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Original Research Article

Study of patients with liver dysfunction during pregnancy and their maternal and perinatal outcomes

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ABSTRACT

Background: Liver dysfunction in pregnancy can be associated with maternal and perinatal morbidity and mortality, therefore early recognition and timely management is of paramount importance to improve the outcome. The studies related to liver dysfunction in pregnancy and its outcome are sparse from this part of India and are retrospective in nature, so present study was planned.
Methods: A total of 80 pregnant patients with liver dysfunction were enrolled as per the inclusion criteria after taking informed consent. Patients were investigated depending on the symptoms and pregnancy related complications with an aim to know the probable cause of liver dysfunction. Maternal and perinatal outcomes were noted in these patients.
Results: Intrahepatic cholestasis of pregnancy was the most common cause of deranged liver function tests (71.3%) followed by HELLP syndrome (21.3%), viral hepatitis (6.3%) and AFLP (1.3%) respectively. The most common maternal complication seen was preterm labour (33.8%) followed by thrombocytopenia (11.3%), postpartum hemorrhage (7.5%), vaginal wall hematoma (7.5%) and coagulopathy (3.8%). 2 patients (2.5%) required ICU admission and both patients expired due to fulminant hepatic failure. The most common fetal complication was prematurity (33.8%). Intrauterine fetal demise occurred in 10% of the patients and there were 12.5% perinatal deaths observed in our study.
Conclusions: The commonest cause of liver dysfunction in our study was IHCP (71.3%) followed by HELLP syndrome (21.3%). In spite of multidisciplinary approach, liver dysfunction during pregnancy was associated with high maternal and perinatal morbidity and mortality.

Keywords: Pregnancy, Liver dysfunction, Intrahepatic cholestasis of pregnancy

INTRODUCTION

Liver dysfunction in pregnancy can be due to pregnancy related liver diseases or exacerbation of pre-existing liver disease or coincidental with pregnancy. Liver dysfunction in pregnancy can be severe enough to cause significant maternal and neonatal morbidity and mortality.[1] Pregnancy related liver disorders occur at a specific period of gestation, while non-pregnancy-related liver diseases can occur at any time.[1] Globally the incidence of abnormal liver function tests (LFTs) in pregnant women is 3-5 % similar to Indian studies which have also quoted the incidence of abnormal LFTs during pregnancy to be 6.7% in a study from Kerala and 3.3% in another Indian study.[2-4]

The timing of clinical manifestations and abnormal liver tests in pregnancy are taken into account before making a

diagnosis and planning treatment strategies. Decisions must be made considering the maternal and fetal implications in mind, and rapid diagnosis followed by immediate delivery will determine maternal and fetal outcome in pregnancy.[5]

A study done by Divyakala et al revealed that pregnancy related liver dysfunction was found to be the predominant cause and of these HELLP accounted for 64.86% of total cases of liver dysfunction during pregnancy.[6] Another study showed cholestasis of pregnancy (54.9%) was the commonest cause followed by HELLP (21.6%) and viral hepatitis respectively.[5] Same study revealed that hepatitis E infection was the commonest cause of viral hepatitis in pregnancy (11.8%) and Intrahepatic cholestasis of pregnancy(IHCP) was the commonest primary liver disorder in pregnant women.

Complications of liver dysfunction in pregnancy can be because of liver derangement per se or because of the combined effect of pregnancy related morbidities with liver derangement. Cholestasis of pregnancy was associated with preterm labour and premature rupture of membrane (27.4%), meconium stained liquor(15.7%), fetal distress (13.7%), and postpartum haemorrhage (2%) in one study.[3] Disseminated intra vascular coagulation (33.3%) was the most common complication in patients of liver dysfunction associated with HELLP syndrome and pre-eclampsia according to one study.[4] Hepatitis E and acute fatty liver of pregnancy are associated with significant maternal and perinatal morbidity and mortality.[2] Other fatal complications of liver dysfunction include acute renal failure, hepatic encephalopathy, DIC, complications of blood and blood products, ICU admission and maternal death.[2]

Hence this prospective study was an attempt to determine the clinical profile of patients with liver dysfunction, its causative factors and their effect on maternal and perinatal outcomes.

