Intrahepatic cholestasis of pregnancy

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ABSTRACT

Intrahepatic cholestasis of pregnancy (ICP) is a rare disease occurring mainly during the last trimester of pregnancy. Pruritus, often accompanied by excoriation of the skin but without other skin lesions, and elevated concentrations of bile acids are characteristic for this disorder. We present a 30-year-old woman with pruritus, elevated bile acids, ASAT and ALAT in the 22\textsuperscript{nd} week of pregnancy. Treatment with ursodeoxycholic acid resulted in complete disappearance of the pruritus and normalisation of the bile acids, ASAT and ALAT. A healthy child was born at term. In the differential diagnosis of liver function abnormalities during pregnancy, ICP should be included. ICP responds very well to treatment with ursodeoxycholic acid, with no detrimental effects for mother and child.

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a rare disease of unknown aetiology, usually occurring during the third trimester of pregnancy in otherwise healthy women. ICP is characterised by skin pruritus and secondary excoriation but without other evidence of skin lesions, abnormal – cholestatic – liver function tests and a characteristic elevation of the concentration of serum bile acids. Except for the, at times extreme, pruritus the disease is benign for the mother and disappears rapidly after delivery.\textsuperscript{4,7} However, ICP has been associated with an increased risk of premature deliveries and stillbirth.\textsuperscript{4,7} Furthermore, it usually leads to an extensive diagnostic work-up to exclude other liver diseases. Ursodeoxycholic acid administration is an effective and safe treatment for early onset ICP, according to a randomised, double-blind study controlled by placebo.\textsuperscript{6} It reduces pruritus, normalises biochemical abnormalities and most importantly improves the outcome of pregnancy.

CASE REPORT

The patient is a 30-year-old female, with a history of cholelithiasis followed by a cholecystectomy in 1987, pregnancy-related hypertension and tachycardia during her first pregnancy in 1996 and hypothyreoidism substituted with levothyroxine since the beginning of 2000. This patient was seen during her second pregnancy in the 22\textsuperscript{nd} week of gestation with severe complaints of pruritus, which developed after a short course of treatment with amoxicillin for an upper respiratory tract infection. The pruritus did not diminish after the amoxicillin had been stopped. She also complained of constant epigastric pain, sometimes accompanied by attacks of colicky-like pains. There was no fever, the urine was not darkly coloured and the faeces were not discoloured. She had not travelled outside the country in the last three months.

On physical examination blood pressure was 135/80, confirmed by automatic blood pressure measurement (mean 135/77). The skin showed many effects of scratching, but no other abnormalities were noticeable. The pregnant uterus was conform gestational age. Palpation of the epigastric...
area caused diffuse epigastric pain. Liver and spleen were neither palpable nor tender. Lungs were clear and heart sounds were normal.

Laboratory evaluation showed normal haematological parameters, thrombocytes 191 × 10^9/l (150-400 × 10^9/l), bilirubin 6 μmol/l (<10 μmol/l) alkaline phosphatase 298 U/l (normal 40-120, during pregnancy 60-200 U/l), γ-glutamyl transpeptidase 71 U/l (5-35 U/l), aspartate aminotransferase (ASAT) 85 U/l (12-35 U/l), alanine aminotransferase (ALAT) transpeptidase 71 U/l (5-35 U/l), aspartate aminotransferase (ASAT) 85 U/l (12-35 U/l), alanine aminotransferase (ALAT) transpeptidase 71 U/l (5-35 U/l), lactate dehydrogenase 429 U/l (200-450 U/l), bile acids 437 U/l (8-40 U/l), and ALAT increased to more than 500 U/l, and the concentration of bile acids rose to 199 μmol/l. The diagnosis of intrahepatic cholestasis of pregnancy was made and we decided to start treatment with ursodeoxycholic acid administration at a dosage of 900 mg/day. Seven days after initiating ursodeoxycholic acid, the itching diminished and after two weeks it disappeared completely. After two weeks of treatment both ASAT and ALAT were only slightly above normal. The bile acid level also returned to normal. At 37 weeks and 5 days a healthy boy was born vaginally after induction with oxytocin drugs, weighing 3570 g, with an Apgar score of 10 after five minutes. Directly after delivery the treatment with ursodeoxycholic acid administration was stopped since all biochemical values remained normal.

The time course of clinical signs and symptoms and the liver function abnormalities in relation to the treatment with ursodeoxycholic acid are shown in figure 1. The rapid clinical and biochemical response to treatment is evident.

### DISCUSSION

We present a case of intrahepatic cholestasis of pregnancy successfully treated with ursodeoxycholic acid. ICP has been identified all over the world, but the prevalence varies greatly according to the country and ethnic origin. The prevalence varies between 0.1 to 1.5% in Europe, to 16% of pregnancies in Chile.\(^7,8\) In native Araucanian Indians in Chile, almost 28% of pregnancies have ICP.\(^7,8\) Typically, intrahepatic cholestasis of pregnancy is a disease of the third trimester of pregnancy.\(^7,8\) Our case is a report of very early onset intrahepatic cholestasis of pregnancy, early in the second trimester.

The differential diagnosis of liver function abnormalities during pregnancy is extensive and includes diseases that are not primarily associated with pregnancies, such as hepatitis and (obstructive) biliary tract diseases and pregnancy-related liver disorders. Diseases with liver function abnormalities related to pregnancy include hyperemesis gravidarum (usually first trimester), toxaemia of pregnancy and HELLP syndrome (usually third trimester), acute fatty liver of pregnancy (often late third trimester or after delivery) and intrahepatic cholestasis of pregnancy. In our case an extrahepatic origin of the liver function abnormalities was excluded by magnetic resonance cholangiopancreatography (MRCP). The epigastric pain followed by colicky-like pain is not characteristic of ICP. Although the MRCP did not show any abnormalities, the possibility of a passed gallstone, even after cholecystectomy, should still be considered.

