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Comparison of foeto-maternal outcome in pregnant women with hepatitis E - A review of 12 years.

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ORIGINAL ARTICLE

Comparison of foeto-maternal outcome in pregnant women with hepatitis E — A review of 12 years

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Abstract

Objective: To compare adverse maternal and foetal outcome in pregnant women with hepatitis E immunoglobulin M reactive versus non-reactive.

Methods: This retrospective study was conducted at the Aga Khan University Hospital, Karachi, and comprised records of pregnant patients at any gestational age with clinical and biochemical evidence of hepatitis E from January 2002 and December 2014. . Maternal and perinatal outcome of the subjects were analysed. SPSS 20 was used for data analysis.

Results: Out of the 200 subjects, 168(84 %) were hepatitis E immunoglobulin M reactive and 32(16%) were non-reactive. The overall mean age was 26.7±4.5 years. Also, 12(7%) patients in the immunoglobulin M reactive group were admitted to intensive care unit compared to no one from the non-reactive group. Similarly fulminant hepatic failure was seen in 12(7.1%) patients in the immunoglobulin M reactive group compared to no one in the other group. Post-partum haemorrhage was more frequent in the immunoglobulin M reactive group compared to the non-reactive group. There were 5(3%) maternal deaths in the reactive group compared to no death in the other group.

Moreover, 34(20.2%) neonates of the immunoglobulin M reactive group needed neonatal intensive care unit admission compared to none in the non-reactive group. There were 4(2.4%) neonatal deaths in the reactive group.

Conclusion: Participants in the immunoglobulin M reactive group had a higher percentage of adverse foeto-maternal outcomes compared to the non-reactive group.

Keywords: Hepatitis E, Fulminant hepatic failure, Maternal mortality. (JPMA 67: 538; 2017)

Introduction

Hepatitis E virus (HEV) is the most frequent cause of acute hepatitis and has become an important public health concern in many developing countries.[1] Hepatitis E virus is a non-enveloped, single-stranded ribonucleic acid (RNA) virus that is approximately 27-34nm in diameter. It has four genomes; genomes one and two are highly virulent as well as prevalent in Asia.[2] In Pakistan, the first reported explosive water-borne epidemics of hepatitis E was in Islamabad in 1994 followed by an outbreak in army garrison in Lahore and then in Karachi.[3] It is usually transmitted through faecal contamination in water, however, pig's internal organ and rodents were also reported to be the means of transmission of disease in sporadic cases in industrialised nations.[4,5] A study conducted by Khuro et al. also claims trans-placental transmission of virus to the foetus.[6]

Hepatitis E presentation is similar to hepatitis A virus including lethargy, anorexia, abdominal pain, jaundice and fever. The disease has a very mild course in men and non-pregnant women. However, in pregnant women this infection is particularly severe and leads to high fatality.[7]

The prevalence of hepatitis E infection during pregnancy is high ranging from 47.4-84.3%.[4,8] It seems to be due to altered immune response, hormonal changes and malnutrition. In fact, the exact mechanism is not well comprehended.[9]

During pregnancy, especially in the third trimester, the infection is worst. It may progress to coagulation defects, fulminant hepatic failure (FHF) and encephalopathy. It also increases pregnancy complications like preterm labour, post-partum haemorrhage (PPH) and maternal mortality.[10]

Maternal mortality ranges from 36-71%.[4,10] In majority of the cases, these women developed FHF, which accounts for 28-70%,[3,5,6] while coagulation defect occurs in 26-79%.[10,11] S. Shukla et al. observed 100 cases of hepatitis and encountered 6 patients who developed hepatitis encephalopathy; no one survived among them.[12] Haemorrhage during and after delivery is also not uncommon as its prevalence is 4% and 27%, respectively.[10] In contrast, the reports from Egypt, Europe

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and the United States show no difference in severity of the disease in non-pregnant and pregnant women.[8,13]

Perinatal mortality ranges from 5-20%.[10,14] The rate of intrauterine death (IUD) is around 5% while neonatal death (NND) occurs in 8% of cases. This could be due to disease itself or prematurity in more than 50% of cases.[10]

The current study was planned to compare maternal and foetal outcome in pregnant women with hepatitis E immunoglobulin M (IgM) reactive versus IgM non-reactive presenting.

