

Review

Intrahepatic cholestasis of pregnancy: molecular pathogenesis, diagnosis and management

Frank Lammert, Hanns-Ulrich Marschall¹, Anna Glantz² and Siegfried Matern

Department of Internal Medicine III, Aachen University of Technology – RWTH, Aachen, Germany, ¹Karolinska Institutet, Department of Medicine, Division of Gastroenterology and Hepatology, Huddinge University Hospital, Stockholm, and ²Department of Obstetrics and Gynecology, Sahlgren's University Hospital, East, Göteborg, Sweden

CHOLESTASIS, or impaired bile flow, is one of the most common and devastating manifestations of hereditary and acquired liver diseases. Intrahepatic cholestasis of pregnancy (ICP) is a reversible form of cholestasis in late pregnancy, persisting until delivery. The first case of unexplained pruritus associated with visible jaundice appearing in the last trimester of pregnancy and clearing shortly after delivery was reported in 1883 (1). The disease remained unnoticed and unnamed until the mid-1950s when the detailed clinical features were described by several Scandinavian clinicians [for a review, see (2)]. Familial clustering and endemic occurrence of cholestasis of pregnancy strongly indicated a genetic basis. Recent progress in molecular dissection of bile secretion has led to the identification of several gene defects that cause cholestatic liver diseases. These genes are now being tested as candidate genes predisposing to cholestasis of pregnancy.

The incidence of ICP in Europe is approximately 10 to 150 per 10 000 pregnancies (Table 1). For pregnant women with cholestasis, quality of life can be impaired by itching, jaundice and fat malabsorption, but the prognosis for the mother is good. In contrast, ICP is a condition with possible lethal outcome for the unborn child if not handled with care. The major consequences of ICP are premature births in 19 to 60% of affected pregnancies (3–5), a high rate of intrapartur fetal distress in 22 to 33% of deliveries (6,7), and stillbirths in 1 to 2% of ICP pregnancies (4,5,8–10). In spite of these substantial risks, ICP is often neglected and treated expectantly, even in obstetric centers. It is therefore es-

sential to increase interest in and knowledge of the disease, and to find a safe medical treatment that improves fetal outcome.

Molecular Pathogenesis

Hormonal factors: estrogens

Genetic predisposition and hormonal factors play key roles in the pathogenesis of ICP. Evidence for a primary role of hormonal factors in ICP was provided by the following observations (2):

- The disease starts in the last trimester which is the period of the highest hormone concentrations.
- Twin pregnancies display both a higher incidence of ICP and more pronounced rises in hormone levels.

TABLE 1

Incidence of intrahepatic cholestasis of pregnancy (*n* per 10 000 pregnancies) (24)

Country	Incidence	Time of survey	Reference
Australia	80	1964–1966	(122)
	150	1968–1970	(123)
	20	1965–1984	(7)
Bolivia	920	1976	(124)
Caucasian	780		
Aimara	1380		
Canada	10	1963–1976	(125)
Chile	1560	1974–1975	(37)
Caucasian	1510		
Araucanian	2760		
	650	1988–1990	(5)
China	10	1950	(126,127)
	30	1981–1983	(126)
Finland	110	1971–1981	(10,55)
France	20	1961–1973	(128,129)
	60	1988–1989	(130)
Poland	120	1964–1966	(131)
Portugal	100	1994–1997	(132)
Sweden	150	1971–1974	(9)
	100	1980–1982	(9)
USA	<10	1932–1960	(133)
	70	1977	(134)

Correspondence: Hanns-Ulrich Marschall, Karolinska Institutet, Department of Medicine, Division of Gastroenterology and Hepatology, Huddinge University Hospital K63, S-141 86 Stockholm, Sweden.
Tel: 46 8 58582492. Fax: 46 8 58582335.
e-mail: hanns-ulrich.marschall@mbb.ki.se

- ICP resolves promptly after delivery, when levels of placental hormones return to normal.
- In further pregnancies, ICP recurs in 45–70% of the patients.

