

## Pregnancy related liver diseases

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### Abstract

The focus of this article is on the most important (prognostic and therapeutic) pregnancy related liver diseases: cholestasis of pregnancy, preeclampsia induced liver dysfunction and intrahepatic cholestasis of pregnancy, eclampsia (including HELLP – hemolysis, elevated liver enzymes, low platelet count) and acute hepatic steatosis. They are completely reversible after delivery and must be distinguished from other intercurrent liver diseases, for which pregnancy is a possible precipitating factor. Intrahepatic (obstetric) cholestasis of pregnancy (ICP) is a unique hepatobiliary condition that manifests itself with itching, jaundice, an increase in the serum concentration of bile acids and poses a risk of complications for both the mother and the baby. ICP is a reversible type of hormonally influenced cholestasis. It develops during the third trimester, when hormone concentrations are at their peak. Ursodeoxycholic acid relieves pruritus and improves liver function tests in pregnant women in intrahepatic cholestasis and largely reduces fetal mortality, but has a secondary role in HELLP syndrome and acute hepatic steatosis during pregnancy, where timely delivery is the key to treatment.

**Keywords:** cholestasis, pregnancy, hormones, eclampsia, HELLP syndrome

### Introduction

Liver diseases associated with pregnancy /cholestasis during pregnancy, liver involvement in pre-eclampsia or intrahepatic cholestasis in pregnancy (ICP), eclampsia (including HELLP syndrome - Hemolysis, Elevated Liver enzyme, and Low Platelet count) and acute hepatic steatosis in pregnancy/ are presents clinically with often non-specific general symptoms such as nausea and vomiting, upper abdominal pain, jaundice and/or pruritus. Often, the precipitating underlying disease (eg, EPH gestosis [EPH, edema (edema), proteinuria, and hypertension]) is clinically foregrounded. The frequency of jaundice as a symptom of liver disease during pregnancy is 1:500 to 1:1,500 pregnancies [1, 2, 4, 5, 7, 10]. The appearance of jaundice is not mandatory (only 25% in cholestasis of pregnancy, 5% in HELLP syndrome, but up to 85% in fatty liver). Acute viral hepatitis is the most common cause of jaundice during pregnancy. It can occur in any trimester, but is most often seen in the last trimester. Differential diagnostic clarification aims to distinguish from hepatobiliary diseases, in which pregnancy may be a possible triggering factor, but which are also observed outside pregnancy (eg, obstructive jaundice in cholelithiasis, Budd-Chiari syndrome) - random intercurrent liver diseases, which, however, sometimes have higher risk of complications during pregnancy (eg hepatitis E, maternal mortality: 20%; herpes simplex virus [HSV] hepatitis: maternal mortality up to 40%) and - hepatological complications during pregnancy with preexisting liver disease [1, 10]

### Preeclampsia and HELLP syndrome Etiopathogenesis

The incidence of preeclampsia is 3-5% in primiparous women and 0.5% in parous women. Preeclampsia is defined by the onset of hypertension and proteinuria in the second half of pregnancy; liver involvement (in the sense of elevated transaminases) occurs in 10 to 20% of pregnant women [1, 5, 6, 7, 9, 10] Seizures are called eclampsia (0.1 to

0.2% of pregnancies), which is generally considered the endpoint of preeclampsia, with liver involvement occurring in 70 to 90%. A pathogenetically important role is played by endothelial activation with vasoconstriction and activation of the coagulation cascade.

Liver damage ranges from minimal histological changes with periportal fibrin deposits and necrosis of liver cells leading to nonspecific elevations of transaminases to HELLP syndrome and hepatic infarction with potentially life-threatening complications of hepatic hematoma or liver rupture. HELLP syndrome is characterized by the presence of hemolysis (schistocytes in the differential blood count, increased LDH and haptoglobin), increased liver enzymes (aspartate aminotransferase - AST > ALT) and thrombocytopenia (low platelets below 50, depending on the degree of severity - up to 150 000 /mm<sup>3</sup>). The clinical symptoms of HELLP syndrome are nonspecific - general malaise and upper abdominal symptoms such as epigastric pain (90%), nausea and vomiting (50%) EPH gestosis with edema, proteinuria and arterial hypertension are usually present in 80% of cases [1, 2, 5, 9, 10]. Ascites (10%) and jaundice (5%) are rare. HELLP syndrome occurs before birth in 69% of cases and after birth in 31%. Additional laboratory tests usually show proteinuria (80%) and signs of hemolysis with thrombocytopenia and activation of intravascular coagulation (elevated D-dimer by about 42%). However, complete consumption coagulopathy is rare (8-15%) [1, 6, 10]

