ORIGINAL RESEARCH

Study of liver diseases in pregnancy & the maternal outcomes

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Received: 11 June, 2023 Accepted: 13 July, 2023

ABSTRACT

Background: The liver is one of the many organs affected by the physiological & hormonal changes that occur during pregnancy. Many hepatic disorders diagnosed before or during antenatal period can stay unaffected, go into remission or get exacerbated during pregnancy. **Materials and methods:** This prospective study was conducted in the department of obstetrics and gynaecology and department of gastroenterology in IPGMER Hospital over a period of one year (July 2020 to June 2021). Pregnant womenwere examined clinically after taking detailed history. History of close contact with cases of viral hepatitis, parentral drug use, multiple drug transfusions, exposure to blood and blood products, history of hemodialysis was specifically asked. Patients underwent routine lab investigations and special investigations like CT & Peripheral blood films. **Results:** We screened a total of 22654 pregnant females & about 940 of them had liver disorders with total overall prevalence of about 4.1%. The prevalence of ICP was most common with 588 cases (2.59%), Hyperemesis gravidarum 120 cases (0.52%), chronic carriers of HBV 104(0.45%), Acute hepatitis A 86 (0.37%), acute hepatitis B 12 (0.052%), hepatitis C 6 cases (0.02%), hepatitis E, 2 cases (0.008%) & HELLP syndrome with 22 cases (0.09%) & no case of AFLP was observed. **Conclusion:** Liver disease can complicate the pregnancy in a dramatic and tragic fashion. Awareness, improved recognition and understanding of liver diseases and multidisciplinary approach can diminish maternal and fetal morbidity and mortality.

Key words: Intrahepatic cholestatsis of pregnancy,hepatitis, hyperemesis gravidarum,HELLPsyndrome,Acute fatty liver of pregnancy.

INTRODUCTION

The liver is one of the many organs affected by the physiological & hormonal changes that occur during pregnancy. Many hepatic disorders diagnosed before or during antenatal period can stay unaffected, go into remission or get exacerbated during pregnancy. Liver disorders like Intrahepatic cholestasis of pregnancy (ICP), toxaemias & HELLP syndrome can adversely affect the maternal &fetal outcomes with increase in both morbidity & mortality (1).

Undiagnosed viral infections can also be transmitted to medical personals, family contacts & the baby (2). Although a firm diagnosis is difficult to make but it should be attempted in a timely manner & optimum treatment protocols should be implemented with help of multidisciplinary team including hepatologists & gynaecologists. (3)

The liver diseases in pregnancy are divided into three major categories : (4,5)

A. Group I- Liver diseases unique to pregnancy:
1. Hyperemesis Gravidarum
2. ICP
3. HELLP syndrome
4. Acute fatty liver of pregnancy (AFLP)

B. Group II- Disease coincident with pregnancy
1. Viral hepatitis
2. Cholelithaisis
3. Budd- chiari syndrome

C. Group III – Preexisting in pregnancy
1. Autoimmune hepatitis
2. Wilson disease
3. Cirrhosis of liver

Hyperemesis gravidarum is the severe end of spectrum of morning sickness& can be defined as intractable nausea & vomiting during pregnancy leading to hospitalisation which complicated about 1-1.5% of all pregnancies. (6) The syndrome is more common in nulliparous, under 25 years of age, multiple pregnancies & commonly seen with in first trimester of pregnancy but insevere cases may extend upto 20th week of pregnancy (7). Raised aminotransferases are seen in about 50% of the

