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SERUM URIC ACID AS MARKER FOR DIAGNOSING PREECLAMPSIA

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ABSTRACT

Hypertensive disorders are important causes of premature delivery, IUGR and intra uterine fetal death. It accounts for 15% to 20% of maternal deaths in developing as well as developed nations. An association of serum uric acid with hypertensive disorders of pregnancy. The main objective of the present study was measuring and evaluating serum uric acid values in normal pregnant and preeclamptic and eclamptic cases to see the trend in the rise of serum uric acid in toxemic cases. Therefore we planned this study. The present study was conducted on Control (15 Normal non pregnant healthy women) and 140 cases they were further sub divided as, 60 Normal pregnant women in different trimesters, 60-Preeclampticcases, 20-Eclampticcases. Then Preeclampsia was divided into3groups (Mild preeclampsia – BP at least 140/90 mmHg. Moderate preeclampsia – BP more than 140/90 but <160/110mmHg. Severe preeclampsia – BP>160/110 mmHg but without convulsions). Estimation of serum uric acid was done at Department of Biochemistry, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand during June 2008 to Sept.2009. The cases were selected from outdoor, indoor and emergency of department of Obstetrics and Gynecology, RIMS, Ranchi. The serum value of uric acid was studied in 60 preeclamptic cases and 20 cases of eclampsia.. The mean ± S.D. values of serum uric acid in normal non pregnant cases was 3.68±0.66, in normal pregnant cases in 1st trimester was 3.60±0.78, normal pregnant cases in 2nd trimester was 3.40±0.33, normal pregnant cases in 3rd trimester was 4.64±0.70. in preeclamptic patients, the mean was 6.70±0.78 and in eclamptic patients it was 7.52±0.95. on doing analysis of this it shows significant changing patterns in serum uric acid level between normal non-pregnant cases and normal pregnant cases in the 3rd trimester. Also there is a good significance between normal cases in 3rd trimester and preeclamptic cases as a whole. The above study undertaken shows a definite rise in serum uric acid level in diseased subjects as early as first and early second trimester, although difference rise in serum uric acid in mild cases when compared to normal cases was not statistically significant. But, it can be concluded that serum uric acid measurement is one of the best markers of the diagnosis as well as severity of preeclampsia and will be a useful index for the management of the same.

INTRODUCTION: The association of hyperuricemia with preeclampsia has been known since 1917 [1]. Hypertension in pregnancy is a major cause of maternal death and also a major source of maternal and perinatal morbidity and perinatal mortality [2]. Uric acid is a component of non-protein nitrogenous substances Asmallfraction of urates is loosely bound to plasma proteins. It is important to identify women who are high risk of developing the disease early in pregnancy [3].

Preeclampsia is a pregnancy specific syndrome of reduced organ perfusion secondary to vasospasm and endothelial activation. Proteinuria is an important sign of preeclampsia and rightfully concluded that the diagnosis is questionable in its absence. It can be defined as a multisystem disorder of unknown etiology characterized by development of hypertension to the extent of 140/90 mmHg or more with proteinuria induced by pregnancy after the 20th week [4].

Hypertensive disorders are important causes of premature delivery, IUGR and intra uterine fetal death. It accounts for 15% to 20% of maternal deaths in developing as well as developed nations [5]. Pregnancy induced hypertension is defined as the hypertension that develops as a result of the gravid state and includes**:** Preeclampsia, Eclampsia and Gestational hypertension [6]. Although the cause of preeclampsia remains unknown, evidence for it begins to manifest early in pregnancy with pathophysiological changes that gain momentum across gestation unless delivery supervenes. These changes ultimately result in multi-organ involvement with a clinical spectrum ranging from barely noticeable to life threatening for both mother and fetus. These adverse maternal and fetal effects develop simultaneously and presumably are a consequence of vasospasm, endothelial dysfunction and ischemia.

The myriad of maternal consequences of the preeclampsia syndrome are described in terms of organ systems, but they frequently overlap. It is enigmatic that there are such wide variations of involvement of these systems in individual pregnancies. Recently, because of uric acid's role in vascular damage and in oxidative stress, hyperuricemia has been evoked as a contributor to the pathogenesis of preeclampsia [7, 8].

In normal pregnancy, serum uric acid level slowly decreases until about 16 weeks of gestation, secondary to plasma volume expansion, increased renal clearance, and the uricosuric effect of estrogen. For most of the 2nd trimester, the uric acid level remains stable, and then increases during the 3rd trimester because of increase catabolism/production [9]. Interestingly, women with a history of preeclampsia also have a higher risk for cardiovascular disease and hypertension later in life [10, 11].

