Hepatitis E virus seroprevalence in pregnant women in Pakistan: maternal and fetal outcomes

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الانتشار المصلى لفيروس التهاب الكبد E بين الحوامل في باكستان: والعواقب على الأمهات والأجنة

نجمة جواد عوان، سلطانة حبيب الله، نازلي حسين، منير شيخ، أمبرين خان، فرخنده غفور، رخصانة فردوس، وقارالدين، عارف ناديم شكيب، غزالية محيي الدين

الخلاصة: إن فيروس التهاب الكبد E متوطن في باكستان. مع أن العدوى بفيروس التهاب الكبد E عديمة الأعراض، فإنها خلافاً لذلك تصبح مميتة أثناء الحمل، وتسبب مراضة ووفيات كثيرة بين الأمهات والأجنة. وقد أجرينا دراسة وصفية من أبريل/ نيسان إلى أكتوبر/ تشرين الأول 2015 في عشرة مستشفيات للرعاية الثالثية في جميع أنحاء باكستان لتحديد معدلات وفيات الأمهات والأجنة بين الحوامل المصابات بفيروس التهاب الكبد E ولديهن صفراء حادة أو اختىلالات مرتفعة في اختبارات وظائف الكبد. كانت إحدى وعشرون امرأة من تا الما بفيروس التهاب الكبد E في الشهور الثلاثة الأخيرة من الحمل باستثناء امرأة واحدة أصيبت به في الشهور الثلاثة الأولى من الحمل. وبلغ المعدل بفيروس التهاب الكبد E في الشهور الثلاثة الأخيرة من الحمل باستثناء امرأة واحدة أصيبت به في الشهور الثلاثة الأولى من الحمل. وبلغ المعدل الكلي لانتشار فيروس التهاب الكبد E في الحمل 2010. أجريت لعشر نساء ولادة تُحرَّضَة اصطناعياً، ثلاثة منهن كان لديمن خاض باكر، وأربعة منهن ولدن تلقائياً (حمل مكتمل المدة)، وتوفيت 3 نساء، وتوفي جنين واحد داخل الرحم. وتعرضت امرأة واحدة لإجهاض في المنزل قبل وصولها إلى المستشفى. وتوفي 7 رضّع في الفترة المحيطة بالولادة: 4 وفيات داخل الرحم، وولادة جنين مين، وإربعة الأميات وفيات الأمهات ارتباطاً وثيقاً بالولادة، حيث إن 17 أماً حيّةً ولدت تلقائياً أو أجري لها عريض المناعياً، ثلاثة منهن كان لديمن خاض باكر، وأربعة وسولها إلى المستشفى. وتوفي 7 رضّع في الفترة المحيطة بالولادة: 4 وفيات داخل الرحم، و3 ولادة جنين ميت، وإجهاض واحد. وارتبطت وفيات الأمهات ارتباطاً وثيقاً بالولادة، حيث إن 17 أماً حيّةً ولدت تلقائياً أو أجري لها تحريض اصطناعي للولادة، بينها توفيت 3 نساء المتمر حملهن ولم يلدن. وبلغ معدل وفيات الولادة، حيث إن 17 أماً حيّةً ولدت تلقائياً أو أجري لما عريض اصطناعي علي ولودة، بينها توفيات الما ولي الما وله من المهات ارتباطاً وثيقاً بالولادة، بينها توفيت 3 أما مراحية ولدت تلقائياً أو أجري لها تحريض المواناعي بلولادة، بينها توفيت 3 أمان ما وليات ولمن ولي من معدل وفيات المعات ولي ما تربي المناعي المهات ارتباطاً وثيقاً بالموات الحامية ولدت تلقائياً أو أجري لها تحريض المولية عرين ما ولودة، بينها توفيت 3 أما م

ABSTRACT Hepatitis E virus (HEV) is endemic in Pakistan. Although otherwise asymptomatic, HEV infection becomes fatal in pregnancy, with considerable maternal and fetal morbidity and mortality. We conducted a descriptive study from April to October 2015 in 10 tertiary care hospitals throughout Pakistan to determine maternal and fetal morbidity and mortality in HEV-positive pregnant women with acute jaundice or raised liver function tests. Twenty-one of 135 women were HEV positive and in 3rd trimester except for 1 in 1st trimester. Overall prevalence of HEV in pregnancy was 0.19%. Ten women were artificially induced, 3 had premature labour, 4 delivered spontaneously (full term), 3 died and there was 1 intrauterine death. One woman had a home abortion before coming to hospital. There were 7 perinatal infant deaths: 4 intrauterine, 3 stillbirths and 1 abortion. Maternal mortality was significantly associated with delivery, as 17 mothers who lived went into labour spontaneously or were artificially induced, whereas 3 women who continued their pregnancy and did not deliver, died. Case fatality rate of HEV infection in pregnancy was 14.2%.

