INTRAHEPATIC CHOLESTASIS OF PREGNANCY

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1. INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a reversible form of cholestasis that appears during the third trimester of pregnancy (rarely before week 26) and resolves spontaneously after delivery. It clinically presents with pruritus without rash and a progressive increase in bile acids.

It is a disease of unknown cause but associated with hormonal, environmental and hereditary factors. ICP is the most frequent liver disease during pregnancy and the second cause of jaundice in pregnancy (the first is hepatitis, and the third is gallstones). Its incidence is from 0.1 to 2%, although with a high geographical variation (more frequent in South America). Maternal age, multiparity, multiple gestation, hepatitis C, and family or personal history of cholestasis are risk factors.

Historically, it has been associated with increased foetal morbidity and mortality, although some data are controversial. ICP is associated with preterm delivery, presence of meconium, neonatal ICU admission, and foetal death, although some adverse perinatal outcomes are related to iatrogenic prematurity. Nevertheless, those cases with an increase in bile acids of more than 100 μmol/L appear to be related to higher likelihood of stillbirth.

2. DIAGNOSIS

The diagnosis of ICP is mainly clinical. It consists of the onset of itching during the third trimester of pregnancy (10% in the first trimester, 25% in the second trimester) associated with liver dysfunction or an increase in total bile acids, although normal values do not exclude the diagnosis. This is a diagnosis of exclusion in which other causes of itching or liver damage must be ruled out. ICP resolves spontaneously a few days after delivery (maximum 4 weeks).

2.1 MATERNAL CLINICAL FEATURES

- Itching (80%): it begins on the palms of the hand and soles of the feet and progresses centrally until it is generalised. It occurs without a rash, although they may present excoriations from scratching. It is often more pronounced at night, causing insomnia and irritability. It can precede the analytical changes by weeks.

- Jaundice (up to 25%): appears 2 weeks (1-4 weeks) after itching, with dark urine and pale stools.
- Nausea, vomiting, discomfort in the right hypochondrium.
- Steatorrhea due to fat malabsorption: is infrequent but, in these cases, the absorption of fat-soluble vitamins such as vitamin K can be altered and cause coagulation disorders.

2.2 LABORATORY INVESTIGATIONS

ICP can alter the following laboratory parameters:

- Bile acids (cholic and chenodeoxycholic acid) > 10 µmol/L. It is the most sensitive diagnostic test, although normal values do not exclude the diagnosis
- Transaminases (ALT/AST) > 35-70 IU/L
- Total bilirubin > 1.2 mg/dl (by the increase of direct fraction)
- Alkaline Phosphatase (ALP) > 500 IU/L
- Gamma-Glutamyl Transferase (GGT) > 40 IU/L.
- Prothrombin time < 70% (due to vitamin K malabsorption, although this is rare)

Therefore, in case of suspected ICP, a laboratory investigation should be undertaken, including: complete blood count, ALT/AST, GGT, bile acids, total bilirubin, glucose, creatinine, Na/K and coagulation screen.

Additional investigations should be considered in pregnant women with an atypical or uncertain picture of ICP (Appendix 1):

- Screening for preeclampsia / HELLP syndrome: angiogenic factors.
- Hepatotropic viral infections (HAV, HBV, HCV, HEV) and non-hepatotropic viral infections (EBV, CMV and HHV-6) if the above are negative.
- Antimitochondrial and smooth muscle antibodies: to rule out autoimmune hepatitis.

If the laboratory investigations are normal and the symptoms persist, it is recommended to repeat every 2-3 weeks, since a significant number of women will experience itching days or weeks before the appearance of liver disorders (confirmation diagnosis).

3. TREATMENT

The role of the treatment in ICP is to improve maternal symptoms (variable and unrelated to bile acid concentration), but there is no evidence that the treatment improves bile acid disorders or perinatal outcomes. A staggered treatment will be carried out, beginning with topical emollients and antihistamines in patients with few symptoms, and reserving ursodeoxycholic acid for those patients with more symptoms or laboratory abnormalities.

