

# Liver Disease in Pregnancy: A Prospective Analysis of Maternal and Fetal Outcomes among 120 Patients at a Tertiary Care Center

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## ABSTRACT

**Background:** Liver disorders during pregnancy pose unique challenges to the managing obstetrician in terms of consequences to the mother and the fetus. The aim of the study is to evaluate the various etiologies, clinical presentation, and to find out the maternal and fetal outcomes in mothers presenting with liver disorders during pregnancy.

**Methods:** The study prospectively analyzed 120 consecutive patients who presented to our tertiary care center and were diagnosed to have some liver disease based on a combination of clinical, serological, or radiological evidence. Patients with liver disorder secondary to sepsis and multiorgan failure were excluded from the study.

**Results:** A maximum number of patients were in the age group of 21–30 (73.3%). In terms of frequency, most common liver disorder was hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome (21.7%) cases followed by pre-eclampsia (19.2%) and Hepatitis E (14.2%). There was high presence of preterm deliveries comprising 64.25% of all deliveries. There were 107 live births and still birth was noted in 13 patients. Among the still birth group, the most common associated liver disease was Hepatitis E in 10 (76.9%) patients. The maternal mortality was 13.3% (16 patients). Hepatitis E was the single most important cause of mortality in all 16 patients.

**Conclusion:** Pregnancy-specific liver disorders were far more common in the study and HELLP syndrome accounted for maximum number of cases. The presence of hepatitis E was the single most important cause of both fetal and maternal mortality.

**Keywords:** HELLP syndrome, Hepatitis E in pregnancy, Liver disease in pregnancy, maternal and fetal outcomes.

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## INTRODUCTION

Liver disease during pregnancy poses potentially serious consequences to the mother and fetus. Its early diagnosis and management are of paramount importance for a favorable outcome. Liver disorders during pregnancy may either be a result of pre-existing liver conditions, liver disease specific to pregnancy or liver disorders diagnosed coincidentally during pregnancy. The incidence of liver disease during pregnancy can range from 0.3 to 3%, and severe liver injury is encountered in even smaller group of patients.<sup>1,2</sup> The widespread role played by liver in synthesis, metabolism, and excretion of substances makes the symptomatology of liver disorders equally widespread ranging from abdominal pain, nausea, and vomiting to signs of frank acute hepatic failure.

Most serum levels of the liver function tests (LFT) experience reduction in levels during pregnancy as compared to the nonpregnant state.<sup>3</sup> This is mainly due to the expansion of the extracellular fluid compartment. This result is noticed for parameters other than alkaline phosphatase (ALP), which is increased during the third trimester due to increased placental production.<sup>4–7</sup> Therefore, any elevation in the LFT parameters is considered abnormal and should be evaluated thoroughly. Similarly,  $\alpha$ -fetoprotein is not routinely found, but it may be elevated due to its production by the fetal liver.<sup>8</sup> The safest and most commonly used radiological modality for diagnosis is the ultrasound of the liver. Magnetic resonance imaging is also considered safe, but the use of gadolinium should be avoided due to its unknown effects on the fetus.<sup>9</sup> A computed tomographic scan is usually avoided owing

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the radiation hazards to the fetus, and the use of liver biopsy for diagnosis is also rarely required.

The successful management of liver diseases during pregnancy requires collaborated efforts by obstetricians, gastroenterologists, and/or hepatologists. There is paucity of literature regarding the maternal and fetal outcomes of patients with liver disorders, and such studies are especially infrequent in the Indian population. Our study aims to prospectively evaluate the maternal and fetal outcomes of patients with various pregnancy- and nonpregnancy-related liver disorders. The various factors relevant for maternal

outcome include antenatal diagnosis, mode of delivery, need for intensive care unit (ICU) admission, requirement of surgical intervention for liver dysfunction, and eventually a measure of maternal mortality, including an analysis of various causes contributing to maternal mortality with liver disorders. The fetal outcome relates to presence or absence of fetal growth retardation (FGR), full-term or preterm births, live or still birth, and the need for neonatal ICU (NICU) stay. This analysis then further allows us to look into the various factors that need specific interventions to improve maternal and fetal outcomes with liver disorders.

