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Title: Maternal and Fetal outcomes in pregnancies complicated by intrahepatic cholestasis

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Abstract

Objective. The aim of study was to report maternal and fetal outcome of pregnancy affected by intrahepatic cholestasis of pregnancy.

Materials and methods. We reviewed maternal and fetal outcome of 70 consecutive women who were delivered XXXXX University Hospital between January 2012 and December 2017. Intrahepatic cholestasis of pregnancy diagnosis clinically and diagnosis confirmed after delivery when all symptoms regressed and laboratory changes returned to normal after delivery.

Results. Liver transaminases were elevated at 61 (87%) of women. The median delivery week was 37(26-42) gestational weeks. Preterm delivery rate was 40%. Eight (11%) women developed preeclampsia There was no stillbirth or neonatal death.

Conclusion. Still birth rate does not increase at pregnancy affected by intrahepatic cholestasis of pregnancy. However, it is needs investigation whether this result related preterm birth or not.

Keywords. Intrahepatic cholestasis of pregnancy, serum transaminases, stillbirth, preeclampsia

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is characterized by elevated serum bile concentrations or elevated aminotransferase levels with pruritus, which usually develops in the late second or third trimester and rapidly regressing after birth. The etiology of the disease is not fully understood, but probably depends on genetic predisposition, hormonal factors and environmental factors. Intrahepatic cholestasis is the most common liver disease specific to pregnancy (1). The incidence of intrahepatic cholestasis worldwide is likely to vary from 1 to 27.6%, depending on geographic variations, differences in sensitivity between ethnic groups and environmental factors (2-4).

The diagnosis of ICP is a diagnosis of exclusion and the diagnosis is confirmed by the regression of symptoms and laboratory changes after birth. The classic maternal manifestation of pregnancy-induced intrahepatic cholestasis is a generalized rash without itching. Itching is a common symptom in

pregnancy. Intrahepatic cholestasis of pregnancy is considered when serum bile acid levels or aminotransferases increase with pruritus. Pruritus of cholestasis distinguishes it from diseases characterized by high transaminase levels such as acute fatty liver of pregnancy, HELLP syndrome or severe preeclampsia. The absence of primary skin lesions together with itching helps to distinguish it from pruritic dermatoses specific to pregnancy and skin conditions not related to pregnancy. Infectious etiology is excluded by serological tests.

There is no solid evidence of an association between ICP and adverse pregnancy outcomes. Observational studies have reported a relationship between pregnancy intrahepatic cholestasis and adverse pregnancy outcomes such as spontaneous preterm labor, meconium passage, fetal distress and stillbirth (4). However, the frequency of adverse pregnancy outcomes in these studies is likely to vary widely depending on the criteria used in the definition of intrahepatic cholestasis in pregnancy, the limited number of patients included in the studies, and changes in the management of cholestasis in recent years. In the last two decades, although it is not evident that it decreases perinatal mortality, ursodeoxycholic acid is widely used and elective termination of pregnancy at 37 weeks of gestation is advised by organizations (4, 5).

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Materials and methods

We reviewed women who diagnosed as ICP at our hospital between January 2012 and December 2105. The diagnosis of ICP was based on clinical examinations. The study was approved by XXXX University Clinical Investigations Ethical Comitee.

All women had generalized pruritus in the absence of any dermatologic condition, viral hepatitis, hypertensive diseases of pregnancy, other hepatobiliary disease and all returned to normal as clinical and laboratory after delivery.

In this clinic, all women who suspected of having ICP had a routine investigation and follow-up. Initially, all suspected women had liver function tests (serum aspartate transferase [AST], serum alanine transferase [ALT], direct/indirect bilirubin, lactic dehydrogenase, alkaline phosphatase [ALP], gamma-glutamyl transpeptidase [GGT]), 24-h urine collection for protein excretion, viral hepatitis serology, and abdominal sonography. All women had normal ultrasonography of the liver and biliary tract. Than women undergo biweekly NST, amniotic fluid (AF) volume assessment using the four quadrant amniotic fluid index (AFI), and liver function tests weekly. All women were given ursodeoxycholic acid (started as 1 g/day and increased up to 20 mg/kg/day as needed) and antihistaminic if needed.

