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Evaluation of Total protein, Albumin, Aspartate Transaminase (SGOT), Urea and Creatinine in Third Trimester of Preeclampsia and Their Effect on Obstetric Outcome: A prospective study

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Abstract
Preeclampsia, a clinical condition manifested by new onset hypertension (=/> 140/90 mm of Hg) after 20 weeks of gestation with proteinuria with or without evidence of multiorgan involvement. Generalized vasoconstriction that occurs in severe preeclampsia and subsequent multiorgan dysfunction secondary to reduced perfusion, hypoxia, activation of coagulation cascade and loss of endothelial integrity causes characteristic clinical features like hypertension, proteinuria, hypoproteinemia, hemolysis, raised liver enzymes, low platelet count and raised level of urea, creatinine and uric acid. Abnormal values of these parameters are considered as markers of severe preeclampsia which badly affect the course of pregnancy and obstetric outcome though no single marker has been established to have high predictive value.

Materials and Method: *This prospective study was carried out for one and half years during the year 2015-16 at a peripheral Medical College of West Bengal, India with Ethical approval. The study population included the antenatal mothers who attended antenatal OPD from the first trimester of pregnancy. The aim of the study was to evaluate the biochemical changes, mainly of liver and kidneys associated with preeclampsia and how it affected the outcome of pregnancy. A total of 100 mothers were taken as case-control study. Group one (n=50) were the mothers having increase systolic pressure >30 mm Hg and diastolic blood pressure >15 mm Hg above their booking blood pressure for two consecutive clinic attendance and presence of proteinuria by dipstick test, serve as case; group two (n=50) were the mothers with normal systolic and diastolic blood pressure throughout the pregnancy ,serve as control; All biochemical and hematological investigations were done in central pathological lab of the Institution and ultrasonography at the Department of Radiology. All other data collected from Labour Room Record Book, Antenatal Record Book, Logbook, OT Registrar and Bed Head Ticket and data analyzed at the end of the study.*

Results & Analysis: *According to parity, 42 out of 50 mother in preeclampsia group were primigravida (p value 0.046) rectify nulliparity is a risk factor. There was significant proteinuria among preeclampsia mothers compared to normotensive mothers (P value< 0.05).The study showed preeclampsia group have statistically less Hb% (p value <0.05), less mean total protein (p value< 0.05), less mean albumin (p value< 0.05), abnormal rise of AST (aspartate aminotransferase) (p value< 0.05) and significant rise of blood urea (p value <0.05) at term in comparison to normotensive group. There was higher incidence of LUCS delivery (p value< 0.05) and preterm, IUGR and low birth weight (LBW) babies (p value< 0.05) among preeclampsia mothers than that of normotensive mothers. In evaluation of birth conditions per Apgar score index, relative risk of life expectancy was greater in preeclampsia group (P*

value< 0.05) than that of normotensive group. In this regard, SNCU admission in preeclampsia group was much higher than normotensive group (P value< 0.05). The duration of hospital stay was more in preeclampsia mother compared to normotensive mother (p value< 0.05) and significant number of mother admitted to ICU in preeclampsia group than that of normotensive group (P value< 0.05).

Conclusion: *In preeclampsia, involvements of multiorgan complicate the course of pregnancy more severely. In this connection, evaluation of different parameters like degree of proteinuria, gestational age, available Hb%, biomarkers like serum total protein, serum albumin, AST, serum urea and creatinine should be justified for the timing delivery in preeclampsia mother and thus a better obstetric outcome could be ascertained.*

Keyword: *Preeclampsia, Normotensive, Proteinuria, Aspartate aminotransferase (AST), Low birth weight (LBW).*

