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Relationship Between Pregnancy-Induced Hypertension and Liver Function Test: An Observational Study

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ABSTRACT

Background: Liver damage accompanying preeclampsia may range from mild hepatocellular necrosis with serum enzyme abnormalities (aminotransferase and lactate dehydrogenase) to the ominous hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome.

Methods: The study was undertaken at Department of Obstetrics and Gynecology, NIMS Medical College and Hospital, Rajasthan for the period of 1 year on 100 patients diagnosed with PIH.

Results: Variable degree of proteinuria was seen in patients of Pre Eclampsia whereas in Eclampsia group it was of 3+ or more. Mean SGOT, SGPT, Alkaline Phospatase, Total bilirubin was elevated in patients with PE and E group and were in normal range in GTN group. Mean Total protein was lower in patients with eclampsia group only.

Conclusion: Inclusion of LFTs with routine investigations leads to early prediction of severity of PIH and subsequent complications. The primary aim of antepartum monitoring is timely recognition of maternal & fetal complications by special investigation (LFT); and to take appropriate in time intervention to prevent further serious complications to both mother and fetus.

Keywords: Pregnancy-Induced Hypertension, Liver Function Test, Third Trimester.

INTRODUCTION

The diagnosis of gestational hypertension is made in pregnant women whose blood pressure reaches 140/90 mm Hg or greater for the first time during pregnancy but in whom proteinuria is not identified. Gestational hypertension is also called transient hypertension if preeclampsia does not develop and the blood pressure has returned to normal by 12 weeks postpartum. In this classification, the final diagnosis that the woman does not have gestational hypertension is not made until several weeks after delivery. Thus, gestational hypertension is a diagnosis of exclusion.2 Importantly, some women with gestational hypertension may later develop other findings of preeclampsia, for example, symptoms such as headaches or epigastric pain, proteinuria, or thrombocytopenia, all of which influence management.[1,2] Pre-eclampsia (PE), a multi-system disorder, defined as gestational hypertension associated with significant proteinuria (> 300 mg/L or >500 mg/24 hours urine or on dipstick 2 + or more proteinuria), occurs usually after 20 weeks of gestation. It is a pregnancy specific syndrome of reduced organ perfusion secondary to vasospasm and endothelial activation.[3-5]

Abnormal laboratory findings indicating impairment of renal, hepatic and hematological function increase the certainty of preeclampsia in addition to persistent premonitory symptoms such as head ache and epigastric pain. The symptoms of the pre eclampsia are usually resolved within six weeks after delivery. PE complicates 5-6% of all pregnancies, the figure may rise up to 25% in women with pre-existing hypertension.[6]

Based on the classification of American College of Obstetrician & Gynaecologist (ACOG), the pre-eclampsia can be categorized into Mild (140-159 /90-109 mm Hg) and severe (≥160 /110).[7]

Epigastric or right upper quadrant pain is thought to result from hepatocellular necrosis, ischemia, and edema that stretch the Glisson capsule. This characteristic pain is frequently accompanied by elevated serum hepatic transaminase levels and usually is a sign to terminate the pregnancy. The pain presages hepatic infarction and hemorrhage or catastrophic rupture of a subcapsular hematoma. Fortunately, hepatic rupture is rare.[8,9]

Superimposed HELLP syndrome develops in 4-12% of women with pre-eclampsia or eclampsia. HELLP syndrome is severe form of pre-eclampsia, which poses a significant threat to both mother and fetus. This acronym HELLP was first coined by Weinstein, in 1982, to emphasize the triad of hemolysis, elevated liver, and low platelets. Based on the lowest observed maternal platelet count,

HELLP syndrome is classified into three classes: Class 1 - If platelet count < 50,000/cumm, Class 2 - If platelet count is >50,000 and <100,000/cumm and Class 3 - If platelet count >100,000 and <150,000/cumm.[10]

