Objectives: To determine the frequency of Hepatitis E virus in Fulminant Hepatic Failure and to gauge its associated mortality

Patients and Methods: This cross-sectional study included ninety-five patients who presented with Fulminant Hepatic Failure during pregnancy. Pregnant ladies, less than forty years of age, with gestational amenorrhea of more than three months duration were included. Besides a detailed medical history, all patients underwent a complete medical examination. Investigations performed included a Blood CP, urine routine examination, liver function tests, prothrombin time/INR, serum urea and creatinine, blood glucose levels along with an abdominal and pelvic ultrasound. Hepatitis viral serology was also sent and included IgM for Hepatitis E virus. Those who had co-morbid diseases like cardiac failure and chronic liver disease, or those developing pre-eclampsia and eclampsia were excluded from the study. All patients received antibiotics, mainly from Imipenem/Cilastatin group. Data was collected on a specifically designed proforma and entered into SPSS version 10 for analysis.

Results: Of the ninety-five cases of fulminant hepatic failure, fifty-six (58.9%) were found to be IgM positive for of Hepatitis E virus. The ages ranged from 20 to 38 years, with mean age of 28.12 years ± 4.92SD. Among the total 95 patients, 31.6% presented in the first week after developing FHF, 44.2% in second week and 24.2% in the third week of FHF or later. Fulminant hepatic failure occurred in most patients in {66(69.5%)} between 25 to 32 weeks of gestation. Maternal mortality was 30% in the HEV positive females.

Conclusion: Hepatitis E viral infection in the third trimester of pregnancy frequently leads to fulminant hepatic failure and is associated with poor maternal and fetal outcomes.

Key Words: Fulminant Hepatic Failure, Hepatitis E virus, Pregnancy, Third trimester

Introduction

Acute Liver Failure (ALF) is an uncommon but dramatic clinical syndrome, characterized by sudden and massive hepatic necrosis that results in jaundice, coagulopathy (INR>1.5) and hepatic encephalopathy (any degree of altered mentation) in the absence of pre-existing liver disease. It may be fulminant or sub-fulminant. Fulminant Hepatic Failure (FHF) is characterized by the development of hepatic encephalopathy within eight weeks after the onset of acute liver disease while in sub-fulminant hepatic failure, these findings appear between eight weeks and six months. Both carry a poor prognosis. Hepatitis E is a single stranded, non-enveloped RNA virus with an incubation period of 2 to 9 weeks. It spreads through faeco-oral route and is considered to be endemic in parts of Asia, Africa, the Middle East and Central America, where large outbreaks are associated with inadequate sanitation and water-borne infections. HEV Genotype 1 is hyper-endemic in Asia and Africa, where it causes outbreaks, sporadic acute hepatitis, acute hepatic failure and acute-on-chronic hepatic failure. Genotype 2, with similar epidemiological and sporadic features, has been reported from Mexico and Nigeria. Genotypes 3 and 4 are prevalent in the industrialized and developed nations. Whereas the reservoir for genotype 1 and 2 has been identified to be human, that of genotype 3 and 4 seems to be pigs, and therefore zoonotic transmission is more prevalent in these regions. Genotypes 3 and 4 have not been implicated in causing severe liver disease but more studies are required to further clarify this observation. A provisional diagnosis is based on a positive Hepatitis E IgM. Hepatitis E may cause catastrophe in females who are pregnant. Fulminant hepatic failure is the most serious outcome in pregnancy because of prolonged duration of HEV viremia. FHF in pregnant women caused by HEV is an explosive disease with a short pre-encephalopathy period, rapid development of cerebral edema and high occurrence of disseminated intravascular coagulation. Women with HEV associated acute hepatitis during pregnancy have poor
maternal and fetal outcomes. A study by Kumar et al in New Delhi found that in FHF during pregnancy, 81% cases were due to HEV. Another study carried out in Riyadh, Saudi Arabia reported 76 pregnant women developing FHF of which 69.2% were in the HEV group. In Pakistan, a study conducted by Hamid and Jafri found Hepatitis E to be the most frequent cause of acute hepatic failure in pregnant women, and associated with high morbidity and mortality. Jaiswal et al reported 57.5% cases of FHF in pregnancy due to HEV infection.

