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HEPATITIS E INFECTION AND PREGNANCY: A FATAL COMBINATION

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ABSTRACT

Maternal death has serious implications to the family, society and the nation. Death of mother is a tragic event. An autopsy study on maternal deaths carried out by our department 4 years back revealed Hepatitis-E infection as the number one cause of maternal death (Jashnani *et al.*, 2009). Has the situation improved over the time? An audit was also carried out during that time with guidelines recommended to be followed during autopsy procedure. Are these guidelines being followed? To get answers, we carried out a prospective study of maternal deaths. In a three year period, there were a total of 118 maternal deaths. Autopsy was carried out in 58 cases. Fulminant liver failure due to Hepatitis E infection was still the predominant cause of maternal death highlighting a very dismal picture. Raising awareness and mobilising resources for prevention of Hepatitis-E infection in pregnant women will go a long way. Simple measures like healthy diet and maintaining good personal hygiene would definitely reduce the disease occurrence in the first place.

Keywords: Maternal Mortality; Hepatitis- E Infection; Fulminant Hepatic Failure; Improved Sanitation; Hepatic Necrosis

INTRODUCTION

28th July is celebrated worldwide as World Hepatitis Day every year by World Health Organisation (WHO) to increase awareness and understanding of viral hepatitis. Clinical outcomes associated with HEV infection are quite diverse. It most commonly manifests as self-limiting, acute icteric hepatitis, which is indistinguishable from acute hepatitis caused by other hepatotropic viruses. The illness usually lasts for a few weeks, although some patients have a somewhat prolonged illness with prominent cholestatic manifestations. In a proportion of patients, the illness is particularly severe and presents as fulminant hepatitis (acute liver failure). Pregnancy is associated with increased risk of severe disease. In a few cases, subacute liver failure can also occur (Dalton et al., 2008; Navaneethan et al., 2008; Sookoian, 2006). The cause of fulminant hepatitis (acute liver failure) in pregnant women may be reduced immunity or altered hormonal status in pregnancy. Pregnancy is associated with high levels of steroid hormones (oestrogen and progesterone). These hormones may promote viral replication. It also has a direct inhibition on hepatic cells which may predispose to hepatic dysfunction/failure when exposed to infectious pathogens. Alterations in the hormonal status and of T & B cell ratios during pregnancy are responsible factors for viral virulence (Strelkauskas et al., 1978). Fulminant hepatitis- E infection was the leading cause of maternal deaths in our previous study (Jashnani et al., 2009). It is still a predominant cause as found in our present study. With regard to high mortality rate of jaundice in pregnancy, especially HEV infection, simple measures like healthy diet and maintaining good personal hygiene, would definitely reduce the disease occurrence in the first place.

MATERIALS AND METHODS

This was a prospective study over a period of three years. The study was carried in a tertiary care hospital which serves as a major referral centre. Complete autopsy was performed in all 58 cases after obtaining relative or police permission. These cases underwent a detailed external and in-situ examination with

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special emphasis on pulmonary thromboembolism, especially in cases with healthy mothers collapsing suddenly. Organs were dissected and looked for specific gross findings and then preserved in 10% formalin. Frozen section with special staining for fat demonstration was done in 2 cases of gross yellow liver with detection of acute fatty liver of pregnancy. Blood culture and swabs for Gram's stain, Ziehl Neelson stain or Giemsa/Wright's stain were done during autopsy wherever essential. Information regarding age, hospital stay, trimester of pregnancy, parity, presenting symptoms etc was collected from indoor papers or autopsy protocol papers. A thorough histopathologic examination was carried out by first two authors and final cause of death was given. The causes of maternal deaths were divided into direct and indirect causes.

