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Original Article

Perinatal Potential Hazards of Hepatitis; a Tertiary Care Study

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ABSTRACT

Objective: To explore the frequency of HEV infection in pregnancy, associated risk factors and its prenatal and maternal consequences.

Study Design: Prospective longitudinal study

Place and Duration of Study: Department of Gynaecology Obstetrics, Divisional Head Quarter Hospital, Multan, Pakistan from Nov 2021 to Jun 2023.

Methodology: The research comprised 100 patients, 50 pregnant patients who met the criteria for eligibility. For seroprevalence, anti-HEV antibodies (IgG) were detected. Hepatic profile, CBC, coagulation markers, and standard workup/protocol were also assessed for prenatal fetomaternal hemorrhage.

Results: Data was gathered using pre-designed questionnaires. Of the 50 patients, 31 (62%), were HEV positive with mean age 26.90±4.16 year. Serum bilirubin levels >1.5 mg/dL in 47 patients (94.00%) with SD1.68±0.28, AST (SD85.87±51.878), ALT (SD149.42±71.90) in 38 (76.00%), low platelet count in 24 cases. There were 6 cases (9.35%) IUD, 3 (8.75%) fetal distress and 4 (12.09%) maternal distress, preterm deliveries 4 (12.09%) and 3(2.5%) neonatal deaths. Mortality rate was (38.7%) 12 cases, due to hepatic comma and intravascular coagulation and Fulminant hepatic failure.

Conclusion: Hepatitis E (HEV) infection during gestation may result in serious consequences such as elevated hepatic profiles, acute anemia, low platelet count, IUD, premature delivery, and postpartum issues, which are primarily caused by inadequate sanitation and a contaminated water source. Maternal fatalities and fetal consequences are exacerbated by HEV infection.

Keywords: Hepatitis E, hygiene condition & compliance, pregnancy complications, viral transmission, water borne diseases.

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INTRODUCTION

Hepatitis E virus (HEV) is a silent killer disease that significantly contributes to morbidity and mortality, particularly in developing countries. Infection with HEV leads to a serious epidemic, causing an estimated 3 million acute liver diseases and 57,000 fatalities worldwide each year [1,2]. WHO reported that HEV infection was responsible for 44,000 fatalities globally in 2015, accounting for 3.3% of all viral hepatitis deaths [2]. The worldwide impact of HEV among expectant mothers is now unrecognized for HEV, and it has been largely unexplored and often neglected or misdiagnosed by physicians[3,4]. In expecting women, liver failure is a significant cause of fatalities, particularly when preexisting liver disease is present [5]. The mortality rate among expectant women increases from 10% to 25% during the third trimester [1,5]. There are eight classes of HEV, with predominant genotypes (HEV-1) and (HEV-2) infecting humans through feco-oral transmission due to meager hygiene, while (HEV-3) and (HEV-4) are prevalent zoonotically. Transmission of genotype 3 occurs by undercooked meat, shellfish, rabbits, and deer. Genotype[3,4]. prevail in industrial countries, with sporadic and clustered cases in infected regions [6,7]. HEV genotype 2 was active in Pakistan in 2005, according to serological evidence. HEV genotype 2 was detected in Pakistan's sewage water, posing a significant risk to the Pakistani population, despite previous vaccination efforts failing [8]. Hepatitis E (HEV) infection is similar to acute viral hepatitis, with acute liver failure being the most common complication. Pregnant women with HEV suffer from jaundice and worse obstetric complications. The immune-compromised patients are more susceptible to viral replication, leading to chronic liver disease[9,10].

In Pakistan, pregnant women are not frequently screened for Hepatitis E virus (HEV). The rationale behind this study is to determine the prevalence of HEV, its incidence, source of dissemination, serological affirmation, maternal and fetal outcomes. Which will address the rigorousness of the endemic

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and its consequences. Subsequently, the diagnosis, monitoring, and strict adherence to hygiene preventative measures could be better implicated among masses.

