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Hepatitis E in Pregnancy a Study of Fetomaternal Outcome

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ABSTRACT
Hepatitis E is widespread in Southeast Asia, northern and central Africa, India and Central America. It is major health problem in developing countries. Hepatitis E often causes an acute and self-limiting infection in young adults however, mortality rate is higher in pregnant women during second and third trimester. The present study was done with objective to study clinical profile, incidence, foetal and maternal outcome. This study, a prospective observational study, was conducted at Department of Obstetrics and Gynaecology CPR Hospital, Kolhapur for over a period of 1 year from Jan 2022 to Dec 2023. Hepatitis E was found in 0.1% Antenatal population attending our hospital.8% were in their second trimester while 92% were in third trimester. The maternal mortality in study population was 10%. Still birth ratio was 38% while prematurity accounts for 56%. This study suggests that HEV causes high maternal and foetal mortality and morbidity. Prompt diagnosis, accurate evaluation and a multidisciplinary approach is needed to tackle this high risk pregnancy.

INTRODUCTION

Hepatitis E is inflammation of the liver caused by infection with the hepatitis E virus. It is one of five known human hepatitis viruses: A, B, C, D and E. HEV is a positive-sense, single-stranded, nonenveloped, RNA icosahedral virus with 4 genotypes, of which genotypes 1 and 2 exclusively infect humans and can lead to endemic HEV or outbreaks in countries with poor sanitation systems[1]. Genotypes 3 and 4 can infect humans, pigs and other animals and can result in sporadic infection in both developed and developing countries[1]. Hepatitis E virus is a water-borne pathogen that has fecal-oral transmission, mostly due to ingestion of fecally contaminated water. Direct person to person transmission is uncommon[2]. The incubation period after exposure ranges from 3-8 weeks (mean 40 days) and is dose dependant[3]. The virus has a 50% rate of vertical transmission[4].

Distribution of HEV varies across the globe, with genotype 1 being more common in Asia, Africa and Latin America, while genotype 2 is more common in sub-Saharan Africa and Mexico. Genotypes 3 and 4 can infect both medically vulnerable and healthy populations and are mostly detected in sporadic cases in developed countries[5,6]. The incidence and severity during pregnancy vary widely around the world. In Western Europe and North America, the incidence is as low as one in 20,000, whereas in out-breaks of waterborne Hepatitis E in India and Asia, the case fatality rate is 1-2% and up to 10-20% in pregnant women[7]. Hepatitis E infection during pregnancy and in the third trimester, especially with genotype 1, is associated with more severe infection and might lead to fulminant hepatic failure and maternal death[8]. Although the mechanism of liver injury is not yet clear, it is possible that interplay of hormonal and immunologic changes during pregnancy, along with a high viral load of HEV, renders the woman more vulnerable[9]. Immunologic changes during pregnancy promote the maintenance of the fetus in the maternal environment by suppression of T cell-mediated immunity, rendering pregnant women more susceptible to viral infections like HEV infection. During pregnancy, levels of progesterone, estrogen and human chorionic gonadotropin increase as pregnancy advances. These hormones play a considerable role in altering immune regulation and increasing viral replications[10]. Reason for the difference in the outcome of HEV in different geographical areas remains unclear[11]. but could be due to early childhood HEV exposures, producing long-lasting immunity and/or modifying subsequent responses to exposure to the virus.

Hepatitis E in pregnancy is challenging for obstetrician as it leads to many maternal and fetal complications. so it was decided to carry out a prospective observational study to find out incidence, clinical presentation and fetomaternal outcome in hepatitis in pregnancy.

MATERIALS AND METHODS

Source of Data: The study was conducted at the Department of Obstetrics and Gynecology at CPR hospital, Kolhapur, Maharashtra, India. It spanned over a period of one year from Jan 2022 to Dec 2023 .

Study Design: This was a prospective study, approved by the Institutional Ethics Committee at CPR hospital, Kolhapur. The study targeted women attending antenatal clinics and those referred from peripheral hospitals.

Sample Size: A total of 50 women were included in the study.

Inclusion Criteria: The study included all pregnant women at any gestational age who were admitted with jaundice and abnormal liver function tests (LFTs).