patients & the babies of patients with dehydration & electrolyte imbalances can suffer from low birth weight or intrauterine growth retardation (IUGR). (8)
pregnancy (ICP) is the most common of liver diseases & ICP is second only to viral hepatitis for jaundice & pruritis & usually affects about 20% of the pregnancies. Incidence rates vary with geographic location & race. Highest incidence rates seen about 12% in Chile, 9 % in Bolivia, 2-3% in Sweden. The exact cause of ICP is unknown but genetic, hormonal & exogenous factors do play a role in the pathogenesis. (9) Pruritus with or without jaundice is the hallmark of ICP with disappearance after parturition. Maternal outcomes are usually good but fetal outcomes can show increased incidence of prematurity, Intrapartum fetal distress &fetal death. (10) Careful assessment of fetal distress should be done as the prematurity risk is directly proportional to onset of pruritus.
Viral hepatitis is the most fearsome infections with unpredictable course & poor nutritional value of patients with hepatitis leads to poor maternal &fetal outcomes. Patients may be infected with HAV, HEV, HBV, HDV & HCV.
HAV is a small RNA virus with fecooroal transmission with good maternal &fetal outcomes. (11). Acute HBV infection occurs in 2/1000 & chronic HBV infection or relapse occurs in 5-15/1000. (2) 85-95% undergo complete resolution, 10% become carriers & rest <1% develop fulminant hepatic failure. Transmission rates to neonates is extremely high in HBV infection- 10% in 1st, 80-90% in 3rd trimester & about 90% with HbeAg positive mothers; therefore, timely detection & treatment is of utmost importance. No relation was found between mother with HBV & increased prevalence of abortion, still birth or prematurity.
HCV infection is transmitted from mother to infant prenatally & can lead to cirrhosis, Hepatocellular carcinoma, hepatic failure & death. The vertical transmission is correlated to HCV RNA titre in mother. The presence of HCV infection during gestation does not adversely affect fetal& maternal outcomes(12).
HEV is usually feco orally transmitted with 2-6 weeks incubation period. During epidemics, icterus occurs 9 times more common in pregnant females than non pregnant. The disease is much severe in third trimester with mortality rates ranging from 20-80% (13)
Toxaemia, HELLP & AFLP usually occur in 3rd trimester & present with raised liver enzymes, coagulopathy & DIC.
HELLP syndrome both partial & complete affects approximately 0.2% -0.6% of all pregnancies (14). Onset occurs in approx. 2/3rd cases during antepartum majorly 3rd trimester & 1/3rdpost partum. The maternal mortality rate ranges from 1-25% & perinatal mortality rate 10-60%; due to these high rates any patient suspected of HELLP should be investigated for HELLP irrespective of BP. (15).
Acute fatty liver of pregnancy is the least common & most serious liver disease of pregnancy occurring in 3rd trimester. The disease can progress rapidly to FHF, encephalopathy, coagulopathy, bleeding & death. Early recognition & timely treatment is the cornerstone of survival & good prognosis.(16)

MATERIALS AND METHODS

This prospective crossectional study was conducted in the department of obstetrics and gynaecology and department of gastroenterology in IPGMER Hospital over a period of one year (July 2020 to June 2021).
Pregnant women with liver diseases formed the subject for the study. Patients were examined clinically after taking detailed history. History of close contact with cases of viral hepatitis , parentral drug use, multiple drug transfusions, exposure to blood and blood products , history of hemodialysis was specifically asked. Patients underwent routine lab investigations and special investigations like CT & Peripheral blood films. The liver diseases were diagnosed according to their specific cirterias:

CRITERIA FOR HYPEREMESIS GRAVIDARUM

- Nausea and vomiting of unusual severity necessitating admission upto 20 wks period of gestationaccompanied by weight loss exceeding 5% of pre pregnancy body weight and ketonuria unrelated to any other cause.
- Other causesof nausea and vomiting ruled out.

CRITERIA FOR INTRAHEPATIC CHOLESTATSIS OF PREGNANCY

Positive criteria

1. Itching during pregnancy.
2. Disappearence of itching after delivery.
3. Itching during previous pregnancy or after contraceptive pills in patients , mother or sister.
4. Itching should be associated with deranged LFT.Sometimes liver function test becomes deranged after one or 2 weeks of itching.

Negative criteria

1. No signs of dermatological disease.
2. No recurrent itching except during pregnancy or use of contraceptive pills
3. No other active liver disease.

CRITERIA FOR DIAGNOSIS OF VIRAL HEPATITIS

1. Evaluation in terms of history, physical examination and course of disease.
2. Recent onset of jaundice with conjugated hyperbilirubinemia.
3. Raised transaminases
4. ELISA marker for viral hepatitis.

5. Exclusion of other diseases like exposure to drugs,toxins known to induce liver disease, cholestatic jaundice of pregnancy and eclampsia.

CRITERIA FOR DIAGNOSIS OF HELLP SYNDROME

1. Hemolysis :-any 2 of the following:
a. Serum bilirubin >1.2mg/dl
b. Peripheral blood film showing schistocytes or helmet cells
c. Increased LDH (>600 mg/dl) or decreased hepatoglobin (<25 mg/dl).
d. Presence of severe anemia not explained by any other cause.
2. Elevated liver enzymes : SGOT/ SGPT > 70 IU
3. Platelet count < 1 lakh /mm^3

CRITERIA FOR THE DIAGNOSIS OF ACUTE FATTY LIVER OF PREGNANCY

1. Increased liver enzymes 5 to 10 times the upper limit.
2. Increased serum bilirubin.
3. Increased serum creatinine.
4. Increased white cell count
5. Increased ammonia
6. Derranged coagulation prpfile.
7. Decreased glucose levels.
8. Peripheral blood film show fragmented red cells, burr cells, helmet cells or schistocytes.

