



# **Intra-Hepatic Cholestasis of Pregnancy and Its Consequences: A Review**

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## **Authors' contributions**

*This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.*

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## **ABSTRACT**

**Background:** The most common cause of liver illness in pregnancy is intrahepatic cholestasis (IHCP). It has a varying incidence due to geographic variance; factors such as advanced age, multiple pregnancy, family history, and previous pregnancy cholestasis have demonstrated a higher prevalence in these patients. Cholestasis in pregnancy has an aetiology that is currently unknown. It usually occurs after ovarian hyperstimulation syndrome in early pregnancy and coincides with growing oestrogen levels in the second half of pregnancy [1]. The ABCB4 gene mutation is largely associated in a subtype of progressive familial intrahepatic cholestasis, where disease clustering in first-degree relatives increases hereditary predisposition. Itchy palms and soles with elevated liver enzymes and bile acids are the most common symptoms. Some of the reported maternal problems in these patients include preterm labour, HELLP syndrome, acute fatty liver of pregnancy, and postpartum haemorrhage [2]. There are no precise antenatal foetal monitoring tests that can predict foetal fatalities in the womb. To reduce perinatal death with expectant treatment beyond this gestation, it is recommended that a pregnancy be terminated near 36–37 weeks of pregnancy.

**Keywords:** *Intrahepatic cholestasis; hyperstimulation; precise; terminated.*

## 1. INTRODUCTION

Pruritus and an increase in blood bile acid concentrations characterise intrahepatic cholestasis of pregnancy (ICP), which often develops in the late second and/or third trimester and resolves quickly after birth. Itching is a frequent pregnancy symptom that affects about 23% of women [3]. Itching is usually a slight discomfort brought on by changes in the skin, particularly the skin of the abdomen [4]. Itching can, however, be a symptom of ICP in some cases. Itching can occur anywhere on the body, while it is most commonly found on the palms of the hands and the soles of the feet. Intrahepatic cholestasis of pregnancy is most frequent in the third trimester of pregnancy, but it can start at any time. The majority of women with this syndrome experience itching without a rash throughout the third trimester (but it can occur as early as week seven). Itching is most commonly found on the palms of hands and soles of feet, but it can occur everywhere on the body [5,6]. The most typical: Itching of the palms of the hands and soles of the feet, but not confined to them, without the presence of a rash Itching that becomes more prominent in the evening, Urine that is darker. Less frequently used: Stools that are lighter in weight, The time it takes for blood to coagulate has increased (due to possibly associated vitamin K deficiency), Fatigue, Nausea has increased, Appetite decreases, Jaundice is a type of jaundice that occurs (less than 10 percent of women), Pain in the upper right quadrant [7].

### 1.1 Incidence Rate

Among all 62 pregnant women with prevalence rate of 5.64% have been found to be suffering from ICP. The most frequently affected (22, 35.48%) age-group with ICP were belong to age > 35 years. The prevalence ranges from 0.02 percent to 2.4 percent of all pregnancies, with large regional variations [8]. Although the maternal prognosis is usually favourable, severe foetal outcomes such as meconium staining of amniotic fluid, foetal bradycardia, and even foetal loss can occur. Anti-histaminic therapy had a poor response. Ursodeoxycholic acid has the best response in reducing pruritus in mothers, and it may also have a role in preventing perinatal problems [9].

### 1.2 Mechanism of Action

The origins of intrahepatic cholestasis in pregnancy are unknown, however they are

thought to be produced by a combination of genetics and environment. Hormones and the surrounding environment Hormones, the environment, and hereditary factors are all thought to play a role in the disease [10]. ICP is most common during the third trimester, when hormone levels are at their peak. ICP is more common in twin and triplet pregnancies, which are linked to increased hormone levels. When placental hormone production stops after delivery, ICP resolves quickly. ICP symptoms may be caused by older high-dose oestrogen oral contraceptive tablets [11]. Estrogens in animal experiments, Estrogens, particularly glucuronides like estradiol-17-D-glucuronide, have been found to produce cholestasis via lowering bile acid uptake by hepatocytes. Progesterone treatment with progesterone during the third trimester of pregnancy has been linked to the development of ICP, and levels of progesterone metabolites, particularly sulphated progesterone, are higher in ICP patients than in unaffected women, implying that progesterone may play a larger role in ICP than oestrogen. Aspects of genetics clustering of ICP cases in families, geographic variation in incidence of ICP, and recurrence of ICP in 45-70 percent of subsequent pregnancies all point to the condition having a genetic component [12]. In cases of ICP, genetic mutations in the hepatic transport protein ABCB4 (MDR3), which regulates phosphatidylcholine release into bile, have been discovered. Patients with increasing familial intrahepatic cholestasis have also been discovered to have genetic abnormalities affecting hepatic bile salt transport molecules [13]. It has been discovered that mothers of patients with this condition had a greater rate of ICP, implying that heterozygote carriers of these genes are also at risk. External influences environmental variables may have a role in ICP, according to a number of aspects of the disease, ICP is more common in the winter than it is in the summer, according to reports. In Chile, the prevalence of ICP has decreased from 14% in 1975 to 4% in 2016. In 60% to 90% of future pregnancies, ICP recurs. Although the role of selenium in bile secretion is unknown, ICP has been associated to low serum selenium levels [14].