3.1 TOPICAL EMOLLIENTS

Topical emollients are safe agents. Although their efficacy has not been proven, they can produce temporary relief from itching.

- **Calamine lotion**
- **Menthol 0.25% aqueous creams**: postpartum discontinuation due to risk of neonatal apnoea

3.2 ANTIHISTAMINES

Although the effectiveness of antihistamines is uncertain, consider their use for sedative effect at night.

- **Dexchlorphenamine**: 2-6 mg every 6-12 hours
- **Hydroxyzine**: 25-50 mg every 8 hours

3.3 URSODEOXYCHOLIC ACID

Dose of 15 mg/Kg/day (maximum dose of 21 mg/Kg/day)

Usual dose: 600-1200 mg orally every 24 hours divided into two daily doses.

It is the treatment of choice in pregnant women with moderate-severe itching and laboratory abnormalities compatible with ICP. Well tolerated (most frequent side effects: transient nausea and intestinal discomfort). It produces a reduction in maternal itching and decreases maternal plasmatic bile salts and transaminases.

3.4 VITAMIN K

Dose: 10 mg intramuscular every 7 days.

Vitamin K is recommended in pregnant women diagnosed with ICP who presented coagulation disorders (prolonged prothrombin time). In the absence of coagulation disorders, no correlation with postpartum haemorrhage has been observed.

In cases of contraindication of the intramuscular route (patients with anticoagulant treatment), the alternative regimen would be 10 mg orally every 24 hours, although absorption is low.

3.5 OTHER AGENTS

- **Rifampicin** (second-line treatment): very limited experience, in some studies improvement of itching and a reduction of bile acids and transaminases. Dose of 150-300 mg every 12 hours. Potentially serious adverse effects (nausea, anorexia, haemolytic anaemia, renal failure and hepatitis).
- **Cholestyramine** and **dexamethasone** are not currently recommended treatments.

4. MANAGEMENT

4.1 MATERNAL FOLLOW-UP

Frequency of maternal monitoring should be based on a woman's discomfort and laboratory abnormalities:

- **Every 2-3 weeks** if good symptom control, normal laboratory investigations and bile acids < 40 µmol/L
- **Every 1-2 weeks** if progression of symptoms, laboratory abnormalities or bile acids ≥ 40 µmol/L

Recommended laboratory investigations during follow-up:

- Blood count, ALT/AST, GGT, total bilirubin, glucose, creatinine, Na/K and coagulation screen
- **Bile acids:** due to its prognostic role, it will be investigated at diagnosis, at 36-37 weeks' gestation and every 1-2 weeks after 37 weeks' gestation.

4.2 FOETAL FOLLOW-UP

ICP has been associated with preterm delivery (spontaneous and iatrogenic), presence of meconium, neonatal ICU admission, and stillbirth. Although there are controversial data, the most recent evidence shows a significantly higher incidence of stillbirth in those cases with a bile acid level ≥ 100 µmol/L. Stillbirth could be related to an arrhythmogenic effect of bile acids on the foetal heart.

There is no evidence of any test that ensures foetal well-being, but, despite the limitations, it is recommended:

- **Control of foetal movements** and notification of any reduction or change to their maternity unit
- Ultrasound control: usual controls according to gestational age. There is no evidence of placental insufficiency in ICP, so we do not recommend additional Doppler studies.
- Weekly **CTG** from 38-39 weeks' gestation.
- **Functional echocardiography** if bile acids ≥ 40 µmol/L. The increase in bile acids has been associated with adverse effects on cardiomyocytes. Several studies show that ICP can produce an increase in the AV interval and/or left ventricular dysfunction in the foetus, mainly an alteration of the myocardial performance index or TEI index (see functional specific protocol), which has been related to an increase of perinatal adverse events. In the echocardiography, a complete morphometric and functional evaluation will be carried out, including the measurement of the AV interval. In the case of prolongation of AV interval > 2 SD and/or the presence of signs of heart dysfunction, the case will be assessed according to the gestational age and maternal symptoms.

