A Prospective Study on Acute Viral Hepatitis in Pregnancy; Seroprevalence, and Fetomaternal Outcome of 100 cases

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ABSTRACT

OBJECTIVE: To determine the seroprevalence, risk factors and coinfection of hepatitis A, B, C, D and E among pregnant women with acute viral hepatitis and its influence on the mother and fetus.

METHOD: Hundred pregnant women with clinical and biochemical evidence of hepatitis admitted in SSKH hospital in their second or third trimester were studied prospectively from December 2006-January 2008. The etiology, clinical course and fetomaternal outcome were observed. The sera were tested for IgM Anti HAV, HBsAg, IgM Anti HCV, IgM Anti HEV markers and those that were positive for HBsAg were further tested for the IgM Anti HDV. All analyses were performed using commercial kits based on ELISA methodology.

RESULTS: Hundred pregnant women (mean age 23.85±2.5 yrs) with clinical and biochemical evidence of hepatitis were included. Majority (75%) were in third trimester with a median gestational age of 29.38±3.9 weeks. Primigravidae (41%) constituted the largest group of pregnant population with hepatitis. The total infective pathology due to acute viral hepatitis was 57%, with Hepatitis B (HBV) being the major cause of infection i.e. 37%, followed by Hepatitis E (HEV) in 18%, Hepatitis C (HCV) in 4%. However, none of the mothers were infected with Hepatitis A (HAV). Six patients were coinfected with dual hepatitis virus infection. Four out of 37 (10.8%) HBsAg positive mothers were coinfected with HDV and 2 out of 37 (5.4%) HBsAg positive mothers were coinfected with HCV. All the patients (100%) presented with complaints of yellowish discoloration of sclera and urine. Loss of appetite was described by 62% and fever by 43% of patients. 6 percent of them had hepatic encephalopathy with abnormal sensorium and died. Out of 100 mothers with hepatitis, 94 recovered completely. Among them 29.7% underwent caesarean section, 17% had preterm delivery and 6% had an intra uterine death. Among the neonates of the ninety-four mothers who recovered, 5.3% had a neonatal death and 30.8% had low birth weight.

CONCLUSION: Viral Hepatitis is the commonest cause (57%) of jaundice in pregnant women with clinical evidence of hepatitis. In the study group, 37 out of 57 (64.9%) infective hepatitis cases were due to HBV. Since HBV was the most common cause of hepatitis in pregnant women, and is preventable by vaccine, it is recommended that women in the reproductive age group (before the first pregnancy) should receive full course of hepatitis B vaccine. HEV was associated with a high mortality rate among pregnant women. Public awareness, complete immunization against viral hepatitis, better sanitation facilities, safe drinking water, increased availability of antenatal care for early detection and well equipped hospitals for intensive care will go long way in the reduction of viral hepatitis in pregnancy and also its associated maternal and perinatal mortality and morbidity.

1. INTRODUCTION

Hepatitis is among the most important causes of loss of healthy life years in women. Hepatitis is one of the important causes of hepatocellular malignancy and acute and fulminant hepatitis in developing country. Among pregnant women, these illnesses can lead to coagulation defects, postpartum haemorrhage, organ failure and high maternal mortality and poor outcomes of their newborns such as still births, neonatal deaths (NND), acute and chronic liver disease and hepatocellular carcinoma. For all these reasons, the early intervention
and prevention of these illnesses is a priority today and therefore, included in universal screening programmes in antenatal visits and part of reproductive health programmes.

Pregnancy with jaundice is considered as a high risk pregnancy. Viral hepatitis is the most common cause of jaundice in pregnant women. Incidence of hepatitis varies greatly around the world. In developed countries, the incidence is around 0.1% whereas in developing countries it can range from 3-20% or higher. There is no difference in the course of the disease in pregnant and non-pregnant women in developed countries. However, in developing countries, there is a higher incidence of maternal mortality with fulminant hepatitis.1,2

HEV and HBV infections were most frequent cause of fulminant hepatic failure in pregnancy.3,4,5 As far as developing countries like India is concerned, Hepatitis E is the most common cause of fulminant hepatic failure. Fulminant hepatitis was seen in high percentage in third trimester pregnant women with high maternal mortality ranging from 15%-45%.6,7

