

# **INTRAHEPATIC COLESTASIS OF PREGNANCY. A REVIEW OF EPIDEMIOLOGY, CLINICAL FEATURES, FETAL RISKS, TREATMENT AND MANAGEMENT**

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## **REZUMAT**

Colestaza intrahepatică de sarcină este o formă reversibilă de coleastăză care apare la pacienți cu predispoziție genetică în ultimele luni de sarcină. Ea se caracterizează clinic prin prurit și leziuni tegumentare exclusiv secundare. Semnificația cunoașterii acestei dermatoze constă în asocierea ei cu riscuri fetale precum nașterea prematură, mortalitatea fetală perinatală și stress-ul fetal. Această asociere face necesară cooperarea interdisciplinară între medici dermatologi, gastroenterologi, obstetricieni și pediatri. Scopul acestui articol este de a sublinia caracteristicile clinice, de laborator și management-ul colestezei intrahepatice de sarcină, în vederea evitării riscurilor fetale.

**Cuvinte cheie:** coleastăză intrahepatică de sarcină, dermatoze de sarcină, icter

## **ABSTRACT**

Intrahepatic cholestasis of pregnancy is a reversible form of cholestasis, in genetically predisposed individuals, in late pregnancy. It is clinically characterised by the presence of pruritus and exclusively secondary skin lesions. The importance of knowing this dermatosis lies in the fact that is associated with fetal risks like prematurity, stillbirth and fetal distress. This is the reason why an interdisciplinary management between dermatologists, gastroenterologists, obstetricians and paediatricians is necessary. The purpose of this article is to delineate the clinical features, laboratory findings, and the management of intrahepatic cholestasis of pregnancy in order to avoid fetal risks.

**Key Words:** intrahepatic cholestasis of pregnancy, dermatoses of pregnancy, jaundice

## **INTRODUCTION**

Intrahepatic cholestasis of pregnancy (ICP) also called cholestasis of pregnancy, pruritus gravidarum, prurigo gravidarum, or jaundice of pregnancy is a specific dermatosis of pregnancy. It is a reversible form of cholestasis, in genetically predisposed individuals, in late pregnancy. It is clinically characterised by the presence of pruritus and exclusively secondary skin lesions and is usually associated with fetal risks like prematurity, stillbirth or fetal distress.

The specific dermatoses of pregnancy are a heterogeneous group of severely pruritic inflammatory skin diseases specifically related to pregnancy and/or the immediate puerperium period.

The most recent classification of the specific dermatoses of pregnancy, proposed by Ambros-Rudolph et al in 2006, includes the following diseases: pemphigoid gestationis (PG), polymorphic eruption of pregnancy (PEP), intrahepatic cholestasis of pregnancy (ICP), and atopic eruption of pregnancy (AEP).<sup>1</sup> While some of them are pruritic but otherwise harmless, others may be associated with an increased risk for mother and child.

This review article proposes to study ICP in order to establish a better understanding of this disease. Because of the lack of information in the Romanian literature, we consider that this article will be helpful for the practitioners. They need to understand how to challenge ICP in order to avoid the main fetal risks. In ICP an interdisciplinary management between dermatologists, gastroenterologists, obstetricians and paediatricians is absolutely necessary.

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## **HISTORICAL DATA**

In 1883, was reporting for the first time, a case of unexplained pruritus associated with visible jaundice in a pregnant woman, during the last trimester of pregnancy. The symptoms persisted until delivery and resolved spontaneously afterwards. The disease remained unnamed until the mid-1950's, when several Scandinavian clinicians described the clinical features in detail.<sup>2</sup>

In 1998, Shornick included ICP into the classification of the specific dermatoses of pregnancy.

## **EPIDEMIOLOGY**

The incidence of ICP is higher in South America and Scandinavia, but the highest rate was detecting in Chile (16%).<sup>3</sup> In Middle Europe, the prevalence is approximately 0.2 - 2.4%. There are no available data concerning this impairment in Romania. The endemical occurrence and the positive family history in up to 50% of cases indicate a genetic background of the disease.