RESULTS AND DISCUSSION

Results

Of the total 58 autopsy cases, maximum 51 deaths (88%) occurred with a hospital stay of less than 7 days. 48 cases (83%) belonged to age group of 21-40 years of age. 21 deaths (36%) occurred in third trimester of pregnancy followed by 19 deaths (33%) in postpartum period. 35 deaths (60%) were seen in multigravida while 23 deaths (40%) occurred in primigravida. Maternal deaths were divided into direct and indirect causes (Table I). Fulminant hepatic failure (FHF) due to submassive to massive hepatic necrosis on histopathologic examination was the predominant cause of death in 16 cases with positive serology for HEV infection in 6 cases (Figure 1, 2). All these 16 patients had presented with jaundice and variable levels of consciousness, ranging from mental confusion state to hepatic coma. Liver function tests like SGOT and SGPT were elevated with values ranging from 450 units/dl to 1600 units/dl. This was followed by Acute Respiratory Distress Syndrome (ARDS) - 9 cases (15.52%) and Tuberculosis - 6 cases (10%) as indirect causes of death (Refer Table I). Amongst the direct causes, puerperal sepsis - 5 cases (9%) followed by Acute Fatty Liver of Pregnancy (AFLP) - 4 cases (7%) and Disseminated Intravascular Coagulation (DIC) - 4 cases (7%) were common. Occasional cases of spontaneous rupture of rudimentary horn of gravid uterus and superior sagittal sinus thrombosis were also noted. There was a single case of bilateral contracted kidneys showing 75-85% glomeruli with crescents as a cause of renal failure in chronic renal disease (Figure 3). This case was being clinically managed as pre-eclampsia.

Of the 29 cases of intrauterine foetal deaths (IUFD), 19 were fresh stillbirths. Sections from placenta in these cases showed evidence of dense acute chorioamnionitis in one case. Rest all showed features of mature placenta for its gestational age. Pituitary was sectioned in 36 cases with evidence of coagulation necrosis in 5 cases and calcification in one case. Of the 60 maternal deaths where autopsy was not carried out, the cause of death in 37 cases (almost 55%) was Fulminant hepatitis (Chart I). Laboratory diagnosis of hepatitis- E infection was available in 23 of these cases. The rest 23 cases had died of ARDS, DIC, Tuberculosis, Malaria etc. All the maternal deaths were also classified into preventable and non-preventable deaths during the local institutional meeting held between the representatives from different departments like Obstet/Gyn, Medicine, Pathology and Anaesthesia. 31 maternal deaths due to various causes like Anaemia, tuberculosis, pneumonia, etc were classified as preventable deaths. 87 Maternal deaths due to DIC, FHF due to Hepatitis E infection, Rheumatic heart disease with mitral stenosis, Crescentric glomerulonephritis, etc were classified as non-preventable deaths of the total 118 maternal deaths (with and without autopsy).

Discussion

The fatality rate among pregnant woman with Acute Liver Failure (ALF) is reported to be high in India at 22.2% with the maximum severity occurring during the third trimester (41.4%) (Kumar *et al.*, 2001). In a study from Kashmir (Khuroo *et al.*, 1981), acute liver failure was reported in 22.2% cases of pregnant women and 3% in nonpregnant women. The hepatitis was more common and severe in late pregnancy. 9% women developed hepatitis in first trimester. In the second and third trimester, this was raised to 19%. Maternal deaths (44%) only occurred in late pregnancy. Hepatitis- E infection in pregnancy is also associated with high rates of spontaneous abortion, intrauterine death in preterm labour. We have compared the present study with our previous study and found no differences. The maternal mortality rate

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is still higher, which continues to be due to large numbers of complicated referral cases received from private as well as peripheral hospitals. 91 cases (77%) out of total 118 maternal deaths were late referrals from peripheral hospitals. Maternal Mortality Rate (MMR) was high -1386 per 1, 00,000 live births for 118 maternal deaths against a total of 8,514 total live births. This however should be considered as maternal mortality ratio as the exact denominator is not known since a large number of deaths occurred in referred or transferred patients. Fulminant hepatic failure due to Hepatitis-E infection continues to be the leading cause of maternal mortality. The guidelines for autopsy on maternal deaths provided by the previous study are meticulously followed during each and every autopsy. Acute fulminant hepatitis was the predominant cause of death in 41.5% cases where autopsy had been performed in our previous study. The present study showed FHF as cause of death in total (autopsy and non-autopsy) 53 cases (44.9%) with positive serology for Hepatitis E infection in 29 cases. Association of HEV and viral hepatitis with pregnancy has been reported earlier in many studies (Ahmed et al., 2008; Beniwal et al., 2003; Jilani et al., 2009; Kumar et al., 2001; Purcell and Emerson, 2008). Jaiswal and colleagues (2001) in central India and Aziz and associates (1997) in Pakistan have reported that HEV is responsible for 58% and 62% of cases of acute viral hepatitis in pregnant women, respectively. Two studies from New Delhi Kumar et al., (2001), Singh et al., (2003) reported slightly lower prevalence (45% and 37%) and a study of sporadic HEV infection in the context of multiple HEV epidemics in Kashmir reported a prevalence of 86% among pregnant patients with acute viral hepatitis (Khuroo et al., 1995). Patra and colleagues (2007) in a study on pregnant women with jaundice and acute viral hepatitis caused by HEV infection concluded that, they had a higher maternal mortality rate and worse obstetric and foetal outcomes than did pregnant women with jaundice and acute viral hepatitis caused by other types of viral hepatitis. Similar case reports are reported from other parts of world (Goumba et al., 2010). There is an excellent article by Navaneethan et al., (2008) who described mechanisms responsible for the severity of Hepatitis E in pregnancy. They have described the immunological changes of pregnancy which lead to viral hepatitis. The maternal immune system is altered during normal pregnancy to tolerate a genetically different fetus that is considered as a paternally derived allograft. The placenta expresses an enzyme, indoleamine 2, 3-dioxygenase which inactivates and depletes tryptophan, an amino acid essential to T-cell function. This suppresses cellmediated immunity at the fetus-placental interface. That is why; pregnancy is a state of relative immunosuppression which may lead to the increased severity of infection.