Introduction

Preeclampsia is a clinical condition manifested by new onset of hypertension on two or more occasions at least 6 hours apart and proteinuria during pregnancy, usually after 20 weeks[1], is a major cause maternal and neonatal morbidity and mortality [2] though the exact etiology still remains unclear. Many observations about the disease process have been made, but none have yet resulted in a clear elucidation of its pathogenesis. Newer definitions also include maternal organ dysfunction, such as renal insufficiency, liver involvement, neurological and hematological complications, utero placental dysfunction or intrauterine growth restrictions (IUGR) [3, 4]. Though the early stage of preeclampsia is asymptomatic, placental vascular abnormality, i.e. defective trophoblastic invasion has noted during first trimester of pregnancy and the magnitude of this defect positively correlate with the severity of hypertensive disorder in later stage[5].Plasma Endothelin-1, a potent vasoconstrictor, maintaining a much higher level in preeclampsia than normotensive pregnant women[6] though the source found to be arise from systemic endothelial activation, not from the placental material[7]. Vasoconstriction occurs in women with overt preeclampsia and subsequently multiorgan dysfunction secondary to reduced perfusion, hypoxia, activation of coagulation cascade and loss of endothelial integrity[8] causes characteristic clinical features like hypertension, proteinuria with hypoproteinemia, hemolysis, raised liver enzymes, low platelet counts, acute kidney injury and eventually eclampsia. In many cases, though patients remain asymptomatic, there is much elevation of liver enzymes, namely aspartate aminotransferase (AST) and alanine aminotransferase (ALT)- are considered markers for severe preeclampsia[9]. Regarding fetal outcome, preeclampsia itself to be an independent risk factor for low birth weight baby and mothers who delivered LBW babies are five times more likely to have had pregnancy induced hypertension[10]. Moreover, it is a major cause of maternal and perinatal morbidities, preterm and late preterm births and NICU admissions[11].

Materials & Methods

The study was carried out within a period of 18 months during the year 2015-16 at a peripheral Medical College of West Bengal, India after being approved by the Ethics Committee. The study was prospective and observational in nature and the study population was among the antenatal mothers who attending antenatal OPD from the first trimester of pregnancy. As the natural history of preeclampsia is to progress at an unpredictable rate till the delivery, the patients were closely monitored. Though there is frequent association of multiorgan involvement and no single biomarker has high predictive value, application of multiple biomarkers allows easy grouping of preeclampsia patients into different categories based on severity of symptoms, and thus proper and timely intervention with medical management could improve the outcome of pregnancy.

The aim of the study was to evaluate the biochemical changes, mainly of liver and kidneys associated with preeclampsia and how it affected the outcome of pregnancy.

A total of 300 patients were recruited on their booking day in preparation of antenatal care with an informed consent. Inclusion criteria includes:

1) all antenatal mother attended antenatal clinic before 20 weeks of gestation. 2) BP less than 140 mm 0f Hg systolic and less than 90 mm of Hg before 20 weeks of gestation. Exclusion criteria includes: 1) hypertensive or epileptic before pregnancy 2) known diabetic 3) smoker and alcoholic 4) known history of renal disease 5) mother not willing to participate.

The gestational age was determined using the first day of last menstrual period and confirmed using pelvic ultrasound in all patients. A dipstick urine measurement for protein was performed on urine specimen collected from the patient on the clinic days. Testing was performed with multitask reagent strips. Proteinuria classified as 0 or absent (<300mg/L), 1+ or 2+(level between 300 - 3000mg/L) and high grade 3+ /4+ (level >3000mg/L). General and physical examination included body weight, pallor, edema, pulse, BP, heart sounds and urine for dip stick test along with obstetrical examination done at each antenatal visit. Data collected for routine hematological and serological test for pregnancy along with LFT, thyroid function test, urea, creatinine and pelvic ultrasound examination. All mothers under selection counseled about the abnormal signs and symptoms with advice to attend the clinic even earlier if she feels such symptoms. At each visit, the blood pressure was determined using mercurial sphygmomanometer in sitting position with the arm rested. The first and fifth korotkoff sounds were used as systolic and diastolic blood pressure respectively. Hypertension was defined as systolic and diastolic pressure of >/= 140 mm mercury and >/= 90 mm Hg respectively on two occasion at least 6 hours apart.

After completion of the study, total 100 mothers were taken as case-control study. They were divided into two groups, group one (n=50) with normal systolic and diastolic blood pressure served as control; group two (n=50) included the mothers having increase systolic pressure >30 mm Hg and diastolic blood pressure >15 mm Hg above their booking blood pressure for two consecutive clinic attendance and presence of proteinuria by dipstick test served as case. Apart from hypertension and proteinuria, other parameters did not differ much. All biochemical and hematological investigations were done in central pathological lab and ultrasonography at the Department of Radiology of the Institution. All other data collected from Labour Room Record Book, Antenatal Record Book, Logbook, OT Registrar and Bed Head Ticket.

Statistical analysis was done after data had entered in MS Excel and analyzed using SPSS (statistical package of social sciences).Descriptive characteristics were expressed as mean and standard deviation. Mean values between the two groups were compared using T-test and P-value were measured. Statistical significance was set at p value < 0.05 providing a 95% confidence interval.