The various maternal complications associated with viral hepatitis are preterm labour, obstetric haemorrhage, fulminant hepatitis, hepatic encephalopathy, renal failure, DIC and death. The various foetal complications are intrauterine death, prematurity and risk of vertically transmitting the hepatitis infection.8,9

The prevalence and etiology of viral hepatitis still remains debatable in developing and developed countries. The exact prevalence of acute viral hepatitis and fulminant hepatic failure due to HEV in pregnancy is still a matter of conflict. There is little information about the magnitude of HDV in pregnancy.

2. METHOD & METHODOLOGY:

Hundreds of pregnant women with clinical and biochemical evidence of hepatitis admitted in SSKH hospital in their second or third trimester were studied prospectively from December 2006-January 2008.

Criteria for inclusion: Recent onset of jaundice in the absence of any chronic liver disease or past history of jaundice and Serum bilirubin > 2.5 mg/dl with an increase in serum transaminases more than two times the normal. Criteria for exclusion-HELLP syndrome (Haemolysis, elevated liver enzymes, low platelet count), acute fatty liver of hepatitis and Intrahepatic cholestasis.

Study of socio-demographic profile and medical history, obstetric details and risk factors for hepatitis was assessed through a questionnaire. The etiology, clinical course and fetomaternal outcome were observed. The sera were tested for IgM Anti HAV, HBsAg, IgM Anti HCV, IgM Anti HEV markers and those that were positive for HBsAg were further tested for the IgM Anti HDV. All analyses were performed using commercial kits based on ELISA methodology. The data were statistically analyzed.

3. RESULTS:

Hundred pregnant women (mean age 23.85±2.5 yrs) with clinical and biochemical evidence of hepatitis were included. Majority (75%) were in third trimester with a median gestational age of 29.38±3.9 weeks. Primigravidae (41%) constituted the largest group of pregnant population with hepatitis. The total infective pathology due to acute viral hepatitis was 57%, with Hepatitis B (HBV) being the major cause of infection i.e. 37%, followed by Hepatitis E (HEV) in 18%, Hepatitis C (HCV) in 4%. However, none of the mothers were infected with Hepatitis A (HAV). Six patients were co
# TABLE 1.
**PREVALENCE OF VIRAL HEPATITIS IN PREGNANT WOMEN WITH ACUTE VIRAL HEPATITIS**

<table>
<thead>
<tr>
<th>Hepatitis</th>
<th>Our Study Group N=100</th>
<th>Indian Study</th>
<th>International Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAV</td>
<td>0%</td>
<td>Nayak et al*(Delhi 1989)*</td>
<td>Extremely uncommon.*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Singh, S et al*(Delhi 2003)*</td>
<td>0%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patra S et al*(Delhi 2005)*</td>
<td>0.5%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Beniwal et al*(Delhi 2003)*</td>
<td>5.2%*</td>
</tr>
<tr>
<td>HBV</td>
<td>37%</td>
<td>Nayak et al*(Delhi 1989)*</td>
<td>17%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Singh, S et al*(Delhi 2003)*</td>
<td>17%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patra S et al*(Delhi 2005)*</td>
<td>33%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Jaiswal et al*(M.P./Indore 2001)*</td>
<td>19%*</td>
</tr>
<tr>
<td>HCV</td>
<td>4%</td>
<td>Beniwal et al*(Delhi 2003)*</td>
<td>10%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Singh, S et al*(Delhi 2003)*</td>
<td>10%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patra S et al*(Delhi 2005)*</td>
<td>10%*</td>
</tr>
<tr>
<td>HEV</td>
<td>18%</td>
<td>Beniwal et al*(Delhi 2003)*</td>
<td>47.4%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kumar A et al*(Delhi 2004)*</td>
<td>45.2%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Singh, S et al*(Delhi 2005)*</td>
<td>37.0%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Jaiswal et al*(M.P./Indore 2001)*</td>
<td>57.5%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patra S et al*(Delhi 2005)*</td>
<td>60%*</td>
</tr>
<tr>
<td>Co-infection</td>
<td>HBV+HDV 10.8%</td>
<td>Ashok et al(Delhi 2007)*97</td>
<td>HBV + HCV = 4.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HBV + HDV = 0%*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Beniwal et al*(Delhi 2003)*</td>
<td>HBV + HDV = 1.03%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HBV + HEV = 4.1%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HAV + HEV = 3.1%</td>
<td></td>
</tr>
</tbody>
</table>