The pregnancy-related liver diseases can be broadly classified into those of early pregnancy including hyperemesis gravidarum (HG), those of late pregnancy like acute fatty liver of pregnancy (AFLP), pre-eclampsia with hepatic involvement including HELLP syndrome, liver rupture/infarction, and intrahepatic cholestasis of pregnancy (ICoP).

**HG:** It is usually defined as intractable vomiting, resulting in dehydration, ketosis, and weight loss greater than 5% usually requiring admission and hydration. It is a reversible condition causing no permanent hepatic damage.

**ICP:** Typically presenting in the third trimester with pruritus worse on palms and soles with elevated levels of serum bile salts. It may be associated with spontaneous preterm labor, still birth, and admissions to NICU.

**Pre-eclampsia:** A multisystem disorder diagnosed as new hypertension after 20th week of pregnancy in combination with proteinuria (>300 mg/day) and other maternal organ dysfunction such as renal insufficiency, liver involvement, uteroplacental dysfunction, and fetal growth restriction.

**HELLP syndrome:** It is most commonly diagnosed with the help of Tennessee criteria: evidence of hemolysis, AST >70 IU/mL, thrombocytopenia (platelets <100000/mm<sup>3</sup>), and AST.

**AFLP:** It is a medical and obstetric emergency as it can be fatal for both the mother and the fetus if diagnosis is delayed and appropriate management is not started early. It is commonly diagnosed with Swansea criteria:<sup>10</sup> vomiting, abdominal pain, polydipsia/polyuria, encephalopathy, bilirubin >0.8 mg/dL (14 kmol/L), hypoglycemia <72 mg/dL (4 mmol/L), uric acid >5.7 mg/dL (340 kmol/L), leukocytosis >11 × 10<sup>6</sup>/L, ascites or bright liver on sonogram, aspartate aminotransferase and alanine aminotransferase >42 IU/L, ammonia >27.5 mg/dL (47 kmol/L), creatinine >1.7 mg/dL (150 kmol/L), coagulopathy [prothrombin time (PT) >14 s or activated partial thromboplastin time (aPTT) >34s], and microvesicular steatosis on liver biopsy. Six or more of these terms are required to diagnose AFLP.

Pre-existing liver diseases and pregnancy comprise mainly chronic hepatitis B virus infection and chronic hepatitis C virus infection as diagnosed with serological tests.

Acute viral infections arising with pregnancy are the most common causes of jaundice occurring in pregnancy worldwide.<sup>11</sup> The diagnosis of hepatitis E is done by positive immunoglobulin M (IgM) anti-hepatitis E virus (HEV).

## MATERIALS AND METHODS

### Patients

We conducted a single center prospective analysis of patients after obtaining institutional ethics committee approval. Appropriate consent was obtained prior to enrollment in the study. The patients

were enrolled at a single tertiary care center in the department of obstetrics and gynecology, after a diagnosis of liver dysfunction during antepartum, intrapartum, or postpartum period. Patients attending the outpatient clinics or indoor services from January 2018 to December 2019, with a clinical, hematological, or radiological diagnosis of liver dysfunction were included in the study (mentioned subsequently). Patients with pre-existing liver disease not related to pregnancy and patients with a diagnosis of liver disease during pregnancy, both were included in the study. Pregnant women with liver dysfunction secondary to sepsis and multiorgan failure were excluded from the study. Similarly, patients not willing to participate were also excluded.

### Parameters

All patients in the final inclusion group were examined by standard technique as per the institutional protocol. Clinically, the presence of abdominal pain, nausea, vomiting, ascites, pedal edema, and palpable hepatomegaly was chosen as signs and symptoms requiring further hematological and radiological investigations. The following abnormal hematological investigations were used for diagnosis as per institutional protocol: serum bilirubin ≥25.6 mmol/L (1.5 mg/dL), alanine transaminase ≥40 IU/L, aspartate transaminase ≥40 IU/L, and ALP ≥306 IU/L. Serum albumin levels, PT, aPTT, bleeding time, and clotting time were also measured for each patient. Patients with abnormal LFT were subjected to further serological testing and ultrasonography to reach a diagnosis. Maternal outcome was studied in terms of demographic profile, antepartum characteristics, and mode of termination of pregnancy. We looked at the patients with spontaneous onset of labor or those requiring induction of labor, outcome in terms of vaginal delivery or need for cesarean section, need for forceps or vacuum device for augmentation of labor, and the various causes for cesarean section. We identified the various causes and their contribution to the number of patients with liver disorder during pregnancy. We also looked at various maternal complications, reasons for maternal ICU admissions, and maternal end result in terms of presence or absence of maternal mortality due to the liver disease. Fetal outcome was assessed by presence or absence of FGR, full-term or preterm births, live or still birth, and the need for NICU stay.