The purpose of this study was to seek independent confirmation of the frequency of HEV infection causing FHF in pregnancy in our region and to gauge the associated mortality, so as to take appropriate measures to counter it.

Patients and Methods
This cross-sectional study included 95 patients presenting with FHF during pregnancy in the public sector teaching hospitals in Punjab over one-year span. Pregnant ladies, less than forty years of age, with gestational amenorrhea of more than three months duration were included. Fulminant Hepatic Failure was defined as hepatic failure characterized by the development of hepatic encephalopathy, coagulopathy (INR>1.5) and jaundice within 8 weeks after onset of ALF. Besides a detailed medical history, all patients underwent a complete medical examination. Investigations performed included a Blood CP, urine routine exam, L.F.Ts, Prothrombin time/INR, serum urea and creatinine, blood glucose levels along with an abdominal and pelvic ultrasound. Hepatitis viral serology sent included IgM for Hepatitis E virus.

Patients with cardiac failure in NYHA (New York Heart Association Functional Classification) class 2 to 4 and those known to be suffering from chronic liver disease were excluded from the study. Moreover, those who developed pre-eclampsia (defined by blood pressure more than 140/90, proteinuria and edema feet) as well as ladies with eclampsia (defined by convulsions in addition to the above criteria) were excluded from the study. All patients received antibiotics, mainly from Imipenem/Cilastatin group. All data was collected on a specifically designed proforma and entered into SPSS version 10 for analysis. Qualitative data like age (in years), gestational weeks and duration of FHF was presented as mean and standard deviation and quantitative data like Hepatitis E as frequency and percentage. Confounding factors impact was controlled by data stratification with regards to age, gestational weeks and duration of FHF.

Results
Of the ninety-five females suffering from fulminant hepatic failure, fifty-six (58.9%) were found to be IgM HEV positive while 39(41.1%) were negative for HEV. The age ranged from 20 to 38 years, with 80% ladies falling between 20 to 34 years (Table 1). Mean age was 28.12 years ± 4.92 SD. Among the total 95 patients, 31.6% presented in the first week after developing FHF, 44.2% in second week and 24.2% in the third week of FHF or later (Table 2).

Fulminant hepatic failure occurred in most patients between 25 to 32 weeks of gestation, i.e. in 66(69.5%) patients while 37.9% were in gestational weeks 25 to 27, 31.6% in gestational weeks 28 to 32 and 26.3% in gestational weeks 33 to 37 (Table 3). Maternal mortality was 30% in the HEV positive females (as 17 out of 56 patients who were IgM for HEV positive did not survive).

<table>
<thead>
<tr>
<th>Age Range (in years)</th>
<th>Number of Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-24</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>25-29</td>
<td>38</td>
<td>40</td>
</tr>
<tr>
<td>30-34</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>35-38</td>
<td>19</td>
<td>19</td>
</tr>
</tbody>
</table>

Table 2: Duration of Fulminant Hepatic Failure at Presentation (n 95)

<table>
<thead>
<tr>
<th>Duration of disease</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>One week</td>
<td>30</td>
<td>31.6</td>
</tr>
<tr>
<td>Two weeks</td>
<td>42</td>
<td>44.2</td>
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<tr>
<td>three weeks or more</td>
<td>23</td>
<td>24.2</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Gestational weeks</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-27</td>
<td>36</td>
<td>37.9</td>
</tr>
<tr>
<td>28-32</td>
<td>30</td>
<td>31.6</td>
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<tr>
<td>33-37</td>
<td>25</td>
<td>26.3</td>
</tr>
<tr>
<td>38-42</td>
<td>4</td>
<td>4.2</td>
</tr>
</tbody>
</table>