METHODS

This prospective observational study was conducted in the Department of Obstetrics and Gynaecology in collaboration with the Department of Biochemistry at Government Medical College and Hospital-32, Chandigarh after approval from the Institution Ethics Committee. Pregnant women with liver dysfunctions fulfilling the inclusion criteria were enrolled in the study. During the study period, clinical profile and maternal and perinatal outcomes were studied in the pregnant women with liver dysfunctions.

Inclusion criteria

Pregnant women with liver dysfunction at any period of gestation. Women willing to come for a follow up and likely to deliver at our institute.

Exclusion criteria

Women with liver disorder before pregnancy. Women with liver dysfunction reporting in the postpartum period.

A total of 80 patients as calculated by sample size estimation and as per the inclusion criteria were enrolled in the study after informed consent of the patient. A detailed antenatal, previous obstetric and medical history especially related to symptoms pertaining to liver dysfunction (jaundice, fever, loss of appetite, abdominal pain etc.), was taken in detail.

General physical examination and systemic examination including signs of liver dysfunction (icterus, hepatomegaly, abdominal tenderness, palmar erythema, spider angiomas etc.) was done. Patients were investigated and appropriate investigations (hemogram with platelet count, LFTs, viral markers, USG whole abdomen, coagulation profile etc.) were done depending on the symptoms, pregnancy related complications and associated co-morbidities with an aim to know the probable cause of liver dysfunction.

Investigations were repeated as and when required to know the progression or regression of disease. Patients were managed medically and obstetrically in the ward or in the out-patient department as per protocols of the diagnosis made but some patients required multi-disciplinary management. Patients were followed up till the time of discharge after delivery. Maternal and perinatal outcomes were noted as per the proforma in these patients.

Statistical analysis

Pregnant women with liver dysfunctions were recruited and their symptoms, clinical signs and biochemical evidence were described using proportions and percentages. Continuous data were given as mean±Standard deviation. Significance of association between two groups was tested by Chi square test. Normal tests of proportion and percentages were used to compare outcomes in women with IHCP, HELLP and hepatitis. Data analysis was done using IBM SPSS statistics (version 22.0).

RESULTS

The mean age of pregnant women with liver dysfunction was 25.55±3.36 years, minimum being 19 years and maximum being 35 years. Maximum number of patients i.e., 51.3% belonged to the lower middle class; 23.8% belonged to the upper middle class, 17.5% to the lower class and 7.5% belonged to the upper class according to modified kuppuswamy scale. 41% patients were obese, 34.6% were overweight and 24.4% had normal BMI. Mean BMI was 25.1±3.21 kg/m2. 52.5% women were primigravida and rest were multigravida. 47.5% patients were booked at our institute and the rest were unbooked or referred cases (Table 1).

Most common symptom in the study population was itching (65%) followed by fever (5%), yellowish discoloration of sclera (5%), vomiting (3.8%) and clay-coloured stools (5%).

Table 1: Demographic and baseline characteristics.

Demographic variables		Cases (n=80)	%	Mean
Age	15-20	5	6.3	25.55
	21-25	34	42.5	
	26-30	35	43.8	
	31-35	6	7.5	
Socioeconomic status	Class 1 (upper class)	6	7.5	
	Class 2 (upper middle class)	19	23.8	
	Class 3 (lower middle class)	41	51.3	
	Class 4 (upper lower class)	0	0	
	Class 5 (lower class)	14	17.5	
BMI	Underweight (<18.5 kg/m2)	0	0	25.1 kg/m2
	Normal (18.5-22.9 kg/m2)	20	25	
	Overweight (23-24.9 kg/m2)	28	35	
	Obese (>25 kg/m2)	32	40	
Parity	G1	42	52	
	G2	24	30	
	G3	7	8.8	
	> G3	7	8.8	
ANC care	Booked	38	47.5	
	Unbooked	42	52.5	

Table 2: Mean TSB, SGOT and SGPT.

