Outcome of Hepatitis-E Virus Infection among Pregnant Women Admitted in a Tertiary Care Hospital

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Author’s Contribution
\begin{itemize}
\item Conception of study
\item Experimentation/Study conduction
\item Analysis/Interpretation/Discussion
\item Manuscript Writing
\item Critical Review
\item Facilitation and Material analysis
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Objective: To evaluate hepatitis E infection outcomes among pregnant women admitted to a tertiary care hospital.

Materials & Methods:
\textbf{Study Design:} Cross-sectional study
\textbf{Study Setting:} Department of Gynecology and Obstetrics Unit I, Services Institute of Medical Sciences, Lahore
\textbf{Study Duration:} May 2019 to Feb 2020, after approval from Institutional Review Board.
\textbf{Data Collection Procedure:} 30 Pregnant women with Hepatitis E confirmed on ELISA IgM, fulfilling the inclusion criteria age, 25 – 40 years of age in any trimester of pregnancy will be included in the study through Non-probability/convenience sampling. Data was entered and analyzed in SPSS ver: 25.0 Qualitative variables like Socio-demographic details and Clinical variables like the feto-maternal outcome were presented as frequency and percentages. The outcome was cross-tabulated with a demographic and clinical profile. The Chi-square test was applied with p < 0.05 and was taken as statistically significant.

Results: 30 patients were recruited for the study. 96.7% were between the age of 18 - 40 years. 43.3% were primigravida. 76.7% were delivered through spontaneous vaginal delivery. 66.7% had coagulation defects, Fetal outcomes showed 63.3% were alive, 20.0% were stillbirth and 16.7% had ENND. The maternal outcome was 96.7% recovered from Hepatitis E. 14.3% of pregnant women who were delivered with LSCS died which was statistically significant. (p=.045)

Conclusions: The present findings suggest a high Hepatitis E infectivity in pregnancy results in considerable high maternal and fetal morbidity and mortality. This high disease burden can be minimized by the provision of clean drinking water and access to better sanitary conditions for pregnant women.

Keywords: HEV, Hepatitis E infection, HEV infection, Pregnancy.
Hepatitis E virus (HEV) infection in developing countries is one of the main reasons for morbidity and mortality among pregnant women and there are disproportionate mortality rates in low-income and developing countries among pregnant women.\(^1\) Hepatitis E infection among pregnant women poses a great challenge for the obstetrician due to severe pregnancy-related complications including Maternal complications like preterm labour, preterm premature rupture of membrane (PPROM), antepartum hemorrhage (APH), postpartum hemorrhage (PPH), and maternal coagulopathy and Fetal complications like meconium stained liquor and intrauterine fetal death.\(^2\)

The situation of the Hepatitis E virus (HEV) in Pakistan is endemic in nature although most cases among young adults are asymptomatic. But Hepatitis E infection becomes fatal in pregnancy and there is substantial maternal and fetal morbidity and mortality.\(^3\)

The Hepatitis E vaccine trials have been successfully conducted in the southern Asian population and results have been very promising, results have shown that the candidate vaccines are very effective and well-tolerated but the availability of these vaccines to susceptible populations has still not been accessible to populations.\(^4\)

In a study done by Parsad et al., they recruited pregnant women who were anti-HEV IgM-positive and were symptomatic to evaluate maternal and fetal outcomes in these pregnancies, 5.0% of women died due to complications, among fetal complications 11.0% had PROM, 80.0% had prematurity and one antenatal death with the rate of vertical transmission of 28.0%. This high maternal morbidity and mortality among the Asian population warrant a need for further studies of virus genotyping and its infectivity and virulence.\(^5\)

The data collected during 2001-2007 surveillance of more than 110,000 pregnancies among 650,000 women in rural Bangladesh showed 9.8% of pregnancy-related deaths due to acute hepatitis and the majority of these deaths were attributed to hepatitis E. The findings of this and other similar studies show that as many as 10,500 maternal deaths each year are mainly due to HEV infection during pregnancy and can be prevented by the use of HEV vaccines.\(^1,6,7\)

HEV infection among pregnant women is very prevalent in low and middle-income countries mainly due to very limited access to clean potable water, poor sanitation, hygienic condition, and limited access to health services.\(^8,9\) HEV infection among these pregnant women occurs both as sporadic cases and seasonal outbreaks in these areas. These outbreaks' main reason is fecal contamination of drinking water supplies and usually, several hundred to several thousand persons are affected. Also, some of these outbreaks are more prevalent in areas where there are humanitarian emergencies like a refugee situation, internally displaced persons, or areas of war zones, where clean and safe water supply is difficult and challenging.\(^10\)

Objective: To evaluate hepatitis E infection outcomes among pregnant women admitted to a tertiary care hospital.

