CORRELATION OF BIOMARKERS IN PREDICTING FETOMATERNAL COMPLICATIONS IN HYPERTENSIVE DISORDERS OF PREGNANCY – PROSPECTIVE HOSPITAL BASED OBSERVATIONAL STUDY

Dr. Nahid Khanam[1], Dr. G Prasanna[2], Dr. Jyochnamayi Panda[3], Dr. Neha Khanam[4]
[1]Post Graduate 3rd Year, Department of Obstetrics and Gynaecology, Kalinga Institute of Medical Sciences, Bhubaneswar.
Email: itsnahidkhanam@gmail.com
[2]Associate Professor, Department of Obstetrics and Gynaecology, Kalinga Institute of Medical Sciences, Bhubaneswar.
[3]Professor, Head of Department, Department of Obstetrics and Gynaecology, Kalinga Institute of Medical Sciences, Bhubaneswar.
[4]Post Graduate, Department of Obstetrics and Gynaecology, Saraswati Institute of Medical Sciences, Hapur, UP.

Corresponding Author: Dr. Nahid Khanam

Abstract
Pregnancy induced hypertension is one of the leading medical disorder of pregnancy and contributes significantly to poor maternal and perinatal outcome. The early detection and effective management play a beneficial role in the outcome of pregnancy, both for the mother and the baby. Incidence of Pre-eclampsia is 3-6% of all pregnancies and 1.5 to 2 times higher risk in primigravida.
Materials and Methods: This study was hospital based observational prospective study from September 2020 to August 2022. Total 150 pregnant women included in the study and fetomaternal outcome were noted and statistical analysis done using SPSS-20.
Results: Majority of patients were in age group 21-25 years in both the groups i.e. 44% in study group and 46.7 % in control group. In study group around 58.7% were preterm deliveries. In our study in group A with deranged biomarkers and group B with normal biomarkers, developed abruption placenta in 26.7 v/s 2.7%, eclampsia in 18.7% v/s 1.3%, HELLP syndrome in 8% v/s 0%, ARF in 4% v/s0% respectively. In our study perinatal complications developed in group A and group B were IUGR (20% v/s 8%), fetal distress(37.3% v/s 20%), NICU admission(49.3% v/s 29.3%), MSL (12% v/s 20%) and IUD (9.3% v/s 1.3%) respectively.
Conclusion: Hypertensive disorders of pregnancy with deranged hepatic biomarkers are correlated with more adverse maternal and perinatal complications compared to normal hepatic biomarkers. Such cases require more frequent antenatal check-ups with serial ultrasonography.
Keywords: Fetomaternal Outcome, Biomarkers, Pregnancy, HELLP Syndrome

INTRODUCTION

Pregnancy induced hypertension is one of the leading medical disorder of pregnancy and contributes significantly to poor maternal and perinatal outcome. The early detection and effective management play a beneficial role in the outcome of pregnancy, both for the mother and the baby. [1]
Abnormal tests for biochemical markers helps to detects changes in the body which further increase in the presence of any pathology like diabetes mellitus,hypertension, cardiac and

kidney disorders. Liver shows no significant change during a normal pregnancy, however hepatic blood increases during pregnancy.
Incidence of Pre-eclampsia is 3-6% of all pregnancies and 1.5 to 2 times higher risk in primigravida. [2] In India, the incidence of preeclampsia amongst the admitted patients is around 7-10 % of all antenatal admissions [3]
Vasoconstriction and thickening of the vessel wall, which reduce vascular capacity and raise peripheral resistance, are the primary causes of preeclampsia. Multiple organ systems undergo dysfunction including the renal, hepatic, pulmonary, central nervous and hematologic systems. In addition, blood components including platelets and fibrinogen are deposited subendothelally as a result of systemic endothelial cell damage, which promotes interstitial leakage. The subendothelial zone of resistance arteries changes ultrastructurally, and endothelial junctional proteins are also disturbed (Suzu ki, 2003; Wang, 2002).
Endothelial damage causes pathologic capillary leak which lead to rapid gain weight or have non-dependent edema in women hands or face or have pulmonary oedema.
Reduced uteroplacental blood flow caused by the damaged placenta can have impact on the developing foetus. Clinically, this reduction in perfusion may seem as non-reassuring CTG, oligohydramnios or IUGR.
HELLP syndrome is full blown picture of hemolysis, elevated liver enzymes and low platelet count and has serious complications. Detection of increased LFT in cases of hypertensive disorder is a risk category. Such cases need special attention with early detection and referral to higher center with better facilities of NICU set up to reduce the complications & mortality.

MATERIAL AND METHODS:

Sample Size: 150 consists of two groups, 75 Study group and 75 Control group.

Place of Study: The study was conducted in the Department of Obstetrics and Gynaecology of Pradyumna Bal Memorial hospital, KIMS, Bbhubaneswar.

