

## Maternal and neonatal outcome in pre-eclamptic mothers with elevated liver enzymes: A prospective analytical study

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### Abstract

**Introduction:** Hypertensive disorders during pregnancy may cause damage to liver which may manifest biochemically as a deranged liver function test and subsequent maternal morbidity and mortality any elevation in liver enzymes in a pre-eclamptic patient is significant and influences fetomaternal outcome this study evaluates the liver enzymes as a diagnostic and therapeutic tool in the management of preeclampsia and establishes a correlation between severity of liver function test derangement and severity of fetomaternal complications and use it as a predictive tool of severity of preeclampsia and for termination of pregnancy.

Aim was to evaluate maternal and neonatal outcome in pre-eclamptic mothers with and without transaminitis.

Primary objective of the study was to compare the maternal and neonatal outcome in pregnant women with preeclampsia in singleton pregnancies with gestational age >24 weeks with and without transaminitis.

Secondary objective was to correlate the severity of liver enzyme derangement in preeclamptic mothers with adverse maternal and / or fetal outcome and use it as a predictive tool of severity of preeclampsia and for termination of pregnancy

**Materials and Methods:** This prospective cohort study was conducted on 281 patients after approval by the institute ethics committee informed consents were taken from patients inclusion and exclusion criteria were met all enrolled patients were classified into mild, moderate and severe hypertension and managed as per standard guidelines. Specific investigations were performed if during any visit ast >25 iu/l and/or alt >32iu/l and/or alp > 418 iu/l, patients were called again after a week and blood pressure and fetomaternal well-being was assessed termination of pregnancy was done as per standard guideline statistical analysis done and hypothesis established.

**Results:** From the present study it can be derived that at ast >66 iu/l and alt > 64 iu/l poor maternal outcome is expected with ast >60 iu/l and alt>64 iu/l adverse fetal complications are likely to occur.

**Conclusion:** From the present study it can be concluded that severity of liver function test derangement is directly related to severity of preeclampsia which in turn is related to severity of fetomaternal complications.

**Keywords:** Elevated liver enzymes, Preeclampsia, Maternal, Neonatal outcome.

### Introduction

Hypertensive disorders are common medical problems encountered during pregnancy with reported incidence between 5-10%.<sup>1</sup> They form one of the deadly triad along with haemorrhage and infection contributing to maternal and fetal morbidity and mortality.<sup>1-4</sup> Altered biochemical markers signify changes in the body which become intensified in the presence of some pathology like hypertension, diabetes, cardiac and renal disease. The severity of changes is related to the severity of pathology. There is no significant change in liver size during a normal pregnancy, however hepatic arterial and portal venous blood flow increase substantially.<sup>6</sup> Alterations in the liver enzymes are also minimal. The aminotransferases (AST and ALT), gamma glutamyl transpeptidase (GGT), total bilirubin, and serum bile acid level remain almost same as non-pregnant value. The only significant change observed is doubling of total alkaline phosphatase which is mainly placental in origin, that to near third trimester. The albumin level is lower as compared to nonpregnant women and the cholesterol level higher.<sup>7</sup> So, any elevation in aminotransferases or

gamma GGT signifies some pathology and should prompt a search for disease.<sup>5</sup>

Alanine transaminase levels between 2 and 25 U/L and aspartate transaminase levels between 4 and 32 U/L are taken as normal during pregnancy.<sup>8-11</sup> ALP values ranging between 130 and 418 U/L are also considered normal during antenatal period.<sup>12,13</sup> Whenever the values are outside this range, it signifies derangement of liver function which can have multiple causes.

Although there is evidence to prove that severity of liver function test derangement is directly related to severity of preeclampsia which in turn is related to severity of fetomaternal complications but it has not been used as a diagnostic and therapeutic tool in classification and management of preeclampsia. Blood pressure and urine albumin are used as denominators for management and termination strategies till now.

