An outbreak of hepatitis E and high maternal mortality at Port Sudan, Eastern Sudan

Duria A. Rayis¹, Ammar M. Jumaa², Gasim I. Gasim², Mubark S. Karsany³, Ishag Adam¹

¹Faculty of Medicine, University of Khartoum, Sudan, ²Faculty of Medicine, Red Sea University, Port Sudan, Sudan, ³College of Medical Laboratory Sciences, Karary University, Khartoum, Sudan

During 4 months (November 2010–March 2011) of an outbreak of hepatitis E virus (HEV), 39 pregnant women presented at Port Sudan Hospital, Sudan, with various symptoms of viral hepatitis. The diagnosis of viral hepatitis was confirmed by serology using ELISA anti-HEV IgG and IgM. The mean (SD) maternal age and gestational age were 24.0 (4.2) years and 33.6 (3.7) weeks, respectively. Eight (20.5%) women were primigravidae. There were 11 (28.2%) maternal deaths, 14 (36.0%) intrauterine fetal deaths, and eight (20.5%) cases of postpartum haemorrhage. There were nine (23.0%) cases of preterm (<37 weeks of gestation) deliveries. Fulminant hepatitis with hepatic encephalopathy was the most common cause of death among these patients. Nine of these women died before delivery and the other two died immediately following the delivery due to severe haemorrhage. There were no significant differences in clinical and biochemical data between the women who died (11) and those who survived.

Keywords: Pregnancy, Viral hepatitis, Hepatitis E virus, Sudan

Introduction

Hepatitis E virus (HEV) is a major public health problem, especially in resource limited countries. In an annual estimate in 2005, there had been 20.1 million HEV infections, resulting in 70 000 deaths and 3000 intrauterine fetal deaths, and a possibility of 0.019 and 0.198 mortality in symptomatic illness for non-pregnant and pregnant patients, respectively.¹ HEV infections can occur either in the form of epidemics or sporadic cases.² Epidemics of HEV have been reported in African countries, including Sudan, Ethiopia, Somalia, Chad, the Democratic Republic of the Congo, and Uganda.^{3–6}

HEV infection in pregnancy can progress to fulminant hepatitis with a high mortality rate among pregnant women.^{7–9} A recent study showed that pregnant Indian women with acute hepatitis E virus infection had a three times higher relative risk for fulminant hepatic failure and a six times higher risk for mortality.¹⁰

While there is much published literature on HEV infection during pregnancy from other African countries,^{11,12} there are few published data on HEV infection during pregnancy in Sudan.^{13,14} The current study was conducted to investigate the epidemiology, and maternal and perinatal outcomes of HEV

infection among pregnant women at Port Sudan Hospital, Eastern Sudan to provide a better understanding of maternal and perinatal outcomes of communicable diseases in general, as well as viral hepatitis, during pregnancy in this region of Sudan.^{14,15} Information obtained from this study could be useful for preventative measures and adding to the information of previous different epidemics and outbreaks in Sudan.^{16,17}

Patients and Methods

All pregnant women with clinical features suggestive of viral hepatitis who presented at Port Sudan Hospital during 4 months from November 2010 through March 2011 were reviewed retrospectively. Port Sudan is the third city (the main sea Port) in Sudan located on the Red Sea, 950 km from Khartoum, with 550 000 inhabitants. A specialized maternity ward was created for the care of hepatitis infection at Port Sudan Hospital, which is a tertiary care hospital. All suspected cases were referred to this ward regardless of their gestational age. The medical and obstetrical files of all pregnant women with HEV infection were reviewed. Patients' records were retrieved and socio-demographic characteristics (age, parity, and gestational age), various clinical symptoms and signs (fever, headache, vomiting, nausea, backache, abdominal pain, dizziness, diarrhea, and jaundice), obstetrics, perinatal outcomes

Correspondence to: I. Adam, PO Box 102, Faculty of Medicine, University of Khartoum, Khartoum, Sudan. Email: ishagadam@hotmail.com

(miscarriage, preterm labour, stillbirth, and perinatal and maternal deaths), and haematological and biochemical characteristics (complete blood count, serum bilirubin, alanine aminotransferase levels, and aspartate aminotransferase levels) were recorded. A case was defined to have HEV based on symptoms and signs (jaundice, dark urine, elevated serum transaminases), and anti-HEV-positive (both IgG and IgM). ELISA anti HEV IgG and IgM antibody capture techniques were used to confirm the diagnosis of HEV (Diagnostic Automation, Inc., Calabasas, CA, USA).

