Obstetric cholestasis

Intrahepatic cholestasis of pregnancy (ICP) is the most common hepatic disorder related to pregnancy in women. It usually develops within the third trimester of pregnancy and presents with pruritus as well as elevated levels of bile acid and/or alanine aminotransferase. The underlying cause is not known but is likely to consist of a combination of both genetic and environmental factors.

The importance of ICP relates to the risks associated with this condition:

- There is an increased risk of intrauterine death. For singleton pregnancies, the prevalence of stillbirth is reported as 0.13% of 2,310 intrahepatic cholestasis of pregnancy cases in women with serum total bile acids of less than 40 µmol/L but 0.28% of 1,412 cases with total bile acids of 40-99 µmol/L and 3.44% of 524 cases for bile acids of 100 µmol/L or more [1] .
- ICP increases the risk of premature delivery (20-60%), intrauterine asphyxia (up to 44%), meconium staining of the amniotic fluid, and fetal bradycardia [2] .
- Maternal morbidity due to intense itching and lack of sleep.

Epidemiology

The incidence and prevalence of ICP vary with ethnicity and geographical distribution. ICP incidence rate is between 0.2% to 2% of pregnancies [3] . It is more common in South American and northern European continents. Research has described ICP in 0.2% to 0.3% of pregnancies in the USA.

Genetic susceptibility and reproductive hormones, especially oestrogen, are found to be the principal contributing factors to the development of intrahepatic cholestasis of pregnancy.

Risk factors

- Past history of obstetric cholestasis. It tends to recur in a more severe form in 45-90% of subsequent pregnancies [2] .
- Family history of obstetric cholestasis - eg, mother.
- Multiple pregnancy.
- Presence of gallstones.
- Hepatitis C.

Presentation

ICP usually presents in the late second trimester to the early third trimester. The most common complaint is generalised intense pruritus, which usually starts after the 30th week of pregnancy. Pruritus can be more common in palms and soles and is typically worse at night.
Other symptoms of cholestasis, such as nausea, anorexia, fatigue, right upper quadrant pain, dark urine, and pale stool, can be present.

Clinical jaundice is rare but may present in around 15% of patients after 1-4 weeks of the onset of pruritus [3] .

Some patients also complain of insomnia secondary to pruritus. Generally, the physical examination is unremarkable except for scratch marks on the skin from pruritus. Pruritus is a cardinal symptom of ICP and may precede biochemical abnormalities.

Sometimes, fatty stools due to absorption disorders, especially lipid malabsorption, are observed in ICP patients. As a consequence, shortages of fat-soluble vitamins, including vitamin K, develop, possibly leading to elongated prothrombin times and causing perinatal haemorrhages as well as bleeding into the fetal central nervous system (CNS) [2] .

The morbidity rate increases with age and the multiplicity of pregnancy [4] .

Investigations

- The most sensitive and specific marker for ICP is the total serum bile acid using a cut-off value of 10 micromol/L. Most studies use an upper limit of bile acids between 10 and 14 micromoles/L for the diagnosis of ICP.

- The risk for fetal complications increases in severe cholestasis with increased serum bile acid levels, usually over 40 micromol/L. Fasting blood samples should be used to check for the total bile salt acid level as it can become elevated in the postprandial state.
- Other liver function tests, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST), are usually mildly elevated and do not exceed two times the upper limit of normal value in pregnancy.
- Serum alkaline phosphatase can be elevated physiologically - at some times up to four times the upper normal value - but this has little diagnostic significance in ICP.
- Elevated bilirubin can present in 25% of cases but rarely exceeds 6 mg/dL.
- High prothrombin time can be present because of vitamin K deficiency (decreased fat-soluble vitamins), but postpartum haemorrhage is rare.

Differential diagnosis

Other clinical conditions affecting the liver in pregnancy include:

- Hyperemesis gravidarum.
- Pre-eclampsia and HELLP syndrome (= **h**aemolysis, **e**levated **l**iver enzymes, **l**ow **p**latelet count).
- Acute fatty liver of pregnancy.
- Chronic liver diseases, including cholestatic liver disease, autoimmune hepatitis, and Wilson's disease, and viral hepatitis may also be seen in pregnancy.

Conditions causing pruritus include[5] :

- Pemphigoid gestationis
- Pruritis gravidarum
- Prurigo in pregnancy
- Atopic dermatitis

- Allergic reactions

See also the separate article Jaundice in Pregnancy.

Management

Monitoring

LFTs should be monitored weekly. If they return to normal or soar (into the 100s), the diagnosis needs to be revised. Following the delivery, wait at least 10 days before re-checking to avoid the confounding factor of the normal fluctuations in LFTs during this time following normal pregnancies. There are no current guidelines regarding specific fetal monitoring that might reduce the risks described above.

Treatment

Topical emollients are safe for both mother and baby but their efficacy is unproven. Ursodeoxycholic acid (UDCA) is the mainstay of medical management, but it has not been shown to reduce adverse perinatal outcomes in women with ICP. Therefore, some call for its routine use for this condition be reconsidered[6] . A Cochrane review showed that when compared with placebo, UDCA administered to women with ICP probably shows a reduction in pruritus[7] . However, the size of the effect is small and for most pregnant women and clinicians, the reduction may fall below the minimum clinically worthwhile effect.

Vitamin K can be offered (daily supplement of water-soluble preparation), particularly if there is steatorrhoea or a prolongation of the prothrombin time. Dexamethasone has been studied in small clinical trials but is not recommended due to adverse neurological effects in the fetus/neonate.

Delivery

There are no current data supporting the blanket recommendation of the popular practice of inducing an early labour and delivery (aimed at reducing a late stillbirth). The biochemical results are not helpful in predicting outcome, but continuous fetal monitoring during labour should be offered. However, perinatal and maternal morbidity increase from 37 weeks of gestation onwards, and induction of labour should be considered from this point onwards. This is probably more so in those with more severe disease and higher levels of transaminases and bile acids. The guidelines of the Royal College of Obstetricians and Gynaecologists include a recommendation to induce premature delivery in ICP-complicated pregnancies in patients with severe biochemical disorders at 37+0 weeks [8] .

Prognosis

This is a condition that should settle spontaneously following delivery [5] . Follow-up should be long enough to ensure a normalisation of LFTs, and it is reasonable to check the LFTs at six weeks. If, after six months, there is no improvement, further specialist input will be required. Women should be advised that there is a significant risk of recurrence. There is an increased risk of adverse fetal outcome.

Further reading

- Manzotti C, Casazza G, Stimac T, et al; Total serum bile acids or serum bile acid profile, or both, for the diagnosis of intrahepatic cholestasis of pregnancy. Cochrane Database Syst Rev. 2019 Jul 5;7:CD012546. doi: 10.1002/14651858.CD012546.pub2.
- Arthuis C, Diguisto C, Lorphelin H, et al; Perinatal outcomes of intrahepatic cholestasis during pregnancy: An 8-year case-control study. PLoS One. 2020 Feb 19;15(2):e0228213. doi: 10.1371/journal.pone.0228213. eCollection 2020.

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