Duration of Study: September 2020 to August 2022

Study Design: Prospective hospital based observational study

Study Subject: All antenatal cases presenting at OPD with predefined inclusion / exclusion criteria.

Inclusion Criteria- Singleton pregnancy after 20 weeks of gestation with BP >/=140/90 mmHg.

Exclusion criteria- Pregnant women with:
1. BP <140/90 mmHg
2. Presenting before 20 weeks
3. Chronic liver disease and drug induced abnormal liver function test
4. Known case of essential hypertention, chronic kidney disease and vascular diseases
5. Multiple gestation

STUDY PROCEDURE

Informed written consent was obtained from all the patients, after confirmed the inclusion and exclusion criteria for the study were made certain. A detailed history along with the physical examination was followed.

Study subjects was divided into two groups on the basis of normal and abnormal LFT reports. They will be followed up till delivery and 1 week postpartum and their fetomaternal outcome were compared.
All study subjects underwent certain biomarkers parameter testing as under: Aspartate transaminase (AST), Alanine transaminase (ALT), Alkaline phosphatase ALP), total bilirubin, direct bilirubin, platelet count, PT/INR and peripheral blood smear.
5 ml of venous blood was collected in plain vacutainer tube from all patients under aseptic condition. Serum was used for the estimations of AST, ALT, LDH. Estimation done using a fully automated Vitrous 5600 system in which UV without P5P, enzymatic calorimetric and biuret methods are used.
Platelet count in our laboratory done by Sysmex XN1000 Beckman Coulter using optical light scatter method.

Fetomaternal complications which was noted in the above groups were
A. HELLP syndrome
B. Eclampsia
C. Renal complications
D. Abruptio placentae
E. deliveries requiring NICU admission
F. Intrauterine growth retardation
G. Fetal distress
H. MSL (Meconium stained amniotic fluid)
I. Intrauterine growth restriction

STATISTICAL ANALYSIS
Demographic profile and descriptive variables of all patients were extracted with mean and standard deviations and were jotted down in tabular and diagrammatic form. Bar chart, Pie Diagrammed, Multiple bar chart, Column chart was graphically represented at the appropriate places. Comparisons between categorical variables were tested by the use of contingency tables and by the calculation of the Chi-square test. Mean ccomparison of the two groups for quantitative variables was done using the independent t test after checking the assumption of the normality otherwise Mann-Whitney test. All calculated *P* values were 2 sided and $P < 0.05$ were considered statistically significant. The Data Entry was performed on Microsoft Excel Software (Window-10). Statistical analysis was done using the Statistical Package for Social Science for Windows (SPSS-20).

RESULTS:
The majority of patients were in the age group 21-25 years in both groups i.e. 44% in the study group and 46.7 % in the control group. It has been seen that both groups were comparable. The mean age was 29.31 and 29.56 in the study and control groups respectively.In group A (cases) primigravida constitute 53.3 % and multigravida 46.7% while In group B (controls) primigravida constitute 52% and multigravidas 48% . P value is 0.87 which is not significant.

TABLE 1: Distribution of the Patients for Preterm and term delivery

Preterm/Term	**Control Group n(%)**	**Case Group n(%)**	**Total**	χ^2	**P value**
Preterm	23 (30.7%)	44 (58.7%)	67	11.895	0.001
Term	52 (69.3%)	31 (41.3%)	83		

In Group A : preterm deliveries (58.7%) were more compared to term deliveries(41.3%), whereas in Group B :term deliveries (69.3%)were more compared to preterm deliveries(30.7%).

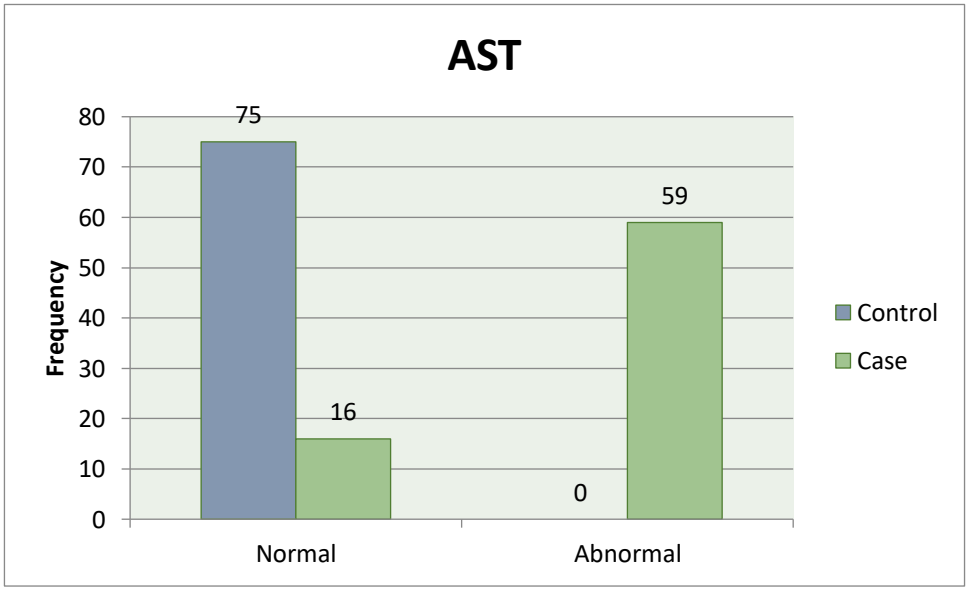
TABLE 2: Mean of Liver Function Test of the patients