Materials and Methods

The study was conducted at the Department of Obstetrics and Gynaecology in collaboration with the Department of Gastroenterology at the Aga Khan University Hospital (AKUH), Karachi, and comprised records of pregnant women who developed jaundice and hepatitis E from January 2002 to December 2014. The AKUH is one of the largest tertiary hospitals in the private sector, with more than 4,500 deliveries per annum. Approval for the study was obtained from ethics review board of the institution. Patients presenting with jaundice, serum bilirubin >2.5mg/dl, increase in serum transaminases more than twice than normal with reactive hepatitis E immunoglobulin G (IgG) and IgM were included. Women - diagnosed with haemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome, obstetric cholestasis and positive hepatitis A, B or C were excluded. Participants were managed according to the management protocol of the institution.

The study variables were age, parity and gestational age at the time of presentation, mode of delivery, complications related to hepatitis E and obstetric complications along with maternal and foetal outcome. Liver function test including alanine aspartate aminotransferases,[10] alanine aminotransferases (ALT), alkaline phosphatase, bilirubin, complete blood count (CBC), blood urea nitrogen (BUN) and creatinine and prothrombin time (PT) were also noted.

Participants were divided into two groups; group A included all women who were IgM reactive, while group B comprised women who had IgM non-reactive but IgG reactive for hepatitis E. Women were labelled as having acute liver failure if they developed severe acute liver injury with impaired liver function test and hepatic encephalopathy within four weeks of onset which is characterised by mental changes progressing from confusion to stupor and coma as a result of severe impairment of hepatic function, without any history of pre-existing liver disease.[15]

SPSS 20 was used for data analysis. Mean and standard deviation (SD) were calculated for continuous variables, such as maternal age, gestational week at delivery, birth weight of baby, biochemical test, etc. Frequency and proportions were calculated for categorical variables, such as mode/type of delivery, admission to intensive care unit (ICU), occurrence of PPH, etc. Differences between means were checked through t-test and association between categorical/nominal variable was assessed through chi-square/ Fisher's exact test as appropriate. $P<0.05$ was considered significant.

Results

Of the 50,037 deliveries during the study period, 200(0.4%) pregnant women developed presented with jaundice and positive hepatitis E antibodies and they comprised the study sample. Of them, 95(47.5%) were aged 25-30 years, 64(32%) were aged below 25 years and 41(20.5%) were aged above 30 years. The overall mean age was 26.7±4.5 years. Moreover, 112(56%) subjects were primigravidas.

In 159(80%) cases, the baby was delivered after 34 weeks' gestation. Besides, 193(96.5%) participants presented in the third trimester, whereas 183(91.5%) came to the hospital in stable condition. Also, 115(57.5%) participants had lower segment caesarean section (LSCS). There was intrauterine foetal death in 11(5.5%) cases. Out of the 189(94.5%) patients whose foetuses were alive at the time of admission, 4(2.1%) died in the neonatal period. In addition, 34(17%) neonates needed neonatal intensive care unit (NICU) admission.

Furthermore, 16(8%) patients had PPH and 2(1%) had prolonged labour. Moreover, 12(6%) participants had FHF and 2(1%) had hepatic encephalopathy. Besides, 12(6%) required ICU admission while 86(43%) were admitted to high dependency unit (Table-1).

The mean bilirubin level was 8.12±5.1 and 8.25±6.5in IgM reactive and non-reactive group, respectively; the difference was not significant. In regard to the values of SGPT, SGOT, Alkaline phosphatase, GGT PT, APTT and INR the data was skewed therefore median value and range was calculated (Table-2).

There were 168(84%) participants in the IgM reactive group compared to 32(16%) in the non-reactive group. Moreover, 76(45.2%) participants in the IgM reactive group were in the age group of 25-30 years compared to 19(59.4%) in the non-reactive group (p=0.34). In the IgM reactive group, 98(58.3%) were primigravidas compared to 14(43.8%) in the IgM non-reactive group (p=0.09).

Gestational age at delivery was significantly different in

Table-1: Characteristics of patients infected with hepatitis E.

