**ORIGINAL ARTICLE**

# Maternal and Fetal Outcome - Pregnancies Affected by Hepatitis E Virus - A Case Series

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## ABSTRACT

**Aim:** To present our experience in managing hepatitis Ein pregnancy and to find association between maternal mortality and advanced gestational age.

**Methods:** A total of 10 cases of pregnant females were selected who reported with HEV Ig M positive in tertiary care hospital from Jan 2019 to June 2019. Detailed history and examination were taken and course of disease followed in all ten cases with maternal and foetal outcome.

**Results:** Mean age of patients at presentation was 25.9 years. Mean gestational age at time of presentation was 30 weeks. Yellow discoloration of sclera was the presenting complaint in 90%of the patients. Five out of ten patients needed ICU admissions and among them 3 needed mechanical ventilation. Maternal mortality was 3 out of total ten patients. All of the patients who expired were in their third trimester. Two patients had intra uterine foetal deaths at time of presentation and there were four early neonatal deaths due to prematurity.

**Conclusion:** The study showed that pregnant females affected by hepatitis E virus in their third trimester had increased risk of maternal mortality. There is also increased risk of pre term delivery in patients with hepatitis E virus infection.

**Keywords:** Maternal mortality, Foetal outcome, pre term labour, Hepatic failure

## INTRODUCTION

Hepatitis E virus is a single stranded RNA virus. It has four genotypes.Genotype 1 and 2 affects human beings and 3&4 infects humans and animals both. It is transmitted by feco oral route Hepatitis E virus infection is of greater concern in pregnancy as it increases the maternal mortality rates because of its fulminant nature.[1-3]There are estimated 20 million cases with 3.3 million symptomatic cases and accounting for mortality rate of 3.3% due to viral hepatitis.[4]

There was an epidemic of Hepatitis E virus infection in Lahore Punjab Pakistan in year 2019. A large number of pregnant females affected by Hepatitis E virus reported in hospitals. Hepatitis E virus infection in Pregnant females resulting in maternal mortalities and foetal deaths because of fulminant nature of disease in pregnancy[1,5]. It also increases maternal and foetal morbidities i.e., ICU admissions, Ventilatory support.

The exact cause of different course of disease in pregnancy is still unclear. An interplay of immunologic, hormonal factors play their role[6-7] Pregnant females with hepatitis E virus infection in their third trimesters has increased mortality rates because of fulminant hepatic failure[1].

The aim of the study is to detect effects of HEV infection in pregnant women i.e., both maternal and foetal outcomes involving hospital stays, ICU admission pregnancy loss, still births, pre term delivery, and development of fulminant hepatic failure and DIC, maternal &neonatal deaths. The objective of present series is to present our experience regarding course of hepatitis E virus infection in pregnancy and correlation of maternal and foetal outcome with gestational age at time of onset of hepatitis E virus infection.

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## MATERIALS AND METHODS

This study was conducted in Department of Gynaecology and Obstetrics Shalamar Hospital (tertiary care hospital) Lahore for a duration of 6 months from January, 2019 to June, 2019. It is a descriptive study. Study population was all pregnant females reporting with hepatitis E infection with a positive HEV Ig M. Other causes of liver diseases in pregnancy excluded. Ten cases were selected randomly.

Proforma was designed which included detailed history, examination, investigations, course of disease, need of ICU admissions for mother and new born. Data collection was done by on duty medical officers, house officers. Detailed history which included age, gravidity, parity, gestational amenorrhea, last menstrual period, presenting complaints were taken examination of patients done. All the investigations including liver function tests, coagulation profile, complete blood count, abdominal ultrasound, obstetric ultrasound of patients was reviewed. Treatment given to the patient during hospital stay, need of FFP and whole blood transfusions, need of ICU admissions for both mother and new born, ventilatory support for both, mode of delivery, gestational age at delivery, intra and post-partum complications, maternal or neonatal mortality were studied.Patients were followed till complete recovery/expiry or delivery of foetus.

