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Outcome of intrahepatic cholestasis of pregnancy: Case report

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ABSTRACT

We present a patient diagnosed with intrahepatic cholestasis of pregnancy at 30 weeks 6 days of gestation. She presented with complaint of pruritus associated with hepatic cytolysis and elevated transaminases revealed by laboratory tests. The emphasis must be laid on importance of early diagnosis of intrahepatic cholestasis of pregnancy to improve the fetal prognosis and to eliminate other severe conditions associated with hepatic cytoloysis syndrome and pruritus.

Keywords: Intrahepatic cholestasis of pregnancy, pruritus, transaminases, hepatic cytolysis

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INTRODUCTION:

Intrahepatic cholestasis of pregnancy (ICP) has a potentially severe impact on maternal and fetal prognosis. Usually it appears in second and third trimester of pregnancy and is characterized by pruritus, elevation of transaminases, bilirubin levels, biliary enzymes and abnormal liver function tests[1].The pruritus of obstetric cholestasis is typically worse at night, is often widespread and may involve palms and soles and it may precede the laboratory abnormalities. Pruritus can range in

severity from mild to moderate (where sleep is disrupted) and to extreme(when the lifestyle of the patient is completely disrupted).

The etiology of intrahepatic cholestasis of pregnancy is unknown, but genetic, hormonal and environmental factors are involved.[2] The genetic variation around ABCB4 and ABCB11 encoding multidrug resistance protein(MDR3)and bile salt export pump(BSEP),respectively, have been reported as key factors related to etiology and severity of ICP.[3] Oestrogen is known to have role in cholestasis of pregnancy. Cholestasis is more common in twin pregnancies, which are associated with higher levels of circulating oestrogen than in singleton pregnancies. It can also be associated with altered metabolism of progesterone and progesterone administration may be a risk for cholestasis.[4]

The fetal consequences of ICP include spontaneous preterm labour, fetal distress and intrauterine death due to increased levels of serum bile acids (>10µmol/L) which cause direct toxic effects on myocardium leading to arrhythmias.[5]Early diagnosis and treatment with ursodeoxycholic acid (UDCA) and maturation of fetus lungs are necessary for both maternal and fetal outcome. Postnatal resolution of symptoms and biochemical abnormalities is required to confirm the diagnosis of intrahepatic cholestasis of pregnancy.

CASE REPORT:

A 25 years old patient, G2P1L0 with period of gestation 30 weeks 6 days was admitted in Obstetric and Gynaecology Department of Sri Guru Ram Das Hospital, Amritsar in Aug 2019. She complained of severe pruritus and jaundice. She had a similar episode in previous pregnancy and had intrauterine death at 28 weeks of gestation but it was not investigated.

Clinical examination was performed. Her blood pressure was normal i.e. 110/70 mmHg and pulse rate was 70 bpm. She had mild icterus. No nausea, vomiting, headache or fatigue were noted. Laboratory investigations revealed increase in serum transaminases, alanine aminotransferase– 209.8 U/L, aspartate transaminase – 282.2 U/L, modestly increase in total bilirubin – 2.09 mg/dL and direct bilirubin 0.70 mg/dl (superior cut of values 1 mg/dl and 0.3 mg/dl respectively). Lactate dehydrogenase – 294 U/L, alkaline phosphatase – 132.5 U/L, total cholesterol – 246 mg/dl, triglyceride – 167 mg/dl. There was no proteinuria and coagulation profile were within normal limits. Her total bile acid levels were 19µmol/L at the time of admission. No haemolysis or thrombocytopenia was observed and tests for viral markers including hepatitis A, B and C and E were negative. Autoimmune markers including antinuclear, antimitochondral and anti-phospholipid antibodies were negative. Based on laboratory investigations other liver disorders relating to pregnancy like viral hepatitis, chronic liver disease, HELLP syndrome, Acute fatty liver of pregnancy were excluded. The skin was inspected and other causes of pruritus like eczema, atopic eruptions, pruritic folliculitis were excluded.

