Intrahepatic cholestasis of pregnancy. Case report

Abstract

We present a patient diagnosed with intrahepatic cholestasis of pregnancy which was reported in the context of a series of 10 similar cases diagnosed and monitored within 1 year in two obstetrics and gynecology centres of Bucharest. The particularity of the case is a differential diagnosis in the case of 32 weeks pregnant patient, accusing pruritus associated with hepatic cytolysis and elevated transaminases revealed by laboratory tests. An emphasis must be put on the importance of early diagnosis of intrahepatic cholestasis of pregnancy and elimination of other severe conditions associated with hepatic cytolysis syndrome and pruritus.

Keywords: intrahepatic cholestasis of pregnancy, liver failure, hepatic cytolysis, pruritus, acute fatty liver of pregnancy

Introduction

Intrahepatic cholestasis of pregnancy (ICP) appears in the second and third trimester of pregnancy and is characterized by pruritus and an increase of serum bile acid concentration.

Cholestasis is associated with many hepatic-biliary disorders that produce extrahepatic biliary tract obstruction and/or intrahepatic biliary perturbation. A key symptom associated with cholestasis is pruritus, and could range in severity from mild to moderate (i.e. where sleep is disrupted) and to extreme (i.e. when the lifestyle of the patient is completely disrupted).

Incidence of ICP varies considerably in different reports (between 0.1 and 15.6%), for reasons that are not completely understood. Geographical variations in rates may reflect differences in disease susceptibility between ethnic groups. Incidence of ICP is increased in Bolivia and is the most recorded among Araucanos Indians in Chile. In a Swedish study, which covered 1.2 million births between 1997 and 2009, an incidence of 0.5% of all births was estimated. Different reports from the United States of America showed an incidence rates ranged from 0.32% recorded at Bridgeport Hospital, Connecticut, to 5.6% for the Latin majority population in Los Angeles. For reasons unknown, the condition is more common in colder months in Chile and Scandinavia. The cause of ICP is unknown, but genetic, hormonal and environmental factors are probably involved. Environmental factors may also influence the manifestation of the disease.

Genetic factors might explain familial cases and the higher incidence in some ethnic groups. The adenosine triphosphate binding cassette, subfamily B, member 4 gene, encoding drug resistance-associated (a canalicular phospholipid translocator) protein is mainly involved in a subtype of progressive familial intrahepatic cholestasis called PFIC3. Heterozygous mutations in this gene have been reported in a large consanguineous family. Several women had pregnancy repeated episodes of cholestasis.

Oestrogens are known as cholestasis causal factors in both experimental and clinical conditions, probably having a role in cholestasis of pregnancy. ICP occurs mainly in the third trimester, when serum concentrations of oestrogen are at maximum level. Cholestasis is more common in twin pregnancies, which are associated with higher levels of circulating oestrogen than in singleton pregnancies.

Cholestasis of pregnancy may be associated with altered metabolism of progesterone and progesterone administration may be a risk for cholestasis. In a study conducted on 50 women with cholestasis of pregnancy in France, 64% were treated with oral natural progesterone to prevent preterm delivery. The onset of cholestasis of pregnancy is usually marked by the development of pruritus. It is often generalized but predominates on the palms and soles and manifests more violently at night. Pruritus may precede laboratory abnormalities. Total serum concentration of bile acid increase in cholestasis of pregnancy and may be the first or only laboratory abnormality. Serum cholic acid increases more than chenodeoxycholic acid, resulting in a marked increase in the ratio cholic acid/chenodeoxycholic acid compared to pregnant women without cholestasis of pregnancy.

Other laboratory results reflecting cholestasis may also be present. These include increases in alkaline phosphatase (ALKP) serum concentrations, 5' nucleotidase, and concentrations of total and direct bilirubin. Total levels of bilirubin infrequently go beyond 6 mg/dl. However, uncommonly, serum levels of gamma-glutamyl transpeptidase (GGT) are normal or slightly elevated, which is unusual in many other forms of cholestatic liver disease in which GGT levels are similar to other cholestatic markers.

Most women are diagnosed in the second or third trimester. Cholestasis of pregnancy diagnosis is based on the presence of pruritus associated with elevated levels of total serum bile acids and/or aminotransferase...
rases, and the absence of other diseases that can cause similar symptoms and laboratory results, the diagnosis being one of exclusion. The main feature of cholestasis of pregnancy (e.g. pruritus) helps to distinguish from other types of liver diseases, which may share similar laboratory features (such as pre-eclampsia or early HELLP syndrome).

Liver biopsy is rarely necessary for diagnosis. When it is performed, histopathology is characterized by cholestasis without inflammation\(^{[16]}\). Portal circulation is not affected.

**Case report**

A 33 year old patient, normal weight, teacher, known with a 32 weeks pregnancy comes to the emergency room of the University Hospital from Bucharest accusing pruritus and is admitted with the following diagnosis: IIG, IIP, 32-weeks pregnancy in development with scarred uterus after a C-section performed in 2008, cholestatic syndrome and hepatic cytolysis, for investigations and specialized treatment. The patient states that she had a similar episode in the previous pregnancy, but it was not investigated.

Specialized clinical examination was performed, blood pressure values are normal, i.e. 110/70 mmHg at a normal heart rate of 70 bpm. From the laboratory test, relevant is the increase in serum transaminases within 10 days of the onset of pruritus, alanine aminotransferase = 1111 U/L, aspartate transaminase = 662 U/L, modestly increase of total bilirubin = 1.09 mg/dL and direct bilirubin = 0.68 mg/dL (superior cut-off values 1mg/dl, and respectiv 0.3mg/dl), lactate dehydrogenase = 294 U/L, total cholesterol = 305 mg/dL, triglycerides = 325 mg/dL, and mild elevations in the serum concentrations of ALKP = 181U/L (superior cut-of value 136U/L). We noted absent proteinuria and unchanged coagulation samples.

