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# Pregnancy And Liver Disease: A Challenging Issue

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**ABSTRACT**

**Background:** The diagnostic work of abnormal Liver Function Test (LFT) in pregnancy is challenging. Biochemical and hematological indices taken during pregnancy need to be interpreted in light of the altered normal range for test result in pregnancy. The pathological derangement in the liver functions may be related or may coexist with pregnancy and may be divided into three major groups

**Material and Method:** All pregnant women who met WHO set of severity markers for near miss mortality (NHM) with deranged LFT were studied prospectively. 60 such women were included in the study.

**Results:** There were 60 women with deranged LFT amongst 504 admissions giving the incidence of 11.90% in our study. 81.66% women had pregnancy specific liver dysfunction whereas 18.33% women had liver disorder which was not specific to pregnancy.

**Conclusion:** Pregnancy specific disorders are the leading cause of abnormal LFT during pregnancy particularly in the third trimester.

**Key words:** Liver function, Pregnancy, Eclampsia

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## INTRODUCTION

The diagnostic work of abnormal Liver Function Test (LFT) in pregnancy is challenging as the conditions peculiar to pregnancy have to be considered in addition to the causes affecting the nonpregnant population. Biochemical and hematological indices taken during pregnancy need to be interpreted in light of the altered normal range for test result in pregnancy.[1]

Maternal Alkaline Phosphatase (ALP) increases in the third trimester when ALP is produced both from placenta and a as result of fetal bone development. Other common biochemical and hematological tests including, urea, hemoglobin levels and the prothrombin time remain unchanged or slightly reduced due to hemodilution. Elevation in transaminase, bilirubin or the prothrombin time is abnormal and indicates a pathological state which requires further assessment.[2]

The pathological derangement in the liver functions may be related or may coexist with pregnancy and may be divided into three major groups. First group includes liver disorders that are specific to pregnancy such as hyperemesis gravidarum, pre-eclampsia, eclampsia, syndrome of hemolysis , elevated liver test and low platelets (HELLP) and acute fatty liver of pregnancy (AFLP), Intra hepatic cholestasis of pregnancy (ICP). Second group includes intercurrent liver diseases occurring during pregnancy such as viral hepatitis and herpes simplex. Third group include pregnancy with preexisting liver diseases such as chronic hepatitis, portal hypertension, cirrhosis of liver.[3], [4]

Liver diseases during pregnancy are relatively poorly studied and pose a challenge for the consulting gynecologist and hepatologist. Nearly 3% of pregnancies are complicated by some form of liver diseases. They are associated with significant morbidity and mortality of both mothers and infants in severe cases.[5], [6]

The present study was done with the objective to study the possible causes of deranged LFT, incidence, clinical profile, maternal and fetal outcome in all cases of near miss mortality (NHM) with deranged LFT at the tertiary care hospital of Faridkot.

## MATERIAL AND METHOD

This study was conducted in the department of Obstetrics and Gynaecology, Guru Gobind Singh Medical College, Faridkot over a period of one year from 1st January 2018 to 31st December 2018. All pregnant women who met WHO set of severity markers [7] for near miss mortality (NHM) with deranged LFT were studied prospectively. 60 such women were included in the study. After obtaining the demographic, menstrual and obstetric details, the

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specific symptoms related to liver dysfunction such as pruritus, persistent vomiting, yellow discoloration of urine, blurring of vision, upper abdominal discomfort, anorexia were noted.

A thorough general and obstetric examination was carried out in all women. All available LFT including LDH were asked. Some other definitive test like platelet count, viral serology, peripheral blood smear and hemoglobin electrophoresis were done whenever required to aid investigation of underlying cause.

Diagnostic criteria for different underlying pathology were based upon following parameters.

**HELLP Syndrome:** Raised bilirubin elevated (ALT, AST >70 IU/C) low platelet count <100000/ml, hemolysis, (suggestive smear with red cell fragmentation along with increased reticulocytes.

Pre-eclampsia associated liver dysfunction: elevated transaminases or bilirubin in the presence of Hypertension to the extent of 140/90 mmHg or more on two occasion >6hr apart proteinuria (1+) after 20 weeks of pregnancy.

Intrahepatic Cholestasis of Pregnancy (ICP) includes pruritus without any skin problem or allergy with elevated transaminase and scrum bile acid.

Acute fatty liver of pregnancy (AFLP):[8] Swansea diagnostic criteria for the diagnosis of acute fatty liver of pregnancy include six or more of features in the absence of other aetiolgy.

