e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2022; 14(7); 826-834

Original Research Article

Maternal and Fetal Outcome in Pregnancies Complicated by Liver Disease - A Prospective Study

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Received: 15-04-2022 / Revised: 20-05-2022 / Accepted: 05-06-2022
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Conflict of interest: Nil

Abstract

Background: Liver disease in pregnancy is rare. Pregnancy related liver diseases can be a serious threat to maternal and fetal wellbeing. In normal pregnancy many physiological and hormonal changes occur within the human body, some of which can mimic those seen in women with liver disease. The spectrum of disease and presentation varies hugely leading to delays in diagnosis and appropriate management. Hence once women with liver disease become pregnant, it is essential that they have rapid referral to specialised physicians with experience of managing hepatic disorders in pregnancy.

Aim: The aim of the study was to evaluate the maternal and fetal outcomes in pregnancy complicated by liver disease.

Methods: This was a prospective observational study conducted in the department of Obstetrics and Gynaecology, Gandhi Medical College, Bhopal, a tertiary care centre in central India. The study was conducted in 320 women admitted in the hospital with diagnosis of liver disease in pregnancy over a period of 12 months, starting from February 2020 to January 2021.

Results: The incidence of liver disease in pregnancy was found to be 2.7%. Majority of the patients belonged to the age group of 18 to 25 years (48.41%) and most of them belonged to rural areas (72.5%). 51.6% among them were primigravida. Hypertensive disorders of pregnancy were the most common cause of liver disease in pregnancy (59.4%) closely followed by viral hepatitis (52.5%). 31.3% required transfusion of blood products. Majority of the patients had vaginal delivery (75.6 %).15.9% of the total deliveries had postpartum hemorrhage (PPH); 2.5% of patients had traumatic PPH and 13.4% patients had atonic PPH. Ninety patients (28.1%) required intensive care support. Maternal mortality rate was 17.8%. 14.1 % patients died within six weeks of delivery. Perinatal mortality rate was 32.5%. 19.4% had low APGAR score at birth, 23.7% were stillborn and there were 8.8 % neonatal deaths. Hypertensive disorders of pregnancy were the cause of highest mortality among patients (73.7%) followed by viral hepatitis (59.6%).

Conclusion: Liver disease in pregnancy can pose a serious threat to maternal and fetal outcome and requires intervention by the hepatologist and obstetrician early during the disease process which can dramatically improve the maternal and neonatal prognosis.

Keywords: Liver Disease, Primigravida, Transfusion, Postpartum Haemorrhage.

Background

Incidence of liver dysfunction in pregnancy is up to 3% [1]. Liver disease is a serious complication of pregnancy and poses a challenge for the obstetrician and hepatologist. Due to the physiological changes in pregnancy, is difficult to timely diagnose and manage liver diseases in pregnancy. Liver diseases in pregnancy can be classified as [2].

1. Pregnancy related liver disease:

    1. Hyperemesis gravidarum
    2. Intrahepatic cholestasis of pregnancy
    3. Hypertension related liver diseases like preeclampsia, eclampsia, HELLP syndrome, liver infarction or liver rupture
    4. Acute fatty liver of pregnancy

2. Non pregnancy related liver diseases

a. Pre-existing liver diseases

    1. Viral diseases
    2. Cirrhosis & portal hypertension
    3. Post liver transplant
    4. Autoimmune liver disease

b. Coincidentally with pregnancy

    1. Autoimmune liver diseases
    2. Viral liver diseases
    3. Vascular (Budd Chiari Syndrome)
    4. Drug induced hepatotoxicity

The main factors that determine maternal prognosis depends on the type of liver disease, the degree of impaired synthetic, metabolic and excretory liver function and timing of delivery [3-5]. The disorders are complex, and patients benefit from multi-disciplinary input by experienced physicians in specialized centres. As there is a considerable overlap in the clinical and laboratory characteristics among the subsets of liver diseases in pregnancy and also the morbidity due to this is high, there is a need to identify factors associated with poor outcome. This will enable the treating physician to identify those who survive with supportive measures and those who require advanced care and transfer or referral to higher centres. Among women with pregnancy related liver disease, mortality rates of zero to 25% have been reported [6,7]. Maternal and fetal prognosis is improving because of ongoing research, improved guidelines and our better understanding of pre-conception risk stratification, disease mechanisms and therapeutic options. Evolving data has been beneficial in expanding insights into the impact of liver disease on maternal and fetal health.