Interdisciplinary examinations refute cholecyst impairment and obstructive syndrome, and the infectious diseases exam conducted at the "Matei Bals" Infectious Diseases Institute from Bucharest, Romania refutes viral aetiology through extensive testing for hepatitis A, B, C, D, E, F, G.

It was administered treatment with ursodeoxycholic acid (Ursofalk) divided in three doses of 250 mg, two tablets in the morning and one in the evening. Under this treatment, within two weeks, liver enzymes decrease by 200-300 IU/day, blood chemistry normalizes. Pruritus was relieved and subsequently remitted.

The patient was admitted again at 38 weeks of pregnancy in labour and gives birth by cross-sectional caesarean for imminence of uterine rupture on scarred uterus, to a living foetus, male, weighting 3270 g.

Subsequently, one month after delivery the biochemical and blood picture where within normal values.

**Discussion**

We gave particular importance for quick identification of ICP associated with a 32 weeks pregnancy, in a symptomatic context dominated by pruritus and associated with hepatic cytolysis syndrome. We also considered eliminating other severe pathological conditions that could be associated with the clinical and laboratory picture of the patient.

To reach the diagnostic of ICP, we first eliminated pregnancy pruritus, pruritus gravidarum, where the test show normal hepatic function and normal bile acids, gestational pemphigoid, rare autoimmune condition characterized by IgG complement fixation antibodies with rashes that develop into high tensioned blisters, associated with an increased risk of preterm delivery and small for gestational age, ectopic pregnancy eruption showing dry red rashes, with or without small blisters which typically affect the trunk and flexions of the limbs, prurigo of pregnancy with red-brown groups of papules on the abdomen and inner surfaces of the limbs, pruritic folliculitis of pregnancy with acneiform rash on the shoulders, upper back, thighs and arms, follicular papules and pustules that can be filled with pus, the culture being usually sterile, rashes improve with advancing pregnancy.

We have also eliminated the serious conditions that can be associated with hepatic cytolysis syndrome and pruritus, when the life of mother and foetus are at risk.

We refer to specific causes of liver failure in pregnancy, acute fatty liver of pregnancy (AFLP) with the emergence of nausea and vomiting in the III trimester which are not caused by *hyperemesis gravidarum*, patients with AFLP are often associated with renal failure, coagulopathy, hypoglycemia and pre-eclampsia. HELLP syndrome where hypertension and proteinuria in which are the main characteristics. *Hyperemesis gravidarum* that occurs in early pregnancy with nausea, vomiting, affected hepatic samples which normalize with drug treatment.

We have also discussed viral hepatitis, but the interdisciplinary examination conducted by the "Matei Bals" Infectious Diseases Institute refutes presence of infection and also pre-pregnancy hepatic impairment such as primary biliary cirrhosis or sclerosing cholangitis with symptoms onset before pregnancy and presence of autoantibodies, biliary obstruction with abdominal pain and ultrasound changes of the liver and not least veno-occlusive disease which would have meant ultrasound documented thrombosis.

After outlining the diagnosis we decided to administer a concentrated treatment for reducing symptoms and preventing maternal and fetal complications, the most promising option being ursodeoxycholic acid (Ursodiol), administered twice a day. It increases bile flow and has been used to relieve pruritus and improve biochemical hepatic tests and in cholestatic liver diseases such as primary biliary cirrhosis. In our case, liver aminotransferases decreased within two weeks after initiation of therapy, with approximately 300 IU/day, the biochemical picture becoming normal.

A number of other treatments for cholestasis of pregnancy may be beneficial in selected cases:
Hydroxyzine (25 to 50 mg/day) may alleviate pruritus, but antihistamines may worsen respiratory difficulties in premature infants; and

Cholesteryamine (8 to 16 g/day) decreases the absorption of ileal bile salts, thereby increasing the faecal excretion. Treatment should be initiated at a low dose and gradually increased. Its effect on the pruritus is, however, limited.

Maternal prognosis of cholestasis of pregnancy is often tolerated(13). Pruritus usually disappears within the first few days after delivery, accompanied by normalization of serum bile acids concentrations and other liver tests. McMenamin’s study suggests that women affected register an increase in liver sequelae, including gallstone disease, hepatitis C, fibrosis and cholangitis(13). Biochemical liver tests and bile acids concentration monitoring is recommended for six to eight weeks after delivery to confirm that the anomalies previously identified were remitted. If laboratory abnormalities are not remitted, the patient should be referred to a specialist to assess for hepatobiliary diseases.

Conclusions

In patients with pruritus and abnormal serum liver tests, especially in advanced stage of pregnancy, intrahepatic cholestasis of pregnancy should not be disregarded. The affected pregnancies have an increased risk of prematurity and in utero fetal death. In this case it is highly recommended to consider the treatment with ursodeoxycholic acid and to try to deliver after 34 weeks of pregnancy.

The main conditions incriminated in differential diagnosis and which should be considered in the context of an advanced pregnancy, especially in the third trimester, are: acute fatty liver of pregnancy, preeclampsia, HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count). Liver biopsy is rarely necessary in the diagnosis of liver diseases that occur during pregnancy.

The risk of recurrence in subsequent pregnancies is variable. There is a possibility that the risk for intrahepatic cholestasis’ occurrence in subsequent pregnancies cannot be accurately predicted.