Original Article

Clinical spectrum and outcome of pregnancy with liver diseases – A prospective study

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Abstract

Objective: Liver diseases constitute a family of diseases in pregnancy which are less often studied individually. Spectrum of liver diseases directly or indirectly related to pregnancy comprise 3% of all pregnancies. The biggest challenge is to arrive at a diagnosis in such cases. With this study we aimed to study the prevalence of different Liver diseases in pregnancy in our population and its effect on fetomaternal outcome. **Material and Methods:** This was a prospective observational study carried out from March 2018 to March 2020. A total of 184 pregnant women with diagnosis of some form of liver disease as evident from their symptoms, signs or biochemical investigations were included in study cohort. **Result:** Primigravida accounted for majority of study cohort (44.02%). Approximately 90.21% belonged to 20-35 yrs. Age group. Intrahepatic cholestasis of pregnancy (IHCP) was the most common liver ailment (66.84%) followed by viral hepatitis (10.32%), Hyperemesis gravidarum (7.06%) and HELLP syndrome (6.52%). There was one case of Acute fatty liver of pregnancy (0.54%), four cases of Pre-eclampsia with liver dysfunction (2.17%), seven cases of Jaundice in pregnancy (3.80%) and 3 cases of pre-existing liver diseases (1.63%). 5 cases (2.71%) of antepartum eclampsia, 5 cases (2.71%) of postpartum eclampsia and 1 case (0.54%) of post-partum HELLP was seen. 33.33% patients were delivered early by induction or caesarean section because of liver dysfunction.14.67% required blood or blood products transfusion.1.63% had postpartum hemorrhage.1.08% mothers required intensive care admissions. Neonatal outcome was poor with 6.41% being growth restricted, 9.61% premature, 8.97% were intrauterine dead fetuses, 2.56% had early neonatal deaths and 7.05% needed neonatal intensive care unit admissions. **Conclusion:** Timely admission, quick diagnosis and appropriate management of patients with liver diseases in pregnancy can make a significant difference in mortality and morbidity rates due to liver ailments in pregnancy.

Keywords: AFLP, cholestasis, HELLP, hyperemesis, liver diseases

Introduction

Liver diseases constitute a family of diseases in pregnancy that are less often studied individually. They are a diverse group of ailments which usually have a common symptomatic profile but can be differentiated biochemically. The spectrum of liver diseases directly or indirectly related to pregnancy comprises 3% of all pregnancies.[1] The biggest challenge is to arrive at a diagnosis in such cases. The management for each disease may vary, making it more crucial for the life of mother and fetus. They are sometimes responsible for the mortality of either the mother or fetus in up to 25% of the cases.[1,2] The clinical and biochemical findings can be confused with normal physiological changes in pregnancy, like increase in alkaline phosphatase, dilutional hypoalbuminemia, increase in clotting

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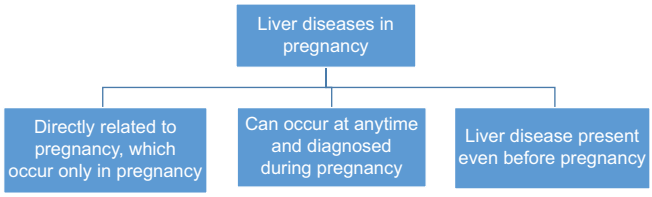

Figure 1: Categories of liver diseases in pregnancy

factors, and findings like spider naevi and palmar erythema due to hyperestrogenic state. However, the values of transaminases, gamma glutamyl transferences, total bilirubin, serum bile acids, and prothrombin time may be slightly lower or may remain within normal range. Any abnormality in these parameters may raise the suspicion of liver disease in pregnancy. With the constant evolution in the diagnosis and prognostication of pregnancy with liver diseases, there is utmost need to understand every detail of the etiopathogenesis with expression of pregnancy with liver diseases. To evaluate the safety and utility of preexisting and newer therapeutic modalities, research is still going on. It is, therefore, important for the general clinicians too to be familiar with this common disorder, so that prompt diagnosis and referral to specialized multidisciplinary team can be done for further management and better feto-maternal outcome.