Typical for intrahepatic cholestasis of pregnancy are the pruritus, classically starting at the palms and soles, worsening during the evening and night, and the high concentration of serum bile acids with increased levels of ALAT, ASAT and normal bilirubin as was the case in our patient.\(^5,9,11\) Bile acids are abnormally high in 90% of ICP patients. However, ALAT and ASAT values are abnormal in 55 and 60% of patients, respectively. Alkaline phosphatase is abnormal in 70% of patients and bilirubin value in 25%.\(^9,11\) Liver biopsy is not generally necessary. If a biopsy is taken for differential diagnostic purposes, the histology shows mild focal irregular intrahepatic cholestasis with bile plugs in the canaliculi and small amounts of bile pigment in centrolobular hepatocytes and macrophages.\(^2,11\) What is difficult in the differential diagnosis is that about 10% of ICP patients develop jaundice.\(^2,11\) Some patients may develop steatorrhoea with decreased absorption of fat-soluble vitamins.

Increased rates of postpartum haemorrhage have been reported,\(^1,14\) possibly related to vitamin K deficiency.\(^2,15\) The aetiology of ICP is not completely elucidated. Historically, ICP has been associated with the cholestatic effects of oestradiol metabolites and progesterone.\(^2,12,16,18\) Recent findings in other cholestatic liver diseases such as progressive familial intrahepatic cholestasis (PFIC) and benign recurrent intrahepatic cholestasis (BRIC) suggest malfunction of...
biliary canalicular transporters.1,2,10-20 PFIC is a disorder characterised by the onset of cholestasis in early childhood which can progress to cirrhosis and liver failure before adulthood.19,20 PFIC can be classified in three subclasses (PFIC1-3). PFIC1 and 2 have low concentrations of biliary bile acids and low to normal γ-GT values in the serum.19 whereas PFIC3 patients have high serum levels of γ-GT and bile acids which lack phospholipids but have a normal biliary bile acid concentration.19-22 Homozygote mutations of multidrug resistant 3 (MDR-3) gene have been described in three pedigrees with PFIC3.22-23 MDR-3 is a protein responsible for secretion of phospholipids. The clustering in families24,25 and the endemic occurrence of ICP suggest there is also a genetic basis in this disease. ICP is more common in families with PFIC3.19-23 In some ICP patients with a raised serum γ-GT heterozygous MDR-3 missense mutations have been found.19 However, some patients have normal γ-GT values. It is possible that other biliary canalicular transporters are involved in these patients. For example, ICP is also more common in BRIC patients,20,26 in whom mutations in the familial intrahepatic cholestasis 1 (FIC1) gene have been described.27 ICP is considered a benign disease for the mother, but has been associated with an increased risk of premature delivery and stillbirth.44,45 The pathophysiological mechanisms have to be defined, but some evidence suggests that the foetal consequences might be caused by the increased maternal and foetal bile acid concentration. High bile salt levels were associated with more frequent occurrence of foetal distress.2,35-38 Moreover, high bile acid levels are reported to worsen cardiac rhythm33 and to induce vasoconstrictive effects on isolated human placent al chorionic veins.34 Various treatments, such as antihistamines, anion exchange resins (e.g. cholestyramine), phenobarbital and corticosteroids, have been tried for ICP, however with disappointing results.39-41 S-adenosylmethionine (SAM) has also been used. In two studies39,40 beneficial effects have been shown, but negative results were found in a double-blind, placebo-controlled study.41 Ursodeoxycholic acid (UDCA) is a naturally occurring hydrophilic bile acid41 that improves clinical and biochemical indices in a variety of cholestatic liver diseases.41,44 At present, Ursodeoxycholic acid seems to be the best treatment option for ICP.2,6-45,46 In a placebo-controlled double-blind trial of ursodeoxycholic acid in the treatment of ICP, all infants born to the eight women treated with ursodeoxycholic acid were born near or at term, and no stillbirths occurred.47 However, in the placebo-treated group five out of seven women delivered prematurely, including one stillbirth. No toxicity was observed up to three months after delivery in mother or child. In another small double-blind randomised study, treatment with UDCA was associated with improved clinical and biochemical results.48 However, the literature about the effectiveness is still not conclusive.19,55 It has been demonstrated that treatment with UDCA does not increase meconium levels of potentially toxic metabolites of UDCA.31 It seems to have no adverse effects on the baby.6,31-34,46

The mechanism of action of UDCA is not completely clear. It might be that the hydrophilic UDCA protects against injury by hydrophobic bile acids and stimulates the excretion of these and other potentially hepatotoxic compounds.2,45 Furthermore, UDCA is able to reverse the impairment of bile acid transport across the trophoblast, which might contribute to favourable foetal outcome.49 Our patient was successfully treated with ursodeoxycholic acid and a healthy child was born. After delivery, treatment was stopped and liver functions remained normal during follow-up for one year. In affected mothers the symptoms classically disappear within two days.19 In patients in whom ICP develops very late in the third trimester, delivery might be awaited without treatment. However, this decision should be taken with due care, as different groups conclude that ICP is associated with adverse perinatal outcome not predicted by conventional foetal surveillance.47,50 It should be reminded that patients with a past history of ICP are at risk for recurrence during subsequent pregnancies in 60 to 70%, or rarely during the use of oral contraceptives.5,51 In conclusion, intraha hepatic cholestasis of pregnancy has to be included in the differential diagnosis of patients with pruritus and liver function abnormalities during pregnancy, especially when concentrations of bile acids are increased. ICP can be treated successfully with ursodeoxycholic acid.

REFERENCES