Uric acid levels correlate with plasma rennin activity [12], hyperuricemia predicts the development of hypertension in the general population [13]. This research work aims at measuring and evaluating serum uric acid in normal pregnant cases and in preeclamptic and eclamptic cases to see the trend in the rise of serum uric acid in toxemic cases when compared to the control group and comparative study with patients.

MATERIAL AND METHODS: A Total of 155 patients were registered in the Department of Biochemistry, Rajendra Institute of Medical Sciences, Ranchi, during June 2008 to Sept.2009. The cases selected from outdoor, indoor and emergency of Dept. of Obstetrics and Gynecology, RIMS The cases studied were 15, (Normal non pregnant healthy women) control.60-Normal pregnant women in different trimesters,60-Preeclamptic cases, 20-Eclamptic cases. Preeclampsia was divided into 3 groups. As diet has effect on serum uric acid level, the samples were to be collected in fasting state.

Hence, the patients were advised to fast overnight and if not possible then at least for 4 hours. In the morning between 8 A.M. to 10 A.M. 3ml of venous blood samples were collected by a dry sterilized syringe into a dry plain vial. The samples were allowed to clot for separation of serum. Then serum was centrifuged for 10 minutes at 3000 rpm. The clear supernatant serum was pipetted into a clean dry test tube for uric acid estimation. Estimation of uric acid by Uricase/Pap method supplied by crest biosystems a division of coral clinical system [14]. Enzymatic conversion of uric acid and oxygen by Uricase to allantoin and hydrogen peroxide. Hydrogen peroxide and phenolic chromogens are converted by peroxidise to a red color compound, whose concentration is proportional to the amount of uric acid in the specimen and is read at 500 nm (range

492-550) the final color is stable for 15 minutes. Intensity of the color formed is directly proportional to the amount of uric acid present in the sample [15].

Another parameter like Detailed menstrual history, Clinical examination, Cycle Flow (Any related complaint such as pain, Last menstrual period (LMP) Expected date of delivery), Obstetrical history (Gravida parity, history of previous pregnancy, detail about previous babies), Medical and Surgical history (Hepatic disorder, Renal disorder, Cardiovascular-hypertension, Heart disease, Respiratory disorder, Metabolic diseases such as Diabetes Mellitus, Epilepsy, Malaria), family history (Multiple pregnancy, Diabetes mellitus, Hypertension, Congenital heart disease), physical Examination, General examination (Body built Height, Pallor, Blood pressure Pulse Oedema), Systemic examination (chest, CVS), Abdominal examination, (Inspection, Palpation, Fetal heart rate) were recorded during the study period when patients had continuous periodical referral to the Dept. of Obstetrics and Gynecology, RIMS.

Statistical analysis was performed using GraphPad Prism version 5.00 for Windows, GraphPad software, San Diego California USA, www.graphpad.com.

RESULTS: Preeclampsia is a major complication of human pregnancies, affecting 5-7% of pregnant women. Preeclampsia is characterized by an increase in vascular tone (vasospasm) that is frequently associated with enhanced platelet aggregation and therefore, reduced utero-placental flow. In addition, coupling of these factors with disturbed renal function worsens perinatal outcome. Preeclampsia usually is well established before the patient develops symptoms.

She may be aware of some puffiness of the fingers and face, which is common in normal pregnancy, but hypertension, proteinuria and increase in uric acid level in blood and decrease in clearance tests, may be present for days or weeks before she has any subjective complaints. Hence, the importance of perinatal care primary objective of which is the early detection of the signs and laboratory parameters in preeclampsia. **Table 1 and figure 1** shows that the serum value of uric acid was studied in 60 preeclamptic cases and 20 cases of eclampsia.

The results obtained in control subjects and in toxemic patients had been shown in the above table. The mean and ±S.D. values of serum uric acid in normal non pregnant cases was 3.68 ± 0.66, in normal pregnant cases in 1st trimester was 3.60±0.78, normal pregnant cases in 2nd trimester was 3.40±0.33, normal pregnant cases in 3rd trimester was 4.64±0.70. In pre- eclamptic patients, the mean was 6.70±0.78 and in eclamptic patients was 7.52±0.95.

Table 2 and figure 2 shows that significant changing patterns in serum uric acid level between normal non-pregnant cases and normal pregnant cases in the 3rd trimester. The p-value obtained< 0.01, which was statically significant. There was significance between normal cases in 3rd trimester and pre-eclamptic cases as a whole. Other groups compared were not statistically significant.