The complication rate of HELLP syndrome is 38% [9]: pulmonary edema (10%), placental abruption (10%), DIC (disseminated intravascular coagulation) (8%), eclampsia (6%), renal failure (5%), intrahepatic hemorrhage (1.6%). A rare but life-threatening complication is the rupture of a subcapsular hepatic hematoma (in 1-2% of patients with HELLP syndrome) [5]. According to recent studies, the maternal mortality rate of HELLP syndrome is up to 1% [1, 5, 6, 9, 10], the possible causes of which are ischemic cerebral strokes, myocardial infarctions, consumption coagulopathy

or very rarely liver failure. Stillbirth [1, 9, 10]; infant mortality is 10 to 35%. In general, HELLP syndrome is completely reversible, with possible onset 24 to 48 hours after birth. It should be borne in mind that HELLP syndrome appears after birth in one third of cases. From a hepatological point of view, supportive measures are at the fore. Patients often require intensive care. The administration of glucocorticoids may be indicated not only in terms of inducing lung maturity but also in improving the condition of the liver. Unlike dihydrolazine and labetalol, nifedipine is not an antihypertensive agent of first choice, but in addition to the desired antihypertensive effect, it also has a possible positive effect on liver function.

In case of severe pre-eclampsia, eclampsia and HELLP syndrome, the obstetrician should aim for immediate delivery, especially if steroid therapy does not have the desired effect [1, 10].

**Acute hepatic steatosis in pregnant women**

Fatty liver during pregnancy is a rare complication with an incidence of 1:7,000 to 1:16,000 pregnancies. Pathogenetically, the defect in mitochondrial beta-oxidation of fatty acids and the hormonally induced increase in free

fatty acids during pregnancy are at the forefront [1, 2, 5, 7, 9, 10]. Fetal enzyme defects in long-chain 3-hydroxyl-acyl CoA dehydrogenase (LCHAD) are present in 10 to 20% [8]. This leads to decompensation of the heterozygous mother from the homozygous fetus, which "floods" the mother with fatty acids (metabolites). Initially, the main clinical symptoms are non-specific - such as fatigue, exhaustion, followed by upper abdominal pain, nausea and vomiting [1, 2, 9, 10]. Jaundice (86%) and hepatic encephalopathy (56%) are common in the course of the disease, and the full picture of acute liver failure may be present.

Gastrointestinal/oesophageal bleeding can also occur as a result of reflux esophagitis or Mallory-Weiss syndrome, and ascites or pancreatitis are sometimes seen. Laboratory tests show elevations in transaminases (usually 350 to 500 U/L) and bilirubin (5-15 mg/dL). An increase in the substances necessary for the kidneys (creatinine, uric acid, urea) and the appearance of leukocytosis, thrombocytopenia and schistocytes in the differential blood count are also characteristic. There is usually a coagulation disorder that is hepatogenic and caused by consumption coagulopathy (Table 1).

**Table 1**

<b>Differences between HELLP-syndrome and acute steatosis of pregnancy</b>		
	<b>HELLP</b>	<b>AFLP</b>
Nausea and vommitus	+	+++
Pain in the upper abdomen	++	++
Icterus	(+)	+++
Hepatic encephalopathy	((+))	++
EPH gestosis	+++	++
AST / ALT	AST>ALT - LDH ↑	AST<ALT
Thrombocytopenia	+++	++
Coagulopathy	+(DIC syndrome)	++++(DIC+LF) +
Azotemia	+	+++

DIC- Disseminated intravascular coagulation LF – Liver failure EPH - Edema, proteinuria, hypertension HELLP – Hemolysis, Elevated Liver enzymes and Low Platelets AFLP – Acute fatty liver, in pregnancy

**ICP Epidemiology**

The prevalence of intrahepatic cholestasis in pregnancy is influenced by genetic burden, environmental factors and varies among populations worldwide. It occurs in 0.1-0.2% of pregnancies. In the US, 1-2 pregnancies per 1,000 are affected by ICP, and in the Latino American population it is 5.6%. In Chile, 2.4% of all pregnancies are affected, and in the Araucanian subpopulation the prevalence is 5% [12]. The condition is also more common in women from India and Pakistan - 1.2-1.5%, while in England obstetric cholestasis affects 0.7% of pregnancies in a multicultural population.

