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ORIGINAL ARTICLE

Obstetric Outcome in Women with Chronic Liver Disease

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Abstract

Aim This study determines the prevalence, causes and outcome of pregnancy in women with chronic liver diseases in a tertiary level teaching institute in Southern India.

Methods Retrospective analysis of case records was carried out between December 2010 and May 2015 in the departments of Obstetrics and Gynecology and Gastroenterology including pregnant women diagnosed to have chronic liver diseases prenatally or during pregnancy.

Results The frequency of chronic liver disease in pregnancy was 50 among 10,823 deliveries (0.4%). Twenty-six women with chronic liver disease had 50 pregnancies during the study period. Fifty percent of the women had cirrhosis. Maternal complications occurred in 22% of the study group. Variceal hemorrhage occurred in 4%, and

hepatic decompensation occurred in 16%. There were two maternal deaths (4%). Obstetric complication such as preeclampsia, postpartum hemorrhage and puerperal infection occurred in 18, 14 and 18%, respectively. Abortion occurred in 34%, 55% in cirrhotic and 4.8% in non-cirrhotic. Live birth rate of 76% was significantly higher ($p < 0.014$) in the non-cirrhotic group compared to cirrhotic group.

Conclusion Pregnancies in chronic liver disease are associated with high rate of abortions. Live birth rates are better and complications such as variceal bleeding or decompensation of liver disease are less common than previously reported.

Keywords Chronic liver disease · Cirrhosis · Pregnancy · Hepatic decompensation · Variceal hemorrhage

Introduction

Pregnancy in the setting of preexisting liver disease is not rare. Cirrhosis was earlier thought to lead to infertility from disruption of the hypothalamic-pituitary axis together with disturbed estrogen metabolism leading to anovulation and amenorrhea [1]. Advances in diagnosis and treatment of chronic liver disease (CLD) have resulted in higher conception rate and successful pregnancy outcomes [2]. Given the advances in the care of patients with CLD, increasing number of pregnancies will be encountered and create dilemmas in the management and prognosis of such cases. Studies focusing on the complications arising from this unique combination in mother and neonate are rare [3–5]. We therefore analyzed our experience with regard to the course of pregnancy and maternal–fetal outcome in women with CLD at a tertiary medical college teaching hospital, in Southern India.

Methods and Material

We conducted a retrospective case review of women admitted with pregnancy in departments of Obstetrics and Gynecology and Gastroenterology, St. John's Medical College, Bangalore. The study was approved by the institutional ethics committee. As it was a retrospective study, consent from participants was waived, but confidentiality was maintained. CLD was diagnosed either prenatally or during pregnancy in women attending the inpatient or outpatient services of the departments of Obstetrics and Gynecology and Gastroenterology during the study period. Women with pregnancy-specific liver diseases such as hyperemesis gravidarum, acute fatty liver of pregnancy, intrahepatic cholestasis of pregnancy, hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome and acute viral hepatitis were excluded from the study.

Chronic liver disease was defined as any liver disease of more than 6-month duration. Detailed history and relevant investigations were extracted from the case records. These included complete hemograms, liver function tests, renal function tests, coagulation profile, hepatitis viral markers, antinuclear antibody, serum ceruloplasmin, urinary copper levels, Doppler ultrasonography findings, upper gastrointestinal findings. MELD score (model for end-stage disease) was calculated for each of these patients [6]. Cirrhosis was diagnosed on the basis of clinical and imaging findings including ultrasonography features showing liver of typical or reduced size in the presence of one or more of the following findings: coarse liver, irregular liver, decreased ratio of the right to left lobes suggested cirrhosis [7].

EHPVO was diagnosed on the basis of the following criteria: (1) presence of portal cavernoma on Doppler ultrasound, (2) hypersplenism, (3) endoscopic evidence of upper gastrointestinal varices [8, 9]. The diagnosis of NCPF was based on evidence of portal hypertension, patent portal vein on ultrasound and absence of cirrhosis [10]. Budd–Chiari syndrome was diagnosed on the basis of CT scan abdomen findings showing hepatic vein outflow obstruction or inferior vena cava obstruction [11]. Wilson's disease was diagnosed by standard criteria [12]. Autoimmune hepatitis was diagnosed by characteristic clinical features, exclusion of other causes of chronic liver conditions and presence of characteristic autoantibodies including antinuclear antibody, smooth muscle antibody, anti-liver kidney microsomal (LKM) antibody and hypergammaglobulinemia specifically IgG [13].