Statistical analysis

Data were entered in a computer using SPSS for Windows version 16.0. Means and proportions were compared by the Student's *t*-test and the Chi-squared test, respectively. $P < 0.05$ was regarded as significant.

Ethics

This was a retrospective study in which the data of the patients were analysed anonymously and no new personal data were required. The study was approved by the local ethical board of the institution.

Results

During the 4 months of the HEV epidemic, 39 pregnant women presented at the hospital with various symptoms, including fever, headache, epigastric pain, nausea, vomiting, itching, and jaundice. The mean (SD) maternal age and gestational age were 24.0 (4.2) years and 33.6 (3.7) weeks, respectively (Table 1). Eight (20.5%) women were primigravidae and the majority (33; 84.6%) of women were rural residents.

There were 11 (28.2%) maternal deaths, 14 (36.0%) intrauterine fetal deaths, and eight (20.5%) cases of postpartum haemorrhage. There were nine (23.0%) cases of preterm (<37 weeks of gestation) deliveries. Fulminant hepatitis with hepatic encephalopathy was the most common cause of death among these patients. Nine of these women died before delivery and the other two died immediately following the delivery due to severe haemorrhage. There were no significant differences in the clinical and biochemical data between the women who died (11) and those who survived (Table 1). The mean (SD) of patients

stay in the hospital was 6.3 (2.7) days. These women had no other infections, e.g. malaria.

Discussion

In the current study, the main findings were a high maternal mortality and intrauterine fetal death from HEV. Recent reports have shown that there are three maternal deaths out of eight cases of HEV infection among pregnant women in Khartoum, Sudan.¹⁴ In Darfur, Western Sudan, a case to fatality ratio of 17.8% was found in HEV outbreak, with a ratio of 31.1% among pregnant women.¹³ In neighbouring Ethiopia, while none of the 423 men with hepatitis developed fulminant hepatic failure or died,³ 19 pregnant women had acute HEV infection and there were eight maternal deaths and six fetal deaths during an epidemic.¹⁸ A high maternal mortality rate in the range of 30–45%,^{19–21} or even as high as 70%,²² has been reported among HEV-infected pregnant women. There are no published data on the maternal mortality in Port Sudan. However, in the nearby state (Kassala), there is a high maternal mortality (713.6/100 000 live births) and acute febrile illness (9.4%) is among the common causes of maternal mortality in Kassala in the Eastern Sudan.²³

We found six out of 39 fetal deaths in the current study. HEV infection during pregnancy has also been reported to be associated with premature delivery, low birth weight, and an increased risk of perinatal death.^{10,21}

In the current study, as well as another study in Ethiopia,¹⁸ clinical and biochemical features (amino-transferase and bilirubin levels) were not different between women who died and those who survived. The severe course of HEV infection during pregnancy might be due to host factors, such as malnutrition, diminished cellular immunity, and high levels of steroid hormones during pregnancy.²⁴ HEV genotypes are another important factor (which was not investigated in the current study) that might influence the severity of infection (e.g. genotypes 3 and 4 are less virulent, while genotype 1 is more pathogenic), and this might explain the severity of HEV infection in India.^{25,26}

In a recent report from India, over half of the cases of viral hepatitis in pregnant women were due to

Table 1 Demographic, biochemical, and outcome data of Sudanese pregnant women with hepatitis E virus infection

