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Is serum uric acid level a predictor for maternal and foetal outcome in pregnancy induced hypertension?

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ABSTRACT

Objectives: Aim of this study was to identify the correlation between serum uric acid level and maternal and foetal outcome in pregnancy induced hypertension

Materials and methods: This prospective study was done in eclampsia unit of Dhaka Medical College and Hospital between January 1998 and April 2001. Five hundred cases of pregnancy induced hypertension (PIH) were reviewed. Among them 418 cases were eclampsia and 82 cases were imminent eclampsia between the gestational age of 28–40 weeks. Serum uric acid, 24 hours urinary total protein (UTP), serum urea, creatinine, SGOT, SGPT and platelet count was estimated. A simple regression analysis was done between serum uric acid and other maternal and foetal parameters to find out any significant correlation between them. A p value of <0.5 was considered significant.

Results: Serum uric acid level was 3.5 mg/dl-9.89mg/dl with a mean value of 6.4mg/dl ± 1.20. Correlation of uric acid with birth weight r = .02, intrauterine death (IUD) r = .25, Diastolic blood pressure r = .15, Systolic blood pressure r = .09, platelet count r = .17, maternal death r = .07 and UTP r = .31. In all this cases p is not significant except UTP where p = .02.

Conclusion: High serum uric acid level might bear a bad prognostic value but only high serum level of uric acid is not predictive for foetal and maternal outcome.

Key words: Uric acid level, maternal and foetal outcome, pregnancy induced hypertension

INTRODUCTION

Hypertension during pregnancy has significantly greater influence on maternal and foetal mortality and morbidity[1]. It has been emphasized that the clinical syndrome is the manifestation of an illness which starts early in pregnancy[2]. There is evidence that impaired trophoblastic invasion into maternal spiral arterioles plays an important pathogenetic role. This incomplete remodeling of the spiral arteriolar wall occurs at 16-20 weeks gestation as a result of failure of the second wave of trophoblastic invasion[2,3].

Diagnosis of hypertensive disorder of pregnancy in its initial clinical stages can be difficult since the only clinical sign is hypertension. Thus many attempts have been performed to find out useful clinical and biochemical tests for an early diagnosis. Since the pathogenic mechanisms behind pregnancy induced hypertension (PIH) are totally different from other hypertensive disorders of pregnancy, biochemical markers are generally chosen on the basis of peculiar pathophysiological aspects of the disease. Therefore, since the pathophysiology of PIH includes endothelial

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damage[4], a number of potentially useful biochemical markers of endothelial damage have been proposed.

The oldest and probably most often studied laboratory test, other than urinary protein determination, in the investigation of PIH is the serum concentration of uric acid[5]. Whether the cause of increased serum uric acid concentration in PIH is secondary to a true tubular damage because of the renal vasoconstriction and ischemia, or to a pure functional adaptation due to the well known hypovolemia existing in this disease, is not known. Despite the fairly large number of reports dealing with uric acid in patients with diagnosed PIH, few data are available with regard to the predictive value of uric acid serum concentration for this disease.

Pregnancy induced hypertension (PIH) is a multiorgan disorder and approximately 30-60% of patients with disorder show evidence of renal involvement with elevated serum uric acid and creatinine levels[6]. There is an association between elevated serum uric acid levels and eclampsia preeclampsia and it has been suggested that the serum uric acid concentration is the most sensitive indicator of eclampsia and preeclampsia available to clinician[7]. Evidence suggests that decreased glomerular filtration rate and renal tubular excretion may be responsible for the rise in serum uric acid levels in PIH. This lesion may lead to tubular necrosis and renal failure and residual renal function impairment[8,9]. Many investigators documented a correlation between hyperuricemia and severity of disease and neonatal morbidity and they found serum uric acid as a better predictor for low birth weight than other parameters[10–13]. Therefore we performed this study to determine the correlation between serum uric acid with maternal and foetal outcome in terms of mortality and morbidity in PIH.