infected with dual hepatitis virus infection. Four out of 37 (10.8%) HBsAg positive mothers were co infected with HDV and 2 out of 37 (5.4%) HBsAg positive mothers were co infected with HCV. All the patients (100%) presented with complaints of yellowish discoloration of sclera and urine. Loss of appetite was described by 62% and fever by 43% of patients. 6 percent of them had hepatic encephalopathy with abnormal sensorium and died. Out of 100 mothers with hepatitis, 94 recovered completely. Among them 29.7% underwent caesarean section, 17% had preterm delivery and 6% had an intra uterine death. Among the neonates of the ninety-four mothers who recovered, 5.3% had a neonatal death and 30.8% had low birth weight.

### 4. DISCUSSION:
Hepatitis in pregnant women may be consequent to infection with hepatitis viruses A, B, C, D and E. Hepatitis E is the most common infecting accounting for 50-70 % of all patients with sporadic viral hepatitis. Studies from the developed countries conclude that pregnant state perse has no adverse effect on the course of hepatitis, provided nutrition is adequate. However increase in fetomaternal mortality has been reported mainly from the developing countries.

The age of women included in the study was in the range of 19-35 years. The mean age of the patients in the study group was 23.85±2.5yrs. Similar study was conducted in our hospital by Patra et al in the year 2003-2005 on 220 pregnant women presenting with jaundice caused by acute viral hepatitis had found mean age to be 24.3±3.3 yrs. The mean age of the patients in our study is comparable to another Indian study conducted by Kumar et al who studied prevalence of HEV and its complication in 62 pregnant women with
acute viral hepatitis in their third trimester admitted in Delhi tertiary hospital in the year 2003 was seen to be 24.13±3.6 yrs. It is consistent with other international studies conducted by Miranda et al\textsuperscript{17} (23.8±6 yrs) who studied seroprevalence of HBV and HIV and associated risk behaviors among 1608 attending antenatal attendees of Vitoria, Brazil in the year 1999 and by Surya et al\textsuperscript{14} (27±5yrs) who screened 2,450 pregnant mothers in the year 2003 at Bali, Indonesia for seroprevalence of HBV, HCV, HEV and HIV infections.

In our study it was seen that approximately 70% of pregnant populations were literate with majority of them having education up to middle level and 30% of population was illiterate. Similar literacy status was observed by Ashok et al\textsuperscript{15} in 2006 after evaluating 8130 women attending antenatal clinics. They reported 76.4% pregnant women attending antenatal clinics and 73.8% women with hepatitis viral seromarker positive were literate.

Study conducted by Jose Luis et al\textsuperscript{16} in Mexico who studied seroprevalence of HBV infection and risk factors associated with HBsAg positive mothers. They included 9992 antenatal attendees, and reported 78% of pregnant women had more than elementary education. Study from Brazil by Miranda et al\textsuperscript{17} reported only 1.2% illiterate pregnant women in their population. Whereas study from Ethiopia by Awole\textsuperscript{18} et al reported 61% illiterate out of 493 antenatal attendees.

86% of the patients in our study belonged to low socio-economic class. Majority of the patients in the study by Kumar et al\textsuperscript{13} from Delhi on 62 pregnant women with clinical hepatitis belonged to low socio-economic class. Similar Study from Ethiopia by Awole\textsuperscript{18} et al reported 88.9% pregnant women had low income.

