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ORIGINAL ARTICLE

Etiology, clinical profile, and outcome of liver disease in pregnancy with predictors of maternal mortality: A prospective study from Western India

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Abstract
Background The aim of this study is to study the etiology, clinical profile, and prognostic factors related to maternal and fetal health in pregnant patients with liver disease in Western India.
Methods This study included 103 consecutive pregnant patients with liver dysfunction from August 2013 to July 2015, who underwent regular biochemical tests, viral markers, ultrasound of abdomen, etc. and were followed up for 6 weeks postpartum or until death.
Results Pregnancy-specific causes of liver dysfunction were found in 39 % (40/103) patients. Liver diseases were most frequent in third trimester 69.9 % (72/103). Etiologies in third trimester were viral hepatitis 36.1 % (26/72), pregnancy induced hypertension (PIH) 30.5 % (22/72), intrahepatic cholestasis of pregnancy 11.1 % (8/72), acute fatty liver of pregnancy (2/72), etc. Hepatitis E was the commonest agent among viral hepatitis 71.8 % (28/39). Causes of maternal mortality ($n = 25$) were hepatitis E 40 % (10/25), PIH 32 % (8/25), and tropical diseases 20 % (5/25). Fetal mortality ($n = 31$) was 38.7 % (12/31) in hepatitis E. Maternal mortality was significantly associated with presence of jaundice, fever, abdominal pain, oliguria, anemia, leukocytosis, and coagulopathy. Model for end-stage liver disease (MELD) score >21 predicted maternal mortality with 80 % sensitivity and 91 % specificity (area under the receiver operating characteristic curve = 0.878 and $p < 0.001$).
Conclusions Liver disease was most common in the third trimester of pregnancy. Hepatitis E was the most common cause of liver disease in pregnant women in western India with significant maternal mortality, predicted by high MELD score.

Keywords Hepatitis E · Liver function tests · Pregnancy-induced hypertension · Viral hepatitis

Introduction

Liver dysfunction in pregnancy is a rare disorder with incidence of 0.3 % to 3 % [1]. It can be of three types: liver diseases specific to pregnancy, liver diseases coincidental to pregnancy, and pregnancy in patients with preexisting liver diseases. Liver disease can have significant impact on pregnancy, and pregnant state itself can lead to certain liver diseases which are specific to pregnancy. Viral hepatitis is endemic in developing countries, and hepatitis E in particular is a cause of significant maternal mortality and fetal loss. Data is scarce regarding etiology, clinical presentation, and prognostic factors related to maternal and perinatal mortality in liver disease in pregnancy in Western India.

Model for end-stage liver disease (MELD) score has been shown to have a prognostic value in patients with pregnancy-specific liver diseases [2]. However, studies evaluating MELD score for predicting outcome of other etiologies of liver dysfunction in pregnancy are few. This study aims to identify the factors affecting maternal as well as perinatal mortality. Utility of MELD score in predicting maternal mortality has also been evaluated.

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Methods

Patients

This prospective observational study was carried out in a tertiary care referral center in Western India from August 2013 to July 2015. One hundred and three consecutive pregnant patients with liver dysfunction developing during pregnancy were included. Informed written consent was obtained from all. The study protocol conformed to the ethical guidelines of the 1975 declaration of Helsinki and was approved by the appropriate institutional review committee.

Methods

All patients underwent frequent clinical examinations, biochemical tests, viral markers for hepatitis like hepatitis B surface antigen (HBsAg), antibody against hepatitis C virus (anti-HCV), IgM antibody against hepatitis E virus (anti-HEV), IgM antibody against hepatitis A virus (anti-HAV), ultrasound of abdomen, and special biochemical tests as and when required. Frequent monitoring of liver function throughout pregnancy and until 6 weeks postpartum or until death was done.

Definitions

Abnormal liver function tests (LFTs): serum bilirubin level ≥25.6 mmol/L (1.5 mg/dL), alanine transaminase (ALT) ≥40 IU/L, aspartate transaminase (AST) ≥40 IU/L, alkaline phosphatase (ALP) ≥306 IU/L. Higher than the normal range as defined by local laboratory.