Intrahepatic cholestasis of pregnancy shows seasonal variation, occurring more frequently in the winter months than in the summer [20, 21]. There is thought to be an environmental cause for the condition, such as reduced exposure to sunlight or a change in diet. Selenium deficiency may play a role in ICP as it acts as a cofactor for several enzymes in oxidative metabolism in the liver [19]. In Chile, elimination of selenium deficiency significantly reduced the incidence of ICP.

Other risk factors for obsteric cholestasis include advanced maternal age, personal or family history of cholestasis with oral contraceptive use, and multiple pregnancy [22]. In addition, women with twin pregnancies are 5 times more likely to develop ICP than women with singleton

pregnancies [23]. The risk is increased in women who have had *in vitro* fertilization (IVF) and those who have had previous liver damage or problems. The likelihood of recurrence in future pregnancies is 60 to 90%. Some studies show that women with ICP tend to develop cholelithiasis.

**Pathophysiology**

Susceptibility to obsteric cholestasis is inherited in an autosomal dominant pattern. Affected individuals have a defect involving the excretion of bile salts, resulting in elevated serum concentrations of bile acids. They are deposited in the skin, causing severe itching [11].

Up to 15% of ICP cases are associated with the adenosine triphosphate binding cassette, subfamily B, member 4 (ABCB4/abcb4) gene [13, 18]. This gene, known as multidrug resistance protein 3 (MDR3), encodes a transporter for phospholipids across the canalicular membrane of hepatocytes. The lack of available phospholipids to bind bile acids results in the accumulation of toxic bile acids, which can impair liver function, including the regulation of bile flow. Up to 10 different MDR3 mutations have been identified. Even one copy of the altered gene in each cell is sufficient to increase the risk of developing the disease [14, 15, 16, 17]. ICP occurs more frequently in heterozygous mothers of homozygous children with progressive familial

cholestasis in weak forms of the MDR3 defect at a later age under the stress of pregnancy.

Genetic mutations in the ABCB11 gene reduce the function of the hepatocellular bile salt export pump (BSEP), leading to impaired biliary excretion and features of ICP. Steroids, estrogen, progesterone, and corticosteroids increase during pregnancy 1000-fold at term compared to the non-pregnant state [18]. Estrogens, and especially glucuronides, such as estradiol-17B-D-glucuronide, have been shown to cause cholestasis in animal studies by reducing bile acid uptake by hepatocytes. In patients with a history of obstetric cholestasis, estrogen-containing oral contraceptives should be used with caution and at the lowest possible dose. Exogenous estrogen

in these patients may lead to reactivation of the disease [12]. Progesterone treatment in the third trimester of pregnancy has been shown to be associated with the development of ICP, and levels of progesterone metabolites, particularly sulfated progesterone, are higher in patients with ICP. Studies by Abu-Hayyeh *et al* found that sulfated progesterone metabolites are a prognostic indicator of ICP and can help predict the onset of ICP and distinguish it from benign fetal pruritus. Therefore, both genetic mutations in hepatocyte proteins involved in biliary secretion and excretion, together with their inhibition by high levels of hormonal metabolites during pregnancy, may have a role in the pathogenesis of ICP.

**Table 2:** Risk factors in ICP.

Contributing factor	Risc
Genetic predisposition: especially: ABCB4, ABCB11, ATP8B1, ABCC2, NR1H4, TJP2	unclear, the effect is more likely to be strong [30, 31]
Liver disease:	
Hepatitis C	OR 20,40 (95% CI 9,39 – 44,33) [32]
Hepatitis B	OR 1,68 (95% CI 1,43 – 1,97) [33]
Cholelithiasis	OR 3,29 (95% CI 2,02 – 5,36) [34]
Multifetal pregnancy	6-9% [35, 36]
Elevated estrogen/progesterone levels	Unclear
Stimulation in assisted reproductive technology (ART)	RR 3,8 (95% CI 1,0-15,0) [37]
Nutritional deficiencies	Vitamin D [38] Selen [39]
Environmental factors	unclear, more common in winter months [40]
ICP in previous pregnancy (risk of recurrence)	45-70% [4]

**Clinical picture**

Symptoms can vary in severity and appearance, but the most common include itching without a rash, which usually appears in the second or third trimester and can affect all parts of the body. It usually starts on the soles of the feet and palms of the hands and progresses over the body and face [28]. It often worsens at night and can be so severe that it affects the patient's quality of life, even leading to suicidal thoughts. Icterus appears in up to 25% of cases within 1 month of itching. Steatorrhea and vitamin deficiency. K can also occur due to fat malabsorption [28]. If the deficiency of vit. K is not corrected until the moment of delivery, postnatal hemorrhage may follow (8% of cases).