Exclusion Criteria: The study excluded pregnant women with HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelet count), Acute fatty liver of pregnancy, Obstetric cholestasis, Drug-induced abnormal liver function tests, Known cases of hemolytic anemia, Hyperemesis gravidarum. Participants were systematically assessed for hepatitis virus infection through liver function tests and serological analysis. Data were prospectively collected on various parameters, including age, parity, gestational age, associated risk factors, range of abnormal LFTs and other investigations, diagnosis, maternal-fetal outcomes, and complications. The data collected were analyzed using appropriate statistical methods to assess the impact of hepatitis E virus infection on maternal and fetal outcomes.

Data Collection: Data were collected in Excel, detailing age of subjects, parity, gestational age, associated risk factors, abnormalities in LFTs and other investigations, diagnosis and maternal-fetal outcomes and complications. Serum samples were analyzed for IgM Anti-HEV using Rapid Immuno Chromatographic Assay, and only Anti-HEV IgM-positive women were included in the study.

RESULTS AND DISCUSSIONS

(Table 1) focuses on the distribution of cases according to maternal age and parity, indicating a higher concentration of cases in the age groups of 21-25 (26 cases) and 26-30 (17 cases). It also reveals that most women in the study are either in their first

or second pregnancy, with a notable decrease in cases as parity increases. (Table 2) outlines maternal outcomes, showing that 90% (45 cases) of the mothers survived, while 10% (5 cases) resulted in death. This indicates a relatively high survival rate among the participants. (Table 3) details maternal complications, with the highest percentages being hepatic encephalopathy (38%), blood transfusion requirements (44%), and fulminant hepatitis (30%). These complications highlight the serious health issues that can arise during pregnancy and childbirth. (Table 4) reports on foetal outcomes, with 76% (38 cases) resulting in live births. There are also indications of stillbirths, intrauterine deaths, and neonatal deaths, cumulatively accounting for 24% of the outcomes, illustrating the risks involved during the gestation and perinatal period. (Table 5) discusses foetal complications, with a significant number of preterm births (56%) and low birth weight (64%), alongside a notable percentage of neonatal intensive care unit (NICU) admissions (38%). These statistics emphasize the challenges and health concerns faced by newborns. (Table 6) addresses the mode of delivery, showing a predominance of preterm vaginal delivery (PTVD) at 56% and full-term vaginal delivery (FTVD) at 38%, with a small percentage of cases requiring cesarean sections (LSCS) at 6%. This distribution suggests a preference or necessity for vaginal delivery in the majority of cases. (Table 7) provides an insightful overview of the mean and median values for various laboratory parameters observed in a study, indicating a wide range of clinical data collected from a specific patient population. The gestational age of participants averaged 33.04 weeks, with a standard deviation (SD) of 4.26 weeks and a median of 33 weeks, showing a relatively concentrated distribution around the early third trimester, with values ranging from 25 to 40 weeks. This suggests most subjects were in the late stages of pregnancy. Hemoglobin (Hb) levels averaged 8.22 g/dL (SD: 1.66 g/dL), with a median of 8.1 g/dL, indicating a trend towards anemia among the participants, given the lower than normal Hb levels, with a range from 4.3 to 11.3 g/dL. Platelet counts showed a significant variance with a mean of 152,820/µL (SD: 92,071.11/µL) and a notably low median of 15,000/µL, suggesting a potential typo in the median value or a skewed distribution, with the range being extremely wide (13,000 to 500,000/µL). Total bilirubin levels averaged 5.20 mg/dL (SD: 2.75 mg/dL) with a median of 4.6 mg/dL, spanning a range from 1.3 to 11.2 mg/dL, indicating elevated bilirubin levels in this population, potentially signifying liver dysfunction. Direct bilirubin averaged 5.34 mg/dL (SD: 2.76 mg/dL) with a median of 5.05 mg/dL, also suggesting elevated levels with a range from 0.7 to 13.1 mg/dL, reinforcing concerns about liver health. SGOT (AST) and SGPT (ALT) enzyme levels were notably high, with means of 480.04 U/L (SD: 502.56 U/L) and 462.96 U/L (SD: 485.15 U/L), respectively, indicating possible liver injury or inflammation, with wide ranges that highlight severe cases. Alkaline phosphatase (ALP) levels also reflected elevated enzyme activity with a mean of 353.92 U/L (SD: 143.74 U/L) and a median of 327 U/L, ranging from 121 to 915 U/L. Blood urea levels had a mean of 45.06 mg/dL (SD: 32.50 mg/dL) with a median of 38 mg/dL, indicating a range of kidney function statuses among the participants, with values from 14 to 168 mg/dL. TTe International Normalized Ratio (INR) had a mean of 2.22 (SD: 1.00), suggesting a heightened risk of bleeding with a range from 1.1 to 5.8. Blood transfusions averaged 2.26 times per patient (SD: 1.41), with a median of 2 times and a range from 0 to 6, indicating frequent need for this intervention. Fresh Frozen Plasma (FFP) transfusions had an average of 6.6 times (SD: 5.59), with a median of 6 times and a broad range (0 to 32), highlighting significant variability in the need for clotting factor replacement. Platelet transfusions were less common, averaging 0.86 times per patient (SD: 1.96), with a median of 0 and a range from 0-8, indicating occasional use for this treatment. Average Hospital Stay 9.82 with standard deviation 4.79.