4.3 TIMING OF BIRTH

Despite the lack of an evidence-based recommendation, taking into account the risks of iatrogenic prematurity and the increase in adverse perinatal outcomes (basically stillbirth) in cases with elevated bile acids, the following is suggested (see Figure 1 in section 7):

- **Planned birth after 40 weeks' gestation:** if there is good control of symptoms and bile acids < 40 µmol/L.

- **Planned birth after 37 weeks' gestation:**
  - Bile acids ≥ 40 µmol/L
  - Poorly controlled symptoms despite treatment and/or worsening liver function tests
  - History of ICP and stillbirth
- **Planned birth before 37 weeks' gestation**: in selected cases (bile acids > 100 µmol/L), planned birth should be considered before 37 weeks' gestation. In these cases, a lung maturity test (quantusFLM®) and/or eventual foetal lung maturation (see specific protocol) should be planned.

5. POSTPARTUM FOLLOW-UP

The itching resolves during the first postpartum days. It is not recommended to request laboratory investigations in the immediate postpartum period because liver disorders can persist up to 10 days after delivery. In cases with laboratory abnormalities during pregnancy, it is recommended to perform an analytical control after the puerperium (complete blood count, liver profile, bile acids and coagulation profile).

Routine puerperium control at high-risk obstetrical unit to:

- Evaluate that the itching and the rest of the maternal symptoms have resolved.
- Check normalisation of laboratory tests at 6-8 weeks postpartum. Other causes of liver disease should be ruled out in women with progressively worsening liver function tests or persistently elevated bile acids.
- Report the risk of recurrence in subsequent pregnancies (40-60%). In a small group of patients, combined hormonal contraceptive treatment can cause recurrent cholestasis, so we recommend prioritising non-hormonal contraceptives, followed by non-oestrogenic ones (preferably those with local action).

6. NEONATAL FOLLOW-UP

A neonatal ECG (in the first 48 hours after birth) will be performed on those newborns of mothers with bile acids ≥ 40 µmol/L, to confirm the normality of the PR interval.

