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Study of estimation of serum uric acid levels in the 1st trimester as a predictor of preeclampsia

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Abstract
Background and Objective: Pre eclampsia is a life threatening multisystem disorder, unique to pregnancy, complicating approximately 28% of pregnancies in developed countries and approximately 5-8% in developing countries. It is the 2nd most important cause of maternal mortality in the world.
Materials and Methods: 200 pregnant women attending ANC, at ESIC MC PGIMSR HOSPITAL, Banglore who were in the 1st trimester (up to 12weeks period of gestation) were included in the study from January 2018 to june2019. Routine laboratory investigations are done, along with the serum uric acid. (1st trimester) serum uric acid level was measured by auto analyser. These patients were regularly followed up in the antenatal OPD once in the 4 weeks till 28 weeks then once in two weeks till there is delivery the patients who developed preeclampsia are grouped as preeclampsia Cohort. The patients who are normotensive till delivery are grouped as normal cohort. In our study, for 200, pregnant women the serum uric acid analysis was done in first trimester for prediction of preeclampsia. 92 patients were positive where uric acid level is >_4.2mg/dl of which 59(37.3%) were normotensive and 33(78.6%) were preeclamptic respectively, and remaining 108 patients were negative (where serum uric acid is _-<_ 4.2mg/dl) which among 99(62.7%) and 9(21.4%) were normotensive and preeclampsia patients respectively.so maximum number of patients were positive in preeclampsia patients that is 78.6% out of 42 patients where p value is 0.0001 which is significant
The biometric level of serum uric acid among cohort(preeclampsia) were in the mean of 4.3+- 0.81(mild), and 4.6+_0.83 for severe preeclampsia and no preeclampsia was 3.67+_0.83 by the two independent t test, both are statistically significant. Receiving operating Curve denotes optimal cut off criterion is > 4.2 for preeclampsia patients. The area under curve is 0.777 with p value of 0.0001 statistically significant.
In our study risk for both maternal and fetal complications assessed with serum uric acid positive pregnant women (>4.2mg/dl) of that P value is statistically significant in severe preeclampsia, Gestational hypertension, HELLP syndrome, mode of delivery (> by LSCS 70.7%), NICU admissions, babies of low Apgar score at 1 minute, Mean birthweight.
Conclusion: First trimester elevated uric acid was associated with later preeclampsia Assessment of uric acid is convienent and costeffective method for determination of preeclampsia and its severity and can be used as prevalent marker for risk assessment in preeclampsia(PET) or PIH.

Keywords: Pregnancy, high risk, pre-eclampsia, uric acid, pregnancy complication

Introduction

Hypertensive disorders i.e PET complicates about 5-10%of all pregnancies, it is one of the member of the deadly triad along with haemorrhage and infection that contributes maternal mortality and morbidity. Preeclamptic toxaemia occurs after 20 weeks of gestation in a singleton pregnancy and resolves afterdelivery.[1] according to many studies, preeclampsia is associated with abnormal trophoblastic invasion of uterine vessels, abnormal immunological tolerance between maternal, placental(paternal) and fetal tissues and maladaption to cardiovascular inflammatory changes of normal pregnancy. Genetic factors like inheriting predisposing genes also play a role in etiology of PET [2] pathophysiological changes which includes abnormal trophoblastic invasion, spiral artery narrowing, atherosis, infarcts, endothelial cell injury seen in placenta, are seen in preeclamptic women [3].
Vasospasm [4] endothelial cell injury [5] increased pressor response [6] prostaglandins involvement and derangement [7-8]. Nitric oxide production and endothelial production [9] are involved in all organs of the body. (William's). All the pathophysiological changes begins with early pregnancy i.e in the 1st trimester of gestation that is when early invasion of trophoblastic changes takes place. During early pregnancy measurements of various biological, biochemical markers implicated in the pathophysiology of PET has been proposed to predict its development.
The biochemical marker which are been proposed which are suggestive of renal dysfunction are seen. Uric acid, microalbuminuria, urinary calcium, microtransferrin urea,

cystatin C, etc [10].

Serum uric acid in the 1st trimester can be a good predictor of preeclampsia and its estimation is a simple, biochemical screening test to predict the development of preeclampsia [11].

Aims and Objectives

Estimation of serum uric acid levels in first trimester as prediction of preeclampsia.

1. To assess ad compare serum uric acid in pregnancy induced hypertension and normal pregnant women.
2. Determine the diagnostic efficiency of uric acid as a predictive marker of severity in PIH.