The primary outcome measures assessed were incidences of variceal hemorrhage needing endoscopic treatment during pregnancy or immediate postpartum, rate of hepatic decompensation such as ascites, hepatic encephalopathy or flare of disease with jaundice, hepatorenal syndrome, hypoglycemia, coagulopathy, transfusional requirement of blood and blood products, intensive care unit admission rate and incidence of maternal mortality. The secondary outcome measures evaluated were associated obstetric complications such as abortion, hypertensive disorders of pregnancy, intrauterine growth restriction, postpartum hemorrhage, puerperal sepsis and neonatal outcomes measures like stillbirths, neonatal death, Apgar score, prematurity, low birth weights, need for neonatal intensive care unit (NICU) admission. Postpartum follow-up details of all these women were recorded.

Statistical Analysis

Categorical variables were summarized using frequency and percentages. The continuous variables were

summarized using mean and standard deviation or median and interquartile range as appropriate. Chi-square test was used for comparative analysis.

Results

A total of 50 pregnancies occurred in 26 women with chronic liver diseases during the study period December 2010 to May 2015. The demographic details and mode of presentation are depicted in Table 1. The mean age of the patients was 25.6 years (range 19–38). There were equal number of primigravidae and multigravidae. Nineteen percent ($n = 5$) had Wilson's disease and were on treatment with penicillamine and zinc. Esophageal varices were present in 65% ($n = 17$), and endoscopic treatment (variceal ligation in two and sclerotherapy in three) had been carried out in five (19.2%) prior to pregnancy. Anemia, thrombocytopenia secondary to hypersplenism and coagulation abnormalities were present in 78, 76 and 16%, respectively. Ascites, jaundice and portal hypertension were present in 34, 16 and 90% of the study cohort at booking visit. The median MELD score calculated at the onset of pregnancy was 6, with the 25th and 75th percentile being 6 and 10, respectively.

Table 1 Demographic features of women with chronic liver disease in pregnancy

Demographic details	*n*	%
Age range (years)		
<20	2	7.6
20–30	21	80.7
>30	3	11.5
Gravidity		
Primigravidae	13	50
Multigravidae	13	50
Duration of disease (years)		
5–10	8	30.7
1–5	11	42.3
<1	7	26.9
Drug treatment		
Penicillamine/zinc	5	19.2
Propranolol	4	15.3
Azathioprine/wysolone	3	11.5
Tenofovir/lamivudine	2	7.6
Endoscopic treatment prior to gestation	5	19.2
Associated features at booking		
Anemia	39	78
Esophageal varices	32	64
Ascites	17	34
Jaundice	8	16
Portal hypertension	45	90
Splenomegaly	42	84
Thrombocytopenia	38	76
Abnormal INR	8	16

Table 2 Etiologic distribution of the 26 women with chronic liver disease

	No.	Percentage
Group A without cirrhosis (50%)		
EHPVO	12	46.1
Non-cirrhotic portal fibrosis	1	3.8
Group B with cirrhosis (50%)		
Wilson's disease	5	19.2
Autoimmune hepatitis	2	7.6
Budd–Chiari syndrome	2	7.6
Hepatitis B-related disease	2	7.6
Cryptogenic liver disease	2	7.6

The etiologic distribution for the women with chronic liver disease in pregnancy is shown in Table 2. Fifty percent of our study group (13 women with 28 pregnancies) had cirrhosis and included five (19.2%) women with Wilson's disease. The remaining 50% were women with EHPVO (46%) ($N = 12$) and NCPF (3.8%) ($N = 1$).