**Risks**

Obstetric cholestasis poses a greater risk to the fetus than to the mother. It is associated with an increased likelihood of stillbirth (intrauterine fetal death), preterm birth, neonatal respiratory distress, meconium staining, preeclampsia, and gestational diabetes.

Cholestasis increases the risk of postpartum respiratory distress syndrome (RDS). Elevated bile acids are thought to interfere with the formation of surfactant, which allows the lungs to expand after birth.

Sometimes (often in response to fetal distress) meconium passes into the amniotic fluid before or during labor. If the baby then inhales the contaminated fluid, breathing problems can occur - meconium aspiration syndrome (MAC).

There is an increased risk of spontaneous preterm birth, with most studies reporting 30-40%. Spontaneous preterm labor occurs when bile acids rise above 40 mmol/l [27].

A stillbirth usually occurs in the last few weeks of pregnancy. Even with modern treatment, the risk of fetal

death can vary from 2-11%. It is thought to be due to cardiac arrhythmia caused by increased bile acids (passage of taurocholate into the fetal compartment) and decreased contractility with a prolonged P-R interval [19, 22, 26]. When bile acid levels are above 100 mmol/L, the risk of stillbirth increases to over 3%.

**Diagnosis**

Recommended laboratory tests for the diagnosis of obstetric cholestasis include: serum total bile acid, cholic, chenodeoxycholic acid, total bilirubin, transaminases, GGT, PT, PTT, and INR. The most specific and sensitive marker of ICP is total serum bile acid (BA) levels above 10 micromoles/L [29]. Healthy pregnant women have a normal fasting bile acid level of 6-10 µmol/L and a postprandial level of 10-14 µmol/L. The meta-analysis by Ovardia *et al.* in fasting pregnant women with ICP (n=1726) showed a median of 23.0 µmol/L (IQR 14.7-41) versus 32.0 µmol/L (IQR 19.0-61.5) in fed subjects (n=2795) 39. Regardless of fasting and UDCA therapy, various analyzes showed that an elevated total serum bile acid level was a sensitive and specific marker (OR=4.17, p=0.0037, AUC=0.62, p=0.046) in the diagnosis of ICP and associated adverse perinatal outcome. Recent studies have shown that two bile acids (taurocholic and taurodeoxycholic) are specifically elevated in ICP. The level of cholic acid is significantly increased, while the level of chenodeoxycholic acid is slightly increased, resulting in an increase in the ratio of cholic to chenodeoxycholic acid [30]. Davies *et al* stated that in the presence of pruritus without rash, alanine aminotransferase (ALT) is the most sensitive of the conventional liver tests for the diagnosis of ICP [31]. Palma *et al* also used ALT and aspartate aminotransferase (AST) values above 40 IU/L as partial criteria for the diagnosis of ICP. Serum gamma GT

activity is normal or only mildly elevated, which may be helpful in differential diagnosis. Familial gene mutations, e.g. ABCB4 (MDR3), associated with ICP, can manifest with elevated levels. Due to the expression of the placental isoenzyme with subsequent elevated levels, alkaline phosphatase does not play a role in the diagnostic workup of ICP.

Studies by Kremer *et al* reported that elevated serum autotaxin activity is a highly sensitive, specific, and stable diagnostic marker for obstetric cholestasis and can differentiate ICP from other pruritic disorders of pregnancy and pregnancy-related liver disease.

Patients with ICP should undergo regular antenatal examinations (starting at 32-34 weeks of gestation), taking into account Doppler flow studies of the umbilical artery [25]. Once the diagnosis of ICP is made, total bile acid levels can be monitored every 2-3 weeks to guide therapy and timing of delivery. In addition, coagulation studies and transaminase levels should be monitored to measure disease progression.

Thus, the diagnosis of ICP can be made in the presence of pruritus without rash in the absence of other liver disease in a pregnant patient after 25 weeks' gestation with elevated serum BA and/or aminotransferase levels.

