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Intrahepatic cholestasis of pregnancy

Colestasis Intrahepática gestacional

Omar F. Yanque Robles[1,a,*]

Abstract

The intrahepatic cholestasis of pregnancy (ICP) is characterized by pruritus in the pregnant and elevated levels of serum bile acids, in addition it is associated with increased obstetric events such as preterm labor, meconium stained amniotic fluid and intrauterine fetal death. Its incidence is variable, being the South American and Asian countries, where the highest rates are reported. There is no known cause, but there are risk factors as well as well-studied genetic defects. The diagnosis should help to its classification, an early onset of ursodeoxycholic acid (UDCA) and a counseling regarding complications and termination of pregnancy.

Keywords: gestational cholestasis, intrahepatic cholestasis of pregnancy, obstetric cholestasis.

Resumen

Gestational intrahepatic cholestasis (IGC) is characterized by pruritus in the pregnant woman and elevated levels of serum bile acids, in addition it is associated with increased obstetric events such as premature delivery, meconium stained amniotic fluid and intrauterine fetal death. Its incidence is variable, being the South American and Asian countries, where the highest rates are reported. There is no known cause, but there are risk factors as well as well-studied genetic defects. The diagnosis should help its classification, an early onset of ursodeoxycholic acid (AUDC) and counseling regarding complications and termination of pregnancy.

Palabras clave: gestational cholestasis, gestational intrahepatic cholestasis, obstetric cholestasis.

[1]Department of Obstetrics and Gynecology, Edgardo Rebagliati Martins National Hospital, EsSalud, Perú.

[a]Fellow of the American College of Obstetricians and Gynecologists

ORCID:
[*]https://orcid.org/0000-0002-3431-2016

Corresponding author:
Omar Fernando Yanque Robles
Address: Av. Edgardo Rebagliati 490, Jesus María, Lima, Perú,
Telephone: +51 991215280.

Email: omaryanque@gmail.com

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Introduction

The intrahepatic cholestasis of pregnancy (ICP) is a liver disease that is exclusive to the pregnancy. It is clinically characterized by maternal pruritus without apparent cause, with high levels of bile acids in the blood and / or transaminases at the end of the second trimester and third trimester of pregnancy. After the childbirth, the pruritus and the impaired liver function are resolve, with a faster clinical resolution (1, 2, 3, 4).

Unlike other dermatoses that are accompanied by pruritus during the pregnancy, the ICP is particularly interesting by the increased risk of adverse fetal events. The initial observational studies, with a limited number of patients, consistently found an association between ICP and adverse fetal outcomes, such as spontaneous preterm labor, meconium stained amniotic fluid, fetal distress, and intrauterine fetal death (stillbirth). A research made in Sweden between 1999-2002 showed that these adverse events were more related to serum bile acid values above 40 µmol / l (2, 4).

Older studies about PCI reported a percentage of stillbirths of up to 15%, decreasing this value to 3.5% or less, in more recent studies (1, 2, 3, 4). The evolution of the diagnosis and management of this entity is a perfect example of the reason for the inconsistency of the data on fetal risk, compared to older studies.

Epidemiology

The incidence of ICP shows variation between different countries and populations. In South America, Chile reported an incidence of 14% (4), although later its reports decreased to 1.5 - 4% (5). In Northern Europe, the incidence is approximately 1 - 1.5% of the pregnancies (7, 8). In France and Italy, the percentage ranges from 0.4 - 1% (9, 10). In the United Kingdom, the ICP affects only 0.6% of Caucasian pregnant women, while 1.4% of Asian pregnant women have the disease (11). In China, the ICP is considered common, with an incidence

of 2.3 to 6% (12). The variable incidences can be explained by the differences regarding the diagnostic criteria used, as well as environmental and genetic factors specific to each population.

The risk factors for developing ICP, which have been described in the literature, are distributed in Table 1. The genetic defects of canalicular transporters, which have been associated with ICP, are found in Table 2.