Liver Function Test		**Control Group**	**Case Group**	**T Value**	**P value**
AST	**Mean±sd**	**38.05±15.02**	**109.88±42.34**	-13.84	<0.01
ALT	**Mean±sd**	**43.76±20.84**	**111.44±39.29**	-13.18	<0.01
ALP	**Mean±sd**	**127.99±23.74**	**223.11±79.14**	-9.97	<0.01

The above Table 1 and 2 shows the mean and standard deviation of liver enzymes. In Group A : mean and SD of AST,ALT and ALP were 109.88±42.34 , 111.44±39.29 & 223.11±79.14 respectively, while in Group B: :Mean and SD of AST,ALT and ALP were 38.05±15.02 , 43.76±20.84 & 127.99±23.74 respectively.

Table 3: Distribution of AST:

AST	Control **n (%)**	Case **n (%)**	Chi Square	P Value
Normal	75 (100.0)	16 (21.3)	97.25	<0.001
Abnormal	00 (0.0)	59 (78.7)		



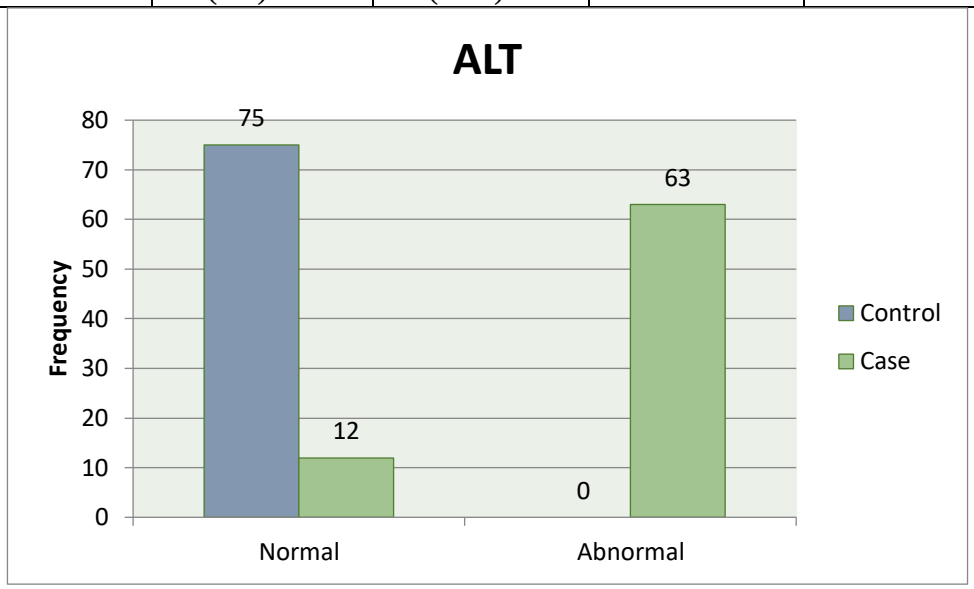
Graph 1: show AST levels among Group A and Group B.

The above table 3 and graph 1 show a comparison of AST levels among Group A and Group B. In group A (cases), 59 patients showed raised AST levels, whereas none of the patients in group B had raised AST levels. P value is 0.001 (statistical significance) Mean and standard deviation of group A (cases) were 109.88 and 42.34 respectively, while in group B (controls) were 38.05 and 15.02 respectively.