METHODOLOGY

The Prospective longitudinal study was conducted at Gynaecology Obstetrics Department, Divisional head quarter Hospital, Multan, Pakistan, from November 2021 to June 2023. Ethical oversight was provided by Ethical Review Committee of Government Shahbaz Sharif DHQ hospital Multan (Letter No GSSDHQM/HR/5811). Sample size was calculated by WHO sample size calculator at 95% confidence level, taking frequency of HEV in pregnant femlaes as 12.4% and margin of error 12% was 50.[11] Screening for HEV antigen in pregnancy is advised by the Royal College of Obstetricians and Gynecologists and other obstetric and gynecologist colleges.[12] Among 50, 31 patients were HEV positive.

Inclusion Criteria: Pregnant patients reported with symptoms of myalgia, anorexia, pruritus, abdominal pain and lethargy and clinical diagnosis of jaundice, were enrolled for study, who underwent routine diagnostic investigations and were screened for anti HEV antibodies through direct ELISA.

Exclusion Criteria: Pregnant women without significant complication and without hepatitis E infection were excluded from the study, while Hepatitis A, B, C and patients were also excluded.

Patients either referred from outdoor department or brought from rural site to Gynae obstetrics service were included in study by convenience sampling technique. Demographic details were collected, all patients signed informed consent proforma on assurance of confidentiality to participate in Hepatitis E identification [13]. Venous blood samples were drawn for biochemical and hematological parameters analysis. Patients were screened for HEV virology by IgG quantification by direct ELISA technique. Blood biochemistry included LFTs, CBC and coagulation parameter to reveal hepatic profile through micro lab, and spectrophotometricaly [9-13]. Depending upon their ALT/ AST values and encephalopathy i.e. few were also kept admitted or followed in outpatient clinics.

The statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 25.0. Qualitative variables were summarized as Mean±SD, while qualitative variables were summarized as frequency and percentages.

RESULTS

Patients reported with symptoms of myalgia, anorexia, pruritus, abdominal pain and lethargy were enrolled for study. Most of the pregnant patients had developed jaundice. HEV has an incubation period of 2 to 10 weeks. Mean age of patients was 26.90±4.16 years with age ranging from 18 to 35 years. As far as prevalence of HEV holds importance, those areas which had poor sanitation were focused for study. The patients revealed that transmission of HEV from unhygienic surrounding was 20(64.5 %), while some of patients remained in contact with the Hepatitis E positive victim during last few months before presentation to hospital. Pregnant patients of HEV infected via family member were 3(9.7%). On the other hand, (25.8%) of women had blood transfusion during last 9-12 months (Table-I).

Table-I: Details of Patients under study, Gestational Period and their Percentage (n=31)

Parameters	n(% age of patients)
Mean age (years)	26.90±4.16
Gestational age(months)	
Ist Trimester	10(32.25)
II nd Trimester	6(19.35)
III3rd Trimester	15 (48.38)
Control involved	
1st and 2nd trimester	9(18)
Late pregnancy	11(22)
Gravidity of HEV positive subjects = 31(100)	
One to two Three to 5	5(16.12) 26(83.87)
HEV from surrounding	20(64.5%) 8(25.8%)
HEV from blood transfusion	
HEV via family	

HEV=Hepatitis E virus

Of the 50 subjects, 31 cases (62%) were serologically positive for IgG antibodies Among these 10(32.25%) had IgG antibodies in 1st trimester, while 6 cases (19.35 %) were in 2nd trimester, 15 cases (48.38%) had reported with symptoms of nausea and jaundice e.t.c. in late pregnancy (Figure-1). At least 31 of them tested positive for IgG using ELISA for serology. Twenty subjects who were pregnant but negative for the hepatitis virus served as a control group. Twelve of the 31 patients died.

Hemorrhagic consequences were observed in 4, 3 patients in (Postpartum and antepartum) respectively. While 3 pregnancies with hepatitis E had premature rupturing of membrane during second trimester. The

vast majority of fatalities went through premature labour, which either occurred naturally or was induced for medical reasons. IUDs and maternal distress were the worst-case situations (19.35%).