Variables (%)	Frequency
Age Mean ± SD	26.7±4.5
< 25 Years	64 (32.0)
25-30 Years	95 (47.5)
> 30 Years	41(20.5)
Gravida	
PrimiGravida	112 (56.0)
Multi Gravida	88 (44.0)
Gestational age at delivery	
< 34	41(20.5)
> = 34	159 (79.5)
Trimester	
II Trimester	7 (3.5)
III Trimester	193 (96.5)
Patient condition on arrival	
Stable	183 (91.5)
Unstable	17 (8.5)
Mode of delivery	
SVD	78 (39.0)
LSCS	115 (57.5)
Not deliver in AKU	7 (3.5)
Condition of foetus on arrival	
Alive	182 (91.0)
Dead	11(5.5)
Not deliver in AKU	7 (3.5)
Condition of baby at the time of delivery	
Alive	178 (89.0)
IUD	11(5.5)
NND	4 (2.0)
Not deliver in AKU	7 (3.5)
NICU admission *	
No	148 (78.3)
Yes	34 (17.8)
Not deliver in AKU	7 (3.7)
Complications due to hepatitis	
Fulminant hepatic failure	12 (6.0)
Hepatic encephalopathy	2 (1.0)
No complication	186 (93.0)
Complication during labour	
PPH	16 (8.0)
Prolong labour	2 (1.0)
Others	12 (6.0)
No complication	170 (85.0)
ICU/Special care admission	
No	102 (51.0)
Yes	12 (6.0)
Special care	86 (43.0)
Maternal Outcome	
recovered and discharged	195 (97.5)
Died	5 (2.5)

*IUDs were excluded from the denominator (n; 189)
SVD: Spontaneous vaginal delivery. LSCS: Lower segment caesarean section.
AKU: Aga Khan University. IUD: Intrauterine death.
NND: Neonatal death. NICU: Neonatal intensive care unit.
ICU: Intensive care unit. PPH: Post-partum haemorrhage.
SD: Standard deviation.

Table-2: Analysis of laboratory parameters in Hepatitis E, IgM reactive and IgM non-reactive.

Laboratory parameters	IgM reactive Mean ± S.D	IgM non- reactive Mean ± S.D	P value
Bilirubin	8.12±5.1 (mg/dl)	8.25±6.5	0.272
Direct	5.24±2.7 (mg/dl)	6.0±3.5	0.223
Indirect	3.40±2.4 (mg/dl)	4.72±2.9	0.597
SGPT	264.5 IU/L(120-2690)	270.5(100-2015)	*
SGOT	219.0 IU/L(105-4038)	333.0(102-2760)	*
Alkaline phosphatase	214.5 IU/L(102-1140)	207.0(140-499)	*
GGT	28.0 IU/L(4-129)	28.0(10-102)	*
PT	11.3(10-70) Seconds	12.3(11-70)	*
APTT	27.5(11.0-150.0) Seconds	30.2(20.4-47.7)	*
INR	1.27(0.80-11.0) Ratio	1.04(0.94-6.6)	*
HB	10.9±1.1 g/dl	11.3±1.5	0.238
HCT	32.5±3.8%	33.0±5.6	0.387
RBC	3.8±0.4* 10 E12/L	4.2±0.7	0.524
WBC	13.5±5.8* 10E9/L	14.7±10.2	0.383
Neutrophils	66.4±13.1%	71.9±12.8	0.520
Platelets	271.7±125.3 10E9/L	239.±89.7	0.447

*Median (Range)
IgM: Immunoglobulin M
SGPT: Serum glutamic-pyruvic transaminase
SGOT: Serum glutamic oxaloacetic transaminase
GGT: Gamma-glutamyltransferase
PT: Prothrombin time
APTT: Activated partial thromboplastin time
INR: International normalized ratio
HB: Haemoglobin
HCT: Haematocrit
RBC: Red blood cells
WBC: White blood cells
BUN: Blood urea nitrogen.

both the groups. All patients in the IgM non-reactive group were more than 34 weeks compared to 127(75.6%) in the IgM reactive group (p=0). On arrival 16(9.5%) patients were unstable in the IgM reactive group compared to 1(3.1%) in the other group (p=0.20). Also, 102(60.7%) patients in the IgM reactive group underwent LSCS compared to 13(40.6%) in the non-reactive group (p=0.02). The number of intrauterine deaths was 9(5.4%)in the reactive group vs. 2(6.3%) in the non-reactive group.