Table 4: Distribution of ALT:

ALT	Control **n(%)**	Case **n(%)**	Chi Square	P Value
Normal	75 (100.0)	12 (16.0)	108.62	<0.001

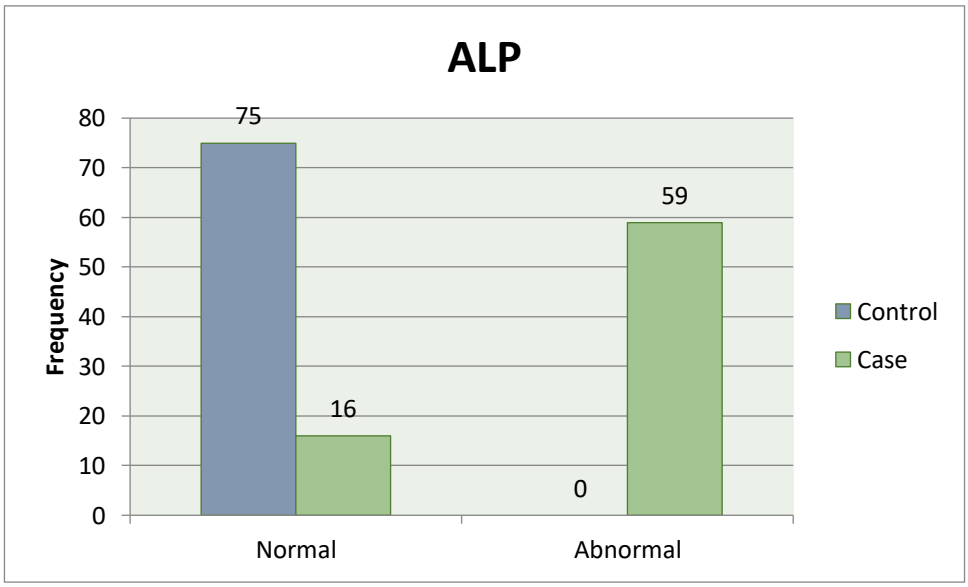
Abnormal	00 (0.0)	63 (84.0)		



In Group A (case): 84 % (63)of patients showed abnormal ALT while 12% (16) showed normal ALT while none of the patients in Group B showed raised ALT, statistically significant(p value<0.001).The mean and standard deviation of group A (cases) were 111.44 and 39.29 respectively, while in group B (controls) were 43.76 and 20.84 respectively.

Table 5: Distribution of ALP:

ALP	Control **n(%)**	Case **n(%)**	Chi Square	P Value
Normal	75 (100.0)	16 (21.3)	97.25	<0.001
Abnormal	00 (0.0)	59 (78.7)		



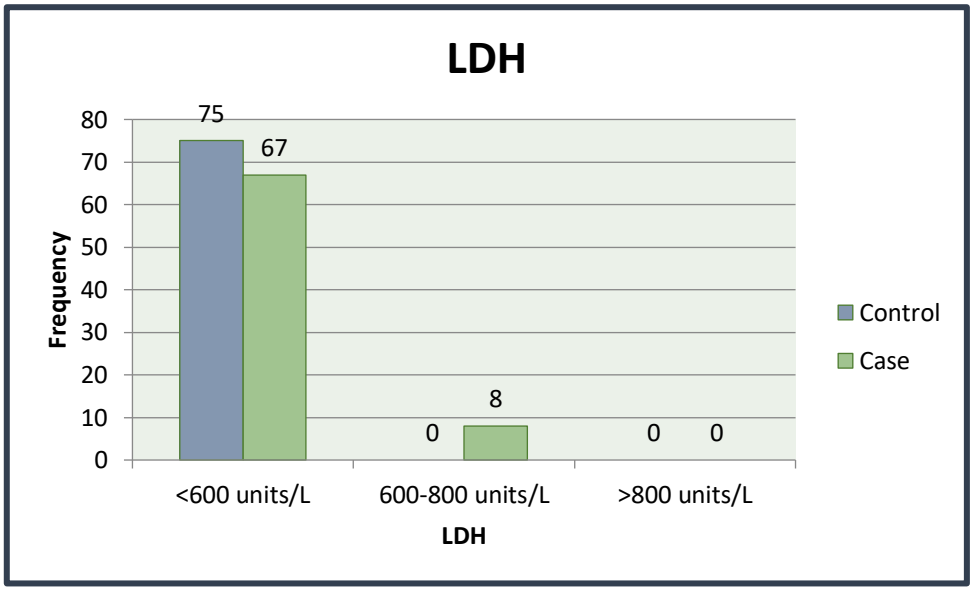
Graph 2: Shows Sr ALP distribution among Group A and Group B

The above table 5 and graph 2 shows Sr ALP distribution among Group A and Group B.Group A showed normal ALP in 21.3%(n=16) and abnormal ALP in 78.7% (n=59) while no patient in group B showed abnormal ALP.The mean and standard deviation of group A (cases) were

223.11 and 79.14 respectively, in group B (controls) were 127.99 and 23.74 respectively.P value (<0.001) is statistically significant.