The onset of convulsion in a woman with preeclampsia which is not due to other cause is termed as eclampsia. The seizures in eclampsia are generalized and may appear before, during, or after labour. Older studies indicate that about 10% of eclamptic women, especially nulliparas, seizures did not develop until after 48 hours post-partum. As prenatal care improved, many ante partum and intrapartum cases are now prevented, and a recent study reported that a fourth of eclamptic seizures are developed beyond 48 hours after the delivery.[11]

Liver damage accompanying preeclampsia may range from mild hepatocellular necrosis with serum enzyme abnormalities (aminotransferase and lactate dehydrogenase) to the ominous hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome, with markedly elevated enzyme levels and even subcapsular bleeding or hepatic rupture. The latter syndrome represents serious disease and is associated with significant maternal morbidity.[12,13]

The aim of present research is to study deviations in liver function tests in pregnancy induced hypertensive patients in third trimester of pregnancy and, so that treatment can be planned to reduce maternal morbidity and mortality.

MATERIALS AND METHODS

A Prospective type of cross-sectional study is done in Obstetrics & Gynaecology Department of NIMS Medical College, Jaipur for a period of one year on 100 pregnant women in third trimester (after 28 weeks of gestation) diagnosed with pregnancy induced hypertension.

The clearance from institutional ethics committee was taken before the study was started. Finally after making diagnosis from clinical examination and investigations; patients were divided into 3 groups: gestational hypertension, preeclampsia and eclampsia.

The Liver Function Test of the patients was done and following parameters were measured:

1) SGOT catalyses the following reaction

Ketoglutamate + L – Aspartate → L – Glutamate + Oxaloacetate

Oxaloaacetate so formed is coupled with 2, 4-Dinitrophenyl hydrazine (2,4-DNPH) to give hydrazone which gives Brown colour in alkaline medium and this can be measured colorimetrically. (Reference range: 12-38 IU/L)

2) SGPT is carried out using 2,4-DNPH as coloring reagent SGPT catalyses the following reaction

α - Ketoglutamate + L – Alanine → L – Glutamate + Pyruvate

Pyruvate so formed is coupled with 2,4-Dinitrophenyl hydrazine (2,4 -DNPH) to give hydrazone which gives Brown colour in alkaline medium and this can be measured colorimetrically. (Reference range: 7-41 IU/L)

3) Alkaline Phosphatase: ALP catalyzes the hydrolysis of ρ-Nitrophenyl phosphate (pNPP) to ρ-Nitrophenol. pNPP is colorless but ρ-Nitrophenol has a strong absorbance at 405 nm. The rate of increased absorbance at 405 nm is proportional to the enzyme activity. The procedure is standardized by means of the millimolar absorptivity of ρ-Nitrophenol (18.75 at 405 nm) under the specified conditions. The results are based on the change in absorbance per unit of time. One International Unit (IU/L) is defined as the amount of enzyme that catalyzes the transformation of one micromole of substrate per minute under specified conditions. (Reference range in third trimester of normal pregnancy is 38-229U/L).

4) Total, Direct and Indirect bilirubin: Alkaline methanolysis of bilirubin followed by chloroform extraction of bilirubin methyl esters and later separation by chromatography and spectrophotometric determination at 430 nm. (Reference range, Total: 0.1 – 1.0 mg/dl, Direct: 0.1 – 0.4 mg/dl, Indirect bilirubin: 0.2 – 0.9 mg/dl).

5) Total Protein: The peptide bonds of the protein react with copper II ions in alkaline solution top form a blue violet ion complex, each copper ion complexing with 5 or 6 peptide bonds. Tartarate is added as a stabilizer whilst iodide is used prevent auto reduction of the alkaline copper complex. The colour formed is proportional to the protein concentration and is measured at 546 nm. (Reference range: 6.7-8.6 g/dl).