Materials and Methods

Sources of Data

200 Pregnant women attending regular ANC OPD in ESIC MC PGIMSR hospital, Rajajinagar, Bengaluru.

Study Design

- Prospective Cohort Study.

Inclusive Criteria

1. Primi/ multigravida with singleton pregnancy with gestational age upto 12 weeks.
2. All selected patients between the age group of 18-35 will be screened for serum uric acid in the early first trimester and will be followed up tilldelivery.

Exclusion Criteria

1. Multiplepregnancy
2. Women with history of renal disease hypertension, diabetes mellitus, hypothyroidism or hyperthyroidism.

Study Period

- -From November 2017 to April 2019(18 months)

Samplesize

As it is a time bound study of 200 patients who fulfill the inclusion criteria aretaken.

Methods of Collection of Data

This study will be undertaken at ESIMC & PGIMSR, Rajajinagar, Bangalore. Pregnant women attending regular ANC visitsin OPD in ESIMC and PGIMSR, whoareinthe1st trimester (upto 12 weeks period of gestation) are included in the study from November 2017 to April 2019.

Methodology

1. Minimum of 200 pregnant women attending regular ANC check up in the department of Obstetrics and Gynaecology, ESIMC & PGIMSR, Bangalore are selected based on the inclusion criteria after obtaining theirconsent.
2. All selected women are subjected to detailed history comprising of age, parity, body weight and height, LMP, medical history, drug history, previous obstetric history, previous history of preeclampsia.
3. They are subjected to clinical examination and BP will be recorded. Routine laboratory investigations are done.
4. On the next day fasting sample was taken from these patients for measuring serum uric acid level.
5. Serum uric acid level will be measured by auto analyser.
6. These patients are regularly followed up in the the antenatal OPD once in the 4 weeks till 28 weeks then once in two weeks till there is delivery and through clinical examination done focusing their blood pressure and urine albumin.
   All the details are noted. The patients who developed preeclampsia are grouped as preeclampsiaCohort.
7. The patients who are normotensive till delivery are grouped as normal cohort.
8. The factors taken for analysis are age, distribution, obstretic score, body mass index, history of preeclampsia in previous pregnancies, serum uric acid, outcome-mode of delivery, APGAR score, birth weight, NICU admission.
9. The productive value of serum uric acid is determined by ROC Curve.

Statistical Analysis

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 21 version software. Categorical data was represented in the form of Frequencies and proportions. Chi-square test was used as test of significance for qualitative data. Continuous data was represented as mean and standard deviation and independent t test was used to calculate p value for continuous variables.

Graphical representation of data: MS Excel and MS word was used to obtain various types of graphs such as bar diagram, Pie diagram and Scatter plots. p value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

Results and Observations

Table 1: Distribution of Serum Uric Acid analysis among both the groups

		GROUP			
		Normal (n=158)		Preeclampsia(n=42)	
		Frequency	%	Frequency	%
Serum Uric acid test	Negative (<_4.2mg /dl)	99	62.7%	9	21.4%
	Positive (>_4.2mg /dl)	59	37.3%	33	78.6%

Chi square = 22.706 p= 0.00

In our study, 200 pregnant women serum uric acid analysis was done. 92 patients were positive (where uric acid level is >_4.2mg/dl) of which 59(37.3%) were normotensive and 33(78.6%) were preeclamptic respectively and remaining 108 patients were negative (where uric acid <_4.2mg/dl) which among 99(62.7%) and 9(21.4%) were normotensive and preeclampsia patients respectively. So maximum number of patients were positive in preeclampsia patients that is 33(78.6%) out of 42 patients where p value is 0.0001 which is statistically significant.

Table 2: Distribution of frequency of proteinuria among study groups

		Serum Uric acid test			
		Positive(n=92) (>_4.2mg/dl)		Negative(n=108) (<_4.2mg/dl)	
		Frequency	%	Frequency	%
Proteinuria A	1+	1	1.1%	3	2.8%
	2+	19	20.7%	1	0.9%
	3+	18	19.6%	5	4.6%
	bsent	54	58.7%	99	91.7%

Chi square = 36.73 p= 0.0001

Out of 92 patients with positive serum uric acid (>_4.2mg/dl), proteinuria 1+ was present in 1(1.1%), 2+was seen in 19(20.7%), 3+ seen in 18(19.6%) and absent proteinuria in 54(58.7%). Out of 108 patients with negative uric acid (<_4.2mg/dl), proteinuria1+ was present seen in 3(2.8%), 2+ in 1(0.9%), 3+ in 5(4.6%) and absent proteinuria was seen in 99(91.7%). The p value is 0.0001 which is statisticallysignificant.