Estrogens, in particular glucuronides like estradiol-17 β -D-glucuronide, were found to be cholestatic in animal studies where they diminished the uptake of bile acids at the basolateral membrane of hepatocytes. An increased permeability of tight junctions (11) and a decreased fluidity of the sinusoidal membrane (12) have been suggested as underlying mechanisms. Decreased membrane fluidity lowers the Na⁺/K⁺-ATPase activity (13), which results in a reduction of the sodium gradient that is necessary for the sodium-dependent bile acid uptake into the hepatocyte. However, these mechanisms may not be primary but secondary effects due to cholestasis (13,14).

Bile secretion depends on the sequential action of several proteins responsible for the specific transport of the main components of bile, i.e. bile acids, other organic anions, phospholipids such as phosphatidylcholine (lecithin), and cholesterol. These translocating proteins are localized at the basolateral and canalicular membranes that are functionally and biophysically distinct domains of the hepatocyte plasma membrane (Fig. 1). In experimental cholestasis in rats, inhibition of basolateral bile acid transport proteins (Na⁺-dependent taurocholate cotransporting polypeptide, NTCP; organic anion cotransporting polypeptides, OATP) occurs at the transcriptional level (15). Biliary excretion of estradiol-17 β -D-glucuronide is performed by the canalicular multispecific conjugate export pump (multidrug resistance related protein, MRP2) which causes a *trans*-inhibition of the canalicular bile acid export pump (BSEP) (16). Furthermore, estradiol-17 β -D-glucuronide suppresses the expression of MRP2 at the posttranscriptional level (17).

Hepatic biotransformation of the major estrogen in pregnancy, estradiol, includes sulfation and glucuronidation (Fig. 1). These conjugation reactions are typical phase II detoxification reactions, which help to diminish the cholestatic effect of estrogens (18). However, the estrogen conjugate that increases most in pregnancy, estriol-16 α -D-glucuronide (19), was itself found to be cholestatic, at least in animals (20). Beside decreased biliary excretion of estrogen metabolites, impaired hepatic sulfation was observed in ICP patients, using a xenobiotic surrogate compound (21).

Hormonal factors: progesterones

In the pathogenesis of ICP, progesterone metabolites seem to play an even more important role than estro-

gens (22). An early observation described the development of ICP-related symptoms after the administration of progesterone in a woman with a history of ICP (23), and recent studies showed that progesterone treatment during the third trimester was associated with ICP (24). The profile of progesterone metabolites in plasma from patients with ICP is markedly different from that seen in normal pregnancy (25,26). It has been discussed whether the changes can be explained on the basis of cholestasis alone or by specific derangements of the reductive metabolism of progesterone or the sulfation of its metabolites. It is noteworthy that pregnant women with cholestasis due to viral hepatitis have a normal profile of steroid sulfates in blood (27), suggesting that the typical pattern of sulfated progesterone metabolites may only be attributable to ICP.

During pregnancy, 250 to 500 mg of progesterone are synthesized in the placenta per day. In the liver, progesterone is reduced to pregnanolone and pregnanediol (Fig. 1). Four different isomers, 3 α /3 β and 5 α /5 β , are formed, which are further metabolized by hydroxylation and conjugation with sulfate and glucuronic acid. Mono- or disulfated progesterone metabolites are the most prevalent steroids during pregnancy with plasma levels of 10 to 15 μ mol/l (28). These compounds are substantially increased in patients with ICP, in particular the 3 α ,5 α -isomers (25,29). The different ratio of 3 α - and 3 β -hydroxy steroids is most characteristic for ICP (30). Both biliary and fecal excretion of sulfated and glucuronidated progesterone metabolites are decreased in patients with ICP (31,32). Substantial amounts of sulfated progesterone metabolites in urine of pregnant women are additionally conjugated with *N*-acetylglucosamine (GlcNAc) (30,33). The formation of these metabolites is selective for 7 β -hydroxy bile acids such as UDCA (34), which is used to treat ICP (see below). GlcNAc-conjugates are also the major urinary metabolites of UDCA in health (34,35) and cholestatic liver diseases (36) including ICP (30).

