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Study of Hepatitis - E in Pregnancy: Maternal and Fetal Outcome

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Abstract: ***HEV infection, a major public health concern, is known to cause large scale epidemic and sporadic cases of acute viral hepatitis in developing countries. The infection primarily occurs in young adults and is generally mild and self-limiting, case fatality is higher when it occurs during pregnancy specifically in 2nd and 3rd trimester. Hepatitis E infection during pregnancy, especially in the third trimester, is characterized by a more severe infection that sometimes results in fulminant hepatitis, increasing maternal and fetal mortality and morbidity.***

Keywords: Hepatitis E infection, pregnancy 3rdtrimester, Hepatic Encephalopathy, Maternal and prenatal morbidity and mortality

1. Introduction

Hepatitis E virus (HEV) is an emerging infectious agent causing acute viral hepatitis worldwide. Each year more than 20 million estimated cases of HEV infection occur globally, resulting into 70 000 deaths. Hepatitis E virus was first recognized in 1978 during an epidemic in Kashmir Valley in northern India, with 52 000 cases of hepatitis resulting in 17 000 deaths. Hepatitis E is a single-stranded RNA 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. Genotypes 3 and 4 can infect humans, pigs, and other animals, and can result in sporadic infection in both developed and developing countries. Distribution of HEV varies across the globe, with genotype 1 being more common in Asia, Africa, and Latin America, while genotype 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. Hepatitis E virus is a water-borne pathogen that has fecal-oral transmission, mostly due to ingestion of focally contaminated water. Direct person-to-person transmission is uncommon. The incubation period ranges from 15 to 64 days with a mean of 6 weeks. The virus has a 50% rate of vertical transmission Hepatitis E infection with genotype 1 during the third trimester can lead to maternal mortality in up to 15% to 25% of cases..

2. Hepatitis E in pregnancy

There is increasing evidence that HEV is an important contributor to maternal morbidity and mortality in South Asia, especially if infection occurs in the third trimester with genotype 1, which is associated with more severe infection and might lead to fulminant hepatic failure and maternal death.

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

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.

3. Breastfeeding in mother with hepatitis-E

Breastfeeding is considered safe in asymptomatic women infected with HEV despite the presence of anti-HEV antibodies and HEV RNA in the colostrums.

However, it is considered unsafe if the mother has acute hepatic disease or an increased viral load. In these cases, feeding formula is advised, as there is a possibility of transmission from infected breast milk or lesions on the nipple through suckling.

4. Aims and Objectives

To study the maternal and fetal complication due to hepatitis –E in pregnant women during 3rdtrimester

5. Materials and Methods

This prospective observational study was done at B.J.medical College and civil hospital Ahmedabad, tertiary care hospital and research Centre. From April 2015 to March 2017 to study fetomaternal complication due to hepatitis E in 3rdtrimester. Incidence of hepatitis –E in civil hospital during this study period was o.27 %(total 45 cases noted and total 16134 delivered including LSCS and vaginal delivery

6. Sample Design

All pregnant women in 3rd trimesterpresenting with icterus were systematically assessed for hepatitis virus infection by liver function tests and serologic analysis.

The serum was analyzed for IgM AntiHEV by Rapid Immuno chromatographic Assay (Insight Device), and only Anti-HEV IgM-positive women were included in our study.

Patients with clinical evidence of jaundice due to other causes, e.g., HELLP syndrome, Hemolysis, Acute Fatty Liver of Pregnancy, Biliary tract disorders, and Drug induced hepatitis, were excluded.

None of the patients had a history suggestive of chronic liver disease

Maternal features such as gestational age at the time of first detection of infection, clinical progression of the disease, worsening or otherwise of laboratory parameters, and obstetric outcomes were noted in detail. These patients were observed for viral hepatitis symptoms such as fever, edema, ascites, paralytic ileus, nasal and gastrointestinal hemorrhage, level of consciousness, and altered sensorium.

Fetal well-being was monitored by ultrasonography and CTG. Further evaluation was done on an individualized basis.

All patients were managed by a team of obstetricians, physicians, intensivists, and neonatologists.