Vomiting, abdominal pain, polydipsia/polyuria, encephalopathy, leukocytosis elevated bilirubin and transaminase, marked hyperglycemia, renal impairment coagulopathy, elevated urate, ascites or bright liver on ultra sound.

**Hepatitis:** elevated transaminases or bilirubin in the presence of positive hepatitis viral serology.

Sickling: Positive Hemoglobin electrophoresis

All the results were recorded in Microsoft excel sheet and were analyzed by SPSS software.

## RESULT

During this period of study there were a total of 504 admissions under criteria laid by WHO used in material near miss assessment. There were 60 women with deranged LFT amongst 504 admissions giving the incidence of 11.90% in our study.

Majority of the women were young and age less than 30 years, were unbooked of low socio-economic status. 85% of women presented in the third trimester of pregnancy. The most women, presenting complaints were edema 48.33%, Headache 30% followed by vomiting, yellow discoloration of urine and visual symptoms (table 2, 3).

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In our study 81.66% women had pregnancy specific liver dysfunction, of these pregnancy induced hypertension related disorder 38.33% had preeclampsia, 20% had HELLP syndrome and 15% were diagnosed with eclampsia. Other causes under this category were acute fatty liver of pregnancy and ICP, whereas 18.33% women had liver disorder which were not specific to pregnancy and consisted of infective hepatitis, malaria and sickle cell diseases. Three patients had borderline derangement in LFT but with profound increase in TLC count so were taken under sepsis (table 3 and 5).

The mean value of all LFT abnormalities is shown in table 6. The mean value of bilirubin in Hypertensive disorders of pregnancy ranged from 2.12 to 4.14 whereas it was between 6 and 11 for ICP and AFLP and it went to very high level >10 in cases of infective hepatitis. Transaminase value was highest in infective hepatitis whereas alkaline phosphatase was highest in ICP. Test for S. bile acid was not available in the inside lab so were asked in selected cases. It come out to 36□mol/L in ICP. LDH levels were markedly elevated in ICP and HELLP syndrome.

Out of five women in second trimester, 3 had intrauterine death (IUD) and the other two were terminated because of severity of PE. Majority of women i.e. 63.33% delivered vaginally whereas 36.66% underwent lower segment caesarean section (LSCS) needing delivery urgently due to worsening fetal or maternal conditions or due to various obstetric reason. Most of the vaginal delivery were induced 29/38 (76.31%).

Table 7 shows the various complication faced by these women. Most common come out to be pulmonary edema 20%, acute renal failure 20%, DIC and PPH. There were total four maternal deaths mainly become of ICP, AFLP and Fulminant HELLP.

22% of women had IUD including five cases of second trimester. Out of 38 live birth, 42.10% were small for dates infants and 39.47% were preterm either induced or spontaneously delivered.

**Table 1: WHO set of severity markers (life threatening conditions) used in maternal near-miss assessments**

| Clinical conditions | Less risk (SOFA category 1, 2) | Greater risk (SOFA category 3, 4) |
|---|---|---|
| Cardiovascular dysfunction | Shock | pH <7.1 |
| | Lactate >5 | Use of continuous vasoactive |

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| | | |
|---|---|---|
| | | drugs Cardiac arrest |
| | | Cardio-pulmonary resuscitation |
| Respiratory dysfunction | Acute cyanosis | Gasping |
| | Respiratory rate >40 or <6 per min | PaO2/FiO2 <200mmHg |
| | Oxygen saturation <90 % for □60min | Intubation and ventilation not related to anaesthesia |
| Renal dysfunction | Oliguria non-responsive to fluids or diuretics | Creatinine □300 mmol/I or □3.5 mg/dl<br>Dialysis for acute renal failure |
| Clothing/hematological dysfunction | Clothing failure<br>Transfusion of □5 units of blood/red cells | Acute thrombocytopenia (<50,000 platelets) |
| Hepatic dysfunction | Jaundice in the presence of pre-eclampsia | Bilirubin >100 mmol/1 or >6 mg/dl |
| Neurological dysfunction | Metabolic coma<br>Status epilepticus/uncontrolled fits/total paralysis | Coma/loss of consciousness for 12 h or more |
| Uterine dysfunction | Hysterectomy due to infection or hemorrhage | |

**Table 2: Demography and Presenting symptoms**

| Demographic feature n = 60 | | Number | % |
|---|---|---|---|
| Age | <20 | 2 | 3.3 |
| | 21-30 | 46 | 76.66 |
| | >30 | 12 | 20 |
| Parity | P0 | 4 | 6.66 |
| | P1 | 38 | 63.33 |
| | P2 and above | 18 | 30 |
| Socio-economic status | 1 & II | 8 | 13.33 |

