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Research Article

High Serum Uric Acid Levels in Preeclampsia and Perinatal Outcome

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Abstract

Hypertensive disorders of pregnancy are the most frequent medical condition that comes across during pregnancy and the medical and economic burden of the condition on the women and society is very high. The working group of the NHBPEP- National High Blood Pressure Education Program classified hypertensive disorders of pregnancies as: Gestational Hypertension, preeclampsia and eclampsia syndrome, preeclampsia superimposed on chronic hypertension and chronic hypertension. Uric acid is a product of purine degradation catalyzed by the enzyme xanthine oxidase and in humans most circulating uric acid is produced in the liver. Uric acid concentrations are influenced by several factors like high protein diet, alcohol consumption, and increased cell turn over, enzyme defects in purine metabolism, altered kidney function, etc. The serum level of uric acid rises preceding the signs and symptom of preeclampsia. Various biomarkers have been tried to predict the outcomes of preeclamptic pregnancies but poor sensitivity and specificity.

The objective of this study is to find the relation of raised uric acid and fetal outcome in preeclamptic women, to estimate serum uric acid levels in preeclampsia and to compare the fetal outcome of preeclampsia with normal uric acid and raised uric acid level in terms of Birth weight, APGAR scores, NICU admissions. This study is a hospital based prospective case control study conducted at Paropakar Maternity and Women's Hospital, Thapathali, Kathmandu with total 92 sample size taken for study. There was a total of 5003 obstetric admission and a total of 429 hypertensive disorders of pregnancies were identified. There was a total of 183 preeclamptic cases and among those cases only 92 patients that met the inclusion criteria were enrolled into the study. The incidence of hypertensive disorder was found to be 8.5%. Adverse perinatal outcomes in preeclamptic patients with serum uric acid more than 5.5mg/dl had 17% low birth weight, 11% NICU admission and 30% had low APGAR score. And the amount of low birth weight observed was statistically significant. Hypertensive disorders of pregnancy are common medical disorders affecting 5 to 10% of pregnancies. These are associated with adverse perinatal outcomes. The Incidence of hypertensive disorder in current study was 8.5%. Perinatal morbidity in terms of low birth weight, NICU admissions and Low APGAR scores were higher in preeclamptic patients with serum uric acid more than 5.5mg/dl. But only the difference in low birth weight was statistically significant.

Keywords: *Adverse Perinatal Outcome; Preeclampsia; Serum Uric Acid; Hypertensive Disorder; Nepal*

Abbreviations

NICU: Neonatal Intensive Care Unit; APGAR: Appearance, Pulse, Grimace, Activity, and Respiration

Introduction

Hypertensive disorders complicate 5% 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 [1,2].

Preeclampsia (PE) is a multi-system disorder unique to human pregnancy characterized by hypertension more than 140/90 mmHg and proteinuria more than 300mg in 24 hours urine and involvement of one or more other organ systems and/or the fetus after 20 weeks of gestation. This condition is best described as a pregnancy-specific syndrome of reduced organ perfusion secondary to vasospasm and endothelial activation [3].

Despite advances in care, preeclampsia remains a leading cause of maternal and perinatal morbidity and mortality worldwid. Preeclampsia affects multiple organ systems and can lead to severe renal, hepatic, neurological, and cardiopulmonary complications. Often the fetus is affected, and adverse perinatal outcomes include preterm birth, intrauterine growth restriction, and death. Preeclampsia, associated with gestational onset of hypertension and proteinuria, is responsible for 10 - 15% (50,000) maternal death yearly worldwide [4]. The challenge in caring for women with preeclampsia is to identify those who are at increased risk for complications so that appropriate and timely delivery can be offered [5].

A frequently reported laboratory finding in women with preeclampsia is elevated serum uric acid. Most accept that hyperuricemia in women with preeclampsia is primarily a result of a reduction in glomerular filtration rate, although others have suggested a possible role for elevated uric acid levels in the pathogenesis of preeclampsia, via endothelial dysfunction [5]. Observations have showed the severity of preeclampsia increases with increasing uric acid levels [1,5]. The association of preeclampsia and hyperuricemia is well documented and was first reported in 1917AD while a correlation between hyperuricemia and severity of preeclampsia was first postulated in 1934AD [6].

The hyperuricemia that shows a pathogenic role in preeclampsia develops before development of hypertension and proteinuria in pregnancy. During healthy early pregnancies the serum uric acid levels are low (≤ 3 mg/dl) due to the effects of estrogen and progesterone which increases the renal blood flow, while the levels in women who are on the verge of developing preeclampsia are relatively high even during their first trimester.[1] 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.[1] Reduced serum uric acid (SUA) clearance secondary to reduced glomerular filtration rate, increased reabsorption, and decreased secretion may be at the origin of elevated serum levels in women with preeclampsia [7].