In our study, 75% of pregnant women were in third trimester of pregnancy. The mean gestational age was 29.38±3.9 weeks. Our findings are similar to the observations seen in other studies by Jaiswal et al\textsuperscript{19} (72%), Singh S et al\textsuperscript{20} (72%) and Patra et al\textsuperscript{12} (72%) who reported more than 70% of pregnant women with acute viral hepatitis presented in their third trimester. Primigravidae constituted the largest group of pregnant women (41%). The study by Veronica et al\textsuperscript{21} in the year 2006 conducted at Ludhiana tertiary hospital on 65 pregnant women with jaundice observed 48% population as primigravidae. Miranda et al\textsuperscript{17} observed 51.2% pregnant women to be primigravidae in a Brazilian hospital study. Our findings are not consistent with Mexican and African studies done by Jose Luis et al\textsuperscript{16} (11.6% primigravidae) and Elsheikh et al\textsuperscript{22} (17.5% primigravidae) respectively as maximum pregnant women presented during the second gravida.

Total infective pathology was detected in 57 out of 100 cases of clinical jaundice in our study. 37% of cases with clinical jaundice were infected with Hepatitis B. Prevalence of HBV infection in pregnant women with acute viral hepatitis reported is consistent with other Indian studies. An earlier study conducted in our hospital by Patra et al\textsuperscript{12} in the year 2003-2005 on 220 pregnant women presenting with jaundice caused by acute viral hepatitis had found 33% prevalence of HBV.

Other hepatitis viral markers positive in pregnant women with clinical jaundice were anti HEV and anti HCV antibodies. The prevalence of HEV antibody was found to be 18% in Four studies from New
Delhi reported prevalence of HEV as 37%, 45.2%, 47.4% and 60%. Jaiswal et al. in central India and Aziz et al. in Pakistan reported that HEV is responsible for 58% and 62% of cases of acute viral hepatitis in pregnant women, respectively. Strands et al. in Angola, Africa in 2003 reported 40% of prevalence of HEV in a case control study on 20 pregnant women with acute viral hepatitis and 40 antenatal attendees. Khuroo et al. in Saudi Arabia reported 49.6% prevalence after evaluating 76 pregnant women with hepatitis.

HCV was found to be 4% in cases of pregnant women with clinical evidence of hepatitis in our study. This is in accordance with the earlier studies of Patra et al. (5%) in the same institution. However, in the past studies from India have not implicated HCV prevalence in pregnant women with acute viral hepatitis. Beniwal et al. (n=97; 2003) and Singh et al. (n=50; 2003) both in tertiary care Delhi hospital found zero prevalence, probably the number of cases studied was too low. Study outside India conducted by Khuroo et al. from Saudi Arabia also reported low prevalence of HCV (1.7%).

None of the mothers were infected with Hepatitis A. Our observation is similar to the results on HAV prevalence studies done in Delhi by Singh et al. (0%) and Nayak et al. (extremely uncommon) whereas Patra et al. found a prevalence of only 0.5% after screening 220 pregnant women with hepatitis. The number of cases screened was large (220) perhaps explaining the detection of the single case as compared to other studies who have screened far less number of cases.

Low prevalence in pregnant women has been observed studies outside India by Khuroo et al. in Saudi Arabia (1.5%) and Aziz et al. in Pakistan (4%).

It was seen that six patients of the 100 pregnant women with clinical evidence of hepatitis were co infected with another hepatitis virus. Four out of 37 (10.8%) HBsAg positive mothers were co infected with Hepatitis D viruses and 2 out of 37 (5.4%) HBsAg positive mothers were co infected with HCV. Similar coinfection study on pregnant women in Delhi by Ashok et al. showed HBV and HCV coinfection to be 4.8%. Studies outside India in Saudi Arabia and Africa have reported HBV and HDV coinfection as 1.5% and as 15.6% (details are given in table 1).

All the patients presented with complaints of yellowish discoloration of sclera and urine. Loss of appetite was described by 62% of pregnant mothers in this group. Fever was the presenting symptoms in 43% of mothers. It was observed that 6% of patient had abnormal sensorium and went into hepatic encephalopathy and died. All six patients who died had Hepatitis E infection. Other presenting complaints were malaise in 34% of patients, and vomiting in 15% of patients. In a study on pregnant women with acute viral hepatitis by Kumar et al. it was found that fever was the most common presenting symptom (75%). Malaise and vomiting were also seen.