## **PATHOGENESIS**

The pathogenesis of ICP seems to be multifactorial. The main factors considered to contribute to the manifestation of ICP are hormonal factors like estrogen and progesterone metabolites, genetic factors, and exogenous factors.<sup>4</sup>

Some clinical and epidemiological observations support the role of hormonal factors in the pathogenesis of ICP. These are:<sup>4</sup>

- An onset of the disease in the last trimester of pregnancy, which is a period with highest hormone concentrations;

- A recurrence of ICP in subsequent pregnancies in 45-70% of cases;

- The fact that the disease resolves after delivery, when the levels of placental hormones return to normal.

The major estrogen in pregnancy is estradiol. Estradiol metabolites like estradiol-17 $\beta$ -D glucuronide and estriol-16 $\alpha$ -D glucuronide, were found to be cholestatic in animal studies. They diminished the uptake of bile acids at the basolateral membrane of hepatocytes.

The excretion of estradiol-17 $\beta$ -D glucuronide in the biliary canals is realised within the canalicular multispecific conjugate export pump (MRP2), where

in ICP cases was observed a trans-inhibition of the canalicular bile acid export pump (BSEP). The result is a decreased biliary excretion of estrogen metabolites.<sup>4,5</sup>

Progesterone metabolites play an even more important role in the pathogenesis of ICP compared to estrogen metabolites.<sup>4</sup> Hepatic biotransformation of progesterone includes pregnanolone and pregnanediol. There are four isomers 3 $\alpha$ /3 $\beta$  and 5 $\alpha$ /5 $\beta$  which are formed and then metabolized by hydroxylation and conjugation with sulfate and glucuronic acid.

The most prevalent steroids during pregnancy are mono- or disulfated progesterone metabolites. The levels in plasma are between 10 to 15 $\mu$ mol/l.<sup>4,6</sup> These steroids are highly increased in the serum of patients with ICP, especially the 3 $\alpha$  and 5 $\alpha$ -isomers.<sup>4,7,8</sup> Thus, in ICP, the biliary and fecal excretion of sulphated and glucuronidated progesterone metabolites are decreased.<sup>4,9,10</sup>

The existence of a genetic predisposition for ICP has been supported by the observation that the condition shows an endemic occurrence and a positive family history in up to 50% of the cases. In addition, there is also a higher incidence of ICP in mothers and sisters of the patients with ICP.<sup>4,11,12</sup>

Because of the genetic mutations in other cholestatic disorders, researchers are looking for a genetically defined aberration in structure or function of hepatic transport proteins. Ropponen et al, in a study over a small number of patients with ICP, identified mutations in the ABCB4 gene and ATP8B1 gene.<sup>13</sup> Because of this, it has been suggested that genetical factors determine a mild malfunction of the canalicular transporters, which only leads to clinical symptoms of cholestasis when the capacity of the transporters to secrete is exceeded. With normal hormone levels, this defect has no clinical implications but becomes only evident with high hormone levels in pregnancy.<sup>14</sup>

In the pathogenesis of ICP, environmental and alimentary factors may increase the risk of ICP in predisposed women. It has been suggested that decreased serum selenium levels could influence the bile secretion. In the liver, selenium is a cofactor of several enzymes in the oxidative metabolism.<sup>15,16</sup>

## **CLINICAL FEATURES**

Usually, ICP starts in the third trimester of pregnancy, but in 25% of cases, it appears as early as the late second trimester of pregnancy, or even much

earlier, in the first trimester of pregnancy, in 10% of the cases.<sup>17</sup>

Of importance, in ICP here are no primary skin lesions. Pruritus is the most common symptom. Typically starts on palms and soles and then quickly becomes generalized with the evolution of the disease. It persists throughout the duration of pregnancy. Only 10% of the ICP cases will present jaundice.<sup>18</sup> Jaundice only complicates the most severe and prolonged episodes.

