Association of Clinico-Epidemiological and Biochemical Parameters Affecting Materno- Fetal Outcome in Acute Liver Injury and Failure in Pregnancy

Abstract

Introduction: Liver disease in pregnancy may range from mild asymptomatic transaminitis to fatal and irreversible deterioration in liver function leading to significant morbidity and even mortality.

Aims and objectives: To analyse the association of clinical and biochemical parameters affecting maternal and fetal outcome in acute liver failure & acute liver injury in pregnancy.

Materials & Methods- It was **a** prospective observational study conducted over one year involving 135 pregnant patients between 19- to 40-year-old with raised liver enzymes with or without coagulopathy or altered sensorium

Results: Our study demonstrates that pregnancy specific liver disorders are leading cause of abnormal liver function tests particularly in third trimester with most common cause being intra hepatic cholestasis of pregnancy and acute viral hepatitis and requires a multidisciplinary team consisting of obstetrician, neonatologist, intensivist and hepatologist as these disorders are associated with high fetal and maternal morbidity and mortality.

Keywords: Acute liver injury, Acute Liver failure, Pre-eclampsia, Jaundice, HELLP Syndrome

INTRODUCTION

Liver disease in pregnancy is a worldwide health problem today and it encompasses a diverse range of problems. Elevated liver biochemical and function tests in pregnant patients may pose a challenge for the patient as well as for the consulting clinician. Liver abnormalities detected during pregnancy require diagnostic evaluation which is also related by gestational age and clinical and physiologic changes of pregnancy. Pregnancy-related diseases are the most frequent causes of liver dysfunction during pregnancy and show trimester-specific occurrence during pregnancy. Differentiation of liver dysfunction as that related to and just incidental to pregnancy is the key to management, especially when liver dysfunction is encountered after 28 weeks of pregnancy **[1]**. It can be judged from the fact that delivery remains the cornerstone of management of pregnancy-related diseases. The spectrum of liver disease may range from mild asymptomatic transaminitis to fatal and irreversible deterioration in liver function leading to significant morbidity and even mortality. Acute liver injury (ALI) is characterised by elevated serum transaminases, jaundice and INR > 1.5 which usually precedes encephalopathy. Acute liver failure (ALF) is defined as the development of coagulopathy, usually with an internationalised normal ratio (INR)

more than 1.5, and any degree of mental alteration (encephalopathy) in a patient without pre-existing liver disease. The overall outcome of ALF in pregnancy depends on the aetiology, early diagnosis, prompt management and early referral to a centre equipped in managing medical, obstetric, surgical or neonatal complications. The fetal outcome is most commonly affected by the stage of pregnancy in which the mother has a development of the liver function, with a worst prognosis associated with first or second trimester liver failure**[2]**.This causes multiple organ failure which is associated with a high mortality. Viral hepatitis E accounts for more than 50% of acute viral hepatitis in young adults in developing countries and carries a mortality rate of 20-30% among infected pregnant woman, primarily those in their third trimester **[3]**. The diagnostic or therapeutic intervention must ensure the safety of both the mother and the foetus. The maternal outcome should take precedent over foetal well being in life-threatening situations. Intensive care management of ALF patient should be focused on the diagnosis and aetiology specific treatment. Although the mechanism of liver injury is not clear yet, it is possible that interplay of hormonal and immunologic changes during the pregnancy along with high viral load of hepatitis virus renders the women more vulnerable. Immunologic changes during pregnancy promote maintenance of foetus in maternal environment by suppression of cell mediated immunity, renders the woman more susceptible to infections like hepatitis virus infections. During pregnancy, the levels of progesterone, oestrogen, human chorionic gonadotropin increase and these hormones play a considerable role in altering immune regulation and increasing viral replication.

AIM AND OBJECTIVES

Aim

- To analyse the association of clinical and biochemical parameters affecting maternal and fetal outcome in acute liver failure & acute liver injury in pregnancy

Objectives

- To study the epidemiological profile of pregnant woman presenting with acute liver injury & acute liver failure.

- To assess the various etiological factors responsible for acute liver injury and acute liver failure during pregnancy.
- To assess the maternal and fetal outcomes in pregnancies with acute liver injury and acute liver failure.

MATERIAL AND METHODS

It was **a** prospective observational study conducted over one year at Department of Obstetrics & Gynaecology in PGIMS Rohtak in which 135 pregnant patients between 19 to 40 year old with raised liver enzymes with or without coagulopathy or altered sensorium were included whereas who were having pre-existing medical /surgical disorder or liver disease were excluded. All the women who presented with acute liver injury as characterised by elevated markers of liver damage like, serum aspartate transaminases (AST) >40 U/L serum alanine aminotransferase (ALT) >40 U/L serum alkaline phosphatase (ALP) >117 U/L, serum bilirubin > 0.8 and INR > 1.5, which usually precedes encephalopathy and/or acute liver failure which was defined as the development of coagulopathy, usually with an internationalised normal ratio >1.5, and any degree of mental alteration (encephalopathy) in a patient without pre-existing liver disease to labour room of department of obstetrics & gynaecology were enrolled in the study. After an informed written consent, detailed history and general physical examination were carried out, accurate period of amenorrhea was calculated, detailed obstetrical examination was carried to assess the gestational age of the patients. All the subjects were subjected to routine antenatal investigations and specific liver functions tests & viral markers. Detailed sonography including upper abdomen and fetal growth parameter was done. Neurological assessment was done periodically to assess the grade of encephalopathy and all the investigations were done depending upon the clinical status of the patients. All the women were managed as per standard protocols and were being followed till recovery/discharge/delivery and maternal and fetal outcomes were noted on pre-structured proforma. Blood sample were taken for complete hemogram, prothrombin time and international normalised ratio, total bilirubin, serum protein, serum albumin, alanine transaminases, aspartate transaminases,

alkaline phosphatase, blood urea, serum creatinine, serum electrolytes with viral serology including IgM-HAVAb, HBsAg, Anti-HCVAb, Anti-HEVAb by ELISA Method. All pregnant women were being followed up till delivery for occurrence of complications and adverse maternal outcome and fetal outcome.The maternal outcome was determined by gestational age at delivery, mode of delivery (spontaneous/induced, vaginal/operative),disseminated intravascular coagulation (DIC), acute renal failure (ARF), postpartum haemorrhage (PPH), mortality, ICU admission and hepatic encephalopathy. The fetal outcome was determined by prematurity, stillbirth, birth asphyxia, meconium aspiration syndrome, neonatal deaths, gestational age at birth, birth weight, APGAR score, neonatal ICU admission, IUD, still birth, neonatal jaundice or any complications.

