ORIGINAL ARTICLE

Factors influencing occurrence of postpartum haemorrhage in pregnant women with hepatitis E infection and deranged coagulation profile

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Summary: Coagulopathy is an important complication associated with hepatitis E virus (HEV) infection in pregnant women. Postpartum haemorrhage (PPH) remains a serious risk while managing the labour of these women. The aim of this paper is to study the factors influencing the occurrence of PPH in pregnant women with hepatitis E infection with coagulopathy. The labours of 38 pregnant women with hepatitis E and deranged coagulation profile were followed. Factors that may predict postpartum bleeding complications in women with HEV infection and deranged coagulation profile were statistically analysed. Of 38 pregnant women with acute viral hepatitis due to HEV, 13 (34%) suffered a PPH while 25 (66%) did not. On univariate analysis low alanine aminotransferase ($P = 0.016$), high international normalized ratio ($P = 0.003$), high levels of D-dimer ($P = 0.008$), presence of hepatic encephalopathy ($P = 0.028$), intrauterine fetal death ($P = 0.001$) and gastrointestinal bleeding ($P = 0.004$) were found to predict PPH. However, on multivariate analysis the only independent variable that predicted PPH was the presence gastrointestinal (GI) bleeding (odds ratio [OR] 11.363; 95% CI: 1.003, 125; $P = 0.050$). Women with GI bleeding have 11 times higher risk of PPH than those without a GI bleed; however, the confidence interval is very wide. Administration of fresh frozen plasma in the peripartum period reduces the risk of PPH. In conclusion, early recognition of factors which predict the risk of PPH and timely intervention with judicious use of blood and blood components in the peripartum period can improve the outcome of pregnant women with HEV infection with deranged coagulation.

Keywords: hepatitis E, coagulopathy, haemorrhage, infection, maternal mortality, pregnancy

INTRODUCTION

It is now well established that hepatitis E virus (HEV) infection causes severe hepatic illness in pregnant women and adversely affects the feto-maternal outcome. It is associated with increased rates of fulminant hepatic failure (FHF) with associated maternal mortality.[1,2] Complications like deranged coagulation profile, renal dysfunction, cerebral oedema, abruptio placentae, intrauterine death (IUD) and postpartum haemorrhage (PPH) further add to the morbidity.[1] The mechanism underlying increased severity of HEV infection in pregnancy is not clear. The course of infection is variable; in the majority of pregnant women it resolves spontaneously but in some it runs a fulminant course. Coagulopathy remains an important complication associated with viral hepatitis E infection.[1,3] Pregnancy is the most significant prognostic factor for the occurrence of disseminated intravascular coagulation (DIC).[1,4] However, the pathogenesis of DIC in pregnant women with viral hepatitis is not known. Pregnant women with HEV infection and deranged coagulation profile pose a real obstetric challenge. Hence, there is reluctance and delay in decisions for termination of pregnancy even for obstetric indications. The importance of peripartum correction of deranged coagulation cannot be overemphasized. However, the usefulness of correction of deranged coagulation in women who are not in labour is debatable.

There is a paucity of literature on the study of the effect of coagulopathy and the factors influencing the occurrence of PPH in pregnant women with hepatitis E infection and coagulopathy. This prospective study aimed to look into these issues.

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PATIENTS AND METHODS

This study was conducted in the Departments of Obstetrics and Gynecology and Hematology of Lady Hardinge Medical

College New Delhi, a tertiary care hospital, in collaboration with the Department of Gastroenterology, GB Pant Hospital, New Delhi, from January 2006 to January 2008. Pregnant women presenting with acute viral hepatitis in the third trimester of pregnancy were systematically assessed with complete haemogram, liver function tests, coagulation profile including prothrombin time (PT), activated partial prothrombin time (APTT), thrombin time, serum fibrinogen, D-dimer and international normalized ratio (INR). All were subjected to viral hepatitis serology including IgM antibody to hepatitis A virus (anti-HAV IgM), hepatitis B surface antigen, IgM antibody to hepatitis B core antigen (anti-HBc IgM), antibody to hepatitis C virus (anti-HCV), IgM antibody to hepatitis delta virus (anti-HDV IgM), and IgM antibody to HEV (anti-HEV IgM).