Incidence of preeclampsia is around 3.9% of all pregnancies, [8] and upto 18% in developing countries [1,4]. The incidence of preterm birth due to preeclampsia is around 15% [5]. The incidence of preeclampsia was 3% in Paropakar Maternity and Women's Hospital.

PE is still regarded as a disease of theories and its etiology has remained poorly understood. However, endothelial dysfunction has been considered to play a central role in the pathophysiology of preeclampsia [9]. Many researches have been done to identify a unique screening test that would predict the risk of developing PE before the classic symptoms appear. One of the most accessible and easiest screening tests is serum uric acid measurement [7]. Several studies have demonstrated a correlation between elevated maternal serum uric acid levels and adverse fetal outcome [9]. A number of studies have evaluated several tests and parameters, including UA, during the first or second trimester of pregnancy, as potential predictors of preeclampsia, with mixed results, and generally with unsatisfactory sensitivity and/or specificity [7,10].

Materials and Methods

A hospital based prospective study was carried out. The study group for this study was 92 preeclamptic women with high uric acid levels (> 5.5 mg/dl). We compared preeclamptic women with high uric acid level and normal uric acid level. The study was conducted at Paropakar Maternity and Women's Hospital in Kathmandu, Nepal. Study population consisted of all singleton term pregnant women with pre-eclampsia and who fulfilled the inclusion criteria. The inclusion criteria were all primi and multigravida patient with BP ≥ 140/90 mmHg and Proteinuria more than 300µg in 24 hours or 1+ in dipstick urine test at 37 completed weeks of gestation. Similarly, exclusion criteria set were women with a history of renal disease, cardiac disease, liver disease, women with history of chronic hypertension, multiple pregnancy, intra uterine fetal demise, known fetal abnormality in ultrasound and non-approval to participate in study. Pre-testing was done in 10 patients to determine the patient's response, validity of the study, time taken for collecting the sample and obtaining the result from hospital laboratory. After the approval from IRB, data collection was done. Informed consent was taken from all the women taking part in the study.

The patient's weeks of gestation was calculated from their last menstrual period and verified by an early ultrasound scan, if available. Detailed history including patient's name, age, gravida, parity, gestational age, medical history, family history, drug history, was taken. Symptoms of preeclampsia like headache, blurring of vision, epigastric pain and swelling of limbs was asked. A detailed clinical and systemic examination was done and recorded. Per vaginal examination was done as per requirement.

The cases were enrolled from admission unit all 7 days in a week and during hospital hours. Cases admitted after hospital hours were followed up the next morning. After fulfillment of inclusion and exclusion criterion cases were enrolled into study. Only those patients were chosen for whom termination of pregnancy had been decided. The enrolled patients with high uric acid levels were allocated into study group until the sample size was achieved. Patients in control group were allocated by lottery method. Lottery was done by pulling out cheats from a vessel containing cheats three times the number of sample size. One third of cheat contained a 'Yes' for enrollment into study and two thirds contained a 'No' for the study.

Lab investigations like blood grouping, Rhesus typing, hemoglobin, platelet count, prothrombin time, renal function test and liver function test urine routine examination, were sent at the time of admission and the result were recorded. Serum Uric acid was measured using Pap colorimetric enzymatic method. Venous blood was collected at the time of admission. Serum uric acid measurement was done within 24 hours of delivery if patient delivered before blood sample had been drawn. All The enrolled participants and their babies were followed till discharge and any adverse events of baby during delivery or hospital stay was recorded. Special attention was given to LBW (< 2.5kg), Low APGAR (< 7 at 1 and 5 minutes), ICU admission. Babies admitted to baby unit for routine care because of maternal ill health was not taken as ICU admission.

Results and Discussion

Patients with serum uric acid levels less than 5.6mg/dl were put in control group and required sample size of 46 was achieved. Similarly, patients with uric acid levels more than and equal to 5.6 mg/dl were classified as study group and a sample size of 46 was achieved. Adverse perinatal outcome was seen with low APGAR scores in 30% vs 15% in study group and control group. Low birth weight 17% vs 7% in study group and control group and NICU admissions 11% vs 4% in study group and control group. However only the low-birth-weight finding was statistically significant.

The table shows distribution of age in each group was found to be similar and finding was not significant. Mean age was found to be 27.

Age in Years	Study group		Control Group		P Value
	No	%	No	%	
<15	0	0%	0	0%	0.217
15 – 19	2	4%	1	2%	
20 – 24	14	30%	14	30%	
25–29	18	39%	14	30%	
30-34	9	20%	10	23%	
35-39	3	7%	7	15%	
40 above	0	0%	0	0%	
Total:	46	100	46	100	

Table 1: *Age Distribution.*

The number of patients in study and control group were similar based on the period of gestation. The Mean gestational age of all the participants was 38 weeks and 3 days. There was no difference in the gestational age group among the control group and study group which was 38 weeks 4 days and 38 weeks 2 days respectively.