Statistical Analysis

The presentation of the Categorical variables was done in the form of number and percentage (%). On the other hand, the quantitative data were presented as the means ± SD and as median with 25th and 75th percentiles (interquartile range). The data normality was checked by using Kolmogorov-Smirnov test. The cases in which the data was not normal, we used non parametric tests. The association of the variables which were quantitative and not normally distributed in nature were analyzed using Mann-Whitney Test (for two groups) and Kruskal Wallis test (for more than two groups) and variables which were quantitative and normally distributed in nature were analyzed using independent t test (for two groups) and ANOVA (for more than two groups). The association of the variables which were qualitative in nature were analyzed using Chi-Square test. If any cell had an expected value of less than 5 then Fisher's exact test was used. The Spearman rank correlation coefficient was used for correlation of birth weight with liver function test parameters. The data entry was done in the Microsoft EXCEL spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, version 25.0. For statistical significance, p value of less than 0.05 was considered statistically significant.

OBSERVATIONS

One hundred and thirty-five pregnant women of age 19 to 40 years with raised liver enzymes with or without coagulopathy or altered sensorium were included in the study. Overall incidence of liver disorders of pregnancy in our institute was 1.21%. All the women were followed till recovery/discharge/delivery and maternal and fetal outcomes were noted and results are as follows.

Table 1: - Distribution of diagnosis of study subjects.

Diagnosis	Frequency (n=135)	Percentage
Acute liver injury (ALI)	130	96.29%
Acute liver failure (ALF)	05	3.71%

Out of 135 pregnant women, 130 women presented with acute liver injury (ALI) while only 5 women had features of acute liver failure. Majority of patients (73.33%) belonged to age group 21-30 years followed by 31-40 years (14.07%). Only 17 women belonged to 19-20 years of age group. The mean age of women in the present study was 26.09 ± 4.5 with range of 19-40 years. Majority sixty patients (44.4%) were primiparous followed by nulliparous, 36.3% women. Maximum number of patients (72.59%) had body mass index(kg/m²) in the range of 18.5 to 24.99 kg/m² (Normal BMI). BMI was in range of 25 to 29.99 kg/m² in 36 women i.e. 26.67% and in one woman, it was <18.5 kg/m². Mean value of body mass index(kg/m²) of study subjects was 23.81 ± 1.92.

Table 2: -Distribution of clinical presentation of study subjects.

Clinical presentation	Frequency	Percentage
Pallor	20	14.81%
Icterus	39	28.89%
Pedal edema	47	34.81%
Asymptomatic	29	21.40%

According to table 2, pedal edema was presenting symptom in majority of women (34.81%) followed by Icterus (28.89%) and pallor (14.81%) and rest were asymptomatic.

Table 3: -Distribution of liver Aetiology amongst the patient.

Liver Aetiology	Frequency (n=135)	Percentage
Intra hepatic cholestasis of pregnancy	68	50.37%
Preeclampsia	32	23.70%
Acute viral hepatitis	27	20.00%
HELLP syndrome	7	5.19%
Hyperemesis gravidarum	1	0.74%
Total	135	100.00%

According to table 3, intra hepatic cholestasis of pregnancy was the etiological factor in majority of women (50.37%) followed by preeclampsia (23.70%), acute viral hepatitis (20.00%) and HELLP syndrome (5.19%). Diagnosis of Hyperemesis gravidarum was seen in only 1 out of 135 patients (0.74%). The mean value of SGOT(U/L), SGPT(U/L), ALP(U/L) and serum bilirubin(mg/dL) of study subjects was 311.07± 577.01 U/L, 240 ± 309.18U/L, 303.79±162.36 U/L and 2.37±2.34mg/dL respectively and mean value of PT(seconds) and INR of study subjects was 20.97 ± 6.21 seconds and 1.31±0.38 respectively. The viral markers were negative in majority of women. IgM HAV & HEV was positive in one patient each, HBsAg in four and Anti-HCV Ab was positive in eight women. In majority of patients (114), ultrasound findings of liver was normal. The mean value of gestational age on admission (weeks) and gestational age on delivery (weeks) of study subjects was 37.47±1.5 and 37.71±1.46 with median (IQR) of 37.6(36.86-38.43) and 37.86(37-38.571) respectively. The mode of delivery was vaginal in majority (62.22%) of women, while it was caesarean section in 37.78% women. The labor was induced in majority of women (49.63%) while 40 women had spontaneous onset of labor (29.63%) and twenty-eight women out of 135 women underwent direct caesarean section. In group with induced labour, 47(70.15%) patient had successful vaginal delivery while 20(29.85%) patients underwent LSCS. In patients with spontaneous labour, 37(92.50%) patients had successful vaginal delivery and 3(7.50%) patients underwent LSCS. The indication for caesarean was fetal distress in majority of patients

[23(45.10%)] followed by HELLP syndrome with poor bishop [7(13.73%)], impending Eclampsia with poor bishop score [5(9.80%)], breech [5(9.80%)], previous two caesarean [4(7.84%)], previous caesarean [3(5.88%)], severe IUGR [2(3.92%)]. Antepartum Eclampsia with poor bishop score and antepartum haemorrhage were indication for caesarean only in one patient each.

Table 4: -Distribution of maternal complications of study subjects.