TSB Range (mg/dl)	Cases (n=80)	%	Mean TSB range (mg/dl)
<1	51	63.8%	1.40 mg/dl
1 - 2	16	20.0%	
2 - 3	6	7.5%	
>3	7	8.8%	
Serum alkaline phosphatase			**Mean alkaline phosphatase**
Normal	63	78.8%	330.83 IU/L
Abnormal	17	21.3%	
SGOT range			**Mean SGOT range**
<100	7	8.8%	264.88 IU/L
100-300	56	70%	
300-500	8	10%	
>500	9	11.3%	
SGPT range			**Mean SGPT range**
<100	8	10%	350.23 IU/L
100-300	46	57.5%	
300-500	16	20%	
>500	10	12.5%	

Mean total serum bilirubin was 1.40mg/dl and mean serum alkaline phosphatase in the study population was 330.83 IU/L. Mean SGOT and SGPT values were 264.88 IU/L and 350.23 IU/L respectively (Table 2). Majority of women with deranged LFTs were due to pregnancy related liver dysfunction (93.8%) while 6.3% were non related to pregnancy (Table 3). Intrahepatic cholestasis of pregnancy was the most common cause of deranged liver function tests (71.3%) followed by HELLP syndrome (21.3%), viral hepatitis (6.3%) and AFLP (1.3%).

Table 3: Final Diagnosis in study population.

Final diagnosis	Cases (n=80)	%
Pregnancy related	75	93.8%
Pregnancy non-related	5	6.3%

Table 4: Distribution of causes of deranged LFTs.

Causes	Cases (n=80)	%
IHCP	57	71.3%
HELLP	17	21.3%
Hepatitis E	3	3.8%
Hepatitis A	2	2.5%
AFLP	1	1.3%

Hepatitis E and Hepatitis A were seen in 3.8% and 2.5% patients respectively (Table 4). 33.8% women had preterm delivery while 66.3% delivered at term. 43.8% of women in the study population went into spontaneous labour, 51.3% patients were induced and 5% patients underwent

elective LSCS. Out of total 80 patients recruited, 49 (61.3%) had normal vaginal delivery, 25 patients (31.3%) underwent emergency LSCS and 4 (5%) had elective LSCS. 2 patients (2.5%) had instrumental delivery.

Table 5: Maternal complications

Maternal complications	Cases (n=80)	%
Preterm labor	27	33.8%
PROM	9	11.3%
Thrombocytopenia	9	11.3%
Coagulopathy	3	3.8%
Abruption	0	0.0%
Abortion	1	1.3%
PPH	6	7.5%
ICU admission	2	2.5%
Maternal mortality	2	2.5%
Others (vaginal wall hematoma)	6	7.5%

Table 6: Fetal complications.

Fetal complications	Cases	% of total patient
Meconium	19	23.8%
Pre term	27	33.8%
IUFD	8	10.0%
Low APGAR	5	6.3%
FGR	5	6.3%
NICU Admission	3	3.8%
Perinatal death	10	12.5%
Neonatal Jaundice	13	16.3%
Sepsis	9	11.3%

The most common maternal complication seen was preterm labour (33.8%) and other complications were thrombocytopenia (11.3%), premature rupture of membrane (11.3%), postpartum hemorrhage (7.5), vaginal wall hematoma (7.5%) and coagulopathy (3.8%). 2 patients (2.5%) required ICU admission, one was seen in hepatitis E and the other was seen in AFLP and both of these patients expired due to fulminant hepatic failure (Table 5).

Out of total 80 deliveries, 72 babies were born alive and 8 had intrauterine foetal death.4 intrauterine deaths were seen in patients with IHCP, 2 with acute hepatitis,1 with HELLP syndrome and 1 with AFLP. Mean birth weight of neonates was 2.62 ± 0.53 kg. The most common fetal complication was prematurity (33.8%). Intrauterine fetal demise was observed in 10% patients and 23.8% had passage of meconium. 75 neonates were appropriate for their gestational age while 5 neonates had fetal growth restriction, 3.8% babies required NICU admission, 16.3% developed neonatal jaundice, 11.3% had neonatal sepsis, and 6.3% had low apgar score (Table 6). There were 12.5% perinatal deaths observed in our study. In our study, patients of IHCP who developed fetal distress had significantly higher mean SGOT and SGPT levels (155 IU/L and 169 IU/L respectively) as compared to patients of IHCP who did not develop fetal distress (p value -0.02 and 0.01). However, there was no statistically significant difference in the mean TSB, SGOT and SGPT levels between the patients who developed preterm labour, PROM, passage of meconium, IUFD and PPH versus the patients of IHCP who didn't develop these complications.

Table 7: Comparison of maternal complications.