Table 3 and figure 3 shows that the difference in uric acid concentration was not statistically significant when parity was compared. The groups were formed according to parity in normal pregnancy. The serum uric acid (mg %) in all these groups were obtained as follows in table (Results are expressed in terms of mean ± S.D. values t value & p value). In 1st gravid normal pregnant cases, mean was 3.52±0.02, and in 3rd gravid normal pregnant cases, it dipped down to the mean of 3.40±0.49. When compared, the difference in serum uric acid is not statistically significant when parity was compared.

Table 4 and figure 4 shows that the difference in uric acid in different age group between normal and toxemic age group 18-25 years, the mean was 3.6±0.48, in 26-30 years age group, the mean was 3.73±0.75 and in age group 30 and above, mean was 3.8±1.11. In toxemic cases, in 18-25 years age group, the mean serum uric acid was 6.3±0.32, in 26-30years age group, the mean was 7.5±0.38 and in 30 and above age group, the mean was 8.2±0.37. The difference in uric acid in different age group between normal and toxemia is statistically significant but when compared between different age group within control or cases. It increases as age advances, but was not found significant.

Table 5 and figure 5 shows that the gradual fall of serum uric acid levels towards lower values after parturition in each group of case. Mean value of serum uric acid during pregnancy in eclamptic cases was 9.55±0.95 and after 6-12 hours after delivery, it was 6.90±1.17. The different between the two group show the p-value <0.01, which was statistically significant.

Table 6 and figure 6 shows that statistically significant difference in the changing pattern (rise) in uric acid when mild, moderate and severe pre-eclamptic were compared in a group of two, was statistically significant. The p-value obtained from mild and moderate cases was <0.001, which was highly statically significant. But when severe pre-eclamptic cases were compared with eclamptic cases, the difference in uric acid was not statistically significant.

TABLE 1: URIC ACID IN MG% IN NORMAL NON-PREGNANT, NORMAL PREGNANT IN DIFFERENT TRIMESTER PREECLAMPTIC & ECLAMPTIC

S. No.	Types of cases	No. of cases (N size)	Range	Mean	S.D.	S.E.
1	Normal non- pregnant cases	15	2.8-5.2	3.68	±0.66	0.1041
2	Normal Pregnant (1st trimester)	10	1.9-5.2	3.60	±.78	0.1090
3	Normal Pregnant (2nd trimester	30	1.0-5.0	3.40	±.33	0.1312
4	Normal Pregnant (3rd trimester	20	2.5-6.3	4.64	±.70	1.54
5	Preeclamptic	60	3.7-9.00	6.70	±.78	0.1130
6	Eclamptic	20	7.1-9.54	7.52	±.95	1.1402

TABLE 2: ANALYSIS OF THE ABOVE DATA IN TABLE 1

Between	T – value	P – value	Significance
1 & 2	1.86	<0.10	Not significant
1 & 3	1.58	<.10	Not significant
1 & 4	3.98	<0.01	Significant
4 & 5	7.04	<.01	Significant
5 & 6	0.34	<0.1	Not significant

TABLE 3: SHOWING SERUM URIC ACID LEVELS IN DIFFERENT TYPES OF PATIENTS ACCORDING TO THEIR PARITY IN NORMAL PREGNANCY SERUM URIC ACID (mg/100 ml)

Group	N. Size	Range	Mean	S.D.	S.E.	t-value	p-value	
Gravida 1	29	1.9-6.2	3.52	±0.02	.1401	1.58	<.1	Not significance
Gravida 2	17	1.9-6.3	3.57	±0.02	.1205			
Gravida 3 or more	15	2.0-5.5	3.40	±.49	.0902	1.60	<.1	Not significance

The difference in uric acid concentration is not statistically significant when parity is compared.

TABLE 4: SHOWS ANALYSIS OF THE SERUM URIC ACID IN MG% IN DIFFERENT AGE GROUP OF PATIENTS

Age Group	Age group in years	Normal	Range	Mean	Serum uric acid in mg%			
					S.D.	S.E.	t-value	p-value
18-25	Normal	38	1.9-6.1	3.6	±0.48	0.201	2.32	<0.05
	Toxaemic	34	3.7-8.5	6.3	±0.32	0.101		
26-30	Normal	22	2.0-6.0	3.73	±0.75	0.25	2.40	<.01
	Toxaemic	34		7.5	±0.38	0.15		
30 and above	Normal	9	2.8-5.6	3.8	±1.11	0.35	2.33	<.01
	Toxaemic	16	3.2-9.2	8.2	±.37	0.26		

TABLE 5: SHOWING THE CHANGING PATTERN OF SERUM URIC ACID CONCENTRATION IN ECLAMPTIC CASES DURING PREGNANCY AND AFTER DELIVER (6-12 HOURS)

Group	Normal size	Range	Mean	S.D.	S.E.	t-value	p-value	
Eclamptics during pregnancy	20	7.1-9.54	9.55	±0.95	0.1402	3.30	<.01	Significant
Eclamptics after 6-12 hours of delivery	20	6.0-8.5	6.90	±1.17	0.1509			

TABLE 6: SERUM URIC ACID IN MG%, IN MILD, MODERATE & SEVERE PREECLAMPTIC CASES

Group	Normal	Range	Mean	S.D.	S.E.	t-value	p-value	Significant
Mild	22	5.2-8.2	6.7	±0.603	0.26	4.58	<0.001	Highly Significant
Moderate	18	5.5-9.2	7.05	±0.402	0.77			
Severe	20	6.2-8.5	7.30	±0.81	0.28	1.28	<0.05	Significant
Eclamptic	20	6.2-8.2	7.16	±0.28	0.16	.52	<0.05	Significant

