Research Article

Pregnancy Outcome in Acute Viral Hepatitis E

Rashida Sultana[1], Shamsa Humayun[2], Sofia Manzoor[3], Sara Humayun[4]

[1]Department of Obstetrics & Gynaecology, Sharif Medical & Dental College, Lahore; [2,3]Department of Obstetrics & Gynaecology, FJMU/ Sir Ganga Ram Hospital, Lahore; [4]Central Park Medical College, Lahore

Abstract

Objective: To evaluate maternal and fetal outcome among pregnant women who have positive serology for hepatitis E IgM.

Study Design: Descriptive

Place and duration of study: Department of Obstetrics & Gynaecology, Sir Ganga Ram Hospital over a period of seven years.

Methodology: Data of women with clinical presentation of jaundice during pregnancy and who were diagnosed as acute hepatitis E was collected on pre-structured questionnaire after their consent. It was entered in Statistical Package for Social Sciences for analysis.

Results: Three hundred and thirty three women had positive serology for hepatitis E IgM. Out of these three hundred were in last trimester of their pregnancy. The gestational age of two hundred and thirty two (77%) women was less than 37 weeks at presentation. Six (2%) pregnancies ended up in miscarriage, fifty four (16 %) had fetal demise in maternal womb while two hundred and seventy three (82%) were viable fetus. One third of live born babies were kept in NICU. Indications of neonatal admission were respiratory distress in 57(72%), jaundice neonatorum in 12(15%), asphyxia neonatorum in 9(12%), while one (1%) had transient tachypnea. Neonates who died in first week of their life were 18(23%).The cause of neonatal death was respiratory distress in 12 (67%) and anoxia in remaining 6 (33%) neonates. Most of the women were discharged home however maternal mortality was recorded in 80(24%) patients, mainly in postpartum period 73(91%).

Conclusion: Pregnant women with acute hepatitis E have more complicated course of this viral infection with adverse fetal and maternal implications.

Corresponding Author | Dr. Rashida Sultana, Associate Professor, Department of Obstetrics & Gynaecology, Sharif Medical & Dental College, Lahore **Email:** drrashidasultana@gmail.com

Key words: Acute hepatitis, feto-maternal, hepatitis E, morbidity, mortality, perinatal, pregnancy, viral hepatitis

Introduction:

Literature reveals that about 20 million cases infected with hepatitis E virus occur worldwide annually, of which 3.3 million are symptomatic leading to morbidity and mortality[1]. Infection is confirmed by detecting antibodies to Hepatitis E virus or Hepatitis E virus RNA. It is unique to hepatitis E that it has different characteristics in different regions in the world. There are 4 different serotypes. Sero type I is commonly found in developing countries and associated with disease outbreaks. It is transmitted by feco-oral route and risk of infection is more in developing countries especially in areas of poor sanitation. Other types of viral hepatitis can co-exist especially hepatitis A virus infection. Both are transmitted by RNA virus via feco-oral route but infection with later is mild[2]. Route of transmission in developed countries is mainly sporadic and zoonotic[3].

Severity of disease varies from asymptomatic to severe illness. It may present with jaundice, fever, nausea, vomiting, malaise, loss of appetite. It has long incubation period ranging from two weeks to two months. Virus continues to excrete in stool fifteen days after clinical presentation[1,2]. Although it is an acute self-limited

illness however it may result in fulminant hepatic failure especially in pregnancy leading to maternal mortality in up to 20% of cases[4,5]. It is due to altered immune status in pregnant women. More over viral factors also play a part[6]. Literature also reveals association of hepatitis E and altered progesterone level in pregnant women[7].

Hepatitis E is associated with very poor feto-maternal outcome. Major fetal complications are prematurity, low for gestation birth weight, in utero growth restriction, in utero feat demise and still birth all contributing to high fetal morbidity and mortality. Maternal complications are fulminant hepatic failure and multi-organ dysfunction[8]. Pregnant patients with acute hepatitis E usually require hospital admission and monitoring with liver functions test and clotting profile[9]. Treatment is symptomatic, supportive with fluid replacement and rest[10].

The objective of the study is to evaluate fetal and maternal outcome among pregnant women who have positive serology for acute hepatitis E. Viral hepatitis is prevalent in developing countries and acute infection with hepatitis E may take fulminant course in pregnancy. Extensive literature on viral hepatitis and hepatitis E in pregnancy is available but in local context little data is available on hepatitis E in pregnancy covering all its aspects in terms of patient demographics, its clinical manifestations in pregnancy, maternal and fetal outcome. The rational for this study is to bridge the knowledge gap and to assess the feto-maternal implications of disease in local context.