Also as definitive management of preeclampsia is termination of pregnancy with ultimate aim of achieving optimal fetomaternal well-being therefore an attempt is being made to evaluate the liver enzymes as a diagnostic and therapeutic tool in the management of preeclampsia and to establish a correlation between

severity of liver function test derangement and severity of fetomaternal complications.

### Aims and Objectives

Aim of the study was to evaluate maternal and neonatal outcome in pre-eclamptic mothers with and without transaminitis.

Primary objective of the study was to compare the maternal and neonatal outcome in pregnant women with preeclampsia in singleton pregnancies with gestational age >24 weeks with and without transaminitis.

Secondary objective was to correlate the severity of liver enzyme derangement in preeclamptic mothers with adverse maternal and/or fetal outcome and use it as a predictive tool of severity of preeclampsia and for termination of pregnancy.

### Materials and Methods

This prospective cohort study was conducted in the department of Obstetrics and Gynaecology at a tertiary care level hospital between September 2016 to June 2017. The study was approved by the Institute Ethics Committee and informed consents were taken from patients before inclusion in the study.

#### Study Population

**Inclusion Criteria:** All preeclamptic women with gestational age >24 weeks with singleton pregnancy and an elevated liver enzymes were included as cases, whereas those without an elevated liver enzymes were included as controls.

**Exclusion Criteria:** Twin pregnancy, antepartum hemorrhage, preterm onset of labour, rhesus negative pregnancy, intrahepatic cholestasis of pregnancy, acute fatty liver of pregnancy, viral hepatitis, liver cirrhosis, portal hypertension with esophageal varices, hemochromatosis, wilson's disease, congenital liver disease, autoimmune hepatitis, hepatic adenomas, hepatocellular carcinomas, non-alcoholic fatty liver disease. Mothers with any systemic illnesses were also excluded.

**Clinical Data:** Detailed baseline information of maternal and neonatal variables were recorded in a predesigned proforma including age of mother, socioeconomic status, number of antenatal visits (booked pregnancy was defined as  $\geq 4$  and unbooked as  $< 4$  antenatal visits), gestational age at delivery, maternal medical and reproductive history, mode of delivery, still birth, Apgar scores at 1 and 5 min, meconium staining of liquor and duration of NICU stay. Weight of the newborn was recorded immediately after delivery in an electronic weighing scale with an accuracy within 5 g.

IUGR status was defined as discrepancy between gestational age assessment by clinical examination and antenatal scans of >3 weeks and/or estimated fetal

weight <10th centile as per standards using antenatal scan.

Maternal complications in the form of severity of Preeclampsia, eclampsia, HELLP syndrome, Placental abruption, intensive care admission and duration of stay, requirement of transfusion, hepatic failure [Hepatic Encephalopathy with deranged INR], renal failure, postpartum haemorrhage, PRES syndrome, fetal distress, requirement of magnesium Sulfate Prophylaxis were also recorded

All enrolled patients were classified into mild, moderate and severe hypertension and managed as per RCOG guideline.<sup>14</sup> Specific investigations were performed including a complete blood count, liver function tests (LFT), renal function tests and prothrombin time. Fundus examination was also done.

Clinical assessment was done during each visit and LFT was repeated at every two weeks interval. If during any visit AST >25 IU/l and/or ALT >32IU/L and/or ALP > 418 IU/L, patients were called again after a week and blood pressure and fetomaternal well-being was assessed. Termination of pregnancy was done as per the RCOG guideline.<sup>14</sup> LFT was repeated within 48 hours of delivery and compared with the previous values.

**Statistical analysis:** Using a prevalence rate of transaminitis of 24% amongst preeclamptic mothers based upon a previous study with an alpha error of 5% and a 5 % margin of error the minimum required sample size was 281 patients. Categorical variables were represented as numbers and percentages (%) and continuous variables as mean and SD or median with IQR. Normality of data was tested by Kolmogorov-Smirnov test. Unpaired t-test/Mann-Whitney U Test were used to compare between two different groups and paired T test/Wilcoxon rank sum test was used to compare across follow up. Qualitative variables were correlated using Chi-Square test /Fisher's exact test as applicable. Pearson correlation coefficient/Spearsman rank correlation coefficient was used to assess the correlation between the variables as applicable. Receiver operating characteristic curve was used to find out the cut off point of BP and liver enzymes for predicting maternal and fetal complications. A p value of <0.05 has been considered statistically significant.