Variables as mean (SD)	Total (n=39)	Died (n=11)	Survived (n=28)	P
Age (years)	24.0 (4.2)	23.0 (4.3)	24.4 (4.2)	0.3
Parity	1.7 (1.3)	1.4 (1.3)	1.8 (1.3)	0.3
Gestational age (weeks)	33.6 (4.5)	32.9 (3.3)	33.9 (3.0)	0.4
Haemoglobin (g/dl)	9.6 (0.4)	9.6 (0.4)	9.5 (0.4)	0.7
Total serum bilirubin (mg/dl)	5.8 (2.4)	5.7 (2.5)	5.9 (2.4)	0.7
Aspartate aminotransferase (IU)	120.0 (6.8)	119.4 (7.1)	120.3 (7.0)	0.7
Alanine aminotransferase (IU)	157.0 (8.5)	157.2 (8.6)	158.2 (9.2)	0.8
Alkaline phosphatase (IU)	156.0 (10.9)	155.8 (10.0)	156.6 (11.4)	0.7

hepatitis E infection. Fulminant hepatic failure was more common among HEV-infected women who were at higher risk than non-HEV infected women. Additionally, maternal mortality secondary to fulminant hepatic failure was also higher in the HEV infected group.¹⁰ In contrast, in Egypt, while there is a high prevalence of anti-HEV, severe HEV and severe acute viral hepatitis in pregnant women have not been reported.⁹

HEV infection represents an important public health concern in many developing countries, where it is primarily transmitted through the orofecal route due to inadequate sanitary conditions and contaminated water supplies.^{27–29} Recent evidence indicates that HEV is a zoonotic disease, which has raised potential public health concerns.²⁸ In the absence of outbreaks, the HEV prevalence is 4.4% in Ghana, 14.0% in Burundi, 15.3% in South Africa, and 67.7% in Egypt, with a seroprevalence of up to 84.3% among pregnant Egyptian women.^{9,30–32} The clinical features and outcomes in the current study and in a previous report from Darfur, Sudan¹³ reflect the features during an outbreak of HEV. HEV may be widespread among pregnant women in Sudan and it may circulate in the general population. Therefore, a population-based study to confirm or exclude this speculation is urgently required. In addition, the sanitary conditions under which pregnant women live and work need to be improved.