### Materials and Methods

A Cross-sectional study was conducted at the Department of Gynaecology and Obstetrics Unit I, Services Institute of Medical Sciences, Lahore from May 2019 to Feb 2020. After approval from Institutional Review Board. A sample size of 30 was calculated using the WHO calculator that uses formulae i.e. \(n = \left(\frac{z}{d}\right)^2 p (1-p) / d^2\) using a 95% confidence interval with an 8% margin of error assuming 5% mortality among pregnant women with hepatitis E from the study of Parsad et al. Pregnant women with Hepatitis E confirmed using IgM antibody by ELISA among those fulfilling the inclusion criteria of age between 25 - 40 years of age in any trimester of pregnancy will be included in the study through Non-probability/convenience sampling. Pregnant women with hepatitis E and pre-existing conditions like heart diseases and malignancies will be excluded. A detailed demographic history was taken along with complications during pregnancy, obstetric complications due to hepatitis E like antepartum or postpartum hemorrhage, preterm premature rupture of membranes, meconium stained liquor, maternal coagulopathy, and intrauterine death was observed. Delivered babies are followed up to 1 week postpartum to determine the perinatal outcome in form of admission, vertical transmission to baby, cause of ENND, or alive baby. Pregnant women with hepatitis other than hepatitis E, drug-induced hepatitis, cholestasis, jaundice of pregnancy, and acute fatty liver of pregnancy were excluded. SPSS version 25.0 was used for data analysis. Mean and Standard deviation was calculated for variables like age, disease duration, and frequency, and percentages were calculated for variables like Socio-demographic and feto-maternal outcome. Chi-square test was applied to
assess statistical significance for the feto-maternal outcome and demographic variable with p < 0.05 was taken as statistical significant.

**Results**

30 patients were recruited for the study. 96.7% were between the ages of 18-40 years. 43.3% were primigravida. 96.7% were between 27–40 weeks of pregnancy. 53.3% were living in an urban area and 40.0% were from urban slum areas. 76.7% of our respondents were educated having secondary and post-secondary education. 83.3% presented with yellow discoloration of the body, sclera, and itching.

| Table 1: Demographic profile of subjects |
|-----------------------------------------|
| **Variables n=30**                      | **Frequency** | **Percent age** |
| Age                                     |               |                 |
| <18                                     | 1             | 3.3             |
| 18-40                                   | 29            | 96.7            |
| Parity                                  |               |                 |
| primigravida                            | 13            | 43.3            |
| multigravida                            | 17            | 56.7            |
| DOP                                     |               |                 |
| 13-26 weeks                             | 1             | 3.3             |
| 27-40 weeks                             | 29            | 96.7            |
| Residential area                        |               |                 |
| urban                                   | 16            | 53.3            |
| urban slum                              | 12            | 40.0            |
| Rural                                   | 2             | 6.7             |

Clinical profile of subject shows 76.7% were delivered through spontaneous vaginal delivery. Maternal complications showed that 66.7% had coagulation defects, 30.0% developed hepatic encephalopathy, and 3.3% developed fulminant hepatic failure. Obstetric complications showed that 50.0% had a preterm delivery, 20.0% developed PPH, and IUGR was present among 26.7% of pregnancies. The fetal outcome showed that 63.3% were alive, 20.0% were stillbirth and 16.7% had ENND. The maternal outcome was 96.7% recovered from Hepatitis E. (Table 2)