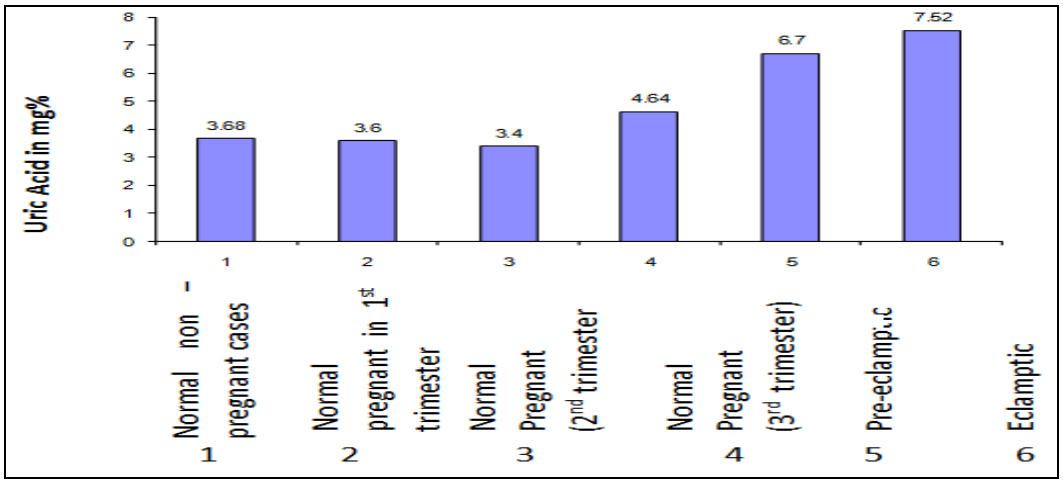

FIGURE 1: TYPES OF CASES

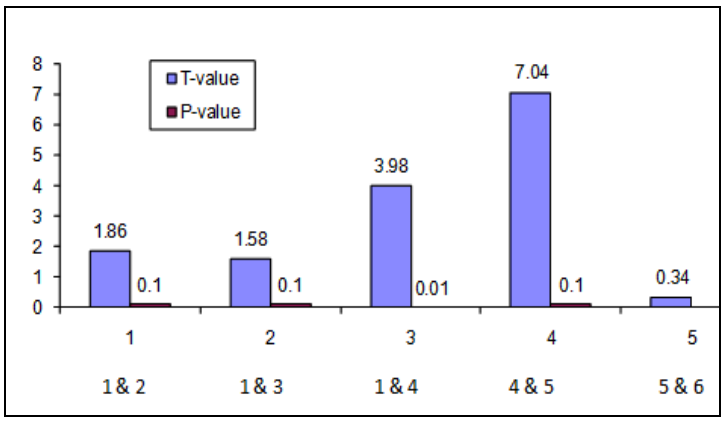

FIGURE 2: ANALYSIS OF THE ABOVE DATA, BETWEEN 1 & 2, 1 & 3, 1 & 4, 4 & 5 AND 5 & 6 OF THE ABOVE TABLE

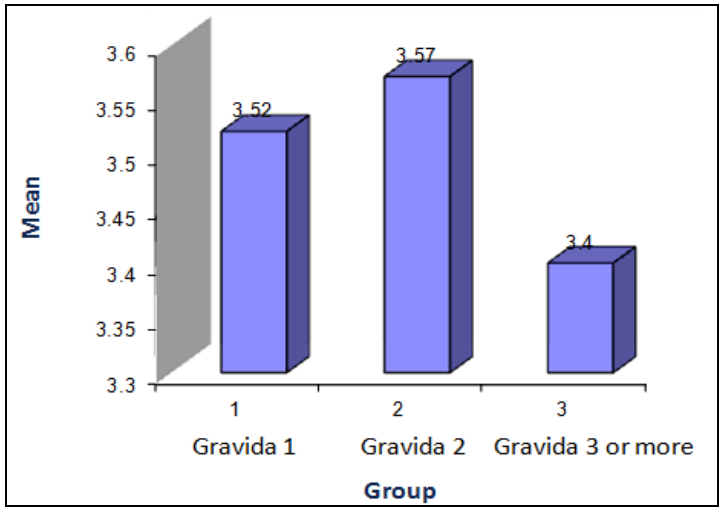

FIGURE 3: SHOWING SERUM URIC ACID LEVELS IN DIFFERENT TYPES OF PATIENTS ACCORDING TO THEIR PARITY IN NORMAL PREGNANCY SERUM URIC ACID (Mg/100 mL)

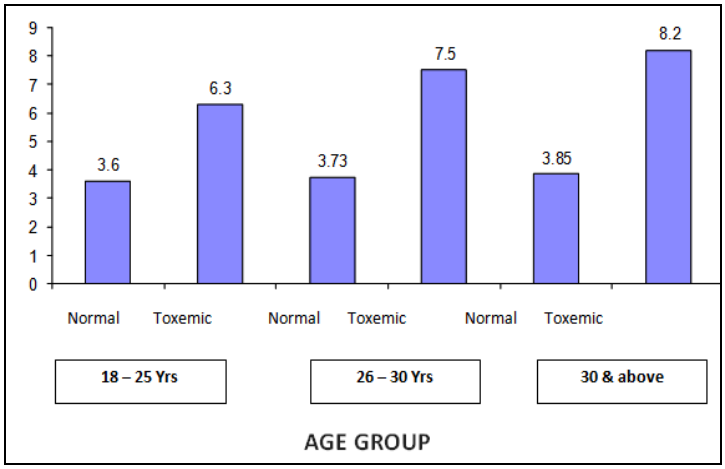

FIGURE 4: ANALYSIS OF THE SERUM URIC ACID IN mg% IN DIFFERENT AGE GROUP OF PATIENTS

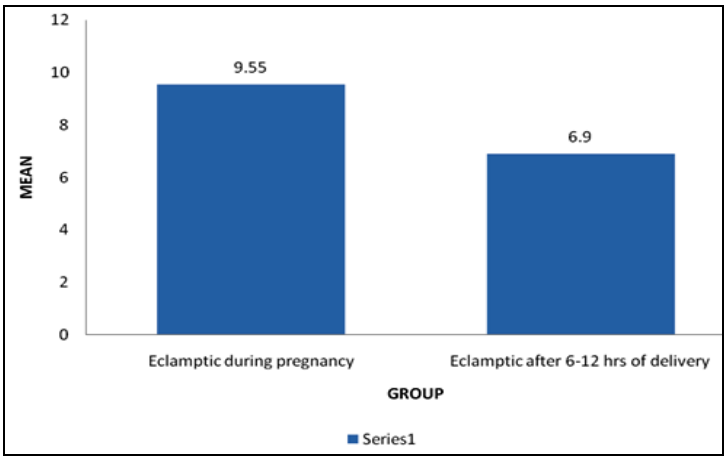

FIGURE 5: SHOWING THE CHANGING PATTERN OF SERUM URIC ACID CONCENTRATION IN ECLAMPTIC CASES DURING PREGNANCY AND AFTER DELIVERY (6-12 HOURS)