Acute hepatitis E: a positive test for IgM anti-HEV.

Hyperemesis gravidarum: Persistent vomiting occurring in the first trimester requiring hospitalization and intravenous hydration.

Preeclampsia: Hypertension developing after 20 weeks of gestation associated with elevated transaminases or bilirubin, proteinuria, and edema [3].

Hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome: Diagnosed using Tennessee criteria. Thrombocytopenia (platelets <100,000/mm^3), AST >70 IU/L, evidence of hemolysis [4].

Acute fatty liver of pregnancy (AFLP): Six or more of the following features in the absence of another explanation (Swansea criteria [1]): ascites or bright liver on hepatic ultrasound, coagulopathy (PT >14 s or aPTT >34 s), elevated serum ammonia levels (>47 μmol/L), elevated serum transaminases (>42 IU/L), elevated serum bilirubin (>14 μmol/L or >0.8 mg/dL), elevated serum urate level (>340 μmol/L or >5.7 mg/dL), encephalopathy, hypoglycemia (<4 mmol/L or <72 mg/dL), leukocytosis (>11,000/mm^3), microvesicular steatosis on liver biopsy, polydipsia/polyuria, renal impairment (creatinine >150 μmol/L or >1.7 mg/dL), and vomiting. Intrahepatic cholestasis of pregnancy (ICP): Pruritus developing in second/third trimester of pregnancy with elevated levels of serum bile acids after exclusion of other causes which improved soon after delivery [5].

Model for end-stage liver disease score was calculated using formula: (9.57 log [creatinine] + 3.78 Log [bilirubin] + 11.20 log [international normalized ratio (INR)] + 6.43) [6].

Patients diagnosed with pregnancy-induced hypertension (PIH)-related diseases were treated with expedited delivery of the fetus and antihypertensives. Patients with ICP were treated with ursodeoxycholic acid (UDCA). Patients with HELLP, AFLP, and critical patients were treated with critical care management. Patients with hepatitis B received antivirals according to the European Association for the Study of the Liver (EASL) guidelines. Reactivation of chronic hepatitis B was ruled out by testing for HBV DNA levels, IgM anti-HBc levels, and HBeAg. Newborn children born to HBsAg-positive mothers were given active and passive immunization against hepatitis B at delivery. Patients with hepatitis E were treated with supportive management and monitored for development of complications (gastrointestinal bleed, ascites, encephalopathy, electrolyte abnormalities, etc.).

Statistical analysis

Statistical analysis was done using Statistical Package for the Social Sciences (SPSS) version 16.0 (SPSS Inc., Chicago, IL, USA). Normal distribution of the data was checked with Shapiro-Wilk test. For parametric and nonparametric continuous data, Student's t test and Mann-Whitney U test were used, respectively. Chi-square test was used for categorical variables. A p-value of ≤ 0.05 was counted as significant. Factors found significant on univariate analysis were analyzed with multivariate analysis by stepwise logistic regression method. The parameters were compared between two most common etiologies of liver dysfunction i.e. hepatitis E and PIH. The parameters were also compared between maternal as well as perinatal survivors and nonsurvivors.

Receiver operating characteristic (ROC) curve was used to derive a cut-off of MELD score to predict maternal mortality. Sensitivity and specificity of MELD score as a predictor of maternal mortality were also determined.

Results

A total of 103 pregnant patients had liver dysfunction during study period. The age of patients ranged from 19 to 35 years (mean 25 years ± 3.8 years). Majority of the patients ($n = 57$) were primigravidae (55.3 %). Liver dysfunction was most common in the third trimester ($n = 72$) (69.9 %), followed by the second trimester ($n = 21$) (20.4 %) and the first trimester

($n = 10$) (9.7 %). Pregnancy-specific causes were found in 39 % patients (40/103).

Etiologies of liver dysfunction in pregnancy (Table 1)

The etiological spectrum is shown in Table 1.