Out of 92 patients, with positive serum uric acid levels (>_4.2mg/dl), 78 patients (84.8%) developed gestational hypertension and 14(15.2%) were normotensive. Out of 108 patients with serum uric acid (<_4.2mg/dl) gestational hypertension was seen in 52(48.1%) and 56 (51.9%) did not develop gestational hypertension, where the p value is 0.0001 which is significant.

Table 3: Distribution of frequency of preeclampsia among study subjects. Tt

		Serum Uric acid test			
		Positive(n=92) (>_4.2mg/dl)		Negative(n=108) (<_4.2Mg/dl)	
		Frequency	%	Frequency	%
Preeclampsia	Absent	59	64.1%	99	91.7%
	Mild	16	17.4%	6	5.6%
	SEVERE	15	16.3%	3	2.8%
	Eclampsia	2	2.2%	0	0.0%

Chi Square = 23.54 p= 0.0001.

Out of 92 patients with positive serum uric acid levels (>_4.2mg/dl), preeclampsia wasabsent in 59(64.1%), mild preeclampsia in 16(17.4%), severe in 15(16.3%) and eclampsia in 2(2.2%). Out of 108 patients with negative serum uric acid (<_4.2mg/dl), preeclampsia absent in 99(91.7%), mild preeclampsia in 6(5.6%0, severe in 3(2.8%), and eclampsia in 0 (0.0%). The p value is 0.0001 which is statisticaly significant.

Table 4: Distribution of HELLP syndrome among study groups.

		Serum Uric acid test			
		Positive(n=92) (>_4.2mg/dl		Negative(n=108) (<_4.2Mg/dl)	
		Frequency	%	Frequency	%
HELLP synd	Absent	87	94.6%	108	100.0%
	Present	5	5.4%	0	0.0%

Chi Square = 6.020p=0.014

Out of 92 patients with serum uric acid positive (>_4.2mg/dl), HELLP Syndrome was absent in 87(94.6%) and was present in 5(5.4%).

Among 108 patients with uric acid negative (<4.2mg/dl), HELLP syndrome was absent. The p value is 0.014 is significant.

Table 5: Distribution of mode of delivery among study groups.

		Serum Uric acid test			
		Positive(n=92) (>_4.2mg/dl)		Negative(n=92) (>_4.2mg/dl)	
		Frequency	%	Frequency	%
Mode of Delivery	Instrumental	2	2.2%	7	6.5%
	LSCS	65	70.7%	44	40.7%
	Vaginal	25	27.1%	57	52.8%

Chi square =26.32p=0.0001

Out of 92 patients with serum uric acid positive (>_4.2mg/dl), Instrumental delivery was seen in 2(2.2%), LSCS in 65 (70.7%), vaginal delivery in 25(27.1%). Out of 108 patients with serum uric acid negative (<_4.2mg/dl), instrumental delivery in 7(6.5%), LSCS was done in 44 (40.7%), vaginal delivery in 57(52.8%). LSCS were more in serum uric acid positive patients (>4.2mg/dl) with p value 0.0001 which is statistically significant. Out of 92 patients with serum uric acid positive (>_4.2mg/dl), babies with no NICU admissions in 58(63.0%) and NICU admission required for 34 babies (37.0%). Out of 108 patients

with serum uric acid negative (<_4.2mg/dl), babies with no NICU admissions were 92(85.2%) and NICU admissions required in 16(14.8%). P value is 0.0001 which is statistically significant.

Table 6: Distribution of mean of serum uric acid in preeclampsia among study groups.

		S. Uric ACID		ANOVA
		Mean	Standard Deviation	
Preeclampsia	Absent	3.67	0.83	F= 18.491 p=0.0001
	Mild	4.3	0.81	
	Severe	4.6	0.83	

Mean uric acid and SD for absent preeclampsia were 3.67+_o.83, for mild preeclampsia was 4.3+-0.81, for severe eclampsia mean uric acid and SD were 4.6+_0.83 where p value shows 0.0001 which is significant.

Table 7: Distribution of mean serum uric acid in eclampsia

	Eclampsia			
	Present		Absent	
	Mean	SD	Mean	SD
Mean Serum Uric Acid Levels	4.6	0.84	3.810	.83

P=0.036 the mean serum uric acid and SD of Eclampsia patient was 4.6 +_0.84 and pregnant women without eclampsia was 3.81+_0.83. The P value is 0.036 which is significant.