6) Serum Albumin: The addition of Bromocresol green with albumin in citrate buffer forms a colored complex. The intensity of the color is directly proportional to the albumin concentration in the sample. (Reference range: Albumin: 3.5-5.5 g/dl, Globulin: 2.0-3.5 g/dl)

7) Proteinuria checked by dipstick method and graded as:

Grade	Concentration
Nil	-
1+	30 mg/dl
2+	100 mg/dl
3+	300 mg/dl
4+	More than300 mg /dl

Statistical Analysis

The data thus collected was compiled by using Excel sheet. The data was transferred to Statistical Package for Social Services (SPSS vs 20). The categorical variables were presented as frequencies and percentages and Quantitative variables were presented as measures of central tendency. Chi square test was used as test of significance for categorical variables. Independent Samples T test was used as test of significance for quantitative variables. P value <0.05 was taken as significant.

Table 1: Distribution of the study groups according to gestational age in weeks

Gestational age in weeks (35.86±1.98)	Gestational hypertension n (%)	Preeclampsia n (%)	Eclampsia n (%)
28 – 32 weeks	0	9 (12.2)	0
32 – 35 weeks	5 (23.8)	10 (13.5)	0
More than 35 weeks	16 (76.2)	55 (74.3)	5 (100)
Total	21	74	5
Mean ± SD	36.2 ± 1.4	35.8 ± 2.1	37.0 ± 0.7

χ^2 value= 5.514; df=4; p value=0.238, NS

Table 2: Distribution of the study groups according to proteinuria

Proteinuria	Gestational hypertension n (%)	Preeclampsia n (%)	Eclampsia n (%)
Nil	21 (100)	0	0
1+	0	23 (31.1)	0
2+	0	8 (10.8)	0
3+	0	23 (31.1)	1 (20.0)
4+	0	20 (27)	4 (80.0)
Total	21	74	5

χ^2 value= 107.798; df=8; p value=0.000, Sig

Table 3: Distribution of the study groups according to SGOT, SGPT & alkaline phosphatase levels

Parameters	Gestational hypertension n (%)	Preeclampsia n (%)	Eclampsia n (%)
SGOT (52.68±17.01)			
Elevated	6 (28.6)	70 (94.6)	5 (100.0)
Normal(12 – 38 IU/L)	15 (71.4)	4 (5.4)	0
Total	21	74	5
Mean ± SD	32.9 ± 6.5	56.1 ± 12.9	86.4 ± 15.4
SGPT (48.9±15.61)			
Elevated	0	66 (89.2)	5 (100.0)
Normal(7 – 41 IU/L)	21 (100)	8 (10.8)	0
Total	21	74	5
Mean ± SD	31.5 ± 4.8	51.1 ± 10.2	89.8 ± 15.5
Alkaline Phosphatase (342.02±167.82)			
Elevated	11 (52.4)	59 (79.7)	5 (100.0)
Normal (38 – 229 U/L)	10 (47.7)	15 (20.3)	0
Total	21	74	5
Mean ± SD	222.0 ± 70.6	353.2 ± 162.2	596.0 ± 92.1

SGOT: χ^2 value= 47.567; df=2; p value=0.000, Sig

SGPT: χ^2 value= 65.347; df=2; p value=0.000, Sig

Alkaline phosphatase: χ^2 value= 8.28; df=2; p value=0.012, Sig

Table 4: Distribution of the study groups according to bilirubin levels

Parameters	Gestational hypertension	Preeclampsia	Eclampsia
Total Bilirubin (1.08±0.53)			
Elevated	4 (19.0)	41 (55.4)	5 (100.0)
Normal (0.1–1.0 mg/dl)	17 (81.0)	33 (44.0)	0
Total	21	74	5
Mean ± SD	0.8 ± 0.2	1.1 ± 0.5	1.9 ± 0.3
Direct bilirubin (0.48±0.41)			
Elevated	17 (81.0)	49 (66.2)	0
Normal (0.1 – 0.4 mg/dl)	4 (19.0)	25 (33.8)	5 (100)
Total	21	74	5
Mean ± SD	0.4 ± 0.1	0.5 ± 0.4	1.1 ± 0.2
Indirect bilirubin (0.603±0.31)			
Elevated	21 (100)	62 (83.8)	3 (60.0)
Normal (0.2 – 0.9 mg/dl)	0	12 (16.2)	2 (40.0)
Total	21	74	5
Mean ± SD	0.4 ± 0.2	0.6 ± 0.3	0.8 ± 0.2

