

# INCIDENCE OF ADVERSE MATERNAL AND FETAL OUTCOMES IN ANTENATAL FEMALES WITH HEPATITIS E VIRUS INFECTION: A COHORT STUDY

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## Abstract

**Objective:** To compare the incidence of adverse feto-maternal outcome in females with hepatitis E virus infection in pregnancy versus normal pregnant females

**Study design:** Cohort study

**Study place and duration:** Department of Obstetrics & Gynecology, Shaikh Zayed Hospital, Lahore for six months (May 2024-02 Nov 2024)

**Methodology:** One hundred pregnant females were included and divided in two groups i.e. exposed with hepatitis E infection and unexposed without hepatitis E infection. Time of delivery and intrapartum and postpartum complications were noted. Relative risk was calculated keeping risk ratio >1 as significant.

**Results:** 100 Individuals were included and divided into two groups. The mean age of females in exposed group was  $30.03 \pm 6.73$  years, while of unexposed group was  $28.60 \pm 5.70$  years. The mean serum bilirubin level was  $8.89 \pm 2.19$  mIU in exposed group and  $2.56 \pm 1.31$  mIU in unexposed group ( $p < 0.05$ ). In exposed females, risk of antepartum hemorrhage was RR: 1.658 (24% vs. 8%, 95% CI: 1.148-2.395), miscarriage was RR: 2.020 (2% vs. 0%, 95% CI: 1.656-2.465), premature rupture of membranes was RR: 1.733 (22% vs. 6.0%, 95% CI: 1.210-2.480), intrauterine death was RR: 1.827 (30% vs. 8.0%, 95% CI: 1.299-2.569), preterm birth was RR: 2.180 (54% vs. 16%, 95% CI: 1.499-3.171), still birth was RR: 2.204 (28% vs. 2%, 95% CI: 1.661-2.923), and maternal mortality was RR: 2.220 (18% vs. 0%, 95% CI: 1.769-2.785).

**Conclusion:** Thus, presence of hepatitis E virus infection is associated with adverse fetomaternal outcome making it an important risk factor for adverse events.

## INTRODUCTION

Human hepatitis E virus infection peaks in the early stages of life in genotype 1 highly epidemic locations, but genotype 3 is endemic in adults and causes around 10% of presumed acute idiopathic infections as well as a number

of subclinical, undetected infections.<sup>1, 2</sup> Hepatitis E virus infection usually remain undiagnosed. This may be because of using low sensitivity serological assays. But few diagnostic tools like nucleic acid-based test have been

upgraded.<sup>3</sup> The prevalence of hepatitis E is high in Pakistan and predominantly is periodic disease.<sup>4, 5</sup> The better understanding of natural history of hepatitis E virus infection was achieved in last 10 years. Many sources and modes of transmission are already recognized.<sup>6</sup> Hepatitis E virus infection during pregnancy increases the rate of hazardous complications and mortality in females, specifically in last trimester and also in postpartum time. Very high number of maternal complications has been reported in pregnant females who present in last trimester, both clinically and disturbed levels of hematological and biochemical markers. Maternal mortality rate due to hepatitis E in pregnancy was 14%, while perinatal mortality rate was 28%.<sup>7, 8</sup>

In pregnancy, hepatitis E virus infection can be severe and have a sudden onset, causing acute hepatic failure, rupture of amniotic membrane, abortions and also still-births. Studies showed that high frequency of hepatitis E virus infection during pregnancy can cause a significant percentage of females to develop severe hepatitis with mortality rate around 30%.<sup>9, 10</sup>

Aim of this study was to compare the incidence of adverse maternal and fetal outcome in females with hepatitis E virus infection versus females with normal pregnancy. Literature has reported that the chances of adverse pregnancy outcome was high in females with hepatitis E virus infection as compared to normal pregnancy. But not much work has been done in this regard. Also, very few local evidence has been reported earlier, but no association-based studies had been conducted before. The incidence of hepatitis E virus infection had been increased from previous decades and affecting high number of pregnancies. So, we wanted to conduct this study to determine the extent of problem in local setting. So that in future, we can be able to screen the symptomatic pregnant females (with symptoms of jaundice), for hepatitis E virus infection to improve the management protocol of pregnant females and improve the outcome of pregnancy. This will help us to improve our practice and reduce the complications of pregnancy with hepatitis E virus infection.