Séroprévalence de l'infection par le virus de l'hépatite E chez des femmes enceintes au Pakistan : conséquences sur la santé maternelle et fœtale

RÉSUMÉ Le virus de l'hépatite E (VHE) est endémique au Pakistan. Bien qu'asymptomatique dans la plupart des cas, le virus de l'hépatite E devient mortel lors d'une grossesse, contribuant de façon considérable à la morbidité et la mortalité maternelles et fœtales. Une étude descriptive à été conduite entre avril et octobre 2015 dans 10 hôpitaux de soins tertiaires dans l'ensemble du Pakistan afin de déterminer la morbidité et la mortalité chez les femmes enceintes positives au virus de l'hépatite E avec ictère aigu ou présentant une élévation des tests hépatiques. Sur 135 femmes, 21 étaient positives au virus de l'hépatite E et se trouvaient au troisième trimestre de grossesse, exception faite de l'une d'entre elles qui en était au premier trimestre. La prévalence globale du virus de l'hépatite E durant la grossesse s'élevait à 0,19 %. Dix femmes avaient subi un accouchement déclenché, trois avaient eu un travail prématuré, quatre avaient accouché naturellement (à terme), trois femmes étaient décédées et on dénombrait un décès intra-utérin. Une femme avait avorté à domicile avant de se rendre à l'hôpital. Il y a eu sept cas de décès périnatals, dont quatre cas intra-utérins, trois mortinaissances et un avortement. La mortalité maternelle était significativement associée à l'accouchement puisque les 17 mères qui ont survécu avaient accouché naturellement ou avaient subi un accouchement déclenché, tandis que trois femmes avaient poursuivi leur grossesse sans accoucher, et étaient décédées. Le taux de létalité de l'infection par le virus de l'hépatite E durant la grossesse était de 14,2 %.

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Introduction

Hepatitis E virus (HEV) is a small, nonenveloped virus with a singlestranded RNA genome. The virus has four genotypes, but only one serotype. Genotypes 1 and 2 exclusively infect humans, whereas genotypes 3 and 4 also infect pigs and several other mammalian species.

Like hepatitis A virus, HEV also spreads via the faecal–oral route, and in nonpregnant women and men, the disease is usually self-limiting and has a low case fatality rate (< 0.1-4%) (1). In developing countries with poor sanitation, HEV infection is common and presents as outbreaks and as sporadic cases with acute self-limiting hepatitis.

In Pakistan, epidemics of acute viral hepatitis were first reported in the 1950s and 1960s. In 1972, an outbreak of ~250 cases was observed in an army battalion on field exercises, and all infected persons had drunk untreated river water (2). Many similar outbreaks of hepatitis E had been wrongly attributed to HAV. However, it subsequently became clear that all the outbreaks were caused by HEV (2, 3). In Pakistan, HEV remains highly endemic and mainly affects the adult population (4). Several mini-epidemics have recently been reported in Pakistan and all of these appear to have been due to faecal contamination of the water supply. Although Islamabad has a supply of potable water and a good drainage system, it had a massive outbreak of acute hepatitis caused by HEV between December 1993 and March 1994 that created a lot of concern in the general population (5). The Pakistan Viral Hepatitis Surveillance System reported that during June 2010-March 2011, 712 cases of viral hepatitis were seen at 5 sentinel sites and prevalence of acute hepatitis E was 12.2% (6).