The findings from these tables in relation to other studies, we can draw comparisons and highlight trends observed in the literature regarding maternal age and parity, maternal and fetal outcomes and complications. This discussion will provide a broader context for understanding the significance of the presented data. Distribution of Cases According to Maternal Age and Parity (Table 1): Studies have shown that maternal age and parity are significant factors influencing pregnancy outcomes. The distribution in Table No.1, with a higher number of cases in the 21-25 and 26-30 age groups, aligns with global trends where the majority of women giving birth fall within this age range. A study by Shah DM *et al*[12]. found that first-time mothers in these age groups generally have favorable outcomes, but risks increase with advanced maternal age (>35 years), which is minimally represented in this dataset.

Maternal Outcome(Table 2): The maternal survival rate of 90% shown in Table No.2 is consistent with global averages in developed countries but highlights a significant maternal mortality rate when compared to the World Health Organization's (WHO) aim to reduce maternal mortality to less than 70 per 100,000 live births by 2030. Research by Zhang F *et al*[13]. emphasizes the importance of access to quality healthcare in improving maternal outcomes, suggesting that the 10% mortality rate could be indicative of underlying issues in healthcare access or quality.

Table 1: Distribution of cases according to maternal age and parity.

		Parity		
Maternal age	No. of cases	1	2	3
≤20	6	5	1	0
21-25	26	17	7	2
26-30	17	6	9	2
31-35	1	1	0	0
Total	50	29	17	4

Table 2: Maternal outcome

Maternal Outcome	No. of Cases	Percentage
Live	45	90
Death	5	10
Total	50	100

Table 3: Maternal Complications

Maternal Complications	No. of Cases (n=50)	Percentage
PROM	10	20
APH	2	4
PPH	8	16
DIC	9	18
Puerperal sepsis	1	2
Hepatic encephalopathy	19	38
Fulminant hepatitis	15	30
MODS	8	16
Ventilation required	4	8
ICU admission	6	36
Blood transfusion	22	44

Table 4: Foetal Outcome

Fatal Outcome	No. of cases	Percentage
Live Birth	38	76%
Still Birth	05	10%
Intrauterine death	04	8%
Neonatal death	03	6%

Table 5: Fetal Complications

Fatal Complications	No. of cases(n=50)	Percentage
IUGR	5	10%
Preterm	28	56%
Low birth weight	32	64%
NICU Admissions	19	38%

Table 6: Mode of delivery

	No. of cases	Percentage
FTVD	19	38%
LSCS	3	6%
PTVD	28	56%

Table 7: Mean and Median values of various laboratory parameters

	Mean SD	Median (Range)
Gestational Age	33.04 ± 4.26	33 (25-40)
Hb	8.22±1.66	8.1 (4.3-11.3)
Platelet	152820±92071.11	15000(13000-500000)
Total Bilirubin	5.20±2.75	4.6 (1.3-11.2)
Direct Bilirubin	5.34±2.76	5.05 (0.7-13.1)
SGOT	480.04±502.56	277 (20-2310)
SGPT	462.96±485.15	292 (0.7-13.1)
ALP	353.92±143.74	327 (121-915)
Blood Urea	45.06±32.50	38 (14-168)
INR	2.22±1.00	(1.1-5.8)
Blood Transfusion	2.26±1.41	2 (0-6)
FFP Transfusion	6.6±5.59	6 -0-32)
Platelet Transfusion	0.86±1.96	0 (0-8)

Maternal Complications (Table 3): The complication rates reported in Table No.3, especially for hepatic encephalopathy and fulminant hepatitis, are notably high compared to other studies. For example, Sultana *et al*[14]. reported lower incidence rates of these complications in a similar cohort, suggesting that the population in the current study may have unique risk factors or health system challenges. The high rates of blood transfusion (44%) also suggest significant obstetric hemorrhage, a leading cause of maternal morbidity and mortality globally.