### 1.3 Diagnostic Evaluation

A serum bile acid test as well as a liver function test are used to diagnose ICP. While most pregnant women feel some itching, itching without a visible rash, or persistent or significant

itching symptoms should be reported to the midwife or obstetrician [15]. The itch in ICP can range from minor to severe, as it does not correspond with bile acid levels (which have been demonstrated to be the most common cause of stillbirth in ICP). A liver function test as well as a serum bile acid test should be requested to confirm an ICP diagnosis. Despite the fact that the ALT level may be elevated, 20% of ICP women will always have a normal LFT test result. This, together with itching in the palms and soles, could be used to diagnose ICP, but only if bile acid levels are abnormally high (however LFTs are not always elevated in ICP patients) [16]. A quantitative assessment of bile acids is used in the serum bile acid blood test for ICP. The treating practitioner should look into other liver disorders that can occur during pregnancy. Preeclampsia, HELLP syndrome, and acute fatty liver of pregnancy are examples of these conditions. Other causes of hepatitis should be investigated as well, such as hepatitis viruses, cancer, and certain drugs [17].

#### 1.4 Treatment Modalities

Ursodeoxycholic acid is frequently prescribed by gynaecologist. Although the most recent experiment, PITCHES, found no overall benefit, some researchers believe that giving Ursodeoxycholic acid to women with bile acids greater than 40 mol/litre may still be advantageous [18]. While there is no cure for ICP and no means to ensure a positive outcome, studies have shown that Ursodeoxycholic acid has a little better foetal and maternal outcome than cholestyramine, which merely seems to reduce itching. Giving water-soluble Vitamin K to a pregnant woman does not appear to reduce the risk of bleeding during birth. If the lady has pale stools, severe ICP (bile acids > 100 mol/litre), or a known clotting problem, experts in ICP will prescribe this [19]. A new study discovered the level of bile acids at which stillbirth risk rises, therefore delivery from 34 weeks may be helpful to lower the chance of stillbirth. According to this study, 90 percent of women with ICP may wait until 39 weeks of pregnancy to be induced, according to The Lancet. This, however, necessitates routine bile acid testing and prompt findings [20].

##### 1.4.1 If left untreated, there are dangers

The following are some of the maternal effects:

Itching that can become excruciating and painful. When bile acids elevate above 40 mol/litre, spontaneous preterm labour occurs.

Among the foetal repercussions are: Distress in the foetus, Consumption of meconium, Stillbirth.

Induction is usually suggested between 34 and 39 weeks in most situations.

Some researchers in the United States believe that inducing labour at 36 weeks reduces the incidence of stillbirth [21].

#### 1.5 Result for the Mother

The prognosis for the mother is good, and symptoms improve quickly after birth, with normalization of relations of serum liver tests. If persistent abnormalities persist, other underlying chronic liver illnesses such as primary biliary cirrhosis, primary sclerosing cholangitis, or chronic hepatitis C should be considered, as they are all linked to the development of pruritus in late pregnancy. ICP recurs in 45–70% of subsequent pregnancies, with varied severity of recurring episodes [22].

What complications might ICP create during and after pregnancy?

- Having a baby too soon. This is when a baby is born before the 37th week of pregnancy, which is considered premature. Kids born this early may have more health issues or require more hospitalisation time than babies born later [23].
- Distressed foetus This occurs when a baby in the womb does not receive adequate oxygen. Reduced foetal movement, changes in your baby's heart rate, and your baby passing meconium are all signs of foetal distress. The first bowel movement of your child is meconium [24].
- Meconium is normally passed after birth, however a kid in foetal distress may pass meconium into the amniotic fluid that surrounds him in the womb before or during labour and delivery.
- Stillbirth: When a baby dies in the womb after 20 weeks of pregnancy, this is known as miscarriage.
- Aspiration of meconium: When a baby inhales amniotic fluid containing meconium, he develops breathing issues. Meconium can obstruct your baby's airways if he breathes it in during birth [25].
- Chronic obstructive pulmonary disease (COPD) is a condition (also called RDS). RDS is a breathing disorder that affects neonates whose lungs have not grown

fully. Surfactant, a slick substance that helps the lungs fill with air and prevents the little air sacs in the lungs from collapsing, is in short supply in babies with RDS. Premature babies are more likely to have RDS.

- Haemorrhage upon childbirth (also called PPH). After giving delivery, you may experience excessive bleeding. It's a severe yet uncommon disease [26].