Moreover, 34(20.2%) neonates in the IgM reactive group needed NICU admission while not a single neonate from the IgM non-reactive group required admission in NICU. There were 4(2.4%) neonatal deaths in the IgM reactive group compared to none in the other group.

Besides, 12(7%) patients in the IgM reactive group were admitted to ICU compared to no one from the IgM non-reactive group. Similarly, FHF was seen in 12(7.1%) patients in the IgM reactive group while no one in the other group developed FHF. PPH was more frequent in

Table-3: Comparison of clinical parameters in Hepatitis E, IgM reactive and IgM nonreactive.

Variables	IgM reactive N 168(%)	IgM non-reactive N 32(%)	P value
Age			0.34
<25 years	56(33.3)	8(25)	
25-30years	76(45.2)	19(59.4)	
>30 years	36(21.4)	5(15.6)	
Gravida			0.09
Primigravida	98(58.3)	14(43.8)	
Multigravida	70(41.7)	18(56.3)	
Gestational age at the time of delivery			0
<34	41(24.4)	0(0)	
>=34	127(75.6)	32(100)	
Trimester			0.28
2nd trimester	7(4.2)	0(0)	
3rd trimester	161(95.8)	32(100)	
Patient condition on arrival			0.2
Stable	152(90.5)	31(96.9)	
Unstable	16(9.5)	1(3.1)	
Mode of delivery			0.02
SVD	59 (35.1)	19(59.4)	
LSCS	102(60.7)	13(40.6)	
Not delivered in AKU	7(4.2)		
Condition of baby at the time of delivery			0.52
Alive	148(88.1)	30(93.8)	
IUD	9(5.4)	2(6.3)	
NND	4(2.4)	0(0)	
Not delivered in AKU	7(3.5)		
NICU admission*			0.007
No	118 (74.2)	32(100)	
Yes	34(21.4)	0(0)	
Not delivered in AKU	7(4.4)		
Complications due to hepatitis			0.092
Fulminant Hepatic failure	12(7.14)	0(0)	
Hepatic Encephalopathy	2(1.2)	0(0)	
Others	0(0)	1(3.1)	
No Complication	154(91.7)	31(96.9)	
Complication during labour			0.66
PPH	14(8.3)	1(3.1)	
Prolong labour	2(1.2)	0(0)	
APH	1(0.6)	0(0)	
Others	5(3.0)	2(6.3)	
No complication	146(86.9)	29(90.6)	
ICU			0.06
special Care	12(7.1)	0(0)	
Yes	67(39.9)	19(59.4)	
Ward	89(53.0)	13(40.6)	
Maternal Out come			0.41
Recovered and discharged	163(97)	32(100)	
Died	5(3)	0(0)	

*IUDs were excluded from the denominator (n; 159)
IgM: Immunoglobulin M. SVD: Spontaneous vaginal delivery.
LSCS: Lower segment caesarean section. AKU: Aga Khan University.
IUD: Intrauterine death. NND: Neonatal death.
NICU: Neonatal intensive care unit. ICU: Intensive care unit.
PPH: Post-partum haemorrhage. APH: Antepartum haemorrhage.

the IgM reactive group compared to the IgM non-reactive group. There were 5(3%) maternal deaths in the IgM reactive group compared to no death in the other group (Table-3).

Discussion

The frequency of hepatitis E was found to be 0.4% in the current study, similar to a study conducted by Sharda Patra that showed overall frequency of jaundice among pregnant women to be 0.6%, out of which 60% were suffering from hepatitis E.[11] However, another study conducted in Chennai, India, demonstrated that only 0.11% deliveries presented with jaundice, out of which two-thirds were due to hepatitis E.[16]

The overall mean age was 26.7±4.5 years in the current study, with majority of the participants aged below 30 years. Another study conducted in Pakistan showed a mean age of 26.4 years.[17]

In our study, more than half of the participants were primigravidas, which is consistent with studies by Shresta et al. and Shukla et al.[10,12]

Majority of patients in our study were in their third trimester, with gestational age being more than 34 weeks in 79.5% cases. This is comparable to other studies done in South Asia in which majority of patients presented in the third trimester.[10,11]

Babies in more than half of the cases were delivered by lower segment caesarean section; this finding is similar to a study conducted in Pakistan.[18] In contrast, another study by Tahira et al. shows only 9% babies were delivered by lower segment caesarean section.[19] However, both the above-mentioned studies had small sample size of 30-33 patients, hence it would be difficult to draw any definitive conclusions.