Viral hepatitis

Viral hepatitis was the commonest etiology of liver dysfunction in pregnancy with 37.8 % patients (39/103). Hepatitis E was the commonest causative agent 71.8 % (28/39), followed by hepatitis B 25.6 % (10/39) and Herpes simplex virus 1 (HSV1) (1/39). Hepatitis E affected 4, 3, and 21 patients and hepatitis B affected 1, 5, and 4 patients in first, second, and third trimesters, respectively. Three patients had high hepatitis B viral load requiring antiviral treatment with tenofovir to prevent perinatal transmission. Viral profiles of only 12 neonates were available. Hepatitis E was found in three neonates and hepatitis B in none.

Table 1 Etiology of liver dysfunction in pregnancy

First trimester (10)	1. Hyperemesis gravidarum (5)
	2. Viral hepatitis (5)
	Hepatitis E (4)
	Hepatitis B (1)
Second trimester (21)	1. Viral hepatitis (8)
	Hepatitis E (3)
	Hepatitis B (5)
	2. Pregnancy induced hypertension related liver dysfunction (3)
	3. Drug induced liver injury (3)
	4. Chronic liver disease (2)
	5. Crigler-Najjar syndrome type II (2)
	6. Choledocholithiasis (1)
	7. Systemic lupus erythematosus with antiphospholipid antibody syndrome (1)
	8. Unknown (1)
Third trimester (72)	1. Viral hepatitis (26)
	Hepatitis E (21)
	Hepatitis B (4)
	HSV 1 (1)
	2. Pregnancy induced hypertension related liver dysfunction (22)
	3. Intrahepatic cholestasis of pregnancy (8)
	4. Acute fatty liver of pregnancy (2)
	5. Tropical diseases (5)
	6. Extrahepatic portal vein obstruction (2)
	7. Wilson disease (1)
	8. Unknown (5)

Number of patients is shown in brackets

HSV 1 herpes simplex virus 1

Pregnancy-specific liver diseases

Pregnancy-specific causes ($n = 40$, 39 %) were PIH-related liver dysfunction ($n = 25$) including preeclampsia, eclampsia, HELLP syndrome, hyperemesis gravidarum ($n = 5$), ICP ($n = 8$), and AFLP ($n = 2$). Ten maternal deaths (25 %) and 13 perinatal deaths (32.5 %) occurred due to pregnancy-specific causes.

Hyperemesis gravidarum accounted for 50 % of cases in the first trimester. They did not have clinical jaundice with bilirubin level <51 μmol/L (3 mg/dL) and transaminases mildly raised (<five times). All patients with ICP presented in the third trimester and had serum bile acid levels raised with mean 23 ± 7.2 μmol/L. They were treated with UDCA 15 mg/kg/day. Pruritus disappeared within 72 h of delivery and LFTs normalized within 10 days.

Patients with PIH-related liver dysfunction included ($n = 25$) preeclampsia ($n = 19$) and eclampsia ($n = 6$). Six patients were diagnosed to have HELLP syndrome. Three and 22 patients presented in second and third trimesters, respectively. The important presenting features of PIH-related diseases were pedal edema ($n = 19$) (76 %), right hypochondriac or epigastric pain ($n = 17$) (68 %), convulsions ($n = 6$) (24 %), oliguria ($n = 6$) (24 %), and encephalopathy ($n = 6$) (24 %). These patients were treated by urgent fetal delivery once fetal lung maturity was attained. Thirteen of the PIH patients delivered preterm (52 %). Two patients had AFLP who were managed by urgent termination of pregnancy and intensive care, but despite that, they developed acute liver failure which resulted in maternal as well as fetal mortality. The diagnosis of AFLP was confirmed with liver biopsy done at autopsy showing microvesicular steatosis.

When two most common etiologies of liver dysfunction in pregnancy, i.e. hepatitis E and PIH-related liver dysfunction, were compared (Table 2), the former presented with jaundice and fever significantly more often, while PIH presented with pedal edema and convulsions more often. Hepatitis E had significant higher levels of serum bilirubin, ALT, INR, and MELD score when compared to PIH, while the latter was associated with higher maternal age.