Patients with fulminant hepatic failure (FHF) were managed in the ICU and monitored for medical and obstetric complications. Fulminant hepatic failure was defined as the rapid development of acute liver injury with severe impairment of the synthetic function and hepatic encephalopathy in a patient without obvious, previous liver disease within 4 weeks

Hepatic encephalopathy, a spectrum of neuropsychiatric abnormalities in patients with liver failure, after exclusion of other known brain diseases includes personality changes, intellectual impairment, and reduced levels of consciousness Treatment included higher antibiotics, parenteral nutrition, and ventilator support, as required. Patients with deranged coagulation profile and bleeding episodes were transfused blood and blood products according to requirement.

All these patients were admitted and were studied regarding pregnancy status, mode of termination, and complications encountered. The decision for termination of pregnancy was taken on an individualized basis

Labor monitoring was conducted as per protocol. Termination of pregnancy was considered for hepatitis per se. All the in-hospital deliveries were attended by the on-call neonatologist and appropriate care was instituted.

In accordance with the institutional ethical committee norms, this study did not require a documented informed consent of the included study subjects as it did not involve any trial of intervention, and a standard treatment protocol was followed for all. Further, strict anonymity has been maintained during analysis.

7. Result

42 pregnant women having hepatitis E were admitted in the civil hospital during the study period with mean age 24 years.

All the patients with pregnancy of more than 28 week gestation are included in this study.

The majority of them were semiliterate and house wives belonging to lower socioeconomic class

Termination of pregnancy was carried out according to the gestational age and maternal situation.

Anorexia, fever, malaise, nausea and vomiting. They were Anti-HEV IgM and IgG positive and were negative serological markers for other viruses like A, B, C and also no history of intake of hepatotoxic agents.

There was no significant different with regards to age and parity status of patients.

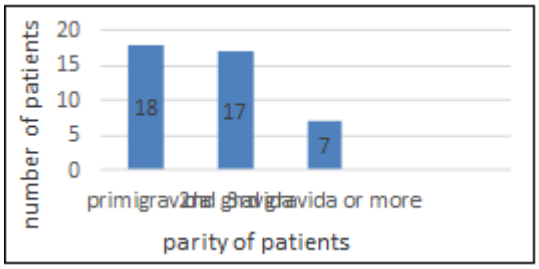

Chart 1: Age distribution of patient

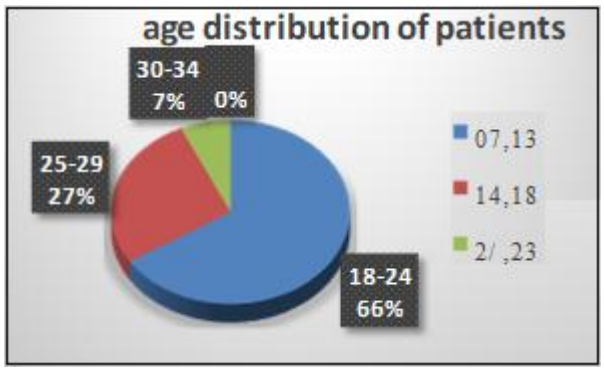

Table 2: Parity distribution of patient

In this study 29(66%) patients in 18-24 year age group, 12 (27%) patients in 25-29 Year age group and 3 (7%) in 30-34 year age group. Majority of patients in this study were from 18-29 year with mean age of 24 year.

In this study 18 patients (42.8%) were primigravida, 17 patients (40.4%) were 2nd gravida and 6 patients (14.28%) were 3rd gravida 1 patient (4.2%) was 5th gravida.