### Results

The data in table 1 and 2 shows maternal and fetal-neonatal complications of the study subjects. It shows that 90% of patients had a normal vaginal delivery, 11.74 % received magnesium sulphate prophylaxis, 3.56 % had abruption, 3.20% had eclampsia, 1.42 % developed HELLP syndrome, 0.71% developed DIC, PE, ARF and 0.36% patients died. Also, 7.11% developed FGR, FD noted in 3.20 % patients, 3.56 % developed MSL, 1.07% had an IUD and NICU stay noted in 12.09 % babies.

The data in table 3 shows comparison of liver enzymes at inclusion and derangement. It shows that there is significant elevation in the levels of SGOT, SGPT and ALP at the time of derangement.

The data in table 4 shows correlation between liver enzymes and blood pressure. It shows that systolic and diastolic blood pressure both at admission/derangement are directly correlated with liver enzymes (SGOT, SGPT).

The data in table 5 shows sensitivity, specificity of liver enzymes for maternal complications. It shows that at 66 IU/L aspartate aminotransferase is 88% specific

and 90% sensitive for predicting maternal complications in preeclamptic patients with deranged liver enzymes. Alanine aminotransferase at 64 IU/L is 88% sensitive and 90% specific for same.

The data in table 6 shows sensitivity, specificity of liver enzymes for fetal complications. It shows that at 60 IU/L aspartate aminotransferase is 94% sensitive and 92% specific for predicting fetal complications in preeclamptic patients with deranged liver enzymes. Alanine aminotransferase at 64 IU/L is 94 % sensitive and 92% specific for same.

**Table 1: Maternal complications at a glance**

Maternal Complications		Frequency	Percentage
Mode of delivery	Hysterotomy	1	0.36%
	LSCS	26	9.25%
	NVD	254	90.39%
Abruption		10	3.56%
Eclampsia		9	3.20%
Magnesium Sulphate		33	11.74%
HELLP		4	1.42%
DIC		2	0.71%
PE		2	0.71%
ARF		2	0.71%
Death		1	0.36%
Total		281	100.00%

**Table 2: Fetal complications at a glance**

Fetal complications	Frequency	Percentage
Fetal growth restriction	20	28.9%
Fetal distress	6	8.69%
Meconium stained liquor	10	14.49%
Intrauterine death	3	4.34%
Nicu Stay (causes)	34	49.20%
Prematurity	16	47.05%
Meconium aspiration syndrome	2	5.88%
Fetal growth restriction	15	44.11%
Extremely low birth weight	1	2.94%
Total	73 (Out of 281)	100.00%

**Table 3: Comparison of liver enzymes at inclusion and derangement**

	At inclusion (n=281)	At Derangement/Admission (n=281)	P value
<b>SGOT</b>			<.0001
Mean ± Standard Deviation	16.05 ± 14.33	31.25 ± 28.27	
<b>SGPT</b>			<.0001
Mean ± Standard Deviation	17.6 ± 15.84	32.75 ± 29.54	
<b>ALP</b>			<.0001
Mean ± Standard Deviation	208.62 ± 32.06	250.99 ± 40.96	

**Table 4: Correlation between liver enzymes and blood pressure**

		SGOT at Derangement /admission	SGPT at Derangement /admission	ALP at Derangement /admission
SBP at Derangement /admission	Correlation Coefficient	.56	.568	0.193
	P value	<.0001	<.0001	0.011
	N	281	281	281
DBP at Derangement /admission	Correlation Coefficient	.573	.558	-0.03
	P value	<.0001	<.0001	.6116
	N	281	281	281