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| | | | |
|---|---|---|---|
| (Mod Prasad classification ) | III & IV | 42 | 70 |
| | V | 10 | 16.66 |
| ANC Care Status | Booked | 16 | 26.66 |
| | Unboked | 44 | 73.33 |
| Gestational Age (Trimester wise ) | I | 0 | |
| | II | 5 | 8.33 |
| | III | 51 | 85 |
| Postpartum | | 4 | 6.66 |

**Table 3: Distribution of cases according to presenting complaint**

| Presenting complaint | No | % |
|---|---|---|
| Pruritus | 4 | |
| Fever | 12 | 20 |
| Headache | 18 | 30 |
| edema | 29 | 48.33 |
| Vomiting | 15 | 25 |
| Yellow urine | 18 | 30 |
| Visual symptoms | 10 | 16.66 |
| Miscellaneous | 05 | 8.33 |

**Table 4: Trimester wise**

**Distribution of cause of abnormal LFT**

| Trimester | No. | % percentage |
|---|---|---|
| **First Trimester** | Nil | Nil |
| **Second Trimester** | | |
| Pre eclampsia | 2 | 8.33% |
| Sickle Cell diseases | 1 | |
| Hepatitis | 2 | |
| **Third trimester & Post-Partum** | | |
| Acute fatty liver | 4 | 91.66% |
| HELLP Syndrome | 12 | |
| Hepatitis | 3 | |

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| | | |
|---|---|---|
| Intra Hepatic cholestasis of pregnancy | 1 | |
| Pre eclampsia | 21 | |
| Eclampsia | 9 | |
| Malaria | 1 | |
| N1H1 (Dengue) | 1 | |
| Sepsis | 3 | |
| Total | 60 | 100% |

Table 6: Mean LFT value with various diseases

| Sr. No. | Diseases | S.bilirubin total | Bilirubin direct | AST | ALT | Alkaline Phosphatase | LDH |
|---|---|---|---|---|---|---|---|
| 1 | Pre eclampsia | 2.12 | 1.43 | 214.04 | 218.35 | 348.63 | 780.56 |
| 2 | Eclampsia | 2.84 | 1.75 | 211.70 | 216.34 | 340.83 | 745.00 |
| 3 | HELLP syndrome | 4.14 | 3.99 | 270.86 | 250.40 | 390.46 | 990.40 |
| 4 | Viral hepatitis | 13.25 | 9.02 | 841.40 | 880.00 | 863.10 | 268.10 |
| 5 | ICP | 4.02 | 3.82 | 124.04 | 128.70 | 1650.00 | 480.00 |
| 6 | AFLP | 9.12 | 8.34 | 770.00 | 788.00 | 710.00 | 940.12 |
| 7 | Malaria | 2.14 | 1.43 | 204.04 | 180.35 | 240.63 | 680.56 |
| 8 | Sepsis | 2.10 | 1.43 | 180.02 | 140.34 | 500.63 | 668.00 |

Table 7: Delivery outcome (N = 60)

| Outcome | | No. | Percentage |
|---|---|---|---|
| 1 | Mode of Delivery | | |
| | Vaginal delivery | 32 | 63.33 |
| | LSCS | 28 | 36.66 |
| 2 | Fetal outcome | | |
| | Live birth | 38 | 63.33 |
| | Preterm | 15 | 39.47 |
| | IUGR | 16 | 42.10 |

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| | | | |
|---|---|---|---|
| | Neonatal admission | 32 | 84.21 |
| | IUD | 22 | 36.66 |
| 3 | Maternal complication | | |
| | DIC | 6 | 9.8 |
| | Acute Renal Failure | 12 | 20 |
| | Abruption | 3 | 5.0 |
| | PPH (Post-Partum Hemorrhage ) | 8 | 13.33 |
| | Pulmonary edema | 12 | 20 |
| | Severe Ascites | 1 | 1.66 |
| | Cerebral Hemorrhage | 2 | 3.33 |
| | Maternal Death | 4 | 6.66 |

**DISCUSSION**

The incidence of abnormal LFT in pregnancy is higher in young age group. In our study majority of women were of low socio-economic status, not booked for antenatal care and as we have analysed the abnormal LFT in a group who fits under the criteria of near miss mortality so these generally got admitted in hospital as emergency cases. Similar demographic facts are observed in other Indian studies [9][ 10] Most common gestational period of abnormal liver function test was third trimester and pregnancy related causes were the commonest cause specially the pre-eclampsia related disorder. This explains the edema (48.33%) and headache (30%) as the leading presenting symptoms, though it is no more a diagnostic criteria.

