REVIEW ARTICLE

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Liver disorders during pregnancy and their management

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INTRODUCTION

During pregnancy, the human body undergoes several changes in the process of its adaptation to the growing fetus. Although these changes are physiological, there is potential for morbidity and mortality to both mother and fetus. Liver is the site of many important metabolic and synthetic functions of the body. In normal pregnancy, the liver is not palpable. Due to hemodilution, biochemical tests may reveal mild increase in liver function tests. Abnormal liver tests occur in 3%-5% of pregnancies, with many potential causes, including coincidental liver disease (most commonly viral hepatitis or gallstones) and underlying chronic liver disease (Table 1). Wide multitudes of liver diseases are encountered in pregnancy. For instance, the liver could be the target of diseases specific to the pregnancy such as intrahepatic cholestasis of pregnancy and acute fatty liver of pregnancy, and there are no available means by which to predict with certainty how and when such illnesses may occur. In tropical countries like India, morbidity and mortality due to liver diseases in pregnancy is very high.[1] In addition, morbidity is more likely in the presence of a preexisting liver disease as in autoimmune hepatitis or when a new onset liver disease occurs during pregnancy as in herpes simplex hepatitis. Several physiologic changes occur during pregnancy and could pose difficulty in evaluating hepatobiliary function because they may be misinterpreted as pathological. For example, the blood volume expands during pregnancy due to retention of salt and water. This

Table 1: Physiological Changes during Pregnancy

Increase	1. Blood volume, heart rate and cardiac output rise by 35%-50% and peak at 32 weeks. Further increase by 20% occur in twin pregnancies 2. Alkaline phosphatase levels rise 3 to 4 fold 3. Clotting factors: 4. Ceruloplasmin 5. Transferrin 6. ESR, CRP, C3 and C4
Decrease	1. Gallbladder contractility 2. Hemoglobin 3. Uric Acid 4. Albumin and total protein 5. Antithrombin III and protein S 6. Systemic vascular resistance 7. Modest decline in blood pressure 8. Modest or no decline in platelet levels
No Change	1. Liver transaminase levels (AST, ALT) 2. GGT 3. Bilirubin level 4. Prothrombin time 5. Blood flow to the liver .

induces a state of hemodilution, an increase in cardiac output, and a reduction in systemic vascular resistance and systemic blood pressure. These changes peak during the second trimester then plateau until delivery. Consequently serum levels of uric acid, albumin, total protein and hematocrit are decreased. On the other hand, serum alkaline phosphatase levels may be elevated three to four folds due to placental production while serum values of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), and bilirubin and prothrombin time remain in the normal range. Estrogens promote biliary cholesterol saturation and inhibit the hepatic synthesis of chenodeoxycholic acid, while progesterone decreases the contractility of the gallbladder and contributes to lithogenicity resulting in sludge and gallstone formation. However, when appropriately diagnosed and managed, the outcome may be favorable and the liver disease in pregnancy could resolve without any chronic consequences.

Liver Disorders in Pregnancy

Liver dysfunction can appear at any point of pregnancy and causes great anxiety to the patient, her family and sometimes her medical attendants[1]. A number of these diseases have been identified which are responsible for morbidity and mortality (Figure 1).

Viral Hepatitis: [2]

Acute viral hepatitis is the most common cause of jaundice in pregnancy. The outcome is usually but not always benign except in viral hepatitis E and Herpes Simplex hepatitis. While infections with viral hepatitis in pregnancy may not always affect the outcome of the pregnancy, transmission to the newborn is always a concern. Diagnosis of viral hepatitis in pregnancy is not different from the diagnosis in the non pregnant state. Viral hepatitis in pregnancy has been a subject of continuing interest and controversy.[3] Reports from Europe and US have shown the course of viral hepatitis during pregnancy to be in no way different from non pregnant women.[4,5] However studies carried out in India , Iran Africa have found the incidence of fulminated hepatitis to be higher in pregnancy. Malnutrition superimposed on the normal demands of pregnancy and inversion of T and B lymphocytes in early pregnancy have been postulated to be the contributing factors.[6,7] In one study of 97 consecutive pregnant patients with acute viral hepatitis, the mortality was seen in 18 patients. Mortality is in the range of 30-45 % and it may be as high as 70%. Majority of cases die undelivered.[7,8] Besides, greater mortality and morbidity has been noted during epidemics of viral hepatitis, particularly in developing countries.[9,10] This may indicate that the nutrition may be involved. About 6 % of women with hepatitis can develop gallstones during their pregnancy.[11,12] The problem of liver diseases in pregnancy is more in women from low socio economic group living in unhygienic surroundings and drinking unfiltered water. If it is considered necessary to confirm the diagnosis, needle biopsy can be performed with all the precautions.[9]

Hepatitis A virus infection

Acute hepatitis A in pregnancy is self limited and maternal fetal transmission is very rare and only reported in a few cases. Transmission may occur if delivery takes place during the incubation period because of viral shedding and contamination during vaginal delivery. The risk of premature labor may be increased in women who are seriously ill during the third trimester. Treatment is supportive. IgG antibodies to HAV infection are passively transmitted to the newborn, which may lead to protection of the infant in the first several months of life. A recent study evaluating the impact of acute hepatitis A on pregnancy over consecutive admission of 79000 patients over a period of 25 years, reported that acute Hepatitis A infection during pregnancy was associated with high risk of maternal complication and

preterm labor.[13] Generally, safety of Hepatitis A vaccine during pregnancy has not been determined.[14]

Hepatitis B virus infection (HBV)
If acute hepatitis B occurs during pregnancy, the outcome of the pregnancy is no different from the non pregnant state. A major concern is the transmission of hepatitis B to the fetus. It is highest and on the order of 90% when the mother is positive for hepatitis B envelope antigen (HBeAg), has high viral deoxyribonucleic acid (DNA) levels or when maternal infection occurs in the third trimester. Rates of transmission average 10% when e Ag is negative or maternal infection occurs in the first trimester**.** Perinatal and early childhood contaminations as a result of the stability of HBV in the environment could result in an estimated 30%-40% of chronic infections. HBV is viable for more than 7 days at room temperature on environmental surfaces and at concentrations as low as 10 2-3 virions/ml even in the absence of visible blood.[15]

Hepatitis C infection
It is a rare problem in pregnancy. The rate of vertical transmission is less than 5%. Spontaneous resolution of infection may occur. Complications may be severe sometimes.[16]

Hepatitis delta virus infection (HDV)
This is the smallest hepatotropic RNA virus that is dependent on HBV for its replication. Coinfection of HBV and HDV together can lead to fulminant hepatic failure. The risk for HDV transmission via breastfeeding is unknown.[16]

Hepatitis E virus infection (HEV)
This is a non-envelope RNA virus responsible for large epidemics in Asia, the Middleast, Mexico, and Africa. It spreads via the fecal–oral route, and has an incubation period of 8-10 weeks. The infection is usually self- limited and does not result in chronic disease. The incidence of acute viral hepatitis E is identical in pregnant and non-pregnant persons. However, pregnant women are at high risk for acute and fulminant hepatitis. Mortality rate in pregnancy can reach 25% whereas it is 0.65% in non-pregnant women.

HEV infection occurs in the late stages of pregnancy, mortality is at its highest. Vertical transmission to the newborn occurs in 50% if mothers are positive for HEV PCR at the time of delivery. Premature deliveries, miscarriages and stillbirths have been reported.[17]

Acute Fatty Liver of Pregnancy (AFLP)
AFLP is a potentially fatal condition of the third trimester with an estimated incidence of one case per 13,000 pregnancies. AFLD may affect pregnant women of any age but is most commonly reported in primiparous women over the age of thirty and in women with multiple fetal gestations and/or carrying a male fetus.[7]

Initial symptoms are typically nonspecific and include nausea, vomiting, epigastric or right upper quadrant abdominal pain mimicking biliary tract disease or acute pancreatitis. Jaundice is a late sign and typically occurs 1-2 weeks after the onset of symptoms. Pruritus is uncommon and should suggest an alternative diagnosis such as intrahepatic cholestasis of pregnancy. Moderate elevations of liver enzymes (ALT, AST) and bilirubin, and elevation of serum creatinine and uric acid are common. The modest abnormality of aminotransferases can be misleading and may not accurately reflect the degree of liver injury. Frank liver failure associated with hepatic encephalopathy, jaundice, renal failure, hypoglycemia and coagulopathy, may present as early as 2 weeks after the onset of symptoms. The etiology and

pathogenesis of AFLP are not clearly understood. It is proposed that the underlying mechanism of AFLP consists of a fatty acid oxidation disorder. Fatty Acid Oxidation Disorders are autosomal recessive disorders involved in the transport and oxidation of fatty acids in the mitochondrion. Byproducts of fatty acid oxidation provide the energy necessary for the growth of the fetus. AFLP occurs in women who have fatty acid oxidation disorder of which the most common is the inherited deficiency of the enzyme LCHAD or Long Chain 3-hydroxylacyl-coA dehydrogenase. This enzyme is involved in the final step of beta-oxidation of fatty acids in the mitochondrion of the hepatocyte. Deficiency of this enzyme is associated with the accumulation of fatty acids in the cell with a resultant lack of energy fuel necessary for the growth of the fetus. In the last trimester of pregnancy, the metabolic demands of the fetus increase, and when affected mothers with one defective allele for LCHAD are pregnant with an affected baby (with 2 alleles, one allele inherited from each parent), acute fatty liver of pregnancy will ensue.9 While not proven, additional triggering factors such as drugs (aspirin and non-steroidal medications) may further impair beta-oxidation.[18]

Autoimmune Hepatitis (AIH)

Autoimmune hepatitis is a progressive liver disease that predominantly affects women of all ages. Women with AIH can become pregnant and carry successful pregnancies to term with the expectation of delivering a normal baby. However the disease activity is unpredictable in pregnancy. Attenuation of disease activity and spontaneous remissions have been reported due to the immune tolerance induced by the pregnancy. Flares of the disease have also been described in 11% of cases during pregnancy and up to 50% in the postpartum period. Maternal deaths due to liver decompensation, variceal bleeding and porto-pulmonary hypertension have been reported especially when treatment is withdrawn. Preterm delivery and fetal loss occur in 24%.[19]

Primary Biliary Cirrhosis and Primary Sclerosing Cholangitis

A few cases of pregnancy have been described in women with primary biliary cirrhosis (PBC). This is partly due to the later age at presentation of the disease. Although reports suggest an increased risk for premature delivery, still births and liver failure, there are no good data on the outcome of pregnancy in women with PBC. When pregnancy occurs, PBC may induce a new onset pruritus. Diagnosis and management are similar to the non pregnant state. There is no indication for termination of pregnancy in these patients.

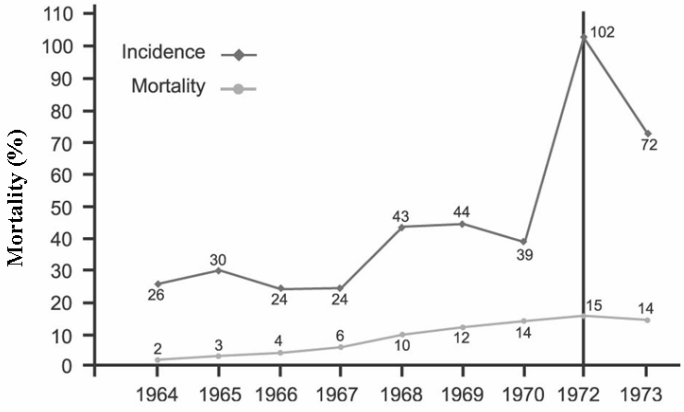

Figure 1: Graph depicting mortality and morbidity due to liver diseases in pregnancy at Calcutta Hospital from 1964-1973

Gallstone Disease in Pregnancy:

The risk for sludge and gallstone formation doubles by the end of gestation in comparison with the first trimester (10% versus 5% respectively), and it is further increased with parity. Gallstones are found in 6.5% to 8.4% of nulliparous women, and in 18.4% to 19.3% of

women with two or more pregnancies. Most sludge and a third of gallstones disappear spontaneously after pregnancy without resulting in symptoms. Acute cholecystitis and gallstone pancreatitis rarely occur during pregnancy (<1/8000) but they require immediate attention. Medical intervention is often effective.[20]

Liver disease in pregnancy may manifest as a benign entity that resolves with delivery of the fetus without any consequences, or a more serious disease that could adversely affect the overall well being of both mother and baby potentially resulting in liver failure and death. Although there are no available clinical markers by which to predict with certainty how and when such situations may be encountered, prior history of liver disease, knowledge of the patient's risk factors for liver disease and the gestational age of the pregnancy are the best guides to a differential diagnosis.

Drug induced hepatitis

While pregnancy is not reported to increase the susceptibility to drug induced liver disease, drug hepato-toxicity should always be considered in pregnant women taking prescription or non prescription medications.

Pregnant women can react to drug causing jaundice in an exaggerated way as manifested with the use of tetracycline, anaesthetic agents, sulfonamides etc. Antitubercular drugs are also known to induce drug related hepatitis. Therefore selection of drug therapy in pregnancy needs to be carefully made.

Management

Liver disease makes a normal pregnancy a high-risk pregnancy. Extreme vigilance is needed to detect early signs and symptoms of liver dysfunction and to distinguish these from the anticipated benign hepatic changes of pregnancy. Prompt management can save the life of the mother and the baby. Management of liver disease in pregnancy requires a concerted effort between the primary care physician, liver specialist, and obstetrician.

Acute liver failure (ALF) in pregnancy is a common challenging clinical problem both in terms of correct diagnosis and management. Acute viral hepatitis is the most common cause of jaundice in pregnancy. The course of acute viral hepatitis is unaffected by pregnancy, except in patients with hepatitis E (HEV), particularly from endemic countries like India, where ALF carries a high mortality. In both HEV infection and herpes simplex infections, maternal and fetal mortality rates are significantly increased. ALF specific to pregnancy including pre-eclampsia, associated with hemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome, acute fatty liver of pregnancy, and hepatic infarction result in increased maternal and fetal mortality if not recognized and acted on early. Early recognition of possible causes and prompt treatment are crucial for successful outcome of ALF in pregnancy. Treatment involves prompt delivery, whereupon the liver disease quickly reverses.

Indigenous drugs

Our team has studied the efficacy and safety of Liv.52 in the management of liver disorders in pregnancy. Our study which was conducted way back in 1974-75 consisted of 84 cases of liver disorder in pregnancy and we were interested to know the efficacy and safety of Liv.52 in the treatment of jaundice in pregnancy. This study, we believe is first of its kind at least in those days because it involved management of pregnant women with jaundice.[21]

In this study population of 84 patients, there were 9 pregnant women who were down with severe viral hepatitis. 21 of eighty four patients had undergone liver biopsy, of course after their written informed consent. Histopathological examinations of these patients of viral hepatitis had indicated extensive periportal round cell infiltration, fibrosis and scaring. All these patients recovered completely after 6 weeks of treatment except one patient (19 years,

second trimester of pregnancy). This patient had also undergone liver biopsy and the histopathology revealed severe round cell infiltration, fibrosis and nodule, all suggestive of cirrhosis. The typing of viral hepatitis of this patient was not conducted since the facility in those days' was not available. This patient initially showed clinical improvement but died after 6 weeks of treatment. Along with Liv.52 she was also receiving Vit. K and B. Complex vitamins. The cause of death in this unfortunate patient was severe acute viral hepatitis with cirrhosis of liver. The cause of death in this patient appears to be due to extentivity of liver pathology and cannot be attributed to any medication. Further, Liv.52 did not produce any adverse effects in any of the 84 patients who underwent Liv.52 drug therapy. Drug therapy with Liv.52 brought down the earlier reported mortality from 26.7% to 1.1% in patients of jaundice with pregnancy. However, a larger trial will be needed to confirm these findings. Liv.52 is a well studied herbal formulation in various diseases.[22,23] It could be a very handy medication in management of Liver diseases in pregnancy.

Liver holds a very important position in the metabolic system of the body. Its active participation in metabolism of carbohydrates, proteins and fats including detoxification of noxious substances gives it a unique position in controlling the metabolic pathways of the body. In spite of tremendous strides in modern medicines, few drugs are known to protect the liver from damage. Liv 52 showed a great promise in this situation as a safet and effective medication.[22,23] Further work in this direction will be highly beneficial.

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