Table 1. Risk factors related to ICP

Hepatitis C Virus Infection [13, 14, 15, 16]
Seasonal start (winter)[17, 18, 19]
Low selenium levels [20]
Low vitamin D levels [21]
Multiple pregnancy [22, 23, 24]
Advanced age (> 35 years) [25]

Table 2. Genetic defects associated with ICP

Canalicular transporters	Chromosome locus	Biochemical / histological characteristics	Clinical spectrum
ATP8B1 (FIC1)	18q21-22	High serum bile salts; decreased gamma-glutamyl transferase / 'soft' cholestasis with coarse and granular bile	ICP, Familial Intrahepatic Cholestasis Type 1, Benign Recurrent Cholestasis Type 1, Byler's disease
ABCB11 (BSEP)	2q24	High serum bile salts; decreased gamma-glutamyl transferase / portal tract fibrosis; proliferation of bile ducts	ICP, Byler's syndrome, Familial intrahepatic cholestasis type 2, Benign recurrent cholestasis type 2, drug-induced cholestasis, transient neonatal cholestasis
ABCB4 (MDR3)	7q21	High serum bile salts; gamma-glutamyl transferase increased / fibrosis, bile duct disappearance syndrome (ductopenia); low phospholipids in bile	ICP, familial intrahepatic cholestasis type 3, cholestasis with low phospholipids, neonatal cholestasis, drug-induced cholestasis
ABCC2 (MRP2)	10q24	Elevated serum conjunct bilirubin / dark liver pigmentation	ICP, Dubin-Johnson syndrome
NR1H4 (FXR)	12q23.1	Elevated serum bile salts	ICP, familial cholelithiasis, idiopathic childhood cholestasis
FGF19	11q13.3	Elevated serum bile salts	ICP, bile acid malabsorption

Modified to[26].

Clinical presentation

The ICP usually manifests during the late second or third trimester of pregnancy, and its main feature is the pruritus. About 80% of cases have been described after 30 weeks of gestation; however, cases as early as 8 weeks of pregnancy have been reported (6).

The characteristics of pruritus are classically described as: generalized, predominantly in palms (hands) and soles (feet), which increases at night and typically becomes progressively more severe as the pregnancy progresses. As the disease progresses and becomes general, secondary skin changes can occur due to scratching, which can range from minor excoriations to severe prurigo nodularis. The injuries generally tend to be concentrated in the extremities, although they may involve sites such as the buttocks and abdomen (6, 26).

Auxiliary exams

The laboratory alteration most frequently found in the patient with ICP is the serum elevation of the concentration of total bile acids. However, the great variability of what are considered abnormal values of total bile acids must be known, which will depend on the method of quantification by the laboratory, the fasting state of the patient, the population studied and the gestational age at the time of diagnosis (6). The suggested diagnostic value for ICP ranges from 10 to 14 µmol / l (6, 26). The level of bile acids in the blood is the most sensitive and specific marker for the diagnosis of ICP, after excluding other causes of cholestasis (27).

The attempt to search for other markers for ICP has led to the study of autotaxin (ATX). The ATX is an essential lysophospholipase-D for the angiogenesis and neuronal development during the embryogenesis. The effects of ATX are largely mediated by the enzymatic formation of lysophosphatidic acid (LPA). The LPA and ATX levels are significantly increased in women with ICP, compared to their controls without disease. Furthermore, high ATX activity has been shown to be a highly sensitive and specific biomarker to differentiate ICP from other liver disorders related to pregnancy or dermatosis accompanied by pruritus. Unlike to the total bile acids, the ATX is influenced neither by food intake nor by circadian rhythm (28).

When there is no availability of dosing total bile acids, it must consider to in most cases of ICP, the liver transaminases will also be elevated. The alanine transaminase (ALT) or glutamic pyruvic transaminase (GPT) is more sensitive than aspartate transaminase (AST) or glutamic oxalacetic transaminase (GOT) in the

diagnosis of ICP, and may be elevated from 2 to 30 times its usual value (29).

