CHOLESTATIC DISEASES OF PREGNANCY

R.O FARO*, O. BADEJOKO+
*600Level Medicine, O.A.U
+Senior Registrar, Department of Obstetrics and Gynaecology, O.A.U.T.H.C Ile Ife

ABSTRACT

Cholestatic diseases of pregnancy (CDP) are also referred to as intrahepatic cholestasis of pregnancy, recurrent cholestatic jaundice of pregnancy, icterus gravidarum and cholestatic hepatosis. It is a form of intrahepatic cholestasis characterized by pruritus and mild jaundice that usually occurs in the third trimester of pregnancy, though occurrence in earlier gestations is encountered occasionally. It is the second most common cause of jaundice occurring in pregnancy, ranking next to viral hepatitis[1].

INCIDENCE and AETIOLOGY

While its incidence ranges between 1:500 and 1:1000 in most countries; it has been reported to complicate up to 4% and 1.5% of pregnancies in Chile and Sweden respectively[2,3]. This variation in incidence is thought to be due to genetic influences arising from mutations in the genes controlling hepatocellular transport systems[4]. Bile formation is a complex sequence of cellular events involving the uptake of bile constituents and xenobiotics at the basolateral plasma membrane of hepatocytes, and secretion of cholephilic compounds across the apical canalicular membrane. The uptake and efflux are mediated by distinct transport systems expressed at the two polar surface domains of hepatocytes. It is the genetically determined alteration of these hepatobiliary transporter functions that underlie individual susceptibility to the development of intrahepatic cholestasis[4]. A novel CDP associated gene

may be located in the vicinity of 2P13LD, encoding FXR which is a bile acid sensor, the genetic variation of which confers susceptibility to CDP[5].

Intrahepatic cholestasis tends to recur in subsequent pregnancies or use of oestrogen containing pills, though the severity may vary; and there does appear to be a seasonal variation in its incidence, with a peak in November[3]. Also, hepatitis C virus positive women appear to be more prone to developing CDP than matched controls[6]. Other implicated factors include oestradiol which has been found to inhibit bile acid transport protein; as well as antidepressants and chlorpromazine[7,8,9].

CDP usually presents clinically in the third trimester, as generalized pruritus worst in the palms and soles; initially nocturnal, and progressing to continuous and bothersome pruritus within two weeks, accompanied by jaundice in about 50 percent of cases[10]. Pruritus worsens with the appearance of jaundice which is usually mild, and persists until delivery. Excoriation marks are a common feature. It is usual for the symptoms to abate within forty eight hours after delivery.

DIAGNOSIS

Differential diagnosis include among others: viral hepatitis, sepsis, HELLP syndrome, drug induced hepatitis, autoimmune hepatitis, acute fatty liver of pregnancy and extrahepatic obstruction.

The diagnosis of CDP is based on the above clinical findings in combination with the characteristic laboratory picture which includes a 5 to 10 fold increase in the level of serum alkaline phosphatase, marginally elevated serum transaminases, increased serum and urinary excretion of sulfated progesterone due to impaired glucuronidation[11], as well as a ten-fold increase in serum bile acids (chenodeoxycholic, deoxycholic and cholic acids). Histologically, the hepatocellular architecture is preserved in CDP. However, the centrilobular areas reveal feathery degeneration of the hepatocytes, and dilated bile canaliculi with atrophy of the microvilli[10]. Some other relevant investigations that may be done include hepatitis serology, hepatic ultrasonography, full blood count, clotting profile, renal function test, and obstetric ultrasonography and cardiotocography for fetal biophysical profile.

TREATMENT

Treatment of CDP is directed primarily at the amelioration of pruritus. The two most recently studied drugs are ursodeoxycholic acid (UDCA) and S-adenyl- methionine (SAM-e). UDCA is a naturally occurring hydrophilic bile acid that works by protecting cholangiocytes from the cytotoxicity of hydrophobic bile acids. It also stimulates bile acid secretion and protects hepatocytes against bile acid induced apoptosis[12]. Its absorption can be impaired by cholestyramine, cholestipol and aluminium hydroxide. UDCA is given in doses of 14 to 16 mg/kg/day[13]. It significantly reduces pruritus and improves liver function. SAM-e is thought to work by reversing the oestrogen induced impairment of bile secretion[10]. Studies have shown that when administered in combination, both drugs are more effective than either one used alone[14].

Older modalities of treatment include the use of diphenhydramine, hydroxyzine, and other antihistamines, to obtain marginal improvement of symptoms. Cholestyramine is an anion binding resin which blocks the enterohepatic circulation. Given at 8 to 16g/day in three to four divided doses, it affords modest relief of symptoms especially when commenced as soon as pruritus is noted. Prolonged usage may result in clotting derangements due to vitamin K deficiency, hence the need for parenteral vitamin K administration. Dexamethasone has also been used in treating CDP. It suppresses fetoplacental oestrogen production which is out of balance in CDP. Phenobarbital and guar gum are some of the other treatment modalities that have been tried[15].

Labour is often induced at 38 weeks because of the increased risk of intrauterine fetal death. Other complications include intrapartum fetal distress, meconium staining of the amniotic fluid with its attendant risk of meconium aspiration syndrome. Maternal complications include steatorrhoea as well as haemorrhage due to deficiency of vitamin K and its dependent clotting factors. The prognosis is good for the mother as pruritus resolves a few days after delivery and the liver functions return to normal. For the fetus, the prognosis is equally good if delivery is timely.

SUMMARY

CDP is a medical disorder with a genetically determined predisposition that is slowly, but steadily being demystified. A great deal remains to be unraveled.

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