Other etiologies

Of tropical diseases ($n = 5$), two patients had Plasmodium vivax malaria, two had leptospirosis, and one had dengue shock syndrome. All presented in the third trimester. All of them developed multiorgan failure and maternal mortality was 100 % (5/5), and perinatal mortality was 80 % (4/5).

Table 2 Comparison of clinical features and biochemical parameters between viral hepatitis E and pregnancy-induced hypertension related liver dysfunction

Parameter	Hepatitis E ($n = 28$)	PIH ($n = 25$)	p-value
Jaundice	20 (71.4 %)	5 (20 %)	<0.001
Fever	22 (78.6 %)	6 (24 %)	<0.001
Abdominal pain	14 (50 %)	17 (68 %)	0.26
Pedal edema	5 (17.9 %)	19 (76 %)	<0.001
Oliguria	5 (17.9 %)	6 (24 %)	0.73
Encephalopathy	3 (10.7 %)	6 (24 %)	0.28
convulsions	0 (0 %)	6 (24 %)	0.008
Vaginal delivery	15 (53.6 %)	7 (28 %)	0.01
Maternal age (years)	23.8 ± 3.75	26.4 ± 4	0.017
Hemoglobin (g/dL)	10.1 ± 2.1	10.4 ± 2.7	0.56
Total leukocyte count (cells/μL)	15300 ± 10165	15200 ± 9050	0.95
Platelet count (cells/μL)	190000 ± 99960	145000 ± 85537	0.08
Creatinine (mg/dL)	1.12 ± 0.69	1.29 ± 0.80	0.40
Serum bilirubin (mg/dL)	7.46 ± 5.67	2.66 ± 2.32	<0.001
AST (IU/L)	662 ± 986	276 ± 327	0.060
ALT (IU/L)	501 ± 611	223 ± 194	0.029
ALP (IU/L)	462 ± 509	303 ± 152	0.14
INR	1.87 ± 0.94	1.39 ± 0.52	0.024
Serum proteins (mg/dL)	5.81 ± 0.53	5.6 ± 0.6	0.18
Albumin (mg/dL)	2.8 ± 0.41	2.8 ± 0.46	0.90
Weight of newborn (g)	1875 ± 627	1687 ± 554	0.25
MELD score	21 ± 7.7	15 ± 7	0.007

Values are presented as mean ± SD, or *n* (%)

PIH pregnancy induced hypertension, *AST* aspartate transaminase, *ALT* alanine transaminase, *ALP* alkaline phosphatase, *INR* international normalized ratio, *MELD* model for end-stage liver disease

Two patients had Crigler-Najjar syndrome type II. They presented with history of jaundice in present pregnancy and had past history of jaundice in childhood.

Maternal and perinatal mortality

Twenty-five maternal deaths occurred. Hepatitis E was the commonest cause (40 %) (10/25), followed by PIH-related diseases, 32 % (8/25), and tropical diseases, 20 % (5/25). Two deaths (8 %) occurred due to AFLP. Disease-specific mortality was 100 % in tropical diseases (5/5) and AFLP (2/2), 35.7 % in acute hepatitis E (10/28), and 32 % in PIH (8/25). On univariate analysis (Table 3), among clinical features, maternal mortality was significantly associated with the presence of jaundice, fever, abdominal pain, and oliguria. Among biochemical parameters, it was significantly associated with anemia, leukocytosis, thrombocytopenia, increased bilirubin levels, raised INR, lower serum proteins, low birth weight, and higher MELD score on admission. On multivariate logistic regression analysis (Table 4) of biochemical parameters found to be significant on univariate analysis, maternal mortality was significantly related to anemia ($p = 0.032$), leukocytosis ($p = 0.003$), and raised INR ($p = 0.031$).

