Editor's Choice

Intrahepatic Cholestasis of Pregnancy

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Introduction:

Intrahepatic cholestasis of pregnancy is a complication in 0.2–2% of pregnancies[1] causing pruritis and increased serum bile acids, liver transaminases, and, occasionally, bilirubin. It is a multifactorial condition. The onset of symptoms is most common in the third trimester, but can be earlier in pregnancy.

It is characterized by pruritus in the absence of a primary skin condition, with abnormal maternal bile acid concentrations. Intrahepatic cholestasis of pregnancy causes minimal risk to the mother except for itching[2]. It has been associated with increased risks of fetus due to prematurity, birth asphyxia, meconium-stained liquor, fetal distress, and unexplained stillbirths[3,4].

Intrahepatic cholestasis has been diagnosed in women based on self-reported itching with an elevation of any of a wide range of liver function tests beyond pregnancy-specific limits.

Serum bile acids may be the only specific laboratory marker for intrahepatic cholestasis in pregnancy. Serum bile acid levels are slightly higher in healthy pregnant women compared to non-pregnant women[5].

There is now increasing evidence that most liver function tests do not reflect the risk of fetal demise and only increased maternal total serum bile acid concentration is associated with an increased risk of stillbirth[6].

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Etiopathogenesis of Intrahepatic Cholestasis of Pregnancy:

Throughout pregnancy, the female body undergoes a multitude of physiological and anatomical transformations to optimize conditions for fetal development. Every system and organ adjusts its functions to support a healthy gestation. Notably, the liver dynamically modifies its metabolism to accommodate the growing fetus. For instance, changes in glucose metabolism occur due to altered insulin sensitivity and increased gluconeogenesis. Hormonal shifts and rising insulin resistance also influence maternal lipid metabolism. Additionally, the liver's role in bile transportation is affected, leading to a gradual elevation in total bile acid (TBA) levels in the bloodstream. While most pregnancies experience a moderate rise within normal ranges, some may encounter excessive increases, indicating intrahepatic cholestasis of pregnancy (ICP).

The exact etiology of ICP remains incompletely understood, with focus primarily on genetic, hormonal, and environmental factors. Genetic elements, particularly mutations affecting the hepatobiliary transport protein-multidrug resistance protein 3 (MDR3), crucial for phospholipid biliary secretion, are implicated in ICP's pathogenesis. MDR3 mutations are detected in around 16% of ICP cases, correlating with disease severity and total bile acid (TBA) levels exceeding 40 μmol/L. However, MDR3 mutations may also manifest in conditions like hereditary low phospholipid-associated cholelithiasis (LPA) and drug-induced cholestasis. Additionally, the multidrug resistance-related protein 2 (MRP2) is implicated in ICP

development. Mutations in other genes such as BSEP, FIC1, and FXR are also associated with ICP[7,8,9,10,11,12].

The role of sex hormones in the development of intrahepatic cholestasis of pregnancy (ICP) is supported by the occurrence of ICP in multiple pregnancies and among individuals using oral contraceptives. Levels of estrogen, progesterone, and their metabolites rise during pregnancy, peaking in the third trimester and declining postpartum, aligning with the course of ICP. However, the precise mechanism by which sex hormones contribute to ICP remains unclear. Higher levels of 17-β-D-estradiol and progesterone sulfates have been observed in pregnant women with ICP as compared to healthy women[13,14].

With respect to the environmental factors, attention is drawn to dietary factors, excess erucic acid from rapeseed oil, selenium deficiency, or the impact of pesticides[15].

Clinical Characteristic of Intrahepatic Cholestasis of Pregnancy:

The primary and most prominent symptom of intrahepatic cholestasis of pregnancy (ICP) is pruritus, typically manifesting in the second or third trimester, often after 30 weeks of pregnancy. This itching is commonly experienced on the palms and soles, although it can affect any part of the body. The pruritus tends to intensify at night, potentially causing insomnia, irritability, and even depression. Occasionally, ICP may present with rare symptoms such as abdominal pain, nausea, and vomiting. In approximately 10–15% of cases, mild jaundice may develop within four weeks of the onset of pruritus. Some ICP patients may also experience fatty stools due to absorption issues, particularly lipid malabsorption. This can lead to deficiencies in fat-soluble vitamins, notably vitamin K, potentially resulting in prolonged prothrombin times and consequent perinatal hemorrhages or bleeding into the fetal central nervous system (CNS). Typically, symptoms resolve spontaneously within 2–3 weeks following delivery. However, ICP poses significant risks to the fetus, including an increased likelihood of premature delivery (20–60%), intrauterine asphyxia (up to 44%), meconium staining of the amniotic fluid, and fetal bradycardia. The risk of adverse fetal effects escalates with maternal blood total bile acid (TBA) levels. Moreover, the risk of stillbirth is elevated in women with ICP, particularly when serum bile acid concentrations exceed 100 μmol/L[16,17].