### Statistical Analysis

Statistical analysis was done using Statistical Package for the Social Sciences (SPSS) version 16.0 (SPSS Inc., Chicago, IL, USA). Comparison of categorical variables was carried out with the help of Chi-square test, and a statistical significance was observed for *p*-value <0.05.

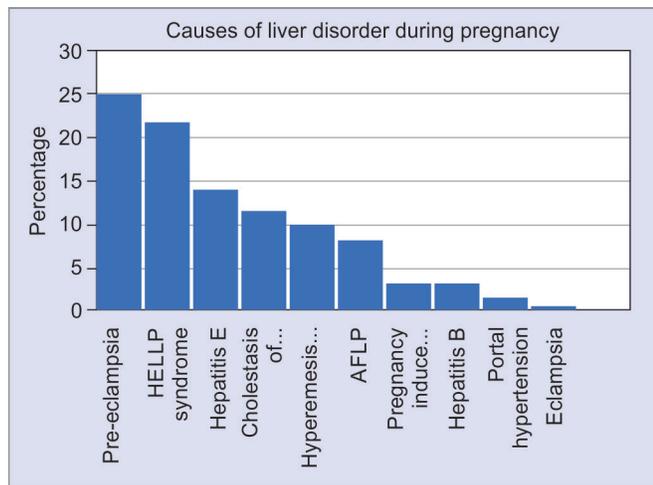
## RESULTS

The study comprises 120 patients after applying the inclusion and exclusion criteria. Out of these, the maximum number (73.3%) of cases was in the age group 21–30 years followed by 9.1% in the 18–20 years group, and 17.5% in the group >30 years. In the study, nearly 52% cases were multigravida and 48% were primigravida. The other demographic data are summarized in Table 1 for better understanding. The most common presenting symptom was abdominal pain (31.7%) and pedal edema (31.7%) followed by vomiting in 24.2% cases. The most common sign of liver disorder was ascites in 42.5% of patients followed by hepatomegaly in 9.2% cases. Out of the entire cohort, pregnancy-specific liver disorders were far more common comprising about 97 (80.8%)

**Table 1:** Depicting the demographic profile of the patients in the study

	Number of patients	%
<b>Age</b>		
18–20	11	9.2%
21–30	88	73.3%
>30	21	17.5%
<b>Rural/Urban</b>		
Rural	77	64.2%
Urban	43	35.8%
<b>ANC</b>		
Booked	51	42.5%
Registered at our institute	69	57.5%
<b>Gravida</b>		
Multi-	63	52.5%
Primi-	57	47.5%
<b>Gestational age</b>		
FT	43	35.8%
PT	77	64.2%

ANC, antenatal care



**Fig. 1:** Summarizing the various causes and the corresponding number of patients for each cause in the study cohort

cases. The most common liver disorder among the study group was HELLP syndrome (21.7%) cases followed by pre-eclampsia (19.2%) cases and hepatitis E in 14.2% cases. Overall, hypertension complicated the course in 63 patients. The various causes and the incidence are well summarized in Figure 1. The patients presented most commonly in the third trimester comprising about 97 cases among the total cohort.

