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EDITORIAL

Hepatic problems during pregnancy

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The liver is one of many organs affected by the physiological changes occurring during gestation. Hepatic excretion of bilirubins may be impaired in the second half of normal pregnancy. However, the liver tests are usually normal. Abnormal liver tests can be found in about 10% of pregnancies.[1] Severe liver disease complicates pregnancy in only 0.1% of the cases.[2] Among the serious liver enzyme abnormalities occurring during pregnancy, acute viral hepatitis is the most common cause, accounting for 40%.[2,3]

Liver diseases found during pregnancy can be categorised into four groups:[4-7]

1. Diseases unique to pregnancy that occur in the context of and exclusively during the pregnancy, such as liver involvement in patients with hyperemesis gravidarum, intrahepatic cholestasis of pregnancy (obstetric cholestasis), liver disorders associated with pre-eclampsia including HELLP syndrome (haemolysis, elevated liver enzymes, and low platelet count), hepatic infarction, intrahepatic haemorrhage/liver rupture and acute fatty liver of pregnancy (AFLP).
2. Liver diseases that are pre-existing in the pregnant patient, including a broad spectrum of liver disorders such as autoimmune hepatitis, Wilson's disease, focal nodular hyperplasia and non-cirrhotic portal hypertension. Worsening of chronic hepatitis B and C has been described; while some women with liver cirrhosis can sustain a normal pregnancy without deterioration of hepatic dysfunction, others develop liver failure. However, it is important to note that women with liver cirrhosis or with chronic liver disease are generally less fertile and have a higher rate of both stillbirths and premature infants.
3. Liver diseases that tend to arise or be exacerbated during pregnancy: cholelithiasis and Budd-Chiari syndrome are more prevalent in pregnant women. Viral infections involving the liver that are usually benign, such as viral hepatitis E and herpes simplex, are more likely to be exacerbated and more likely to develop into fulminant hepatic failure in pregnant women.
4. Liver disease incidental to pregnancy. Pregnant women can have the same liver problems as any one else, such as viral hepatitis or toxic hepatitis.

All liver disorders need to be recognised during pregnancy, because they can affect the wellbeing of the mother and baby. Although an unequivocal diagnosis of hepatic problems during gestation is often difficult to make, it should be attempted to determine the nature of the disease at an early stage so that optimal treatment can be given. Certain disorders such as acute viral hepatitis in pregnancy, AFLP, and intrahepatic haemorrhage or rupture associated with pre-eclampsia should be considered as medical emergencies and delay in diagnosis and treatment will adversely affect maternal and foetal outcomes.
A careful clinical history, physical examination, appropriate laboratory tests including serological investigation and imaging methods should allow a diagnosis to be made within 24 to 48 hours of presentation. Liver biopsy for analysis of hepatic disorders during pregnancy is rarely required.

In this issue of the journal there are three articles devoted to the hepatic problems in pregnancy: Tan *et al.* describe AFLP in a woman during the 39th week of gestation.[8] Labour was induced and she gave birth to a healthy boy.

However, the liver test abnormalities persisted for several weeks after birth. A liver biopsy taken 17 days after birth showed microvesicular steatosis. These findings are indeed consistent with those found in AFLP. AFLP is a late gestational complication with clinical similarities to fulminant hepatic failure. According to recent findings,[9,10] this maternal liver disease is associated with an isolated deficiency of long-chain 3-hydroxy acyl-CoA dehydrogenase (LCHAD) or a complete deficiency of a trifunctional protein that catalyses the last three steps of mitochondrial fatty acid oxidation in the foetus. Liver disease in pregnant women occurs most often when the deficiency of enzymatic activity in the foetus is severe. However, not all women who are carrying a foetus with LCHAD deficiency or trifunctional protein deficiency have liver disease. Moreover, at this moment it is not clear what the molecular mechanism is of the disease that develops in mothers not carrying a foetus with the above-mentioned deficiency, as described in this case report. AFLP may result in marked hypoglycaemia, hyperammonaemia and an increased clotting time. AFLP never resolves before delivery. Therefore induction of labour or caesarean section is the penultimate therapeutic intervention. Nevertheless, maternal mortality is still approximately 12.5% with a corresponding perinatal mortality rate of 9%.[11] The only indication for liver transplantation in patients with AFLP is neurological deterioration in the presence of increased intracranial pressure. In most cases, however, with intensive support patients recover within the first post-partum week.

In the second article, den Dulk *et al.* describe a pregnant woman with severe persisting pruritus which developed in the 22nd week of gestation after a short course of treatment with amoxicillin for an upper respiratory tract infection.[12] Although a diagnosis of intrahepatic cholestasis of pregnancy was made by the authors and treatment with ursodeoxycholic acid was given with success, alternative diagnoses (gallstone disease or amoxicillin drug reaction) were possible, since this patient had constant epigastric pain with several attacks of colicky-like pains, with a past history of cholelithiasis and cholecystectomy. Although no bile duct stones were visualised, the stones could have passed to the intestine before the ultrasonography and MRI were performed. Cholestatic liver disease and pruritus can also be caused by a reaction to a drug such as amoxicillin. Moreover, pruritus in this patient developed at 22 weeks of gestation after an episode of abdominal pain, while in intrahepatic cholestasis of pregnancy, pruritus usually occurs during the third trimester of gestation without abdominal pain. Pruritus generally occurs before any abnormalities are seen in the liver tests.[13] It recurs in 40 to 60% of future pregnancies. Consequently, past history of pregnancy is important for diagnosis. The disease has no serious consequences for the mother, but it is associated with an increased risk of foetal distress, causing premature deliveries and stillbirths. The cause of the disease is unknown. Nevertheless sex hormones, mainly oestrogen and progesterone, appear to be involved in the pathogenesis.[14] Genetic factor(s) may play an important role.[15] Its prevalence is high in Latin America (American Indians) and in Scandinavian countries (Sweden and Finland).[16] According to recent studies,[17] treatment with ursodeoxycholic acid could indeed provide a significant improvement in pruritus and in the biochemical abnormalities with no side effects in the mother and child, as described in this case report.[12]

In the third article, Conchillo *et al.*[18] reported liver involvement in three patients with hyperemesis gravidarum. Although the pathogenesis of the liver injury is still unknown, hypovolaemia, malnutrition and lactic acidosis as the result of hyperemesis are believed to play an important role. The disease is usually benign and occurs in the first trimester of pregnancy in primigravidae.[19] Upon rehydration, enteral or parenteral nutrition, the abnormal liver tests normalise. Symptomatic therapy with antiemetics is, however, required although in most cases the nausea and vomiting would resolve spontaneously after 20 weeks of gestation.

With increasing awareness, especially the early recognition of hepatic problems during pregnancy and prompt appropriate management including early termination of the pregnancy by induction of delivery or by caesarean section, the maternal and child outcomes are improving.

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