Diagnosis of Intrahepatic Cholestasis of Pregnancy:

New onset pruritus in pregnant women, if associated with rash, is unlikely to be ICP. If the itchy skin looks abnormal (other than excoriations) then another cause should be considered. Liver function tests and bile acids are not required routinely. Clinicians should be aware however, that skin conditions (e.g. eczema) and ICP can co- exist. If the itchy skin looks normal, or there is only skin trauma due to scratching, the diagnosis may include gestational pruritus, or ICP and measurement of bile acid concentrations and liver function tests should be undertaken. Currently, the primary biochemical indicator utilized in diagnosing intrahepatic cholestasis of pregnancy (ICP) is the total bile acid (TBA) level, which may serve as the initial or sole laboratory-detected sign. In healthy pregnant women, TBA levels are marginally higher than in non-pregnant counterparts but remain clinically insignificant. The diagnostic threshold for ICP is set at a total bile acid concentration exceeding 19 micromoles/L. If the itchy skin appears normal or shows only minor damage from scratching, the diagnosis may include gestational pruritus or intrahepatic cholestasis of pregnancy (ICP) (refer to Table 1). It is recommended to conduct measurements of bile acid concentrations and liver function tests. A bile acid concentration of 19 micromoles/L or higher during pregnancy supports a diagnosis of ICP. Bile acid measurements should be taken at a convenient time when clinically indicated, and fasting is not necessary. However, a retrospective study by Kondrackiene et al.[17] suggests that TBA levels alone lack sufficient sensitivity and specificity for diagnosing ICP. The authors propose that concentrations of specific bile acids such as cholic acid (CA), chenodeoxycholic acid (CDCA), and their ratio (CA/CDCA) serve as better markers. Notably, analyzing total bile acids without considering the bile acid ratio decreases the accuracy of positive results by over 2%[18].

Table 1: Terminology for pregnant women with itching of normal skin

Diagnosis	Clinical Features
Gestational Pruritus	Itching and peak bile acid concentrations <19 micromol/L[a]
Mild ICP	Itching and raised peak bile acid concentrations 13-39 micromol/L
Moderate ICP	Itching and raised peak bile acid concentrations 40-99 micromol/L
Severe ICP	Itching and raised peak bile acid concentrations ≥100 micromol/L

The elevation in total fatty acids is typically accompanied by an increase in the activity of aminotransferases, notably alanine aminotransferase (ALT) which may rise up to approximately 2–15-fold, occasionally exceeding 1000 IU/L. Nevertheless, determining the reference range for ALT in pregnant women remains a subject of debate. There is a proposal to lower the upper limit of the reference range to enhance the accurate identification of pregnant women with hepatic disorders, including intrahepatic cholestasis of pregnancy. Although ICP patients may exhibit elevated alkaline phosphatase activity (AP), its diagnostic value is limited due to placental and bone production of AP. Also, there is typically no increase in gamma-glutamyltransferase activity in ICP. Dyslipidemia may manifest with elevated total cholesterol, low-density lipoprotein cholesterol, and apolipoprotein levels. However, all maternal serum parameters assessed in liver function tests typically return to normal shortly after delivery.

Previously, the Royal College of Obstetricians and Gynaecologists (RCOG) advocated for routine laboratory and imaging investigations to rule out other potential causes for the clinical presentation of intrahepatic cholestasis of pregnancy (ICP), such as viral and autoimmune tests along with liver ultrasound. However, recent studies suggest that the probability of identifying a viral, autoimmune, or structural cause for the itching and liver abnormalities that were not suspected based on other clinical indicators is exceedingly low and no new diagnoses were discovered following these investigations. Consequently, their routine utilization is no longer recommended. The UK National Screening Committee advises against routine screening for hepatitis C during pregnancy due to a lack of evidence demonstrating benefits. Screening should only be considered in pregnant women with an unusual or unclear presentation of ICP. This may encompass women exhibiting significantly elevated transaminases, early-onset ICP in the first or second trimester, a rapidly deteriorating biochemical profile, any signs of liver failure or evidence of acute infection, or if symptoms persist after childbirth[19,20].

