New Insights on Intrahepatic Cholestasis of Pregnancy

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KEYWORDS

• Intrahepatic cholestasis of pregnancy • Itching • Bile salts • Ursodeoxycholic acid • Cholelithiasis

KEY POINTS

- Intrahepatic cholestasis of pregnancy (ICP) is a disorder of pregnancy occurring in the third trimester, characterized by pruritus, elevated serum transaminases and serum bile acids.
- Fetal delivery results in the resolution of symptoms, but recurrence is common.
- The etiology is likely multifactorial, and includes genetic factors and the influence of several environmental factors.
- Elevated serum bile acids have been shown to be correlated with fetal complications, such as anoxia, prematurity, fetal distress, perinatal death, and stillbirth.
- Ursodeoxycholic acid is the current therapy for this condition, owing to its possible benefits on pruritus, liver function tests, safety, and decreased rates of prematurity and fetal adverse.

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a specific liver disease with onset during pregnancy. It classically presents in the third trimester with pruritus, increased levels of serum transaminases, and high total serum bile acids (BA).[1] The symptoms and biochemical abnormalities resolve rapidly after delivery, but may recur in subsequent pregnancies.

EPIDEMIOLOGY

The incidence of ICP varies worldwide between 0.2% and 25% with the greatest prevalence up to 25% in the Araucanic race in South America.[2] In Europe, the prevalence

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is 0.5% to 1.5% of all pregnancies, and the highest incidence has been reported in Sweden.[3] In China, ICP is considered to be common, with an incidence of 2.3% to 6.0%.[4]

RISK FACTORS

The most important risk factors are reported in **Table 1**. A risk for the development of ICP in hepatitis C virus (HCV)-positive mothers has been described. The first retrospective study reported a highly significant incidence of ICP in HCV-positive pregnant women compared with HCV-negative women.[5] Subsequently, another prospective Italian study confirmed these results and suggested the need to investigate the HCV status in women with ICP.[6] In a study population of 21,008 women with ICP identified from the Finnish Hospital Discharge Register from 1972 to 2000, the incidence of hepatitis C was significantly higher than in controls.[7] More recently, a study analyzing data of women with births between 1973 and 2009, registered in the Swedish Medical Birth Registry, confirmed a strong positive association between ICP and hepatitis C both before and after ICP diagnosis.[8] Moreover, women with HCV infection who developed ICP have been found to exhibit a higher HCV viral load compared with those without ICP.[9] The link between ICP and HCV has not been completely explained so far, although several hypotheses can be suggested, including a defect in the transport of sulphated pregnancy hormones in the liver. In fact, it has been suggested that HCV would downregulate the expression of the ABC transporter multidrug-resistance–protein 2 in the liver, thus inducing a failure in the transport of various toxic substances.[10] Furthermore, another link may be with a defect in ABCB11 gene encoding the bile salt export pump (BSEP).[11]

It was reported from Sweden, Finland, and Chile that the incidence of ICP is higher in the winter than in the summer.[12–14] It has also been suggested that other exogenous cofactors, such as low selenium levels, may act in alteration of oxidative metabolism in the liver.[15] A low vitamin D concentration has also been reported in women with ICP, although its role has yet to be defined.[16] It frequently recurs in multiparous women who previously experienced ICP and is more common in multiple gestations.[17–19] In particular, in the Finnish study[19] the incidence of ICP was 14% in twin pregnancies, and 43% in triplets. Moreover, a relatively advanced age (>35 years) has been shown to be a risk for ICP.[20]

GENETICS

Genetic defects in at least 6 canalicular transporters have been found to be associated with ICP (**Table 2**). Genetic variations may implicate heterozygous or homozygous

Table 1
Risk factors related to intrahepatic cholestasis of pregnancy

Risk Factor	References
HCV	5–8
Seasonal onset (winter)	12–14
Low selenium levels	15
Low vitamin D	16
Multiple gestations	17–19
Advanced age	20