Clinical features in ICP correlate with disease duration. At the beginning of pruritus, the skin appears completely normal, but with disease progression, secondary skin lesions, such as excoriations and prurigo nodules can appear due to scratching. When the patient presents within few days after the onset, the symptoms will consist of linear excoriations or scratch marks. With the progression of the disease, after several weeks, we can find even prurigo nodules.

Skin lesions usually involve the shins and lower arms, but also other sides such as buttocks or abdomen can be affected.

Jaundice present in only 10% of the cases, appears usually after 2 - 4 weeks of evolution and is due to the association of intrahepatic cholestasis with extrahepatic cholestasis. Jaundice can be associated with steatorrhea with decreased absorption of fat-soluble vitamins and weight loss. Therefore, vitamin K deficiency is a possible consequence. In these cases, if the patient is not supplemented with adequate doses of vitamin K, increased intra- and postpartum haemorrhage can occur.

## DIAGNOSTIC TESTS

Due to the intrahepatic cholestasis, total serum bile acids are increased. This feature in combination with pruritus is highly suggestive for the diagnosis of ICP.

For every pregnant woman with pruritus, liver function tests must be performed. An upper abdominal ultrasound must only be considered in cases with abdominal symptoms. It is not necessary to perform a liver or skin biopsy. However, if the liver biopsy is done, the histopathological exam shows mild focal irregular intrahepatic cholestasis with small amounts of bile pigment in centrilobular hepatocytes and macrophages, without necrosis or inflammation.

In ICP, the most common indicator and also the most sensitive one is a rise of serum bile acid levels.

The clinician has to know that pregnancy changes the serum levels of some standard laboratory liver parameters. For example in healthy pregnancies, total serum bile acids are slightly higher ( $6.6 \pm 0.3 \mu\text{mol/l}$ ) and levels up to  $11.0 \mu\text{mol/l}$  are accepted as normal in late gestation. (Table 1) In non-pregnant woman the levels are usually lower ( $5.7 \pm 0.4 \mu\text{mol/l}$ ).<sup>19,20</sup>

Alanine transaminase (ALT) is a very sensitive parameter for intrahepatic cholestasis of pregnancy, too.<sup>21</sup> When the liver cell is damaged, ALT is released into the blood in increasing amounts. Some studies reported that 20-60% of women with pruritus and elevated serum bile acid levels, had 2-10 fold raises in transaminases.<sup>22,23</sup>

Hyperbilirubinemia (up to  $100 \mu\text{mol/l}$  or 5mg/dl) is detected in only 10-20% of cases.  $\gamma$ -GT is usually

**Table 1.** Differences in laboratory tests between normal pregnancy and ICP.

Laboratory tests	Normal pregnancy	Intrahepatic cholestasis of pregnancy
<b>Total serum bile acids</b>	slightly elevated ( $6.6 \pm 0.3 \mu\text{mol/l}$ , up to $11 \mu\text{mol/l}$ accepted as normal)	elevated ( $>11 \mu\text{mol/l}$ )
<b>Alanine transaminase (ALT)</b>	normal	elevated (in 20-60% of cases, with 2-10-fold rises)
<b>Alkaline phosphatase (ALP)</b>	normal	elevated
<b><math>\gamma</math>-GT</b>	lower	normal/slightly elevated (in 30% of cases)
<b>Albumin</b>	normal	slightly lower
<b><math>\alpha</math>2-globulins</b>	normal	moderately elevated
<b><math>\beta</math>-globulins</b>	normal	very elevated
<b>LDL-cholesterol, triglycerides</b>	normal	elevated
<b>HDL- cholesterol</b>	normal	slightly lower
<b>Lipoprotein X (LpX)</b>	absent	present
<b>Bilirubinemia</b>	normal	elevated (in 10-20% of cases)

normal or slightly elevated in ICP patients while in normal pregnancy, it is typically lower.<sup>24</sup>

As already mentioned above, skin biopsy is not necessary. If performed, it shows non-specific changes depending on the clinical appearance. Direct immunofluorescence or indirect immunofluorescence are negative.