Fetomaternal monitoring in ICP :

- **MATERNAL MONITORING :**

  For all women experiencing itching and initial elevated bile acid levels, a second bile acid measurement should be conducted approximately one week later before making any diagnostic or care decisions. This precaution is crucial because many women with bile acid levels exceeding 100 micromol/L or falling within the 40–100 micromol/L range often show subsequent concentrations that are significantly lower[21].

  Subsequent biochemical assessments for women and pregnant individuals will be tailored individually, based on the potential impact of results on further care decisions:

  - Women with mild intrahepatic cholestasis of pregnancy (ICP) and peak bile acids between 19 and 39 micromol/L may consider weekly testing as they approach 38 weeks of gestation to assist in determining the optimal timing for delivery.
  - Those with moderate ICP and peak bile acids ranging from 40 to 99 micromol/L, particularly as they approach 35 weeks of gestation, should consider weekly testing. This approach helps manage the timing of birth should levels reach or exceed 100 micromol/L.
  - In cases of severe ICP with peak bile acids of 100 micromol/L or higher, routine testing may not significantly influence decision-making and thus may not be routinely necessary.

- **FETAL MONITORING :**

  In intrahepatic cholestasis of pregnancy (ICP), evidence indicates that cardiotocography (CTG) monitoring or biophysical profiles do not reliably predict stillbirth. Several studies have documented fetal demise despite intensive surveillance and previously normal ultrasound

scans, including fetal Doppler measurements and CTG monitoring[22,23,24,25].

ICP is not typically associated with fetal growth restriction, as there is no significant difference in birthweight centiles compared to babies born to women without ICP. Therefore, strategies for antenatal monitoring aimed at detecting placental insufficiency are unlikely to provide substantial benefits in cases of isolated ICP.

It is recommended that all pregnant individuals monitor both the quality and quantity of fetal movements regularly. Any reduction or change in fetal movements should be promptly reported to their local maternity unit, aligning with national guidelines.

Management of Intrahepatic Cholestasis of Pregnancy:

- **DRUG TREATMENT IN ICP :** Drug treatment for intrahepatic cholestasis of pregnancy mainly reduces maternal itching, which can vary in intensity and isn't necessarily linked to bile acid levels. However, there's no evidence suggesting that standard medical treatments effectively lower maternal bile acid levels or improve perinatal outcomes[26]. (Level 1 evidence)
  - Topical emollients : It may relieve some of the discomfort associated with itching and has no known harmful effects
  - Antihistamines : The effectiveness of the treatment is uncertain in women and pregnant people with ICP, and relief may be more related to its sedative action than a direct effect. Eg. Chlorphenamine
  - Ursodeoxycholic acid : The drug works by displacing hydrophobic bile acids, thereby protecting hepatocytic membranes. Ursodeoxycholic acid (UDCA) has been demonstrated to enhance the transplacental removal of bile acids from the fetus. It is typically administered orally at a dosage of 300 mg 2–3 times daily (or 10–16 mg/kg/day)[27]. It is effective in reducing alanine transaminases levels but the clinical implications of this are uncertain, as al-anine transaminase levels have no association with stillbirth[28].
  - Vitamin K : It is recommended only if there appears to be reduced absorption of dietary fats (e.g. presence of steatorrhoea) and/or evidence of abnormal prothrombin time if coagulation studies are performed. It is prescribed as a water soluble formulation such as menadiol sodium phosphate at a dose of 10 mg daily[29].
- **TIMING AND MODE OF DELIVERY :**

  The risk of stillbirth is 0.13% in women whose peak bile acids are less than 40 micromol/L, which is comparable to the background population risk. Despite this low risk throughout pregnancy, the benefits of delivering by 40 weeks may outweigh continuing the pregnancy further.

  For women with peak bile acids between 40 and 99 micromol/L, the risk of stillbirth is 0.28%, similar to the overall background population risk, but it appears to increase around 38-39 weeks of gestation. Therefore, it is reasonable to consider planned delivery around this time for these women, especially if other conditions like gestational diabetes or pre-eclampsia are present.