Maternal complications	IHCP		HELLP		Hepatitis	
	Cases	% of IHCP cases	Cases	% of HELLP cases	Cases	% of Hepatitis cases
PPH	4	7	2	11.8	0	0.0
Maternal mortality	0	0	0	0.0	1	20.0
ICU admission	0	0	1	5.8	1	20.0
Others (vaginal wall hematoma)	3	5.3	3	17.6	1	20.0

Table 8: Comparison of fetal and neonatal complications.

Fetal complications	IHCP		HELLP		Hepatitis	
	Cases	% of IHCP cases	Cases	% of HELLP cases	Cases	% of Hepatitis cases
Pre term	19	33.3%	4	23.5%	4	80%
Meconium	12	21.1%	4	23.5%	2	40%
Fetal Distress	8	14.0%	4	23.5%	0	0%
IUFD	4	7.0%	1	5.9%	2	40%
Low APGAR	4	7.0%	0	0.0%	2	40%
FGR	4	7.0%	1	5.9%	0	0%
Neonatal Jaundice	9	15.8%	4	23.5%	0	0%
Sepsis	4	7.0%	5	29.4%	0	0%

Continued.

Fetal complications	IHCP		HELLP		Hepatitis	
	Cases	% of IHCP cases	Cases	% of HELLP cases	Cases	% of Hepatitis cases
NICU Admission	1	1.8%	1	5.9%	1	20%
Perinatal death	5	8.8%	2	11.8%	2	40%

Table 7, 8 depicts comparison of maternal, fetal and neonatal complications in patients of IHCP, HELLP syndrome and Hepatitis.

DISCUSSION

We studied clinical profile, maternal and perinatal outcomes in 80 pregnant patients of deranged LFTs as per the sample size and who were willing to participate in the study from February 2019 to august 2020. The mean age of patients in our study with deranged LFTs was 25.55 years and 52.5% women were primigravidas. A study done in Karnataka in 2014 also reported a similar mean age of 24.78 years in patients with liver disorder.6 Another study by Aparajita et al in 2015 also observed that 52.9% patients with deranged LFTs belonged to the age group of 21-25 years and majority were primigravidas (51%). 4 Itching was the most common symptom observed in patients of liver dysfunction in our study which was reported by 65% of patients. Other symptoms were fever (5%), yellowish discoloration of sclera (5%), clay coloured stool (5%) and vomiting (3.8%). Almost similar results were observed in the study by Aparajita et al in which 76.5% patients presented with pruritus as a chief complaint followed by jaundice (17.6%).[4]

In our study, pregnancy specific disorder was found to be the most common cause of abnormal LFTs (93.8%). Intra hepatic cholestasis of pregnancy was the commonest cause (71.3%) followed by HELLP syndrome (21.3%) which was comparable to the study by Aparajita et al which reported the incidence of IHCP (54.9%) and HELLP (21.6%) in their study.[6] Contrary to our study, study done by Sumangali et al observed that pre-eclampsia was the commonest cause of pregnancy specific liver dysfunction (65%) followed by HELLP syndrome (12%).[3]

In our study, of the total 80 patients with deranged LFTs, 51.3% patients required induction of labour, 61.3% had normal vaginal delivery and 31.3% women underwent emergency LSCS. The results were comparable with the similar study conducted by Umang et al with pregnant women with liver dysfunction showed that 41.2% had normal vaginal delivery and 35.3% patients underwent LSCS.[7] Another study in 2010 in women with intra hepatic cholestasis of pregnancy reported normal vaginal delivery and LSCS in 48.93% and 36.17% women respectively.[8] Thrombocytopenia was observed in 11.3% patients. 7.5% had post-partum haemorrhage and there were 2 maternal deaths (2.5%), one was due to hepatic encephalopathy with hepatitis E infection and another was seen in patient with AFLP. Three patients (3.8%) with liver dysfunction had developed coagulopathy. Contrary to our study, a study conducted in 2015 in pregnant women with liver disorders reported that the most common complication was DIC in 33.3% patients but their study cohort had more patients with HELLP syndrome.[4]