Therefore, early recognition, treatment and timely delivery are imperative. In most cases, an induction of 34 to 39 weeks is usually recommended. In the US, some researchers suggest that the risk of stillbirth is lower if induction occurs at 36 weeks. For all patients with ICP, serum bile acid levels and liver function tests should be monitored 3-6 months postpartum. If bile acid levels remain elevated 6 months postpartum, further evaluation is indicated to rule out an underlying genetic disorder or chronic liver disease.

**Treatment**

Many pharmacological agents have been used in the treatment of intrahepatic cholestasis during pregnancy. These include phenobarbital (100 mg qd), hydroxyzine (25-50 mg qd), the glutathione precursor S-adenosyl methionine (SAME) (800 mg qd IV or 1600 mg qd orally), cholestyramine (8-16 g/d), and dexamethasone (12 mg 4 times a day for 7 days followed by a gradual taper), Vit K 10 mg/day [32, 33, 34]. All of these agents have shown some limited clinical benefit and current recommendations are to refrain from use. UDCA is a naturally occurring bile acid derivative with an anti-cholestatic effect in the human body. UDCA is commonly used off-label in the treatment of ICP. UDCA has several effects in preventing cholestasis, specifically inducing hepatic metabolic enzymes and bile acid transporters, increasing bile acid excretion, protecting biliary epithelial cholangiocytes from bile acid cytotoxicity, and protecting hepatocytes from bile acid-induced apoptosis.

Ursodeoxycholic acid (UDCA) improves clinical symptoms and liver parameters in a number of cholestatic liver disorders [35, 36, 37]. UDCA is thought to engage a key translocator, or transport protein, improving the export of bile salts from the liver and theoretically reducing the risk to the fetus. UDCA (at a daily dose of 600-2000 mg, with the recommended dose being 10-15 mg/kg) is effective in reducing pruritus, lowering total serum bile acid levels, ALT values, and bilirubin levels, and allowing delivery at term -near term [38, 39]. UDCA also improves the cholic acid/chenodeoxycholic acid ratio. UDCA has no significant side effects in the mother and no long-term consequences for the baby.

The *differential diagnosis* of pregnancy-associated hepatopathies is sometimes difficult but mandatory because of differences in maternal and fetal behavior. Based on clinic, gestational age and laboratory indicators (table 3).

**Table 3:** Differential diagnosis of pregnancy-specific hepatopathies - routine laboratory

	<b>ALT</b>	<b>Bilirubin</b>	<b>Bile acid</b>	<b>Uric acid</b>	<b>Platelets</b>	<b>Prothrombin time</b>
HG	1-2 x	<5	Norm.	Norm.	Norm.	Norm
ICP	1-5 x	<5	↑	Norm.	Norm.	Norm./↓
HELLP	1-10 (0) x	<5	Norm.	↑	↑	Norm./↓
AFLP	1-5 x	<10	Norm.	↑	Norm./↓	↓

HELLP – Hemolysis, Elevated Liver enzymes and Low Platelets AFLP – Acute fatty liver, in pregnancy HG – Hyperemesis gravidarum ICP – Intrahepatic cholestasis of pregnancy

**Conclusion**

Hepatological problems in pregnancy are a major differential-diagnostic and therapeutic challenge. An interdisciplinary approach involving a gastroenterologist, gynecologist, neonatologist and resuscitator is necessary. Bile acid levels in the mother's blood should be part of the decision-making process about the best time to give birth. The date of birth is determined individually, after agreement with the expectant mother. A bile acid level  $\geq 100 \mu\text{mol/L}$  is a predictive marker for stillbirth and neonatal complications. Laboratory and clinical changes are completely normalized after delivery. Subsequent pregnancies have an increased risk of recurrence. Outside of pregnancy, the risk of hepatobiliary disorders is increased. Life expectancy is not affected. In case of persistence after a period of 4-8 weeks, the diagnosis of ICP should be questioned. The presence of heterozygous, disease-associated ABCB4 variants favors hepatobiliary

complications. If genetic testing has detected certain ABCB4 variants, lifelong administration of UDCA and annual ultrasound examinations (elastography if necessary) and follow-up of laboratory parameters are recommended. The risk of recurrence of acute steatosis in a new pregnancy is low; if an LCHAD defect is present, it is 25% due to the autosomal recessive mode of inheritance. Information on increased frequency of consequences is mandatory.

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