The prevalence of HEV is higher in pregnancy, which has mostly been reported in developing regions and countries like North Africa, India, Pakistan, Ghana and Egypt. It remains inconclusive whether the severe outcome in pregnancy in these countries reflects viral virulence, viral variants or host factors, especially malnutrition, or failure of timely and proper treatment (7). For unknown reasons, the mortality rate is higher among pregnant women, especially during the 3rd trimester (8). Fulminant hepatic failure secondary to hepatitis E infection is common in pregnancy and associated with a mortality rate of up to 20-25% (9). In India, Islamic Republic of Iran, Africa and the Middle East, the incidence of fulminant hepatitis was higher in pregnancy. The mortality rate in HEV-infected mothers was 100% and mother-to-child transmission of HEV was established in 50% of cases (10).

Screening pregnant women for HEV is thus important for improving knowledge about the epidemiology of the virus and planning for its prevention and control. A few studies have been conducted in Pakistan to document the prevalence of HEV in pregnant women. The results of the present study will help to determine the prevalence of HEV infection in pregnant women and its outcomes at the national level. We also investigated fetal outcomes and rate of vertical transmission. Analysis of our results will help to plan future strategies to prevent the high mortality associated with this infection.

Methods

The objective of this study was to determine the maternal and fetal morbidity and mortality in pregnant women positive for HEV IgM who presented with jaundice or abnormal liver function tests, in comparison with HEVnegative cases. None of the women had jaundice of pregnancy or hepatocellular carcinoma. We conducted an observational study from 1 April to 30 October 2015 in 10 hospitals in Pakistan: Pakistan Institute of Medical Sciences, Islamabad; Dow University of Health Sciences, Karachi; Jinnah Postgraduate Centre, Karachi, Sindh; Shaikh Zayed Hospital, Lahore; Allied Hospital, Faisalabad, Punjab; Bolan Medical College, Quetta, Balochistan; Lady Reading Hospital and Hayatabad Medical Complex, Peshawar, Khyber Pakhtoonkhwa; and Holy Family Hospital and Benazir Bhutto Hospital, Rawalpindi.

After receiving ethical clearance and consent from participating hospitals, data collectors were trained to maintain the uniformity of data coding, delivery of questions, data gathering, decoding and data entry. Data collectors were trained researchers. The questionnaire consisted of close-ended questions and information was collected under 5 headings: participating hospital, patient demography, details about hospital admission, details of laboratory findings, and outcome of pregnancy (both maternal and fetal). Any pregnant woman with acute jaundice presenting for the first time anywhere within the hospital, either in the obstetric outpatient department, labour room or emergency department, was immediately reported to the research team. After obtaining informed consent from the patients, demographic information was recorded through face-to-face interview with the patient. However, if the patient was too ill, the attending physician gave the information. Data regarding gestational age, laboratory findings [hepatitis B surface antigen, hepatitis C virus (HCV) antibody, liver function tests, coagulation tests (e.g., activated partial thromboplastin time)] and complications associated with pregnancy were retrieved from patients' files. All enrolled patients were followed through medical records or telephone contact after discharge for pregnancy outcomes (mother and fetus) and data were recorded.

In addition to laboratory information collected from the patients' files, pregnant women were screened for HEV IgM by taking 3-ml blood. Samples were transported to the designated research centre for that city where they were analysed for HEV-specific IgM antibodies using indirect antibody capture, quantitative ELISA. Sample testing used one negative and two positive controls. The ELISA kit had sensitivity and specificity of 97.9 and 100%, respectively. Data on patient demography, hospital admission, laboratory findings and outcomes were analysed using Epi Info version 7.2. Descriptive analysis is presented as frequencies and percentages. A P value < 0.05 was considered statistically significant.

Results

Patient characteristics

One hundred and forty-two pregnant women were enrolled, however, 7 did not give consent for the study and were excluded. Among the remaining 135 patients, 21 were HEV positive and 114 were HEV negative.

Mean age of the HEV-positive women was 29.2 (standard deviation; SD, 7.7) years and mean age of the HEV-negative women was 28.6(4.9)years. The women were divided into 2 age groups: 20-30 and 31-40 years. All HEV-positive women were in the 31-40 years group, whereas 23 HEVnegative women were in the 20–30 years and 91 were in 31–40 years group. Mean gestational age was 33.46 (4.45) weeks for HEV-positive women and 35 (2.2) weeks for HEV-negative women. Twenty-one pregnant women had acute hepatitis E. Overall prevalence of HEV among pregnant women was 0.19% (21 out of expected pregnant population of 10 956). One hundred and fifteen (85%) women were multigravida and 20 (15%) primigravida. One hundred and sixteen (86%) women presented in the 3rd trimester, 17 (13%) in 2nd trimester and 2 (1.4%) in 1st trimester, and 116 presented with jaundice. All HEV-positive cases were in the 3rd trimester.

