Is pregnancy safe with extrahepatic portal vein obstruction? An analysis

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INTRODUCTION We aimed to analyse the pregnancy outcome of women with extrahepatic portal vein obstruction.
METHODS This was a retrospective observational analysis conducted at the Institute of Postgraduate Medical Education and Research, Kolkata, India, between January 2007 and September 2009. A total of 41 pregnancies in 24 women were evaluated.
RESULTS All women conceived spontaneously (maternal age 20–35 years). 17 women had moderate-to-severe anaemia, and five women had pancytopenia. Variceal bleeding occurred in ten women during pregnancy, which was managed successfully with endoscopic sclerotherapy in eight women and endoscopic variceal ligation in two women. Preterm labour (14.63%), postpartum haemorrhage (7.31%), abortion (4.87%) and pregnancy-induced hypertension (4.87%) were observed in the 41 pregnancies. There were 39 live births and almost all mothers delivered vaginally, except for four who underwent Caesarean section for obstetric indications. Prematurity (15.38%), low birth weight (10.25%), admission to the neonatal intensive care unit (12.82%), stillbirth (2.56%) and neonatal death (2.56%) were noted in the newborns.
CONCLUSION Variceal bleeding during pregnancy coincided with unfavourable outcomes. Although endoscopic obliteration of varices is a safe and effective method for antenatal management of varices in women, prenatal obliteration results in less morbidity. On rare occasions, obliterated varices can bleed in subsequent pregnancies. Therefore, preconception evaluation of the state of varices prior to each pregnancy and their ligation are important aspects of counselling. A successful foetomaternal outcome is achievable with multidisciplinary backup in a tertiary care centre.

Keywords: EHPVO, EST, EVL, portal vein cavernoma, pregnancy outcome
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INTRODUCTION

Prehepatic portal vein occlusion with portal cavernoma formation developing into prehepatic portal hypertension is called extrahepatic portal vein obstruction (EHPVO).[1,2] In developing countries, it is a common cause of non-cirrhotic portal hypertension (NCPH), accounting for up to 30% of all variceal bleeders, and is second only to cirrhosis of the liver (accounting for up to 5% to 10% of variceal bleeders).[1] EHPVO with paediatric origin, which may result from umbilical sepsis, intraluminal trauma due to exchange transfusion, repeated pylephlebitis following intra-abdominal sepsis or necrotising enterocolitis, is responsible for 70% of childhood portal hypertension.[1,3,4] Adult-onset EHPVO occurs due to a thrombotic stimulus, such as pregnancy, oral contraceptive pills, myeloproliferative disorders, or deficiencies of protein C and protein S.[1,4] It generally presents with repeated episodes of variceal bleeding, asymptomatic splenomegaly or features of hypersplenism, and rarely, as jaundice and ascites.[1]

In pregnancy, the hypervolaemic state in women creates increased portal flow, which contributes to high portal pressure being transmitted to the upper gastrointestinal (GI) collateral veins and thus increases the risk of variceal bleeding.[5] Pregnancy has even been viewed as a potential hazard that could cause recurrent variceal bleeding in women with EHPVO that has not been treated properly.[6] Studies have suggested that fertility is near normal among such women with NCPH, and that the number of expected spontaneous abortions and stillbirths in this cohort approaches that in the general population, as liver function usually remains preserved in these patients.[5,7,8] As a majority of patients with EHPVO usually receive medical attention in childhood or adolescence due to associated life-threatening complications, with the advancement of endoscopic interventional therapy, there are increasing numbers of such children reaching adulthood and achieving pregnancy, unlike those with cirrhosis.

The objective of this study was to assess the clinical profile, management and foetomaternal outcome in pregnant women with EHPVO in terms of morbidity and mortality.

METHODS

This retrospective observational study was conducted from January 2007 to September 2009 at the Department of Obstetrics and Gynaecology and the School of Digestive and Liver Diseases (SDLD), Institute of Postgraduate Medical Education and Research, Kolkata, India. A total of 41 pregnancies in 24 women with EHPVO due to portal vein cavernoma were included in the study. EHPVO was diagnosed based on four criteria: (a) the presence of variceal bleeding; (b) presence of splenomegaly; (c)

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Table I. Demographic characteristics of patients with extrahepatic portal vein obstruction (n = 24).