Maternal complications	Frequency(n=135)	Percentage
No complications	102	75.56%
Thrombocytopenia	5	3.70%
Coagulopathy	8	5.93%
Encephalopathy	5	3.70%
ICU stay	20	14.81%
Expired	3	2.22%

Majority [102(75.56%)] of patients did not have complications and rest of them had complications in form of ICU stay [20(14.81%)], coagulopathy [8(5.93%], thrombocytopenia [5(3.70%)] and encephalopathy [5(3.70%)]. Only 3 out of 135 patients (2.22%) expired. Five patients who developed encephalopathy also had ICU stay.

Table 5: -Mean duration of ICU stay (days) of study subjects.

Variable	Mean ± SD	Median (25th-75th percentile)	Range
Duration of ICU stay (days)	4.2 ± 1.67	4(3-5)	2-8

According to table 5, mean value of duration of ICU stay (days) of study subjects was 4.2 ± 1.67 with median (25th-75th percentile) of 4(3-5).

One hundred fourteen (84.44%) neonates had term birth and 21 (15.56%) had preterm birth. It was also observed that majority (68.15%) of neonates, were low birth weight (<2500 gm). Birth weight (grams) was ≥2500 gm was found in 31.85% neonates. Mean value of birth weight (grams) of study subjects was 2325.65 ± 420.73. Majority

of neonates (60.74%) were SGA while 39.26% were AGA. APGAR score at 5 minutes was ≥7 in majority (90.70%) of neonates while the APGAR score was <7 in 9.30% neonates only. Mean value of APGAR score at 5 minutes of study subjects was 7.8 ± 1.09. Only 33 out of 129 neonates (25.58%) required admission to nursery. Majority of neonates i.e. 122 (90.37%) were alive, 7 (5.19%) neonates expired and only 6 out of 135 neonates were IUD.

Table 6: -Distribution of neonatal outcome of study subjects.

Neonatal outcome	Frequency	Percentage
Preterm/term birth		
Preterm birth	21	15.56%
Term birth	114	84.44%
APGAR score at 5 minutes		
<7	12	9.30%
≥7	117	90.70%
Mean ± SD	7.8 ± 1.09	
Median (25th-75th percentile)	8(8-8)	
Range	2-9	
Birth weight(grams)		
<2500 gm	92	68.15%
≥2500 gm	43	31.85%
Mean ± SD	2325.65 ± 420.73	
Median (25th-75th percentile)	2340(2060-2630)	
Range	1200-3450	
Fetal growth parameters		
SGA	82	60.74%
AGA	53	39.26%
Fetal outcome		
Expired	7	5.19%

IUD	6	4.44%
Live	122	90.37%
Admission to nursery	33	25.58%

Table 7: -Association of lab investigations parameters with maternal complications.

Lab investigations parameters	No maternal complications(n=10)	Maternal complications(n=33)	Total	P value
SGOT(U/L)				
Mean ± SD	173.58 ± 178.67	736.06 ± 1023.2	311.07 ± 577.01	**<.0001**§
Median (25th-75th percentile)	132(104.5-186.75)	345(137-780)	143(108.5-204.5)	
Range	38-1475	48-4160	38-4160	
SGPT(U/L)				
Mean ± SD	161.61 ± 111.53	482.3 ± 530.01	240 ± 309.18	**<.0001**§
Median (25th-75th percentile)	127.5(97.25-191.25)	266(138-619)	146(102.5-235)	
Range	45-724	40-2510	40-2510	
ALP(U/L)				
Mean ± SD	291.45 ± 120.2	341.94 ± 250.59	303.79 ± 162.36	0.271‡
Median (25th-75th percentile)	271.5(194.5-364)	285(228-343)	278(198-354.5)	
Range	105-620	120-1452	105-1452	
Serum bilirubin(mg/dL)				
Mean ± SD	1.84 ± 1.41	4.03 ± 3.6	2.37 ± 2.34	**<.0001**§
Median (25th-75th percentile)	1.3(0.9-2.1)	2.7(1.8-4.7)	1.7(1-2.75)	

Range	0.3-8.3	0.4-15.4	0.3-15.4	
PT (seconds)				
Mean ± SD	19.51 ± 4.66	25.5 ± 8.05	20.97 ± 6.21	**0.0002‡**
Median (25th-75th percentile)	19.3(16.2-22.7)	26.1(21.7-29.6)	20.6(16.5-24.5)	
Range	10.4-29.9	8.6-44.2	8.6-44.2	
INR				
Mean ± SD	1.21 ± 0.26	1.64 ± 0.51	1.31 ± 0.38	**<.0001‡**
Median (25th-75th percentile)	1.26(0.962-1.36)	1.59(1.41-1.81)	1.3(1.03-1.435)	
Range	0.8-2.3	0.62-3.21	0.62-3.21	
Viral markers				
Negative	94 (77.69%)	27 (22.31%)	121 (100%)	
Positive	8 (57.14%)	6 (42.86%)	14 (100%)	0.09†
Total	102 (75.56%)	33 (24.44%)	135 (100%)	

‡ Independent t test, § Mann Whitney test, † Chi square test

In the present study, as shown in table 7, it was observed that significant association was seen in SGOT (U/L), SGPT (U/L), serum bilirubin(mg/dL) with maternal complications (p value <.05). Mean values of SGOT, SGPT, serum bilirubin in patients with maternal complications was 736.06 ± 1023.2, 482.3 ± 530.01, 4.03 ± 3.6 respectively which was significantly higher as compared to patients without maternal complications and the mean values were 173.58 ± 178.67 (p value <.0001), 161.61 ± 111.53 (p value < .0001), 1.84 ± 1.41(p value < .0001) respectively. No significant association was seen in ALP(U/L) (p value=0.271) with maternal complications. Mean ± SD of ALP(U/L) in patients without maternal complications was 291.45 ± 120.2 and in patients with maternal complications was 341.94 ± 250.59 with no significant association between them. Mean ± SD of PT (seconds), INR in patients with maternal complications was 25.5 ± 8.05, 1.64 ± 0.51 respectively which was significantly higher as compared to patients without maternal complications 19.51 ±

4.66(p value=0.0002),1.21±0.26(p value<.0001) respectively. Distribution of maternal complications was comparable with viral markers, Negative (22.31%) vs. Positive (42.86%). (p value=0.09).