A total of 31 perinatal deaths occurred. Hepatitis E accounted for 38.7 % perinatal deaths (12/31), followed by PIH 35.5 % (11/31), tropical diseases 12.9 % (4/31), cirrhosis of liver 6.5 % (2/31), and AFLP (6.5 %) (2/31). Disease-specific perinatal mortality was 100 % in AFLP and cirrhosis of liver (2/2 each), 80 % in tropical diseases (4 /5), 44 % in PIH-related diseases (11/25), and 42.8 % in hepatitis E (12/28). Hyperemesis gravidarum, hepatitis B, and ICP had benign courses without any maternal or perinatal mortality. On univariate analysis, fetal mortality was significantly associated with the presence of abdominal pain, oliguria, and encephalopathy. Among biochemical parameters, perinatal mortality was significantly associated with anemia, leukocytosis, thrombocytopenia, increased bilirubin, raised INR, albumin, low birth weight, and higher MELD score on admission. On multivariate logistic regression analysis of biochemical parameters found to be significant on univariate analysis, fetal mortality was found to be significantly related to only leukocytosis ($p = 0.003$).

Mode of delivery

Patients with PIH required delivery by cesarean section significantly more often when compared with hepatitis E as well

Table 3 Comparison of clinical features and biochemical parameters between maternal mortality and survivors

Parameter	Nonsurvivors ($n = 25$)	Survivors ($n = 78$)	p-value
Jaundice	19 (76 %)	29 (37 %)	0.001
Fever	13 (52 %)	20 (25.6 %)	0.025
Abdominal pain	18 (72 %)	26 (33.3 %)	0.001
Pedal edema	6 (24 %)	25 (32 %)	0.617
Oliguria	9 (36 %)	4 (5.1 %)	<0.001
Encephalopathy	5 (20 %)	5 (6.4 %)	0.060
Vaginal delivery	12 (48 %)	46 (59 %)	0.32
Maternal age (years)	25.6 ± 4.7	24.8 ± 3.5	0.425
Hemoglobin (g/dL)	9.1 ± 2.8	10.47 ± 2	0.029
Total leukocyte count (cells/μL)	24,500 ± 12,600	10,000 ± 4412	<0.001
Platelet count (cells/μL)	125,000 ± 102,110	196,000 ± 84,760	0.001
Creatinine (mg/dL)	2.53 ± 4.2	0.91 ± 0.41	0.066
Serum bilirubin (mg/dL)	6.5 ± 6	3.56 ± 3.7	0.028
AST (IU/L)	619 ± 1013	260 ± 430	0.096
ALT (IU/L)	385 ± 529	230 ± 338	0.18
ALP (IU/L)	429 ± 527	346 ± 198	0.25
INR	2.13 ± 0.93	1.21 ± 0.27	<0.001
Serum proteins (mg/dL)	5.6 ± 0.55	5.9 ± 0.61	0.030
Albumin (mg/dL)	2.77 ± 0.38	3.09 ± 0.9	0.089
Weight of newborn (g)	1626 ± 605	2161 ± 471	<0.001
MELD score	25 ± 8	13 ± 5.5	<0.001

Values are presented as mean ± SD, median (interquartile range) or *n* (%)

PIH pregnancy induced hypertension, *AST* aspartate transaminase, *ALT* alanine transaminase, *ALP* alkaline phosphatase, *INR* international normalized ratio, *MELD* model for end-stage liver disease

as other etiologies (Table 2). Fifteen patients (53.6 %) with viral hepatitis E and 7 patients (28 %) with PIH were delivered vaginally, and the rest were delivered by cesarean section ($p = 0.01$). Mode of delivery was not associated with survival (Table 3). Among survivors, 46 patients (59 %) were delivered vaginally and among nonsurvivors, and 12 patients (48 %) were delivered vaginally ($p = 0.32$).

MELD score

All patients' MELD score at admission was calculated. Using ROC curve (Fig. 1), MELD score >21 predicted maternal mortality with 80 % sensitivity and 91 % specificity with area under the ROC curve of 0.878 with $p < 0.001$.

Table 4 Multivariate logistic regression analysis of factors significantly associated with maternal mortality on univariate analysis

Parameter	Odds ratio (95 % CI)	p-value
Hemoglobin	0.457 (0.223, 0.935)	0.032
Total leukocyte count (cells/μL)	1.004 (1.000, 1.001)	0.003
International normalized ratio	92.9 (1.497, 5.76)	0.031

Discussion

Occurrence of liver dysfunction in pregnancy is a rare but potentially fatal disorder. In this study, pregnancy-specific causes were found in 39 % (40/103) patients. The proportion of pregnancy-specific liver diseases varies from 52 % to 89 % in various studies [7, 8].