**Table 5: Cut off value, sensitivity, specificity of liver enzymes for maternal complications**

Maternal complications

	AUC	Standard Error	95% Confidence interval	P value	Cut off point	Sensitivity	Specificity	PPV	NPV
ALP at derangement /admission	0.545541	0.0499	0.485326 to 0.604786	0.361	>292	32	87.45	35.557	85.597
DBP at derangement /admission	0.907965	0.0281	0.867935 to 0.939072	<0.0001	>96	88	88.74	62.84	97.16
SBP at derangement /admission	0.88013	0.0295	0.836306 to 0.915694	<0.0001	>154	74	91.77	66.05	94.22
SGOT at derangement /admission	0.913896	0.0221	0.874779 to 0.943943	<0.0001	>66	88	90.91	67.689	97.223
SGPT at derangement /admission	0.9129	0.0239	0.873627 to 0.943128	<0.0001	>64	88	90.04	65.65897	97.197

At 66 IU/L aspartate aminotransferase is 88% specific and 90% sensitive for predicting maternal complications in preeclamptic patients with deranged liver enzymes. Alanine aminotransferase at 64 IU/L is 88% sensitive and 90% specific for same. Hence an intervention at these levels can prevent fetomaternal morbidity.

**Table 6: Cut off value, sensitivity, specificity of liver enzymes for fetal complications**

Fetal Complications

	AUC	Standard Error	95% Confidence interval	P value	Cut off point	Sensitivity	Specificity	PPV	NPV
Alp at derangement /admission	0.564921	0.0497	0.504748 to 0.623709	0.1913	>290	33.96	86.84	37.49	84.98
DBP at derangement /admission	0.9333	0.0233	0.897508 to 0.959525	<0.0001	>94	94.34	89.47	67.56	98.55
SBP at derangement /admission	0.924942	0.0184	0.887649 to 0.952886	<0.0001	>148	94.34	84.21	58.14	98.46
SGOT at derangement /admission	0.940707	0.0187	0.906347 to 0.965298	<0.0001	>60	94.34	92.54	74.61	98.6
SGPT at derangement /admission	0.938721	0.0203	0.903966 to 0.963761	<0.0001	>64	94.34	92.54	74.61	98.6

At 60 IU/L aspartate aminotransferase is 94% sensitive and 92% specific for predicting fetal complications in preeclamptic patients with deranged liver enzymes. Alanine aminotransferase at 64 IU/L is 94 % sensitive and 92% specific for same. Hence an intervention at these levels may be desirable for better fetomaternal outcome.

## Discussion

Hypertensive disorders of pregnancy are one of the leading causes of maternal and perinatal morbidity and

mortality. Value of liver function tests are rarely used as a cut off criteria for termination. In Indian context, not many studies have been done to evaluate maternal and neonatal outcome amongst pregnant women with

preeclampsia with deranged liver enzymes and to correlate severity of liver enzymes derangement in preeclamptic mothers with adverse fetomaternal outcome. Various significant findings of my study are mentioned below with cut off.

In our study, 26 out of a total of 281 patients (9.25%) underwent lower segment cesarean section. Out of these 26 patients, 76% patients were preeclamptic with deranged liver enzymes and 23% were preeclamptic with normal liver enzymes. Hence, LSCS were performed more in preeclamptic patients with deranged liver enzymes. Also 66% patients with deranged liver enzymes had a normal vaginal delivery which was induced in 50 % patients and spontaneous in the other 50%. Aali BS et al,<sup>16</sup> Yucesoy G et al<sup>17</sup> and Audibert F et al<sup>18</sup> also reported results which are almost similar to our study and P value was noted to be significant.

Out of 69 patients with deranged liver enzymes, 47% required magnesium sulfate prophylaxis, 14% developed abruption, 13% developed eclampsia, 5.79% went into HELLP Syndrome, 2.89% developed DIC, 2.89% pulmonary edema, 0.35% ARF and 0.35% died. As per Loi K et al<sup>15</sup> eclampsia (6%), HELLP (6%), Pulmonary edema (5%), ARF (14%), abruption (2%) maternal complications were noted in preeclamptic patients with deranged liver enzymes.