The primary outcome measures are summarized in Table 3. Variceal hemorrhage requiring endoscopic therapy occurred in 2 out of 50 pregnancies (4%). Hepatic decompensation occurred in 16% ($N = 8$). Acute on chronic liver failure occurred in two patients (4%). One occurred in a woman who developed a flare of autoimmune hepatitis at 20 weeks resulting in maternal death. The other occurred in a woman who developed a flare of hepatitis B with underlying post-hepatitis B liver cirrhosis. Four women developed increasing ascites, and two experienced variceal hemorrhage. Blood and blood products were transfused in 56% of the cases [packed cells in 30%, platelet concentrate in 36% and fresh frozen plasma (FFP) in 12% in 50 pregnancies]. Blood transfusions were generally required in the peripartum period in the event of severe anemia with hemoglobin less than 7 gm%, platelet count lesser than 50,000, INR being more than 1.5 and/or occurrence of postpartum hemorrhage. Women with EHPVO and NCPF had a greater requirement for blood and blood products during their gestation as a result of hypersplenism and thrombocytopenia. Seven of 50 (16%) pregnancies required ICU admission for an average of 5.8 days. There were two maternal deaths (4%) in our study, one following eclampsia and sepsis in the cryptogenic liver disease group and another in a woman with autoimmune hepatitis who developed a spontaneous flare at 20 weeks.

Secondary outcome measures are shown in Table 4. Obstetric complications such as hypertensive disorders of

Table 3 Primary outcome measures in pregnant women with chronic liver disease

Primary outcomes	Total *n* (%)	Cirrhotic *n* (%)	Non-cirrhotic *n* (%)	*p* value
Variceal bleeding	2 (4)	1 (3.4)	1 (4.8)	1.0
Acute liver failure	2 (4)	2 (6.9)	0 (0)	0.5
Hepatic decompensation	8 (16)	6 (20.7)	2 (9.5)	0.44
Blood transfusion	28 (56)	12 (41.4)	16 (76.2)	0.01
ICU admission	8 (16)	4 (13.8)	4 (19)	0.70
Maternal mortality	2 (4)	2 (6.9)	0 (0)	0.503

Table 4 Secondary outcome measures in pregnant women with chronic liver disease

	Total *n* (%)	Cirrhotic *n* (%)	Non-cirrhotic *n* (%)	*p* value
Abortion	17 (34)	16 (55.2)	1 (4.8)	<0.001
Preeclampsia	9 (18)	5 (17.2)	4 (19)	1.0
Postpartum hemorrhage	7 (14)	5 (17.2)	2 (9.5)	0.68
Puerperal infection	9 (18)	4 (13.8)	5 (23.8)	0.464
Growth restriction	4 (8.0)	1 (3.4)	3 (14.3)	0.297
Live birth	28 (56)	12 (41.4)	16 (76.2)	0.014
Still birth	5 (10)	2 (6.9)	3 (14.3)	0.638
Neonatal death	3 (6)	1 (3.4)	2 (9.5)	0.565
Preterm	7 (25)	5 (41.7)	2 (12.5)	0.103
LBW	9 (32)	5 (41.4)	4 (25)	0.432
Low APGAR score	6 (21.4)	3 (25)	3 (18.7)	1.00
NICU admission	10 (35.7)	6 (50)	4 (25)	0.243
Perinatal mortality	8 (24.2)	3 (23.1)	5 (25)	1.00

pregnancy, intrauterine growth restriction, postpartum hemorrhage and puerperal infections developed in 18, 8, 14 and 18% of cases, respectively.

The 50 pregnancies in 26 women resulted in 17 (34%) abortions, 28 (56%) live births, 5 (10%) still births and 3(6.0%) neonatal deaths. The perinatal mortality was 24%. The mean gestational age at delivery was 36.5 weeks (standard deviation 3.3 weeks, minimum 27 weeks and maximum 40 weeks). The mean birth weight was 2.4 kg (standard deviation 0.65 kg, minimum of 1 kg and maximum 3.6 kg). Prematurity, low birth weight and low APGAR was found in 35, 42.8 and 21.4% of the live births. Eleven of these needed NICU care (39.2%), cause for admission to the neonatology unit being prematurity or low birth weight, low APGAR or neonatal jaundice. Outcomes of the 50 pregnancies in women with chronic liver disease are represented in Fig. 1.