Total Bilirubin: χ^2 value=13.912; df=2; p value=0.001, Sig

Direct bilirubin: χ^2 value= 11.8; df=2; p value=0.003, Sig

Indirect bilirubin: χ^2 value= 6.528; df=2; p value=0.038, Sig

Table 5: Distribution of the study groups according to protein levels

Parameters	Gestational hypertension n (%)	Preeclampsia n (%)	Eclampsia n (%)
Total protein (6.08±1.43)			
Decreased	11 (52.4)	47 (63.5)	5 (100.0)
Normal (6.7 – 8.6 g/dl)	10 (47.6)	27 (36.5)	0
Total	21	74	5
Mean ± SD	6.5 ± 0.8	6.1 ± 1.5	3.8 ± 1.4
Serum albumin (3.402±0.88)			
Decreased	9 (42.9)	39 (52.7)	5 (100.0)
Normal (3.5 – 5.5 g/dl)	12 (57.1)	35 (47.3)	0
Total	21	74	5
Mean ± SD	3.6 ± 0.8	3.4 ± 0.9	2.1 ± 0.7
Serum globulin (2.52±0.66)			
Decreased	5 (23.8)	15 (20.3)	3 (60.0)
Normal (2.0 – 3.5 g/dl)	16 (76.2)	59 (79.7)	2 (40.0)
Total	21	74	5
Mean ± SD	2.6 ± 0.5	2.5 ± 0.7	1.8 ± 0.9

Total protein: χ^2 value= 3.961; df=2; p value=0.138, NS

Serum albumin: χ^2 value= 5.304; df=2; p value=0.071, NS

Serum globulin: χ^2 value= 4.184; df=2; p value=0.123, NS

RESULTS

The mean gestational age of patients with gestational hypertension was 36.2 weeks, patients with preeclampsia were 35.8 weeks and patients with eclampsia were 37 weeks. The gestational age of 23.8% of the patients with gestational hypertension was 32 – 35 weeks and 76.2% of the patients were more than 35 weeks. About 12.2% of the patients with preeclampsia had gestational age of 28 – 32 weeks, 13.5% had 32 – 35 weeks and 74.3% had gestational age of more than 35 weeks. The gestational age of all the eclampsia patients was more than 35 weeks. There was no statistically significant difference between the gestational age of the patients with gestational hypertension, preeclampsia and eclampsia (Table 1).

None of the patients with gestational hypertension had proteinuria. In the patients with preeclampsia, 31.1% had 1+ proteinuria, 10.8% had 2+ proteinuria, 31.1% had 3+ proteinuria and 27% had 4+ proteinuria. About 20% of the patients with eclampsia had proteinuria of 3+ and 80% with eclampsia had proteinuria of 4+. There was statistically significant difference between the Proteinuria of the patients with gestational hypertension, preeclampsia and eclampsia (Table 2).

The mean SGOT levels among the patients with gestational hypertension was 32.9 IU, patients with preeclampsia was 56.1 IU and eclampsia was 86.4 IU. About 28.6% of the patients with gestational hypertension, 94.6% of the patients with preeclampsia and all the patients with eclampsia had elevated SGOT levels. This difference in SGOT levels was statistically significant between the patients with Gestational hypertension, pre eclampsia and eclampsia (Table 3).

The mean SGPT levels of the patients with gestational hypertension was 31.5 IU within normal limit. The patients with preeclampsia was 51.1 IU and patients with eclampsia was 89.8 IU. None of the patients with gestational hypertension, 89.2% of the patients with preeclampsia and all the patients with eclampsia had statistically significantly elevated SGPT levels (Table 3).

