

Recurrent Intrahepatic Cholestasis of Pregnancy. A Case Report

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Abstract

Intrahepatic cholestasis of pregnancy (ICP) represents a rare but severe pathology with serious consequences on the outcome of pregnancy. We present the cases of two sisters that came to our clinic with ICP in successive pregnancies. The fetus from a pregnancy with cholestasis can be affected by preterm birth, respiratory distress syndrome, intrauterine death in the third trimester and a possible cerebral damage. Early diagnosis and prednisone treatment have allowed an improvement of the neonatal outcome in the following pregnancies.

Keywords

Intrahepatic cholestasis – pregnancy – premature birth – pruritus.

Introduction

Intrahepatic cholestasis of pregnancy (ICP) represents a rare pregnancy related disorder with potentially severe impact upon maternal and fetal prognosis. The presence of a large number of cases in the same family has raised the possibility of a genetic mechanism that can affect the process of glucoconjugation of bile acids, manifested in particular hormonal states (pregnancy, use of contraceptives).

Case Report

A 27 year old patient, at 28 week of gestation (WG) was admitted to our hospital in March 2000. She complained of uterine contractions, minimal vaginal bleeding, and generalized pruritus.

The obstetrical ultrasound had confirmed a 28 WG monofetal pregnancy and the laboratory evaluation revealed normal values for the complete blood count, glycemia, and creatinine level. Total bilirubin was 2.6 mg/dL, conjugated bilirubin 1.9 mg/dL, AST= 48 IU/L, ALT 35 IU/L, alkaline phosphatase 350 IU/L and total bile acid level 12 mol/L.

The established diagnosis was: Primigesta, primipara 28 WG, severe form of imminent premature labor, cholestatic and hepatocytolysis syndromes. At admission the viral hepatitis markers were negative. The treatment for preventing preterm birth has been initiated and two 12 mg doses of dexamethasone at 12 hours apart were given for accelerating fetal lung maturation.

During the hospitalization, the transaminase values decreased progressively at 35 IU/L respectively 20 IU/L, but bilirubin and alkaline phosphatase remained at high levels. After 10 days of treatment, the uterine contractions reappeared, the labor began and a female newborn of 1,500 g, Apgar score 7 was delivered vaginally.

In the puerperium, pruritus disappeared after 72 hours and all the biochemical parameters normalized. Surfactant was given to the newborn in the Neonatal Intensive Care Unit and she needed assisted ventilation for 72 hours. The child evolved well, with appropriate neuromotor development, but after two years she developed an autistic behavior and was diagnosed with Asperger syndrome.

The same patient was followed in our department for a second pregnancy in 2002. In the second trimester of pregnancy, at the 20 WG she was admitted in the hospital for a severe form of threatened abortion. The laboratory findings were in normal range. An emergency cerclage of Palmer type has been performed. At 27 WG, the patient had symptoms and laboratory findings of cholestasis of pregnancy. The condition was referred as recurrent intrahepatic cholestasis of pregnancy (ICP). Prednisolone was given in a dose of 20-30 mg/day, related to the intensity of cholestasis and of the pruritus, and tocolytic treatment was started. At 37 WG the patient delivered a 2,600 g boy, Apgar score 10. The evolution of the patient during the puerperium was good with the normalization of the biochemical parameters and pruritus disappearance. The evolution of the newborn

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was very good with a normal neuromotor, intellectual and psychical development.

In 2004, one sister of this patient, 32 year old, became pregnant. The patient had been completely investigated from the beginning of the pregnancy. The patient was known with a complete congenital atrioventricular block and had a pacemaker. At 24 WG, a routine laboratory screening showed raised transaminase levels (AST 60 IU/L, ALT 46 IU/L), bilirubin (total 1.8 mg/dL, conjugated 1.2 mg/dL) and alkaline phosphatase. After one week, an intense, generalized pruritus appeared, affecting the sleep and the general state of the patient. The laboratory findings worsened (AST 320 IU/L, ALT 240 IU/L, total bilirubin 4.5 mg/dL, conjugated bilirubin 3.2 mg/dL, alkaline phosphatase 800 IU/L, and total bile acid level 14 mol/L). Promethazine (Romergan®) 60 mg/day and prednisone 25-30 mg/day were administered. The pregnancy evolved with attenuated pruritus, with intermittent cholestatic and hepatocytolytic syndrome until the 37 WG. A cesarean section was performed at this time given the maternal cardiac disease and for the fetus safety. The newborn was a 2,900 g girl, Apgar score 10 and had a good postnatal evolution. After birth, pruritus and the cholestatic and hepatocytolysis syndromes disappeared.

Discussion

Intrahepatic cholestasis of pregnancy is also known as pruritus gravidarum. It is frequent in Chile 21% [1]. In the European countries, its incidence is under 1% of births excepting the Scandinavian countries where it ranges between 1-1.5% [2, 3].