Acute viral hepatitis was diagnosed by symptoms and signs. Cases were defined as pregnant women with a serum bilirubin of $\geq$34.2 μmol/L serum alanine aminotransferase (ALT) of $\geq$2.5 times upper limit of normal and positive acute serology for hepatotropic viruses.[5] Patients with negative viral serology or with dual viral infections were excluded from the study, as were patients with clinical evidence of other causes of jaundice like biliary obstruction, HELLP (haemolysis-elevated liver enzymes, low platelets) syndrome, acute fatty liver of pregnancy, haemolytic jaundice and drug-induced jaundice and those with clinical or laboratory evidence of chronic liver disease. Pregnant women with risk factors for post-PPH like multiple pregnancy, hydramnios, previous caesarean delivery, grand multipara or past history of PPH were also excluded from the study.

Women fulfilling the case definition criteria for acute viral hepatitis were admitted to and managed in the hepatitis ward of the hospital. Pregnant women who were HEV positive and had deranged coagulation profile were included in the study. Deranged coagulation was defined as PT, APTT, INR, more than the normal lab reference range (mean $\pm$ 2SD), which were PT (11.94–14.4 s), APTT (22.5–32.15 s) and INR $\leq$ 1.5. FHF was diagnosed when hepatic encephalopathy developed in a patient with acute viral hepatitis within four weeks of the onset of jaundice.[6] Encephalopathy was graded using the West Haven index.[7]

Women who were HEV positive with deranged coagulation but without FHF were given standard care and remained in the hospital until they either improved or died. They were monitored for the presence of or development of any medical complications including gastrointestinal (GI) bleeding, encephalopathy, renal failure, ascites and obstetric events like the onset of labour, rupture of membranes or IUD. The coagulation status was assessed on admission, prior to delivery, postdelivery and thereafter.

Women with HEV and deranged coagulation with FHF were managed with supportive care in the intensive care unit because liver transplant facilities are not available in our hospital. These patients received lactulose, antibiotics, parenteral nutrition, mannitol 20% and ventilatory support as required. Careful watch was maintained for early signs or symptoms of cerebral oedema, renal dysfunction and electrolyte disturbances. Cerebral oedema in such patients was diagnosed when features of decerebration occurred, along with other clinical signs of raised intracranial pressure. DIC was diagnosed when bleeding occurred from multiple anatomical sites (skin, mucosa, venepuncture sites) along with low levels of fibrinogen $<$2 g/L, thrombocytopenia 100×10^9/L and high levels of D-dimer $>$0.5 mg/L.[8]

Fresh frozen plasma (FFP) was transfused into women with bleeding from any site including gastrointestinal tract, injection sites or bladder and to women in the peripartum period. The initial dose of FFP was 10–15 mL/kg body weight (3–4 units) stat dose followed by two units every eight hours till at least 24 hours after delivery.

The first, second and third stages of labour were managed carefully. Sedative drugs and non-steroidal anti-inflammatory drugs were avoided. Certain practices like sweeping/stretching of perineum during second stage, routine episiotomy and fundal pressure were also avoided. The genital tract was carefully explored for any tears after delivery of the placenta and those who had bleeding due to cervical and/or vaginal lacerations were managed with primary suturing and or vaginal packing for 24 hours. Balloon tamponade was used to control PPH from uterine atony not responding to medical management.

Women with postpartum bleeding complications were compared with those who had no complications. These two groups were statistically compared in terms of clinical profile, laboratory investigations and maternal complications. Multi- and univariate analyses were performed to find out factors that may predict postpartum bleeding complications in women with HEV and deranged coagulation profile.

Statistical analyses

Chi-square test was used to determine the statistical significance between the comparison groups, namely pregnant women with HEV infection, coagulopathy and PPH, and pregnant women with HEV infection, coagulopathy and no PPH. A P value of $<$0.05 was considered as significant. Student's t-test and Mann–Whitney U test were used for parametric and non-parametric data, respectively. Odds ratios (OR) were calculated for all the complications or deaths in these two groups of patients.