The mean values of SGOT, SGPT, serum bilirubin in birth weight <2500 gm was 377.43±682.52, 273.3±361.1, 2.44±2.24 respectively and in birth weight ≥2500 gm was 169.09±150.59, 168.74±121.85, 2.23±2.57 respectively. But there was no significant association between them. Mean± SD of ALP in birth weight <2500 gm was 294.34±136.6 and in birth weight ≥2500 gm was 324.02±207.5 with no significant association between them. There was no correlation seen between birth weight with SGPT, ALP, PT, INR with correlation coefficient of -0.079, 0.078, 0.08, -0.012 respectively. Although non-significant mild negative correlation was seen between birth weight with SGOT and serum bilirubin with correlation coefficient of -0.102 and -0.16 respectively. The maternal mean levels of SGOT, SGPT and ALP in neonates not requiring NICU admission was 191.07±171.83, 175.68±125.52 and 312.7±169.77 respectively as compared to those neonates which required NICU admission which was 501.09±839.6, 324.91 ± 357.49 and 293.48 ± 145.9 respectively with no significant association between them. But significant association was seen with maternal mean level of serum bilirubin which was 2.88±2.23 in neonatal group requiring NICU admission and 2.1±2.34 in neonatal group not requiring NICU admission with p value = 0.005. Out of 14 women with positive viral markers, eleven neonates (78.57%) were SGA, twelve neonates (85.71%) were term and twelve neonates (85.71%) were live. All the women presenting with HELLP syndrome underwent direct caesarean section. Out of 27 patients presenting with acute viral hepatitis, twelve (44.4%) went into spontaneous labour, fourteen (51.85%) were induced after clinical recovery and one patient had direct caesarean section.

Table 8: -Association of liver Aetiology with maternal complications and maternal outcome.

Liver Aetiology	HELLP syndrome	Hepatitis	Hyperemesis gravidarum	Intra hepatic cholestasis of pregnancy	Preeclampsia

No maternal complications(n=102)	1 (14.29%)	13 (48.15%)	1 (100%)	65 (95.59%)	22 (68.75%)
Maternal complications (n=33)	6 (85.71%)	14 (51.85%	0 0%	3 (4.41%)	10 (31.25%)
P value	**0.0008***	**0.0002†**	1*	**<.0001***	0.305†
Expired(n=3)	2 (28.57%)	0 0%	0 0%	0 0%	1 (3.13%)
Live(n=132)	5 (71.43%)	27 (100%)	1 (100%)	68 (100%)	31 (96.88%)
P value	**0.007***	1*	1*	0.119*	0.559*

*** Fisher's exact test, † Chi square test**

It is evident from table 8, that there were three maternal death in present study, two presenting with HELLP syndrome and one presenting with severe preeclampsia (3.13%). No mortality was observed in other etiological groups. The proportion of patients with maternal complications was significantly higher in HELLP syndrome (85.71%, p value=0.0008) and hepatitis (51.85%, p value=0.0002). No significant association was seen in maternal complications with Hyperemesis gravidarum. (p value=1) and Preeclampsia (p value=0.305). Proportion of patients without maternal complications was significantly higher in intra hepatic cholestasis of pregnancy (95.59%, p value<.0001). All the neonates born to HELLP mothers, twenty two (81.48%) born to acute viral hepatitis mothers, 43 (63.24%) born to mother suffering from intrahepatic cholestasis of pregnancy and nineteen (59.38%) born to preeclamptic mother had birth weight <2500 gms and there was no significant difference noted in birth weight regards to the aetiology. Distribution of SGA was comparable between different liver aetiology. [HELLP syndrome (57.14%, p value=1) vs. Hyperemesis gravidarum (0%, p value=0.393) vs. Intra hepatic cholestasis of pregnancy (55.88%, p value=0.244) vs. Preeclampsia (59.38%, p value=0.856)]. There was no difference in APGAR score at 5 minutes <7 when compared with liver aetiology. It was observed that APGAR score <7 was seen in 28.57% of HELLP syndrome followed by 13.04% in patients with acute viral Hepatitis and 12.9% in

preeclampsia. In patients with HELLP syndrome, their neonates required NICU admission was significantly higher (85.71%, p value=0.001). Distribution of requirement of NICU admission was comparable with other liver aetiologies (Hepatitis (26.09%, p value=0.951), Hyperemesis gravidarum (0%, p value=1), Preeclampsia (32.26%, p value=0.328)). Proportion of neonates with no requirement of NICU admission was significantly higher in intra hepatic cholestasis of pregnancy (83.58%, p value=0.013). Higher intrauterine deaths were seen in mothers with acute viral hepatitis as compared to other groups and difference was statistically significant. It was also observed that significant higher level of preterm birth was seen in HELLP syndrome patients (57.14%, p value = 0.011) as compared to other groups. Term births were significantly higher in mothers with intra hepatic cholestasis of pregnancy (91.18%, p value = 0.03). In the present study, it was observed that there is a significant association was seen in SGOT, SGPT, serum bilirubin with liver aetiology (p value <.05). The mean value of SGOT in HELLP syndrome (1432±1286.45) was highest followed by hepatitis (540.33±891.87), intra hepatic cholestasis of pregnancy (177.46±146.56), preeclampsia (163.97±111.38) and mean value of SGOT in Hyperemesis gravidarum 68 ± 0 was lowest (p value=0.0009). The mean value of SGPT in HELLP syndrome (654.86±319.28) was highest followed by hepatitis (408.3±570.18) followed by preeclampsia (178.03±115.01) and intra hepatic cholestasis of pregnancy (162.04±109.46) and mean value of SGPT in Hyperemesis gravidarum 76±0 was lowest (p value=0.0007). The mean value of serum bilirubin in hepatitis (5.33±3.57) was highest followed by HELLP syndrome (2.94±1.25), preeclampsia (1.59±1.04), intra hepatic cholestasis of pregnancy (1.52±0.88) and mean value of liver function test parameters serum bilirubin was lowest in Hyperemesis gravidarum [1.5±0. (p value < .0001)]. No significant association was seen in ALP (p value=0.458) with liver aetiology. Mean± SD of ALP in HELLP syndrome was 348.14±231.95, 346.74±265.24 in hepatitis, 183±0 in Hyperemesis gravidarum, 291.15±109.93 in intra hepatic cholestasis of pregnancy and 288.5±123.65 in preeclampsia, with no significant association between them.