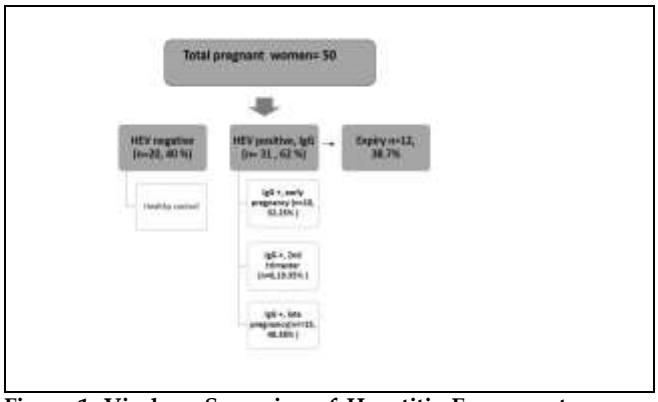

Figure-1: Virology Screening of Hepatitis E pregnant women through ELISA

Among the LFTs, serum bilirubin was raised in 28(90.34%) patients while SGPT (ALT) level SD 85.87±51.878 was above the 100 IU/L in 19(61.29 %) pregnant women. Maximum AST level was > 100 IU/ L with SD149.42±71.90 in 20(64.51%) cases. Bilirubin level determined was > 1.5 mg/ dL with SD 1.68±0.28 (Table-II). The variables (parameters) had been tested with 95% confidence interval. showed moderate anemia to severe anemia due to Hepatitis E. Majority of pregnancies were facing severely anemic condition, 13(41.9%) had (Hb<5 mm Hg) Hb level during Hepatitis E as compared to the cases showed normal (Hb≥10 mm Hg) Hb level, in 5 (19.35%). Very low platelet count < 50000 was recorded in the 20(64.51%) patients, 11(35.48%) had Pt >50000, 13 cases (26.00%) had pt count <50000. Further functioning of liver, was evaluated among all patients by (PT) prothrombine time, almost 19(61.5%) patients had raised >12.5 sec PT, indicative of the liver disease and abnormal clotting coagulopathies. While 12 cases (38.7%) had PT (11-12.5 sec) with less coagulopathies (Table II). Whereas 12(38.7%) maternal expiries, and fetal outcomes revealed that only 19(61.29 %) pregnancies were successful, in carrying to term with no issues. On the other hand, 25(49.75 %) patients experienced sever complication.

The consequences of a Hepatitis E infection might be either acute and severe or long-term and debilitating. Acute Hepatitis E progressed to fulminant Hepatitis progressing towards mortality. HEV infections are self-limiting in a small percentage of patients.

The primary health care units working in periphery are not well equipped so samples were drawn from the pregnant women and transferred to tertiary health care unit. Our data reveals extremely disastrous fetal out comes of 20 patients as 6 cases (9.35%) intra-uterine deaths, 3 cases (8.75%) fetal

Table-II: Hepatic Profile and Biochemical Parameters of HEV+ Pregnant Patients, (n=31)

Biochemical Markers	Clinical Parameters	No of cases and % Age on Different Levels of Parameter		
LFTs	Serum Bilirubin	>1.5 mg/dL 28 (90.34%)	< 1.0 mg/dL 3(32.25%)	
	SGPT (ALT)	<50 IU/L 12(38.7 %)	>100 IU/L 19(61.29 %)	
	SGOT (AST)	< 50 IU/L 11(35.48 %)	>100 IU/L 20(64.51%)	
CBC	Hb	Normal >10mmHg 5 (19.35%)	Anemia 5- 7mmHg 12(38.7%)	Severe anemia 5mmHg 13 (41.9%)
	Platelet count	>50000 pt/µL 11 (35.48%)	<50000 pt/µL 20(64.51%)	
Coagulation profile	Prothrombin time	>12.5 sec 19(61.5 %)	11-12.5sec 12(38.7%)	
Standard Deviation	Hepatitis positive	Hepatitis negative	*p*-value	
Bilirubin	1.68±0.28	1.56±0.28	0.960	
ALT	149.42±71.90	127.84±69.66	0.303	
AST	85.87±51.878	87.89±74.043	0.910	
Hb	6.60±3.19	5.96±3.31	0.503	
Platelets	159927.00±274400.081	118886.37±57007.380	0.525	