The mean serum uric acid and SD for pregnant women with HELLP (Hemolysis, elevated liver enzymes, low platelet count) syndrome was 4.72 +_0.85 and pregnant women without HELLP syndrome was 3.82+_0.83. The mean value is 0.0176 which is statistically significant.

The mean serum uric acid and SD at delivery was 4.5+_0.89 at <28weeks, between 28 to 37 weeks was 4.34+_0.84 and >37weeks was 3.6+_0.83.The P VALUE of 0.0001 is significant. The mean of serum uric acid and SD of birth weight of babies less than 2.5kg was 4.23+_0.84 and birth weight >2.5kg was 3.64+_0.83. The p value of 0.0001 is significant. The mean of serum uric acid and SD of APGAR score at 1 minute, at less than 5 score was 4.25+_0.84 and more than 5 score was 3.67+_0.84.The p value of 0.0001 is significant.

ROC Curve: For Preeclampsia

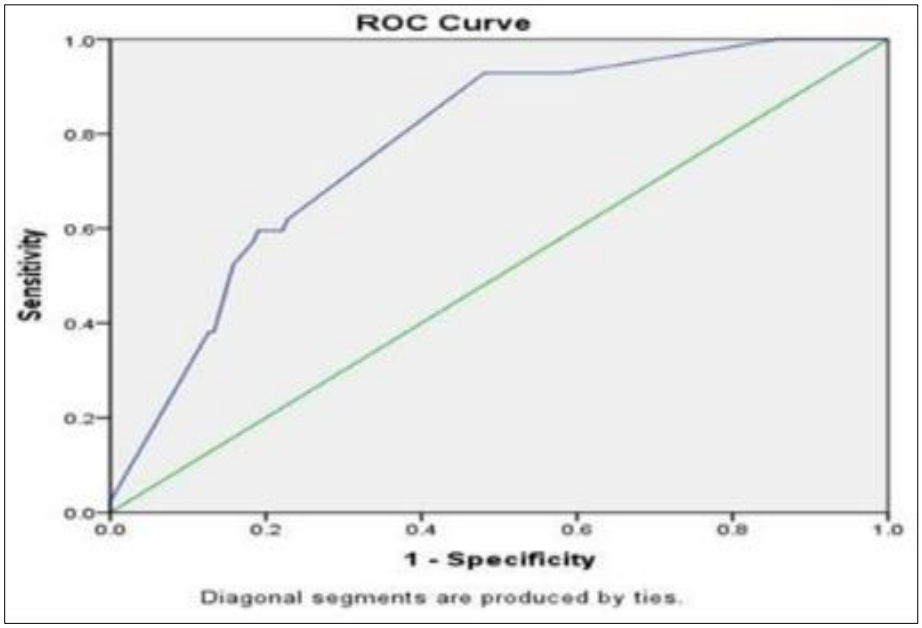

Fig 1

Table 8

Area Under the Curve				
Test Result Variable(s): S.URIC ACID				
Area	Std. Errora	Asymptotic Sig.b	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.777	.037	.000	.705	.849

On applying ROC Curve to check the Diagnostic ability of the Serum Uric Acid level in predicting the Occurrence of Pre eclampsia was found to be statistically significant with p value of 0.0001 and the area under the curve to be 0.777. For the Cut of value of 4.2 of serum uric acid the Sensitivity was found to be 59.5% and Specificity was21.5%.

Disscusion

Present study is concerned with association of elevated serum uric acid level in prediction of preeclampsia and study of maternal and perinatal outcome in elevated serum uric acid levels.

In non-pregnant women serum uric acid level is 2.5-5.6mg/dl is the reference range for females. During pregnancy serum uric acid for the first trimester is 2.0-4.2mg/dl, second trimester 2.4-4.9mg/dl and third trimester is3.1-6.3mg/dl.

There is decrease trend of serum uric acid level in first trimester and second trimester and third trimester of pregnancy. The cited reasons for this change of decreasing trend of uric acid level are (i) due to haemodilution and increase renal plasma flow. (ii) Decreasing oncotic pressure in the blood. (iii) Increase in glomerular filteration rate.

There is a pathological changes in trophoblastic invasion is a known factor as a cause of preeclamptic toxaemia (PET).This pathological changes takes place well before the clinical manifestation. Hence assessment of uric acid in the first trimester is necessary as a predictor of preeclamptictoxemia.