**Outcomes**

When considering the outcome of pregnancy, it was found that 66 cases required induction of labor whereas 54 had spontaneous onset of labor. Among the induced category, vaginal delivery and delivery by cesarean section were noted in 33 cases each. On the contrary, among the spontaneous labor onset group, 47 (87.03%) patients underwent vaginal delivery and cesarean section was used in only 7 out of 54 patients. Highest indication for cesarean section was meconium-stained liquor with fetal distress (emergency). Overall, vaginal delivery was the most common method in 80 patients. Out of these 80 patients, forceps were used in 11 (13.7%) patients and vacuum-assisted delivery was utilized in 5 (6.2%) patients. A staggering 77 (64.2%) mothers had preterm children and only 43 (35.8%) had full-term babies. When analyzing the causes of various liver disorders among the preterm group, it was found that the most common liver disorder was HELLP syndrome in 29.6% of cases followed by hepatitis E infection in 17 (23.9%) cases as compared to the full-term group in 4 (10.3%) and 0 cases, respectively. This was statistically significant ( $p < 0.01$ ). This is summarized in Table 2 for better understanding. We further analyzed the overall fetal morbidity and mortality. There were 107 live births and still birth was noted in 13 patients. It was found that a total of 78 patients were diagnosed to have prematurity. Early neonatal deaths were observed in 18 patients among the total live births. The overall rate of NICU admission was 45% (54 cases). The relationship between need for NICU admissions and the various causes of liver disorders during pregnancy is shown in Figure 2. Among the still birth group, the most common associated liver disease was hepatitis E in 10 (76.9%) patients. Among the live birth group, the most common single liver disease was HELLP syndrome in 25 (23.4%) cases. The difference was statistically significant with  $p$ -value = 0.002. This is summarized in Table 3 for ease of understanding. Among the total study group of 120 patients, FGR was found in 25 patients. The most common liver disease associated with FGR was HELLP syndrome

**Table 2:** Depicting the relationship between full-term/preterm birth vs the various causes of liver disorders during pregnancy

Full-term/Preterm birth	Diagnosis					Total
	COP	HELLP	Hepatitis E	Pre-eclampsia	Others	
<b>FT</b>						
No. of patient	4	4	0	11	20	39
%	10.30%	10.30%	0.00%	28.20%	51.30%	100%
<b>PT</b>						
No. of patient	10	21	17	10	13	71
%	14.10%	29.60%	23.90%	14.10%	18.30%	100%
<b>Total</b>						
No. of patient	14	26	17	23	40	120
%	11.70%	21.70%	14.20%	19.20%	33.30%	100%

$\chi^2$ , 37.075;  $p$ -value, 0.0001; FT, full-term; PT, preterm

in eight patients (32%) followed by pre-eclampsia in five cases. This difference was not significant with  $p = 0.50$  (Table 4). Similarly, the most common associated liver disorder with early neonatal death was HELLP syndrome in 38.9% cases followed by hepatitis E in 27.8% cases. Among the various NICU admissions, HELLP syndrome was again the single most common association in 35.2% cases

followed by pre-eclampsia (16.7%) and hepatitis E (11.1%) (Table 5). The overall mortality among the mothers due to liver disorders of pregnancy was 13.3% (16 patients) among the total study group of 120 patients. Hepatitis E was the single most important cause of mortality in all 16 patients. In total, hepatitis E was diagnosed in 17 patients, and the overall mortality rate due to hepatitis E was found in 16 out of 17 patients. The various causes of maternal mortality in patients with liver disorders during pregnancy is shown in Figure 3.

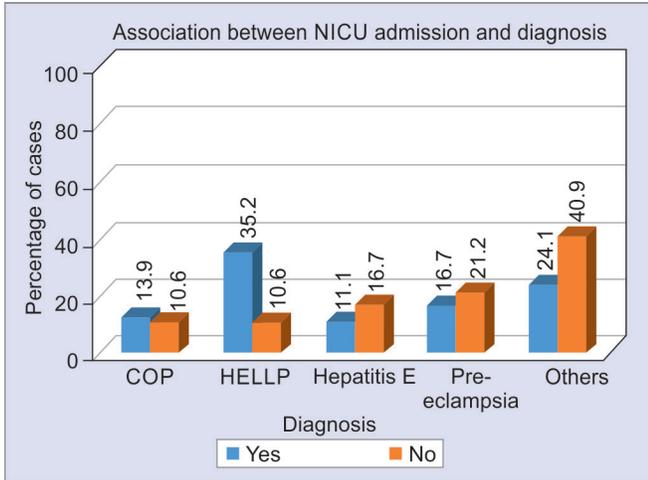


Fig. 2: Depicting the relationship between need for NICU admissions and the various causes of liver disorders during pregnancy