As per Aali BS<sup>16</sup> HELLP (5%), pulmonary edema (3.6%), ARF (5.4%), Abruption (5.6%) were noted in patients with complicated severe preeclampsia. A study by Yucesoy G et al<sup>17</sup> noted eclampsia (11%), abruption (1.5%) and maternal mortality in 3% patients. Studies by Haddad B,<sup>9</sup> Wodeselsassie,<sup>20</sup> Menezies et al,<sup>21</sup> Kozic et al<sup>22</sup> support these results.

Out of 69 preeclamptic patients with deranged liver enzymes, 28.90 % developed FGR, 8.69 % developed FD, 14.49% MSL, 4.34% IUD, 49.20 % NICU stay because of Prematurity in 47.05 % babies, MAS in 5.88%, FGR in 44.11% and ELBW in 2.94 % neonates. Aali BS<sup>16</sup> noted 47% premature births, 6% IUD and LBW in 34% preeclamptic patients with deranged liver enzymes.

Yucesoy G et al<sup>17</sup> noted FGR in 29.4% and LBW in 34% preeclamptic patients with elevated liver enzymes. Verhaeghe et al,<sup>23</sup> Menezies et al<sup>21</sup> and Abramovici et al<sup>24</sup> noted similar results as our study

SGOT at derangement had a cut off value 66 IU/L with sensitivity of 88%, specificity 90% for maternal complications, P value was significant for same <0.0001. SGPT at derangement had a cut off value 64 IU/L with sensitivity of 88%, specificity 90% for maternal complications and P value was significant <0.0001.

SGOT at derangement had a cut off value 60 IU/L with sensitivity of 94% and specificity 92% for fetal complications with a significant p value. SGPT at derangement had a cut off value 64 IU/L with

sensitivity of 94%, specificity 92% for fetal complications with P value being significant <0.0001.

A study by Haddad B<sup>19</sup> calculated ALT/AST values as 70/70 as a cut off, Wodeselsassie<sup>20</sup> calculated ALT /AST as 60/43, Menezies et al<sup>21</sup> calculated ALT/AST as 40/55 and Audibert F et al<sup>18</sup> calculated ALT/AST as 70/70 as a cut off for liver function tests which are similar to our study.

In the preeclampsia patients under study, 81% with deranged liver enzymes landed up with a premature delivery as a strategic intervention. 28% babies were admitted to neonatal intensive care unit and 72% were shifted motherside. Out of the admitted, 94.75% were discharged after 2-3 day NICU stay and some continued. Three babies expired due to respiratory distress syndrome. At one month follow up of the babies, all were healthy and doing well. Gladstone M et al,<sup>26</sup> Engmann et al<sup>25</sup> reported neonatal mortality rate in premature babies between 1.6-7.3% which are almost similar to our study. Above findings support that early intervention although increases the prematurity rate but outcome of such premature babies is satisfactory and one month follow up also reveals that all babies are doing well who would have otherwise landed up as an IUD or developed more fetal complications than noted in our study.

## Conclusion

From the present study it can be concluded that severity of liver function test derangement is directly related to severity of preeclampsia which in turn is related to severity of fetomaternal complications.

These complications were noted in the form of severe. Preeclampsia, impending eclampsia, eclampsia, HELLP syndrome, placental abruption, intensive care unit stay, liver failure, renal failure, hepatic encephalopathy, post partum haemorrhage. Fetal complications were noted in the form of meconium stain, fetal growth restriction, fetal distress, intrauterine death and neonatal intensive care unit stay of the baby

From the present study it can be derived that at AST >66 IU/L and ALT > 64 IU/L poor maternal outcome is expected. With AST >60 IU/L and ALT>64 IU/L adverse fetal complications are likely to occur.

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