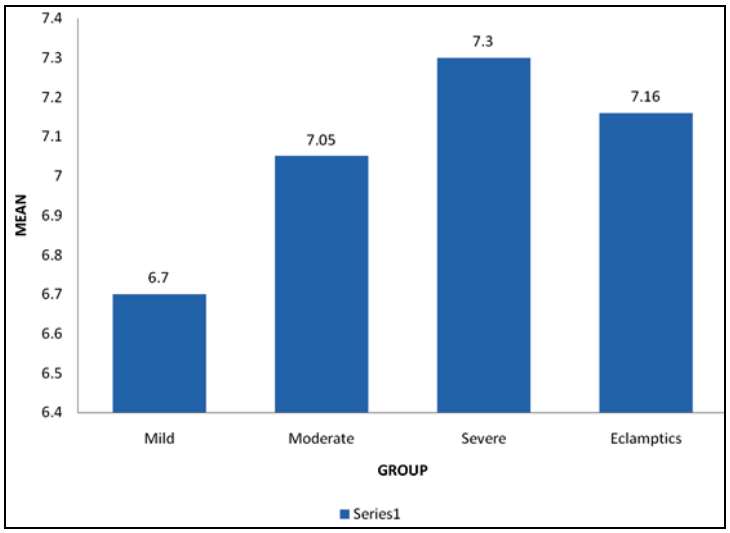

FIGURE 6: SERUM URIC ACID IN MILD, MODERATE AND SEVERE PRE-ECLAMPTIC CASES

DISCUSSION: In the present study, estimation of serum uric acid was done in normal pregnant women and patients with pregnancy induced hypertension (i.e. Preeclamptic and Eclamptic patients). The assessment of the severity of the toxemia of pregnancy was based on the clinical examination of the patients and presence of proteinuria. For the diagnosis of preeclampsia, till date, two of the three factors should be essentially present viz. Hypertension to the extent of 140/90 mmHg or more with edema or proteinuria or both, induced by pregnancy after 20th week of gestation.

In only rare circumstances, do the Preeclamptic features appear before the 20th week as in cases of hydatiform mole and acute polyhydraminos. Serum uric acid, as has been well documented by past workers and confirmed in the present study is definitely raised in toxemia of pregnancy. Also, one of the latest concept is increase in oxidative stress (due to ischemia) when there is more formation of free radicals than the body defense system can handle. This leads to tissue breakdown. When purine component of nucleic acid breaks down, there were increased formations of uric acid.

In the present work, it was established whether the biochemical marker, serum uric acid level can be used as a screening test to predict the later development of the disease. Plasma uric acid levels constitute a better indicator than blood pressure as prognosis for fetal outcome[16].

In the present study estimations of serum uric acid levels were done in normal pregnant women in different trimesters, Preeclamptic toxemic cases and eclamptic cases.

The assessment of the severity of the toxemia of pregnancy is based on the clinical examination of the patients and proteinuria. But these did not give much clue regarding the systemic damage caused by the disease. The clearance values of endogenous creatinine and serum uric acid estimation has been long considered as an accurate index for the early diagnosis of toxemia of pregnancy and in evaluating fetal and maternal prognosis in such cases.

In the present series, study of serum uric acid level in non-pregnant was done not only to compare the results with other series, but also to regard our figures as control. In the present study, the mean for serum uric acid was 3.68± 0.606 while this value was differing from HAWKE and BERGIM value, 2.95mg/dl [17].

The present study also pointed out that as blood pressure increases the level of serum uric acid also increases. When diastolic BP was <90 mmHg, there was no increase in serum uric acid levels (provided other factors do not fluctuate beyond normal limits). There was a positive correlation between the increase in serum uric acid levels and diastolic BP. In our study serum uric acid concentration were analyzed in relation to the different age groups and parity of the patients.

It was found that there was no relation of serum uric acid either with the increasing age or parity. Serum uric acid was analyzed in linear age group for this; entire subjects have been divided into 3 linear reproducible age groups. The mean serum uric acid level was found to be increased with increase in age, but was statistically insignificant. In the first age group (18-25 yrs) the mean Serum uric acid was found to be lowest (3.6 ± 0.48 mg %).

In the age group (26-30 yrs.), the mean Serum uric acid level in normal control cases was 3.73 ± 0.75 and in age group 30 yrs. And above, the mean serum uric acid value was 3.8 ± 1.1. The difference between the above group increases with the increase in age but was not statistically significant.

CONCLUSION: In conclusion that the serum uric acid measurement was one of the best markers of the diagnosis as well as severity of preeclampsia and will be a useful index for the management of the same. In all cases of toxemias (eclamptic) of pregnancy, the estimation was undertaken for uric acid levels. It was found that serum uric acid level gradually declined and came to normal limits by the 6th day of delivery Parity if the patients have no relation with significant increase in serum uric acid levels. Serum uric acid increases with age but is not significant statistically.

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