Genetic factors

The incidence of ICP shows striking geographic and ethnic differences (Table 1). ICP is most common in Scandinavia and South America. The highest rates of ICP are detected in Chile (16%), especially in women with overt Araucanian Indian descent (28%) (37). The heterogeneous incidence in women of different ethnic origin, familial clustering as documented in several pedigree studies (38,39), and higher incidences in mothers and sisters of patients with ICP (40–42) clearly indicate a genetic predisposition for ICP. A high prevalence of the HLA haplotype Aw31B8 in patients with ICP was found in one kindred (38), but could not

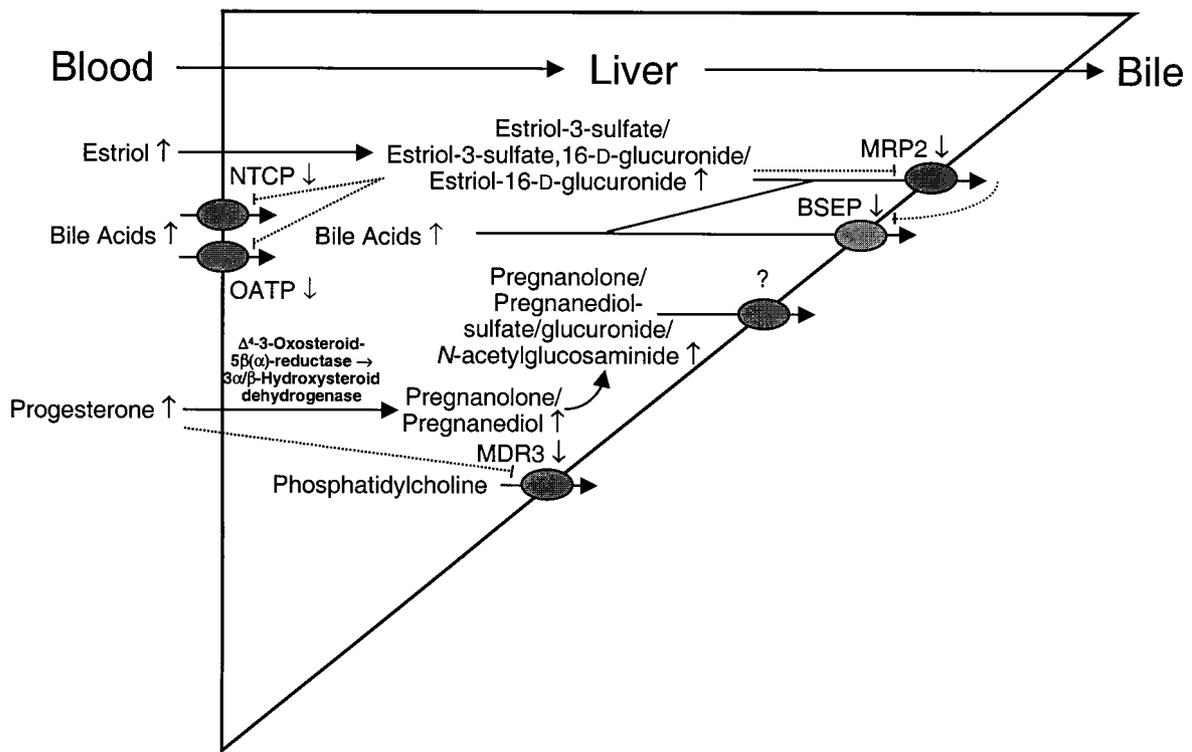


Fig. 1. Schematic diagram of the hepatic metabolism of hormonal factors that contribute to intrahepatic cholestasis of pregnancy (ICP). Hepatic estrogen conjugates inhibit bile salt uptake via the Na⁺-dependent taurocholate cotransporting polypeptide (NTCP) and organic anion cotransporting polypeptides (OATP). Estrogen-glucuronides are excreted via the multidrug resistance associated protein 2 (MRP2) into bile, where they trans-inhibit the bile salt export pump (BSEP). Key enzymes of the hepatic progesterone metabolism include Δ⁴-3-oxosteroid-5β(α)-reductase and 3α/β-hydroxysteroid-dehydrogenase, which convert progesterone to pregnanolone and pregnanediol. These metabolites are conjugated with sulfate, glucuronic acid, and/or N-acetylglucosamine. The export pump for sulfated progesterone metabolites is unknown but might be related to multidrug resistance associated proteins (MRP). Progesterone binds to and modulates the activity of the phosphatidylcholine translocase MDR3.

be confirmed in a later study (42). Thus, the genetic base of ICP is still under investigation.