| Table 2: Socio-demographic profile and maternal outcome Cross-tabulation |
|-----------------------------------------------------------------------|
| **Maternal outcome**                                                  | **P value** |
| **Recovered**                                                          | **Death**   |
| **Frequency** | **Percentage** | **Frequency** | **Percentage** |        |
| Age | <18 years | 1 | 100.0 | 0 | 0.0 | .850 |
| | 18-40 years | 28 | 96.6 | 1 | 3.4 |       |
| Parity | primigravida | 13 | 100.0 | 0 | 0.0 | .374 |
| | multigravida | 16 | 94.1 | 1 | 5.9 |       |
| Residential area | urban | 16 | 100.0 | 0 | 0.0 | .460 |
| | urban slum | 11 | 91.7 | 1 | 8.3 |       |
| | Rural | 2 | 100.0 | 0 | 0.0 |       |
| Education | illiterate/elementary | 1 | 100.0 | 0 | 0.0 | .315 |
| | matric/F.A | 22 | 95.7 | 1 | 4.3 |       |
| | Graduation/above | 6 | 100.0 | 0 | 0.0 |       |
| Mode of delivery | SVD | 23 | 100.0 | 0 | 0.0 | .045 |
| | LSCS | 6 | 85.7 | 1 | 14.3 |       |

The outcome was cross-tabulated with demographic and clinical characteristics. The death occurred in 3.4% of pregnant women 18-40 years. (p=.850) and 5.9% of multigravida women (p=.374). 8.3% of deaths were in urban slum areas. (p=.460) and 4.3% of pregnant women who were educated. (p=.315). 14.3% of pregnant women who were delivered with LSCS died because of fulminant hepatic failure which was statistically significant. (p=.045). (Table 3)

| Table 3: Clinical profile of subjects |
|---------------------------------------|
| **Variables n=30**                     | **Frequency** | **Percent age** |
| Mode of delivery | SVD | 23 | 76.7 |
| | LSCS | 7 | 23.3 |
had Singh et al study also depicted that 76.7% of women presenting in tertiary care hospitals who were living in high endemic areas where maternal and fetal complications. These findings suggest similar findings in contrast with other studies evaluating the burden of disease where a high burden of HEV infection among pregnant women in tertiary care hospitals who were living in high endemic areas where maternal and fetal complications are poor and a high rate of vertical transmission.11-15

Singh et al study also depicted that 76.7% of women had a spontaneous vaginal delivery and among them, 52.0% had in the second trimester among pregnancies in the third trimester 50% had a fulminant hepatic failure, also no statistically significant association was found in fatality rates and HEV infected pregnant women who presented between the second and third trimesters (66.6% vs. 71.43%) respectively.11

In our study maternal complications showed that 66.7% had coagulation defects, 30.0% developed hepatic encephalopathy, and 3.3% developed fulminant hepatic failure. Obstetric complications showed that 50.0% had a preterm delivery, 20.0% developed PPH, and IUGR was present among 26.7% of pregnancies. The fetal outcome showed that 63.3% were alive, 20.0% were stillbirth and 16.7% had ENND.

In a study by Parsad et al5 maternal mortality was evaluated among pregnant women with HEV infection and 5.0% of women died including one antenatal death. 80.0% of the newborn were premature and PROM was present in 11.0% and were the commonest fetal complications noted. The vertical transmission rate of HEV infection in this study was 28.0%. In our study maternal outcome was 96.7% who recovered from Hepatitis E and the fetal outcome showed 63.3% were alive, 20.0% were stillbirth and 16.7% had ENND consistent with Parsad et al study.5 Similar feto-maternal outcomes and risk factor prevalence have been reported by Solanki, Sahi, and Obiri-Yeboah et al studies.20-22

Kumar et al study findings are also consistent with our study findings. The researcher included 32 anti-HEV immunoglobulins M-positive pregnant women who were analyzed for feto-maternal outcomes. The most common fetal complications were intrauterine demise with prematurity and among maternal outcome maternal mortality and premature rupture of membranes was the frequency and there was a statistically significant association with Hepatitis E infection.23 Similarly study Helema et al conducted to determine the frequency of Hepatitis E in pregnancy, its clinical presentation, maternal morbidity, mortality and perinatal outcome. the maternal mortality rate of 29.3% and the rest were discharged safely. The perinatal mortality rate was 30.3 per 1000 live births. Our study findings also reflect high feto-maternal complications.34