Material & methods

This was a single-centre study, conducted in the Department of Obstetrics and Gynaecology, Gandhi Medical College, Bhopal, a tertiary care centre in central India. The study was conducted in women admitted in the hospital with diagnosis of liver disease in pregnancy over a period of 12 months, starting from February 2020 to January 2021.

Inclusion criteria

1. All pregnant females admitted in Sultania Zanana Hospital with diagnosis of Liver disease in pregnancy.
2. Patients in third trimester of pregnancy.
3. Patients giving consent for the study.

Exclusion criteria

1. Patients managed on outpatient department basis were excluded.
2. Patients in first and second trimester of pregnancy.
3. Patients not giving consent.

There was a total of 320 patients fulfilling the inclusion and exclusion criteria. After getting clearance from ethical committee

all pregnant patients presenting with liver disease and satisfying the inclusion and exclusion criteria were enrolled in the study. The diagnosis of liver disease in pregnancy was based on standard criteria. Informed consent was taken from the patients and patients were reassured regarding the expertise and confidentiality. Detailed history taking and clinical examination of the patients was done on admission. Patients were managed as per the departmental protocols for the management of different conditions in pregnancy. Ultrasonography was done and blood and urine samples of the patients were collected and send for laboratory investigations. Details of the mode of delivery were recorded. Maternal outcomes were recorded in terms of ICU admission, requirement of blood transfusion, whether or not the patient landed up in postpartum hemorrhage and mortality. Neonatal outcomes were also recorded in terms of jaundice, low APGAR score at birth, intrauterine fetal demise, stillborn and neonatal death. Postnatal visits were explained to the patient as per the guidelines followed for different liver diseases in pregnancy. Patients were telephonically contacted on monthly basis till 3 months post-delivery to ensure patients and infant's wellbeing.

Observation chart

Table1: Age wise distribution of study participants

Age wise distribution		Count	Percentage (%)
Age Groups	18-25 Years	155	48.4%
	26-30 Years	84	26.3%
	31-35 Years	45	14.1%
	≥ 36 Years	36	11.3%

Table 2: Distribution of study participants according to residence

Distribution of Residence		Count	Percentage (%)
Residence	Urban	88	27.5%
	Rural	232	72.5%

Table 3: Distribution of study participants according to parity

Distribution of Parity		Count	Percentage (%)
Parity	Primigravida	165	51.6%
	Multigravida	151	47.2%
	Grandmulti-gravida	4	1.2%

Table 4: Distribution of study participants according to etiology of liver diseases

		Count	Percentage (%)
Hypertensive Disorder	Present	190	59.4%
	Absent	130	40.6%
Viral Hepatitis	HbsAg Reactive	167	52.2%
	HCV Reactive	1	0.3%
	No	152	47.5%
Intrahepatic Cholestasis of Pregnancy	Present Hepatitis	3	0.9%
	Absent	317	99.1%
Acute fatty liver of pregnancy	Present	1	0.3%
	Absent	319	99.7%

Table 5: Distribution of study participants according to blood transfusion

		Count	Percentage (%)
Packed Red Blood Cell	Yes	59	18.4%
	No	261	81.6%
Fresh Frozen Plasma	Yes	58	18.1%
	No	262	81.9%
Platelets	Yes	33	10.3%
	No	287	89.7%
Blood or Blood Product Transfusion	Yes	100	31.3%
	No	220	68.8%

Table 6: Distribution of study participants according to mode of delivery

		Count	Percentage (%)
Mode of Delivery	Normal Vaginal Delivery	242	75.6%
	LSCS	78	24.4%

Table 7: Distribution of study participants according to postpartum haemorrhage

		Count	Percentage (%)
Postpartum haemorrhage	Postpartum haemorrhage	51	15.9%
	No Postpartum haemorrhage	269	84.1%
Postpartum haemorrhage type	Traumatic	8	2.5%
	Atonic	43	13.4%
	No Postpartum haemorrhage	269	84.1%

