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Management of Severe Hepatitis E Infection in Pregnancy: Assessing Early Delivery as a Safe and Effective Intervention for Improving Maternal and Neonatal Outcomes

Dr. Javairiya Butt[1], Dr. Ghzanfar Ali Awan[2], Dr. Asma Nasrullah[3], Dr. Ayesha Abdul Qayyum[4], Dr. Mominah Gul[5], Dr. Fiza Shabir[6]

1. Poonch Medical College, Rawalakot, Azad Jammu & Kashmir, Pakistan.
2. Poonch Medical College, Rawalakot, Azad Jammu & Kashmir, Pakistan.
3. Azad Jammu & Kashmir Medical College, Muzaffarabad, Azad Jammu & Kashmir, Pakistan.
4. Fatima Jinnah Medical University, Lahore, Punjab, Pakistan.
5. Fatima Jinnah Medical University, Lahore, Punjab, Pakistan.
6. Ayub Medical College, Abbottabad, Khyber Pakhtunkhwa, Pakistan.

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Abstract

Background: There have been reports that around 70% of pregnant women who have acute hepatitis E quickly progress to acute liver failure with a short period of pre-encephalopathy. Acute liver failure presents with decreased synthesis of proteins from the liver causing coagulopathy, encephalopathy and other neurological complications.

Objective: Comparison of maternal and fetal outcomes in pregnant females with moderate and severe hepatitis E infection

Materials and Methods: The approval from institutional review board of ethics was taken for this study. This prospective study was done in collaboration with Department of Gastroenterology and Department of Gynaecology, Fatima Memorial Hospital, Lahore for a period of 1year from 2020-2021. All pregnant females with serologically detected Hepatitis E.Pregnant females with deranged liver function tests with other causes than Hepatitis E Pregnancy related liver diseases.

Results: 87 patients were enrolled in the study. At the time of diagnosis, the patients in the first trimester were 7%, in the second trimester were 23% and in the third trimester were 57%. The patients below 30yrs of age were 77 patients (88.5%) while more than 30yrs old were 10 patients (11.5%). These patients were grouped according to severity of disease, which showed that 47 patients (54%) patients had severe liver disease due to hepatitis E as compared to 40 patients (46%) who had moderate disease. Majority of the patients with severe disease were in their third trimester of gestation.

Conclusion: Although there are no guidelines for management of pregnant patients with HEV infection, however if early delivery of the fetus is possible to prevent maternal mortality, it should be tried. Further randomized controlled studies are needed to decide the best way of managing these patients with HEV infection in pregnancy.

Keywords: Severe Hepatitis E, Pregnancy, Early Delivery, Safe and Effective, Treatment Option.

Introduction

Hepatitis E virus (HEV) infection causes significant morbidity and mortality during pregnancy in women in resource poor and developing countries, mortality rate are disproportionally high as

compared to developed world and the mortality rate can reach up to 20% in pregnant women with hepatitis E. 13 Hepatitis E infection among pregnant women poses a great challenge for the obstetrician due to high risk of acute liver failure and severe pregnancy-related complications including Maternal complications like preterm labor, preterm premature rupture of membrane (PrePROM), antepartum hemorrhage (APH), postpartum hemorrhage (PPH), and maternal coagulopathy and fetal complications like meconium stained liquor and intrauterine fetal death, with highest risk of fatality during the second and third trimester of pregnancy. 1, 14 Lot of work has been done so far to understand the aggressive behavior of HEV during pregnancy. During pregnancy, maternal mortality in HEV infection is correlated with the levels of estrogen and its receptor ESR2β. 2 HEV infected pregnant women with fulminant hepatic failure found to have lower CD4 count, higher CD8 counts and lower CD4/CD8 cell ratio with significantly higher steroid hormones levels as compared to healthy women creating a state of immunosuppression.3 The increase in fetal mortality might be due to transmission of hepatitis E in-utero causing hepatitis in fetus. 4 There have been reports that around 70% of pregnant women who have acute hepatitis E quickly progress to acute liver failure with a short period of pre-encephalopathy. Acute liver failure presents with decreased synthesis of proteins from the liver causing coagulopathy, encephalopathy and other neurological complications. 5

Objective

Comparison of maternal and fetal outcomes in pregnant females with moderate and severe hepatitis E infection

Materials and Methods

The approval from institutional review board of ethics was taken for this study. This prospective study was done in collaboration with Department of Gastroenterology and Department of Gynaecology, Fatima Memorial Hospital, Lahore for a period of 1year from 2020-2021.