Demographic	No. (%)
Age range (yrs)	
< 20	8 (33.33)
20–30	12 (50.00)
> 30	4 (16.66)
Gravidity	
Primigravidae	13 (54.16)
Multigravidae	14 (5.83)
Presenting complaint	
Variceal bleeding	19 (79.16)
Abdominal lump	22 (91.66)
Jaundice	2 (8.33)
Ascites	2 (8.33)
Clinical history	
Previous abdominal surgeries	4 (16.66)
Umbilical sepsis	5 (20.83)

presence of portal vein cavernoma on Doppler ultrasonography; and (d) endoscopic evidence of upper GI varices.[1] The women were divided into two groups: patients with EHPVO already registered at the SDLD, who subsequently conceived (prenatally diagnosed patients); and antenatal women presenting to the Department of Obstetrics and Gynaecology with acute symptoms of EHPVO, who were diagnosed with EHPVO thereafter (antenatally diagnosed patients). Women with diagnoses of liver cirrhosis, altered liver function test, Budd-Chiarri syndrome, portal vein thrombosis, non-cirrhotic portal fibrosis and hepatocellular carcinoma, as well as those positive for hepatitis B and C, were excluded from the analysis.

Careful history taking and relevant investigations, such as Doppler ultrasonography and upper GI endoscopy, were performed to confirm the diagnosis of EHPVO in accordance with the criteria mentioned above. Laboratory investigations, including total haemogram, liver function test, renal function test, coagulation profile, hepatitis B surface antigen and anti-hepatitis C virus tests, were performed for all patients. Data were compiled from patient history and the existing medical records for prenatally diagnosed patients to determine the frequency and duration of variceal bleeding before and during pregnancy, with details of endoscopic interventions, in these patients. Maternal outcome was analysed based on disease-associated and obstetric outcomes. Foetal outcome was evaluated using determinants, such as Apgar score, birth weight, asphyxia at birth and definitive events (stillbirth and neonatal deaths).

Informed consent was obtained prior to the procedures. The varices were graded and variceal bleeding was managed using endoscopic sclerotherapy (EST) or endoscopic variceal ligation (EVL) in accordance with institutional protocols that follow the American Society of Gastrointestinal Endoscopy guidelines.[5] Varices of grade III and IV, with or without bleeding, were managed by endoscopic interventions. EST was done by injecting a sclerosing agent (absolute alcohol) directly onto the varices or paravariceal areas, carried out at 2–3 week intervals till obliteration was complete. EVL was done using a multiple band applicator mounted on the upper GI endoscope. Maternal and foetal well-being were closely watched and supportive therapies were provided for variceal bleeding as required. Informed consent for participation in the study was obtained from each patient. The data were statistically analysed using Graph Pad Prism version 4 (Graph Pad Software Inc, Santiago, CA, USA). The categorical variables between the prenatally and antenatally diagnosed patients were compared using Fisher's exact test. A p-value < 0.05 was considered statistically significant.

RESULTS

A total of 226 patients with EHPVO were registered at the SDLD during the study period, of which 67 were women. 24 (35.82%, 24/67) women conceived, resulting in 41 pregnancies. The mean age of the patients was 26.7 (range 19–35) years. Of these 24, 13 (54.16%) patients were primigravidae (Table I). Variceal bleeding was the presenting complaint in 19 (79.16%) women, 10 of whom presented during pregnancy, while features of hypersplenism were seen in five (20.83%) patients. A childhood history of umbilical sepsis (n = 5, 20.83%) or abdominal surgery (cholecystectomy/appendectomy; n = 4, 16.66%) was seen in some patients.

Haematological investigations at presentation revealed microcytic hypochromic anaemia (haemoglobin 6–10 g/dL) in 17 (70.83%) women and pancytopenia in five (20.83%) women (Table II). Two patients among the five with pancytopenia had an abnormal coagulation profile (total platelet count $< 1.5 \times 105/mm^3$, international normalised ratio [INR] > 1.5). Upper GI endoscopy showed oesophageal varices in all 24 patients and concomitant gastric varices in 18 (75.00%) women.