Table 6(a): Distribution of LDH:

LDH	Control n(%)	Case n(%)	Chi Square	P Value
<600 units/L	75 (100.0)	67 (89.3)	8.45	0.004
600-800 units/L	00 (0.0)	08 (10.7)		
>800 units/L	00 (0.0)	00 (0.0)		



Graph 3: Distribution of Mean SR LDH of the patients

Table 6(b): Distribution of **Mean SR LDH** of the patients

SR LDH	Control Group	Case Group	T Value	P value
Mean±sd	**257.84±64.04**	**383.31±152.58**	-6.57	<0.01

The above table 6a and 6b and graph 3 shows SR LDH distribution among both the groups.In group A (cases): majority of subjects belonged to ≤ 600 IU LDH class interval (n=67, 89.3%) followed by 601-800 IU LDH class interval (n=8, 10.7%). In group B (control): majority of subjects belonged to ≤ 600 IU LDH class interval (n=74, 86.7%) none have LDH value of >600 IU. The mean and standard deviation of group A (cases) are 383.31 and 152.58 respectively, while in group B (controls) are 257.84 and 64.04 respectively.

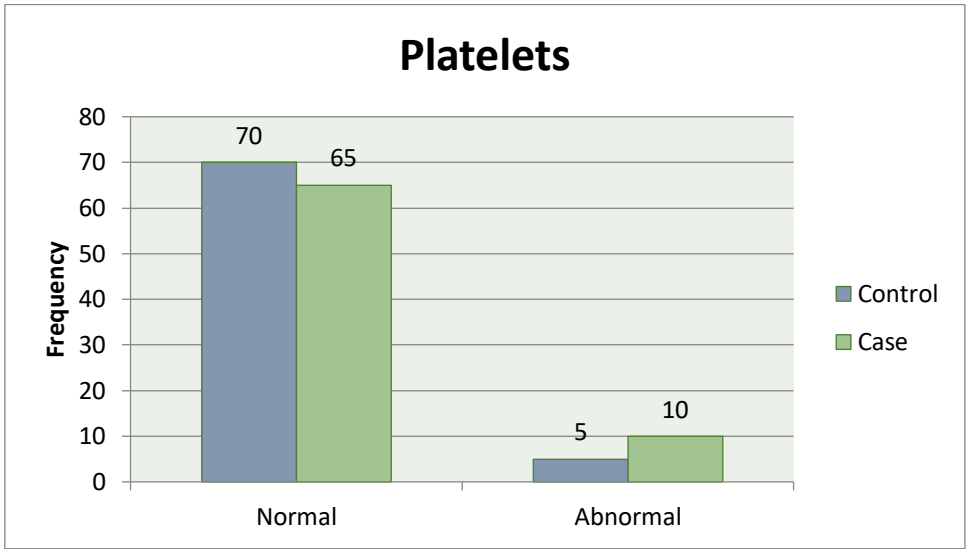
TABLE 7: Distribution of Mean **Bilirubin** of the patients

Bilirubin		Control Group	Case Group	T Value	P value
Bilirubin Total	**Mean±sd**	**0.62±0.76**	**0.69±0.23**	-0.77	0.44
Bilirubin Direct	**Mean±sd**	**0.21±0.13**	**0.33±0.17**	-4.71	<0.01

In Group A: Mean and SD of total and direct bilirubin were 0.69±0.23 and 0.33±17respectively. Group B: Mean and SD of total and direct bilirubin were 0.62±0.76 and 0.21±13respectively

TABLE 8: Distribution of Platelets:

Platelets	Control **n(%)**	Case **n(%)**	Chi Square	P Value
Normal	70 (93.3)	65 (86.7)	1.85	0.174
Abnormal	5 (6.7)	10 (13.3)		

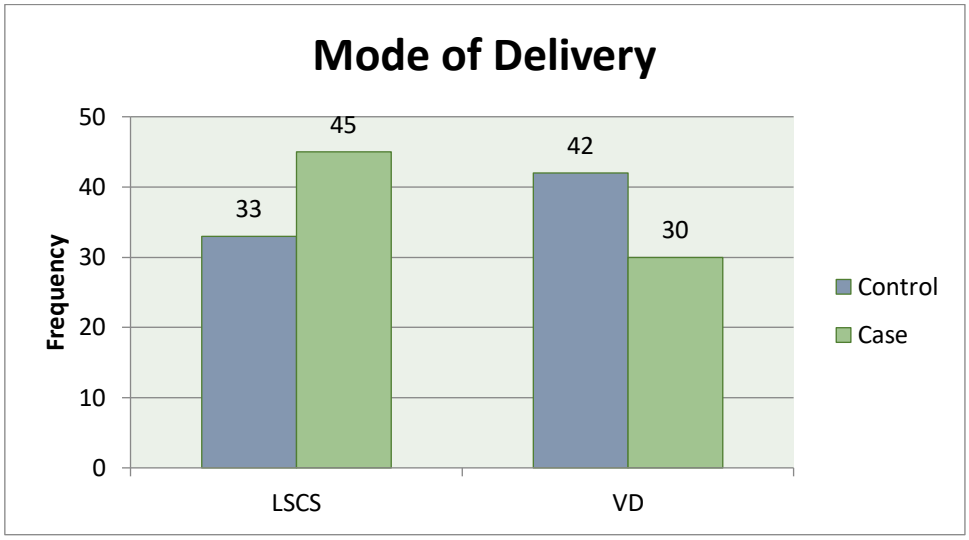


Graph 4: Shows Platelet distribution among Group A and Group B.

The above table 8 and graph 4 shows platelet distribution among group A and group B.
In group A: 13.3% (n=10) patients showed reduced platelet count, out of which 6 patients had mild thrombocytopenia and 4 patients had moderate thrombocytopenia. Out 4 moderate thrombocytopenia 3 developed HELLP syndrome & 1 severe pre-eclampsia. In group B6.7%(n=5) patients showed mild thrombocytopenia. P value is statistically not significant.

Table 9: Distribution of Mode of delivery of the patients

Mode of Delivery	Control **n(%)**	Case **n(%)**	Total	Chi Square	P value
LSCS	33 (44.0%)	45 (60.0%)	78	3.85	0.05
VD	42 (56.0%)	30 (40.0%)	72		



Graph 5: Distribution of Mode of delivery of the patients

Indications of Caesarean section among group A and group B were previous LSCS not willing for VBAC, previous 2 LSCS, fetal distress, malpresentation, failure of induction of labour, cephalopelvic disproportion. In group A (cases), majority underwent LSCS (60%) and 40% underwent VD, while in group B (controls), majority of patients underwent VD 56% and 44% underwent LSCS.

TABLE10: Distribution of Birth weight of the baby

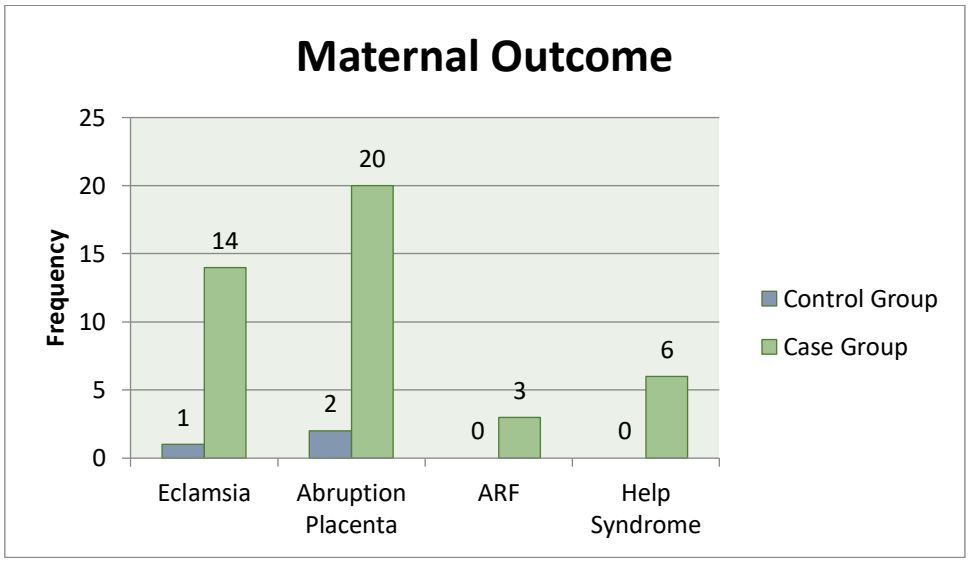
Birth Weight (in grams)	Control **n(%)**	Case **n(%)**	Total	Chi Square	P Value
≤999	0(0.0)	3(4.0)	3	14.86	0.002
1000-1999	10(13.3)	23(30.7)	33		
2000-2999	35(46.7)	36(48.0)	71		
≥3000	30(40.0)	13(17.3)	43		

The above table 10 shows the distribution of birth weight of babies. The majority of babies' birth weights were between 2-2.9 kgs in both the groups. In group A (cases) 13 babies were more than 3 kgs whereas in group B (controls) 30 babies were more than 3 kgs. In group A (cases) 3 babies were born with a birth weight of less than 1 kg, whereas none of the babies had a birth weight of less than 1 kg.