Table 8: Distribution of study participants according to ICU admission

		Count	Percentage (%)
ICU admission	Yes	90	28.1%
	No	230	71.9%

Table 9: Distribution of study participants Maternal Outcome

		Count	Percentage (%)
Maternal Outcome	Alive	263	82.2%
	Mortality	57	17.8%
Maternal Mortality	Within first 3 months	12	3.8%
	Within first 6 weeks	45	14.1%
	Alive	263	82.2%

Table 10: Distribution of study participants Neonatal Outcome

		Count	Percentage (%)
Neonatal Outcome	Alive and Healthy	154	48.10%
	Low APGAR	62	19.40%
	Stillborn	76	23.70%
	Neonatal death	28	8.80%
Neonatal Jaundice	Yes	148	46.30%
	No	172	53.80%

Table 11: Association between maternal diseases and outcomes

Maternal Disease		Maternal Outcome				χ2 Value	p Value
		Alive		Mortality			
Hypertensive Disorder	Present	148	56.3%	42	73.7%	5.887	.015*
	Absent	115	43.7%	15	26.3%		
Acute fatty liver of pregnancy	Present	0	0.0%	1	1.8%	4.628	.031*
	Absent	263	100.0%	56	98.2%		
Viral Hepatitis	HbsAg Reactive	133	50.6%	34	59.6%	1.703	0.427
	HCV Reactive	1	.4%	0	0.0%		
	No Hepatitis	129	49.0%	23	40.4%		
Cholestasis of liver	Present	3	1.1%	0	0.0%	0.656	0.418
	Absent	260	98.9%	57	100.0%		

Results

Total 320 patients were enrolled in the study. Majority of the study participants (48.4%) belonged to age group of 18-25 years followed by 26.3% of study participants who belonged to the age of 26-30 years.14.1% and 11.3% of study participants belonged to age group of 31-45 years and ≥ 36 years respectively. It was found that 72.5% of the participants were from rural community and 27.5% of participants belonged to the urban community. It was found that 51.6% of the participants were primigravida, 47.2% were multigravida and grand multigravida were 1.2%

Patients with hypertensive disorder (including HELLP Syndrome) were 59.4%, 52.5% of participants were found to have viral hepatitis. Intrahepatic cholestasis of pregnancy was found in 0.9% of the patients, acute fatty liver of pregnancy was found in 0.3% of the participants.31.3% of the patients needed blood or other blood component transfusion. Out of these patients, 18.4% of patients were transfused packed red blood cell. 18.1% of participants were transfused fresh frozen plasma, 10.3% of participants were transfused platelet concentrate.

75.6% of the participants had normal vaginal delivery and 24.4% of the patients underwent LSCS. Total 15.9 % of patients had postpartum haemorrhage. Out of these 13.4% of the patients had atonic postpartum haemorrhage and 2.5% had traumatic postpartum haemorrhage. 28.1% of patients were admitted to ICU. Of all patients, 17.8% had mortality. Out of all the mortalities, 12 occurred within first 3 months and 45 occurred within 6 weeks of delivery. Rest 82.2% of the participants were discharged. Among all neonates, 48.1% of them were alive and had APGAR score ≥ 7/10.19.4% of had low APGAR score <6/10. There were 23.70%, 8.8%, stillborn and neonatal deaths respectively. 48.1% of neonates had neonatal jaundice.

Highest mortality was seen in patients with hypertensive disorders of pregnancy (HELLP syndrome) (73.7%) followed by viral hepatitis (59.6%). Statistically significant association was found between acute fatty liver of pregnancy and maternal mortality.

Statistical analysis

The collected data was entered in Microsoft office excel 2016 for windows keeping research question, proposed hypothesis, aims and objectives of study in mind. Descriptive Analysis and Analytical Analysis was done. SPSS version 20.0

software was used to analyse the collected data. p value of <0.05 was considered to be statistically significant.

Discussion

Clinical care in pregnant women with liver disease can be challenging. There are physiological changes in pregnancy that modify liver function, diagnosis and critical follow up. For this reason, this study was conceptualized, designed and carried out in the Department of Obstetrics and Gynaecology, Gandhi Medical College, Sultania Zanana Hospital, Bhopal.