No significant association was seen in PT, (p value=0.123) with liver aetiology. Mean± SD of in Hyperemesis gravidarum was 26.5±0, PT in HELLP syndrome was 24.39±11.21, in hepatitis was 22.87±7.91, in intra hepatic cholestasis of pregnancy was 20.28±4.82 and in preeclampsia was 19.91±5.54 with no significant association

between them. Significant association was seen in INR with liver aetiology, (p value <.05). Mean± SD of INR in HELLP syndrome (1.54±0.53) was highest followed by hepatitis (1.5±0.51), Hyperemesis gravidarum (1.32±0), intra hepatic cholestasis of pregnancy (1.25±0.26) and mean± SD of coagulation profile INR in preeclampsia (1.25 ± 0.41) was lowest (p value=0.018).

DISCUSSION

In our study, majority of women were in age group 21-30 year i.e. 99(73.33%). Mean value of age (years) of the present study subjects was 26.09±4.5. In a study by Singla A et al, the mean age of study subjects was 27.3±4.3 years **[4]**. In another study which was conducted by Chaitra S et al, similar group of age (21-30 years) had the highest prevalence (70.1%) of disease in pregnancy which is consistent with the present study **[5]**. Most of the women in our study were primiparous i.e. 60(44.44%) followed by nulliparous i.e. 49 (36.30%). Chaitra S et al conducted a study and they also concluded that most of the women in their study were primigravida (57.01%) **[5]**. Kumari A et al conducted a study and in their study, they found out that 69% of enrolled women were nulliparous **[6]**. Majority of women (54.07%) got education till high school followed by middle school (26.67%) and 3.70% patients were illiterate. A study by Tiwari A et al observed that maximum number of patients i.e. 91(42.52%) got education till primary school and 22.9% study subjects were illiterate **[7]**. In the present study, a hundred and seventeen women (86.67%) were housewives followed by 8.89% women whom had private job. Out of 135 women, seventy-three were educated up to high school which comprises 54.07% of total cases and 26.67% were educated up to middle school. Guerrier G et al conducted a study in which out of 419 cases, 87% women were housewives **[8]**. Patel BJ et al observed that maximum number of women (34.6%) were educated up to primary school and 26.5% women were illiterate in their study **[9]**. Dsouza et al conducted a study in which they observed that out of 51 women, 68.6% were housewives and 31.4% women were illiterate **[10]**. Out of total 135 patients, 72.59% patients had normal BMI (18.5 – 24.99 kg/m^2) followed by 26.67% patients who were overweight (25 – 29.99 kg/m^2) with mean value of 23.81 ± 1.92. A study by Arthuis C et al showed that one hundred forty women had BMI in the range of 21-27.2 with mean value 23.6kg/m^2 **[3]**. The mean value of systolic blood pressure(mmHg) and diastolic blood pressure(mmHg) of study subjects was 136.34 ± 18.78 and 88.8 ± 11.9 respectively. Gasem T et al

involved 64 women and in contrast they found the blood pressure was raised more than 160/110 mm Hg in 62.5% patients **[11]**. The mean value of gestational age on admission (weeks) and at delivery (weeks) of study subjects was 37.47 ± 1.5 and 37.71 ± 1.46 respectively. A study was conducted by Tiwari A et al and they reported that 71.02% patients presented at term with liver diseases associated with pregnancy **[7]**. Similar results were found in a study by Mishra N et al in which 87.5% women presented at third trimester of pregnancy with abnormal liver function test **[12]**. The most common clinical presentation was pedal edema seen in 34.81% women followed by Icterus in 28.89% women and pallor in 14.81 % of women. Similar results were found in the study by Mishra N et al in which 25 % pregnant women presented with pedal edema and headache was observed in 13% study subjects **[12]**. In contrast to the above study, Icterus and yellow discolouration of urine was seen in all the study subjects with pedal edema seen only in 46% subjects in a study by Choudhary N et al **[13]**. In our study, majority of patients were diagnosed to be of intra hepatic cholestasis of pregnancy (50.37%) followed by preeclampsia (23.70%) and acute viral hepatitis in 20% patients. While HELLP syndrome was diagnosed in 5.19% patients and only one patient had Hyperemesis gravidarum, this patient of Hyperemesis gravidarum presented in first trimester and being followed upto term gestation. In a study by Satia and Jandhyala, sixty two percent women had viral hepatitis followed by intra hepatic cholestasis of pregnancy in 23.6% women **[14]**. In contrast, the most common aetiology in a study by Joshi H et al was HELLP syndrome (40%) **[15]**. Jain M and Thaker H conducted a study and found that majority of patients were of acute viral hepatitis (36.3 %) followed by intra hepatic cholestasis of pregnancy (29.9%) **[16]**. A study by Agarwal M et al showed that maximum 33.6% cases were diagnosed as preeclampsia while intra hepatic cholestasis of pregnancy and hepatitis cases were seen only in 23.70% and 17.20% respectively **[17]**. In our study, mean value of SGOT, SGPT, ALP and serum bilirubin of study subjects was 311.07 ± 577.01, 240 ± 309.18, 303.79 ± 162.36 and 2.37 ± 2.34 and mean value of PT (seconds) and INR of study subjects was 20.97 ± 6.21 and 1.31 ± 0.38 respectively. The range of serum bilirubin in present study was 0.3-15.4 mg/dL. In a study by Agarwal M et al, they observed that more than half of cases had SGOT levels in the range of 100-500 (59%) followed by <100 (24.6%) and >1000 (9.8%) and 501-1000 (6.6%). However, SGPT was 100- 500 among 52.5% cases and <100 in 23% of cases. ALP was between 100-500 among about half of the cases (49.1%) and PT and INR were abnormal in 45.9%