Methods:

This case series was carried out in OBGY unit of Sir Ganga Ram Hospital from April 2013 to March 2020 and was approved by Institutional Ethical Review Board; ERB No. 229. All pregnant patients who presented with jaundice in pregnancy either through outpatient department or emergency were enrolled using non probability purposive sampling technique. Their 2ml venous blood sample was taken for viral serology. Samples were sent to hospital laboratory for testing IgM and IgG for viral Hepatitis. Seropositive patients for hepatitis E IgM were included in the study after their consent. Women with jaundice due to non-viral causes like cholestasis of pregnancy, acute fatty liver of pregnancy, inflammation of bile ducts, gall stones, infiltrative disease, pre-eclampsia, haemolytic disease, hepatitis A, B or C and non-pregnant patients were excluded from the study.

All patients were admitted in hospital, and managed using multidisciplinary approach involving obstetrician, physician, haematologist, and neonatologist. During hospital stay, maternal management included supportive care, monitoring with liver function tests and clotting studies. For fetal surveillance obstetric ultrasound, cardiotochography and fetal kick-count charting were used. Mode of delivery was based on obstetric indications. All patients were followed till discharge from hospital or death whichever occurred first. Newborns were followed till first week of their life.

Data was collected after informed consent on a self-designed structured proforma. Maternal data included age of women, gravidity, gestational age, presenting symptoms, duration of symptoms, pregnancy outcome, and birth route, need of intensive care, mortality and cause of maternal death. Fetal data regarding fetal maturity, fetal outcome in terms of NICU admissions, early neonatal morbidity, and causes of early neonatal death, and perinatal mortality was collected.

Data was entered in SPSS 23 for analysis. Numerical data such as age, gravidity and gestational age, duration of symptoms were analyzed using descriptive statistics like mean and standard deviation. Qualitative variables were presenting symptoms, pregnancy outcome, mode of delivery, causes of early neonatal admission, cause of death of neonate and mother. Qualitative variables were calculated in percent and frequency. Chi square was applied as test of significance; p value ≤ 0.05 was considered statistically significant.

Results:

Three hundred and thirty three women had positive serology for hepatitis E IgM. Of these, 320 (96%) had only acute hepatitis E, 8(2.4%) had co-existent hepatitis A, 3(1%) had co-existent hepatitis C, 1(0.3%) had simultaneous hepatitis B and 1(0.3%) patient was positive for hepatitis A, B, C and E simultaneously.

Mean age of patients was 25 ± 4.2 years ranging from 18 to 39 years. Their mean parity was 2.3 ± 1.4 ranging from 1 to 7. Mean gestational age was 31.3 ± 4.9 weeks with a range from 8 to 40 weeks. Majority of 3rd trimester pati-

Table I: *Demographic and Obstetric Variables*

Variables		Number	%age
Age (Years)	< 20	053	16
	21-25	132	39.6
	26-30	121	36.3
	31-35	022	6.6
	>35	005	1.5
	Total	**333**	**100**
Parity	Primipara	120	36
	Multipara	184	55.3
	Grand multipara	029	8.7
	Total	**333**	**100**
Presenting complaints	Yellow discoloration, fever & GI symptoms	330	99.1
	Altered sensorium	003	0.9
	Total	**333**	**100**
Duration of symptoms (Days)	≤ 7	205	61.6
	8-14	078	23.4
	15-21	045	13.5
	22-30	005	005
	Total	**333**	**100**
Gestational age at presentation	1st Trimester	006	1.8
	2nd Trimester	027	8.1
	3rd Trimester	300	90.1
	Total	**333**	**100**
Pregnancy Outcome	Conservative	082	24.6
	E&C	006	1.8
	LSCS	062	18.7
	SVD	176	52.8
	Undelivered	007	2.1
	Total	**333**	**100**
Maternal outcome	Discharged	253	76
	Expired	80	24
	Total	**333**	**100**
Fetal maturity	Term	068	22.6
	Preterm Mild	126	42
		078	26
	Severe	028	9.4
	Total	**300**	**100**
Fetal Outcome	Missed miscarriage	006	1.8
	Alive	273	82
	IUD	054	16.2
	Total	**333**	**100**
NICU	RDS	57	72.2
Admission	Jaundice	12	15.2
	ANN	09	11.4
	TTN	01	01.2
	Total	**79**	**100**
Early	RDS	12	66.67
Neonatal	ANN	06	33.33
Death	**Total**	**18**	**100**

Appendix table I: GI: Gastrointestinal, E & C: Evacuation and Curettage, LSCS: Lower Segment Cesarean Section, SVD: Spontaneous Vaginal Delivery, IUD: Intra Uterine Death, RDS: Respiratory Distress Syndrome, ANN: Asphyxia Neonatorum, TTN: Transient Tachypnea of Newborn.