TABLE 11: Distribution of maternal outcome among Group A & Group B

Maternal outcome	**Group A (Case) n (%)**	**Group B (Control) n (%)**	χ^2	p value
Eclampsia	14(18.7)	1(1.3)	12.52	<0.01
Abruptio placenta	20(26.7)	2 (2.7)	17.26	<0.01
ARF	3(4.0)	0 (0.0)	3.06	0.24
HELLP syndrome	6(8.0)	0 (0.0)	6.25	0.03

Group A with deranged biomarkers and group B with normal biomarkers, developed abruption placenta in 26.7 v/s 2.7%, eclampsia in 18.7% v/s 1.3%, HELLP syndrome in 8% v/s 0%, ARF in 4% v/s0% respectively

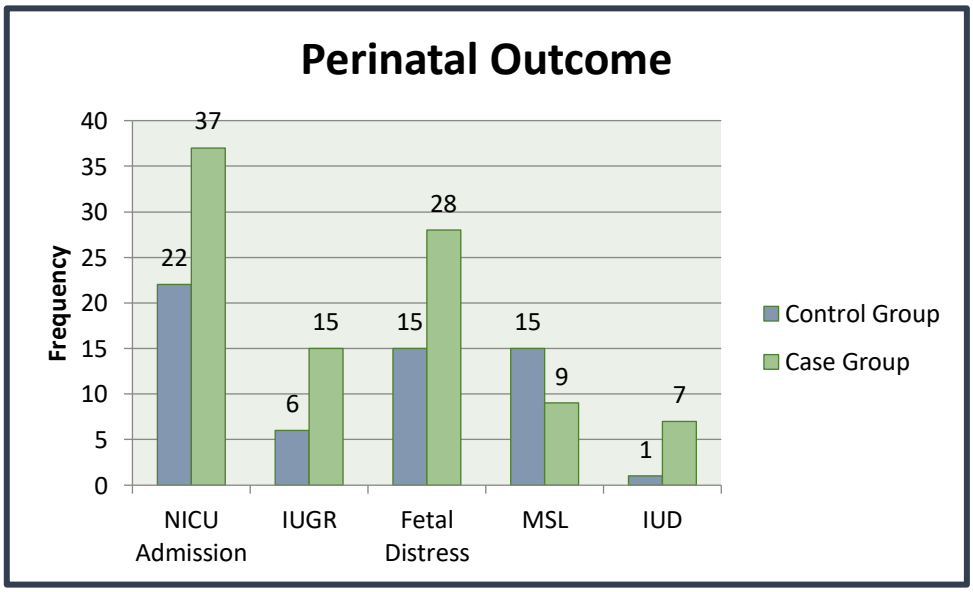


The above graph 6 shows maternal complications in group A and group B.

TABLE 12: Distribution of perinatal outcome among Group A & Group B

Perinatal Outcome	**Control Group n (%)**	**Case Group n (%)**	χ^2	p value
NICU Admission	24 (32.0)	34 (45.3)	2.81	0.09
Fetal distress	15 (20.0)	22 (29.3)	1.76	0.18
MSL	15 (20.0)	09 (12.0)	1.76	0.18
IUGR	6 (8.0)	15 (20.0)	4.48	0.034
IUD	01 (1.3)	07 (9.3)	9.75	0.03

Group A with deranged liver biomarkers and Group B with normal liver biomarkers. Perinatal outcome observed were IUGR (20% v/s 8%), fetal distress (29.3% v/s 20%), NICU admission(49.3% v/s 29.3%), MSL (12% v/s 20%) and IUD (9.3% v/s 1.3%) respectively.



The above graph 7 shows perinatal outcome in both the groups

Discussion

In this study total 150 sample were taken, which was divided into two groups. Group A and Group B on the basis of levels of normal and abnormal hepatic biomarkers respectively. Majority of patients were in age group 21-25 years in both the groups i.e. 44% in study group and 46.7 % in control group. The mean age was 29.31 and 29.56 in study and control group respectively. This is comparable with the study by N.R. Hazari et al in which mean age among controls was 25 and among cases was 23[4].

In the present study primigravida were more compared to multigravida i.e. 53.3 % v/s 46.7% respectively in group A, and 52% primigravida v/s 48% multigravida in group B which is consisted with the study by Manjusha Sajith et al, 2014 in which incidence of primigravida was 53.8% with hypertension[5]. Study by Pillai SS et al reported primigravida is a risk factor for severe preeclampsia which was also supported by Conde Agudelo and by Saxena et al. [6,7,8]

In the present study preterm deliveries (58.7%) were more compared to term deliveries (41.3%) in study group. While in control group term deliveries (69.3%) were more compared to preterm deliveries (30.7%), which is consisted with an observational study on fetomaternal outcome by Kennady G et al in 2017 reported 52.4% preterm deliveries [9].

Mean gestational age in control group was 37.36 wks while in case group was 35.20 wks indicate deranged hepatic biomarkers is a risk factor for preterm delivery .which is consistent with the study by Bridwell M., Handzel E., Hynes, M. *et al.* Who found 392 (4.9%) stillbirths, 738 (9.3%) preterm deliveries, and 1240 (15.6%) low birth weight babies (10).