Gestational Age in weeks	Study group		Control Group		P Value
	No.	%	No.	%	
37 - 38	16	35%	18	39%	0.443
38 - 39	14	30%	11	24%	
39 - 40	9	20%	7	15%	
40 - 41	6	13%	7	15%	
41 - 42	1	2%	3	7%	
Total:	46	100%	46	100%	

Table 2: *Gestation Age in Weeks.*

Distribution according to parity was similar in study group and control group. The distribution according to parity in this study had a trend towards nulliparity and primiparity with almost 80% of the participants being nulliparous or primiparous in both the control and study groups.

Parity	Study Group		Control Group		P Value
	No.	%	No.	%	
Nullipara	21	46%	16	35%	0.409
P_1	15	33%	19	42%	
P_2	8	17%	8	17%	
P_3	1	2%	2	4%	
$P_{\geq 4}$	1	2%	1	2%	
Total:	46	100%	46	100%	

Table 3: *Parity Distribution.*

Instrumental delivery and LSCS was found only in study group whereas control group had all vaginal deliveries. However, the finding was not statistically significant.

Characteristics	study Group		Control Group		P value
	No.	%	No.	%	
Normal	39	85%	46	100%	0.859
Instrumental	4	9%	0	0%	
LSCS	3	6%	0	0%	
Total:	46	100%	46	100%	

Table 4: *Mode of Delivery.*

Most common indication for LSCS was fetal distress (66%) and CPD (33%) as illustrated in bar diagram.

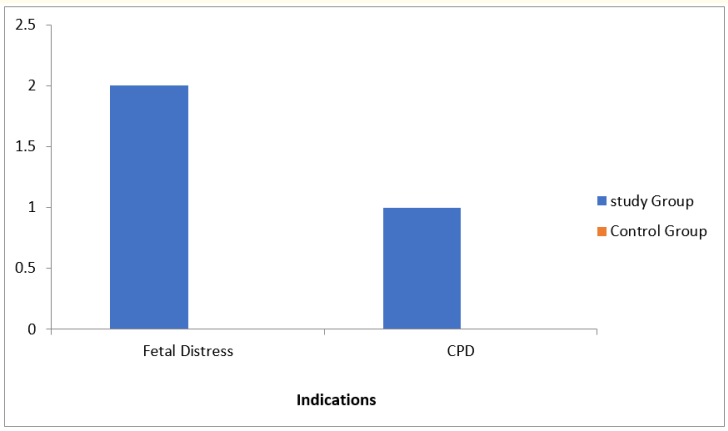

Figure 1: *Indications for Cesarean Section.*

Vacuum delivery was conducted in 4 study group patients. Vacuum was applied for fetal distress (thick meconium).

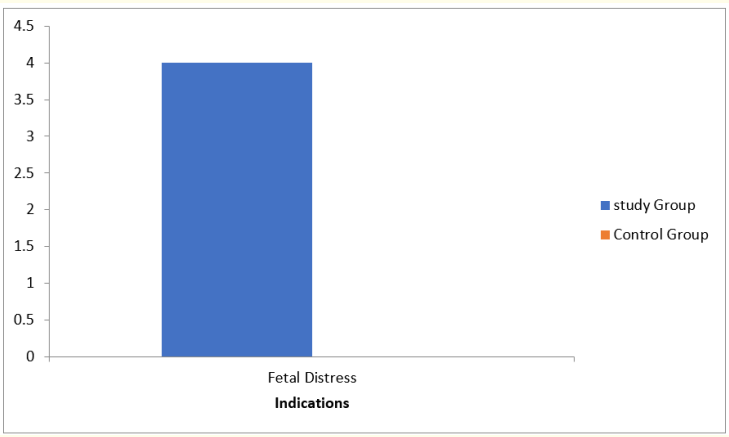

Figure 2: *Indications for Instrumental Delivery.*

There was 17% low birth weight in study group and a low birth weight of 7% in control group. Similarly, low APGAR scores were found 30% in study and 15% in control group. Special care baby unit admissions were 11%in study and 4% in control group.

Characteristics	Study Group		Control Group		P value
	No.	%	No.	%	
Low Birth weight	8	17%	3	7%	0.792
Low APGAR	14	30%	7	15%	
SCBU admission	5	11%	2	4%	

Table 5: *Adverse Perinatal Outcome in relation to Serum Uric acid.*

A total of 7 babies were admitted in NICU in which the most common indication was low APGAR score. N=3 (60%) among study group.