References

- Rein DB, Stevens G, Theaker J, Wittenborn JS, Wiersma ST. The global burden of hepatitis E virus. *Hepatology*. 2012; 55:988–97.
- Aggarwal R, Naik S. Epidemiology of hepatitis E: current status. *J Gastroenterol Hepatol*. 2009;24:1484–93.
- Tsega E, Krawczynski K, Hansson BG, Nordenfelt E, Negusse Y, Alemu W, et al. Outbreak of acute hepatitis E virus infection among military personnel in northern Ethiopia. *J Med Virol*. 1991;34:232–6.
- Mushahwar IK, Dawson GJ, Bile KM, Magnus LO. Serological studies of an enterically transmitted non-A, non-B hepatitis in Somalia. *J Med Virol*. 1993;40:218–21.
- Benjelloun S, Bahbouhi B, Bouchrit N, Cherkaoui L, Hda N, Coursaget P, et al. Outbreak of enterically-transmitted hepatitis due to hepatitis A and hepatitis E viruses. *J Hepatol*. 1998; 28:745–50.
- Nicand E, Armstrong GL, Enouf V, Guthmann JP, Guerin JP, Caron M, et al. Genetic heterogeneity of hepatitis E virus in Darfur, Sudan, and neighboring Chad. *J Med Virol*. 2005; 77:519–21.
- Kumar RM, Uduman S, Rana S, Kochiyil JK, Usmani A, Thomas L. Sero-prevalence and mother-to-infant transmission of hepatitis E virus among pregnant women in the United Arab Emirates. *Eur J Obstet Gynecol Reprod Biol*. 2001;10:9–15.
- Navaneethan U, Al Mohajer M, Shata MT. Hepatitis E and pregnancy: understanding the pathogenesis. *Liver Int*. 2008;28:1190–9.
- Stoszek SK, Abdel-Hamid M, Saleh DA, El Kafrawy S, Narooz S, Hawash Y, et al. High prevalence of hepatitis E antibodies in pregnant Egyptian women. *Trans R Soc Trop Med Hyg*. 2006;100:95–101.
- Patra S, Kumar A, Trivedi SS, Puri M, Sarin SK. Maternal and fetal outcomes in pregnant women with acute hepatitis E virus infection. *Ann Intern Med*. 2007;147:28–33.
- Adjei AA, Tettey Y, Aviyase JT, Adu-Gyamfi C, Obed S, Mingle JA, et al. Hepatitis E virus infection is highly prevalent among pregnant women in Accra, Ghana. *Virol J*. 2009;6:108.
- Caron M, Kazanji M. Hepatitis E virus is highly prevalent among pregnant women in Gabon, central Africa, with different patterns between rural and urban areas. *Virol J*. 2008;5:158.
- Boccia D, Guthmann JP, Klovstad H, Hamid N, Tatay M, Ciglenecki I, et al. High mortality associated with an outbreak of hepatitis E among displaced persons in Darfur, Sudan. *Clin Infect Dis*. 2006;42:1679–84.
- Ahmed RE, Karsany MS, Adam I. Brief report: acute viral hepatitis and poor maternal and perinatal outcomes in pregnant Sudanese women. *J Med Virol*. 2008;80:1747–8.
- Elsheikh RM, Daak AA, Elsheikh MA, Karsany MS, Adam I. Hepatitis B virus and hepatitis C virus in pregnant Sudanese women. *Virol J*. 2007;4:104.
- Adam I, Jumaa AM, Elbashir HM, Karsany MS. Maternal and perinatal outcomes of dengue in Port Sudan, Eastern Sudan. *Virol J*. 2010;7:153.
- Abdallah TM, Ali AA, Karsany MS, Adam I. Epidemiology of dengue infections in Kassala, Eastern Sudan. *J Med Virol*. 2012;84:500–3.
- Tsega E, Krawczynski K, Hansson BG, Nordenfelt E. Hepatitis E virus infection in pregnancy in Ethiopia. *Ethiop Med J*. 1993;31:173–81.
- Khuroo MS, Kamili S, Jameel S. Vertical transmission of hepatitis E virus. *Lancet*. 1995;315:1025–6.
- Jaiswal SP, Jain AK, Naik G, Soni N, Chitnis DS. Viral hepatitis during pregnancy. *Int J Gynaec Obstet*. 2001;72:103–8.
- Kumar A, Beniwal M, Kar P, Sharma JB, Murthy NS. Hepatitis E in pregnancy. *Int J Gynaecol Obstet*. 2004; 85:240–4.
- Singh S, Mohanty A, Joshi YK, Dwivedi SN, Deka D. Outcome of hepatitis E virus infection in Indian pregnant women admitted to a tertiary care hospital. *Indian J Med Res*. 2001;113:35–9.
- Mohammed AA, Elnour MH, Mohammed EE, Ahmed SA, Abdelfattah AI. Maternal mortality in Kassala State — Eastern Sudan: community-based study using reproductive age mortality survey (RAMOS). *BMC Pregnancy Childbirth*. 2011;11:102.
- Jilani N, Das BC, Husain SA, Baweja UK, Chattopadhyaya D, Gupta RK, et al. Hepatitis E virus infection and fulminant hepatic failure during pregnancy. *J Gastroenterol Hepatol*. 2007;22:676–79.
- Emerson SU, Purcell RH. Hepatitis E virus. *Rev Med Virol*. 2003;13:145–54.
- Mizuo H, Yazaki Y, Sugawara K, Tsuda F, Takahashi M, Nishizawa T, et al. Possible risk factors for the transmission of hepatitis E virus and for the severe form of hepatitis E acquired locally in Hokkaido, Japan. *J Med Virol*. 2005;76:341–9.
- Worm HC, van der Poel WH, Brandstaetter G. Hepatitis E: an overview. *Microbes Infect*. 2002;4:657–66.
- Purcell RH, Emerson SU. Hepatitis E: an emerging awareness of an old disease. *J Hepatol*. 2008;48:494–503.
- Meng XJ. Recent advances in Hepatitis E virus. *J Viral Hepat*. 2010;17:153–61.
- Tucker TJ, Kirsch RE, Louw SJ, Isaacs S, Kannemeyer J, Robson SC. Hepatitis E in South Africa: evidence for sporadic spread and increased seroprevalence in rural areas. *J Med Virol*. 1996;50:117–9.
- Aubry P, Niel L, Niyongabo T, Kerguelen S, Larouze B. Seroprevalence of hepatitis E virus in an adult urban population from Burundi. *Am J Trop Med Hyg*. 1997;57:272–3.
- Martinson FE, Marfo VY, Degraaf J. Hepatitis E virus seroprevalence in children living in rural Ghana. *West Afr J Med*. 1999;18:76–9.