Table: Maternal morbidity and obstetric complications

Maternal complication	Present study (%)
Hepatic encephalopathy with Fulminant hepatic failure(FHF)	05 (11.9 %)
Ascites	15 (35.7%)
Rénal failure	06 (14.28%)
Disseminated intravascular coagulation (DIC)	12 (28.5%)
ICU admission	08 (19.04%)
Blood transfusion	18(42.85%)
Gastrointestinal hemorrhage	02(7.76%)
Maternal mortality	5(11.90)
Postpartum hemorrhage	11(26.19%)
Premature rupture of membrane (PROM)	08(19.04%)
Intrauterine fetal death(IUFD)	06(16.66%)
Preterm labor	11(26.19%)

There were 5 (11.9%) maternal death; all 5 women had fulminant hepatic failure and multiorgan dysfunction. Other medical complications were as cites in 15 patients (35.7%),Disseminated intravascular coagulation(DIC) in 12 patients (28.5%), renal failure in 6 (14.28%) patients, Gastrointestinal hemorrhage in 2 (7.76%), 18 patients (42.85%) required blood product transfusion, 8 patients (19.04%) required intensive care, 11 women developed post-partum hemorrhage, 8 women had premature rupture of membrane, 11 women had preterm labor pain and 6 women had intrauterine fetal death.

Table 4: Laboratory parameters

Lab parameters	Present study (%)
Mean hemoglobin (gm %)	8.81 gm/dl
Mean leukocyte count	15.3 × 10^3/ cmm
Mean platelet count	110 × 10^3/cumm
Mean serum bilirubin level	7.4 mg/dl
Mean SGPT level	70 U/l
Median prothrombin time	32 second
Median INR	2.5
Mean serum albumin level	2.3 gm/dl
Mean serum creatinine level	0.8 mg/dl

Among this study serum total bilirubin and prothrombin time were significantly increased ranging from 1.2 – 26 mg/dl with mean value of 7.4mg/dl and prothrombin time range from 15-64 second with mean value of 32 second and INR ranging from o.9 -5.4 with mean value of 2.5

Other investigations were mean hemoglobin 8.82gm/dl,mean leukocyte count 15.3×10^3/cumm, mean platelets count were 110×10^3/cumm, mean albumin 2.3 mg/dl and mean serum creatinine 0.8mg/dl

Table 5: Fetal outcome

Fetal outcome	Result of study (%)
Intrauterine death(IUD)	07(16.66%)
Preterm babies	11(26.19 %)
Still birth	03 (7.14%)
Live birth	32(76.19%)
Low birth weight	16(38.09%)
Meconium stained liquor	08(19.04%)
NICU admissions	14(33.3%)
Neonatal mortality	10(23.80%)

There were 32 women with hepatitis –E delivered live baby, there were 7 intrauterine death, 3 still birth, 11 preterm delivery, 16 low birth weight, 8 meconium stained liquor and 14 babies admitted in NICU and neonatal mortality were 10.

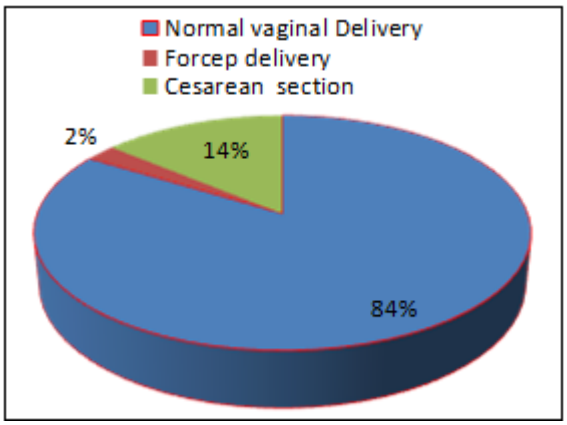

Chart 2: Mode of delivery

36 women delivered vaginally including 1 forceps delivery and 6 women delivered by Cesarean section. All cesarean were done for obstetric indications like fetal distress, primi breech and placenta Previa

8. Discussion

Hepatitis E viral infection occurring in young adults is a known phenomenon with predisposition to pregnant women. Although high mortality and morbidity of both mother and fetus have been reported the exact mechanism still remain unexplained

Out of 68 women with icterus 42 cases were attributed to hepatitis –E.(61.7%).which is comparable to south Indian study but lower than northern Indian reported rates.

The difference as well as similarities between this study and reported cases from the above quoted Indian studies cannot be overemphasized in view of referral bias as well as small restricted sample and region difference.