ents were preterm i.e. 232(77.4%) and only 68(22.6%) women attained maturity till term. Four (66.67%) of the 1st trimester patients were managed conservatively and 2(33.33%) ended up in evacuation and curettage due to missed miscarriage. Of 2nd trimester patients, 19(70.3%) were managed conservatively, 4(14.8%) had evacuation and curettage, 3(11.1%) had spontaneous vaginal expulsion, and 1(3.8%) was expired. Of 3rd trimester, 59(19.66%) women were managed conservatively, 62(20.67%) had abdominal delivery, 173(57.67%) had vaginal delivery and 6(2%) remained undelivered. Thirty eight (62%) caesarean sections were done due to scarred uterus, 14(22%) due to fetal distress, 4(6.4%) due to breech presentation and, remaining 6(9.6%) due to other indications. Of total 176 vaginally delivered patients, 144(82%) underwent spontaneous labour and 32(18%) were induced due to obstetric indication. The common indication for induction of labour was intrauterine death in 15(47%) patients followed by ruptured amniotic membranes in 8(25%), pre-eclampsia in 6(18.7%) and deterioration of maternal condition in 3(9.3%) patients.

Ninety three (28%) patients were shifted to ICU. Maximum mortalities were in the postpartum period i.e. 73(91%) while 7 (9%) during antepartum span. Of these antenatal expiries, one patient was in 2nd trimester and 6 were in early 3rd trimester i.e. <28 weeks. The cause of maternal mortality was fulminant hepatic failure with multi-organ involvement in all patients. Fetal outcome is detailed in table I. Perinatal mortality was 21.6.

Maternal abnormal laboratory parameters were significantly associated with maternal mortality as shown in table II. Mean number of blood transfusions in discharged versus expired patients were 2.3±1.2 versus 3.4±1.4, whereas mean number of transfused

Table II. *Laboratory parameters among recovered and expired mothers*

Investigations		Recovered		Expired		P value
		No.	%age	No.	%age	
Haemoglobin (gram/dl)	≤11	162	64%	67	83.8%	0.00
	>11	091	36%	13	16.2%	
Platelets (10^9/L)	≤150	020	7.9%	14	17.5%	0.02
	>150	233	92.1%	66	82.5%	
Serum Bilirubin (10mg/dl)	≤10	159	62.8%	20	25%	0.00
	>10	094	37.2%	60	75%	
ALT (U/L)	≤1000	211	83.4%	39	48.8%	0.00
	>1000	042	16.6%	41	51.2%	
AST (U/L)	≤1000	203	80.2%	44	55%	0.00
	>1000	050	19.8%	36	45%	
PT (seconds)	Normal	112	44.2%	04	5%	0.00
	Prolong	141	55.8%	76	95%	
aPTT (seconds)	Normal	055	21.7%	03	3.8%	0.00
	Prolong	198	78.3%	77	96.2%	

Appendix table II: ALT: Alanine Transaminase, AST: Aspartate aminotransferase, PT: Prothrombin Time, aPTT: Activated Partial Thromboplastin Time, U/L: Units per Liter

FFPs were 4.5±3.6 versus 8.7±3.1 respectively.

Discussion:

Hepatitis E infection causes acute self-limiting illness with low morbidity and mortality in general population, but may lead to severe illness and fulminant hepatic failure in pregnancy.[10] In present study, (320) 96% patients presented with acute hepatitis E, while 2.4% had co-existent hepatitis A, 1% had co-existent hepatitis C, 0.3% had hepatitis B and 0.3% had hepatitis A, B, C, and E simultaneously. The results of study done in North India showed that 6.95% cases of Hepatitis A, 30.5% cases of Hepatitis E, 20.8% cases of co-existent Hepatitis A and E,1.38% patients with HEV and HBV infection and 1.38% had positive serology for hepatitis A, B and E. Co-infection with HEV and HAV may be due to their common route of transmission. Variations in the results may be due to short duration of study, and has small study population as compare to our study[6].

Mean age of patients was 25±4.2 years in current study. Similar results were observed in other studies i.e. 22.2 years and 23.85 ± 2.9 years[5,6]. Mean gestational age was 31.3±4.9 weeks which is similar to the study by Gowri et al i.e. 32.6 ± 3.37 weeks[5]. Majority of patients (64%) in our study were multiparous. According to another study conducted in Pakistan, most of the patients 55 (83.7%) were multiparous however sample size was small in this study[11].

A comparative study conducted in Agha Khan Hospital Pakistan on pregnant patients with reactive Hepatitis E IgM versus non-reactive Hepatitis E IgM reveals that pregnant patients with reactive Hepatitis E IgM had higher percentage of adverse fetomaternal outcome as compare to the women with non-reactive IgM[12].

Majority of the patients (99.1%) presented with jaundice, gastrointestinal symptoms and fever. The initial presentation in a study in a developed country is of non-specific symptoms like malaise, myalgia and vomiting followed by jaundice[13]. This difference of presentation may be due to late attendance of pregnant women for care in current study. Moreover they have studied the general population including pregnant ladies while we enrolled only pregnant patients.