Results and Analysis

After satisfying all inclusion and exclusion criteria 50 preeclampsia and 50 normotensive mothers were included as case and control under study. Both the group have almost same level of socio economic status i.e. mainly of lower middle and middle class group. Regarding parity, most mother of preeclampsia group was primigravida in comparison to normotensive group with a p-value 0.046 which correlates the association between preeclampsia and primigravidae. There was also a positive correlation of pedal edema with preeclampsia mother compared to normotensive mother (p-value 0.000) which indicates a strong association.

Figure: 1 Distribution of study group according to their urinary protein excretion among normal and preeclampsia group

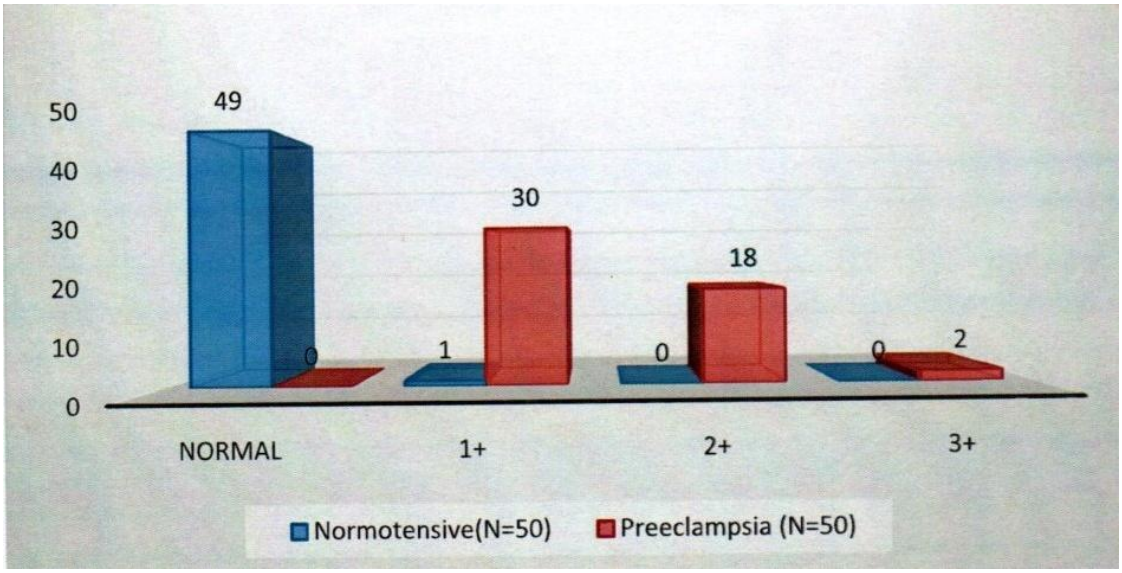

Figure: 2. Mean serum total protein level among normotensive and preeclampsia group at booking and third trimester

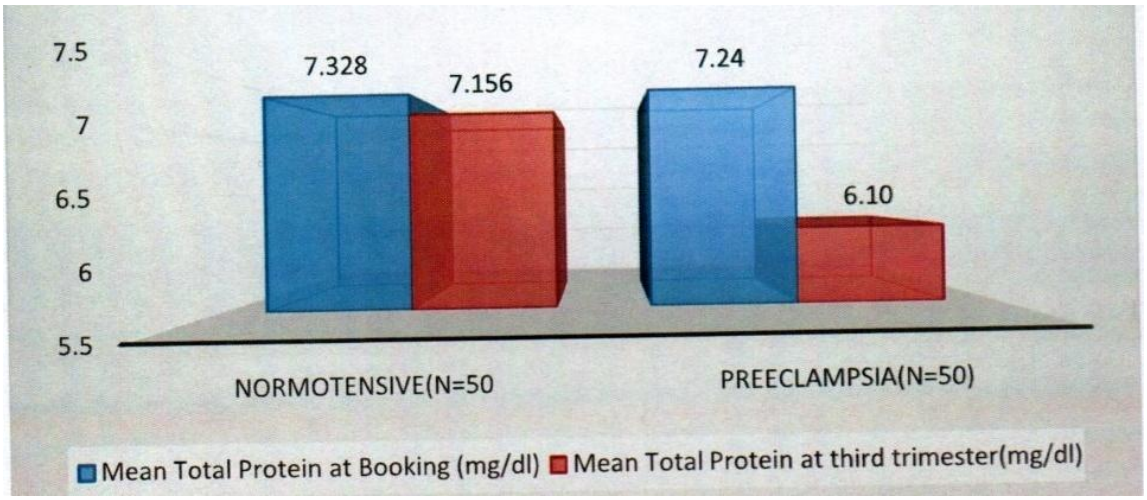

Figure: 3. Mean AST level among normal and preeclampsia group at booking and third trimester