Data was collected from 320 patients who fulfilled the inclusion criteria after attaining the written consent. The study included all antenatal women with liver disease presenting in third trimester in our institute during the study period. Incidence of liver disease in pregnancy was found to be 2.7%. The mean age of participants (in years) was 27 ± 6 with the incidence of liver diseases in pregnancy decreasing steadily with the increasing age of the participants. The age of maximum incidence was earlier in our study with majority of the patients 155(48.4%) belonging to the age group of 18-25 years followed by 26-30 years which included 84 patients (26.3%) followed by 31-35 years which included 45 patients (14.1%). There were 36 patients (11.3%) in age group of more than 36 yrs.

Prospective study by HY Wong *et al* (2004) found that the mean age of incidence was 31 yrs [8]. Swati Sharma *et al* (2016) also reported that most of the pregnant females with deranged liver profile belonged to the age group of 25-29 years (68.69%) [9]. Aparajita *et al* (2015) recorded the peak age of incidence of liver diseases between 21-25 years [10].

Here in this study, majority of the patients 232 (72.5%) belonged to rural areas and 88 (27.5%) belonged to urban areas which was consistent with the finding of the study conducted by Amrita *et al* (2016) where 66.82% belonged to rural areas and 33.18% belonged to urban areas [11]. Prospective study by Swati *et al* (2016) reported majority of the patients were from urban areas that had better awareness of the possible complications during pregnancy, leading to less maternal mortality [9].

The current study showed that the incidence of liver disease was highest in primigravida accounting for a total of 51.6 % (165 cases). Multigravida accounted for 47.2% (151 cases) of the total and grand multigravida contributed to 1.2% (4 cases). This showed good agreement with the study conducted by Swati *et al* (2016) where primigravida constituted 66% of the total cases gravida-2 constituted 26.7 % and gravida 3 contributed 6.7 % of the total cases [9]. Amrita *et al* (2016) also recorded that 53.73% of the patients were primigravida and 46.26% of the patients were multigravida [11]. Aparajita *et al* (2015) reported the majority of the patients with liver disease in pregnancy were primigravida (51%) [10]. On the contrary, HY Wong *et al* (2004) reported that 46% of the patients were primigravida [8].

Hypertensive disorders of pregnancy were the most common cause of liver disease in pregnancy accounting to 190 cases (59.4%) followed by viral hepatitis in which there were 168 cases accounting to 52.2 % of the total cases. There was a single case of acute fatty liver of pregnancy (0.3%) and 3 cases of intrahepatic cholestasis of pregnancy (0.9%). Among hypertensive disorders of pregnancy, HELLP syndrome was the most common complication accounting for 18.4 percent (152 cases). Hepatitis B was the most common cause of viral hepatitis in pregnancy accounting for 167 (52.2%) cases in our study.

Amrita *et al* (2016) reported that hypertensive disorders of pregnancy were the most common abnormality (66.35%). Hepatitis B was the most common cause of infective hepatitis in pregnancy [11].

whereas in the prospective study done by Swati *et al* (2016) viral hepatitis was the most common cause of liver disease in pregnancy and was found in 46.7 % of cases among which hepatitis B was the most common cause of acute hepatitis (26.7%). 33.33% cases of pre-eclampsia were reported and 6.7% cases of intrahepatic cholestasis of pregnancy (ICP) were found [9]. Another study conducted by Umang *et al* (2007) reported the pregnancy induced hypertension related disorders were the commonest cause of liver dysfunction in third trimester followed by viral hepatitis in which Hepatitis E was the most common (11%) [12]. On the contrary in the study conducted by Aparajita *et al* (2015) cholestasis jaundice was found to be the most common of liver dysfunction in pregnancy [10].

In the current study, 100 patients (31.3%) required blood or other blood component transfusion out of which 59 patients (18.4 %) were transfused PRBC, 58 patients (18.1 %) were transfused fresh frozen plasma and 33 patients (10.3%) were transfused platelet concentrate. All patients who went into postpartum hemorrhage were managed with blood transfusion. Platelet concentrates were mainly transfused in patients with HELLP syndrome. In the study by Swati *et al* (2016) 60% of the patients received blood and blood component therapy [9]. Amrita *et al* (2016) reported that 43.75% patients required blood transfusion [11]. This was in contrast to another prospective study done by Aparajita *et al* (2015) blood transfusion was done in only 12% patients [10].