To simplify the study of various diseases, liver diseases in pregnancy can be divided into three categories [Figure 1]. Those directly related to pregnancy are diseases which can occur only during pregnancy, and their time of occurrence is different for each. The diagnosis is also established based on in which trimester it is seen. They include hyperemesis gravidarum, acute fatty liver of pregnancy (AFLP), hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome, and intrahepatic cholestasis of pregnancy. Liver diseases which can occur at any time but were diagnosed during pregnancy or those which were preexisting include viral hepatitis (hepatitis A, B, C, D, E, herpes simplex virus, Epstein–Barr virus), autoimmune liver diseases, portal hypertension, nonalcoholic fatty liver disease, liver cirrhosis, and liver transplantation.[1]

Objectives of the study:

1. To study the frequency of different liver diseases in pregnancy in our population
2. To study the other comorbidities and complications associated with liver diseases in pregnancy
3. To study the outcome of pregnancy with liver disease.

Materials and Methods

This was a prospective observational study conducted over a period of 2 years from March 2018 to March 2020. All the pregnant women who got admitted in the obstetric ward of our institute with diagnosis of some form of liver disease as evident from their symptoms, signs, or biochemical investigations were included in the study. A written informed consent was taken from all patients after explaining to them the details and purpose of the study. Further workup of the patient was done by taking proper and detailed history of the patient, which included her period of gestation, last menstrual period, presenting complaints, previous menstrual history, obstetric history of previous pregnancies and current pregnancy, past medical or surgical history, and family history. Height (cm) and weight (kg) of the patient were noted, and body mass index (kg/m^2) was calculated. Detailed head to toe general physical examination, systemic examination, and per abdominal examination were done. Relevant blood investigations with blood grouping, complete blood count including hemoglobin (g/dl) and platelet count (per mm^3); liver function tests including total, direct bilirubin (mg/dl), alanine aminotransferase (ALT; IU/ml), aspartate aminotransferase (AST; IU/ml), and alkaline phosphatase (IU/ml); prothrombin time; hepatitis B surface antigen (HbsAg) antigen; anti-hepatitis C virus (anti-HCV) antibody; renal function tests; random blood sugar (mg/dl); urine routine and microscopy; and thyroid function tests were carried out. Ultrasound obstetrics to look for fetal well-being and ultrasound upper abdomen to look for any liver pathology were done. All the details were entered into a structured proforma.

After taking into consideration all the details and laboratory findings, liver disease in participants were divided into two categories as follows:

1. Those specific to pregnancy (hyperemesis gravidarum, HELLP syndrome, AFLP, intrahepatic cholestasis of pregnancy [IHCP])
2. Liver diseases not specific to pregnancy – included those that were diagnosed in pregnancy but could occur anytime (viral hepatitis, autoimmune liver diseases) and those which were preexisting in the patient (portal hypertension, liver cirrhosis, and liver transplantation).

A probable diagnosis was made with all possible differential diagnoses, and management was done accordingly. Our objective is to study the prevalence of different liver diseases in our population and to study the complications associated with it. An Excel spreadsheet was prepared using all the above data, and statistical analysis was done.

Results

In our study, a total of 184 patients with liver disease in pregnancy were included and divided into different categories. During the specified time period, there were 1810 deliveries. This resulted in prevalence of liver diseases as 10.16% in our hospital.

In our study, most of the patients were primigravida (44.02%) and most commonly belonged to the age group of 20–35 years (90.21%). We can also see in Table 1 that most patients presented to us in their third trimester of pregnancy. It was seen that these patients had many risk factors associated with pregnancy other than liver diseases, like bad obstetric history, anemia, pancytopenia, gestational diabetes mellitus, thyroid disorders, oligohydramnios and polyhydramnios, antepartum

Table 1: Demographic characteristic of mothers in pregnancy

	No. of cases (*n*=184)	Percentage
Parity		
G1	81	44.02
G2	45	24.45
G3	36	19.56
G4 or more	22	11.95
Age group		
≤20 years	9	4.89
21-35 years	166	90.21
>35 years	9	4.89
Trimester of presentation		
First trimester	10	5.43
Second trimester	14	7.60
Third trimester	160	86.95
Risk factors of pregnancy		
Bad obstetric history	6	3.26
Anemia	11	5.97
Pancytopenia	2	1.08
Gestational diabetes mellitus	5	2.71
Hypothyroidism	17	9.23
Hyperthyroidism	2	1.08
Oligohydramnios	11	5.97
Polyhydramnios	3	1.63
Antepartum hemorrhage	7	3.80
Fever	3	1.63
Rh-negative pregnancy	9	4.89
Past medical illness		
Diabetes mellitus	4	2.17
Hypothyroidism	7	3.80
Tuberculosis	3	1.63
Heart disease	2	1.08
Gastrointestinal disorders	4	2.17

Table 2: Frequency of liver diseases in pregnancy

	Number	Percentage
Pregnancy-specific diseases	153	83.15
Liver diseases not specific to pregnancy	31	16.84

hemorrhage, fever, and Rh-negative pregnancy. Out of all these, hypothyroidism (9.23%) was the most associated factor.