The exact etiology is not known. The presence of a family history and the occurrence of intrahepatic cholestasis in the same patient while administering oral contraceptives suggest a hereditary factor, validated in the presence of a hormonal context. Several mutations of the genes *ABCB11*, *ABCB4* and *ATP8B1* [4-6] have been involved in the development of ICP. These genes encode for the proteins involved in the transport of bile acids, phosphatidylcholine

and aminophospholipids [7].

In ICP, the serum and urinary levels of the sulfated progesterone metabolites are increased, while the levels of glucuronidated metabolites remain unchanged [8]. Occurrence of ICP in 64% of the patients that had taken natural micronised progesterone for preventing an imminent premature labour has been described [9].

The alkaline phosphatase is usually elevated 5-10 times while the bilirubin levels are moderately increased up to 5 mg/dL. The transaminases are usually in normal range but can increase up to 200-400 IU/L. Bile acid level is elevated 10-100 times. If bile acid values are higher than 40 micromoles/L, there is an increased risk of fetal complications, although there seems not to exist a correlation between the severity of maternal symptoms and the level of the bile acids [10]. Serum cholesterol and triglycerides can be elevated [11].

The differential diagnosis has to be done with other liver disorders related with pregnancy (Table I), most frequently with viral hepatitis, cholelithiasis, chronic liver disease and Gilbert syndrome [12].

Obstetrical complications related to ICP can be both maternal and fetal. The fetus is exposed at a high risk of preterm birth, intrapartum fetal distress or even in utero fetal death. The cause of fetal death before the labor onset is unknown, but it was hypothesized to be the result of the direct toxic effect of the bile acids upon the myocardium leading to arrhythmias [13]. Taken into consideration the risk of sudden intrauterine fetal death, many authors suggest that pregnancy should be terminated after reaching fetal lung maturity [14]. The newborn from pregnancies complicated with ICP is exposed at a higher risk for developing acute respiratory distress syndrome, like in our first case [15].

The treatment is addressed to both the pregnant patient and the fetus. The main objective for the pregnant patient is attenuation of the pruritus. An intense monitoring of the fetus status is mandatory. The Cochrane review has concluded that there is not enough evidence for recommending a certain therapy or for recommending an association of several

Table I. The differential diagnosis of hepatic disorders that can occur during pregnancy

	Incidence	Trimester affected	Total bilirubin mg/dL	Transaminases IU/L	Renal abnormalities	Specific features
Intrahepatic cholestasis of pregnancy	1:1000-1:10000	usually III	<5	<300	No	Intense pruritus Elevated bile acid levels
Acute fatty liver	1:700-1:16000	usually III	2-10	<1000	Could be present	Hypoglycemia, fatty liver (biopsy) Overlapping with preeclampsia
HELLP syndrome	1:500	Late second or typically third	<5	50-2000	Could be present	Hypertension Proteinuria trombocytopenia
Viral hepatitis	1-2:1000	Any time	>5 up to 30 in case of fulminant hepatitis	500-3000	No	Serologic diagnosis

therapies so that further studies are necessary [16].

Antihistamines such as diphenhydramine hydrochloride (Benadryl®) have been administered for the control of the pruritus. Cholestyramine acts by fixing the bile acids. By consequence, steatorrhea can be aggravated. It has no effect upon the hepatic function or upon the fetus [17]. Phenobarbital has been administered given its enzyme induction effect, but it does not lead to an amelioration of the pruritus and can favour neonatal acute respiratory distress [17]. Dexamethasone has been proposed for ICP treatment, but it is less efficient than ursodeoxycholic acid in ameliorating the bile acid levels and the hepatic function [18, 19]. S-adenosyl-L-methionine (SAME) reduces pruritus and bilirubin level [20, 21]. SAME is as efficient as ursodeoxycholic acid against pruritus. Ursodeoxycholic acid has been considered the elective therapy for ICP. In a retrospective study of a 12 year period of administration of ursodeoxycholic acid (Ursofalk®), 15 mg/ kg/day in 34 patients as compared to 14 historical controls with no treatment, the pruritus has been ameliorated and also the serum level of bilirubin and transaminases decreased. The incidence of premature birth was lower [22, 23].

In conclusion, in our patient, family aggregation and the occurrence of ICP at successive pregnancies suggest a genetic factor. Other two sisters of the same family had no liver disorders during pregnancy or at oral contraceptive use. This suggests that the genetic anomaly of this case, which we could not investigate, has an incomplete penetrance. The risk of ICP recurrence is about 60-70% for the next pregnancy [24].

The occurrence of intrahepatic cholestasis during pregnancy can determine complications such as preterm birth and a higher incidence of acute respiratory distress syndrome of the preterm newborn. The treatment of ICP is not yet standardized, but it allows an improvement of the fetal prognosis.

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