Ninety percent of patients presented in 3rd trimester of pregnancy. Similarly literature revealed that 92-96% patients reported in last trimester of pregnancy.[5] According to a study conducted in China hepatitis E affected in 2nd and 3rd trimesters of pregnancy[14]. Majority of the 3rd trimester patients had preterm labour i.e. 77.4%, and only 22.6% of patients' attained maturity till term. Study by Sharda et al in New Dehli revealed that hepatitis E is associated with preterm delivery in 84% while 16% had full-term delivery[4]. Antenatal complications like pre-

term labor was reported in 77 %, and premature rupture of membranes in 11 % of patients[5]. Commonly observed antenatal complication in a Chinese study was preterm labour[14]. Of all the patients, 24.6% were managed conservatively, 1.8% had E & C due to miscarriage, 18.7% delivered by caesarean section, 52.8% delivered by SVD and 2.1% remained undelivered. Spontaneous miscarriage corresponds to 1.8% in a study conducted in India[5]. The common indications for caesarean section in our study were scarred uterus followed by fetal distress, mal-presentation. The obstetric indications observed for cesarean sections were scarred uterus, transverse lie, placenta previa and fetal distress in the study by Gowri et al[5]. The most common indication for induction of labour was intrauterine death in 47% followed by preterm rupture of membranes in 25% cases.

In our study, the percentage of IUD was 16.2% and fetuses born alive were 82% which is comparable to results of an Indian study i.e. 9% and 95% respectively.[5] Similarity may be due to Asian ethnicity in both studies. Of those admitted in NICU, 22.8% had early neonatal death due to different complications of prematurity like RDS, JNN, ANN etc. Neonatal death is comparable to another study done in Pakistan i.e. 21.1%[11].

According to a systemic review; hepatitis E virus infection may result in premature births, small for gestation, stillbirth, and intrauterine death. However this review does not show any association with miscarriage in contrast to current study. Moreover proportion of Hepatitis E vertical transmission was quite high ranging from 13.3 to 64.2[15].

The number of patients recovered and discharged after conservative management were 253(76%). However maternal mortality was seen in 80(24%) patients in our study. Most common cause of mortality was fulminant hepatic failure. Abnormal laboratory parameters have significant association with maternal mortality. Literature reveals that low income countries have more prevalence of hepatitis E in pregnancy leading to fulminant hepatic failure with maternal mortality up to thirty percent cases[15]. Mortality rate of up to 30% is observed in another study with most frequent maternal complications leading to maternal death were disseminated intravascular coagulation and fulminant hepatic failure[3]. In this study maximum number of mortalities was in the postpartum period i.e. 73(91.25%) while seven (8.75%) patients expired in the antenatal period[3]. Maternal death occurred in 24.2% females in the study by Asghar S et al[11]. In another study maternal mortality was observed in 3 patients in postpartum period, 2 were infected with Hepatitis E only and one was infected with both Hepatitis E and Hepatitis A. The cause of mortality was fulminant hepatic failure in all the patients[6].

The number of patients requiring intensive care was 93(28%), and those observed in the study of Gowri were around 10%. In current study 32% patients required blood and blood products transfusion[5]. The mean number of transfusions of blood and blood products was significantly high in patients who had abnormal laboratory parameters and were expired. The reason for this fulminant nature of hepatitis E in pregnancy is unclear. An immunomodulation from TH1 to TH2 may be an underlying factor for serious disease implications among pregnant women. Moreover hormonal changes during pregnancy also weaken cellular immunity and exaggerate the process of viral replication resulting in high morbidity and mortality[4,7].

Presently, only supportive management is helpful for this condition[16,17]. China has launched a vaccine against hepatitis E that is being used for Chinese population. This vaccine is not licensed by WHO so not available in other parts of the world[18]. This vaccine is effective in general population; however its safety and efficacy in a large population of pregnant women needs to be determined[19]. The other preventive strategies include improving education, creating public awareness regarding hygienic measures for sanitation and clean drinking water sources. Screening, monitoring and patient education regarding potential fetal side effects is crucial with close follow up[20]. Vast span of severity of this viral disease demands in-depth genomic level exploration. Phase of clinical transition to chronicity is still poorly understood and require more research[21].

Strengths and Weaknesses

This is a large case series but single centered descriptive study. Moreover aspect of vertical transmission has not been addressed in this study.

Conclusion:

Pregnant women with positive serology for hepatitis E

IgM have wide range of mild to serious disease implications in both mother and fetus. Moreover it results in significantly high maternal mortality especially in postpartum period.

Ethical Approval: Given

Conflict of Interest: The authors declare no conflict of interest.

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