## CASE PRESENTATION

**Case 1:** This is a case of 28 years old female primigravida with gestational age of 31+1week admitted with complaint of fever 3 days.It was associated with yellow discoloration of sclera.Her blood pressure was raised and she was having proteinuria and oedema.Her LFT's and coagulation profile was deranged. She was HEV IgM positive. Obstetric ultrasound showed intrauterine death while abdominal

ultrasound was normal. On her first admission day she suddenly became short of breath and then shifted to ICU. Patient shifted on ventilator and 15 FFPS AND 4 whole blood transfusions done. Emergency caesarean section performed for delivery of dead foetus. Despite delivery of dead foetus her condition worsened and she developed DIC along with fulminant hepatic failure and expired .Her hospital stay was of 2 days.

**Case 2:**This is a case of 26 years old female patient G2P1A0 at 36+6weeks admitted with complaint of yellow discoloration of sclera and labour pains. She was vitally stable with jaundice present. Her LFT's were deranged. Emergency caesarean section performed due to foetal distress.Alive female baby of 2.5kg delivered and shifted to mother.Patient was discharged on second post operative day.She was readmitted on her 7$^{th}$post operative day with wound discharge and massive wound hematoma.Her LFT'S were still deranged.Wound curettage done and dressing with antiseptic done.Patient discharged and wound healed by secondary intention.

**Case 3:**This is a case of 23 years old female G3P2A0 at 25+4 weeks presented with complaint of yellow discoloration of sclera for 6 days.It was associated with loss of appetite. On examination she was vitally stable with jaundice present.Her LFT'S and coagulation profile was not within normal range. She was HEV IgM positive. Obstetric Ultrasound was normal but abdominal ultrasound shows liver parenchymal changes of acute hepatitis.During her hospital stay 15 FFP and 3 whole blood transfusion were given to patient.She went into labour at 26+6 weeks and delivered a 0.7 kg male baby that remained on ventilator in NNU and expired after 2 days. Maternal condition improved post delivery and she was discharged after a hospital stay of 18days.

**Case 4:**This is a case of 34 years old female G3P2A0 at 35+4 weeks of gestation presented with yellow discoloration of sclera for 4 days.It was associated with fever and vomiting.She was vitally stable and GCS was 15/15,jaundice was present. Her LFT's and coagulation profile was markedly deranged.She was seropositive for HEV IgM. Obstetric ultrasound showed alive foetus. Abdominal ultrasound was normal. Her condition deteriorated rapidly and GCS dropped to 7/15 and she went into hepatic encephalopathy Grade2.She was shifted to ICU and 15 FFP and 3 whole blood transfused. Mechanical ventilation started and decision was made to terminate pregnancy.Emergency caesarean section performed and alive female baby of 2.4kg delivered shifted to NNU and expired after 3days.Patient remain admitted in ICU for 5 days and expired due to fulminant hepatic failure.She remain admitted in hospital for 7 days.

**Case 5:** A 28 years old female primigravida at 26+3 weeks presented with yellow discoloration of sclera for 7 days. It was associated with vomiting and loose motions. On examination she was vitally stable with jaundice. She was sero positive for HEV IgM. Her LFT's and coagulation profile was deranged.Obstetric ultrasound was normal but abdominal ultrasound showed changes of acute hepatitis in liver. She remain admitted in ICU and 2 FFPs and 1 whole blood transfused. Pre term labour started and she had given birth to 0.7 kg male baby vaginally. Neonate remain admitted in NNU on ventilator for 3 days and then expired. She was discharged after 8 days of hospitalisation.