MATERIALS AND METHODS

We reviewed 500 patients of PIH prospectively in a special eclampsia care unit of Dhaka Medical College and Hospital. Among them 418 were patients with eclampsia and 82 were imminent eclampsia between the gestational age of 28-40 weeks. Disease was documented by high blood pressure, proteinuria, oedema, blurred vision, headache, and convulsion. All patients had a live foetus at the time of enrollment. Samples were collected for 24 hours urinary total protein (UTP), serum urea, uric acid, creatinine, SGOT, SGPT and platelet count from all antepartum patients. A few patients whose gestational age was <37 weeks and patients were completely stable within 24 hours observation with satisfactory test results were treated conservatively and others terminated either by induction followed by vaginal delivery or caeserean section or by elective caeserean section. Ultrasonography was performed in patients who were treated conservatively and the laboratory investigations were repeated weekly or biweekly depending on initial values. Pregnancy was terminated either by completion of 36 weeks or due to failure to respond to treatment like uncontrolled blood pressure in spite of adequate antihypertensive therapy, persistent headache, epigastric pain, or due to development of any complications like vaginal bleeding, ruptured membrane, recurrent fit, foetal distress, foetal death and static foetal growth. Analysis was made on level of serum uric acid and its correlation with foetal and maternal outcome. A simple regression analysis was done and a p value of <0.5 was considered significant.

RESULTS

Most of the patients were young primiparous. The average age was 22.40 ± 4.21 and 72.77% patients were primiparous. Table 1 shows the value of uric acid. SGOT, SGPT, UTP, Platelet count, SBP, DBP. The mean serum uric acid value was 6.4 ± 1.20. Table 2 shows the correlation of serum uric acid values with selected clinical outcome like blood pressure and platelet count, UTP of mother and birth weight and still birth rate of foetus. There is a correlation between uric acid and all the parameters mentioned but it is not significant. Correlation with birth weight r = .02, intra uterine death (IUD) r = .25, DBP r = .15, SBP r = .09, platelet count r = .17, maternal death r = .07. In all these cases p is not significant. Only UTP showed a significant relationship r = .31 p = .02.

TABLE 1
Patient's parameters at admission

Parameter	Range	Mean±SD
Systolic blood pressure	140–190	155.04 ± 12.52
Diastolic blood pressure	90–135	110.54 ± 11.56
24 hour UTP (g/24h)	0.15–7.45	2.50 ± 6.76
Urea (mg/dl)	20–65	42.45 ± 7.35
Creatinine (mg/dl)	0.7–3.8	1.35 ± .65
Uric acid (mg/dl)	3.5–8.89	5.4 ± 1.23
SGOT (IU/L)	10–45	18.78 ± 8.05
SGPT (IU/L)	8–42	20 ± 10.58
Platelet count (n/mm^3)	50–350	200 ± 50.52

TABLE 2
Correlation of uric acid level with maternal and foetal parameters

Parameters		r	p
Birth weight (Kg) Mean ±	2.1 ± 0.47	.02	.91
Still birth (%)	23.02	.25	.06
SBP (mmHg) Mean ± SD	155.04 ± 12.52	.09	.53
DBP (mmHg) Mean ± SD	110.54 ± 11.56	.15	.27
Platelet count (n/mm^3) Mean ± SD	200 ± 50.52	.17	.22
Urinary total protein (g/24h) Mean ± SD	2.50 ± 6.76	.31	.02
Maternal death %	4.6	.07	.83

DISCUSSION

Uric acid excreted through kidney with difficulties due to its relative insolubility. A rise in plasma uric acid may indicate renal involvement or impairment when other metabolic end product such as plasma creatinine and urea remain within normal range. It is primarily secreted by the distal tubules and the secretion is dependent upon the renal blood flow. In hypertensive disorder of pregnancy as there is generalized vasospasm renal blood flow also reduced due to spasm, which causes renal damage and impairs function. As a result uric acid levels rise due to defective excretion through kidney. So high level of serum uric acid is an indicator of renal dysfunction. Redman et al[14] suggested that serum uric acid is a useful indicator of the risk of perinatal mortality in women with hypertension in pregnancy.