## DISCUSSION

Liver disorders during pregnancy comprises a wide spectrum of diseases. The mode of presentation, its diagnosis, and the further management are dependent upon the type of disease. The age group of patients presenting to us with liver disorders during pregnancy was 21–30 years (73.3% cases), which is similar to previous studies done by Sharma et al.<sup>13</sup> where the peak incidence is reported in 21–25 years age group and by Jain et al.<sup>14</sup> who have reported the mean age to be 25.4 years. In our study, the majority of patients (57.5%) were referrals from outside hospitals. These data are comparable with the study of Tiwari et al.<sup>12</sup> and Sharma et al.<sup>13</sup> In our study of 120 patients, liver disorders developed in 57 (47.5%) primigravida patients and 63 (52.5%) multigravida patients. AFLP presented more commonly in multipara (80%) so as pre-eclampsia (60.86%), whereas cholestasis of pregnancy (COP) (71.42%), hepatitis E (82.35%), and HG (83.33%) were seen more

Table 3: Depicting the relationship between live birth and still birth vs the various causes of liver disorders during pregnancy

Fetal outcome	Diagnosis					Total
	COP	HELLP	Hepatitis E	Pre-eclampsia	Others	
Live/Still birth						
Live						
No. of patients	14	25	7	23	38	107
%	13.1%	23.4%	6.5%	21.5%	35.5%	100.0%
Still						
No. of patients	0	1	10	0	2	13
%	0.0%	7.7%	76.9%	0.0%	15.4%	100.0%
Total						
No. of patients	14	26	17	23	40	120
%	11.7%	21.7%	14.2%	19.2%	33.3%	100.0%

$\chi^2$ , 47.750;  $p$ -value, 0.002

Table 4: Depicting the relationship between IUGR and the various causes of liver disorders during pregnancy

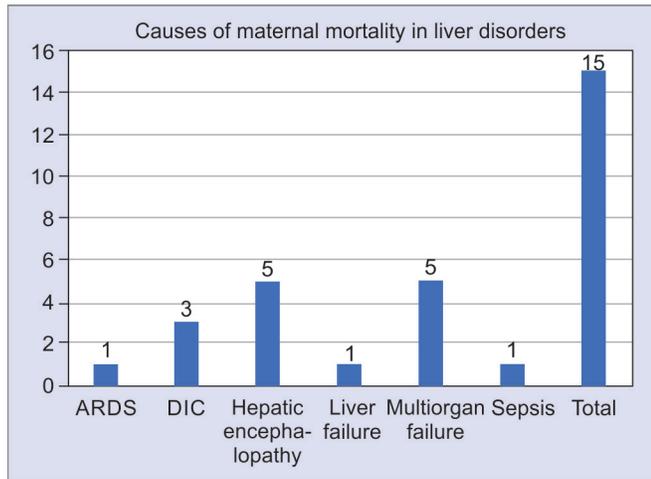
IUGR	Diagnosis					Total
	COP	HELLP	Hepatitis E	Pre-eclampsia	Others	
Yes						
No. of patients	3	8	4	5	5	25
%	12.00%	32.00%	16.00%	20.00%	20.00%	100.00%
Total						
No. of patients	14	26	17	23	40	120
%	11.70%	21.70%	14.20%	19.20%	33.30%	100.00%

$\chi^2$ , 3.330;  $p$ -value, 0.50

**Table 5:** Demonstrating the various causes of NICU admissions in mothers with liver disorder during pregnancy

Reason of MICU/EMS admission	Diagnosis					Total
	COP	HELLP	Hepatitis E	Pre-eclampsia	Others	
<b>ARDS</b>						
No. of patients	0	2	0	0	0	2
%	0.00%	100.00%	0.00%	0.00%	0.00%	100.00%
<b>DIC</b>						
No. of patients	0	1	4	0	5	10
%	0.00%	10.00%	40.00%	0.00%	50.00%	100.00%
<b>Encephalopathy</b>						
No. of patients	0	0	9	0	1	10
%	0.00%	0.00%	90.00%	0.00%	10.00%	100.00%
<b>Ventilatory support</b>						
No. of patients	0	0	2	0	1	3
%	0.00%	0.00%	66.70%	0.00%	33.30%	100.00%
<b>Renal failure</b>						
No. of patients	0	0	0	0	3	3
%	0.00%	0.00%	0.00%	0.00%	100.00%	100.00%
<b>Sepsis</b>						
No. of patients	0	0	2	0	1	3