**Case 6:** A 20 years old female G2P1A0 at 31+2weeks admitted with complaint of yellow discoloration of sclera for 5 days.On examination she was febrile with tachycardia.Jaundice and pallor were present. Liver function tests and coagulation profile was deranged. Her HEV IgM was positive. Obstetric ultrasound was normal while abdominal ultrasound showed increased parenchymal echogenicity of liver.9 FFP and 2 whole blood transfusions were given.Because of her worsening labs decision was made to terminate pregnancy. Emergency caesarean section done at 32+2 weeks and alive male baby of 1.9kg baby delivered.Baby was shifted to NNU and was on ventilator but recovered and shifted back to mother after 1 week.Total hospital stay was of 9 days.

**Case 7:** A case of 18years old primigravida at 12+5weeks admitted with complaint of yellow discoloration of sclera for 1 week.She was vitally stable with jaundice present on examination. She was HEV IgM positive. Her LFT's were deranged but coagulation profile was normal.Her abdominal ultrasound showed liver parenchymal changes.Supportive treatment was given and patient's condition improved. Her hospital stay was for 8 days. She was followed till term and had given birth vaginally to alive female baby of 2.4kg at term.

**Case 8:**This is a case of 25years old female G2P1A0 at 38+5weeks admitted with complaint of yellow discoloration of sclera for 7 days. She was vitally stable with only jaundice present.Her LFT's and coagulation profile was deranged.Her obstetric ultrasound and abdominal scan were normal.She was at term and decision was made to deliver her through elective caesarean section.Alive female baby of 3.1 kg delivered.Patient's condition also improved and she was discharge after5 days of hospital stay.

**Case 9:** This is a case of 27 years old G4P2A1 at 36+2weeks (IUD) admitted with complaint of yellow discoloration of sclera for a week.It was associated with nausea and vomiting. Her HEV Ig M was positive. Her LFT'S and coagulation profile were deranged.She was admitted in ICU with mechanical ventilation.26 FFP and 4 whole blood transfusions given.Her condition deteriorated and elective caesarean section performed to deliver an IUD foetus of 2.4kg.She died on her 8$^{th}$ admission day due to hepatic failure.

**Case 10:** This is a case of 30 years old female G4P3A0 at 26weeks with complaint of yellow discoloration of sclera for 7 days. It was associated with nausea and vomiting. On examination she was vitally stable with marked jaundice. Her LFT's and coagulation profile was markedly deranged and she was HEV IgM positive.3 fresh frozen plasma transfused. She went into pre term labour and had given birth to 0.8kg female baby expired at 5 min of life by SVE.Her hospital stay was of 3 days.Her LFT'S improved post-delivery.

## RESULTS

In our study all patients were HEV IgM positive. Mean age of the patient at time of presentation was 25.9 years. Three patients were primigravida while 7 were multigravida. 90% presented with presenting complaint of yellowing of sclera.

Mean gestation age at time of presentation was 30 weeks with 6 patients presented in their 3rd trimrester.3 patients had HEV infection in their second trimester while 1 patient had presented in 1st trimester (Table 1).

Haemoglobin was between 6.8g/dl to 14.9g/dl with a mean value of 10.32g/dl. Total bilirubin ranged from6.4mg/dl to 22.8mg/dl with a mean of 12.58mg/dl. ALT range was between 223IU/L to 3275IU/L with a mean of 1317.8IU/L.AST was between 378 IUL/L to5208IU/L with a mean of 2012.3IU/L.INR has a range of 1.0 to 5.0 with a mean of 2.24 (Table 2).

5 patients needed ICU admission. 3 of them needed mechanical ventilation. There were 3 maternal deaths and all of them were in their 3rd trimester. All 3 women had fulminant hepatic failure leading to encephalopathy and multi organ failure (Fig. 1).