RESULTS

From January 2006 through January 2008, a total of 110 pregnant women were admitted with acute viral hepatitis. Of these 75 (68%) were hepatitis E positive and 56 of these 75 (74.6%) had deranged coagulation profile. The study group comprised 38 of these 56 women with HEV infection and deranged coagulation profile who delivered. Thirteen (13/38) of these had postpartum bleeding complications (Group 1) and the rest, 25/38 women, had no postpartum bleeding complications (Group 2). Only 46% of Group 1 women with PPH received peripartum FFP transfusion compared with 80% of the women in Group 2 without PPH. The mean interval from admission to the delivery was five hours in the women with PPH and three days in the group without PPH, thus explaining the reason why women in the PPH group did not receive FFP. This difference in the admission–delivery interval was highly significant ($P < 0.001$).

The clinical characteristics show that age and parity were comparable in the two groups. The median gestational age at admission was 34 weeks in both the groups (Table 1).

On analysing the clinical presentation (Table 1) it was observed that 62% of the women with PPH and 24% without PPH were in hepatic encephalopathy prior to delivery ($P = 0.028$). A significant percentage of women with PPH had

Table 1 **Comparison of clinical characteristics of women with and without PPH**

Parameters	All women ($n = 38$)	Women with PPH ($n = 13$) Group 1	Women without PPH ($n = 25$) Group 2	*P* value (Group 1 versus 2)
Median gestation age (range), weeks	34 (24–41)	34 (24–39)	34 (26–41)	0.939
Parity (%)				
Primigravida	18 (47%)	5 (62%)	13 (52%)	0.327
Multigravida	20 (53%)	8 (38%)	12 (48%)	
Median parity (range)	2 (1–5)	2 (1–5)	1 (1–3)	0.362
Hepatic encephalopathy (%)	14 (37%)	8 (62%)	6 (24%)	0.028
IUD (%)	14 (37%)	7 (54%)	7 (28%)	0.001
GI bleed (%)	7 (18%)	6 (46%)	1 (4%)	0.004
Died	9 (24%)	5 (38%)	4 (16%)	0.012

PPH, postpartum haemorrhage; IUD, intrauterine death; GI, gastrointestinal

intrauterine fetal death prior to delivery compared with the women without PPH (54% versus 28%, $P = 0.001$). Approximately 50% of the women with PPH had bleeding from other sites, most commonly GI bleeding, compared with only 4% in women without PPH. This difference was statistically highly significant ($P = 0.004$), suggesting that the majority of the women who had PPH had DIC in addition to synthetic dysfunction of the liver. On univariate analysis hepatic encephalopathy, IUD and gastric bleeding significantly affected the occurrence of PPH in women with HEV with coagulopathy. However, on multivariate analysis hepatic encephalopathy (OR 3.257; 95% CI: 0.462, 22.727; $P = 0.236$) and IUD (OR 1.458; 95% CI: 0.981, 1.222; $P = 0.323$) did not correlate with the occurrence of PPH. The only independent variable which predicted PPH was GI bleed. Women with GI bleed had 11 times more risk of PPH than those without GI bleed (OR 11.363; 95% CI: 1.003, 125; $P = 0.050$) but the confidence interval is wide.

The baseline coagulation profile of all the 38 pregnant women with HEV infection and deranged coagulation profile is summarized in Table 2. A high INR was present in all women with a median value of 4.4 (range 1.6–15). The median D-dimer and serum fibrinogen levels of the study population were 4 μg/L (range 2–64 μg/L) and 1.15 g/L (range 0.5–2.66 g/L), respectively.

The median serum levels of bilirubin were significantly higher ($P = 0.003$) in the women with PPH compared with those without PPH, 342 versus 234.2 μmol/L. On the contrary, serum ALT levels were significantly lower (269 versus 664 U/L, $P < 0.01$) in the former compared with that in the latter group (Table 1) pointing towards extensive liver dysfunction in the group with PPH, possibly associated with release of thromboplastins and DIC. However, on multivariate analysis a low-serum ALT did not correlate with the occurrence of PPH (OR 0.999; 95% CI: 0.998, 1.001) (Table 3). There was no significant difference in the serum albumin levels ($P = 0.108$) although it was low in both the groups (22 versus 24 g/L) indicating a contribution of synthetic dysfunction of the liver to derangement of coagulation profile in both groups.