Majority of the patients belonged to preeclampsia class (60%), followed by gestational hypertension (21.3%), eclampsia (18.7%) in the study group A while In control Group B majority of patients belonged to gestational hypertension i.e. 88 %(n-66), followed by preeclampsia10.7 %(n-8), eclampsia1.3%(n-1). which is consistent with the study by Sengodan SS found 47.4% gestational hypertension, 32.6% preeclampsia, chronic hypertension 8.2% and preeclampsia superimposed on chronic hypertension 11.8%(13).

In our study serum AST,ALT, LDH values significant differ between group A with deranged biomarkers and group B with normal biomarkers with p value of <0.001, which is consistent with study by Hazari NR et al ascertained that the levels of serum AST and ALT were significantly increased i.e. 40 % and 45% respectively in women with preeclampsia . Romero R. et al (11) also observed the liver dysfunction as determined by AST was 21% in patients with pregnancy induced hypertension. Girling J.C. (12) also noted 54% of abnormal LFTs in preeclampsia by measuring liver transaminases.The activity of ALP in severe preeclampsia was higher than mild preeclampsia.

In our study majority of the women have raised Sr LDH in group A compared to group B.10.7% patient in study group had Sr LDH>600 u/l associated with severe pre-eclampsia and Hellp syndrome. Demir SC et al. (14) observed a statistically significant correlation between high LDH levels and maternal complications. Jaiswar et al (15) also showed significantly raised LDH level in preeclampsia and eclampsia.

Study by K Maryam et al (16) reported mean LDH level in mild and severe preeclampsia, were 337.89±173.15IU/l and 556.41±193.02IU/l respectively which is consistent with our study.

In the current study rate of LSCS was found to be more in study group (A) 60%(n-45) compared to vaginal delivery i.e. 40%(n-30). In control group(B) vaginal delivery occurred more than LSCS (56%,42 v/s 44% ,33 respectively) which is consistent with the study by Puneeta Mahajan et al (17)in which 26 patients who had LSCS, 76% had preeclampsia and abnormal liver enzymes, while 23% had preeclampsia and normal liver enzymes. Aali BS et al., (18), Yucesoy G et al., (19), and Audibert F et al., (20) likewise according findings that are nearly identical to those of our investigations and P value was regarded as important in each case.

In our study in group A with deranged biomarkers and group B with normal biomarkers, developed abruptio placenta in 26.7 v/s 2.7%, eclampsia in 18.7% v/s 1.3%, HELLP syndrome

in 8% v/s 0%, ARF in 4% v/s0% respectively. This is consistent with the study by Mahajan P et al who found that 14% of pregnancies ended in abruption, 13% in eclampsia, 5.79% in HELLP syndrome, 2.89% in DIC, 2.89% in pulmonary oedema, and 0.35 % in ARF and maternal fatalities. According to Loi K et al. (21), maternal consequences in pre-eclampsia women with abnormal liver biomarkers included abruption (2%) and ARF (14%), eclampsia (6%), HELLP (6%), pulmonary edoema (5%), and ARF (14%).

According to Aali BS (18), patients with complicated severe preeclampsia experienced pulmonary edoema (3.6%), HELLP syndrome (5%), ARF (5.4%), and Abruption (5.6%). Eclampsia (11%), abruption (1.5%), and maternal death (3% of patients) were all found in a research by Yucesoy G et al (17). These findings are supported by research by Haddad B, Wodeselsassie (22) Menezies et al (23) and Kozic et al(24).

In our study perinatal complications developed in group A with deranged liver biomarkers and group B with normal were IUGR (20% v/s 8%), fetal distress(29.3% v/s 20%), NICU admission(49.3% v/s 29.3%), MSL (12% v/s 20%) and IUD (9.3% v/s 1.3%) respectively. This is consistent with study by Patra KK (25)2022 who also found NICU admission in 42.4%, MSL in 6.9% and IUFD in 5.6%.

Also study by Mahajan P et al (17) noted 14.49% MSL, 8.69% FD, 28.90% FGR development, 49.20% NICU admission, and 4.34% IUD. Aali BS (18) noted in pre-eclampsia patients with abnormal liver enzymes 47% preterm births, 34% LBW, and 6% IUD. LBW was found in 34% and FGR in 29.4% of preeclamptic women with abnormal liver enzymes, according to Yucesoy G *et al* (19). Similar findings were found by Menezies et al. (23), Verhaeghe et al. (22), and Abramovici et al. (24)

CONCLUSION

Hypertensive disorders of pregnancy with deranged hepatic biomarkers are correlated with more adverse maternal and perinatal complications compared to normal hepatic biomarkers. Such cases require more frequent antenatal check-ups with serial ultrasonography in order to catch the complications at early stage and prevent further diminution in the maternal and fetal well-being. So use of hepatic biomarkers play a significant adjunct for predicting fetomaternal outcome and help in taking timely and appropriate intervention.

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