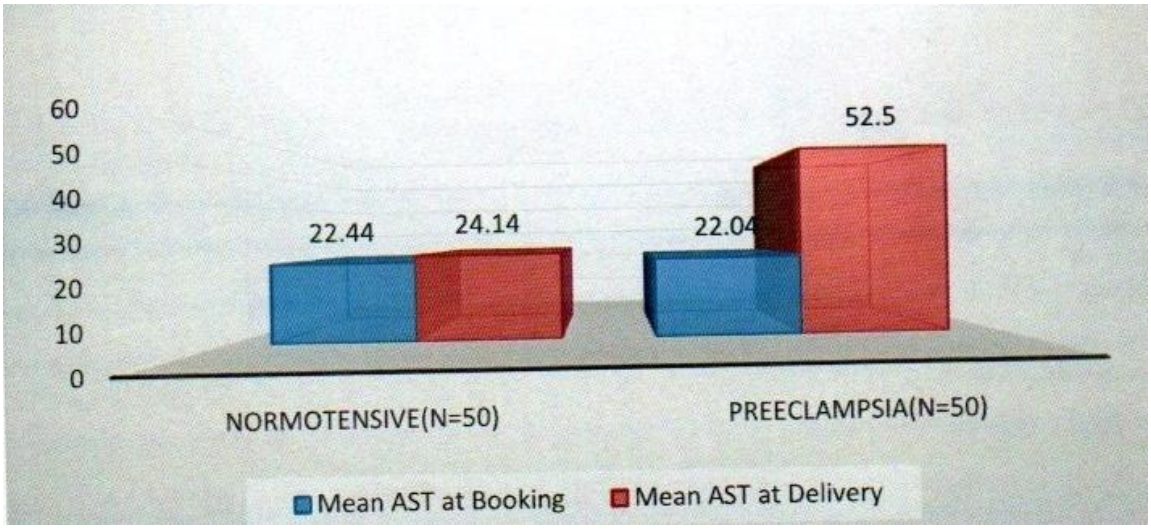

Figure: 4 Distribution of study group according to mode of delivery among normal and preeclampsia group.

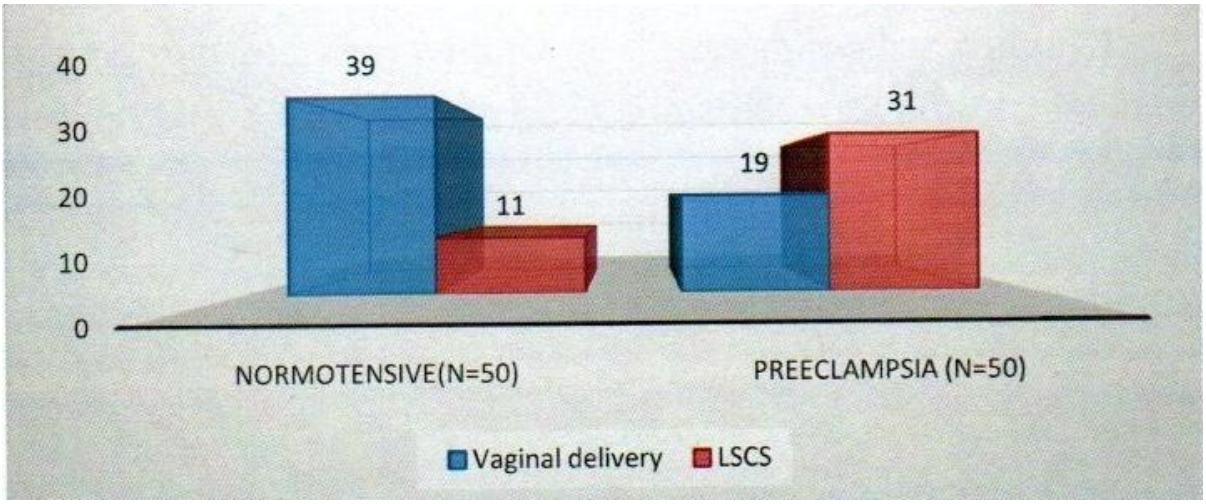

Figure: 5 Distribution of study group according to their outcome of the baby among normal and preeclampsia group