After diagnosing intrahepatic cholestasis of pregnancy patient was treated with ursodeoxycholic acid (UDCA) 300 mg twice a day and after two weeks levels of alamine aminotransferase increased to 290 U/L and aspartate transaminase increased to 424 U/L and alkaline phosphatase was raised to 188 U/L and her pruritus was not relieved and total bile acid levels were increased to 25 µmol/L. The dose of UDCA was increased to 300 mg thrice a

day. Fetal monitoring was done by doing daily nonstress test, weekly biophysical profile and Doppler study. Within next two weeks pruritus was decreased, liver transaminases also showed decline, but bile acid levels further increased to 51.0µmol/L. At 35 weeks of gestation uterine contractions started spontaneously. Continuous electronic fetal monitoring revealed late decelerations and on amniotomy, meconium was confirmed and she underwent emergency caesarean section and a male baby 2000 gm was delivered with Apgar score 7. The biochemical parameters normalized and pruritus disappeared within 2 weeks of delivery. The newborn had normal neuromotor and intellectual development.

DISCUSSION

The exact etiology of intrahepatic cholestasis is not known. There can be abnormal metabolism of bile acid due to high secretion of oestrogen during pregnancy. Various mutation of genes ABCB11, ABCB4 and ATP8B1 have been involved in development of ICP.[6] These genes encode for proteins involved in transport of bile acids, phosphatidylcholine and aminophospholipids.[7] The patients who had taken micronised progesterones for preventing imminent premature labour, ICP was found in 64% of cases.[8]Serum cholesterol and triglycerides can also be elevated in patients of ICP.[9]

In our patient ICP was diagnosed at 30 weeks 6 days, in symptomatic context dominated by pruritus and was also associated with hepatic cytolysis syndrome and increased levels of bile acids at time of admission. We also considered eliminating other pathological conditions like pregnancy pruritus where tests show normal hepatic function and normal bile acids. Her serum markers showed no evidence of any other hepatic diseases, like HELLP syndrome, acute

fatty liver of pregnancy, autoimmune liver diseases or chronic hepatitis.

The most frequent complications in ICP to fetus is preterm delivery and the risk is higher if TBA >40µmol/L as found in our patient and she delivered at 35 weeks gestation. The cholelic acid activity result in increased sensitivity of uterine muscles to oxytocin and increased oxytocin receptor expression. There is increased incidence of intrapartum fetal distress or even intrauterine death. It can probably be due to direct toxic effects of bile acids upon the myocardium leading to arrhythmias.[10] No correlation seems to exist between severity of maternal symptom and levels of bile acids.[11]

Administration of ursodeoxycholic acid has been encouraged for ICP to reduce pruritus and improve hepatobiliary enzyme levels and to reduce the risk of fetal death.[12] In our case, UDCA was effective for improving symptoms. In some studies therapeutic use of dexamethasone and S.adenosyl-L-Methionine (SAME) has been described. In comparison to UDCA these therapies did not give better

outcomes with regard to reduction of laboratory parameters and clinical signs of cholestasis.[13,14]Hydroxyzine(25-50mg) can alleviate pruritus but causes respiratory difficulty in premature infants. Cholestyramine (8-16mg/day) decreases the absorption of ileal bile salts and increase the fecal excretion. Its effect on pruritus is limited.

Pruritus disappears within first few days after delivery and there is normalization of serum bile acid concentrations and other liver function tests. McMenamin's study suggests that woman affected register an increase in liver sequelae, including gallstone disease, hepatitis, fibrosis and cholangitis.[15] Biochemical liver tests and bile acid levels should be monitored six to eight weeks after delivery. If laboratory anomalies are not remitted, the patient should be referred to hepatologist to assess hepatobiliary disease.

CONCLUSION:

The patients with pruritus and abnormal serum transminases, especially in advanced stage of pregnancy can be having intrahepatic cholestasis of pregnancy. The affected pregnancies have increased risk of prematurity, fetal distress and intrauterine fetal death. The

patient is treated with UDCA which lead to attenuation of pruritus and resolution of deranged biochemistry. UDCA normalises increased bile acid and reduces plasma concentration and urinary excretion rates of sulphate steroid metabolites. Intense monitoring of fetus status is mandatory. As there is risk of sudden intrauterine fetal death, pregnancy should be terminated after reaching the fetal lung maturity. Although treatment of ICP is not yet standardized, but it helps in improvement of fetal prognosis.

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