Discussion

There are limited data available on the obstetric outcome in women with chronic liver diseases. Similarly, the effects of pregnancy in CLD are also limited. Recent literature including results from this study demonstrates that the fetomaternal outcome partly depends on the etiology and the severity of the underlying liver disease. The better results in this study compared to some earlier ones could possibly be because a significant proportion (50%) of our cohort had EHPVO or NCPF. Even in the remaining 50% with cirrhosis; comprising of Wilson's disease (19%), autoimmune hepatitis (7.6%), hepatitis B cirrhosis (7.6%), Buddchiari syndrome (7.6%) and cryptogenic liver disease (7.6%) the fetomaternal outcome was favourable. The low risk of variceal bleeding and mortality is highlighted in our study and likely is a result of better control of portal hypertension before and during pregnancy. This is supported by a recent study where adequate control of portal hypertension in EHPVO results in better outcome [14].

The two deaths in our series, one in a patient with autoimmune hepatitis and another in a woman with hepatitis B, highlight the spontaneous flare that may occur with these diseases. Both these women were unaware of the disease before pregnancy, and the diagnosis was only made during the occurrence of jaundice in pregnancy. Flares of both diseases have been described in pregnancy and perhaps can be prevented by continuation of treatment throughout pregnancy and postpartum period [15].

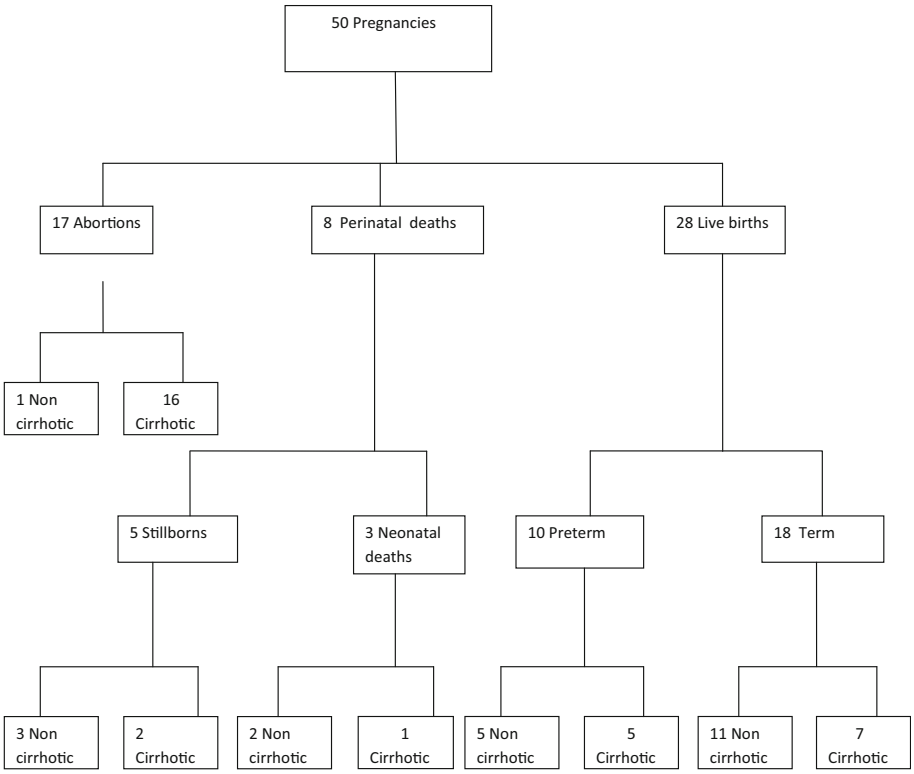

Fig. 1 Algorithm demonstrating the outcomes of 50 pregnancies in women with chronic liver disease

Although treatment was started soon after diagnosis, the disease state was advanced and treatment duration too short to make a difference. The effect of adequate treatment is highlighted by the excellent outcome in five women with Wilson's disease who received treatment before and during pregnancy resulting in successful outcome for both the mothers and babies. This is again in line with some recent experience [16]. In fact, all five women with Wilson's disease tolerated pregnancy well and had a live birth rate of 53%.

The optimal management of pregnancy with cirrhosis and portal hypertension is ill defined. Most patients with advanced cirrhosis have low fertility; but successful pregnancy may be completed in those with well-compensated disease and mild portal hypertension. We found the live birth rate to be 76% in the non-cirrhotic group (12 women with EHPVO and 1 with NCPF) in our study cohort. Women with cirrhosis had abortion rate of 55% and live birth rate of 42%. The main maternal risk associated with pregnancy in cirrhosis is from portal hypertension and can result in maternal complications in 30–50% of patients [17]. In our study cohort, it was found to be 22%.