Table 3 **Factors for the prediction of PPH (multivariate analysis)**

Variable	*P* value	Odds ratio	95% confidence interval
ALT	0.402	0.999	0.998, 1.001
INR on admission	0.866	1.027	0.755, 1.397
D-dimer	0.581	1.020	0.952, 1.092
Hepatic encephalopathy	0.236	3.257	0.462, 22.727
IUD	0.323	1.458	0.981, 1.222
GI bleed	0.050	11.363	1.003, 125.000

PPH, postpartum haemorrhage; GI, gastrointestinal; INR, international normalized ratio; ALT, alanine aminotransferase; IUD, intrauterine death

In women with HEV infection and deranged coagulation, the chances of developing bleeding complications, particularly postpartum bleeding complications, were much higher in women who had associated DIC. The median INR and D-dimer levels differed significantly between the two groups (6.4 versus 2.7 and 8 mg/L versus 4 mg/L (range 2–64 mg/L), $P = 0.003$, $P = 0.008$ respectively). Although the serum fibrinogen level was lower in the PPH group, the difference was statistically not significant (0.96 versus 1.28 g/L, $P = 0.171$). Similarly, the platelet count was lower in PPH group compared with no PPH group (187×10^9/L versus 214×10^9/L, $P = 0.100$) but the difference was not statistically significant. On multivariate analysis ALT, INR and D-dimer did not correlate with the occurrence of PPH.

Most of the women in both the groups went into spontaneous labour (92% versus 84%); labour was induced in five women, 4/5 (16%) in the non-PPH group and 1/5 (8%) in the PPH group. The indications for induction of labour were IUD ($n = 3$) and prolonged pregnancy >41 weeks ($n = 2$) (Table 4). The coagulation profile was corrected prior to induction.

Nine out of 38 women died, five (38%) women in the PPH group and four (16%) in the non-PPH group (Table 1). The OR for death was 2.2 (95% CI: 1.4, 3.2; $P = 0.012$) in the PPH

Table 2 **Comparison of biochemical parameters in women with and without PPH (univariate analysis)**

Parameters	All women ($n = 38$), median (range)	Women with PPH Group 1 ($n = 13$), median (range)	Women without PPH Group 2 ($n = 25$), median (range)	*P* value (Group 1 versus 2)
Serum bilirubin (μmol/L)	263.3 (102.6–485.6)	342 (106–485.6)	234.2 (102.6–427.5)	0.003
Serum AST) (U/L)	566 (49–2632)	377 (49–2632)	622 (89–2595)	0.113
Serum ALT (U/L)	492 (42–4430)	269 (42–2120)	664 (140–4430)	0.016
Serum albumin (g/L)	24 (19–31)	22 (19–31)	24 (21–29)	0.108
Median INR on admission (range)	4.4 (1.6–15.0)	6.4 (3.4–15.0)	2.7 (1.6–10.6)	0.003
Serum D-dimer (mg/L)	4 (2–64)	8 (2–64)	4 (2–32)	0.008
Serum fibrinogen (g/L)	1.15 (0.5–2.66)	0.96 (0.53–2.34)	1.28 (0.50–2.66)	0.171
Platelet count (10^9/L)	202 (20–614)	187 (20–275)	214 (60–614)	0.100

PPH, postpartum haemorrhage; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio

Table 4 **Comparison of peripartum factors in women with and without PPH (univariate analysis)**

Parameters	All women (n = 38)	Women with PPH (n = 13) Group 1	Women without PPH (n = 25) Group 2	P value (Group 1 versus 2)
Median INR before delivery (range)	3.4 (1.0–11.0)	6.4 (3.0–10.0)	2.0 (1.0–11.0)	0.003
Predelivery FFP transfusion (%)	26 (68%)	6 (46%)	20 (80%)	0.040
Median admission to delivery interval (range), days	2.00 (0.04–15.00)	0.24 (0.04–12.00)	3.00 (0.04–15.00)	<0.001
Induced labour (%)	5 (13%)	1 (8%)	4 (16%)	0.433
Median onset to delivery interval (range), hours	4 (1–11)	4 (1–11)	4 (2–10)	0.901
Post-delivery FFP required (%)	22 (58%)	13 (100%)	9 (36%)	<0.001
Median INR after delivery (range)	2.0 (0.9–10.3)	4.2 (1.1–10.3)	1.3 (0.9–4.5)	0.001