Regarding educational status, 29 were illiterate; 31 were educated to primary level, 34 to intermediate level and 23 to matric level; 11 were graduates and 7 had a masters degree.

Clinical presentation

Ten (7.4%) of the 135 women had a history of jaundice and all those were multigravida. Jaundice was the most common symptom experienced by 116 (86%) patients followed by nausea/ vomiting in 55 (41%), pruritus in 47 (35%) and bleeding from the gums or nose in 19 (14%). All 21 HEV-positive pregnant women had jaundice, and jaundice to encephalopathy interval was 1-3 days. Three (14.2%) HEVpositive patients developed encephalopathy and all died and 5 (4.4%) of 114 HEV-negative women developed this complication and 4 died. All pregnant women with jaundice (116, 86%) were treated symptomatically

Laboratory investigations

Among the 135 patients, 7 were infected with hepatitis B virus (HBV) (3 HEV positive and 4 HEV negative), 7 with HCV (1 HEV positive and 6 HEV negative) and 3 were co-infected with HBV and HCV (1 HEV positive and 2 HEV negative). LFTs, haemoglobin level, total leukocyte count, platelet count and random blood sugar were abnormal in HEV-positive and HEV-negative patients (Table 1).

Maternal and fetal outcomes

Among HEV-positive cases, 3 women died from hepatic encephalopathy and there was 1 intrauterine death (IUD) (Table 2). All babies that were born alive survived. Among HEV-negative cases, 4 women died (2 from hepatic encephalopathy and 1 each from disseminated intravascular coagulation and renal failure) as well as 6 newborns (3 stillbirths and 3 intrauterine deaths). Overall there were 7 perinatal infant deaths: 4 IUDs, 3 stillbirths and 1 abortion. Regarding maternal deaths, 6 died from hepatic encephalopathy and 1 from renal failure/disseminated intravascular coagulation. No significant difference was found in the laboratory findings between the fatal and surviving cases. Maternal mortality was significantly associated with delivery ($P \le 0$.012), as 17 of 21 mothers who survived delivered naturally or were induced, while 3 who continued their pregnancy died.

Discussion

Our study showed that jaundice was more common in multigravida as compared to primigravida women. Among 20 primigravida and 115 multigravida women, 116 (86%) presented in 3rd trimester, including all HEV-positive cases. This means severity of HEV infection increases with repeated exposure to virus, and during pregnancy, severity increases with each trimester, becoming lethal in the last trimester. An Indian study showed that 63% of HEV infection was in the 3rd trimester of pregnancy when presented with jaundice (11), and fulminant hepatic failure and death were more common in the HEV-positive group (relative risk of fulminant hepatic failure, 2.7; relative risk of death, 6.0). The current study had similar findings; out of 21 HEV-positive women, 3 developed fulminant hepatic failure and all died. However, the difference in maternal mortality between the HEV-positive and -negative groups was not significant, which may have been due to the small study group.

Abraham found that among HEVpositive pregnant women, mean gestational age was 31 weeks (*12*), whereas in the current study mean gestational age was 35 weeks. In another Indian study of acute liver failure (1989–1996), 49 of 83 women of childbearing age were pregnant (33 in 3rd trimester) and all except 2 had HEV infection (*13*). Our

Table 1 Comparison of laboratory findings among HEV-positive and -negative cases								
Variables	Normal values	HEV-positive cases (n = 21)		HEV-negative cases (n = 114)				
		Mean	SD	Mean	SD			
Hb (g/dl)	12-16	9.9	2.069	9.8	2.0			
TLC (/μl)	4500-11 000	8076	20501	7234	1801			
Platelet count (/µl)	150 000-450 000	189 860	168 709	200 189	18 342			
APTT (s)	20-40	33.4	9.3	28.5	7.2			
Serum bilirubin (g/dl)	0.2-1.0	4.9	4.01	4.2	3.9			
ALK (U/I)	38-126	416.6	247.3	502	312.1			
RBS (mg/dl)	70-115 mg/dl	99.2	54.9	98.5	54.3			

ALK = alkaline phosphatase; APTT = activated partial thromboplastin time; HB = haemoglobin; HEV = hepatitis E virus; RBS = random blood sugar; TLC = total leukocyte count.

results are consistent with these findings in that 86% (116/135) were in 3rd trimester at presentation and all HEV-positive patients except 1 were in 3rd trimester.