All patients underwent endoscopic interventions (Table III). 16 women were prenatally diagnosed with EHPVO, among whom EST was performed for six women and EVL for eight women prior to pregnancy. Two women, for whom EST failed, required EVL antenatally. All women diagnosed with EHPVO during pregnancy underwent antenatal EST. Instances of preterm labour (n = 6, 14.63%), postpartum haemorrhage (n = 3, 7.31%), abortion (n = 2, 4.87%) and pregnancy-induced hypertension (n = 2, 4.87%) were observed in the 41 pregnancies (Table IV). The disease-associated morbidities observed included variceal bleeding (24.39%), ascites (2.43%), pancytopenia (12.19%) and jaundice (4.87%). Ten women had antenatal variceal bleeding (first trimester n = 2; second trimester n = 3; third trimester n = 5). Most women delivered vaginally, and of the 18 institutional deliveries, Caesarean sections were performed only on four women due to obstetric indications. Complications due to ascites, jaundice and pancytopenia resulted in one maternal death, where the patient succumbed to postpartum haemorrhage, disseminated intravascular coagulation and multiorgan failure (maternal mortality n = 1, 4.16%).

There were 39 live births (Table V). The median gestational ages at delivery in the prenatally and antenatally diagnosed groups were 38 (range 28–42) weeks and 34 (range 28–37) weeks, respectively. The median birth weights in the prenatally and antenatally diagnosed groups were 2.824 (range 2.403–

Table II. Findings of investigations done at the time of presentation.

Finding	No. (%)
Blood indices	
Anaemia (< 11 g/dL)	17 (70.83)
Leukopenia (< 4,000/mm^3)	11 (45.83)
Thrombocytopenia (< 1.5 × 105/mm^3)	5 (20.83)
Abnormal coagulation profile (INR > 1.5)	2 (8.33)
Pancytopenia	5 (20.83)
Ultrasonography	
Splenomegaly	24 (100.00)
Ascites	2 (8.33)
Portal cavernoma	24 (100.00)
Upper gastrointestinal endoscopy	
Gastric varices	18 (75.00)
Grade II	6
Grade III	8
Obliterated	4
Oesophageal varices	24 (100.00)
Grade III	8
Grade IV	6
Obliterated	12

INR: international normalised ratio

Table III. Details of therapeutic endoscopic interventions performed for patients.

Therapy	No. (%)
Therapy prior to pregnancy (prenatally diagnosed patients)	16
EVL	8 (50.00)
EST	6 (37.50)
EVL + EST	2 (12.50)
Therapy during pregnancy (antenatally diagnosed patients)	10
EVL	8† (80.00)
EST*	2 (20.00)

*Patients who had rebleeding in spite of EST prior to pregnancy.
†Eight patients were diagnosed with extrahepatic portal vein obstruction during pregnancy.
EVL: endoscopic variceal ligation; EST: endoscopic sclerotherapy

3.565) kg and 2.156 (range 1.260–2.943) kg, respectively. For 37 babies, the Apgar scores at five minutes were 8–9. Foetal outcome was varied – prematurity (gestational age < 37 weeks; n = 6, 15.38%), low birth weight (weight < 2.5 kg irrespective of gestational age; n = 4, 10.25%) and admission to the neonatal intensive care unit (NICU; n = 5, 12.82%) were noted among the newborns. Reasons for admission to the NICU ranged from prematurity and jaundice to low birth weight. Perinatal mortality included stillbirth (n = 1, 2.56%) and neonatal death (n = 1, 2.56%) due to extreme prematurity and birth asphyxia.

DISCUSSION

EHPVO is a vascular disorder of the liver, which is characterised by features of recent thrombosis with portal cavernoma as a sequela of portal vein obstruction.[9] It is an important cause of NCPH, especially in Third World countries.[4] In India, EHPVO is more frequent due to childhood aetiologies, such as umbilical sepsis and pylephlebitis, and rarely, following home deliveries in rural, backward areas.[6] Unlike in women with cirrhosis and chronic active hepatitis, conception in women with EHPVO is reported to be mostly spontaneous, as normal liver function is usually preserved in these patients.[1,7,8,10] Our results supported this observation.

Most women in our series were anaemic (70.83%), and five patients had pancytopenia due to hypersplenism. Haemoglobin levels were 6–10 g/dL in the anaemic patients. An atypical presentation noted in our patients was icterus in two patients due to portal biliopathy, which is generally defined as abnormalities in the extrahepatic and intrahepatic bile ducts of patients with EHPVO, and is very rarely symptomatic in adulthood.[1,9] Variceal bleeding was the commonest feature on presentation (79.16%), especially in the later stages of pregnancy. Similar to the observations of Aggarwal et al,[11] most patients with a prenatal diagnosis of EHPVO in our series presented with fewer varix-related morbidities. However, two women in our study with previously obliterated varices had recurrence of variceal bleeding during pregnancy.