cases, also in 64.7% patients had serum bilirubin level >10 mg/dL **[17]**. In a study by Mitta P, the level of serum bilirubin varied widely between 2.4 to 20.05 mg/dL with serum bilirubin levels more than 10 mg/dL in 14.28% subjects. SGPT and SGOT levels more than 200 U/L were seen in 11.90% patients each. Serum alkaline phosphatase was more than 200 U/L in 74% of cases **[18]**. In a study by Mishra N et al, AST and ALT elevations upto levels of 500 IU/L were found in almost 90% patients. About forty seven percent women had elevation of serum bilirubin (mg/dL) more than 2.5. Majority of women (83.75%) had elevations of alkaline phosphatase in the range between 141 and 564 IU/L **[12]**. In the present study, majority of patients delivered vaginally (62.22%) and rest of the patients (37.78%) underwent caesarean section. Similar results were found by Kumari A et al involving 126 pregnant women where vaginal delivery was observed in 65% and caesarean section in 33% women while only 2 patients remain undelivered **[6]**. In contrast to present study, Singla A et al analysed a study on 82 pregnant women and found that 96.3% patients delivered vaginally and only 3.7% patients underwent caesarean section **[4]**. In a study by Joshi H et al, 44% pregnant women had caesarean section **[15]**. Chaitra S et al observed in a study that maximum number of patients 71(62.2%) underwent caesarean section and 43(37.7%) patients delivered vaginally **[5]**. Rizvi SM et al observed in their study that 69% patients had caesarean section and 24% pregnant women had normal vaginal delivery **[19]**. In the present study, fetal distress was major indication for caesarean section found in 45.10% patients followed by HELLP syndrome with poor bishop in 13.73% patients. In a study conducted by Vinaya chandran and Anaswara involving 52 women, forty four percent women underwent caesarean section with previous caesarean in majority women(n=7) followed by HELLP syndrome with poor bishop score and AFLP with poor bishop score (n=4 each). Only two women had caesarean for fetal distress **[20]**. A study by Mishra N et al involving 80 patients, twenty-four patients had caesarean section with most common indication being preeclampsia in 41.6% followed by HELLP syndrome in 33.3% patients **[12]**. As per the present study, labour was induced in majority of women (49.63%) while 40 women had spontaneous onset of labour (29.63%) and twenty-eight women out of 135 women underwent direct caesarean. In group with induced labour, 47(70.15%) patients had successful vaginal delivery while 20 (29.85%) patients underwent LSCS. In patients with spontaneous labour, 37(92.50%) patients had successful vaginal delivery and 3(7.50%) patients underwent LSCS. Twenty-eight (20.74%) patients underwent direct

caesarean. In a study by Kumari A et al, it was observed that out of one hundred twenty-six women, 115 women were admitted in labour, of which 65.3% delivered vaginally, 33% women underwent caesarean section and two died undelivered. Most common indication for caesarean was found to be previous caesarean in 36.80% patients followed by failed induction in 34.20% and only 13.10% patients underwent caesarean section because of fetal distress **[6]**. In a study by Satia and Jandhyala enrolling 55 patients, total vaginal deliveries were 79% and 19% patients underwent lower segment caesarean section and 1 patient had instrumental (vacuum) delivery. In total 9 caesarean sections, 3 were elective sections and 6 were for emergency sections in which five were for fetal distress and one was for previous LSCS **[14]**. We observed in our study that majority of patients didn't have any complications. Hepatic encephalopathy was found out in 5 patients, including these 5 patients a total of twenty patients were admitted in ICU. Eight patients had signs of coagulopathy and 5 patients had thrombocytopenia. Out of five patients who developed hepatic encephalopathy, maternal death occurred in three women. Maternal death rate of 13.02% was seen and reported in a study by Tiwari A et al out of which majority were due to hypertensive disorders (21 out of 25) **[7]**. In a study by Jain and Thaker involving 55 pregnant women, eight (14.5%) maternal death were seen with acute viral hepatitis being the most common cause in more than 50% patients followed by preeclampsia and HELLP Syndrome. DIC and encephalopathy was observed in 18.8% and 5.4% respectively **[16]**. Out of 135 patients, only 20 required ICU stay comprising of 14.81% of total patients. Mean duration of ICU stay was 4.2 days. Sharma S et al analyzed that all patients were kept in ICU for intensive monitoring **[21]**. Joshi H et al analyzed in their study that 40% patients required ICU admission **[15]**. Out of total 135 patients, only 43 patients (31.85%) required blood and blood products transfusion with average 71 packed cell volume, 163 fresh frozen plasma and 54 platelet rich plasma were transfused as per requirement. Tiwari A et al reported in their study that 43.75% patients needed blood transfusion.[37] In a study by Sharma S et al it was concluded that 60% patients received blood and its components.[47] A study by Joshi H et al reported that 36% patients required blood transfusion **[15]**. A study by Rizvi and Raina analyzed that 20% patient required blood transfusion **[19]**. Mitta and Rao conducted a study and observed that about 21.42% patients received blood transfusion of various components. It was also observed that one patient with HELLP syndrome and DIC received 8 PCV ,12 FFP