The mean alkaline phosphatase levels in patients with gestational hypertension was 222 IU, in the patients with preeclampsia was 353.2 IU in patients with eclampsia was 596 IU. In About 52.4% of the patients with gestational hypertension, 79.7% of the patients with preeclampsia and all the patients with eclampsia had elevated alkaline phosphatase levels. This difference in alkaline phosphatase levels was statistically significant between the patients with gestational hypertension, preeclampsia and eclampsia (Table 3).

The mean total bilirubin levels of the patients with gestational hypertension was 0.8 mg/dl, patients with preeclampsia was 1.1 mg/dl and eclampsia was 1.9 mg/dl. About 19% of the patients with gestational hypertension, 55.4% of the patients with preeclampsia and all the patients with eclampsia had elevated total bilirubin levels. This difference in total bilirubin levels was statistically significant between the patients with gestational hypertension, preeclampsia and eclampsia (Table 4).

The mean direct bilirubin levels of the patients with gestational hypertension was 0.4 mg/dl, in patients with preeclampsia was 0.5 mg/dl and in patients with eclampsia was 1.1 mg/dl. The direct bilirubin level was elevated in 81% of the patients with gestational hypertension, 66.2% of the patients with preeclampsia and none of the patients with eclampsia. This difference in levels of the direct bilirubin levels was statistically significant between the patients with gestational hypertension, preeclampsia and eclampsia (Table 4).

The mean indirect bilirubin levels in patients with gestational hypertension was 0.4 mg/dl, the patients with preeclampsia was 0.6 mg/dl and eclampsia was 0.8 mg/dl. All the patients with gestational hypertension, 83.8% of the patients with preeclampsia and 60% of the patients with eclampsia had elevated indirect bilirubin levels. There was no statistically significant difference between the indirect bilirubin levels of patients with gestational hypertension, preeclampsia and eclampsia (Table 4).

The mean total protein levels of the patients with gestational hypertension was 6.5 g/dl, in the patients with preeclampsia was 6.1 g/dl and among the patients with eclampsia was 3.8 g/dl. About 52.4% of the patients with gestational hypertension, 63.5% of the patients with preeclampsia and all the patients with eclampsia had depleted total protein levels. This difference in total protein levels was statistically not significant between the patients with gestational hypertension, preeclampsia and eclampsia (Table 5).

The mean serum albumin levels among the patients with gestational hypertension was 3.6 g/dl, among the patients with preeclampsia was 3.4 g/dl and among the patients with eclampsia was 2.1 g/dl. The mean serum albumin level was decreased in 42.9% of the patients with gestational hypertension, 52.7% of the patients with preeclampsia and all the patients of eclampsia. There was no statistically significant difference between the serum albumin levels of the patients with gestational hypertension, preeclampsia and eclampsia (Table 5).

The mean serum globulin levels of the patients with gestational hypertension was 2.6 g/dl, among the patients with preeclampsia was 2.5 g/dl and among the patients with eclampsia was 1.8 g/dl. About 23.8% of the patients with gestational hypertension, 20.3% of the patients with preeclampsia and 60% of the patients with eclampsia had depleted serum globulin levels. This difference in serum globulin levels between the patients with gestational hypertension, preeclampsia and eclampsia was not statistically significant (Table 5).

DISCUSSION

Abnormalities in liver function test (LFT) occur in 3% of the pregnancies and preeclampsia is the most frequent cause. The hepatic dysfunction in preeclampsia ranges from the presence of mild hepatic enzyme elevations in the serum to the more extreme HELLP syndrome, sub capsular bleeding or even hepatic rupture.[10]

About 28.6% of the patients with gestational hypertension, 94.6% of the patients with preeclampsia and all the patients with eclampsia had elevated SGOT levels. The mean SGOT levels among the patients with gestational hypertension was 32.9 IU, patients with preeclampsia was 56.1 IU and eclampsia was 86.4 IU. In a study by Aref et al[14], the mean SGOT level among the patients with pregnancy induced hypertension was 97.3 IU. In a study by Munazza et al[15], the mean SGOT level was 41.34 IU among the cases. In a study by R. Anuradha et al[16], the mean SGPT level was 39.3IU among the cases. In a study by Patil et al[17], the mean SGPT level was 42.5 IU in milder preeclampsia group and 60.51 IU in severe preeclampsia group. Discrepancy in mean value of SGOT in other studies to present study may be due to large difference in study in regard of no. of cases and inclusion of study subjects.