It is widely known that the altered physioanatomy of normal pregnancy causes hypervolaemia and raises cardiac output in women while decreasing venous return via the inferior vena cava, especially toward full term. These factors ultimately increase the splanchnic and portal venous pressures, resulting in a transient increase in the oesophageal variceal pressure, thus leading to its bleeding.[10,12] Upper GI varices in our patients were treated by endoscopic procedures, such as EST and EVL, especially in women with grade III and IV varices. Ten women with bleeding varices were managed antenatally, eight of whom received EST; EVL was required for two patients, as recurrent variceal bleeding was seen in spite of the EST performed.

EST is widely believed to help achieve subsequent successful pregnancy outcomes in women with EHPVO, as it does not interfere with conception when performed prenatally and is also considered a safe and effective antenatal procedure.[1,7,8,13] Our results support these findings and suggest that EVL is an equally safe and effective procedure for pregnant women for whom EST has failed. International consensus on EHPVO is that oesophageal varices, if detected during gestation, should be banded or obliterated to prevent rebleeding.[1] Prevention of variceal haemorrhage should be undertaken when the patient develops medium- to large-sized varices.[14] Although the current literature suggests that EVL is more effective than EST in controlling variceal bleeding,[15] our results indicate that both procedures are safe and effective for pregnant women. According to the recent report of the Baveno V consensus workshop, EVL is the recommended form of endoscopic therapy for acute oesophageal variceal bleeding, although sclerotherapy may be used in the acute setting, if ligation is technically difficult.[9]

Variceal bleeding was an important predictor of pregnancy outcome in the present analysis, with other predictors being comorbidities, such as maternal jaundice, ascites and pancytopenia. The only maternal mortality encountered in our series was a patient with pancytopenia, ascites and jaundice, who died due to postpartum haemorrhage, subsequent disseminated intravascular coagulation and multiorgan failure. This patient had

Table IV. Maternal outcome of the 41 pregnancies.

Maternal outcome	No. (%)			p-value
	Pregnancies with prior diagnosis and treatment (n = 33)	Pregnancies without prior diagnosis and treatment (n = 8)	Total	
Disease-associated complication				
Variceal bleeding	2 (6.06)	8 (100)	10 (24.39)	< 0.001
Ascites	0	1 (12.5)	1 (2.43)	0.195
Pancytopenia	1 (3.03)	4 (50.0)	5 (12.19)	< 0.001
Jaundice	1 (3.03)	1 (12.5)	2 (4.87)	0.356
Obstetric event				
Abortion	1 (3.03)	1 (12.5)	2 (4.87)	0.356
Pregnancy-induced hypertension	1 (3.03)	1 (12.5)	2 (4.87)	0.356
Preterm labour	1 (3.03)	5 (62.5)	6 (14.63)	< 0.001
Postpartum haemorrhage	1 (3.03)	2 (25.0)	3 (7.31)	0.019
Mortality	0	1 (12.5)	1 (4.16)	0.195

Table V. Foetal outcome of the 41 pregnancies.

Foetal outcome	No. (%)			p-value
	Pregnancies with prior diagnosis and treatment (n = 33)	Pregnancies without prior diagnosis and treatment (n = 8)	Total	
Live birth	32 (96.96)	7 (87.50)	39 (95.12)	0.356
Preterm birth	1 (3.12)	5 (71.42)*	6 (15.38)	< 0.001
Low birth weight	0	4 (57.14)*	4 (10.25)	< 0.001
Admission to the neonatal intensive care unit	0	5 (71.42)*	5 (12.82)	< 0.001
Neonatal death	0	1 (14.28)*	1 (2.56)	0.195
Stillbirth	0	1 (14.28)*	1 (2.56)	0.195

*There was one abortion in the antenatally diagnosed group.

a prior history of abortion (n = 1) and stillbirth (n = 1), and was diagnosed with EHPVO during her third pregnancy. Antenatally diagnosed patients had worse foetomaternal outcome in comparison with those diagnosed prenatally. The incidences of variceal bleeding (relative risk [RR] 16.5, 95% confidence interval [CI] 4.31–63.24) and preterm labour (RR 20.63, 95% CI 2.78–152.98) were higher among antenatally diagnosed women. Although there was no significant difference between the number of live births in these two groups, poorer foetal outcomes were seen for antenatally diagnosed patients (preterm labour 71.42%, low birth weight 57.14%, perinatal death 28.57%).