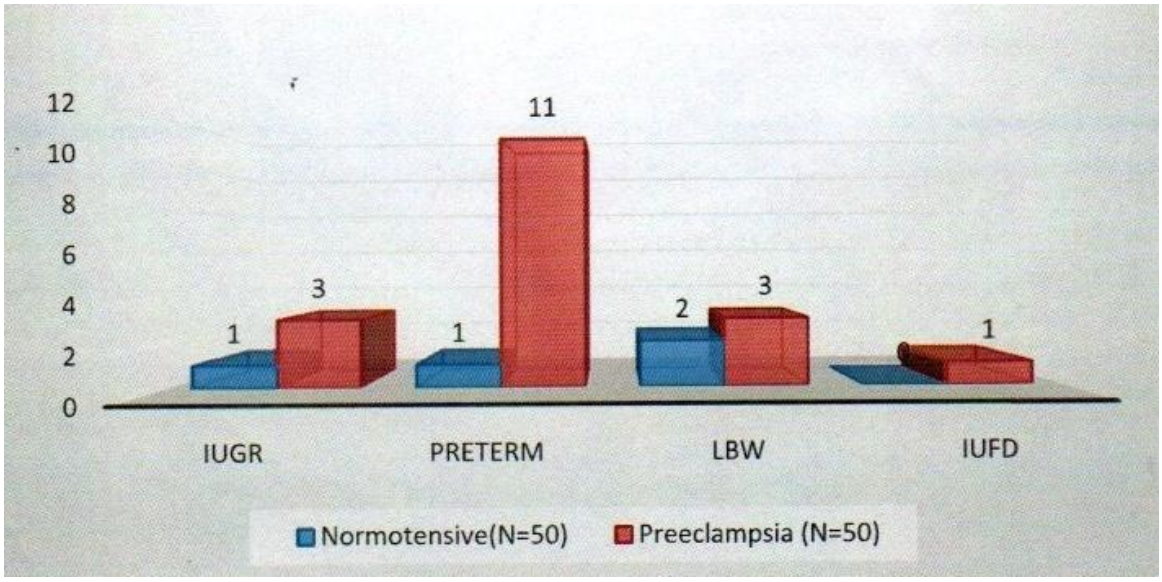

Figure: 6 Distribution of study group according to their outcome of baby among normal and preeclampsia group in terms of Apgar score.

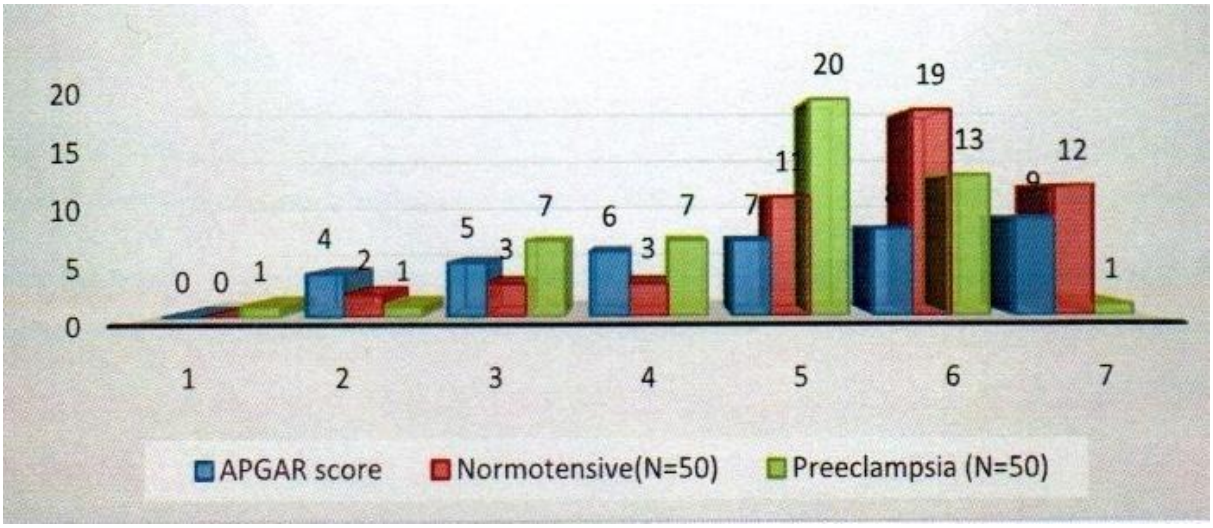

Table -1 Distribution of study group according to presence of protein in urine

Urinary protein	Normotensive(n=50)	Preeclampsia(n=50)	total	p-value
normal	49 (100%)	00 (0%)	49	0.000
1+	01 (3.2%)	30 (96.8%)	31	
2+	00 (0%)	18 (100%)	18	
3+	00 (0%)	02 (100%)	02	