RESULTS

During the course of the study, we screened a total of 22654 pregnant females & about 940 of them had liver disorders with total overall prevalence of about 4.1%. The prevalence of ICP was most common with 588 cases (2.59%), Hyperemesis gravidarum 120 cases (0.52%), chronic carriers of HBV 104(0.45%), Acute hepatitis A 86 (0.37%), acute hepatitis B 12 (0.052%), hepatitis C only 6 cases (0.02%), hepatitis E 2 cases (0.008%) & HELLP syndrome with 22 cases (0.09%) & no case of AFLP was observed.

Table no. 1: Prevalence of various liver disorders in pregnancy

Disorder	No. of cases	Prevalence
Hyperemesis gravidarum	120	0.52%
Intrahepatic cholestasis of pregnancy	588	2.59%
Viral hepatitis A	86	0.37%
Acute viral hepatitis B	12	0.052%
Chronic carriers of HBV	104	0.45%
Viral hepatitis C	6	0.02%
Viral hepatitis E	2	0.008%
HELLP syndrome	22	0.09%
Acute fatty liver of pregnancy	Nil	-

In hyperemesis gravidarum cases, 108 (90%) cases present between 6-10 weeks of gestational age. The most common maternal complications seen were dehydration 18% , electrolyte imbalance about 10%, preterm labour about 5% & abruptio placentae in 1.6%.

In Intrahepatic cholestasis of pregnancy cases, the prevalence was most commonly seen in third trimester 530 cases (90.1%) & 58 cases (9.86%) during 2nd trimester. Pruritus (83.1%) was the most common symptom, jaundice was seen in 11.3% & both the symptoms were seen in 5.4%. Maternal complications were seen in 26.9% of cases with preterm labour about 17.3 % & PPH in 9.6%.

In viral hepatitis cases, HBV was the most common infection 116 (55.2%), Hepatitis A were seen in 86 (40.9%) & HEV in 0.95% & HCV in 2.8%.

51% cases of HAV were seen during 32-36 weeks of gestational age & about 75.8% cases of HBV were diagnosed after 36 weeks of gestational age.

Table no. 2: Frequency distribution of symptoms in viral hepatitis

Clinical feature	HAV(n)	HBV (n)	HCV (n)	HEV(n)
Jaundice	54 (62%)	24 (20%)	2 (33%)	2 (100%)
Vomiting	12 (14%)	14 (12%)	4 (66%)	2 (100%)
Anorexia	34 (39%)	76 (65%)	5 (83%)	2(100%)
Dark urine	26 (30%)	22 (19%)	1 (16%)	1 (50%)
Light stools	18(20%)	12 (10%)	Nil	1 (50%)
Fever	44 (51%)	10 (8%)	1 (16%)	Nil
Abdominal pain	08(9%)	05 (4%)	2 (33%)	2 (100%)
Nausea	66 (76%)	55 (47%)	4 (66%)	2 (100%)
Epistaxis	2 (2%)	nil	Nil	1 (50%)
Antepartum hemorrhage	Nil	6 (5%)	Nil	1(50%)

Preterm labour was the most common maternal complication seen in HBV 27% &post partumhemorrhage was the most common complication with HAV 25%.

Table no. 3: Maternal complications in viral hepatitis.

Complication	HAV(n)	HBV (n)	HCV (n)	HEV(n)
Preterm labor	18 (21%)	32 (27%)	1 (16%)	Nil
Post partum hemorrhage	22 (25%)	17 (14%)	Nil	1(50%)
Puerperal sepsis	8 (9%)	11 (9%)	1 (16%)	Nil
Antepartum hemorrhage	nil	6 (5%)	Nil	1(50%)
Hepatic encephalopathy	nil	nil	Nil	1 (50%)
Maternal death	nil	nil	Nil	1 (50%)

In HELLP syndrome cases, maximum number of cases were seen in 32-37 weeks of gestational age 63%. The most common signs & symptoms were hypertension 86%, Nausea & vomiting 63% , headache 54% & epigastric pain in 45%. HELLP syndrome has very high maternal mortality rate about 4.5% with DIC about 9%, acute renal failure in 13% & pulmonary edema in 27%.

Table no. 4: Frequency distribution of symptoms in HELLP syndrome.

Symptoms	No. of cases	Percentage
Nausea and vomiting	14	63%
Hypertension	19	86%
Right upper quadrant or epigastric pain	10	45%
Visual changes	3	13%
Headache	12	54%
Jaundice	7	31 %
Convulsions	2	9%
Disorientation	1	4.5%
Decreased urine output	2	9%
Hemetemesis / malena	1	4.5%

Table no. 5: Maternal complications in HELLP Syndrome.

Complications	No. of cases	Percentage
Meconium stained liquor	6	27%
Post partum hemorrhage	9	40%
Abruptio placentae	4	18%
Acute renal failure	3	13%
Pleural effusion	5	22%
Intravascular coagulopathy	2	9%
Pulmonary edema	6	27%
Maternal death	1	4.5%

DISCUSSION

The occurrence of hepatobiliary disease with or without jaundice during pregnancy poses a threat 7 urgent diagnostic challenge for a hepatologist &gynaecologist. Early termination of pregnancy is the ideal treatment for toxaemia & HELLP & AFLP syndromes. Whereas, early detection of HBV infection decreases the transmission of HBV to fetus from mother.

940 pregnant females were diagnosed with liver diseases in our study with prevalence of 4.1%. The prevalence of ICP was most common with 588 cases (2.59%), Hyperemesis gravidarum 120 cases (0.52%)&chronic carriers of HBV 104(0.45%).

The prevalence of hyperemesis gravidarum was ranging from 0.02-1% in Hallak et al (17) whereas in our study, the prevalence was 0.52%; the lower prevalence can be explained by lower age group of the females in our study about 75% were below 25 years of age. The onset of symptoms were seen 90% between 6-10 weeks which was similar to Susan et al (18) who found about 13% below 10 weeks. Electrolyte imbalance was seen in 10 % of the patients in our study almost similar observations were made by Jacqueline et al (1).

The prevalence of ICP was seen 2.58 % in our study almost in concordance with Yannik et al (19). 90% of patients developed ICP in third trimester also similar to findings of Yannik et al (19). Preterm labour was seen in 17.6 % cases of our study in contrast to Nicholas et al (20) which observed about 44% of prematurity; the cause of lower preterm labour might be due to lower number of multipara patients included in our study.

The prevalence of HAV is about 1/1000 pregnant females as seen in our study with higher incidence in 3rd trimester about 73 % in Zhang et al (21); also anorexia & vomiting were the most common symptoms in both the studies. Jaundice was also seen in 62% cases in accordance to Zhang.

In our study,116 patients were shown to be HBV positive with 104 chronic cases & about 12 were acute hepatitis. Nausea & vomiting were the most common symptoms as seen by hieber et al (22). Preterm labour was seen in 27% in our patients which was similar in the study by Hieber et al (22). PPH was seen in 14 % of cases which was also in accordance to other observations.

We found 2 cases of HCV & 6 cases of HEV in our study , about 25% maternal mortality rate was seen in third trimester of patients with HEV which was about 15 % in our study in accordance to Trivedi et al (23) which also showed prevalence of encephalopathy in almost all patients with fulminant hepatic failure associated with mortality.

HELLP syndrome occurs in 0.2-0.6% of all pregnancies, in or study the prevalence was 0.09%; out of 22 cases, 16 were partial HELLP & 6 were complete HELLP with more prevalence in primigravidae & similar findings were seen by Bassan et al (24). Nausea &vomiting , epigastric pain & headache were the most common symptoms in our study which was similar to Audibert et al (25).

Abruptio placentae in 18 % & DIC was seen in 9% of patients which was similar to findings of Bassan et al (24) &pulmonary edema of 27% was higher than Audibert findings of 8.3%, which might be due to higher number of complicated cases in our study.

CONCLUSION

Liver disease can complicate the pregnancy in a dramatic and tragic fashion.Pruritis in pregnancy should be evaluated. Raised transaminases levels in pregnancy should be evaluated further.The various liver diseases in pregnancy should be distinguished as early delivery doesnot affect the course of a patient but early delivery is thetherapy of choice for AFLP and HELLP Syndrome. Awareness , improved recognition and understanding of liver diseases and multidisciplinary approach can diminish maternal and fetal morbidity and mortality.

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