As per Table 2, in our study, patients with liver diseases (83.15%) specific to pregnancy were more common compared to patients with preexisting liver diseases (16.84%).

Table 3 shows the frequency of various types of liver diseases in pregnancy. IHCP was the most common liver ailment (66.84%), followed by viral hepatitis (10.32%), hyperemesis gravidarum (7.06%), and HELLP syndrome (6.52%). We had one case of AFLP (0.54%), four cases of preeclampsia with liver dysfunction (2.17%), seven cases of jaundice in pregnancy (3.80%), and three cases of preexisting liver diseases (1.63%). The mean age of presentation was almost similar in all the patients (around 27 years). Patients with hyperemesis gravidarum presented mostly in their first and early second trimesters, whereas all others presented in the late second and third trimesters of pregnancy. The values of AST and ALT were the highest in patients with IHCP and hyperemesis gravidarum. Among the patients who presented with jaundice, total bilirubin was as high as 6.2 mg/dl and direct bilirubin was 4.6 mg/dl.

From Table 4, we can infer that pregnancy was terminated before 34 weeks in about 14.10% of patients, between 34 and 37 weeks in 19.23%, and after 37 weeks in 66.66% of patients. Twenty-eight women out of 184 did not deliver in our hospital; hence, their maternal and fetal outcome could not be included. Early termination was done owing to presence of complications in mother or fetus. In two patients, induced vaginal delivery was done at 24–25 weeks in view of maternal morbidity and antepartum eclampsia. In one patient, emergency cesarean hysterectomy was done in view of (i.v.o) placenta percreta with active bleeding per vaginum.

It was found that 47.43% of babies were males and 52.56% were females. Most babies weighed 2.6–4 kg (55.76%) at birth. Low birth weight (<2.5 kg) was seen in 43.48% babies. There were 15 cases of prematurity (9.61%), 14 cases of intrauterine death (8.97%), 11 cases needed neonatal intensive care unit (NICU) admission after birth (7.05%), 10 cases of intrauterine growth restriction (IUGR; 6.41%), and four cases of early neonatal death (2.56%) [Table 5].

From Table 6, it is evident that 27 patients needed either blood or blood products in the peripartum period (14.67%). Among all, 9.78% patients had severe preeclampsia, five patients had antepartum eclampsia (2.71%), and five patients had postpartum eclampsia (2.71%). Three patients had postpartum hemorrhage (1.63%), and two patients needed intensive care unit (ICU) admission (1.08%). In our study, there was no case of maternal mortality, which can be attributed to the availability of immediate and good ICU care.

Discussion

The frequency of liver diseases in pregnancy is a topic which is to be explored more as there is a high rate of maternal or fetal mortality directly or indirectly due to associated comorbidities, which may be a cause or the result of liver dysfunction.

In our study, the prevalence of liver disease was 10.1%. This is similar to a study by García-Romero *et al.*[3] in which it was 11%. But in studies by Kohli *et al.*[4] and Tiwari *et al.*,[5] liver diseases were present in 2%–3% of all pregnancies. In our study, pregnancy-specific liver diseases were more common than preexisting liver diseases. This is similar to the reports of Tiwari e*t al.*[5] (85.98%), Mishra *et al.*[6] (83.25%), and Rathi *et al.*[7] (52.3%), whereas in a study by Solanke *et al.*,[8] pregnancy-specific causes accounted for only 39% pregnancies and nonspecific causes of liver diseases were more common.