The maternal outcome was good in our study. The overall incidence of variceal hemorrhage 4% (3.5% in cirrhosis and 4.5% in non-cirrhosis) is much lower as compared to some earlier studies that have reported variceal hemorrhage in up to 42% of pregnant women with cirrhosis [18–20]. Indeed prior to the era of prophylactic therapy with banding or beta blockers, bleeding rates as high as 78% were described [21]. Our results are supported by two studies with bleeding rates between 2.2 and 5% [4, 22], illustrating the efficacy of proper control of portal hypertension before pregnancy resulting in reduced complications of variceal bleeding. The two patients out of 26 women in our study group developed esophageal variceal bleeding at 19 weeks and another at postpartum and were controlled with endoscopic variceal ligation. It has been recommended that routine endoscopic evaluation and treatment should be carried out prior to conception for medium to large varices [8, 14]. Although pregnancy does not worsen liver disease specifically, previous studies have reported that hepatic decompensation can develop in 15–24% of women with cirrhosis [3, 4, 20]. Our incidence of hepatic decompensation was 16% women.

The greatest need for blood transfusion occurs in the peripartum period [23]. Fifty-six percent of our study group needed transfusion of blood and its products, with postpartum hemorrhage being the largest indication in 18% of women. Obstetric complications such as pregnancy-induced hypertension (18%), intrauterine growth restriction (8%), puerperal infections (18%) and postpartum hemorrhage (14%) occurred whose frequencies are in line with a

recent survey [4]. Although splenic artery rupture is said to affect up to 2.6% of pregnancies in patients with cirrhosis [18, 20], none were reported in our study.

Based on sparse data available, maternal mortality in women with cirrhosis and portal hypertension is estimated at 10–18% [17] which is higher than maternal mortality of 7.8% described in post-hepatitis liver cirrhosis [5]. The maternal mortality was 4% in our cohort of cirrhotic women, which is even lower and suggests the improved preconception control of disease status prior to conception.

The optimal mode of delivery in a woman with chronic liver disease is controversial and is dependent on the presence or absence of large esophageal varices, degree of liver dysfunction or presence of thrombocytopenia. Rasheed et al. [5] concluded that variceal bleeding during vaginal delivery was the most frequent cause of mortality among patients in their cohort. Contrary to this, in our study 70% of deliveries (26 women with chronic liver diseases who had 33 viable pregnancies) were delivered vaginally and 30% were subjected to cesarean section which was carried out for obstetric indications. There were no cases of mortality or complication from vaginal delivery. Even in the cirrhosis group the incidence of vaginal delivery was fairly high (61.5%), suggesting that vaginal delivery is safe and variceal bleeding during delivery is an overstated and rare event. This could be achieved with improved obstetric services, multidisciplinary approach and intensive care facilities. A similar conclusion was reached in a study of 53 and 38 patients with cirrhosis and non-cirrhosis, respectively [19].

However, the high incidence of fetal wastage in women with chronic liver disease continues to challenge the care of these patients [24]. Thirty-four percent of the 50 pregnancies in our study cohort resulted in abortions mostly in the cirrhotic group (55%). In the non-cirrhotic group abortion rate was only 4% (p value <0.001). Live birth rate in the non-cirrhotic group was higher (76%) against 42% in the cirrhotic group. Prematurity, intrauterine growth restriction and NICU admission frequently complicate pregnancies in women with CLD, and their occurrence was 20, 8 and 39% in our study cohort, respectively [4].

In conclusion, our experience demonstrates that pregnancies in women with chronic liver disease including those with cirrhosis result in a good outcome with minimal mortality and complications of hepatic decompensation. Vaginal delivery can be safely recommended with cesarean section dictated by obstetric indications. Proper management of portal hypertension with beta blockers and variceal banding before pregnancies prevents the serious complication of variceal bleeding. Proper coordination across different specialties including obstetrician, gastroenterologist, neonatologist and intensivists will optimize pregnancy and neonatal outcome.

Compliance with Ethical Standards

Conflict of interest Pinky Jena, CN Sheela, Rao Preethi Venkatachala and Harshad Devarbhavi declare that they have no conflicts of interest.

Ethical Statements The study has received institutional ethics committee approval. By virtue of being a retrospective case record review, informed consent for the same has been waived.

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