  In women with peak bile acids of 100 micromol/L or more, the risk of stillbirth rises to 3.44%, which is higher than the background population rate. This risk appears to increase starting from 35-36 weeks of gestation and hence, it is reasonable to plan delivery around this time[30].

BILE ACIDS LEVEL	RECOMMENDATION
19– 39 micromol/L	Consider options of planned birth by 40 weeks' gestation or ongoing antenatal care according to national guidance in women with mild ICP
40– 99 micromol/L	Consider planned birth at 38– 39 weeks' gestation in women with moderate ICP
100 micromol/L or more	Consider planned birth at 35– 36 weeks' gestation in women with severe ICP

Pregnant women with ICP do not have increased rates of assisted or operative birth compared with women without ICP. Mode of birth should therefore be based on usual obstetric or medical indications[31].

- **MONITORING IN LABOUR :**

  When considering intrapartum care, it is important to assess any pre-existing obstetric or medical conditions that could influence fetal

monitoring decisions during labor. For women with mild intrahepatic cholestasis of pregnancy (ICP) (peak bile acids 19-39 micromol/L) and no other risk factors, intrapartum care can align with national guidelines[32].

In cases of moderate ICP (peak bile acids 40-99 micromol/L), decisions should be individualized. The uncertainty regarding the benefits of continuous electronic fetal monitoring should be discussed, taking into account the presence of additional risk factors.

For women with severe ICP (peak bile acids 100 micromol/L or higher), given evidence indicating heightened risks of adverse perinatal outcomes, continuous electronic fetal monitoring should be recommended.

- **CONTRACEPTION AND FUTURE PREGNANCIES :**

The 2016 UK Medical Eligibility Criteria (UKMEC) for Contraceptive Use indicate that copper-bearing intrauterine devices, levonorgestrel-releasing intrauterine systems, progestogen-only implants, progestogen-only injectables, and progestogen-only pills are suitable for use without restriction in women with a history of intrahepatic cholestasis of pregnancy (ICP) (UKMEC category 1).

Combined hormonal contraception can be considered in women with ICP (UKMEC 2), provided they do not have a history of cholestasis related to contraception. Previously, concerns existed that women with a history of ICP might have an increased risk of cholestasis with estrogen-containing hormonal contraception, but this risk is unlikely for most women. The 2016 UKMEC advises that for women who have had ICP, the benefits of using these estrogen-containing methods outweigh this theoretical risk (UKMEC category 2), allowing them to choose this method if desired[33].

Women and individuals of reproductive age with history of intrahepatic cholestasis of pregnancy (ICP) in previous pregnancy have a higher likelihood of developing ICP again in subsequent pregnancies compared to the general population. However, the exact extent of this increased risk remains uncertain.

Differential diagnosis & management of Pruritus in pregnancy

Pruritic Dermatoses of pregnancy	Areas affected	Risk factors	Recurrence risk	Management	Pregnancy outcome
Intrahepatic cholestasis of pregnancy	scalp, anus, vulva, abdominal skin	Indian- Asian origin, Pakistani- Asian origin, previous obstetric cholestasis	60-70 % in future pregnancies	• Ursodeoxycholic acid • Topical emollients • Sedating anti-histamines	Increased risk of stillbirth, Increased risk of PPH, Increased risk of fetal distress, Increased risk of premature birth
Atopic Eruption of Pregnancy	Face, neck, chest, extensor surfaces of limbs and trunk	Family history of atopy	Limited data	• Topical emollients • Topical anti-pruritics • Topical steroids • Antihistamines	No adverse effects on mother of fetus
Polymorphic eruption of pregnancy	Abdominal striae with peri-umbilical sparing, can progress to trunks and extremities, sparing palms, soles and face	Nulliparity, multiple pregnancy, any cause of overdistension of skin	Rarely recurs	• Topical steroids (first line) • Topical emollients • Antihistamines • Oral steroids	No adverse effects on mother of fetus
Pemphigoid Gestationis	Appears around umbilicus, can progress to trunks and extremities, palms, soles sparing mucosa	Recognised correlation with HLA-DR3, HLA-DR4, Other autoimmune conditions	May recur in subsequent pregnancies with earlier onset and increasing severity May recur with oral contraception/ menstruation	• Topical/ oral steroids • Antihistamines • Antibiotics • Immunophoresis • immunosuppressants	IUGR, Preterm labour, Self limiting skin lesions in neonates

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