In this study a simple regression analysis was performed between uric acid and other parameters, which failed to show any strong correlation between levels of uric acid and blood pressure, platelet count, birth weight, stillbirth and maternal death. Correlation with birth weight r = .02, IUD r = .25, DBP r = .15, SBP r = .09, platelet count r = .17, maternal death r = .07. It did not show any significant correlation. Some researchers showed a strong association between hyperurecemia and the severity of the disease[10–12,15]. Lim and associates[16] found a weak correlation between serum uric acid levels and maternal blood pressure and birth weight of the baby. They concluded that the utility of measuring serum uric acid levels in hypertensive diseases of pregnancy is limited. Begum et al[17] showed that severe uricemia had no effect on mother. Regarding foetal outcome they showed live birth with average weight baby when uric acid level was high (7.8 mg/dl). On the other hand IUD occurred in the case where uric acid level was quite normal (4.30 mg/dl). So it is difficult to say that level of serum uric acid is a good predictor for foetal and maternal outcome. In this series we also failed to show the direct correlation of high serum uric acid with bad maternal and foetal prognosis. Although low birth weight and IUD were there, uric acid level was normal in many of the cases. On the other hand a number of patients with high serum uric acid had birth average weighted alive foetuses. There was no strong correlation of hyperuricemia with maternal blood pressure and platelet count.

Uric acid is the end product of purine metabolism in humans and other primates. In other species uric acid is further degraded to allantoin and urea. Xanthine oxidase/dehydrogenase degrades the purines, xanthine and hypoxanthine, to uric acid. Xanthine dehydrogenase/oxidase has two forms. One (xanthine dehydrogenase) requires nicotinamide adenine dinucleotide and the other (xanthine oxidase) requires oxygen. The dehydrogenase form produces uric acid and reduced nicotinamide adenine dinucleotide and the oxidase form produces uric acid and superoxide. The two forms of the enzyme coexist in vivo. Under certain conditions, including ischemia-reperfusion[18–20] and hypoxia[21], there is increased conversion of the dehydrogenase form to the oxidase form. Increased conversion to the oxidase form promotes production of reactive oxygen species[22].

Normal cellular metabolism includes degradation of purines from genomic material, producing xanthine and hypoxanthine, which ultimately leads to production of uric acid by xanthine dehydrogenase/oxidase.

The placenta is a cellular organ with some cells turning over rapidly. The placenta is therefore a rich source of purines for the generation of uric acid by xanthine dehydrogenase/oxidase. Higher hypoxanthine concentrations are present in peripheral blood during than before labor[23], and much higher concentrations

of purines are present in the uterine vein than in peripheral veins in this setting. This is felt to result from accelerated ATP degradation during parturition. In preeclampsia cellular turnover and ATP degradation are further increased[24]. Increased trophoblast shedding occurs as evidenced by larger numbers of trophoblast cells in maternal blood[25] and in lungs of preeclamptic patients at autopsy[26]. This breakdown of placental tissue likely provides an additional source of purines for xanthine dehydrogenase/oxidase utilization. Furthermore, the shallow implantation characteristic of preeclampsia should lead to reduced placental perfusion[24,27] and increased substrate for xanthine dehydrogenase/oxidase utilization. This postulate is consistent with increased adenosine in the placenta of preeclamptic patients[28], implying reduced ATP recycling. The increased concentration of adenosine is not uniformly distributed throughout the placenta but is focal, perhaps reflecting local narrowing or obliteration of the spiral arteries supplying the placenta[29,30].

The fetus is also a potential source of substrate for xanthine dehydrogenase/oxidase. Reduced placental blood flow reduces nutrient and oxygen delivery to the fetus with subsequent hypoxia. Studies of hypoxic fetuses indicate increased blood concentrations of purine metabolites in these infants[23, 31–33], and some reports have considered these as markers of fetal asphyxia and potential adverse outcome[34]. The increased hypoxanthine can cross the placenta[35], providing substrate for maternal xanthine dehydrogenase/oxidase.