Figure 1: Gross photograph of small shrunken and limp liver slice with wrinkled capsule

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Figure 2: Microphotograph of liver showing submassive hepatic necrosis (H & E, 100X)



Figure 3: Microphotograph of kidney showing almost 75-85% of glomeruli with crescents (H & E, 400X)



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Screening every expecting mother for HIV, HBsAg and VDRL are mandatory. The policy of not screening for HEV antibodies in pregnant women is based on its perceived low prevalence and on the low lifetime risk of its associated diseases.

Table I: Classification of deaths into direct and indirect causes based on final histopathological diagnosis

Causes of Deaths	Number of cases (n=58)
I] Direct Causes	17 (29.31%)
1) Puerperal sepsis	05 (8.62%)
2) Acute fatty liver of pregnancy	04 (6.90%)
3) DIC	04 (6.90%)
4) Miscellaneous causes:	
a) Spontaneous rupture of uterus	02 (3.45%)
b) Eclampsia	01(1.72%)
c) Superior saggital sinus thrombosis	01(1.72%)
II] Indirect causes	41(70.69%)
1) Viral hepatic necrosis	16(27.59%)
2) Tuberculosis	06(10.34%)
3) Acute respiratory distress	09(15.52%)
syndrome/Pneumonia	
4) Anaemia	02(3.45%)
5) Pyelonephiritis	03(5.17%)
6) Rheumatic heart disease	02(3.45%)
7)Miscellaneous causes:	
a) Intestinal perforation	01(1.72%)
b) Bilateral renal cortical necrosis	01(1.72%)
c) Crescentic glomerulonephiritis	01(1.72%)

Should screening for HEV, after appropriate counselling, be recommended as part of the routine antenatal screening programme? The answer may be No. As no specific therapy is capable of altering the course of acute hepatitis -E infection, prevention is the most effective approach against the disease. As almost all HEV infections are spread by faecal-oral route, good personal hygiene, high quality standards for public water supply and proper disposal of sanitary waste can result in a low prevalence of HEV infections in general population as well as pregnant state. At present, no commercially available vaccine exists for the prevention of Hepatitis- E. However, several studies for the development of an effective vaccine against Hepatitis- E are in progress.

Availability of vaccine in HEV-endemic country will be a major milestone on the road toward protecting vulnerable women in disease-endemic areas from HEV infection, foetal loss, and neonatal death or even maternal deaths (Labrique *et al.*, 2012; Shrestha *et al.*, 2007). Till the time of availability of vaccine, it is the authority's job to look into proper disposal of sanitary waste and make provision for safe drinking water. Awareness programmes for pregnant woman should be held regularly like hand washing, drinking boiled and cooled water. Pregnant woman should avoid drinking water and/or ice-cream of unknown purities, and eating uncooked an unwashed fruits or vegetables that are not peeled. Determinations of source of infection, detection of outbreak and spread containment are some other functions of the authority. Thus in addition to providing good antenatal and obstetric care and early referrals of complicated cases, these above measures may bring down the maternal mortality rate.

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