Characteristics	study Group		Control Group		P value
	No.	%	No.	%	
Low APGAR Score	3	60%	0	0%	0.319
Low Birth Weight	1	20%	0	0%	
Suspected Sepsis	1	20%	2	100%	
Total:	5		2		

Table 6: *Indications for NICU Admission.*

This table shows that among all participants 11 pregnant women had low birth weight babies in which n=8 (17%) had low birth weight in study group which was statistically significant (p = 0.032). overall incidence of low birth weight was 11 which consisted of a low-birth-weight percentage of 12%. The incidence of low birth weight was more in the study group which was 17% while the incidence of low birth weight in control group was only 7%. This difference was statistically significant as depicted by p value 0f 0.032.

Birth weight in kg	Study Group		Control Group		P value
	No.	%	No.	%	
<2.5	8	17%	3	7%	0.032
2.5 –3	17	37%	27	59%	
3 – 3.5	17	37%	13	28%	
3.5 – 4	4	9%	3	7%	
>4	0	0%	0	0%	
Total:	46	100%	46	100%	

Table 7: *Birth weight in relation to Serum Uric Acid.*

The Incidence of hypertensive disorder of pregnancy in this study was 8.5% which is almost same as the study done by Yucesay., *et al* who found the incidence of hypertensive disorder of pregnancy 8.49%. This incidence is higher than that the study done by Arju Chand Singh., *et al*. which was 3.3%, the study done by Vatten and Skjaerven which was 2.6% and the study done by Lawler J 1.1% [16-19]. The higher incidence found in this study is probably due to the study being conducted at the tertiary maternity referral hospital of Nepal.

Also, there is high number of nulliparas and young patients being enrolled in the study that might also account for the higher incidence of pregnancy induced hypertension.

The mean gestational age in this study is greater than the study done by Razia Sultana., *et al* [9]. and A.C. Urato., *et al* [11] which was 33.5 ± 2.55 weeks in the cases and 33.6 ± 2.95 weeks in control. The mean gestational age in the group with uric acid less than 4 mg/dl was 34 weeks and 5 days, uric acid 4.1 – 6 mg/dl was 32 weeks and 5 days and the group with uric acid level ≥ 6 mg/dl was 31 weeks and 6 days [11]. Such grouping has been done in our study with a uric acid cutoff value of 5.5mg/dl. Similarly the mean gestational age in this study was similar to that study conducted by Vaidyanathan G., *et al.* where the mean gestational age was 37 ± 3weeks [13].

This distribution of parity was similar to the distribution observed W Visser et al. where nullipatity contributed to 74% of all participants [14]. In a study by Loi K., *et al.* they observed equal distribution of participants in to nulliparity and multiparity [12]. Similarly, in a study by A.C. Urato., *et al.* there was a diverse inclusion of participants in regards to parity distribution with 51% nullipara, 28% primipara, 13% para2, 5% para3 and 3% para4 or more [11].

In this study the overall incidence of low birth weight was 11 which consisted of a low-birth-weight percentage of 12%. The incidence of low birth weight was more in the study group which was 17% while the incidence of low birth weight in control group was only 7%. This difference was statistically significant as depicted by p value 0f 0.032. This outcome was similar to the study conducted by Joel R livingstone., *et al.,* where the total cohort had a low birth weight incidence of 8.4%.[5] Also the findings of current study is supported by the finding of study by A Ramana Priya., *et al.* where they concluded that a uric acid value of greater than 5.5 mg/dl in patients of GHTN is associated with low birth weight which is statistically significant ($p < 0.004$) [15]. Similarly, the study done by A.C. Urato, which had findings of decreasing values of birth weight with increasing values of uric acid is also in correlation with the findings of this study [11]. The incidence of low birth weight in this study is much lower than the incidence seen in a study by Alan K Snover., *et al.* where the incidence of low birth weight was 46% in control group and 89% in the study group [1]. The findings are also in unison with the findings by Norvald Sagen., *et al.,* where they found a significant association of serum urate levels with low birth weight 3 [6].

The relative lower incidence of adverse perinatal morbidities observed in this study is probably due to the inclusion of women after completion of 37 weeks of gestation at which most of the fetuses have grown to full maturity.

Conclusion

Hypertensive disorders of pregnancy are common medical disorders affecting 5 to 10% of pregnancies. These are associated with adverse perinatal outcomes. The Incidence of hypertensive disorder in current study was 8.5%. Perinatal morbidity in terms of low birth weight, NICU admissions and Low APGAR scores were higher in preeclamptic patients with serum uric acid more than 5.5mg/dl. But only the difference in low birth weight was statistically significant.

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Conflict of Interest

There is no any form of conflict of interest.

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