All patient printed and electronic files were reviewed and demographic data and pregnancy outcome measures were collected retrospectively. Descriptive statistics were used to analyze data. One sample Kolmogorov-Smirnov test was used to test normal distribution. All analyses were done by SPSS 23 Statistical Package program (IBM, NY, USA).

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Results

A total of 70 consecutive women who have ICP at study period were reviewed. Patient characteristics were given at Table 1. There were 25 (26%) primipar women. The onset of symptoms was after 30 weeks of gestation at 63 (90%) women. There were 19 (27 %) women at ≤32 gestational weeks and 27 (39%) at ≤34 gestational weeks. Four (6%) women had a history of a ICP and three (4%) severe preeclampsia or HELP syndrome. Either of liver transaminases were elevated at 61 (87%) of women and both were elevated at 50(71%) women. ALP and total bilirubin was elevated at most of women.

Follow-up and delivery outcomes were given at Table 2. Despite the ursodeoxycholic acid treatment 10 (14%) women suffered severe pruritus. Eight (11%) women developed preeclampsia. The median gestational weeks at delivery was 37 weeks and the median diagnosis to delivery interval was one week. Number of women who delivered at ≤37, ≤36, ≤34 and ≤32 gestational weeks were 47(67%), 28(40%), 11(16%) and 5(7%) respectively. Ten (14%) women delivered spontaneously at ≤36 gestational weeks. Number of fetus who has a birthweight under 2500 g and 1500 g were 20(29%) and 3 (4%) respectively. There was 3(4%) SGA fetuses at birth**.** Four (6%) fetus has a pH<7,2 and there was no perinatal date. A total three fetuses were hospitalized more than 24 hours at third level neonatal intensive care unit. None has birth asphyxia but delivered before 33 gestational weeks. None of women had uneventful postpartum course.

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Discussion

We reviewed maternal and fetal demographic data and outcomes of 70 women had ICP. Most of women were delivered at ≤37 weeks of gestation. The preterm delivery rate (≤ 36 gestational weeks) and spontaneous preterm delivery rate was high. The incidence of fetuses with SGA was not increased but low birthweight rate was high resembling high preterm delivery rate. A high rate of preeclampsia was detected. No adverse maternal outcome or perinatal death were encountered.

A recent two large retrospective cohort studies from Sweden and Australian reported favorable outcomes associated with ICP (3). The Sweden study reported increased risk of preterm delivery, gestational diabetes and preeclampsia but not of stillbirth (3). Australian study reported generally favorable outcomes associated with ICP, mild or severe, with no stillbirths. They reported a high proportion gestational diabetes, preeclampsia, and/or spontaneous preterm labor compared with the general population. These high rates of preterm delivery but no increased still birth rate are need to be considered in the management of ICP pregnancies. Authors of both cohort studies argues that no increased stillbirth rates were likely secondary to proactive medical management. The American College of Obstetricians and Gynecologists endorse active management protocols for ICP (5). Others, however, were against proactive management (6, 7). They proposed that given the relatively low frequency of population stillbirth, historically reported stillbirth rate for pregnancy with ICP have not sufficient power to accepts that stillbirth rate was increased at ICP (6, 7). The Royal College of Obstetrics and Gynecology does not support routine active management of intrahepatic cholestasis of pregnancy (ICP) affected pregnancies.(7)

The onset of symptoms occurred in the third trimester at 90% of women presenting after 30 weeks of gestation as reported by others (8, 9). Vast majority of women had elevated ST or ALT. In addition to symptoms, elevated serum bile acid levels are used to diagnose ICP at majority of studies.

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However, the onset of pruritus in ICP precedes elevation of bile acids by 3 weeks on average (8). Serum transaminases (ALT and AST) also rise in the majority of women with ICP and their elevation may precede the increase in bile acids by 1 to 2 weeks (8). The relative value of serum bile acids, and serum transaminases for the diagnosis of OC is a matter of debate because it is not yet certain which is the best prognostic indicator (10).

The sample size and retrospective nature of our study limits its results. However, this concerns are generally valid for all literature on ICP. The incidence of ICP is low and that is a barrier for prospective studies. We think that it is needed to clarify whether ICP related prematurity is due to spontaneous or iatrogenic preterm. Given that there is no solid proof of evidence that ICP increases stillbirth rate, we recommend individual management of ICP-affected pregnancies rather than routine early delivery.

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