Table 1: Distribution of Cases as per age

| Age in cases | Number of cases |
|---|---|
| Upto 20years | 2 |
| 21 to 30 | 7 |
| >30 years | 1 |

Table 2: Laboratory parameters

| Cases | Bilirubin (mg/dl) | Hemoglobin(g/dl) | ALT (IU/L) | AST (IU/L) | INR |
|---|---|---|---|---|---|
| Case 1 | 20 | 9.0 | 590 | 378 | 2.1 |
| Case2 | 11.3 | 11.3 | 1576 | 1821 | 1.2 |
| Case 3 | 22.8 | 8.5 | 1403 | 1311 | 5.0 |
| Case4 | 8.5 | 11.0 | 1206 | 1874 | 3.6 |
| Case 5 | 11.2 | 10.0 | 1638 | 3263 | 1.9 |
| Case6 | 6.4 | 9.7 | 664 | 1157 | 1.2 |
| Case7 | 12.4 | 11.2 | 427 | 925 | 1.0 |
| Case 8 | 15.8 | 14.9 | 2176 | 5208 | 1.3 |
| Case9 | 8.0 | 6.8 | 223 | 388 | 2.5 |
| Case10 | 9.4 | 10.8 | 3275 | 3798 | 2.6 |

Fig. 1: Maternal Outcome and Gestational Age

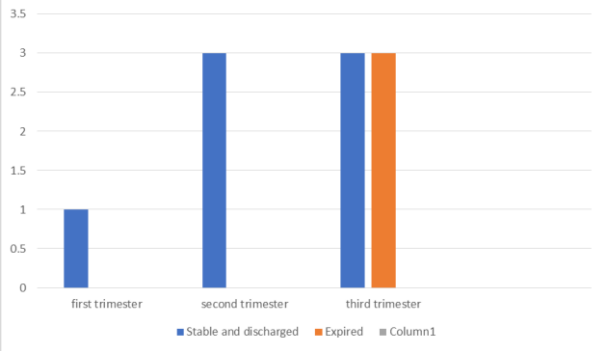


Fig. 2: Fetal Outcome

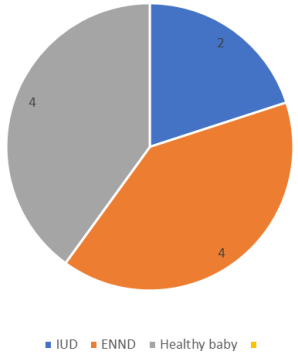


Table 3: Mode of delivery

| Gestational age | Number of patients | ICU Admissions | FFP Transfusions | Mode of Delivery |
|---|---|---|---|---|
| <13weeks | 1 | No | no | SVD |
| 13-28weeks | 3 | 2 | 3 | SVD |
| >28weeks | 6 | 3 | 4 | C section |

## DISCUSSSION

Hepatitis E in pregnancy causes a more severe infection and associated with increase mortality and morbidity.In our study 7 patients were multigravida and 3 were primigravida. Mean gestational age was 30weeks.Presenting complaint in almost all patients was yellow discoloration of sclera. Associated symptoms were nausea and vomiting.Only 1 out of 10 patient was febrile at time of presentation. Jaundice was clinically present in all 10 patients.

Liver function tests and coagulation profile was deranged in all patients. There was increase in total bilirubin with a marked increase in conjugated bilirubin. Alanine aminotransferase and aspartate aminotransferase levels were also high in all cases marking liver necrosis. Prothrombin time and activated partial thromoboplastintime was also raised with deranged International normalized ratio.

In our study ICU admission were 5out of total 10 patients. Three patients needed ventilatory support. The patients who were admitted in ICU has developed fulminant hepatic failure with markedly deranged liver function tests.Out of these 5 ICU admissions 3 were expired.Seven patients had Fresh frozen plasma transfusions to normalise the coagulopathy.Eight patients needed whole blood transfusion for correction of anemia. Six patients delivered withC section whereas 4 patients mode of delivery was vaginal.Maternal mortality was 3 patients out of total 10 patients.There were two received intrauterine deaths, four early neonatal deaths and four neonates were alive and healthy.Mean duration of hospital stay was 7 days.