FFP, fresh frozen plasma; PPH, postpartum haemorrhage; INR, international normalized ratio

group. The majority of women (8 of 9) died of multiorgan failure; however, there was one woman who died of hypovolemic shock consequent to massive atonic PPH. The median time from delivery to death was five days in the PPH group and four days in the non-PPH group.

DISCUSSION

Coagulopathy is a well-known complication which occurs in acute viral hepatitis E infection in pregnancy.[1–5,8] In the present study, 74% of women with HEV infection had coagulopathy. This is similar to observations reported in previous studies.[1,2,8] The importance of coagulopathy in FHF is related to the potential for spontaneous bleeding and the risk of haemorrhagic complications during pregnancy, especially PPH.[8] Hence, it is essential to have a substantial correction of the coagulopathy before delivery. Delivery is safe if the INR is in the normal range (<1.5).[9] However, this level is arbitrary and most of the recommendations are based on small studies rather than large evidence-based data.[9]

In our cohort of 38 pregnant women with HEV infection and deranged coagulation, postpartum bleeding complications occurred in 34%. The cause of PPH was traumatic bleeding from vaginal or cervical tears and episiotomy in most of the cases. There was only one woman with massive PPH from uterine atony. A similar observation of bleeding due to coagulopathy was made in two recent studies from India.[1,2] However, none of the studies mentioned the type of PPH. This is probably the first study that has analysed the clinical characteristics of pregnant women with hepatitis E infection, coagulopathy and PPH.

An interesting observation made in the present study was that women with PPH had abnormal coagulation consequent to deranged synthetic function of the liver as well as consumptive coagulopathy possibly as a result of thromboplastins released by extensive liver damage as in FHF.[8] This was reflected by low albumin, high D-dimer and low fibrinogen levels suggestive of DIC. This was in contrast to the presence of only synthetic dysfunction and the absence of severe DIC in women without PPH. It suggests that the presence of coagulopathy due only to synthetic dysfunction is unlikely to cause any bleeding complications unless complicated by consumptive coagulopathy. An association between the fetus affected by HEV leading to IUD and DIC has already been suggested in one study.[8] We in our study also observed that there were more IUDs (54%) in women with PPH compared with those without PPH.

The importance of the use of FFP prior to delivery and in the peripartum period to correct coagulopathy is evident by the observation that the majority of women whose peripartum period was covered with FFP did not have any postpartum bleeding complications compared with women who did not receive FFP.

Our main objective was to recognize factors that could predict PPH in women with HEV with coagulopathy. The only independent factor on multivariate analysis was GI bleeding. The occurrence of GI bleeding could be an early sign of DIC.[9] The association of DIC with PPH requiring massive transfusions has been previously described.[10] Hence, it appears that pregnant women with HEV infection and coagulopathy consequent to synthetic dysfunction do well in labour regarding bleeding complications in the third stage compared with those with coagulopathy due to synthetic dysfunction and DIC, provided that the peripartum period is adequately covered with FFP. As FHF is often associated with IUD and DIC[8] it would be interesting to research into whether induction of labour is worth considering in pregnant women with a viable pregnancy and worsening hepatitis E where severe DIC has not yet developed. Although this sick cohort of patients did not have access to orthotopic liver transplantation, our data may help clinicians with access to transplantation in their patient selection for superurgent liver transplantation in HEV with particular reference to fulfilling the King's College Hospital Criteria for Acute Liver Failure ('King's Criteria').[11,12]

DECLARATIONS

Conflicts of interest: None.

Contributorship: Conception and design: MP, SST and SKS; Acquisition of data: PS, NM and SS; Analysis and interpretation of data: SP and AK; Drafting the article or revising it critically for important intellectual content: MP; Final approval of the version to be published: MP.

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