## METHODOLOGY

After taking approval from ethical board (SZMC/IRB/Internal/0048/2024 dated 26-04-2024) this Prospective Cohort study was done at Department of Obstetrics & Gynaecology, Shaikh Zayed Hospital, Lahore for six months i.e. from 02 May 2024-02 Nov 2024. Sample size (n) = 100 cases (50 in each group) has been estimated by keeping power of study at 80%, significance level at 5% and percentage of maternal mortality i.e. 14% in exposed. All the patients, who fulfilled following criteria were enrolled after applying Sampling Technique: Non probability, convenience sampling technique.

**Inclusion:** Females aged 20-40 years, parity <5, presenting at any gestational age with or without jaundice (serum bilirubin >5 mIU), with symptoms including nausea and vomiting, dark urine, pale stool, fever (temperature >99°F) were included in the study. Exposed group were those pregnant females who were diagnosed with hepatitis E, assessed by serological analysis i.e. positive IgM. Unexposed pregnant females were without Hepatitis E and normal LFTs. Females attending emergency were enrolled in the study.

**Exclusion:** Females also have hepatitis B or C, with chronic or gestational hypertension, diabetes, asthma, cardiac disease, placenta previa, accrete, increta or percreta, abnormal amniotic fluid index or ectopic pregnancy were excluded from the study.

Demographics like name, age, BMI, gestational age and parity were also noted. Then females were divided in two groups i.e. exposed with hepatitis E virus infection and unexposed without hepatitis E virus infection. All the females were followed-up in OPD and were asked to present in labor room in case of vaginal bleeding or miscarriage. If there were no fetal movement reported by female and no heart beat detected on ultrasound, then intrauterine fetal death was labeled. If female presented with active bleeding (antepartum haemorrhage) or premature rupture of membrane, then it was noted. Females were followed-up till delivery. If delivery will occur before completion of 37 weeks, then preterm delivery was labelled. After delivery, females were followed-up in post-delivery wards and if

bleeding occurs >500ml or >1000 ml then postpartum hemorrhage were labeled. Low birth weight infant with birthweight <2500gm regardless of gestational age was also noted. Maternal mortality, intrauterine death and still birth if baby delivered without signs of life, detected as dead after 24 completed weeks of gestation were also noted, if occur. All the data were gathered in proforma.

Data were statistically analyzed by using Statistical Package for Social Sciences v. 21. Relative risk was calculated to measure the association of hepatitis E virus infection in pregnancy with adverse pregnancy outcomes. Risk ratio >1 was taken as significant.

## RESULTS

In this study total 100 females were enrolled and divided in two equal groups. The mean age of females in exposed group was  $30.03 \pm 6.73$  years, while of unexposed group was  $28.60 \pm 5.70$  years. The mean gestational age at enrollment was  $24.44 \pm 7.90$  weeks in exposed group, and  $22.24 \pm 7.61$  weeks in unexposed group. The mean BMI of females was  $24.86 \pm 5.58$  kg/m<sup>2</sup> in exposed group and  $23.90 \pm 6.34$  kg/m<sup>2</sup> in unexposed group. In exposed group, there were 33 (66%) females of parity 1-2 while 17 (34%) females had parity 3-4. In unexposed group, there were 34 (68%) females of parity 1-2 while 16 (32%) females had parity 3-4. The mean serum bilirubin level of females was  $8.89 \pm 2.19$  mIU in exposed group and  $2.56 \pm 1.31$  mIU in unexposed group. There was significant