ROC Curve (Receiving Operating Curve)

Present study out of 200 patients, 92 patients were uric acid positive (>4.2mg/dl) and 108 patients were uric acid negative (<4.2mg/dl). The mean serum uric acid levels and SD was 4.6+_0.84 compared to negative serum uric acid which was 3.81+_0.83with P value 0.036 is significant.Similar studies was done by APEKSHA NIRAULA, M.D., *et al.* 2015 [15], ninety study participants were included: 45 participants were diagnosed PIH and 45 in control group .They concluded that mean serum uric acid levels was higher in PIH compared to control group (5.46+_1.51 vs 4.03+_0.69) respectively. where p value for both studies shows significant.Similar studies was done by Dr.P.S. JIKKIKALAISELVI *et al.* 2017 [16], the biomarker level of serum uric acid among preeclampsia were in the mean of 5.51 and no preeclampsia patients were 3.570. P value is statistically significant. ROC Denotes Optimal Cut off Criterion Is>4.6 for preeclampsia. Patients. The area under curve is 0.922825, which is atmost perfect prediction with a youden index value=0.7994. they concluded study that first trimester elevated uric acid was associated with later preeclampsia which coordinates with our study where the mean is >4.2mg/dl for preeclampsia and ROC curve 0.777 where the p value is also significant. Similar study was done by CIMONA LYN SALDANHA *et al.* [17] 2018, n=45, where serum uric acid was, >5mg/dl frequency is 44(97.7%), and n=55 where serum uric acid is<5mg/dl frequency was 20(36.3%). The p value is 0.000 which is significant. which coordinate to our study where percentage of proteinuria is increased is raised serum uricacid.In present study among 200 pregnant women, maximum number of patient were belong to age group 26 to 30yrs 62 (39.3%) in normotensive and 21(50.0%) inpreeclampsia respectively. Followed by 51(32.30%) and 10 (23,8%) between age group 21 to 25yrs. Obstretic index among the study subjects, both in normal and preeclampsia belong to primi gravida 84 (53.2%) and 15 (35.7%) followed by Gravida 2 and Gravida 3, 29.7% and 12.7% in normotensive and 17 (40.5%) and 6(14.3%) respectively.

In present study, 200 ANC patients were estimated for serum uric acid levels in first trime ster (up to 12weeks), among them, at gestational age 8 weeks were 6 (3.8%),0 (0.0%),at 9 weeks were 17(10.8%), 3(7.1%), at 10 weeks were 27(17.1%) and 7(16.7%),at11weekswere
63(39.9%) and 15(35.7%) and at 12 weeks were 45(28.5%), 17(40.5%) in normotensive and pre-eclamptic patients. The p value iso.445.

In our study, for 200 pregnant women the serum uric acid analysis was done. 92 patients were positive (where uric acid level is>_ 4.2mg/dl) of which 59 (37.3%) were normotensive and 33(78.6%) were preeclamptic respectively. and remaining 108 patients were negative (where uric acid is <_ 4.2mg/dl) which among 99(62.7%) and 9(21.4%) were normotensive and preeclampsia patients respectively. So maximum number of patients were positive in preeclampsia patients that is 33(78.6%) out of 42 patients where p value is 0.0001 which is highly statistically significant. out of 92 patients mild preeclampsia were 16(17.4%) and severe preeclampsia were 15(16.3%). out of 108 patients 6(5.6%) were mild preeclampsia and 3(2.8%0 were severe preeclampsia. The p value is 0.0001 is significant. The mean uric acid and SD 0f Mild Preeclampsia Was 4.3+_0.81 And For Severe Preeclampsia was 4.6+-0.83 with Pvalue 0.0001 which issignificant. The study correlates with the study done by Elloradevi *et al.* [12], Habibunnisha B. Sirjwaala *et al.* [13] and Hemanth G. Deshpande. *et al.* [14] studies. In present study out of Out of 92 patients with positive uric acid (>_4.2mg/dl), proteinuria 1+ present in 1(1.1%), 2+ proteinuria in 19(20.7%), 3+ proteinuria in 18(19.6%) and absent in
54(58.7%).

Out of 108 patients with negative uric cid (<_4.2mg/dl), proteinuria 1+ present in 3(2.8%), 2+ proteinuria in 1(0.9%), 3+proteinuria in 5(4.6%) and absent in 99(91.7%). The p value is 0.0001 which issignificant.