HEV: Hepatitis E virus, HepE: Hepatitis E, LFTs: Liver function tests, AST: Aspartate transaminase, ALT: Alanine transaminase, ELIZA: Enzyme linked imunosorbent assay, CBC: Complete blood count, SGPT: Serum glutamate pyruvate transaminase, G-6-PD: Glucose 6 Phosphate Dehydrogenase, ALF: Acute liver failiure, IUD: Intrauterine death, TGF: Tumor growth factor, INF: Interferon, IL-6: Interleukin 6, MFP: Materno fetal protein, FHF: Fulminant hepatitis failure

distress, 4 cases (12.09%) maternal distress, preterm deliveries 4 cases (12.09) and 3 cases (2.5%) neonatal deaths were recorded. Concerning the fetal outcomes, 8.75% had obstetric complications. Postpartum hemorrhage (3.75%), which exceeded pre partum hemorrhage (2.5%) in 3 patients delivered with complications along with 3 patients (2.5%) antepartum hemorrhage (Figure-2).

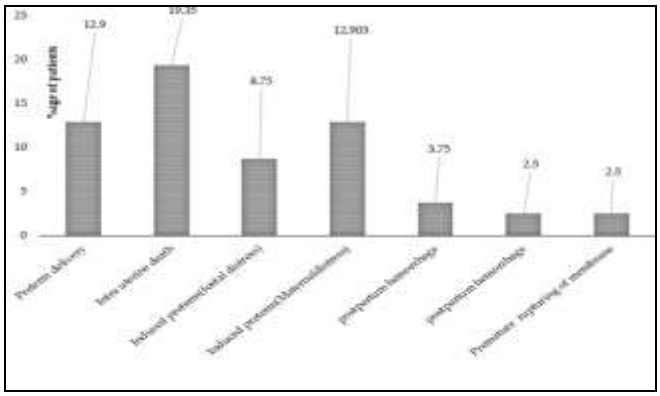

Figure-2: Maternal and Foetal Outcomes of pregnant patients of Hepatitis E ;(n= 31 HEV seropositive)

DISCUSSION

Patients from families with limited resources who were enrolled had no access to clean water for drinking, and lacked sufficient drainage and treatment of sewage. There are over 3,000 stillbirths every year documented as a consequence of HEV infection, and the majority of cases occur in pregnant women since they are more susceptible to the virus and its potentially harmful effects on their health [3-14]. Thirty-one out of 50 pregnant women tested positive for HEV, with high anti-HEV IgG seroprevalence, the percentile in early and middle trimesters, which were significantly lower as compared to the patients during the late pregnancy 48.38 % ($p \leq 0.05$), which corresponds to the findings by Sultana and Alvi studies[15-17]. Patra narrated the case fatality of pregnant women as 20%, and this rate increases during the second and third trimesters, whereas currently (12 cases) 38.7% expiry was recorded. Kamar *et al.*,[16,17] also reported that HEV infection during pregnancy, especially in the third trimester may lead to acute liver failure. Wu also mentioned the highest mortality rate (56%), among the HEV-infected pregnancies of third trimester[7].

As far as prevalence of HEV holds importance, those areas which had poor sanitation were focused for study.[7] The feco-oral route and contaminated drinking water from the environment are the most common vectors for the spread of hepatitis E, Wu's findings provide credence to the idea that blood transfusions and vertical transmission are also involved [7]. Blood transfusion is now considered as a new risk factor for HEV transmission. [18] Cases of Hepatitis E are reported after blood transfusion from HEV positive blood donors as expressed in . Insignificant precautions used while dealing with infected needles, syringes, devices, blood, and tissues in healthcare waste may lead to the transmission of hepatitis E [18].