Parity does not seem to play much of role since we had almost equal distribution in primgravidae and multigravida. With respect to severity of liver failure, present study has small incidence of fulminant hepatic failure, 5/42 (11.9%)

The reason for the difference in outcome of HEV in different geographic area remain unclear but could be due to early childhood HEV exposure, produce long standing immunity and modifying subsequent response to virus, alternatively virulence of HEV genotype could vary in different geographic area.

This virulent ability of genotypes might play role in determining viral subtype which is common in pregnancy and in epidemic outbreaks.
Obstetric complications included preterm labor in 11/42 (26.9%), postpartum hemorrhage (PPH) 11/42 (26.19%), premature rupture of membrane (PROM) 08/42 (19.04%), intrauterine fetal death6/42 (16.6%).

There were 6 cesarean section done for obstetric indications like primi breech, placenta Previa, previous LSCS and fetal distress and one forceps delivery to cut short 2nd stage of labor for fetal distress.

Worsening maternal condition due to infection does not affect cesarean rate in our study. Induction was labor performed for indications such as PROM, Iligohydroamnios, Gestational hypertension and IUD in 12 patients with cerviprime gel 0.5mg and tablet misoprostol 50microgram according to indications.

Medical complications included hepatic encephalopathy in 05 (11.9 %) patients, Ascites in15 (35.7%)patients, renal failure in 06 (14.28%) patients, DIC in 12 (28.5%) patients, requirement for blood transfusion in 18(42.85%) patients, and ICU admission required for 08 (19.04%) patients.

Maternal mortality occurred in 5 women out of 42 (11.9%) with hepatic encephalopathy and fulminant hepatic failure. Among that 3 women diagnosed as IUD and 2 delivered live baby and post-partum hepatic encephalopathy developed. None of them died antenatal.

Maternal mortality was considerably lower in our study as compared to other north Indian study vary from 26-41%, as all the women included in study not developed hepatic encephalopathy and fulminant hepatic failure and cured with medical treatment and blood transfusion.

As regards to fetal outcome preterm 11(26.19 %) and low birth weight 16(38.09%) form bulk of NICU admission14 (33.3%).

As expected almost all patients with fulminant hepatic failure had poor fetal outcome and also preterm neonates had poor prognosis due to higher chances of septicemia.

7 IUFD, 2 still birth and 10 neonatal mortality occur. Which indicates high perinatal mortality. Most common cause of perinatal mortality was preterm birth followed by low birth weight. The severity was higher in patients with IUFD in our study, out of 5 maternal mortality 3 women admitted with IUFD. More severe course in pregnancy with IUFD is probably due to fetal hepatitis and toxins released in maternal circulation.

9. Conclusion

These observed variations in maternal and fetal morbidity and mortality between studies indicate a need to subtype viral genotype according to its virulence and morbidity which are almost exclusive to pregnancy.

This could form the basis for sponsored vaccination programme in epidemic area and susceptible populations. All the pregnant women should avoid taking contaminated foods and water as Hepatitis E was transmitted by fecooral route.
Case fatality was very high once patient developed hepatic encephalopathy. Once hepatitis E diagnosed proper treatment should be started immediately.

Commercially available vaccines should be studied in people as it is most harmful to pregnant women. If mother has active hepatitis in 3rdtrimester chances of preterm labor is more and which leads to IUFD and poor neonatal outcome and higher neonatal mortality.

10. Limitations

Primarily our study had smaller sample size as incidence of hepatitis in 3rdtrimester in our institute was very low.

We cannot deny the possibility of referral bias in our study. Icteric pregnant women and early preterm delivery requiring NICU facility were commonly referred from rural primary health Centre and remote area, and all the women were from lower socioeconomic class and illiterate or semiliterate and don't understand language

Prevalence was HEV not studied as we have included the HEV IgM positive patients.

Patients with minor symptoms and asymptomatic could have been missed on clinical evaluation and were not documented HEV testing in babies not done so that chances of vertical transmission was not studied.

HEV RNA testing was not done in our study which has high specificity in diagnosis.

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