In this study case fatality ratio was 30% while in a study conducted inIndiacase fatality ratio was 8%[3]. 60% patients delivered through c section while 40% delivered vaginally in our study while in other studies rate of vaginal deliveries were more in patients affected by hepatitis

E.Most common age group affected was between 21to 30 years in our study whereas in other study most patients were under 25 years[3]. Prematurity was the commonest obstetric complication in almost 40% of patients while in other study it was present in 80% of cases[10].

Fulminant hepatitis was seen in 30% of our patients while in other study conducted in Israel and other industrialized countries it was seen in 33%cases.[11]Mean gestational age in our study was 30weeks while in other study conducted in Lahore, Pakistan it was 32 weeks.[12] Two were intrauterine deaths in this case series and early neonatal deaths were 40% as compare to study conducted in Lahore,Pakistan in which early neonatal deaths were 14%.[12]In this study one patient had undergone hepatic encephalopathy and maternal mortality was more in patients who were affected in their 3rd trimester similar to study in India in which maternal mortality was seen in patients in their 3rd trimester.[5] In our case series 90% of patients presented with yellow discoloration of sclera as chief complaint whereas in other case series in Ghana 100% of patients presented with yellow discoloration sclera[13].

Average duration of hospital stay in our study was 7days whereas in a study in India Himachal Pradesh it was 10.46.[14]In the same study 30.76% of patients needs ICU admissions while in our study 40%required hospital admissions.[14] The cause of fulminant nature of hepatitis E infection in pregnancy is still unclear. An interplay of hormonal, immunologic and virologic factors play their role in adverse outcomes with hepatis E in pregnancy[6]. A study conducted in China shows that increased oestradiol in pregnancy affected by hepatitis Evirus promotes viral replication[15].

In pregnancy placenta can be the site of extrahepatic replication of Hepatitis E virus.[16]In this study we found a correlation in maternal mortality and advanced gestational age. More patients were reported in their third trimester with hepatitis E virus infection so may be there is increase susceptibility to Hepatitis Evirus infection in third trimester also seen in study in China[17]. There is increase viral load in third trimester because of extrahepatic viral replication in placenta in turn more severe disease in third trimester[18].

In this study we selected 10 cases randomly during a period of 6 months. Other causes of liver diseases were excluded and only patients with HEV IgM positive were included in this case series. All the patients were followed during whole course of disease and till delivery. Both maternal foetal outcomes were traced.There may be selection bias during our study, we randomly selected ten cases that reported in a duration of six months.

This case series sheds light on clinical presentation, course, management, obstetric complications and maternal and foetal outcomes in pregnancies affected by Hepatitis E virus. The exact cause of increase susceptibility and increase mortality due to Hepatitis E virus infection in third trimester of pregnancy needs to be further investigated.

## CONCLUSIONS

There is increase susceptibility of hepatitis E virus infection in pregnant females in their third trimester. The study showed that pregnant females affected by hepatitis E virus in their third trimester had increased risk of maternal mortality. There is also increased risk of pre term delivery in patients with hepatitis E virus infection.

**Recommendations:** The patients who presented in third trimester with hepatitis E virus infection should be delivered electively before commencement of acute hepatic failure and other complications.Because once hepatic failure ensues the maternal outcome does not improve despite termination of the pregnancy.