Inclusion Criteria:

All pregnant females with serologically detected Hepatitis E

Exclusion Criteria:

Pregnant females with deranged liver function tests with other causes than Hepatitis E Pregnancy related liver diseases. The diagnosis of Hepatitis E in pregnant females was made by the clinical history and examination followed by investigations including CBC, LFTS, Coagulation profile, viral serology of anti HAV IgM, anti HEV IgM, HBsAg and anti HCV.

Total 87 patients were enrolled in the study.

The variables of the study included the gestational age at diagnosis of Hepatitis E and gestational age at the time of delivery, mode of delivery, fetal and maternal outcomes, indications of ELSCS at preterm and term, indications of SVD at preterm and term, comparison of maternal fetal outcomes and mortality during ELSC and SVD. The biochemical laboratory parameters i.e CBC, LFTs, INR, RFTs was also recorded. Preterm was defined as delivery before gestational age of 37weeks while term was defined as gestational age between 37 and 41 weeks. SPSS version 23 was used for statistical analysis.

Terminologies used:

Preterm: Delivery of baby before 37weeks of Gestational amenorrhea

Term: Delivery of baby after 37weeks of Gestational amenorrhea Coagulopathy: Encephalopathy

Severe Liver disease: Patient having features of Encephalopathy, coagulopathy or ascites and required admission in ICU for monitoring and management of the disease

Moderate Liver Disease: Patient not having features of Encephalopathy, coagulopathy or ascites and did not require admission in ICU for monitoring and management of the disease

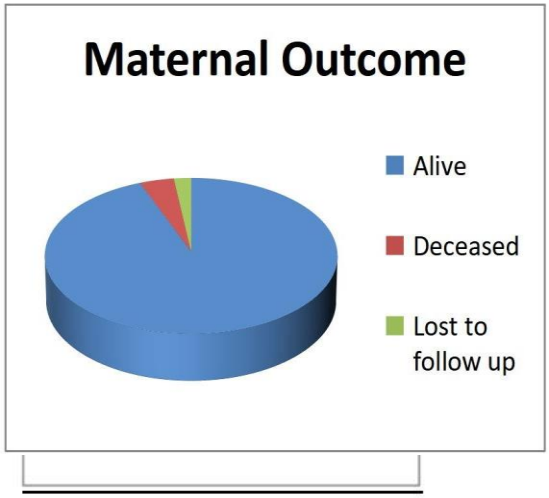
Results:

87 patients were enrolled in the study. At the time of diagnosis, the patients in the first trimester were 7%, in the second trimester were 23% and in the third trimester were 57%. The patients below 30yrs of age were 77 patients (88.5%) while more than 30yrs old were 10 patients (11.5%). These patients were grouped according to severity of disease, which showed that 47 patients (54%) patients had severe liver disease due to hepatitis E as compared to 40 patients (46%) who had moderate disease. Majority of the patients with severe disease were in their third trimester of gestation. The maternal outcomes observed in our data showed that 46 patients (53%) had preterm delivery while 41 patients (47%) had delivery at term (p =1.000). The modes of delivery for these patients were LSCS in 40 patients (45%) and SVD in 47 patients (55%). When these patients were grouped in the preterm and term categories, it showed that 21 patients (46%) had preterm LSCS and 25 patients (54%) had preterm SVD. While 19 patients (46%) had term LSCS and 22 (54%) had term SVD (P=0.698). 79% patients were delivered in their third trimester and 1 delivered during the second trimester.

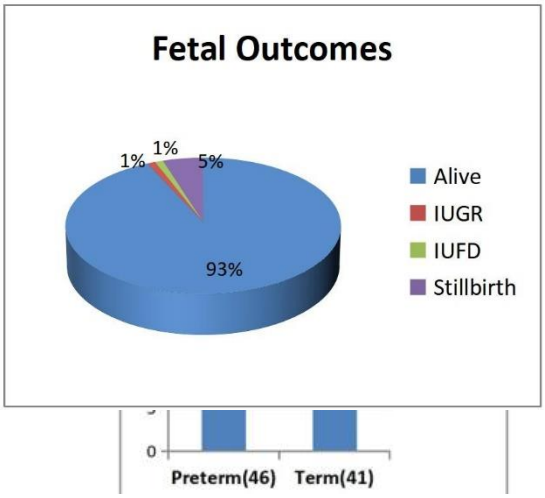
The decision of early delivery and the mode of delivery were made on worsening of mother's condition and fetal distress, with the consensus of hepatologist and obstetrician. There were 25 reported preterm SVD and 22 term SVDs. Maternal outcomes showed that 82 patients were alive and were discharged while 3 patients expired and 2 patients got lost to follow up (P=2.64). Maternal outcome was better with preterm delivery more with LSCS indicating that early intervention in preterm patients was more likely to save mother's lives. However 3 mortalities were seen in the third trimester in patients with severe liver disease due to hepatitis E and its complications who underwent spontaneous SVD. These patient developed encephalopathy and coagulopathy leading to sepsis, DIC and AKI causing deaths