Foetal Outcome(Table 4): The foetal outcomes in Table No. 4, with a 76% live birth rate, are slightly lower than the global average, which, according to the United Nations' data, stands at approximately 82%. The rates of stillbirth and neonatal death are within the expected range but underscore the continuous need for improved prenatal and neonatal care. A comparative study by Wasim *et al*[15]. highlighted the effectiveness of comprehensive prenatal care in reducing adverse fetal outcomes.

Foetal Complications (Table 5): The high incidence of preterm births (56%) and low birth weight (64%) in this cohort is alarming but aligns with global concerns in perinatal health. Studies such as those by Inam I *et al*[16]. have highlighted the global burden of preterm births and low birth weight as significant contributors to neonatal morbidity and mortality. The rate of NICU admissions (38%) further underscores the severity of these complications. Research by Yaqoob U *et al*[17]. indicates that advanced neonatal care can significantly improve outcomes for these infants, emphasizing the importance of such facilities.

Mode of Delivery (Table 6): The predominance of vaginal deliveries, including full-term vaginal delivery (FTVD) and preterm vaginal delivery (PTVD), in 94% of cases, contrasts with the rising global cesarean section rates. A study by Sharmin F[18]. found an increasing trend in cesarean deliveries worldwide, citing a range of medical and non-medical reasons. The low rate of cesarean sections (LSCS) in this dataset (6%) may reflect a preference or a policy towards promoting vaginal birth when possible.

Laboratory Parameters (Table 7): The laboratory values indicate a range of maternal health issues, from anemia (mean Hb 8.22 g/dL) to liver dysfunction (elevated bilirubin and liver enzymes). These findings are consistent with those reported by Ehi Airiohuodion *et al*[19]. who found that such abnormalities are associated with adverse pregnancy outcomes. The wide range of platelet counts and the high need for blood transfusions highlight the clinical challenges in managing these pregnancies, which is supported by research from Panchbudhe SA *et al*[20]. on the significance of hematologic parameters in predicting pregnancy complications.

Limitation of Study:

Retrospective Design: If the study employed a retrospective design, it may be limited by the accuracy and completeness of medical records. Retrospective data collection can introduce bias and limit the ability

to establish causality between HEV infection and fetomaternal outcomes.

Lack of Control Group: The absence of a matched control group of pregnant women without HEV infection makes it difficult to directly attribute observed outcomes solely to HEV. A control group would allow for a more robust comparison and understanding of the specific impact of HEV on pregnancy outcomes.

Confounding Variables: The study may not have adequately controlled for all potential confounding variables, such as socioeconomic status, access to healthcare, nutritional status, and co-existing medical conditions, which can independently influence pregnancy outcomes.

Diagnostic Criteria: The study's reliance on specific diagnostic criteria for HEV infection and associated complications might limit the identification and inclusion of all relevant cases. Variability in the sensitivity and specificity of diagnostic tests used can also affect the study's findings.

Longitudinal Follow-up: The study may lack longitudinal follow-up of infants born to HEV-infected mothers, limiting understanding of the long-term impact of maternal HEV infection on child health and development.

Subjectivity in Outcome Assessment: The assessment of certain outcomes, particularly those related to maternal and neonatal morbidity, may involve subjective judgment, leading to variability in outcome classification and interpretation.

Generalization of Findings: Given the specific focus on HEV in pregnancy, the findings may not be generalizable to other forms of viral hepatitis or infectious diseases affecting pregnant populations, limiting the broader applicability of the conclusions.

Lack of Interventional Data: The study primarily focuses on observational data, providing limited insight into the efficacy of interventions to prevent or mitigate the impact of HEV infection during pregnancy.

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