#### 1.5.1 If you've had ICP before, you're at danger

- ICP affects more than half of pregnant women.
- ICP runs in your family. If your mother or sister have ICP, notify your doctor. To record health information about your family, fill out the March of Dimes family health history form and share it with them [27].
- Have a history of liver problems, such as hepatitis C. Hepatitis C is a disease that causes your liver to swell due to the hepatitis C virus (also known as HVC).
- Hepatitis C is transferred by infected blood in most cases. It can also be passed from mom to kid during childbirth or through unprotected sex with an infected person [28].

These genes aid in the production and use of bile. A gene change refers to a change in the instructions encoded in a gene. A person's gene might alter on its own or be passed down from parents to their children [29].

#### 1.5.2 ICP is treated in a number of ways

Ursodiol is a prescription drug that doctors may prescribe to you. A prescription is a health-care provider's order for medication. Ursodiol reduces bile acid levels in the blood, relieves itchy skin, and may minimise your baby's risk of ICP issues. Prescription medications should not be taken during pregnancy unless your doctor has given you permission [30].

Antihistamines, corticosteroid creams, and lotions are not recommended for itching relief. These drugs are available without a prescription and can be purchased over the counter. Antihistamines are antihistamines that are used to treat allergy symptoms such as rashes on the skin or irritated eyes [31].

They are frequently ineffective, and they may harm your unborn child. Corticosteroid creams

and lotions will not reduce the itching caused by ICP, and they may harm your unborn child. Bathing in lukewarm water might help you relax [32].

Amniocentesis. A sample of amniotic fluid from surrounding your baby in the uterus is taken for this test (also called womb). The test examines your infant for birth abnormalities and hereditary diseases. Ultrasound may be used by your provider to check for meconium in your baby's amniotic fluid or to see if his or her lungs are ready for birth. Ultrasound imaging shows an image of your baby within the womb using sound waves and a computer screen [33].

Monitoring the foetal heart rate (also called a nonstress test or NST). This test measures your baby's heart rate while in the womb and how it varies as he or she moves. This test is used by your doctor to ensure that your baby is getting adequate oxygen [34].

Profile biophysical (also called BPP). A nonstress test and an ultrasound are combined in this exam. BPP can be used by your doctor to determine how much amniotic fluid is in your womb and to monitor your baby's muscle tone and movements. When your provider gives you medicine or breaks your water (amniotic sac) to start labour, this is referred to as inducing labour [35].

## 2. DISCUSSION

ICP during pregnancy might range from 0.1 to 15.6 percent depending on where you live. Obstetricians are being urged to closely monitor impacted pregnancies due to the possibility of poor pregnancy outcomes. One of the difficulties that primary care doctors encounter is making a timely diagnosis of such a dangerous illness, especially when symptoms arise early in pregnancy [36]. The gestational age cut-off for determining whether a pregnancy is early or late is 34 weeks. Elevated oestrogen and progesterone levels are thought to be a contributing factor in the development of ICP. Furthermore, genetic predisposition may cause bile acid transmembrane hepatocyte transporters to fail, resulting in bile acid build-up. In fact, this defect becomes apparent in the presence of hypoestrogenism (i.e., pregnancy or oral contraceptive pill use) and the patient develops the typical symptomatology [37]. Early onset first trimester ICP is associated with supra-physiological oestrogen levels throughout the

first trimester, according to the majority of the studies. If the mother experiences cholestasis during pregnancy, the foetus has a considerably greater chance of preterm birth, albeit the reasons for this remain unknown.

If an infant's lungs aren't fully grown when he or she is born prematurely, he or she may have breathing problems. There's also a greater chance of foetal death. The foetus relies on the mother's liver to eliminate bile acids from the blood throughout pregnancy. This can be passed on to the foetus if the mother has too much bile acid. During birthing, the neonate is also at an increased risk of inhaling meconium, which can cause breathing problems. Because of the potentially catastrophic problems for the infant, doctors frequently induce labour early if the woman has cholestasis during pregnancy. Multiple pregnancies or pregnancies accompanied by ovarian hyperstimulation syndrome are more likely to have increased sex steroid levels. Furthermore, pregnancies produced through ovarian stimulation cycles followed by embryo transfer have a greater risk of developing early-onset ICP [38].

### 3. CONCLUSION

The first three months of pregnancy ICP is a rare illness that doctors should be aware of, especially if symptoms are usual. To date, the cornerstone of treatment to avoid poor new-born outcomes has been attentive follow-up, foetal monitoring, and UDCA. To further understand the pathophysiology of ICP and determine the best treatment, more research is needed. The most common presenting symptom of cholestasis during pregnancy was itching all over the body. After ruling out alternative causes of itching, bile acids should be used to confirm the diagnosis of IHCP in women with normal liver enzymes. This will save money on studies. In the current investigation, there was no link between pregnancy cholestasis, premature labour, or meconium-stained fluid. In women with bile acids >40 mol/L and noncompliant patients, an early termination of pregnancy between 36 and 37 weeks can be considered.

### CONSENT

It is not applicable.

### ETHICAL APPROVAL

It is not applicable.

### COMPETING INTERESTS

Authors have declared that no competing interests exist.

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