Discussion

A very high burden of HEV infection is seen among pregnant women, especially in developing countries in recent years. Infection with hepatitis E virus during pregnancy is usually associated with poor fetal-maternal outcomes with a two to three-fold increase in intrauterine fetal death, a three-fold increase in poor intrauterine fetal maturity, and a significant increase in the likelihood of maternal deaths. Global Burden of Disease6,9 in several studies have estimated the HEV seroprevalence among women of childbearing age (15 to 45 years) to be 5-22% and a high IgM seroprevalence of more than half of HEV infection among symptomatic women depicts an endemic situation of HEV is endemic in these regions.11-17

In our study among pregnant females, 43% were primigravida, and 56% were multigravida. Among these pregnant women, 96.7% were in the third trimester of pregnancy these findings are similar to previous studies where the incidence of HEV infection increases with increased gestational age, and the relation between HEV infection and gravid uterus was not evaluated in previous studies.8,9-11

Singh et al researchers analyzed the rate of HEV infection among pregnant Indian women who were admitted to tertiary care hospitals. A high positivity rate of 40.0% for IgM anti HEV was seen. Other study findings suggest similar findings in contrast with other studies evaluating the burden of disease where a high burden of HEV infection among pregnant women presenting in tertiary care hospitals who were living in high endemic areas where maternal and fetal outcomes are poor and a high rate of vertical transmission.11-15

Our study findings suggest that Hepatitis E infectivity among pregnancy with high feto-maternal morbidity and mortality among pregnant women among women
presenting in tertiary care hospitals. The burden of HEV infection among these pregnant women can be reduced by preventive measures like the provision of a safe water supply and a better sanitary environment for pregnant women.

References

1. Paul RC, Nazneen A, Banik KC, Sumon SA, Paul KK, Akram A, et al. (2020) Hepatitis E as a cause of adult hospitalization in Bangladesh: Results from a jaundice surveillance study in six tertiary hospitals, 2014-2017. PLoS Negl Trop Dis 14(1): e0007586. DOI: https://doi.org/10.1371/journal.pntd.0007586

2. Bigna JJ, Mchyiini AF, Nansseu JR, Amougou MA, Nola M, Kemoe S, et al. Burden of hepatitis E virus infection in pregnancy and materno-fetal outcomes: a systematic review and meta-analysis. BMC Pregnancy and Childbirth 2020; 20: 426 - 430.

3. Javed N, Ullah SH, Hussain N, et al. Hepatitis E virus seroprevalence in pregnant women in Pakistan: maternal and fetal outcomes. East Mediterr Health J. 2017;23(8):559-563. Published 2017 Oct 30.

4. Khuroo MS. Discovery of hepatitis E: The epidemic non-A, non-B hepatitis 30 years down the memory lane. Virus Res. 2011;161(1):3–14.

5. Prasad GS, Prasad S, Bhupali A, Patil AN, Parashar K. A Study of Hepatitis E in Pregnancy: Maternal and Fetal Outcome. J Obstet Gynaecol India. 2016;66(Suppl 1):18-23. DOI: 10.1007/s13224-015-0749

6. World Health Organization. Global Health sector strategy on viral hepatitis 2016–2021: Towards ending viral hepatitis. WHO: 2016. Available from: https://apps.who.int/iris/bitstream/handle/10665/246177/W HO-HIV-2016.06- eng.pdf?sequence=8

7. Javed NA, Ullah SH, Hussain N, Sheikh MA, Khan A, Ghafoor F, Firdous R, Uddin W, Saqib AN, Muhyudin G. Hepatitis E virus seroprevalence in pregnant women in Pakistan: maternal and fetal outcomes. East Mediterr Health J. 2017;23(8):559-63.

8. Singla A, Mehta S, Rajaran S, Shree S. Materno-fetal outcomes with viral hepatitis E in pregnancy. J Obstet Gynaecol India. 2016;66(3):166-9. DOI: 10.1007/s13224-014-0666-5

9. Aggarwal R, Gandhi S. The global prevalence of hepatitis E virus infection and susceptibility: a systematic review. Geneva, Switzerland: World Health Organization; 2010.