and 12 PRP **[18]**. In our study, 114(84.44%) neonates had term birth and 21 (15.56%) had preterm birth, but in majority of neonates (68.15%), birth weight (grams) was low birth weight (<2500 gm). Birth weight (grams) was more than 2500 gm in only 43 neonates (31.85%). Mean value of birth weight (grams) of study subjects was 2325.65 ± 420.73. Majority of neonates i.e. 82 (60.74%) were SGA and 53 out of 135 neonates were AGA. Ninety percent of neonates had APGAR score more than 7 while 10% neonatal APGAR scare was less than 7. Mean value of APGAR score at 5 minutes of study subjects was 7.8 ± 1.09. Only 33 out of 129 patients (25.58%) required admission to nursery. Majority of neonates were alive 122 (90.37%), 7(5.19%) neonates expired after NICU admission and only 6 out of 135 neonates were IUD. In a study by Vinaya Chandran and Anaswara, 36 out of 52 deliveries were preterm (69.2%) and rest were term. This shows a higher incidence of preterm deliveries when compared to the general population. About sixty percent neonates had birth weight less than 2.5 kg. This shows that most of the babies were low birth weight **[20]**. A study by Acharya N et al reported term delivery rate about 51% and preterm delivery rate of 48% and 16.6% neonates were still born. In this study incidence of preterm delivery was higher than our study **[22]**. In a study by Choudhary N et al, it was observed that 55.77% patients had term delivery and 40.38% patients had preterm delivery whilst 3.85% patients had abortions. Still birth rate was about 30%. Most common cause of neonatal mortality in their study was found to be prematurity and low birth weight (42.11%) followed by birth asphyxia (36.84%) and fetal distress (21.05%). NICU admission was required in 31.43% neonates **[13].** Rizvi and Raina in a study involving 100 women found that 70 women delivered at term, out of which 64 were live birth. It was also observed that 30% of neonates had low birth weight **[19]**. In our study majority of women were viral negative. Only fourteen women (10.3%) were viral positive out of which eight women were Anti HCV Ab positive. Four were HbsAg positive and one patient was positive for Anti HAV Ab and Anti HEV Ab each. In a study by Kumari A et al, it was observed that hepatitis was seen in only 5 (4%) cases, and all were Hepatitis B positive with one patient having very high level of HbeAg **[6]**. In a study by Agarwal M et al they concluded that Hepatitis B virus was the most common cause of acute hepatitis comprises 47.6% patients followed by Hepatitis E positive in 28.6%. However, Hepatitis C Virus and Hepatitis A virus were positive in 14.3% and 9.5% of cases respectively **[17]**. A study by Sharma S et al observed that viral hepatitis was the major cause of jaundice in their study (46.7%)

out of which Hepatitis B was the most common cause of viral hepatitis (26.7%) and incidence of hepatitis E was found to be 13.3% **[21]**. Mishra N et al analyzed in a study that 6.2% patients were HEV positive followed by 05% HAV positive patients **[12]**. In our study, significant association was seen in SGOT(U/L), SGPT(U/L), serum bilirubin(mg/dL), PT (seconds), INR with maternal complications (p value <.05). Values of all these parameters were significantly higher as compared to patients without maternal complications. No significant association was seen in ALP(U/L) with maternal complications (p value=0.271). Out of 135 patients, 8 out of 102 patients without any maternal complications were viral marker positive and 6 patients out of 33 patients with maternal complications were positive for viral markers. It is explained by the fact that there is physiological rise in ALP levels during pregnancy. In a study by Agarwal M et al, they concluded that percentage of mortality was 16.7% among whom SGOT was >1000, 57.1% with SGPT >1000, 73.3% ALP >1000, 59.7% with total bilirubin10-15mg% **[17]**. Choudhary N et al analyzed that maternal deaths were directly proportional to the level of the serum bilirubin **[13]**. Joshi H et al also concluded that raised direct bilirubin, SGOT, alkaline phosphatase and low haemoglobin level & thrombocytopenia were found to be significantly associated with adverse maternal outcome among the patients. Maternal deaths were directly proportional to the level of the serum bilirubin **[15]**. In the present study, no significant association was seen between liver function tests and birth weight. A significant association was seen between serum bilirubin(mg/dL) with NICU admission with p value < 0.05 which concludes that mean value of the babies required NICU admission with serum bilirubin of mother were significantly higher than the babies in which NICU admission not required. In a study by Joshi H et al, they analyzed that raised serum total bilirubin level, thrombocytopenia, low haemoglobin level was significantly associated with adverse fetal outcomes. They also observed that most common adverse neonatal outcome was low birth weight (56%) **[15]**. Choudhary N et al observed in their study that jaundice in pregnancy is associated with high maternal and perinatal mortality rates and found that out of 50 delivered cases, 62% babies were alive, 30% stillbirth and early neonatal death in 8% cases. Perinatal mortality in this study was 38%. Prematurity and low birth weight in 42.11% accounted for majority of the deaths **[13]**. In present study, there was no significant association between viral markers with the fetal growth, maturity and fetal outcome. A study by Chaitra S et al showed that out of 114 study subjects, 29.8%

delivered preterm babies and 4% were intra uterine fetal demise and 26.3% were low birth weight **[5]**. Among 70 delivered hepatitis positive patients in the study by Singla A et al, 76.1% had preterm deliveries **[4]**. In the present study, patients with HELLP syndrome underwent direct caesarean section. Out of 27 patients with acute viral hepatitis, twelve (44.4%) went into spontaneous labour, fourteen (51.85%) were induced after clinical recovery and one patient had direct caesarean section. In a study by Mishra N et al involving eighty pregnant women, only 11 patients were of HELLP syndrome out of which eight patients underwent LSCS. In their study the induction rate was high because of many cases with intrauterine foetal deaths and pre-eclampsia related obstetric conditions **[12]**. In a study by Chandni et al, majority of pregnant mothers with viral hepatitis had vaginal delivery (79.78%) and caesarean section was done in only 20.22% cases due to obstetric indications or worsening maternal conditions. However, vaginal delivery is preferred due to the fear of increased bleeding tendency in these patients **[19]**. In the present study, there were three maternal deaths in present study, two presenting with HELLP syndrome and one presenting with severe preeclampsia (3.13%). There was no mortality observed in patients with hepatitis (0%), Hyperemesis gravidarum (0%), intra hepatic cholestasis of pregnancy (0%) (p value=0.007). It is also evident from present study that proportion of patients with maternal complications was significantly higher in HELLP syndrome (85.71%, p value=0.0008) and hepatitis (51.85%, p value=0.0002). No significant association was seen in maternal complications with Hyperemesis gravidarum. (p value=1) and preeclampsia (p value=0.305). Proportion of patients without maternal complications was significantly higher in intra hepatic cholestasis of pregnancy (95.59%, p value<.0001). Similar findings were observed by Mishra N et al that patients with HELLP syndrome were highly associated with maternal adverse outcome. Out of four maternal mortality two women expired with diagnosis of HELLP syndrome **[12]**. In a study by Rathi U et al, they reported that 25% maternal mortality was due to preeclampsia associated liver dysfunction **[23]**. A study by Agarwal M concluded that maternal mortality was 39.3% and hepatic encephalopathy was the main reason for death (64.6%) followed by MODS (10.4%), HELLP + DIC (10.4%), PPH (8.3%). They also observed that mortality was higher in hepatitis cases (47.6%) and was least in preeclampsia cases (19.5%) **[17]**. It was observed in the present study that all the neonates born to HELLP mothers, twenty- two (81.48%) born to acute viral hepatitis mothers, 43 (63.24%) born to mothers suffering from