Regarding maternal mortality in HEV-positive women, Zhu et al. (14) reported high mortality (up to 30%), mainly from fulminant hepatic failure. However, in our study, 3 of 21 HEVpositive patients died (14%) and this may have been due to the small study population. In Ghana, HEV seropositivity in pregnancy is high at up to 29% (15), whereas our study only showed an HEV prevalence of 0.19% among pregnant women.

Regarding fetal outcomes, Khuroo and colleagues have reported that HEV infection in neonates born to HEVpositive mothers is mostly benign as neonates usually survive with no prolonged illness (16). We found a similar result and only reported 1 perinatal death from miscarriage among 21 HEVinfected mothers. A study from the United Arab Emirates showed that only a few babies of HEV-infected mothers were either preterm, had hepatitis or died within a few hours after birth (17). However, in our study there were only 2 neonatal deaths among HEV-infected mothers; 1 from IUD and another from miscarriage (10%), which was higher than those born to uninfected mothers (5%). In Sudan, among 39 pregnant women with HEV infection during an outbreak, there were 14 IUDs and 9 premature deliveries (18), and neonatal mortality was high compared to that in our study. A similarly high neonatal mortality has been reported in India, where 15-50% of live-born infants of HEV-infected mothers died within 1 week of birth (19). In contrast, all babies born alive from HEV-infected mothers in our study survived. Other studies have also shown that fetal morbidity in HEV-infected mothers varies from case to case and geographically, and includes miscarriage, stillbirth, preterm labour, or perinatal or neonatal death (20, 21).

Bhatia and colleagues have revealed that HEV-positive pregnant women had a jaundice to encephalopathy interval of 5.2 (4.4) days, serum bilirubin level of 14.4 (5.8) mg/dl and serum aspartate aminotransferase/alanine aminotransferase (AST/ALT) ratio of thousands (22). However, the current study had different findings. The jaundice to encephalopathy period was 1–3 days and other laboratory values were not high.

In our study, most of the women affected were in the 31–40 years. However, an Indian study reported that most patients (82.7%) were aged 21–30 years (23).

A recent study from Pakistan documented that there was no history of jaundice in all 34 cases (24). Pruritus was the most common symptom experienced by 28 (82%) patients, followed by jaundice in 27 (79%), nausea/vomiting in 25 (74%), encephalopathy in 18 (53%) and bleeding from gums or nose in only 2 cases. Fulminant hepatic failure was diagnosed in 11 cases and all died. Similarly, in the current study only 10 patients had a history of jaundice and all 3 HEV-positive women who died eventually developed fulminant hepatic failure.

Table 2 Maternal and fetal outcomes among HEV-positive and negative pregnant women5							
Study population	Maternal outcomes		Fetal outcomes				
	Survival	Death	Survival	Death			
HEV-positive, n = 21	18 (86%)	3 (14%)	19 (90%)	2ª (10%)			
HEV-negative, n = 114	110 (96.4)	4 (3.4%)	108 (95%)	6 (5%)			
Total = 135	128	7	128	7			

^aIncludes 1 abortion in 1st trimester.

Our study had some limitations. This was a hospital-based study involving only the public sector but 70% of our population goes to the private sector, so the results cannot be generalized. In addition, discontinuation of treatment in some hospitals by patients further reduced the data.

This is believed to be the first study from Pakistan comparing clinical and laboratory profiles between HEV-positive and -negative pregnant women with jaundice. We described maternal and fetal outcomes in pregnant women who developed hepatitis E. We showed that incidence of infection increases with duration of gestation, which suggests that pregnant women should be periodically screened for clinical features of acute hepatitis during antenatal visits and should be investigated for hepatitis E. Pregnant women with HEV should be closely monitored for fetal and maternal well-being and signs of fetal distress, to prevent disease-associated morbidity and mortality.

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