Table 3: Frequency and findings of different categories of liver diseases in pregnancy

	Frequency	Mean age (years)	Min. AST/ALT (IU/ml)	Max. AST/ALT (IU/ml)
Hyperemesis gravidarum	13 (7.06%)	27.15±3.53	19/21	483/512
Acute fatty liver of pregnancy	1 (0.54%)	33	355	237
HELLP syndrome	12 (6.52%)	25.58±2.46	62/58	301/356
Mild	3 (1.63%)			
Moderate	5 (2.71%)			
Severe	4 (2.17%)			
Intrahepatic cholestasis of pregnancy	123 (66.84%)	26.56±4.58	23/23	538/459
Preeclampsia with liver dysfunction	4 (2.17%)	26.75±6.39	93/40	260/264
Jaundice	7 (3.80%)	25.71±3.77	11/22	93/127
Viral hepatitis	19 (10.32%)	27.68±5.62	14/12	422/239
HCV	14 (7.6%)			
HbsAg	5 (2.71%)			
Preexisting liver disease	3 (1.63%)	25.5±5.19	10/20	56/34
Portal hypertension	2 (1.08%)			
Chronic liver disease	1 (0.54%			
Other causes of deranged LFT	2 (1.08%)	28	54/49	88/139
	184 (100%)			

ALT=alanine aminotransferase, AST=aspartate aminotransferase, HbsAg=hepatitis B surface antigen, HCV=hepatitis C virus, HELLP=hemolysis, elevated liver enzymes, low platelet count, LFT=liver function test

Table 4: Mode of delivery in various liver diseases in pregnancy

	<34 weeks	34-37 weeks	>37 weeks	Total
Vaginal delivery	11 (7.05%)	16 (10.25%)	55 (35.25%)	82 (52.56%)
Cesarean section	11 (7.05%)	14 (8.97%)	49 (31.41%)	74 (47.43%)
Total	22 (14.10%)	30 (19.23%)	104 (66.66%)	156 (100%)

Table 5: Fetal outcomes and complications in pregnancy with liver dysfunction (*n*=156)

	Number	Percentage
Male	74	47.43
Female	82	52.56
Birth weight		
<1.5 kg	19	12.17
1.5-2.5 kg	49	31.41
2.6-4 kg	87	55.76
>4 kg	1	0.64
IUGR	10	6.41
Prematurity	15	9.61
IUD	14	8.97
Early neonatal death	4	2.56
Need for NICU admission	11	7.05

IUD=intrauterine demise, IUGR=intrauterine growth restriction, NICU=neonatal intensive care unit

Among pregnancy-specific causes in our study, IHCP (66.84%) was more common, followed by viral hepatitis (10.32%). This is similar to the report of Kohli *et al.*[4] in which IHCP (35.62%) was more common. In the studies of Dang *et al.*,[9] García-Romero *et al.*,[3] Tiwari *et al.*[5] (66.35%), and Mishra *et al.*[6] (81.25%), preeclampsia and associated causes were more common. While in the study by Solanke *et al.*,[8] viral hepatitis was the most common liver disease in pregnancy. In almost all the studies, liver diseases presented in the third trimester of pregnancy and were mostly seen in primigravida. The most common age group of occurrence in all studies is 21–30 years, similar to our study. In our study, transaminases were the highest in IHCP and hyperemesis gravidarum, whereas in the study of Mishra *et al.*,[6] transaminases were the highest in infective hepatitis group. In our study, 52.56% of patients had vaginal delivery and 47.43% of patients had cesarean deliveries. This is similar to that reported in Dang *et al.*[9] (48.93% vaginal deliveries) and Kohli *et al.*[4] (53.42% vaginal deliveries). In our study, preterm termination of pregnancy was done in 33.33% of patients. This is in accordance with the study result of Kohli *et al.*,[4] in which 33.56% of patients had preterm vaginal delivery (7.53%) or preterm lower segment cesarean section (LSCS; 26.03%). In a study by Dang *et al.*,[9] preterm termination of pregnancy was conducted in 19.14% of cases.

If we see the fetal outcomes, in our study, adverse outcomes like prematurity were seen in 9.61% of cases, IUGR in 6.01%, and NICU admission was required in 7.05% of cases. Perinatal mortality with intrauterine fetal death was seen in 14 cases (8.97%), and early neonatal death was seen in four cases (2.56%). Low birth weight, that is, less than 2.5 kg, was seen in 43.58% of cases. In the study by Kohli *et al.*,[4] intrauterine death was found in 1.37% of patients and induced expulsion was done in 4.11% of patients. IUGR was seen in 39.29% of patients, and NICU admission was required in 19.29% of patients. Birth weight was <2.5 kg in 39.2% of babies. In the study by Tiwari *et al.*,[5] fetal complications like prematurity were seen in 32.29% of babies, perinatal mortality was seen in 29.17%, and NICU admission was needed in 24.47% of babies. In the study by Mishra *et al.*,[6] intrauterine death was seen in 41.25% of women.