difference in both groups for mean serum bilirubin level. Table I

In exposed females, risk of antepartum hemorrhage was RR: 1.658 (24% vs. 8%, 95% CI: 1.148-2.395) in exposed females as compared to unexposed females. In exposed females, risk of miscarriage was RR: 2.020 (2% vs. 0%, 95% CI: 1.656-2.465) in exposed females as compared to unexposed females. In exposed females, risk of premature rupture of membranes was RR: 1.733 (22% vs. 6.0%, 95% CI: 1.210-2.480) in exposed females as compared to unexposed females. In exposed females, risk of intrauterine death was RR: 1.827 (30% vs. 8.0%, 95% CI: 1.299-2.569) in exposed females as compared to unexposed females. In exposed females, risk of preterm birth was RR: 2.180 (54% vs. 16%, 95% CI: 1.499-3.171) in exposed females as compared to unexposed females. In exposed females, risk of still birth was RR: 2.204 (28% vs. 2%, 95% CI: 1.661-2.923) in exposed females as compared to unexposed females. In exposed females, risk of low birth weight was RR: 1.556 (56% vs. 34%, 95% CI: 1.047-2.311) in exposed females as compared to unexposed females. In exposed females, risk of postpartum hemorrhage was RR: 1.899 (28% vs. 6%, 95% CI: 1.365-2.641) in exposed females as compared to unexposed females. In exposed females, risk of maternal mortality was RR: 2.220 (18% vs. 0%, 95% CI: 1.769-2.785) in exposed females as compared to unexposed females. Table II

**Table I: Demographic details of females enrolled in the study (n=**

|                             | Exposed          | Unexposed         |
|-----------------------------|------------------|-------------------|
| n                           | 50               | 50                |
| Age (in years)              | $30.03 \pm 6.73$ | $28.60 \pm 5.70$  |
| Gestational age (in weeks)  | $24.44 \pm 7.90$ | $22.24 \pm 7.61$  |
| BMI (kg/m <sup>2</sup> )    | $24.86 \pm 5.58$ | $23.90 \pm 6.34$  |
| Parity                      |                  |                   |
| 1-2                         | 33 (66%)         | 34 (68%)          |
| 3-4                         | 17 (34%)         | 16 (32%)          |
| Serum bilirubin level (mIU) | $8.89 \pm 2.19$  | $2.56 \pm 1.31^*$ |

\* = highly significant (p-value < 0.05)

Table II: Comparison of fetomaternal outcomes in both groups

|                                | Group   |           | Total | RR          | Significance |
|--------------------------------|---------|-----------|-------|-------------|--------------|
|                                | Exposed | Unexposed |       | 95% CI      |              |
| Antepartum hemorrhage          | 12      | 4         | 16    | 1.658       | 0.029        |
|                                | 24.0%   | 8.0%      | 16.0% | 1.148-2.395 |              |
| Miscarriage                    | 1       | 0         | 1     | 2.020       | 0.315        |
|                                | 2%      | 0%        | 1%    | 1.656-2.465 |              |
| Premature rupture of membranes | 11      | 3         | 14    | 1.733       | 0.021        |
|                                | 22.0%   | 6.0%      | 14.0% | 1.210-2.480 |              |
| Intrauterine death             | 15      | 4         | 19    | 1.827       | 0.005        |
|                                | 30.0%   | 8.0%      | 19.0% | 1.299-2.569 |              |
| Preterm birth                  | 27      | 8         | 35    | 2.180       | <0.0001      |
|                                | 54.0%   | 16.0%     | 35.0% | 1.499-3.171 |              |
| Still birth                    | 14      | 1         | 15    | 2.204       | <0.0001      |
|                                | 28.0%   | 2.0%      | 15.0% | 1.661-2.923 |              |
| Low birth weight               | 28      | 17        | 45    | 1.556       | 0.027        |
|                                | 56.0%   | 34.0%     | 45.0% | 1.047-2.311 |              |
| Postpartum hemorrhage          | 14      | 3         | 17    | 1.899       | 0.003        |
|                                | 28.0%   | 6.0%      | 17.0% | 1.365-2.641 |              |
| Maternal mortality             | 9       | 0         | 9     | 2.220       | 0.002        |
|                                | 18.0%   | 0.0%      | 9.0%  | 1.769-2.785 |              |

## DISCUSSION

The primary cause of hepatitis development and death in underdeveloped nations is hepatitis E. It is a leading cause of death, particularly among pregnant women.<sup>3</sup> The single-stranded RNA of the hepatitis E virus is not enclosed. Within the genus Hepatitis E virus, it is the only virus.<sup>11, 12</sup> About thirty years ago, the virus was discovered. In these developing nations where access to clean water is restricted or nonexistent, it poses a grave risk to health, life, and productivity.<sup>13</sup> All around the globe, this pathogen is now an emerging infectious agent that mostly causes acute infections. In tropical and sub-tropical locations, it is also the primary source of sanitary problems and pandemic water-borne diseases.<sup>14</sup>