Table showed single mother among normotensive group had 1+ proteinuria, rest were normal whereas 30 mother had 1+ proteinuria among preeclampsia group, rest 20 had either 2+ or 3+ proteinuria with significant p-value.

Table -2 Mean systolic and diastolic blood pressure in study group

Blood Pressure (mm of Hg)	Time of measurement	Normotensive	Preeclampsia	P value
Mean Systolic BP	At Booking	116.53 +/- 4.392	118.16 +/- 3.893	0.000
	At Delivery	121.64 +/- 6.070	157.48 +/- 13.247	
Mean Diastolic BP	At Booking	73.72 +/- 4.499	76.72 +/- 4.899	0.006
	At Delivery	77.40 +/- 5.704	102.40 +/- 7.825	

The table clearly displayed that the mean systolic and diastolic blood pressure has markedly increased in preeclampsia group in comparison to normotensive group at the time of delivery with significant p-value in both the variety.

Table – 3 Levels of different parameter among the normotensive and preeclampsia group

Different parameter level	Normotensive		Preeclampsia		P Value	Inference
	At Booking	At 3rd Trimester	At Booking	At 3rd Trimester		
Hb% (gm %)	11.472 +/-1.558	10.31 +/-0.652	11.518 +/-0.527	10.04 +/-0.570	0.032	significant
Mean total protein (g/dl)	7.328 +/-0.243	7.24 +/-0.555	7.334 +/-0.313	6.10 +/-0.580	0.000	significant
Mean Albumin(g/dl)	4.176 +/-0.363	3.84 +/-0.486	4.188 +/-0.340	2.82 +/-0.334	0.000	significant
Mean AST(IU/L)	22.44 +/-3.302	24.14 +/-4.794	22.04 +/-3.416	52.50 +/-16.787	0.000	significant
Mean Urea(mg/dl)	19.5 +/-3.985	23.48 +/-5.048	18.76 +/-3.684	33.00 +/-16.512	0.000	significant
Mean Creatinine (mg/dl)	0.324 +/-0.087	0.20 +/-0.404	0.318 +/-0.102	0.94 +/-0.470	0.382	insignificant

The table showed significant decrease in mean Hb% (p value 0.032), serum total protein (p value 0.000) and mean albumin level (p value 0.000) and significant increase level in mean AST (p value 0.000) and urea (p value 0.000) in preeclampsia group compared to normotensive group. The difference in mean Creatinine level (p value 0.382) between the two groups was not significant.

Table – 4 Mean gestational age, mode of delivery and mean birth weight

	Normotensive (n=50)	Preeclampsia(n=50)	Total	P Value
Mean gestational age (weeks) at delivery	39.04 +/- 1.551	36.86 +/- 2.928	100	0.000
Vaginal delivery	39 (67.2%)	19 (32.8%)	58	0.000
LUCS	11(26.2%)	31 (73.8%)	42	
Mean birth weight(kg)	2.78 +/- 0.418	2.58 +/- 0.499	100	0.000

The table showed mean gestational age was 36.86 +/- 2.928 weeks in preeclampsia group; on the other hand, it was 39.04 +/- 1.551 weeks in normotensive pregnancy. Here, p value is 0.000 which is highly significant. In normotensive group, 39 deliveries out of 50 was vaginal and LUCS done in rest 11 cases, whereas in preeclampsia group 19 delivery was vaginal and 31 delivery have done by LUCS. P-value is 0.000, which is highly significant favoring higher percentage of LUCS in preeclampsia group.