## **EVOLUTION AND MATERNAL PROGNOSIS**

The prognosis for the mother is generally good. A considerable discomfort for the patient can appear if pruritus is severe and generalized. In cases of jaundice and fat malabsorption, there is a possible maternal risk for intra- and postpartum haemorrhage. Adequate doses of vitamin K will combat this maternal risk.

After delivery, pruritus and jaundice disappear usually within 1-2 days, but sometimes they may persist for 1-2 weeks.

ICP patients should be informed about the possible risk of recurrence of the disease in subsequent pregnancies, as reported in 45-70% of cases. Furthermore, a minimal risk of recurrence exists related to the intake of oral contraceptives. Despite this, the use of low-dose oral contraceptives after normalization of liver function tests can be considered. The patient should be counselled to stop medication if pruritus and cholestasis occur.

ICP is not associated with an increased risk of early abortion. Breastfeeding is not contraindicated.

## **FETAL PROGNOSIS**

ICP is a disorder with severely increased fetal risks if not handled with care. The most common risk is intrapartum fetal distress with a prevalence of 22 to 33% of deliveries. Other fetal risks are: premature births with an incidence of 16-60% and stillbirths with an incidence of 1-2%.<sup>4,25</sup>

The pathogenesis of the fetal risk is not completely understood. There are some factors thought to be involved such as: an increased flux of bile acids from the mother to the fetus and a reduced ability of the fetus to eliminate bile acids with retention of these.

It has been shown that with higher bile acid levels, in particular if exceeding 40µmol/l, fetal risks are more frequent.<sup>25,26</sup> Therefore, in such cases, an intensive fetal surveillance is necessary.

In ICP, the frequency of malformations is not increased. Birth weights are adequate for gestational age.

In severe cases, complicated by concomitant

extrahepatic cholestasis, there is a high risk of antepartum fetal hemorrhage due to vitamin K deficiency.

## **DIFFERENTIAL DIAGNOSIS**

ICP is a specific dermatosis of pregnancy. Therefore, primarily we have to exclude other specific dermatoses of pregnancy. In PG and PEP we have primary skin lesions and the total serum bile acid levels are not elevated (<11µmol/l).

For the clinician it can be a particular challenge to distinguish ICP from AEP, especially the P-type variant (prurigo-type). An important feature to differentiate the two is the gestational age at onset. AEP usually starts earlier, before the third trimester of pregnancy, while ICP manifests in late pregnancy. If the clinical features overlap, the elevated serum bile acid levels confirm the diagnosis.

The differential diagnosis includes also skin disease with pruritus as major symptom like allergic reactions or scabies.

If the patient presents with jaundice we have to exclude other conditions associated with this sign like acute fatty liver of pregnancy, viral hepatitis, pre-eclampsia with increased liver enzymes, hyperemesis gravidarum, bile duct obstruction, metabolic diseases, haemolytic diseases, drug icterus, or hyperbilirubinemic states.<sup>27</sup>

## **TREATMENT AND MANAGEMENT**

In the majority of obstetric centres, ICP is still often neglected and treated expectantly. First of all, it is important to recognise the disease and then, obstetric surveillance and prompt treatment is the key to avoid fetal risks. In the management of ICP an interdisciplinary collaboration is absolutely necessary. Because ICP starts typically in the third trimester of pregnancy, the side effects of the treatment are usually minimized.

As pointed out before, the fetal prognosis correlates with disease severity. Therefore, the aim of treatment is the reduction of bile acids in order to prolong the pregnancy and reduce both fetal risks and maternal symptoms. Obstetric surveillance is very important and the management consists in:

- Weekly fetal cardiotocographic (CTG) registration, from 34 weeks of gestation;
- Weekly assessment of serum bile acids, transaminases, and bilirubin;
- Control of prothrombin time if the patient suffers from steatorrhea.