The exact causal relationship between disease morbidity and pregnancy outcome could not be established in our study due to the limited number of patients. However, it is possible that anaemia puts pregnant women at risk of haemodynamic compromise in the case of blood loss, and also increases the risk of preterm labour and low birth weight.[16] There were only two abortions in our population, with one abortion seen in each patient group. Our findings on foetal loss in pregnant women with EHPVO are similar to those of Kocchar et al.[8] According to Aggarwal et al, who found 23 women with EHPVO in an analysis of 50 pregnancies (live births 84.2%, stillbirth 15.8%, abortion 17.4%, preterm labour 10.5%, babies that were small in size for gestational age 5.3%),[11] women with variceal bleeding had a higher incidence of abortion and perinatal death. We also found a higher incidence of preterm, low birth weight newborns needing NICU admission among pregnant women who had variceal bleeding. As a majority of our antenatally diagnosed patients hailed from rural areas and had GI bleeding as the chief complaint, the timely referral of such women to a tertiary care centre that has multidisciplinary adult and neonatal backup is of paramount importance.

In another study, Sumana et al, who studied 12 pregnancies in nine women with NCPH, concluded that these patients had normal fertility, no apparent increase in the incidence of haematemesis during pregnancy and no indication for elective Caesarean delivery. The authors did, however, find an increased incidence of babies that were small for gestational age.[17] In our study, all the women, except for four who had obstetric indications for Caesarean section, had vaginal deliveries, and prophylactic forceps were offered in 14 of these institutional deliveries with high-grade varices. Epidural anaesthesia was most frequently used in our operative procedures. It is generally recommended that pregnant women with EHPVO should not be allowed to strain and that the second stage of labour should be electively curtailed by instrumental delivery when feasible.[7,18] Extradural analgesia, which allows progression to lower segment Caesarean section if required later, is the recommended labour analgesia.[18] General anaesthesia, if at all required, should involve extubation of the trachea with an awakened patient in the lateral position, as complications of portal hypertension may include dilated aberrant gastric vessels, haemorrhage and hypotension.[18]

Another important aspect of the management of pregnant women with EHPVO is the role of anticoagulation and antibiotics. In contrast with chronic patients, low-molecular-weight heparin should be started immediately and followed up with oral anti-coagulant therapy in acute symptomatic patients with EHPVO.[9] Anticoagulation should be continued for at least three months, unless an underlying persistent prothrombotic state has been documented, in which case lifelong therapy is recommended.[9] Antibiotic therapy should be instituted on evidence of infection. These recommendations suggest that, as pregnancy is a prothrombotic state, anticoagulant therapy is necessary in pregnant women with EHPVO if the patient presents with symptomatic recent EHPVO. However, the feasibility of instituting anticoagulation when a patient with EHPVO presents with haematemesis and pancytopenia remains debatable. Anticoagulants were not administered to any of our patients with recent EHPVO and no thromboembolic events were encountered in our group. Although anticoagulation in pregnant women with recent EHPVO can be considered, its routine administration in this cohort needs further evaluation through extensive randomised controlled trials.

To summarise, we found adverse foetomaternal outcome to be associated with variceal bleeding, anaemia, pancytopenia and jaundice in pregnant women with EHPVO. Prenatally diagnosed women with EHPVO had favourable foetomaternal outcomes. EST and EVL were both considered to be safe during pregnancy. As recurrent variceal bleeding can occur during subsequent pregnancies in women with EHPVO even after therapeutic endoscopic procedures, a re-evaluation of GI varices prior to each pregnancy is crucial for the adequate prenatal care of such women. Vaginal delivery should be the preferred option for this cohort, unless otherwise indicated by obstetric indications, and the general recommendation of prophylactic instrumental delivery for all pregnant women with varices needs to be further evaluated. Although pregnancy carries a significant risk to the patient with EHPVO, prophylactic obliteration of higher-grade varices prior to conception may result in better outcomes. Thus, preconceptional counselling regarding diagnosis and obliteration of varices, strict antenatal surveillance, proper postnatal follow-up and a multispecialty approach to patient care that involves gastroenterologists, obstetricians and neonatologists are all desirable requisites for achieving successful pregnancy outcomes in patients with EHPVO.

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