Anemic condition of maternal and neonatal are prevalent features in infected pregnant women [16-20]. Anemia is reported in people with glucose-6-phosphate dehydrogenase deficiency, particularly hemolytic anemia documented in up to 23% of patients after HEV infection, possibly escalating to 70% [21,22]. The low hemoglobin level rendered (41.9%) patients from moderate to severe anemic condition, the cases of thrombocytopenia in hepatitis E infected pregnant women are also reported by Seth [23].Hypersplenism, reduced hepatic thrombopoietin synthesis, inhibition of hepatotropic virus, and antiplatelet autoantibodies are the hallmarks of thrombocytopenia, a disease often linked to HEV-associated symptoms [24,25]. The prolonged prothrombin time in 19 individuals (61.5%) is recorded, which is in accordance with the investigations of Rais and Boccia on out break of Hep E from Sudan. They presented similar results of Prothrombin time, which presents defective clotting factors and liver fibrosis.[16-20] HEV accelerates liver fibrosis and lead to decompensated cirrhosis as recommended by Seth [23], that may even cause Fulminant hepatitis failure (FHF). This condition is particularly dangerous for pregnant women, as it results into death rate of up to 30% [16-25]. LFTs showed raised serum bilirubin > 1.5 mg /dL along with profoundly elevated serum ALT, AST, which can result in severe maternal and fetal consequences as explained in a prospective field studies carried out by Kamar, Ahmed et al and Khuroo *et al.*,[8-10]. Kamar also unveiled that 42 % patients had raised serum bilirubin more than 50 mg/ dm 25. LFTs and bilirubin levels are reported in prodromal and icteric phase of viral course, respectively [23,25].

According to a report conducted in Bangladesh, Hep E is connected to 9.8% of postpartum problems, early delivery, stillbirth, abortion, and IUD. A New Delhi research discovered that HEV caused 60% of

acute hepatitis cases among pregnant women, increasing maternal death, antepartum hemorrhage, congenital malformations, and IUD hazards [10-23] , which correlate with our findings.

Gonadotropin hormone raises estrogen and progesterone levels, interleukin flooding cytokines IL-4, IL-10, TNF, INF-γ and TGF production during pregnancy while decreasing the immunological response. Hepatitis E infection may occur during pregnancy due to factors such as a reduction in the number of CD4/CD8 cells, the use of hormonal steroids, and a decrease in the expression of the progesterone receptor. Maternofoetal complications in HEV are more likely to occur in the second and third trimesters of pregnancy [15],. Patients with fluctuating levels of estrogen, progesterone, and beta-HCG are at a greater risk of viral infection and liver injury, the immune response mechanism, which includes increased levels of TGF, IL6, INF-η, and cytokines, also makes pregnant patients more vulnerable to viral invasions. Above all, the MFP protein is the most prominent infecting factor due to the viral heterogeneity of various variants 5. Along with the above scenerio,lack of adequate nutrition also impact the risk of hepatitis E complications during pregnancy. Placental enzymes and cytokines decrease cell-mediated immunity during maternal-fetal interaction, facilitating HEV transmission. There have also been cases of HEV replication within the placenta [23].

The lack of understanding in the path to health objectives necessitates coordination between community and health care systems. The problem requires familiarity with the general public to express the issue's seriousness and emphasize cleanliness in their lives. Due to patient noncompliance and financial constraints, it was not possible to prove the vertical transmission associated with prenatal and intrapartum testing. To accomplish health goals, it is necessary to prioritize immunization and sanitation services in areas with dense populations and to work together effectively[25]. The research was not intended to investigate the frequency of hepatitis E by vertical transfer, although may be a future possibility. Since no financial agency was involved, neither the vertical transmission rate nor the postnatal and fetal research were made public. Patients inhabiting remote regions are particularly susceptible. The inadequate handling of hepatitis E-related problems during pregnancy, on the other hand, presents a difficult clinical picture. The outcomes and complication in results may inspect the deleterious effects of Hepatitis E during pregnancy.

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CONCLUSION

Dreadful outcomes may result from Hepatitis E, an endemic viral disease, when pregnant. The main sources of infection included unsanitary procedures, blood transfusions, and polluted water supplies. Conclusively Hepatic profile parameters such as AST, bilirubin e.t.c, and prothrombine time are elevated in infections caused by HEV. This research found that liver damage, which increases the risk of morbidity and death in HEV-infected pregnancies, manifests itself in severe anemia along with decreased counts of platelets. Hepatitis E during pregnancy was associated with intrauterine devices (IUDs), preterm birth, and problems after childbirth.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

AA & AH: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

NB & NA: Data acquisition, data analysis, approval of the final version to be published.

MHAT & MI: Critical review, concept, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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