This study highlights the high incidence of hepatitis E in pregnant females in western India. There were no hepatitis E epidemics during the study period in the localities where the patients came from and the cases represent sporadic hepatitis E. Hepatitis E was the commonest cause of liver dysfunction in pregnancy with incidence of 27.2 % (28/103). The incidence of hepatitis E in pregnancy varies geographically. A study in Egypt reported an incidence of hepatitis E in pregnancy as high as 84.3 % [9]. Study by Rathi et al. has shown the incidence of 16.5 % in Western India [7]. In North India, incidence of hepatitis E in pregnancy ranges from 37 % to 86 % in various studies [10, 11]. Whereas a study by Rasheeda et al. in South India has shown the incidence of 75 % [12]. The reasons for high incidence of hepatitis E in pregnancy may be that pregnancy is associated with high levels of steroid hormones leading to viral replication and direct inhibitory effect of steroids on hepatocytes [13].

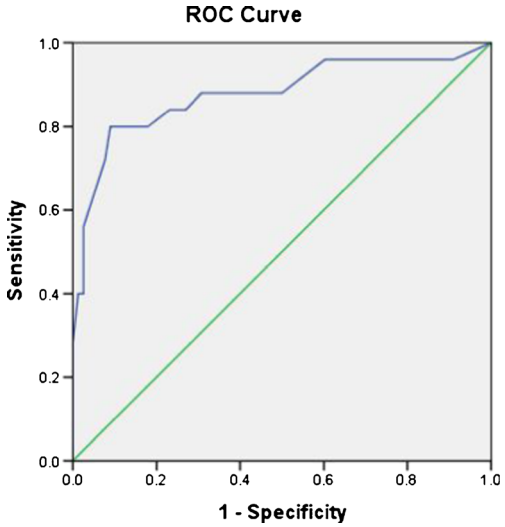

Fig. 1 Receiver operating characteristic curve of model for end-stage liver disease (MELD) score to predict maternal mortality (area under the ROC curve 0.878). MELD score >21 predicts maternal mortality with 80 % sensitivity and 91 % specificity

In the present study, hepatitis E was most prevalent in the third trimester (21/28). The disease-specific maternal mortality was 35.7 % (10/28) for hepatitis E and fetal mortality was 42.8 % (12/28). Such high maternal mortality rates in Western India are similar to North Indian studies ranging from 12 % to 64 % [10, 14]. There is a clear North vs. South divide among maternal mortality in hepatitis E in India. A South Indian study has shown a mortality rate of only 3.4 % despite high incidence [12]. Another study from Bangalore, South India by Devarbhavi et al. noted maternal mortality of 7.5 % in viral hepatitis [15]. Egyptian study had very high incidence of hepatitis E but no maternal mortality [9]. Reasons for geographical differences in the outcome may be early childhood exposures, producing immunity which modifies subsequent acute infections. There is low sero-prevalence of hepatitis E IgG in New Delhi as shown by Begum et al. leading to higher rates of clinical disease and maternal mortality [16]. The geographical differences in the maternal mortality may also be due to genotype shift in India. In a study by Kar et al., high HEV viral load was associated with acute liver failure as compared to acute viral hepatitis patients [17]. However, due to economic constraints, genotyping and viral load of hepatitis E could not be done in the present study.

Second most common etiology among viral hepatitis was hepatitis B ($n = 10$). Four patients were HBeAg-positive (40 %). HBeAg positivity was similar to the study done by Dwivedi et al. who found 56.8 % HBeAg positivity [18], but older studies have shown far less HBeAg positivity rates [19, 20]. Seroprevalence of HBsAg could not be found in the present study as it includes patients with deranged LFTs only. There was no maternal or fetal morbidity as well as mortality among patients with hepatitis B.