In the present study, out of 320 cases maximum cases (242) delivered vaginally constituting 75.6 % of all the cases and 78 cases (24.4 %) had LSCS. In the prospective study by Umang *et al* (2007) 67% of the patients had normal vaginal delivery 28% of the patients underwent LSCS and 5% of the patients died before delivery [12]. Swati *et al* (2016) recorded 100% normal vaginal delivery [9]. Aparajita *et al* (2015) recorded 64.7 percent of vaginal deliveries and 35.3 % of LSCS [10]. In the present study, 51(15.9%) of the total deliveries were complicated by postpartum hemorrhage. Eight (2.5%) patients had traumatic postpartum hemorrhage and 13.4% of the patients (243) landed up in atonic postpartum haemorrhage. All the patients who landed up in postpartum hemorrhage for managed by blood transfusion.

In the study conducted by Swati *et al* (2016) 60% of the patients went into postpartum hemorrhage [9]. Amrita *et al* (2016) reported that 30.7% patients went into postpartum hemorrhage [11]. In contrast to this Aparajita *et al* (2015) recorded that only 2% patients went into postpartum hemorrhage [10]. There were 90 ICU admissions which accounts for 28.1 % of the total patients. Intensive care monitoring was needed in patients with eclampsia preeclampsia and acute fatty liver of pregnancy (AFLP) who ultimately developed serious complications like pulmonary Edema. Amrita *et al* (2016) reported 27% ICU admissions [11]. In the study conducted by Swati *et al* (2016) in Bhopal, all patients were kept in ICU for intensive monitoring [9]. In contrast to this Aparajita *et al* (2015) reported only 3.9 % ICU admissions [10].

Around 17.8% (57) maternal deaths were recorded in which 45 patients (14.1%) died within 6 weeks of delivery and 12 patients (3.8%) died within 3 months of delivery. Rest 82.2 % of the patients were discharged. Amrita *et al* (2016) reported 13.02% maternal mortality (25 out of 192) due to liver disease [11]. This is comparable with 19% overall mortality in prospective study by Umang *et al* (2007) [12]. Swati *et al* (2016) reported one maternal death 3.33% [9].

The current study reported overall perinatal mortality was 32.5%.154 (48.1%) of the neonates were alive and healthy .62

neonates 19.4% had low APGAR score .20.3 % (65 neonates) had intrauterine fetal demise. 11 neonates (3.4 %) were still born and there were 28 (8.8%) neonatal deaths. 154 babies (48.1 %) had neonatal jaundice. This was in concurrence with the findings of other studies.

In the study by Aparajita *et al* (2015) out of 52 babies born, there 49 (94.2 %) live births and 3(5.7 %) fresh stillbirths. There were 57.6 % and NICU admissions. 1.9% cases developed in neonatal hepatitis [10]. Amrita *et al* (2016) reported 29.17 % perinatal deaths, out of which 16.14% babies were still born and 13.54% were IUFD and 13.02% neonatal deaths. There were 24.47% and NICU admissions [11]. Umang *et al* (2007) recorded 35% perinatal deaths [12].

The study recorded highest mortality in patients with hypertensive disorders of pregnancy (including HELLP current syndrome) 73.7 % (42 patients) followed by viral hepatitis 59.6%. (34 patients). Acute Fatty Liver of Pregnancy (AFLP) had the worst prognosis (mortality rate=100%). Statistically significant association was found between hypertensive disorder of pregnancies and Acute Fatty Liver of Pregnancy (AFLP) with maternal mortality (p value=0.15 and 0.31 respectively.

Amrita *et al* (2016) also inferred through her assessment that maximum maternal mortality was because of hypertensive disorders of pregnancy (21 out of 25) [11]. Umang Rathi *et al* (2007) reported that highest maternal mortality was in patients with Acute Fatty Liver of Pregnancy (AFLP) (2/ 3) followed by hepatitis B (4 /6) and hypertensive related liver dysfunction (9/36). Overall maternal mortality was 20% [12].

Conclusion

Liver disease in pregnancy is a cause of concern for both mother and the baby. Some of them with fatal consequences for mother and neonate. A systematic approach is needed for it's diagnosis and treatment. Therapeutic decisions must be taken considering the implications for both the mother and the baby which requires rapid diagnosis in certain liver diseases as immediate intervention can improve the maternal and fetal prognosis.

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