In present study, Out of 92 patients, with serum uric acid positive (>_4.2mg/dl) the gestational hypertension present in 78(84.8%). Out of 108 patients with serum uric acid (<_4.2mg/dl) the gestational hypertension absent in 52(48.1%) and 56 (51.9%). The p value is 0.0001 which issignificant.

In present study, out of out of 92 patients with serum uric acid positive (>_4.2mg/dl), preeclampsia was absent in 59(64.1%), mild preeclampsia present in 16(17.4%), severe preeclampsia were 15(16.3%) and eclampsia in 2(2.2%). Out of 108 patients with serum uric acid negative (<_4.2mg/dl), preeclampsia absent in 99(91.7%), mild preeclampsia present in 6(5.6%), severe preeclampsia were 3(2.8%), and none of them had eclampsia 0 (0.0%). The p value is 0.0001.which is significant.

Out of 92 patients with serum uric acid positive (>_4.2mg/dl), HELLP Syndrome absent were 87(94.6%) and present were 5(5.4%). Among all 108 patients with uric acid negative (<4.2mg/dl), none of the patient had HELLP syndrome.The p value is 0.014 is significant. The study correlates with Cimona lyn Saldana *et al.* study [17].

In present study Out of 92 patients with serum uric acid positive (>_4.2mg/dl), IUGR absent were 87(94.6%) and present were 5(5.4%). out of 108 patients with uric acid negative (<4.2mg/dl IUGR absent were 106(98.1%) and present were 2(1.9%). The Pvalue is statistically not significant. Our study corelates with the study of MARYAM ASGHAMIA. M.D. *et al.* [18].

In present study, 92 patients with serum uric acid positive (>_4.2mg/dl) Abruption absent in 91(98.9%) and present in 1(1.1%). Out of 108 patients with uric acid negative (<_4.2mg/dl) none of them had abruption. The p value is 0.277. The present study correlates with Cimona Lyn SALDANA *et al.* study [17].

In present study, Out of 92 patients with serum uric acid positive (>_4.2mg/dl), Mode of delivery with Instrumental were 2(2.2%), LSCS were 65 (70.7%), vaginal were 25(27.1%). Out of 108 patients with serum uric acid negative (<_4.2mg/dl), the instrumental delivery were 7(6.5%), LSCS were 44 (40.7%), vaginal delivery were 57(52.8%). The maximum deliveries was through LSCS. The P value is 0.0001 is significant. Our study correlates with thestudy

In present study, Out of 92 patients with serum uric acid positive (>_4.2mg/dl), babies with NICU admission absent were 58(63.0%) and present were 34(37.0%). Out of 108 patients with serum uric acid negative (<_4.2mg/dl), babies with NICU admission absent were 92(85.2%) and present were 16(14.8%). P value is 0.0001 is significant. Our study correlates with CIMONA LYN SALDANA *et al*. study [17].

In present study among 92 patients with serum uric acid positive >4.2mg/dl, babies of low APGAR score at 1 minute were 3.2(36.4%) and with serum uric acid negative ie <4.2mg/Dl were 13(12.1%). p value is 0.0001. Present study correlates with CIMONA LYN SALDANA *et al.* study.

In present study among 92 patients with serum uric acid positive >4.2mg/dl mean birth weight is 2.5837 SD of 1.8521 and out of 108 patients with serum uric acid <4.2mg/dl the mean birth weight is 3.1231 SD of 2.9402.The study correlates with CIMONA LYN SALDANA *et al.* [17] 2018 study, where birth weight of new born babies was average of <_2.5kg.And Similar studies was done by Dr.P.S. Jikkikalaiselvi *et al.* [16] 2017, the biomarker level of serum uric acid among preeclampsia were in the mean of 5.51 and no preeclampsia patients were 3.570. P value is statistically significant. ROC Denotes Optimal Cut off Criterion Is>4.6 for preeclampsia. Patients .The area under curve is 0.922825, which is at most perfect prediction with a youden index value=0.7994. they concluded study that first trimester elevated uric acid was associated with later preeclampsia which coordinates with our study where the mean is >4.2mg/dl for preeclampsia and ROC curve 0.777 where the p value is also significant

Conclusion

In present study increased serum uric acid level in first trimester is associated with development of preeclampsia in later weeks of pregnancy and increased risk of HELLP syndrome, abruption of placenta IUGR, low APGAR score and increased NICUadmission.

Routine estimation of serum uric acid level in first trimester is a valuable biochemical marker for prediction of preeclamptic toxemia.

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