Current research on the pathogenesis of ICP focuses on two major questions: Is there a defect in transport proteins disabling the biliary excretion of physiologically occurring metabolites in pregnancy or do quantitatively or qualitatively abnormal metabolites inhibit otherwise normally working transport proteins? The increased amount of sulfated progesterone metabolites in plasma could, for example, saturate the maximal transport capacity of dedicated transport proteins. The search for a genetically defined aberration of structure or function of hepatic transport proteins in patients with ICP is motivated by recent progress in the molecular characterization of other cholestatic disorders (43).

In 1998, mutations in genes encoding biliary transport proteins were identified in patients with progressive familial intrahepatic cholestasis (PFIC) [for reviews see (44,45)]. The first mutations were found in the gene *FIC1* (Familial intrahepatic cholestasis 1). The defect

is prevalent in two cholestatic disorders with quite different prognosis (46): patients with Byler's syndrome (PFIC type 1) develop liver cirrhosis in childhood, whereas in many patients with benign recurrent intrahepatic cholestasis (BRIC) no major complications occur. The gene *FIC1* codes a P-type-ATPase that is expressed in the ileum and in large cholangiocytes. The protein may function as an aminophospholipid translocase and is supposed to play an important role in the enterohepatic circulation of bile acids.

In patients with PFIC type 2, mutations of the hepatic canalicular bile acid translocase (BSEP) have been identified (47). Patients with PFIC type 3 display mutations of the gene encoding the canalicular phosphatidylcholine translocase (Multidrug resistance gene 3, *MDR3*) (48). In contrast to other types of PFIC, patients with PFIC type 3 are characterized by elevated serum γ-glutamyl transferase (γ-GT) levels, which are due to bile acid toxicity in phosphatidylcholine deficient bile.

In mothers of patients with PFIC or BRIC, a higher incidence of ICP has been observed (49–51). This indicates that heterozygote mutations of hepatobiliary transport proteins predispose to ICP. This hypothesis is supported by the finding that in the family of a PFIC type 3 patient, six women with a history of ICP were heterozygous for the same deletion (1712delT) in the *MDR3* gene (52). In addition, DNA sequence analysis identified one woman with ICP and raised serum γ -GT, but with no known family history of PFIC, who displayed a missense mutation (C546A); fluorescence activated cell sorting and Western analysis demonstrated disruption of protein trafficking with a subsequent lack of functional protein at the cell surface (53). However, the most prevalent defects in the majority of ICP patients remain to be defined. The close link between genetic and hormonal factors is corroborated by the finding that progesterone binds to and modulates the activity of MDR-translocases such as the phosphatidylcholin translocase *MDR3* (54).

Exogenous factors

Some characteristics of ICP suggest that in addition to hormonal and genetic factors, environmental and alimentary factors may increase the risk for ICP in predisposed women. This is indicated by the decline of ICP prevalence rates in Chile during the last decades (Table 1), and the fact that ICP recurs in less than 70% of pregnancies in multiparous women. It was also reported from Sweden, Finland and Chile, that the incidence of ICP is higher in winter than in summer (9,55,56). Therefore, exogenous factors may superimpose on the genetic predisposition and lead to manifestation of the disease. Some studies linked ICP to low serum selenium (Se) levels (56,57). Se acts as a cofactor of several enzymes in the oxidative metabolism in the liver but the role of Se in bile secretion has yet to be defined.

Fetal pathophysiology

The pathogenesis of stillbirths in ICP is not fully understood. Autopsies show signs of acute, lethal anoxia with petechial bleeding in pleura, pericard and adrenal glands, but no signs of chronic anoxia (4,10,58). In ICP pregnancies there is a major increase in the incidence of meconium-stained amniotic fluid (6,7,58), with stillborns often lying in heavily stained fluid (4,5). However, fetuses of women with ICP have adequate birthweights for gestational age and normal Doppler umbilical artery velocimetry (59), suggesting that chronic placental insufficiency is not the primary cause of fetal death. Infusion of cholic acid to fetal sheep increases the incidence of meconium passage, indi-

cating stimulation of colonic motility by bile acids (60). In experimental models, it has been shown that meconium can cause acute umbilical vein constriction and lead to a reduction in umbilical flow (61,62).