In most studies the cause of abnormal LFT is reported to be of pregnancy specific disorders and varies from 68% to 84% [11], [12]. Our finding of 81.6% is in agreement with others. Pregnancy related liver disorder in their occurrence, exhibit trimester specific characteristic; whereas non-pregnancy related liver diseases can occur at any time [13]. The timing of the occurrence of clinical manifestation and abnormal lives test is critical in determining diagnosis and treatment strategies. For example hyperemesis gravidarum is a pregnancy related liver disorder of early pregnancy, whereas IHC, Pre-eclampsia, AFL are conditions affecting the liver in late pregnancy [5][13]. Although we did not have any case of hyperemesis gravidarum with abnormal LFT in the first trimester, our second and third trimester cases, followed the same patterns. So, gestational age is an important guide for further evaluation of abnormal LFT in pregnancy.

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In our study group 18.3% were from abnormal LFT with causes non-specific to pregnancy, we had 5 cases of viral hepatitis. It is reported to be common in developing countries and the fulminant hepatitis especially in relation to hepatitis E is higher in pregnancy with higher mortality up to 25% probably influenced by malnutrition. [14]

In our study, only one woman had IHC of pregnancy and her lab-investigation showed marked elevation of Alkaline Phosphatase and serum bile acid with moderate increase in serum bilirubin levels. She was also positive for hepatitis E virus. S. Uric acid is not available from inside lab of hospital so were asked for selective cases where patient chief complaint was excessive pruritus especially during night. Its levels are high in intrahepatic cholestasis of pregnancy. [15][16]

According to recent data, IHC of pregnancy is associated with an increased risk of developing others hepatobiliary diseases and in addition, patients with underlying chronic liver diseases e.g. hepatitis C have increased risk of ICP[17] so it's better testing for Hepatitis C in women with ICP, especially when abnormal LFT do not improve rapidly with in few days postpartum.

In our study out of 60 women 73.3% had pre-eclampsia related disorders and 4 had acute fatty lives of pregnancy. In a series of 28 patient with AFLP castro et al[18] reported that the cardinal feature were that of impaired coagulation and renal impairment. However HELLP too can lead to DIC and renal impairment with a reported incidence of 21% and 7.1% respectively. [19]In our study group renal impairment 20% and DIC 9.8% were the finding. 2nd, it has been suggested that AFL may form the extreme end of the spectrum of pre-eclampsia disease.

In our study group AST and ALT were maximally elevated in viral hepatitis. LDH is less sensitive than AST and ALT as a marker of hepatocellular injury. It represent a marker of hemolysis specially in the presence of raised bilirubin, fragmented ABC on peripheral smear resulting from microangiopathic hemolysis which in the hell mark of HELLP syndrome.[20] S bilirubin was elevated to the range of 10-14 in viral hepatitis and AFLP. ALT and AST in pre eclampsia liver function abnormalities particularly HELLP may be ranging from 70 to 6000 with a mean of 250 [21]. So, the degree of derangement of LFT can guide the approach to diagnose further. In our study the mean value of abnormal LFT was more or less followed the same pattern.

Induction of labor was the most common mode of termination of pregnancy due to severity of cases which can be due to liver diseases or due to associated other comorbidities. LSCS done in 28/60 cases due to various maternal and fetal reasons. Fetal outcome was

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gloomy as 36.66 ended up in 10D. Preterm and IUGR accounted for 63.33 of live births. Similar findings were reported by Mishra et al. and C L Chng.[22][4]

According to the literature a mortality rate of 0-25% has been reported among mothers with pregnancy related liver diseases. AFLP, HELLP, fulminant hepatitis E are well known for grooming maternal and fetal prognosis specially where there is delay in delivery. [24][25] In our study group there occur four maternal death. 2 women died due to multi organ failure having fulminant HELLP syndrome, one died of ICP and other died of encephalopathy and cerebral hemorrhage due to AFLP. Other maternal complications like acute renal failure, PPH, DIC, abruptio were in accordance to other studies. [23][23]

## CONCLUSION

The factors responsible for the higher maternal and fetal morbidity and mortality appear to be due to lack of awareness regarding the pregnancy specific condition which may lead to worsening of the outcome of pregnancy especially in the presence of abnormal liver functioning. Pregnancy specific disorders are the leading cause of abnormal LFT during pregnancy particularly in the third trimester. Pre eclampsia related disorders are the commonest among there. The timing of clinical manifestation and liver test results abnormalities can be critical for determining the diagnosis and treatment strategies. More research is needed to understand the epidemiology of pregnancy related liver diseases and to evaluate the long term maternal outcome.

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