Liver dysfunctions in pregnancy may have a devastating effect not only on the mother but also on the fetus and neonate, in spite of good antenatal and perinatal care provided in tertiary care centres. In our study, 90% of babies delivered were live born, 33.8% were preterm, 10% had intrauterine demise (IUD) and 23.8% had passage of meconium. Out of total 8 IUDs, 4 were due to passage of meconium in patients with IHCP, 2 were seen in acute viral hepatitis, while remaining 2 stillborn were seen in patients with HELLP and AFLP respectively. 56.3% neonates had birth weight in the range of 2.5-3.5 kg and mean birthweight was 2.62 kg. A study done in north kerala by Sumangali et al in women with abnormal LFTs showed similar results of 92% live birth, 3% IUD and higher percentages of preterm (77%).[3] However, study conducted by Divyakala et al in pregnant women with jaundice revealed very high stillbirths rate (46.15%).[6] A retrospective study conducted in 2015 in pregnant women with liver disorders showed prematurity and meconium stained liquor in 27.4% and 15.7% respectively.[4]

In our study, patients of IHCP who developed fetal distress had significantly higher mean SGOT and SGPT levels (155 IU/L and 169 IU/L respectively) as compared to patients of IHCP who did not develop fetal distress (p value -0.02 and 0.01). However, there was no statistically significant difference in the mean TSB, SGOT and SGPT levels between the patients who developed preterm delivery, PROM, passage of meconium, IUFD and PPH versus the patients of IHCP who didn't develop these complications.

Women with IHCP, HELLP and hepatitis were compared for maternal and neonatal complications. The incidence of preterm delivery was much higher in hepatitis (80%) as compared to patients with IHCP (33.3%) and HELLP syndrome (23.5%). 21.1% patients with IHCP had a passage of meconium which was much less as compared to patients with HELLP syndrome (23.5%) and viral hepatitis (40%). 23.5% of patients with HELLP syndrome had fetal distress as compared to 14% patients with IHCP and none of the patients with hepatitis had fetal distress. Incidence of IUFD was much higher in viral hepatitis (40%) as compared to IHCP and HELLP (7% and 5.9% respectively). The incidence of PPH was much higher in patients with HELLP (11.8%) as compared to patients with IHCP and hepatitis (7% and 0.0%) respectively. With the

multidisciplinary approach taken to manage the severe cases of liver dysfunction in our patients, still there were 2 maternal deaths, one died due to complications of hepatitis and other died due to AFLP. Perinatal death was seen in 40% of patients with hepatitis which was comparatively much higher as compared with patients of IHCP (8.8%) and HELLP (11.8%). A prospective study conducted in 2007 in pregnant women with liver dysfunction revealed a much higher rate of maternal mortality in patients with HELLP syndrome (31%) and hepatitis E (27%) while no maternal death was seen in patients with IHCP. The same study reported significantly higher incidence of perinatal mortality in HELLP syndrome (54%) and hepatitis (40%) as compared to patients with IHCP (10%).[7] Another study conducted in 2017 in pregnant women with deranged liver profile revealed 13.02% and 29.17% maternal and perinatal mortality respectively.[9]

The shortcoming of our study was that no control group was taken to compare the maternal and perinatal outcomes and serum bile acids estimation to diagnose IHCP was not routinely available in our hospital, so could not be done in patients of IHCP. HELLP and hepatitis cases were very few in our study, so a conclusive comparison between the maternal and perinatal outcomes among the different causes of liver disorder couldn't be significantly made out. As the data regarding the liver dysfunction in pregnancy is sparse and this condition is associated with significant maternal and perinatal morbidity and mortality, more large-scale studies are required to formulate the guidelines on the management of liver dysfunction in pregnancy which will further help in reduction of adverse maternal and perinatal outcomes.

CONCLUSION

The commonest cause of liver dysfunction in pregnancy in our study was IHCP (71.3%) followed by HELLP syndrome (21.3%), hepatitis (6.3%) and AFLP (1.3%) respectively. Liver dysfunction was more common in primigravida and occurs more commonly in lower middle-class women. The most common maternal complication in our study was preterm labour (33.8%). Other maternal complications were thrombocytopenia (11.3%), PPH (7.5%), coagulopathy (3.8%), maternal death (2.5%) due to fulminant hepatic failure. Perinatal complications in our study were preterm delivery (33.8%), meconium passage (23.8%), intrauterine fetal demise (10%), and perinatal deaths (12.5%). Hence our study revealed that liver dysfunction during pregnancy was associated with high maternal and perinatal morbidity and mortality.

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