During ICP there is an increased flux of bile acids from the mother to the fetus, as indicated by increased bile acid levels in amniotic fluid (63,64), cord plasma samples (65), and meconium (66). Because the high bile salt levels were found to be associated with more frequent occurrence of fetal distress (65), this might be of great relevance for fetal prognosis, although the pathophysiological mechanisms have yet to be defined. Bile acids have been shown to induce vasoconstriction of human placental chorionic veins *in vitro* (67).

Fetal bile acid balance is dependent on the placental transfer capacity for bile acids. Recently, in vesicle preparations of the basal (fetal) and apical (maternal) trophoblast membranes from patients with ICP, a diminished placental transport of bile acids was observed. This is supposed to result in decreased fetal elimination and a retention of toxic bile acids in the fetus (68,69).

Symptoms

In the past, icterus was believed to be the major clinical finding in ICP. However, the most common symptom is severe pruritus, which most typically appears in the third trimester and starts in palms and soles. In 10% of the patients, pruritus develops in the first trimester and 25% of the patients present with pruritus in the second trimester (70). The pruritus is generally more severe at night and can lead to considerable discomfort for the patients. Only 10% of the patients with pruritus develop icterus (5). Thus, the old term *pruritus gravidarum* designates the mild course of ICP, whereas *icterus gravidarum* describes the aggravated course of ICP. Icterus without pruritus is rare. In most patients, pruritus and icterus disappear promptly after delivery, within 1–2 days; sometimes pruritus persists for 1–2 weeks. However, some cases with a protracted course of the disease have been reported (71). Four Puerto Rican sisters had recurrent prolonged cholestasis of pregnancy, which was followed by periportal fibrosis or cirrhosis but was most likely not identical to “classical” ICP (72). This study indicates that patients with prolonged cholestasis during pregnancy should be monitored for evidence of chronic liver disease, should be counseled on the risks of disease recurrence and progression in future pregnancies, and should inform family members at risk of the disease and its possible symptoms.

ICP may rarely cause steatorrhea with decreased absorption of fat-soluble vitamins and weight loss. In

cases with severe steatorrhea, increased intra- and postpartum hemorrhage may occur if the patient is not supplemented with adequate doses of vitamin K before delivery. Abdominal pain or fever are not observed, unless ICP is associated with other diseases like urinary tract infection.

ICP is associated with a predisposition for cholesterol gallstones, and the incidence of ICP is higher among gallstone patients (73–75). Primigravidae with ICP have a 2.7-fold increased risk for gallstones compared to pregnant women without cholestasis (74). Both fasting and postprandial gallbladder volumes are increased in ICP (76,77). This increase indicates gallbladder hypomotility, which is believed to result from cholesterol absorption by the gallbladder wall (78). Interestingly, the ICP candidate genes discussed above have also been established as genetic determinants for cholesterol gallstone disease in animal models (79).

Diagnosis

Liver function tests are to be performed in every pregnant woman who experiences pruritus. The increase of serum bile acids in combination with typical pruritus is highly suggestive of the diagnosis of ICP.

Among standard liver tests, alanine transaminase (ALT) is a very sensitive parameter for ICP (3). Serum transaminase levels are normal until delivery in healthy pregnancies and therefore, any rise should alert and lead to further tests. ALT is released into the blood in increasing amounts when the liver cell is damaged (80). It has been reported that 20–60% of women with pruritus and elevated serum bile acid levels have 2–10-fold rises in transaminases (5,81,82), but there is poor correlation between the levels of serum bile acids and transaminases (83,84).

The most sensitive indicator for ICP is a rise of serum bile acid levels (Table 2). In healthy pregnancies, total serum bile acids are slightly higher in pregnant ($6.6 \pm 0.3 \mu\text{mol/l}$) than in non-pregnant woman ($5.7 \pm 0.4 \mu\text{mol/l}$) (85), and levels up to 11.0 are accepted as normal in late gestation (86). It is important to emphasize that the av-