None of the patients with gestational hypertension, 89.2% of the patients with preeclampsia and all the patients with eclampsia had the elevated SGPT levels.

The mean SGPT levels of the patients with gestational hypertension was 31.5 IU, the patients with preeclampsia was 51.1 IU and patients with eclampsia was 89.8 IU. And total mean of all studied cases (PIH) was 48.9. In a study by Aref et al[14], the mean SGPT levels among the patients with pregnancy induced hypertension was 65.3IU, 32.5 IU among the patients with late normal pregnancy. Munazza et al.[15] studied that mean SGPT level was 55.81 IU among the cases and 15.22 among the controls. In a study by R. Anuradha et al[16], the mean SGPT level was 30.5IU among the cases and 11.4IU among normal pregnant females. In a study by Patil et al[17], the mean SGPT level was 36.6 IU in milder preeclampsia group and 51.94 IU in severe preeclampsia group and 27.31IU in control group30. Discrepancy in mean value of SGPT of present study to some other reviewed studies ex. Aref et al[14] and R. Anuradha et al[16] may be due to different sample size and sample subjects.

About 52.4% of the patients with gestational hypertension, 79.7% of the patients with preeclampsia and all the patients with eclampsia had elevated alkaline phosphatase levels. The mean alkaline phosphatase level in present study of all patients (PIH) was 342.02. Individually in separate groups; in patients with gestational hypertension was 222 IU, in the patients with preeclampsia was 353.2 IU in patients with eclampsia was 596 IU. In a study by Aref et al[14] the mean alkaline phosphatase level was 165.2 IU in patients with pregnancy induced hypertension, 86.1 among the women in later normal pregnancy. In a study by Lang RM et al[12], the mean alkaline phosphatase level was 458.15 IU/ L among the cases and 182 IU/L among the controls. Munazza et al[15] studied, the mean alkaline phosphatase level was 454.16 IU/ L among the cases and 181.34 IU/L among the controls. Mean value of alkaline phosphatase level in present study is different to other studies may be due to different study group in both sample size and studied population.

About 19% of the patients with gestational hypertension, 55.4% of the patients with preeclampsia and all the patients with eclampsia had elevated total bilirubin levels. The mean total bilirubin levels of the present study of all patients (PIH) were 1.08 mg/dl. In each different group patients with gestational hypertension, it was 0.8 mg/dl, patients with preeclampsia was 1.1 mg/dl and eclampsia was 1.9 mg/dl. In a study by Aref et al[14], the mean total bilirubin 0.44 mg/dl among the patients with pregnancy induced hypertension, 0.58 mg/dl in patients with late normal pregnancy and 0.61 mg/dl among the controls. In a study by Sibai et al[3], the mean serum bilirubin level was 10.62 µ mole/L among the cases and 7.81 µ mole/L among the controls. In a study by Munazza et al[15], the mean serum bilirubin level was 10.78 µ mole/L among the cases and 7.92 µ mole/L among the controls. Discrepancy in value of mean total bilirubin level of present study to other studies mentioned here may be due to different sample size & study group.

CONCLUSION

- Variable degree of proteinuria was seen in patients of PE whereas in E group it was of 3+ or more.
- Mean SGOT, SGPT, Alkaline Phospatase, Total bilirubin was elevated in patients with PE and E group and were in normal range in GTN group.
- Mean Total protein was lower in patients with eclampsia group only.

Inclusion of LFTs with routine investigations leads to early prediction of severity of PIH and subsequent complications. The primary aim of antepartum monitoring is timely recognition of maternal & fetal complications by special investigation (LFT); and to take appropriate in time intervention to prevent further serious complications to both mother and fetus.

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