Table – 5 Distribution of baby according to Apgar score among Normal and Preeclampsia group

APGAR score	Normo0tensive group (n=50)	Preeclampsia group (n=50)	Total	P value
0	0 (0.0%)	1 (100%)	1 (100%)	0.007
4	2 (66.7%)	1 (33.3%)	3 (100%)	
5	3 (30 %)	7 (70%)	10 (100%)	
6	3 (30%)	7 (70%)	10 (100%)	
7	11 (35.5%)	20 (64.5%)	31 (100%)	
8	19 (59.4%)	13 (40.6%)	32 (100%)	
9	12 (92.3%)	1 (7.7%)	13 (100%)	

Table: 6. Distribution of study group according to stay in hospital among normotensive and study group

Duration of stay	Normotensive(n=50)	Preeclampsia(n=50)	P Value
2 Days	36(100%)	00(0%)	0.000
3Days	03(25%)	09(75%)	
4Days	01(11.1%)	08(88.9%)	
5Days	00 (0%)	01(100%)	
7Days	09(37.5%)	15(62.5%)	
8Days	1(6.7%)	14(93.3%)	
9Days	00(0%)	03(100%)	

Discussion

The study was carried out on 2015-16 session at a peripheral medical college after ethical approval. Total 100 pregnant mothers were included under the study of which 50 cases were preeclampsia and 50 were normotensive. Both the group had primary or middle school level of education in majority, more than 80% were from Hindu family and mostly from lower middle or middle class group in economic status. According to parity, 42 out of 50 mother in preeclampsia group were primigravida with a p value 0.046 rectify nulliparity is a risk factor. 40 mother of normotensive group had no pedal oedema where as 45 out of 50 preeclampsia mothers had pedal oedema with a p value 0.000 suggest its intimate association with preeclampsia. One normotensive mother had 1+ proteinuria (others without proteinuria) compared to 30 mothers with 1+, 18 mothers with 2 + and 2 mothers with 3+ proteinuria in preeclampsia group. P value is 0.000 which shows statistically highly significant correlation between proteinuria and preeclampsia.

There was no significant difference in systolic and diastolic blood pressure between normotensive and preeclampsia group at booking, but as pregnancy advances towards term, differences become obvious. The mean systolic blood pressure in normotensive and preeclampsia group at booking were 116.53 +/- 4.392 and 118.16 +/- 3.893 mm of Hg respectively and at delivery, it is 121.64 +/- 6.070 and 157.48 +/- 13.247 mm of Hg (p value 0.000). Similarly, the mean diastolic blood pressure in normotensive and preeclampsia group at booking were 73.72 +/- 4.499 and 76.72 +/- 4.899 mm of Hg and at term were 77.40 +/- 5.704 and 102.40 +/- 7.825 mm of Hg respectively (p value 0.006). So in preeclampsia, there is statistically significant rise of both systolic and diastolic blood pressure in advanced pregnancy.

The mean gestation age in terms of week at the time of delivery in normotensive group was 39.04 +/- 1.551 compare to 36.86 +/- 2.928 in preeclampsia group; here p value is 0.000 which is highly significant. Due to high BP, eclampsia, IUGR and PROM, preeclampsia mother needed termination of pregnancy at earlier weeks.

In normotensive mothers, the mean Hb% at booking was 11.472 +/- 1.558 gm% and at third trimester it was 10.31 +/- 0.652 gm%. On the other hand, in preeclampsia, mean Hb% at booking was 11.518 +/- 0.527 gm% but at third trimester it was 10.04 +/- 0.570 gm%. As p value is 0.032, preeclampsia mothers have statistically less Hb% at term.

Preeclampsia is associated with observed proteinuria due to increased capillary permeability secondary to endothelial damage with resultant low serum total protein and albumin levels. In our study, the mean total protein value in normotensive mother at booking was 7.328 +/- 0.243 g/dl and 7.24 +/- 0.555 g/dl at third trimester; where as in preeclampsia mother it was 7.334 +/- 0.313 g/dl and 6.10 +/- 0.570 g/dl respectively. The p value is 0.000, so there is strong association between preeclampsia and less serum protein. The mean serum albumin level in normotensive group at booking was 4.176 +/- 0.363 g/dl and 3.84 +/- 0.486g/dl in third trimester. In preeclampsia group, albumin level at booking was almost similar to that of normotensive group, 4.188 +/- 0.340 g/dl, but at third trimester, the level decreased up to 2.82 +/- 0.334 g/dl. The p value is 0.000, highly significant. These findings corroborate with earlier work done by Bhatia et al and Olooto et al[12,13].