Treatment

The ursodeoxycholic acid (UDCA) it is the drug that has been shown to be effective in reducing the pruritus, improving liver test results, and improving perinatal results. The UDCA dose can be evaluated according to the symptoms, usually recommended between 500mg to 2g per day. The most commonly secondary effects associated to the drug are: nausea, vomiting, or liquid stools; however these effects are described in a small group of pregnant women. (29, 30, 31, 32).

The mechanisms of action attributed to the UDCA are:

- Its hydrophilic properties per se (33).
- The improvement of both the transport and the secretion of bile acids by the liver by increasing the activity of canalicular transporters (33).
- The improvement of the transport of bile acids through the placenta, reducing the exposure of bile acids to the fetus (33).
- Partial reduction of the accumulation of bile acids in the mother, placenta and fetus; showing upregulation of ABCG2 in trophoblast cells (34).

There are studies with rifampicin, S-adenosylmethionine, guar gum (guaran), activated carbon, dexamethasone, cholestyramine, sage, and agents from China, but there is insufficient evidence to indicate its effectiveness alone on ICP (26, 29, 35).

Complications

The ICP has as complications the increased incidence of spontaneous preterm labor, non-reassuring fetal states, meconium-stained amniotic fluid, and intrauterine fetal death (stillbirth). At the date the studies have shown a linear relationship of total bile acid levels with such complications (29). A recent meta-analysis of individual patient data, even with the limitations of this type of review, has determined that the risk of intrauterine fetal death is increased in patients with ICP when total bile acid concentrations are 100 µmol / l or more (36). With all the data provided and the studies reviewed, it is prudent to classify the ICP according to the total bile acid levels: mild (10 - 39 µmol / l), moderate (40 - 99 µmol / l) and severe (≥ 100 µmol / l). The last group being the one most related to severe complications and therefore in which more aggressive management would be justified (36, 37).

Intrauterine fetal death

The pathogenesis of fetal death, related to the ICP is a sudden and unpredictable event not yet well understood. Currently the studies suggest that it is associated with a fetal heart event, rather than chronic placental insufficiency. The in vitro studies in rat cardiomyocytes have shown that elevated bile acids can decrease the frequency of contraction, reduce the amplitude of contraction, prevent cardiomyocyte synchronization, promote loss of cellular integrity, and reduce the duration of action potentials (38, 39, 40, 41). The bradycardia-tachycardia events, increased PR interval and difference in fetal myocardial deformation have been observed in human fetuses of ICP patients (42, 43, 44, 45, 46).

Full-term pregnancy

The most important point regarding the management of ICP is to assess the optimal gestational age to minimize the risk of perinatal mortality. The prenatal fetal monitoring strategies have not been shown to be effective, resulting in a notable variation in the best time to decide the finish pregnancy, due to attempts to balance the risks of intrauterine fetal death against the neonatal and childhood complications, product of preterm labor. Currently, there are two studies that analyzed cohorts to retrospective form and determined that the optimal pregnancy termination strategy (where the risk of fetal mortality is minimized) is given at 36 weeks gestation (47, 48). It is necessary to individualize the case of each patient for the final decision, to evaluate the clinical characteristics, the auxiliary examinations, the comorbidities and, finally, the expectations of the parents.

Conclusion

The pruritus during the pregnancy, particularly in the last trimester it should never be neglected. The diagnostic approach, to exclude or confirm the ICP, it must include in the treatment plan the serum measurement of total bile acid levels, as well as the pertinent examinations to rule out other liver pathologies. The ICP should be classified as mild, moderate, or severe, based on total bile

acid levels. Due to the association with severe fetal risks, this disease must be diagnosed early, start treatment with UDCA and have strict obstetric surveillance. The counseling on complications and the termination of pregnancy should prevail in prenatal care, in the same way as a timely reference to levels of care that have experience in the management of this pathology.

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