Our study clearly shows a significant relation of uric acid with proteinuria r = .31, p = .02. But in many of the cases it was found that uric acid level was 8.7 mg/dl and UTP was 0.70 g/24 hours or uric acid was 4.3 mg/dl and UTP was 6.53 g/24 hours. So it is also variable and does not bear any predictive value. High serum uric acid and high UTP both are indicators of renal function impairment due to renal damage. So these patients might develop renal disease in subsequent period. We were not able to conduct the follow up of these patients except a few who returned after discharge.

There were 23 maternal deaths in this series. Causes of death were pulmonary oedema (6), hepatic failure (5), CVA (4), DIC (5), renal failure (1) and HELLP syndrome (2). In all the cases serum uric acid was slightly increased and was between 4.9 – 5.9 mg/dl except renal failure case whose uric acid level was high (9.8 mg/dl). There was another acute renal failure in this series in a woman whose uric acid level was high (8.5 mg/dl) and this patient was treated by frusemide and did not require dialysis. As patient came with failure we could not measure her previous values and it was not possible to say whether the previous value was predictive for failure. On the other hand patient with very high uric acid (10 mg/dl) did not develop any major complication. So in conclusion it can be said that not any single parameter like serum uric acid levels can predict the foetal and maternal outcome in PIH. As it is a multi organ disorder all test results should be weighted together to assess foetal and maternal outcome.

REFERENCES

1. Chesley LC. Hypertensive disorder in pregnancy. New York. Appleton Century Crofts, 1978, p2.
2. Mushambi MC, Hallingan AW, Williamson K. Recent developments in the pathophysiology and management of pre-eclampsia. Br J Anaesth 1996; 76:133-148.
3. Wang Y, Walsh SW, Kay HH. Placental lipid peroxides and tromboxane are increased and prostacyclin is decreased in women with pre-eclampsia. Am J Obstet Gynecol 1992; 167:946-949.
4. Flavahan NA, Vanhoutte PM. Endothelial cell dysfunction. Am J Hypertens 1995; 8:28S-41.
5. Jaeschke R, Guyatt G, Sackett D. Users' guide to the medical literature, III: how to use an article about a diagnostic test. JAMA 1994; 271:703-7.
6. Schindler M, Gatt S, Isert P, Mogans D, Cheung A. Thrombocytopenia and platelet functional defects in pre-eclampsia implications for regional anaesthesia. Anaesthesia Intensive Care. 1990; 18:169-174.
7. Roberts J. Pregnancy related hypertension. In: Creasy R, Resnik R, editors. Maternal-foetal medicine: principles and practice. 3rd ed. Philadelphia: WB Saunders; 1994. p 804-43.
8. Riff DP, Wilson DM, Dunea G, et al. Adrenocortical necrosis: partial recovery after 49 days of oliguria. Arch Intern Med 1967; 119:518-21.
9. Briggs JD, Kennedy AC, Young LN, et al. Renal function after acute tubular necrosis. Br Med j 1967; 3:513-6.
10. Acien P, Lloret G, Lloret M. Perinatal morbidity and mortality in pregnancy hypertensive disorders: prognostic value of the laboratory findings. Int J Gynaecol Obstet 1990; 32:229-35.
11. Redman C, Beilin L, Bonnar J, Wilkinson R. Plasma urate measurements in predicting foetal death in Hypertensive Pregnancy. Lancet 1976; 1:1370-3.
12. Sagen N, Kjell H, Nilsen S. Serum urate as a predictor of foetal outcome in severe preeclampsia. Acta Obstet Gynaecol Scand 1984; 63:71-5.

13. Schuster E, Weppelmann B, Plasma urate measurements and foetal outcome in preeclampsia. Gynecol Obstet Invest 1981; 12:162-7.

14. Redman C.W.G, Beilin L.J, Bonnar J and Wilkinson R.H (1976) Lancet, I, 1370.

15. Plouin PF, Chatellier G, Breart G, Hillion D, Moynot A, Tchobroutsky C, et al. Factors predictive of perinatal outcome in pregnancies complicated by hypertension. Eur J Obstet Gynecol Reprod Biol 1986; 23:341-8.