It is important to differentiate between viral hepatitis and PIH-related liver dysfunction early, as patients with PIH respond well to early delivery of the fetus. In the present study, PIH-related liver dysfunction has convulsions ($p = 0.008$) and pedal edema ($p < 0.001$) significantly more often, whereas viral hepatitis E has presence of jaundice ($p < 0.001$) and fever ($p < 0.001$) significantly more often. These clinical features should lead to suspicion of the etiology and management accordingly. Devarbhavi et al. noted that presence of ascites and hypertension differentiates pregnancy-associated acute liver dysfunction from viral hepatitis [15]. In the present study, hepatitis E had significant higher levels of bilirubin, ALT, INR, and MELD score when compared to PIH, whereas the latter was associated with higher maternal age (Table 2).

On multivariate logistic regression analysis, maternal mortality was significantly related to anemia ($p = 0.032$), leukocytosis ($p = 0.003$), and raised INR ($p = 0.031$). Mean total leukocyte count was $24{,}500 \pm 12{,}600/\mu L$ in maternal deaths as against $10{,}000 \pm 4412/\mu L$ in survivors. This indicates that maternal deaths had higher incidence of systemic inflammatory response syndrome (SIRS). This finding is similar to that of Sahai et al. [21].

Hepatitis E appears to cause coagulopathy in pregnant females with mean INR of 1.87 ± 0.94. The pathogenesis of coagulopathy in hepatitis E is not known. A Schwartzman-like reaction to viral proteins has been proposed [22]. Mean INR was 2.13 ± 0.93 in maternal deaths as against 1.21 ± 0.27 in survivors. Higher incidence of coagulopathy in maternal deaths correlates with Sequential Organ Failure Assessment (SOFA) score [23]. This finding is similar to that of Sahai and Kiran [24]. Higher prevalence of coagulopathy leading to disseminated intravascular coagulation (DIC) and presence of SIRS leading to multiorgan dysfunction explains high maternal mortality in acute hepatitis E in this study despite nondevelopment encephalopathy as a manifestation of acute liver failure.

Eight maternal deaths (32 %) and 11 perinatal deaths (44 %) occurred in PIH-related diseases. Various other studies have found maternal mortality rates in PIH ranging from 25 % to 44 % [7, 8, 15].

Indian studies have shown significant maternal mortality with AFLP ranging from 31 % to 100 % [25, 26]. Western studies have shown maternal mortality ranging from 0 % to 13 % and perinatal mortality of 0 % to 9 % [1]. The reason for higher maternal and fetal mortality may be that Indian patients present late to the healthcare facility and also higher intake of complementary and alternative medicines by them. A recent Indian experience has shown that with early diagnosis, urgent fetal delivery, and aggressive supportive care, significant reduction in maternal mortality in AFLP is possible [27].

Patients with pregnancy-specific liver diseases like PIH, ICP, and HELLP syndrome had rapid improvement in LFTs after delivery. LFTs came to 50 % of their maximum value in

mean 72 h of delivery and became normal within 2 weeks. This is consistent with findings of Tank et al. and Martin et al. [8, 28]. If LFTs do not show a decreasing trend and do not normalize in 2 weeks, additional causes should be sought.

In the present study, hyperemesis gravidarum accounted for 50 % of liver dysfunction in the first trimester. It is shown to be the commonest cause of liver dysfunction in the first trimester in some studies [7, 29].

In the present study, ICP had a benign course and did not result in maternal or perinatal mortality. It may be due to low mean levels of serum bile acids in our patients. These findings are similar to the study done by Rathi et al. who reported a low maternal mortality in ICP [7]. Of the neonates in ICP, three were preterm (37.5 %). Some studies show premature birth rate in ICP of up to 60 %. The onset of pruritus and higher maternal fasting serum bile acids have been shown to be associated with higher risk for premature delivery [30].

Tropical diseases have been found to cause severe liver dysfunction leading to 100 % maternal mortality. Sappenfield et al. in their systematic literature review have found that pregnant state leads to increased severity of disease for several pathogens like malaria, influenza, HSV, etc. [31]. Immune alteration during gestation impairing pathogen clearance may be the underlying pathophysiologic mechanism.