Maternal outcome:
Out of 100 mothers, 94 recovered completely. Among these 29.7% underwent caesarean section. Hepatitis virus seromarkers in mothers who underwent caesarean section were hepatitis B (42.8%), hepatitis E (17.8%), and hepatitis C (7.1%). The indication of caesarean section in the pregnant mothers with seropositive viral
markers was foetal distress. The majority pregnant mothers had vaginal delivery.

In our study 17(17%) of pregnant mothers had preterm deliveries. Preterm delivery is a common maternal complication of hepatitis in pregnancy and is observed in studies by Medhat et al\textsuperscript{23} (14.9%) after studying 48 pregnant women with acute viral hepatitis in the year 1993 in Egypt, and by Mirghani et al\textsuperscript{30} (20.8%) in a case control study on 50 pregnant women with acute viral hepatitis at a Sudan hospital in the year 1990. It is the important complication observed in Indian studies also by Veronica et al\textsuperscript{21} (56%) in the year 2006 conducted at Ludhiana tertiary hospital on 65 pregnant women with jaundice and by Kumar et al\textsuperscript{13} (66.6%) in the year 2003 conducted at Delhi on 62 pregnant women with acute viral hepatitis.

Six out of 100 pregnant women with clinical evidence of hepatitis developed hepatic encephalopathy and all were infected with hepatitis E virus. This is lower than reported by Khuroo et al\textsuperscript{20} who studied 76 pregnant women with hepatitis at Saudi Arabia in 2003 and found the incidence of hepatic encephalopathy to be 61.8%. All the six who developed hepatic encephalopathy due to HEV died. The maternal mortality rate in pregnant mothers infected with hepatitis E virus as reported by other studies ranges between 14-45\textsuperscript{%} \textsuperscript{30,4,23,19} and may be as high as 70\textsuperscript{%}.\textsuperscript{20} Thus, HEV was associated with a high mortality rate among pregnant women.

**Foetal Outcome**

Six out of 100 pregnant women with clinical evidence of hepatitis in the study group had intra uterine death. All of these mothers had Hepatitis E infection and underwent encephalopathy and died. The findings are consistent with studies by Mirghani et al\textsuperscript{30} (6.3%), Medhat et al\textsuperscript{9} (8.3%), and Kumar et al\textsuperscript{13} (3.8%). Out of ninety-four mothers who recovered from viral hepatitis, 5 (5.3%) had lost their neonates.

Medhat et al\textsuperscript{9} observed 6.3\% of neonatal deaths whereas Nagaria et al\textsuperscript{31} observed it to be 11.8\%. Low birth weight was found in 30.8\% of neonates. Low birth weight in infants born to mothers with acute viral hepatitis has been reported by Kumar et al\textsuperscript{13} (7.6\%) and Veronica et al\textsuperscript{21} (20\%).

**5. CONCLUSION:**

Viral Hepatitis was the commonest cause (57\%) of jaundice in pregnant women with clinical evidence of hepatitis. Majority of mothers (37\%) with clinical evidence of hepatitis were infected with HBV. The prevalence of HEV and HCV among mothers with clinical evidence of hepatitis was found to be 18\% and 4\% respectively. None of the pregnant women were infected with HAV.

Six patients in the study group were co infected with another hepatitis virus. Four out of 37 (10.8\%) HBsAg positive mothers were co infected with Hepatitis D viruses and 2 out of 37 (5.4\%) HBsAg positive mothers were co infected with HCV.

HEV was found to be associated with high maternal mortality as 6 out of 18 (33.3\%) HEV infected mothers died. Forty-two percent of pregnant women infected with viral hepatitis had poor foetal outcome. Among them, 6\% percent of mothers had intrauterine death and all of them were infected with HEV. Whereas 5.3\% and 30.8\% of pregnant women had neonatal death and low birth weight baby respectively. Sixty percent of mothers who had lost their neonates were infected with HBV and 41.3\% of mothers who had low birth weight baby had HEV infection.
Thus to conclude, public awareness and complete immunization against viral hepatitis, better sanitation facilities, safe drinking water and increased availability of antenatal care for early detection and well equipped hospitals for intensive care will go long way in the reduction of viral hepatitis in pregnancy and also its associated maternal and perinatal mortality and morbidity.

6. BIBLIOGRAPHY: