pregnancy induced hypertensive patients and 100 normotensive pregnant women admitted in Antenatal ward, Department of Obstetrics & Gynaecology, RIMS Hospital between September 2014 to August 2016. The blood samples were collected and analyzed for serum uric acid level and foetal outcome of these participants were noted. The serum uric acid was significantly elevated in pregnancy induced hypertensive women compared to normal pregnant women (7.85 ± 2.7 mg/dl vs 3.20 ± 0.81 mg/dl, $p<0.05$). Higher serum uric acid level (>7mg/dl) was significantly associated with bad foetal outcome ($p<0.001$) and lower serum uric acid (<5mg/dl) with good foetal outcome ($p<0.001$). Women with PIH had a higher incidence of assisted deliveries compared to control group (25 vs 4). And blood pressure was not statistically associated with foetal outcome ($p>0.05$). Serum uric acid was elevated in pregnancy induced hypertensive patients and was significantly associated with foetal outcome.

INTRODUCTION

Gestational hypertension is a medical disorder worldwide that complicates approximately 12-22% of the pregnancies [1]. It is one of the leading causes of perinatal morbidity and mortality. It complicates about 5% to 10% of pregnancies in India. It is strongly associated with fetal growth retardation and prematurity [2]. The major risks to the foetus result from decreased placental perfusion which leads to decreased supply of oxygen and nutrients necessary for fetal growth and well being.

Uric acid (UA) is the major end-product of purine metabolism. The cause of hyperuricaemia in pre-eclampsia has been attributed to either a decreased excretion or to an increased production of uric acid. Decreased uric acid

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clearance is reflected by altered tubular function. Increased breakdown of purines in placenta may a be possible explanation of overproduction of uric acid [3].

In 1917, Slemons and Bogert first observed an association between serum uric acid concentration and presence of preeclampsia and Redman was the first to note that high serum uric acid level was associated with increased perinatal mortality rate [4,5].

Hyperuricaemia is one of the most consistent and earliest detectable changes in pre-eclampsia and has been cited as a better predictor of fetal risk than blood pressure [6,7].Severe maternal hypertension without hyperuricaemia is associated with better prognosis of the foetus. Whereas even mild hypertension with hyperuricaemia is always associated with poor prognosis [8].

Despite these findings, uric acid assessment in the evaluation of PIH has fallen into disfavour. A study reported that no significant difference was observed in serum uric acid level between normal and pre-eclamptic women [9].Furthermore, one study also reported that serum uric acid lack sensitivity and specificity as a diagnostic tool [10].

Aims and objects

The present study was conducted in Department of Biochemistry in collaboration with Department of Obstetrics and Gynaecology, Regional Institute of Medical Sciences, Imphal, to estimate the serum uric acid levels in pregnancy induced hypertensive (PIH) patients and in normal pregnant women and to compare the findings between them and also to establish if any significant relation exists between serum uric acid levels and foetal outcome in PIH patients.

MATERIALS AND METHODS

The study was a case-control study comprising of 200 study populations admitted in the Antenatal Ward, Department of Obstetrics and Gynaecology, Regional Institute of Medical Sciences, Imphal during the period from September 2014 to August 2016. Hundred patients who were diagnosed as having pregnancy induced hypertension (PIH) were taken as cases and 100 normal pregnant women of comparable gestational age as controls.

5 ml of venous blood was drawn from antecubital vein from all these patients and analyzed for serum uric acid. The serum uric acid levels were estimated in the Department of Biochemistry, RIMS by Uricase method (enzymatic-colorimetric test) modified by Human Co., Germany [11,12]. Foetal outcome (birth weight, pre-term/term delivery, still birth, apgarscore and referral to neonatal intensive care unit, NICU) were noted from the birth register maintained in the Labour room, Department of Obstetrics & Gynaecology, RIMS. All the cases and controls in the study were subjected to detailed history regarding age, parity, height and weight at the time of blood collection. General physical examination and systemic examination with special reference to oedema and blood pressure were carried out. And all the investigations were recorded in the perfoma designed for the study. Those patients presenting with preexisting hypertension, cardiovascular diseases, renal diseases, diabetes mellitus or chronic diseases were excluded from the study.

Written informed consent was taken from all the participants. Ethical clearance was obtained from Ethical Committee, Regional Institute of Medical Sciences, Imphal. Statistical analysis was performed by using SPSS software, version 16.0.

RESULTS

Table 1. Comparison of serum uric acid (mg/dl) between the study groups

Parameter	Case group	Control group	*P*
S. Uric acid (mg/dl)	7.85 ± 2.70	3.20 ± 0.81	‹ 0.001

Values are given as mean ± S.D. $x^2 = 1.85$; *d.f = 117*

Table1 shows that the mean serum uric acid level in the case group is significantly higher in the case group than the control group with $p<0.001$.

Table 2. Comparison of birth weight (kg) between the study groups

Birth weight(kg)	Case group	Control group	Total
< 2.5	22	9	31(15.5%)
≥ 2.5	78	91	169 (84.5%)

Table 2 shows that the incidence of low birth weights (<2.5 kg) are more in the case group than the controls (22 vs 9) while the incidence of normal birth weight are more in the controls than the case group mothers (91 vs 78).

Table 3. comparison of Apgar score between the study groups

Apgar Score	Study group		Total
	Case (n=100)	Control (n=100)	
0-5	6	0	6
>5-7	22	2	24
>7-10	72	98	170

Table 3 shows that the low Apgar score is found to be more prevalent in infants born to mothers with PIH than in those babies born to normal controls.

Table 4. Comparison of foetal outcome according to serum uric acid level

S. uric acid (mg/dl)	Fetal Outcome		*p-value*
	Bad* (57)	Good** (143)	
<5	7 (12.28%)	110 (76.92%)	<0.001
5-7	6 (10.52%)	20 (13.98%)	<0.001
>7	44 (77.19%)	13 (9.09%)	<0.001

**Bad foetal outcome included Low birth weight (<2.5 kg), pre-term delivery (< 37 weeks of gestation), still birth, low Apgar score (<7) & referral to NICU. **Good foetal outcome included normal birth weight (>2.5kg), term delivery (>37 weeks of gestation), normal Apgar score (>7).*

As is evident from table 4; good foetal outcome is seen in 76.92% patients of the study population whose serum uric acid level is <5 mg/dl while bad foetal outcome has been observed in those patients(77.19%) whose serum uric acid is >7 mg/dl .Serum uric acid was significantly associated with foetal outcome with *p< 0.001*.

Table 5. Comparison of foetal outcome according to blood pressure in the case group only

BP (mmHg)	Foetal Outcome		*P value*
	Bad (n=48)	Good (n=37)	
>140/90 ≤ 160/110	29 (34.11%)	23 (27.05%)	0.956
>160/110	19 (22.35%)	14 (16.47%)	0.400

It can be seen from table 5 that out of the 100 patients in the case group, 85 patients had BP ≥ 140/90 mm Hg. But, when the foetal outcome were compared among these patients with respect to the severity of BP, the difference is found to be statistically insignificant *(p>0.001).*

Table 6. Comparison of mode of delivery among the study groups

Mode of Delivery	Case (n=100)	Control (n=100)
NVD	40	40
NVD + RMLE	35	56
EmLSCS	15	02
Ventouse	09	02
Forceps	01	00

Table 6 shows that the number of assisted deliveries (EmLSCS, Ventouse& Forceps) was more in the case group than the controls.

DISCUSSION

The main aim of this study was to estimate the serum uric acid levels in pregnancy induced hypertension (PIH) patients and in normal pregnancy women of comparable gestational age and to compare the findings between the groups. It has been found that the mean serum uric acid level in the case group was significantly higher than in the control group (table 1). This finding is in accordance with the findings of Akter S et al [13], Aneela K et al [14], and Liggy A et al [15] who reported that the mean serum uric acid level was higher in the toxaemic group as compared to normal pregnancy at equivalent period of gestation.

Uric acid is a terminal metabolite of the degradation of nucleotides. It is influenced by diet, alcohol consumption, increased cell turnover, enzymatic defects in purine metabolism or altered kidney function [16]. In pregnancy uric acid concentration initially fall 25-35% due to effects of estrogen, expanded blood volume and increased glomerular filtration rate [17]. But, concentration slowly rise to those observed in non-pregnant women by term gestation (4-6mg/dl) [18]. However, in preeclampsia, uricemia occurs, which is due to reduced uric acid clearance from diminished glomerular filtration, increased tubular reabsorption and decreased secretion [19].

The present study also aimed to establish a possible correlation between serum uric acid levels and foetal outcome. The study showed that the incidence of low birth weight, low apgar score, assisted deliveries (table 2, 3, 6) were more in the case group than the controls.

When the foetal outcome of the two study groups were compared in relation to the serum uric acid levels, it was observed that patients having relatively lower serum uric acid levels (<5 mg/dl) had good foetal outcome while patients having relatively higher serum uric acid levels had bad foetal outcome (>7 mg/dl) and the difference was statistically significant (table 4). On the other hand, there was no significant correlation between the foetal outcome and the blood pressure levels in the case group (table 5).

Uric acid has recently been shown to reduce endothelial nitric oxide bioavailability and inhibit endothelial cell proliferation [20-22]. Because maternal uric acid passes freely into the placenta [23], a rise in uric acid level could lead to an inhibition of fetal angiogenesis in the third trimester, which might lead not only to a small infant, but also to the inhibition of kidney growth with a reduction in nephron number [20,23]. Indeed, there is also

accumulating evidence that uric acid may have a potential contributory role in the maternal phenotype [24],although other factors, including oxidative stress and circulating inhibitors of vascular endothelial growth factor, likely have a more dominant role [25].

CONCLUSION

The study shows that the level of serum uric acid level is found to be significantly higher in patients with pregnancy induced hypertension (PIH) compared to the normotensive pregnant women. It also shows that the serum uric acid was significantly associated with foetal outcome.

The present study confirms the hypothesis that serum uric acid is better indicator than blood pressure for identifying women at risk of having bad foetal outcome. However, further studies are required to ascertain this hypothesis and to determine a cut-off value of serum uric acid level in PIH patients above which a planned delivery can be initiated to prevent serious maternal complications and give the best possible chance of foetal survival.

STATEMENT OF HUMAN AND ANIMAL RIGHTS

All procedures performed in human participants were in accordance with the ethical standards of the Institutional Research Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals.

CONFLICT OF INTEREST

There is no conflict of interest among the authors.

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