In our study, the most common maternal complication associated with hepatitis E was PPH (8%); this can be attributed to the deranged coagulation present as part of the disease process. This frequency was found to be between 14-27% in other studies.[10,11] This may be due to the routine practice of prophylactic transfusion of fresh frozen plasma and cryoprecipitate just before delivery to avoid bleeding.

Two of our patients developed hepatic encephalopathy, however, both survived. Moreover, 7.1% developed FHF. In other studies the rate of FHF was very high ranging from 55-82%.[1,11] Literature strongly suggests that pregnant women with acute hepatitis E are more prone to develop FHF than non-pregnant and men.[20] However, once FHF develops, its prognosis is similar to non-

pregnant patients.[21]

In our study, 11 patients had intrauterine foetal demise on presentation, while there were four neonatal deaths. Also, 17% neonates required intensive care admission. Most of the babies (80%) were healthy and discharged in satisfactory condition. Other studies show higher rate of stillbirth of 54% and the rate of take-home babies was just 21%.[11] This discrepancy may be due to advance gestational age in our data set and better neonatal services.

In our study, 17% participants were unstable at initial presentation out of which one woman was negative for IgM, but positive for IgG antibodies of hepatitis E. Nevertheless, literature supports that IgM positive suggests acute infection while IgG positive implies convalescence phase. This drew our attention to divide our dataset in IgM positive and IgM negative groups to compare the morbidity. We had 200 women presented with jaundice, out of which 84% were IgM positive while only 16% were IgM negative. Two African studies also enrolled both IgM and IgG positive groups.[14,22] In our study, gestational age was more than 34 weeks among all women who were IgM negative and12% of the IgM positive women. Modes of delivery between both these groups were significantly different, as more babies in the IgM positive group were delivered by Caesarean section. With regard to complications, women in the IgM positive group had more complications like haemorrhage, hepatic encephalopathy and FHF. There was special care admission in 59% of women with IgM negative and jaundice and none required ICU care.

Previous studies in Pakistan have shown high maternal mortality of 29.3%[19] and 35%[17] with hepatitis E. Other studies from our region show similar data with maternal mortality of 32.6% reported by Shinde N.R. et al from India.[23] In our study, overall maternal mortality was 2.5%, with 96.5% patients presenting in the 3rd trimester, out of which 12 had FHF and 5 died. We attribute this low mortality to timely and proactive multidisciplinary approach involving obstetricians, gastroenterologists, anaesthetists and intensivists. Delivery was expedited in all our patients. Though there is conflicting evidence regarding benefit of early delivery in reducing maternal mortality, immediate delivery was the standard of care in our study.

Studies done in Egypt and America show a much milder course of hepatitis E in pregnancy disease, probably due to different genotypes of the disease in industrialised countries.[8,13,22]

The current study was the first in the South Asian region involving pregnant women with hepatitis E with a sample size of 200 and conducted over a period of 12 years. However, one of the limitations of the study was its retrospective nature. The authors have already planned to conduct a prospective study to address the shortcomings of the current study.

Recently, M. Khuroo postulated a possible mechanism to explain the increased severity of the disease in pregnancy. The author suggested that vertical transmission of infection to the developing foetuses causes production of toxic metabolites, which worsens the disease in the mother.[24]

In the start of 2015, results of hepatitis E vaccination phase-three trial were published, showing efficacy of 85% with sustained protection for 4.5 years.[25] In India 300 million people still defecate in the open, though this is not the case in a big metropolitan city like Karachi, nonetheless mixing of water and sewerage lines does commonly occur increasing the chances of being infected with hepatitis E. It is estimated that 1.8 billion people consume faecally contaminated water globally.[24] The government needs to take the initiative to make safe and clean drinking water accessible to everyone. Furthermore, the disease burden can be reduced by the availability of hepatitis E vaccine, especially to pregnant women.

Conclusion

Participants in the IgM reactive group had a higher percentage of adverse foeto-maternal outcomes compared to the ones in IgM non-reactive group.

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