16. Lim KH, Friedman SA, Ecker JL et al. The clinical utility of serum uric acid measurements in hypertensive diseases of pregnancy. Am J Obstet Gynecol 1998; 178:1067-71.

17. Begum MR., Akhter S, Begum A, Khatun M, Quadir E, Choudhury SB. Conservative Management of Eclampsia and Severe Pre-eclampsia – Bangladesh experience. Medscape Women health e Journal 2002; 7(1):1-10.

18. Chambers DE, Parks DA, Patterson G, et al. Xanthine oxidase as a source of free radical damage in myocardial ischemia. J Mol Cell Cardiol 1985; 17:145-52.

19. Vasko KA, DeWall RA, Riley AM. Effect of allopurinol in renal ischemia. Surgery 1972; 71:787-90.

20. Sussman MS, Bulkley GB. Oxygen derived free radicals in reperfusion injury. Methods Enzymol 1990; 186:711-23.

21. Roy RS, McCord JM. Superoxide and ischemia: conversion of xanthine dehydrogenase to xanthine oxidase. In: Greenwald RA, Cohen G, eds. Free radicals and their scavenger system. New York: Elsevier, 1983; 3:145-53.

22. Parks DA, Granger DN. Xanthine oxidase: biochemistry, distribution and physiology. Acta Physiol Scand 1986; 548(suppl):87-99.

23. O'Connor MC, Harkness RA, Simmonds RJ. The measurement of hypoxanthine xanthine inosine and uridine in umbilical cord and fetal scalp blood samples as a measure of fetal hypoxia. Br J Obstet Gynaecol 1981; 88:381-90.

24. Bernischke K, Kaufman P. Placental changes in preeclampsia. In: Bernischke K, Kaufman P, eds. Pathology of the human placenta. 2nd ed. New York: Springer-Verlag, 1990:516-9.

25. Chua S, Wilkins T, Sargent I, Redman CWG. Trophoblast deportation in preeclamptic pregnancy. Br J Obstet Gynaecol 1991; 98:97309.

26. Attwood HD, Park WW. Embolization to the lung by trophoblast. J Obstet Gynaecol Br Emp 1961; 68:611-7.

27. Dixon HG, Robertson WB. A study of the vessels of the placental bed in the normotensive and hypertensive women. J Obstet Gynaecol Br Emp 1958; 65:803-9.

28. Maguire MH, Westermeyer FA, King CR. Measurement of adneosine inosine hypoxanthine in human term placenta by reverse phase high performance liquid chromatography. J Chromatogr 1986; 380:55-66.

29. Maguire MH, Szabo I, Slegel P. Determination of concentrations of adenosine and other purines in human term placenta by reverse phase high performance liquid chromatography with photoiodide array detection: evidence for pathways of purine metabolism in the placenta. J Chromatogr 1992; 575:243-53.

30. Maguire MH, Westermeyer FA, King CR. HPLC determination of adenosine inosine and hypoxanthine in human term placenta. In: Nyhan WL, Thompson LF, Watts WE, eds. Purine and pyrimidine metabolism in man. New York: Plenum, 1985; 5:583-5.

31. Saugstad OD. Hypoxanthine as a measurement of hypoxia. Pediatr Res 1975; 9:158-61.

32. Thiringer K. Cord plasma hypoxanthine as a measure of foetal asphyxia. Acta Paediatr Scand 1983; 72:231-7.

33. O'Connor MC, Harkness RA, Simmonds RJ, Hytten FE. Raised hypoxanthine xanthine and uridine concentrations in meconium stained amniotic fluid and during labor. Br J Obstet Gynaecol 1981; 88:375-80.

34. Pietz J, Guttenberg N, Gluck L. Hypoxanthine: a marker for asphyxia. Obstet Gynecol 1988; 72:762-6.

35. Hayashi T, Garvey BL. Transplacental passage of nucleotides nucleosides and bases. Am J Obstet Gynecol 1968; 109:1154-61.