Mean AST (aspartate transaminase) level in normotensive group at booking was 22.44 +/- 3.302 IU/L and 24.14 +/- 4.794 IU/L in third trimester. In preeclampsia group, AST level 22.04 +/- 3.416 IU/L of early pregnancy sharply increased up to 52.50 +/- 16.787 IU/L at third trimester. P value is 0.000, which is statistically highly significant and suggestive of abnormal liver function and severe preeclampsia. Our study result matched with previous work done by Benoit and Rey and Olooto et al[14,13].

Urea, Creatinine (and uric acid) are non protein nitrogenous metabolites, cleared off by the kidneys through glomerular filtration. These values usually decrease in pregnancy as GFR increases by 50%. So raised values of these parameters commonly indicate abnormal renal function, commonly seen in severe preeclampsia. In our study, mean serum urea level in normotensive group at booking was 19.5 +/- 3.985 mg% and 23.48 +/- 5.048 mg/dl at third trimester. In preeclampsia group, it was 18.76 +/- 3.684 mg/dl and 33.00 +/- 16.512 mg/dl at booking and third trimester respectively. P value is 0.000, which is highly significant and corroborated with previous study[13]. Serum creatinine level in normotensive group was o.324 +/-0.087 mg/dl at booking and 0.20 +/-0.404 mg/dl in third trimester. In preeclampsia group, it was 0.318 +/- 0.102 mg/dl and 0.94 +/-0.470 mg/dl at booking and third trimester respectively. P value in this respect is 0.382, which is statistically not significant. Though different study shows raised creatinine level in preeclampsia and not exceed normal upper limit i.e. 1.2 mg/dl, few studies also observe insignificant change in serum Creatinine level[15, 16].

The mean gestational age was 36.86 +/- 2.928 weeks in preeclampsia group; on the other hand, it was 39.04 +/- 1.551 weeks in normotensive pregnancy. Here, p value is 0.000 which is highly significant. In preeclampsia group 19 delivery was vaginal and 31 delivery have done by LUCS compared to 39 deliveries by vaginal and 11 by LUCS in normotensive group. P-value is 0.000, which is highly significant favoring higher percentage of LUCS in preeclampsia group. Major indications for caesarian section in preeclampsia group was fetal distress, PROM, non progress of labour and prolonged labour. The incidence of preterm, IUGR and LBW babies were much higher in preeclampsia group. The mean birth weight of babies of normotensive mother was 2.78 +/- o.418 kg and that of preeclampsia mother was 2.58 +/- 0.499 kg; p value also significant, 0.000 as preeclamptic mother had more low birth weight baby.

Regarding Apgar score of the babies, normotensive group showed 2 baby with score 4, 3 baby with score 5, 3 baby with score 6, 11 baby with score 7, 19 baby with score 8 and 12 baby scored 9. Where as in preeclampsia group, 1 baby scored with 0, 1 baby with score 4, 7 baby with score 5, another 7 baby with score 6, 20 baby with score 7, 13 baby with score 8 and 1 baby with score 9. In evaluation of birth conditions per Apgar Index, the value equal or less than 7 in 1st and 5th minute of life was more in preeclampsia

group than that of normotensive group and thus relative risk of life expectancy was greater in preeclampsia. P value is 0.007, which is < 0.05 i.e. significant. In this regard, SNCU admission in normotensive group included 8 babies (8/50) compared to preeclampsia group where 17 babies have admitted (17/50) in SNCU mostly due to preterm deliveries. P value is 0.038, means significant, which is suggestive of intimate association between preeclampsia and preterm delivery.

From indoor record book it has found that the duration of hospital stay was more in preeclampsia mother compared to normotensive mother. In normotensive group, 36 mothers stayed hospital for only 2 days where as 15 preeclampsia mother stayed hospital for 7 days and another 14 mother of this group stayed for 8days. P value is 0.000, so hospital bed occupation was significantly higher in preeclampsia group. Moreover, 4 preeclampsia mothers admitted in ICU compared to none in normotensive group. These mothers were admitted due to eclampsia with associated complications. P value is 0.043, <0.05, so significant number of mother admitted to ICU in preeclampsia group.

Conclusion

Though the definitive treatment of preeclampsia is termination of pregnancy, involvements of multiorgan with abnormal biomarker values complicate the course of pregnancy more severely. Though no single marker has been established to have high predictive value[17], evaluation of different parameters like degree of proteinuria, gestational age, available Hb%, platelet count, biomarkers like serum total protein, serum albumin, AST, serum urea, creatinine and clinical condition of mother and baby should be justified for assessing the situation and proper timing of delivery in preeclampsia mother and thus a better obstetric outcome could be ascertained.

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