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**Ethical Approval:**Taken

**Consent:**The patients provided written informed consent for their information and images to be published.

## REFERENCES

1. Chaudhry SA, Verma N, Koren G. Hepatitis E infection during pregnancy. Canadian Family Physician. 2015 Jul 1;61(7):607-8.
2. Changede P, Chavan N, Raj N, Gupta P. An observational study to evaluate the maternal and Foetal outcomes in pregnancies complicated with jaundice. The Journal of Obstetrics and Gynecology of India. 2019 Feb 6;69(1):31-6.
3. Kashyap R, Joshi I, Gupta D, Prashar A, Minhas S. Characteristics and obstetric outcomes in pregnant women with Acute Hepatitis E Virus Infection in tertiary care hospital of Himachal Pradesh. J Assoc Physicians India. 2019 Apr;67(4):20-2.
4. Hepatitis E," 08 07 2019. [Online]. Available: https://www.who.int/en/news-room/fact-sheets/detail/hepatitis-e. [Accessed 12 january 2020].
5. Yadav S, Shirodker S, Kshirsagar S. Maternal and foetal outcome in pregnancy with hepatitis E virus infection. Int J ReprodContracept Obstetric Gynecol. 2016;5(10):3482-90.
6. Navaneethan U, Al Mohajer M, Shata MT. Hepatitis E and pregnancy: understanding the pathogenesis. Liver international. 2008 Oct;28(9):1190-9.
7. Jilani N, Das BC, Husain SA, Baweja UK, Chattopadhya D, Gupta RK, Sardana S, Kar P. Hepatitis E virus infection and fulminant hepatic failure during pregnancy. Journal of gastroenterology and hepatology. 2007 May;22(5):676-82.
8. Bergløv A, Hallager S, Weis N. Hepatitis E during pregnancy: Maternal and foetal case-fatality rates and adverse outcomes—A systematic review. Journal of Viral Hepatitis. 2019 Nov;26(11):1240.
9. Pérez-Gracia MT, Suay-García B, Mateos-Lindemann ML. Hepatitis E and pregnancy: current state. Reviews in medical virology. 2017 May;27(3):e1929.
10. Prasad GS, Prasad S, Bhupali A, Patil AN, Parashar K. A study of hepatitis E in pregnancy: Maternal and fetal outcome. The Journal of Obstetrics and Gynecology of India. 2016 Oct 1;66(1):18-23.
11. Lachish T, Erez O, Daudi N, Shouval D, Schwartz E. Acute hepatitis E virus in pregnant women in Israel and in other industrialized countries. Journal of Clinical Virology. 2015 Dec 1;73:20-4.
12. Sultana R, Humayun S. Fetomaternal outcome in acute hepatitis E. J Coll Physicians Surg Pak. 2014 Feb 1;24(2):127-30.
13. Bonney JH, Kwame-Aryee RA, Obed S, Tamatey AA, Barnor JS, Armah NB, Oppong SA, Osei-Kwesi M. Fatal hepatitis E viral infection in pregnant women in Ghana: a case series. BMC research notes. 2012 Dec;5(1):1-5.
14. Ranjan A, Thakur S, Mokta J, Bhawani R, Ranjan V. Clinical profile and outcome of pregnant patients with acute HEV hepatitis during water borne epidemic in Himachal Pradesh: A hospital based study. J Assoc Physicians India. 2017 Dec;65(12):44-8.
15. Yang C, Yu W, Bi Y, Long F, Li Y, Wei D, Hao X, Situ J, Zhao Y, Huang F. Increased oestradiol in hepatitis E virus-infected pregnant women promotes viral replication. Journal of viral hepatitis. 2018 Jun;25(6):742-51.
16. Knegendorf L, Drave SA, Thi VL, Debing Y, Brown RJ, Vondran FW, Resner K, Friesland M, Khera T, Engelmann M, Bremer B. Hepatitis E virus replication and interferon responses in human placental cells. Hepatology communications. 2018 Feb 1;2(2):173-87.
17. Huang F, Wang J, Yang C, Long F, Li Y, Li L, Jing S, Wang H. Chinese pregnant women in their third trimester are more susceptible to HEV infection. Brazilian Journal of Infectious Diseases. 2015 Dec;19(6):672-4.
18. Bose PD, Das BC, Hazam RK, Kumar A, Medhi S, Kar P. Evidence of extrahepatic replication of hepatitis E virus in human placenta. Journal of General Virology. 2014 Jun 1;95(6):1266-71.