We can see in our study that severe preeclampsia (9.78%) which leads to HELLP syndrome (6.62%); antepartum eclampsia (2.71%), and postpartum eclampsia (2.71%) are the major

Table 6: Maternal complications in pregnancy with liver diseases (*n*=184)

	Number	Percentage
Severe preeclampsia	18	9.78
Antepartum eclampsia	5	2.71
Need for blood or blood products transfusion	27	14.67
Postpartum hemorrhage	3	1.63
Postpartum eclampsia	5	2.71
Postpartum HELLP	1	0.54
DIC	1	0.54
Need for ICU admission	2	1.08
Renal failure	1	0.54
Mortality	0	0

DIC=disseminated intravascular coagulation, HELLP=hemolysis, elevated liver enzymes, low platelet count, ICU=intensive care unit

causes of maternal morbidity. Also, 1.08% patients needed ICU admission and 0.54% patients were complicated by disseminated intravascular coagulation (DIC) and acute renal failure. No case of maternal mortality has been reported in our study. In the studies by Kohli *et al.*[4] and Tiwari *et al.*,[5] ICU admission was needed in 10.2% and 26.56% of patients, respectively, which is much more than that found in our study. In our study, blood or blood component transfusion like Fresh Frozen plasma (FFP) and platelet cryoprecipitate was required in 14.67% of patients, as opposed to 43.75% of patients in the study by Tiwari *et al.*[5] and 20.55% of patients in the study by Kohli *et al.*[4] In our study, postpartum hemorrhage was seen in 1.63% of patients, whereas in the studies by Kohli *et al.*,[4] Tiwari *et al.*,[5] and Dang *et al.*,[9] it was 27.4%, 30.4%, and 29.78%, respectively. Maternal mortality was seen in 13.02% of patients in the study by Tiwari *et al.*,[5] 5% of patients in the study by Mishra *et al*,[6] and 1.37% of patients in the study by Kohli *et al.*[4]

We had no cases of drug-induced liver disease in our cohort. This is seen in nearly 3% of pregnant women and is mostly underreported, with common offenders being antibiotics and antihypertensive agents. Treatment is to identify the causative drug and stop its usage with close monitoring of liver function.[10] Nonalcoholic fatty liver disease is another entity seen in association with gestational hypertension and diabetes, with rates as high as 28.9/100,000.[11]

A major limitation of the study was the absence of a control group. But the strength was that we had a large sample size of women with liver diseases.

Conclusion

We can conclude from the study that timely admission, quick diagnosis, and appropriate management of patients with liver diseases in pregnancy can make a significant difference in the mortality and morbidity rates due to liver ailments in pregnancy. For this, a multidisciplinary approach may be needed with contributions from the gastroenterologists for proper management of the patient. Liver function tests should be advised in a patient with even mild symptoms like itching and vomiting. Blood pressure records should be properly maintained, as it can turn worse at any time during pregnancy. The patients diagnosed with liver dysfunction in early trimesters or those with preexisting liver diseases should be advised regular follow-up and started on medical management as early as possible to prevent complications later in pregnancy.

Abbreviations

- HELLP: hemolysis, elevated liver enzymes, low platelet count
- AFLP: acute fatty liver of pregnancy
- IUD: intrauterine demise
- IHCP: intrahepatic cholestasis of pregnancy
- LFT: liver function test
- LSCS: lower segment cesarean section
- AST: aspartate aminotransferase
- ALT: alanine aminotransferase
- DIC: disseminated intravascular coagulation
- HCV: hepatitis C virus
- HbsAg: hepatitis B surface antigen
- ICU: intensive care unit
- IUGR: intrauterine growth restriction
- NICU: neonatal intensive care unit.

Key points

- Liver disease in pregnancy may be either pregnancy specific, a *de* novo presentation in pregnancy, or a preexisting liver condition.
- Pregnancy-specific physiological changes should be kept in mind while diagnosing liver diseases.
- AFLP and HELLP are obstetric and medical emergencies needing supportive measures with pregnancy termination.

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Conflicts of interest

There are no conflicts of interest.

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