Fetal outcomes were with 79 live births (93%), 4 stillbirths (5%), 1 IUD (1%) and 1 IUGR (1%) (p=1.75). Two stillbirth cases were seen in preterm deliveries moderate disease while 2 were seen with term deliveries severe disease. The IUD and IUGR cases were seen with severe liver diseases in pregnancy. Normal birth weight was reported in 42 fetuses (48%) while low birth weight category included 35 fetuses (40%) with majority having severe maternal disease while 2 patients were lost to follow up. Comparison of maternal mortality from second trimester (1.25%) to third trimester (2.5%) showed a higher mortality rate. Similarly, comparison of fetal mortality from second trimester (1.25%) to third trimester (6.25%) showed a marked raise in mortality.

Maternal Outcomes



Fetal outcomes:



Maternal and Fetal mortality:

	Second Trimester	**Third Trimester**
Maternal Mortality	**1.25%**	**2.5%**
Fetal Mortality	**1.25%**	**6.25%**

Discussion:

Hepatitis E is a self-limiting disease which is of major public health concern in pregnant females and their fetuses due to their effects in pregnancy. According to a study by Singh et al, hepatitis E has a high prevalence rate and it ranges from 47.4%-84.3%.12

Begum et al concluded that hepatitis E is more pronounced in third trimester as compared to second trimester. This is comparable to our data in which 23% females were in second trimester and 57% were in the third trimester.6 Banait et al, did a retrospective study in India on patients with acute liver failure secondary to acute hepatitis E during pregnancy. He concluded that early delivery in patients who had developed encephalopathy secondary to hepatitis E had improved outcome in maternal mortality over natural course. 7 However our research has shown that there is an improved outcome in terms of maternal and fetal outcomes when early intervention for delivery is done. There is also evidence that these women have increased risk of preterm labor and complications which may lead to the decision of early delivery.

Khuroo et al. postulated that vertical transmission of HEV infection causes severe fetal liver disease along with severe maternal liver disease, resembling mirror syndrome. Fetus with severe liver disease may produce toxins which cross to the maternal blood and precipitate Fulminant hepatic failure and disseminated intravascular coagulation in the HEV infected mother.8 Kumar et al. in his study showed that two-third of his patients had preterm delivery. This finding is similar to our findings showing that 53% had preterm delivery before 37weeks of gestational amenorrhea. He also found that there were improved results in mothers with preterm deliveries.9

Bergløv et al. concluded from his study in 2019 that the case fatality rate (CFR) was 26% in pregnant women who were diagnosed with hepatitis E infection, along with 8% neonatal and 33% fetal mortality.10 A study in Pakistan by Ahmed et al. showed that maternal mortality rate goes up to 25% and prenatal mortality goes up to 17.8% in pregnant females with acute hepatitis E especially in 3rd trimester. 11This is higher than what we observed in our study with maternal mortality of 1.25% and 2.5% in second and third trimester respectively. However fetal mortality

was higher, estimated to be 1.25% and 6.25% in second and third trimester. This may be due to the small number of patients and comparatively earlier presentation of patient to the hospital settings. Currently there is not much unanimity regarding treatment of acute hepatitis E in pregnancy, however some studies are showing promising data that whenever possible earlier delivery should be considered in order to reduce the mortality of mother and fetus. Larger randomized researches are needed in future to devise the most appropriate management plan for hepatitis E in pregnancy.

Conclusion

Although there are no guidelines for management of pregnant patients with HEV infection, however if early delivery of the fetus is possible to prevent maternal mortality, it should be tried. Further randomized controlled studies are needed to decide the best way of managing these patients with HEV infection in pregnancy.

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