ARDS, acute respiratory distress syndrome



**Fig. 3:** Depicting the various causes of maternal mortality in patients with liver disorder during pregnancy

commonly in primigravida patients. These results are comparable with the previous studies.<sup>12,13</sup>

Of the 120 patients in our study, pregnancy-specific liver disorders occurred more commonly in 97 patients (80.8%), of which most common liver disorder was HELLP syndrome, which is a part of hypertensive disorders of pregnancy (21.7%), followed by pre-eclampsia (19.2%). Results on similar grounds were observed in the study done by Tiwari et al.<sup>12</sup> This study also showed that hypertensive disorder of pregnancy constituted 66.35% of all liver disorders of pregnancy with HELLP occurring in 15.62% of patients. In a study by Jain et al.,<sup>14</sup> they studied 55 patients in which the incidence of HELLP was 27.2%, which is corresponding with our study.<sup>15</sup>

In our study of 120 patients of liver disorder, 97 (80.8%) patients presented in the third trimester with hypertensive disorder and hepatitis E being the most common causes, whereas HG usually presented in the first trimester. This presentation according to the trimester is comparable with previous studies by Tiwari et al.<sup>12</sup> and Jain et al.<sup>14</sup> The still born percentage in our study of 120 patients of liver disorder was 10.8%, which is nearly same with the study done by Ramola et al.<sup>16</sup> (146 patients, 10.3% patients delivered still born fetuses).

The maternal mortality in our study of 120 patients was 13.3% (16 patients died) and 86.7% (104 survived), which is comparable with other previous studies.<sup>12,14,15</sup> Of the 16 patients who died in our study, the only cause of maternal mortality was hepatitis E. Similarly, in the study by Jain et al.,<sup>14</sup> out of 55 patients, 50% of maternal mortality occurred because of hepatitis E infection and in the study by Ramola et al.,<sup>16</sup> hepatitis E was associated with 33.3% of maternal mortality in liver disorders, which further corroborates that hepatitis E is a leading cause of nonspecific liver disorders related maternal mortality.

The various fetal complications included in our study were prematurity (65%), still births (11.6%), early neonatal death (15%), NICU admission (45%), and intrauterine growth restriction (IUGR) (20.83%). Konareddy and Krithika<sup>17</sup> mention 25% incidence of perinatal mortality in their study while the same in our study was 26.6%, which is comparable. ICU admissions were present in 31 patients (25.83%) in our study; the most common causes were disseminated intravascular coagulation (DIC) (32.25%) and hepatic encephalopathy (32.25%) followed by acute renal failure (ARF) (9.67%) and ARDS (6.4%). These results are comparable with the study of Tiwari et al.<sup>12</sup> in which out of 192 patients, 26.56% required ICU admission, DIC developed in 24.48%, hepatic encephalopathy in 3.64%, and ARF in 15.58% of patients. So, the screening of hepatitis B is mandatory in pregnancy.<sup>18,19</sup>

## Limitations

The most important limitation of the study is the single-center nature. The same needs to be confirmed from other major centers as well to provide better significance to the results. The other limitation is the small sample size, which is inherent due to the incidence of liver disorders during pregnancy. However, the study provides important insights into the behavior of liver disorders in pregnancy and the expected maternal and fetal outcomes.

## CONCLUSION

Pregnancy-specific liver disorders were far more common in the study and HELLP syndrome accounted for maximum number of cases. The presence of liver disease during pregnancy predisposed the mothers to a higher rate of preterm deliveries and overall NICU admissions for the newborn. The presence of maternal hepatitis E was the single most important factor predisposing for fetal and maternal mortality.

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