7. MANAGEMENT ALGORITHM

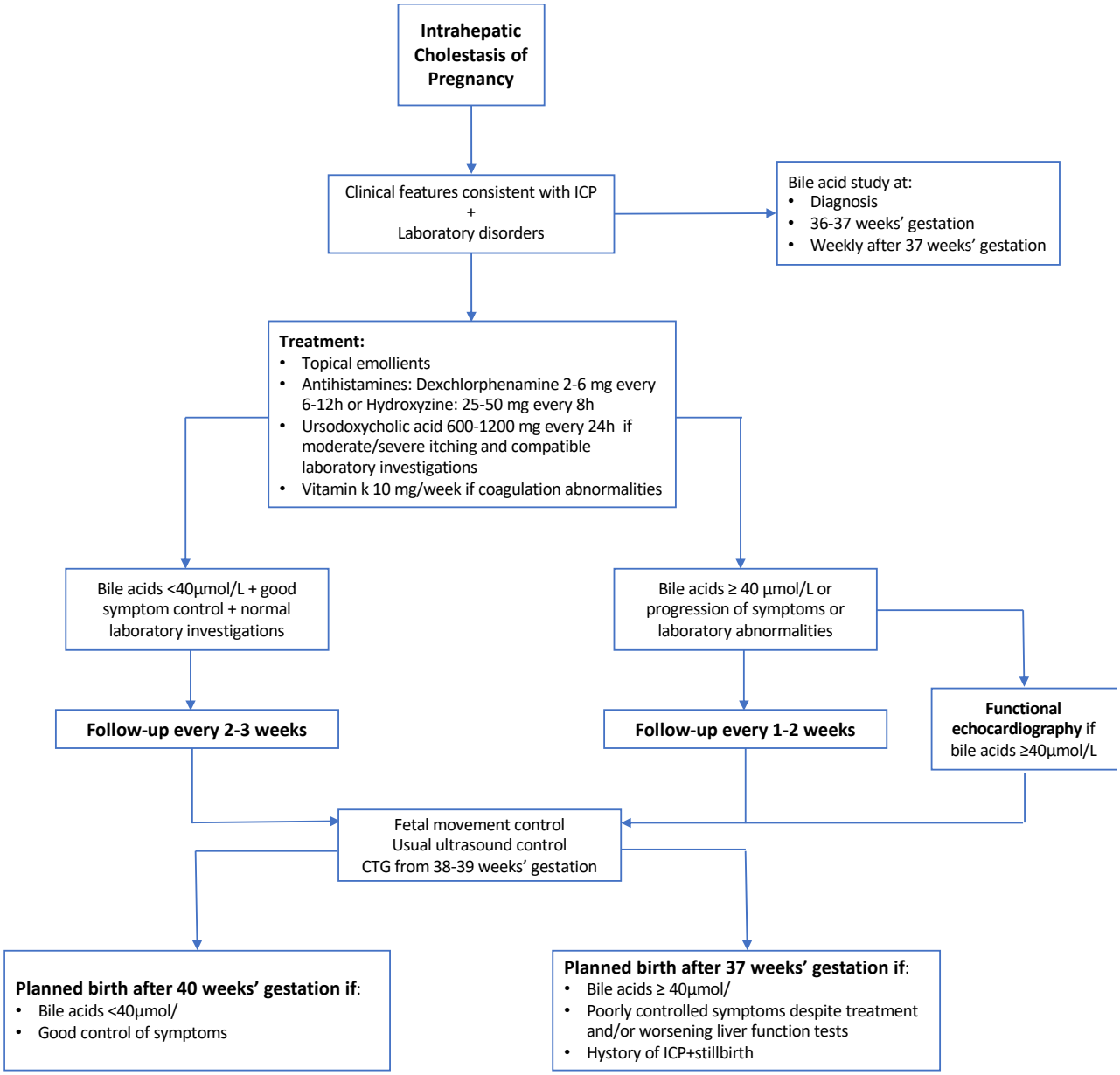

Figure 1. Management algorithm of Intrahepatic Cholestasis of Pregnancy.

APPENDIX 1. DIFFERENTIAL DIAGNOSIS OF INTRAHEPATIC CHOLESTASIS OF PREGNANCY

DIFFERENTIAL DIAGNOSIS	CLINICAL PRESENTATION	COMPLEMENTARY STUDIES
Intrahepatic cholestasis of pregnancy	Itching without rash, onset during third trimester	Increased bile acids, liver dysfunction
Acute fatty liver	Nausea and vomiting, abdominal pain, headache	Renal profile disorder, coagulopathy, hypoglycaemia
HELLP	Hypertension, epigastric pain, photopsias, headache	Proteinuria, thrombocytopenia, angiogenic factors disorder
Viral hepatitis: HAV, HBV, HCV, EBV, CMV	Nausea and vomiting, jaundice, discomfort, abdominal pain	Increased transaminases > 1000 IU/L, specific hepatitis serologies
Autoimmune hepatitis	Nausea, jaundice, lethargy, other autoimmune disorders, symptoms onset before pregnancy	Anti-nuclear (ANA) and smooth muscle (SMA) antibodies
Biliary obstruction	Abdominal pain, dark urine, pale stools	Abnormal liver ultrasound
Primary biliary cirrhosis	Itching, jaundice, lethargy, other autoimmune disorders, symptoms onset before pregnancy	Anti-mitochondrial (AMA) antibodies
Primary sclerosing cholangitis	Jaundice, hepatosplenomegaly, inflammatory bowel disease	Cholangiopancreatography by MRI
Pemphigoid gestationis	Itchy rash progressing to bullous lesions	Anti-complement antibodies
Polymorphic eruption of pregnancy	Papules that coalesce into plaques on abdominal striae	Non-specific complementary studies
Gestational pruritus	Erythematous papules and nodules located on limbs	Non-specific complementary studies