intra hepatic cholestasis of pregnancy and nineteen (59.38%) born to preeclamptic mothers had birth weight <2500 gms and there was no significant difference noted in birth weight regards to the aetiology. Distribution of SGA was comparable with other liver aetiology. There was no difference in APGAR score at 5 minutes <7 when compared with liver aetiology. It was observed that APGAR score <7 was seen in 28.57% of HELLP syndrome followed by 13.04% in patients with acute viral Hepatitis. It was observed in our study that in the patients with HELLP syndrome, their neonates requiring NICU admission was significantly higher (85.71%, p value=0.001). Distribution of requirement of NICU admission was comparable with other liver aetiologies. Proportion of neonates not requiring NICU admission was significantly higher in intra hepatic cholestasis of pregnancy (83.58%, p value=0.013). It was observed that higher intrauterine deaths were seen in mothers with acute viral hepatitis as compared to other groups and difference was statistically significant. It was also observed that significant higher level of preterm birth were seen in HELLP syndrome patients (57.14%, p value = 0.011). Term births were significantly higher in mothers with intra hepatic cholestasis of pregnancy (91.18%, p value = 0.03). In a study by Chandni et al involving 293 pregnant women, 60.7% had acute viral hepatitis, out of which 18 were IUD and 39.89% patients were associated with preterm delivery in majority **[24]**. Jain P and Sapre S observed that hepatitis infections related complications rate was associated with high perinatal mortality rate (35.29%) **[25]**. In a study by Desai A et al, it was observed that perinatal mortality was seen in 16 cases (32%). In which maximum perinatal mortality was seen in cases with viral hepatitis (43.75%). Other causes of perinatal mortality were HELLP (37.5%), Intra hepatic cholestasis of pregnancy (12.5%) and AFLP (6.25%) **[26]**. In the present study, it was observed that there is a significant association was seen in SGOT, SGPT, serum bilirubin with liver aetiology (p value <.05). Mean value of SGOT in HELLP syndrome (1432 ± 1286.45) was highest followed by hepatitis (540.33±891.87), intra hepatic cholestasis of pregnancy (177.46 ± 146.56), preeclampsia (163.97 ±111.38) and least in Hyperemesis gravidarum (68 ± 0) was lowest.(p value=0.0009). Mean value of SGPT in HELLP syndrome (654.86 ± 319.28) was highest followed by hepatitis (408.3±570.18) followed by preeclampsia (178.03±115.01) and intra hepatic cholestasis of pregnancy (162.04±109.46) and least in Hyperemesis gravidarum (76±0) was lowest. (p value=0.0007). Mean value of serum bilirubin in hepatitis (5.33±3.57) was highest followed by HELLP syndrome

(2.94 ±1.25), preeclampsia (1.59 ± 1.04) intra hepatic cholestasis of pregnancy (1.52 ± 0.88) least in HG [1.5 ± 0.(p value<.0001)]. No significant association was seen in ALP(U/L) (p value=0.458) with liver aetiology. No significant association was seen in PT(seconds) (p value=0.123) with liver aetiology. Significant association was seen in INR with liver aetiology (p value <0.05). Mean ± SD of INR in HELLP syndrome (1.54 ± 0.53) was highest followed by hepatitis (1.5 ± 0.51), Hyperemesis gravidarum (1.32 ± 0), intra hepatic cholestasis of pregnancy (1.25 ± 0.26) and mean ± SD of coagulation profile INR in preeclampsia (1.25 ± 0.41) was lowest (p value=0.018). A study by Mishra N et al analysed that the cause of abnormal LFTs is associated with 83.25% pregnancy specific disorders such as intra hepatic cholestasis of pregnancy, pre-eclampsia and HELLP syndrome. This study also quotes that in cases of viral hepatitis, commonly the transaminases are high reaching 500–1000 IU/L and bilirubin often crosses 10 mg % **[12]**. A study by Desai A et al reported that three patients (6%) had bilirubin > 16 mg/dl and eight patients (16%) had SGOT & SGPT more than 500 IU/L. High level of S. bilirubin, SGPT, SGOT levels more than 500 IU/L were associated with viral hepatitis **[26]**. In the study by Sharan and Kumar, it was reported that maternal mortality was in observed in 8% cases and 36 patients (40%) developed several complications. Out of 54 case of hepatitis, seven (7.7%) and three patients (3.3%) developed hepatic encephalopathy hepatorenal failure respectively out of which four patients of hepatic encephalopathy had mortality. It was also observed that atonic PPH developed in 10%, DIC in 6%, and abruption in 5% cases **[27]**.

CONCLUSION

The present study clearly demonstrates that pregnancy specific liver disorders are leading cause of abnormal liver function tests particularly in third trimester with most common cause being intra hepatic cholestasis of pregnancy and acute viral hepatitis. The management of these patients requires a multidisciplinary team consisting of obstetrician, neonatologist, intensivist and Hepatologist as these disorders are associated with high fetal and maternal morbidity and mortality. Improvement in health awareness, regular antenatal checkup, early referral and intensive monitoring of both mother and fetus aids in early diagnosis & careful management of these patients.

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