Discussion
Pregnancy may be complicated by severe liver problems including hepatic failure. Some liver disorders are specific to pregnancy. The two most serious, acute fatty liver of pregnancy and HELLP syndrome (haemolysis, elevated liver enzymes, low platelets), are rare whereas obstetric cholestasis and liver dysfunction associated with pre-eclampsia, are common. Certain other hepato-biliary disorders are also important either because they are more likely to occur in pregnancy, for example, gall stones and hepatic vein thrombosis or because they run a more severe course than in the non-pregnant state, for example acute hepatitis E. Viral hepatitis is the most common cause of jaundice during pregnancy. When it does occur in this setting, it is no different from viral hepatitis in non-pregnant women, with the exception of pregnant women infected with Hepatitis E virus. This virus is one of the most common causes of fulminant hepatic failure in pregnant ladies. Its course in pregnancy is fulminant and the outcome often fatal. The virus causes fulminant hepatitis in about 20% of pregnant women. In fact, approximately 20% of ladies who acquire this virus during the third trimester of pregnancy die as a result. Hepatitis E also increases the risk of fetal complications and fetal death. Currently there is no antiviral medication for Hepatitis E, nor is any vaccine available to
Due to HEV7, which also corresponds to our study. Fulminant hepatic failure occurring during pregnancy are<br>to be 27%6. In our setting, Yasmeen and associates stated it to be 52%.17 Maternal mortality due to HEV was 30% in our<br>study, 61% females were between gestational weeks 20 to 34 years of age. Our observation corresponds to that of Shrestha et al from Nepal, who found 76% such patients to be in this age group.16<br>In our study, HEV was found in 56(59%) patients out of 95 suffering from fulminant hepatic failure during pregnancy. This corresponds to a study conducted by Jaiswal et al in India, where they found it to be 57.5%.9 Another study conducted at Dhaka by Al-Mahtab et al found it to be 56.52%.15 Khuroo et al proved that 61.8% cases of fulminant hepatic failure occurring during pregnancy are due to HEV7, which also corresponds to our study. However, Kumar A et al, in their series found that 81% cases of fulminant hepatic failure were due to HEV.6 This difference is probably due to the fact that they included all patients suffering from jaundice in pregnancy and did not exclude patients suffering from comorbid diseases. In addition, their sample size was smaller than ours. Eighty percent of our patients were 20 to 34 years of age. Our observation corresponds to that of Shrestha et al from Nepal, who found 76% such patients to be in this age group.16<br>In our study, 61% females were between gestational weeks 29 to 42. In India, Yuel et al also showed similar results of 52%.17 Maternal mortality due to HEV was 30% in our study. This figure is close to many previously done studies. Shrestha et al found it to be 27.5%.6 Kumar et al estimated it to be 27%.6 In our setting, Yasmeen and associates stated it to be 29.3%.18 However, the study conducted by Al Mahtab found maternal mortality to be 80%.15 Possible reasons for this could be one of the following:<br>We did not include all those patients in our study who were suffering from either chronic liver disease or other comorbid diseases like heart failure. Majority of females in our population group were less than 35 years. With advancing age, the mortality rises. Early administration of broad spectrum antibiotics has been shown to reduce mortality in patients of fulminant hepatic failure.19 We used antibiotics, mainly of Imipenem/Cilastatin group in all our patients, which could have also prevented mortality from rising further. However, this conclusion cannot be drawn from our study since no parallel group of such patients existed which was denied antibiotics, for comparison. Another possible reason for high mortality in study done by Al Mahtab may have been due to concomitant Hepatitis B Virus.15<br>Thus HEV associated diseases can no longer be brushed under the carpet as a problem of the developing world, where sanitation is inadequate. Due to its global presence, an effective vaccine with long lasting immunity is urgently needed for protection everywhere. This requires the attention of public health experts, academia and the health authorities throughout the world in order to reduce the morbidity and mortality caused by it.<br><br>Conclusion

Hepatitis E viral infection in the third trimester of pregnancy frequently leads to fulminant hepatic failure and is associated with poor maternal and fetal outcomes. Special attention also needs to be directed at prevention besides cure, through better public health facilities and educating the general population, particularly ladies with pregnancy. Investigation based diagnosis is mandatory. The first and foremost should be IgM anti HEV.

References
1. Lee WM. Acute Liver Failure. Semin Respir Crit Care Med 2012; 33; 36-45