10. Xia H, Wahlberg N, Belak S, Meng XJ, Liu L. The emergence of genotypes 3 and 4 hepatitis E virus in swine and humans: a phylogenetic perspective. Arch Virol. 2011;156(1):121-4. DOI: 10.1007/s13224-014-0666-5

11. Singh S, Mohanty A, Joshi YK, Dwivedi SN, Deka D. Outcome of hepatitis E virus infection in Indian pregnant women admitted to a tertiary care hospital. Indian J Med Res. 2001;113:35-39.

12. Gurley ES, Hessain MJ, Paul RC, et al. Outbreak of hepatitis E in urban Bangladesh resulting in maternal and perinatal mortality. Clin Infect Dis. 2014;59(5):658-665. DOI: 10.1093/cid/ciu383

13. Tejada-Strop A, Tohme RA, Andre-Alboth J, Childs I, Ji X, Landgraf DO, De Castro V, Boncy J, Kamilli S. Seroprevalence of hepatitis a and hepatitis e viruses among pregnant women in Haiti. Am J Trop Med Hyg. 2019;101(1):230–2. DOI: 10.4269/ajtmh.19-0020

14. Rein DB, Stevens GA, Theaker J, Wittenborn JS, Wiersma ST. The global burden of hepatitis E virus genotypes 1 and 2 in Hepatology; Baltimore, Md. 2012. 2005;55(4):988–97.

15. WHO: Hepatitis E vaccine: WHO position paper; May 2015. Available at: http://www.who.int/wer/2015/wer9018.pdf?ua=1. Last accessed 14th July, 2020.

16. De Paschale M, Cerviani C, Romanò L, Cerulli T, Cagnin D, Cavallari S, Ndayakye J, Zaongo D, Diombe K, Priuli G, et al. Epidemiology of hepatitis E virus infection during pregnancy in Benin. Trop Med Int Health. 2016;21(1):108–13.

17. Abebe M, Ali I, Ayele S, Overbo J, Asfaha A, Mihret A. Seroprevalence and risk factors of Hepatitis E Virus infection among pregnant women in Addis Ababa, Ethiopia. PLoS One. 2017;12(6).

18. Farshadpour F, Taherkhani R, Ravanbod MR, Eghbali SS, Taherkhani S, Mahdavi E. Prevalence, risk factors and molecular evaluation of hepatitis E virus infection among pregnant women resident in the northern shores of Persian Gulf, Iran. PLoS One. 2018;13(1).

19. World Health Organization. Global Health sector strategy on viral hepatitis 2016–2021: Towards ending viral hepatitis. WHO: 2016. Available from: https://apps.who.int/iris/bitstream/handle/10665/246177/W HO-HIV-2016.06- eng.pdf?sequence=8

20. Solanke D, Rathi C, Pandey V, Patil M, Phadke A, Sawant P. Etiology, clinical profile, and outcome of liver disease in pregnancy with predictors of maternal mortality: a prospective study from Western India. Indian J Gastroenterol. 2016;35(6):450-8. DOI: 10.1007/s12664-016-0704-6.

21. Sahai S, Mishra V, Ganga D, Jatav OP. Viral hepatitis in pregnancy—a study of its effect on maternal and Foetal outcome. J Assoc Physicians India. 2015;63(1):28–33.

22. Obiri-Yeboah D, Asante Awuku Y, Adu J, et al. Seroprevalence and risk factors for hepatitis E virus infection among pregnant women in the Cape Coast Metropolis, Ghana. PLoS One. 2018;13(1):e0191685.

23. Kumar N, Das V, Agarwal A, Pandey A, Agrawal S. Fetomaternal outcomes in pregnant women with hepatitis e infection; still an important fetomaternal killer with an unresolved mystery of increased virulence in pregnancy. Turk J Obstet Gynecol Obstet Dernegi Dergisi. 2017;14(2):106–13.

24. Yasmeen T, Haleema A, Taj H, Taj A. Fetomaternal outcome in Hepatitis E in pregnancy. Journal of the College of Physicians and Surgeons Pakistan 2018, Vol. 23 (10): 711-714