**Table 2.** Key features in ICP.

<b>Incidence</b>	Chile (about 16%) Middle Europe (about 0.2-2.4%)
<b>Onset</b>	- mainly-third trimester of pregnancy - occasionally-second trimester (25% of cases) or - extremely rarely-first trimester of pregnancy (10% of cases)
<b>Clinical features</b>	- positive family history in 50% of cases - intense pruritus - no primary skin lesions - only secondary skin lesions due to the scratching (excoriations, prurigo nodules)
<b>Laboratory findings</b>	Elevated serum bile acid levels Elevated alanine transaminase (ALT) DIF negative Histopathological findings: non-specific
<b>Differential diagnosis</b>	- other specific dermatoses of pregnancy (PG, PEP, AEP) - other hepatic disorders coinciding with pregnancy (acute fatty liver of pregnancy, viral hepatitis, pre-eclampsia with increased liver enzymes, hyperemesis gravidarum, bile duct obstruction, metabolic diseases, haemolytic diseases, drug icterus, or hyperbilirubinemic states)
<b>Treatment</b>	Ursodeoxycholic acid (UDCA): 15mg/kg/day
<b>Prognosis</b>	Mother: - good - recurrence in subsequent pregnancies Fetal: - stillbirths (in 1-2% of cases) - intrapartum fetal distress (in 22-33% of cases) - premature births (in 19-60% of cases)

The obstetricians have to put in balance the risk of premature delivery due to induction of labor against the risk of sudden death in utero. Every premature delivery can be associated with complications.

Many antiprurigen drugs have been proposed as treatment option for ICP patients including antihistamines, anion exchange resins, phenobarbital, S-adenosylmethionine (SAM), and ursodeoxycholic acid (UDCA).

Colestyramine is an anion exchange resin. It binds bile acids and interrupts their enterohepatic circulation. Nowadays, colestyramine is not considered to be first line therapy for ICP, because the fetal risk could not be lowered by this treatment.

S-adenosylmethionine (SAM) is a precursor of glutathione and a methyl group donor. It influences the composition and fluidity of hepatocyte plasma membranes and also the methylation and biliary excretion of hormone metabolites.

In ICP, the use of S-adenosylmethionine is still a matter of debate. Some studies revealed a significant decrease of pruritus, bilirubin, and ALT after daily intravenous application of SAM, but others showed no effect.<sup>28-30</sup>

The use of phenobarbital relieved pruritus in only 50% of patients and had no effect on liver parameters.<sup>31,32</sup>

Hirvioja et al were the only ones who showed a significant clinical and laboratory improvement in patients treated with dexamethasone, a potential inhibitor on fetoplacental hormone synthesis.<sup>33</sup>

UDCA has been successfully used in Chinese medicine for more than 5.000 years in the treatment of various liver diseases. It is a naturally occurring hydrophilic bile acid, which improves the clinical and biochemical tests in a variety of cholestatic liver diseases. UDCA is considered to be the first line treatment option for patients with primary biliary cirrhosis (PBC), where it improves the survival rate without liver transplantation. Because of the positive effect in PBC it was also used in the treatment of ICP.

To reduce maternal symptoms and fetal risks, the recommended dose for UDCA is 15mg/kg/day.<sup>34</sup> (Table 2) Occasionally, mild diarrhea can appear due to treatment.

UDCA has been shown to reduce premature labor, fetal distress, and fetal deaths. The other

drugs like phenobarbital, S-adenosylmethionine, and cholestyramine do not improve fetal prognosis. Therefore, UDCA remains the treatment of choice for patients with ICP.<sup>34</sup>

## **CONCLUSIONS**

ICP is a specific dermatosis of pregnancy associated with fetal risks like: premature births, intrapartum fetal distress and stillbirths.

The positive diagnosis is sustained by the elevation of the total serum bile acids level plus the presence of pruritus and only secondary skin lesions.

In order to reduce maternal symptoms and fetal risks, ursodeoxycholic acid in dose of 15mg/kg/day is the treatment of choice.

An interdisciplinary management between dermatologists, gastroenterologists, obstetricians and paediatricians is absolutely necessarily.

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