In our study, we had four pregnant patients with portal hypertension, two with cirrhosis and two with extrahepatic portal venous obstruction (EHPVO). Pregnancy in cirrhotics is rare due to amenorrhea and anovulation related to metabolic and hormonal disturbances [32]. Both patients with cirrhosis had perinatal mortality in the second trimester, whereas patients with EHPVO could complete term and were delivered with elective cesarean section to avoid aggravation of portal pressure during second stage of labor. No maternal or perinatal mortality occurred due to EHPVO. Aggarwal et al. have shown in a series of 26 pregnancies in 14 patients with EHPVO that these patients can be safely delivered vaginally [33].

Present study includes two patients with Crigler-Najjar syndrome. It is a rare autosomal recessive condition with an incidence of 1 in 1,000,000 births. These patients were treated with low-dose phenobarbitone, and their bilirubin levels were maintained to <8 mg/dL throughout pregnancy as suggested by Passeullo et al. [34]. Both patients had normal deliveries at term and neonates had normal bilirubin.

Two of the three factors used to calculate MELD score, i.e. serum bilirubin and INR, were significantly related to maternal mortality on univariate analysis. So, we tried to find the predictive ability of MELD score for maternal mortality. MELD score >21 predicted maternal mortality with 80 % sensitivity and 91 % specificity with area under ROC curve of 0.87 ($p < 0.001$; standard error 0.05; 95 % CI 0.78–0.97).

In the present study, we have found that maternal mortality remains high in patients with liver failure when MELD score exceeds 21 even if not complicated by development of encephalopathy as a manifestation of raised intracranial pressure. These may represent the patients who are yet to develop acute liver failure. Hence, MELD score >21 helps in early identification of patients at high risk of developing acute liver failure, and such patients should be referred for urgent liver transplantation which can be life saving for the mother as well as fetus. There are reports of successful intrapartum liver transplantation for acute liver failure [35, 36].

Murali et al. have evaluated the predictive accuracy of MELD score in pregnancy-specific liver diseases [2]. They devised a new logistic model based on two variables (bilirubin and INR), which also accurately predicted maternal mortality and was comparable with the MELD score. MELD score has been evaluated to predict outcome of pregnancy in cirrhotic patients by Westbrook et al. [37]. They found that MELD score ≥10 at the time of conception correlates with maternal liver-related complications as well as maternal death with 83 % sensitivity and 83 % specificity, while scores ≤6 conferred no excess risk with no maternal mortality. Present study shows that MELD score has predictive value in all etiologies. Only two cirrhotics were included in the present study, so predictive value of preconception MELD could not be evaluated. These two patients had MELD scores of 6 and 8, respectively, and maternal mortality did not occur in them.

The present study has certain limitations. It was carried out in a tertiary care referral center in Western India, so there is a possibility of referral bias. Viral profile of all neonates could not be done; hence, it was not possible to find the actual rates of vertical transmission.

Conclusions

Liver diseases are most common in the third trimester of pregnancy. Hence, frequent monitoring of liver function is required in the third trimester. Viral hepatitis, especially hepatitis E, is the commonest cause of liver disease in pregnant females in western India with significant morbidity and maternal and fetal mortality. Hence, emphasis should be given to maternal hygiene and clean drinking water. Other important causes of maternal mortality are PIH-related diseases and tropical diseases. Among clinical features, maternal mortality is significantly associated with presence of jaundice, fever, abdominal pain, and oliguria. Among biochemical parameters, maternal mortality was significantly associated with anemia, leukocytosis, and coagulopathy on multivariate analysis. Patients with these features should receive intensive management from the outset.

MELD score is an excellent predictor of maternal mortality in patients with all etiologies of liver dysfunction. MELD score >21 predicts maternal mortality with 80 % sensitivity and 91 % specificity; hence, such patients should be referred

for liver transplantation at the earliest. MELD score can be incorporated as a tool in managing liver disease in pregnancy. Further prospective studies are needed to evaluate utility of MELD score in pregnancy.

Compliance with ethical standards

Conflict of interest DS, CR, VP, MP, AP, and PS, authors of this study, declare that there is no conflict of interest involved.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments.

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