The overall incidence of antibody against hepatitis E virus is high in tropical region while low in sub-tropical regions, but extensive local differences were observed in case of both areas. "Hot spots" of the infection can exist for both strains types in specific areas or in specific people all over the world.<sup>15</sup> Hepatitis E virus infection in pregnancy, particularly during last trimester, is categorized by most severe form of infection, which occasionally can cause fatal hepatitis, rising the frequency of fetomaternal morbidity

and mortality.<sup>16, 17</sup> But, the growth of this virus during pregnancy is different than non-pregnant or other population with mild self-constraining infection described in other populations.<sup>18</sup>

In our study, we observed that the risk of antepartum hemorrhage was RR: 1.658 (24% vs. 8%, 95% CI: 1.148-2.395), miscarriage was RR: 2.020 (2% vs. 0%, 95% CI: 1.656-2.465), premature rupture of membranes was RR: 1.733 (22% vs. 6.0%, 95% CI: 1.210-2.480), intrauterine death was RR: 1.827 (30% vs. 8.0%, 95% CI: 1.299-2.569), preterm birth was RR: 2.180 (54% vs. 16%, 95% CI: 1.499-3.171), still birth was RR: 2.204 (28% vs. 2%, 95% CI: 1.661-2.923), low birth weight was RR: 1.556 (56% vs. 34%, 95% CI: 1.047-2.311), postpartum hemorrhage was RR: 1.899 (28% vs. 6%, 95% CI: 1.365-2.641) maternal mortality was RR: 2.220 (18% vs. 0%, 95% CI: 1.769-2.785) in exposed females as compared to unexposed females.

In a study done in Pakistan, antepartum hemorrhage was reported in 20% cases, postpartum hemorrhage in 30%, premature rupture of membranes in 20% cases, preterm delivery in 65% cases, and maternal mortality in 26.66% cases.<sup>19</sup>

It has been reported that hepatitis E virus infection is associated with adverse pregnancy

outcome. In a study in India, regarding maternal outcome comparing hepatitis E infected females and non-hepatitis E infected females, antepartum hemorrhage was reported in 23% vs. 6% cases, postpartum hemorrhage in 14% vs. 9% cases, premature rupture of membranes in 9% vs. 3% cases, maternal mortality in 41% vs. 1% cases, respectively, while fetal outcome were preterm delivery in 90% vs. 75% cases, still birth in 54% vs. 1%, intrauterine death in 58% vs. 31%, neonatal death in 17% vs. 15%.<sup>20</sup>

In a case study of 25 pregnant women with acute hepatitis E, Sultana and Humayun also found that only 1 (4%) of the pregnancies resulted in a second-trimester missed miscarriage. Of the twenty-one (84%) live infants born, eighteen (86%) were preterm. Three (14%) incidences of early neonatal fatalities and intrauterine deaths each contributed to the 26% perinatal mortality rate. Due to fulminant hepatic failure, there were five maternal fatalities (20%), four (80%) in the postpartum period, and one (20%) in the antepartum period. They came to the conclusion that fulminant hepatic failure in women and premature birth are the main causes of poor fetomaternal outcomes in cases of acute hepatitis E during pregnancy.<sup>21</sup>

Yadav et al. studied 50 pregnant women in India and discovered that pregnant women who had acute viral hepatitis from hepatitis E virus infection and jaundice had a significant death rate (52%), particularly in the third trimester and the postpartum period (82%). Coagulation failure (56%) and acute liver failure (27%) were the most frequent medical complications, with hepatic encephalopathy coming in second (17%). IUFD (24%), APH (8%), and postpartum haemorrhage (42%) were the most frequent obstetric complications. They found that pregnant women who had jaundice and acute viral hepatitis from an infection with the hepatitis E virus had poor obstetric and foetal outcomes and a high death rate, particularly during the third trimester and postpartum period.<sup>22</sup>

## CONCLUSION

Through this study, we observed that hepatitis E virus infection in pregnancy is associated with

adverse feto-maternal outcome. Thus, in future, we will now recommend to implement the screening of pregnant females for hepatitis E virus infection, especially the symptomatic females or jaundiced females and if found positive, we will plan strategies and preventive measures to control the pregnancy outcome and avoid adverse pregnancy outcomes. It will help to reduce the number of unwanted complications of pregnancy and improve the outcome.

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