erage value for total serum bile acids in ICP patients in Table 2 is a consequence of cases with more serious illness; in fact, a number of patients with markedly lower concentrations have been reported (3,10). In ICP, glycine- or taurine-conjugated bile acids, in particular taurocholate, increase by 2- to 5-fold (87,88), with an increased cholic acid/chenodeoxycholic acid (CA/CDCA) ratio of approximately 4:1 (89). In normal pregnancies of the same gestational age as well as in non-pregnant women, the CA/CDCA-ratio is <1.5 (89). The abnormally high ratio in ICP patients might reflect the fact that the less polar bile acid CDCA is preferably sulfated and excreted in the urine. Both in women with ICP and in women with healthy pregnancies, the serum bile acid composition shows a marked predominance of CA and is similar to the biliary bile acid composition, in contrast to bile of non-pregnant women (90). The measurement of bile acid concentrations in serum is particularly helpful in pregnant women with pruritus but normal transaminases. The urinary bile acid excretion is increased approximately 10-fold during ICP (30).

Total serum alkaline phosphatase (ALP) levels rise slightly in normal pregnancies due to high production of placental and bone isoenzymes (91). ALP levels are usually elevated in ICP patients (Table 2), but are of poor diagnostic value. γ -GT, which is generally lower in late pregnancy, is usually normal or slightly elevated in ICP. If γ -GT levels are high, mutations in the *MDR3* gene are suspected, but not routinely tested to date. Hyperbilirubinemia, up to $100 \mu\text{mol/l}$ (5 mg/dl) is only detected in 10–20% of the cases (Table 2). In urine, bilirubin and urobilinogen can be tested positive.

Serum protein electrophoresis reveals slightly decreased albumin, whereas α_2 -globulins are moderately and β -globulins appreciably increased (92). The increase of LDL-cholesterol and triglycerides, which is observed during pregnancy, is more pronounced in cholestatic patients including ICP, whereas HDL-cholesterol may decrease (70). Cholestasis is associated with the appearance of the abnormal lipoprotein X (LpX) in plasma. LpX are 40–100-nm vesicles, which

TABLE 2
Laboratory findings in intrahepatic cholestasis of pregnancy (135)

Test	Number of patients	Percent of women with abnormal values	Average value	Maximum value
Alanine transaminase	321	55	$2.2 \pm 1.6 \mu\text{kat/l}$ ($131 \pm 96 \text{ U/l}$)	$17.2 \mu\text{kat/l}$ (1030 U/l)
Aspartate transaminase	409	60	$2.0 \pm 0.9 \mu\text{kat/l}$ ($119 \pm 51 \text{ U/l}$)	$12.3 \mu\text{kat/l}$ (736 U/l)
Alkaline phosphatase	575	70	$2.4 \pm 1.1 \mu\text{kat/l}$ ($146 \pm 66 \text{ U/l}$)	$12.5 \mu\text{kat/l}$ (750 U/l)
Bilirubin	558	25	$17 \mu\text{mol/l}$ (1.0 mg/dl)	$315 \mu\text{mol/l}$ (8.4 mg/dl)
Bile acids	128	90	$47 \mu\text{mol/l}$	$430 \mu\text{mol/l}$
Cholic acid	64	70	$17 \mu\text{mol/l}$	$109 \mu\text{mol/l}$

contain unesterified (free) cholesterol. Using mice with a disrupted *Mdr2* gene (murine homolog of *MDR3*), Oude Elferink et al. (93) demonstrated that the appearance of LpX is dependent on the presence of the canalicular translocator for phosphatidylcholine (*MDR2*) and that abnormal excretion of biliary vesicles into blood occurs during cholestasis.

An upper abdominal ultrasound is considered in ICP patients with abdominal symptoms or puzzling laboratory controls. Liver biopsy in general is unnecessary. Histology would show mild focal irregular intrahepatic cholestasis with bile plugs in the canaliculi and small amounts of bile pigment in centrilobular hepatocytes and macrophages. Necrosis or inflammation is absent. Electron microscopy revealed dilated bile canaliculi and loss of microvilli as well as mitochondrial alterations, including enlargement, irregular shape, and lamellar inclusions (94).

Differential Diagnosis

The main differential diagnoses of pruritus of ICP without icterus are skin diseases, allergic reactions and pruritus related to abdominal striae. Only 0.07% of all pregnant woman develop visible icterus (95). The clinician distinguishes *icterus in graviditate*, the coincidence of icterus and pregnancy, from *icterus e graviditate* as a specific complication of pregnancy (Table 3). The acute fatty liver of pregnancy presents with transaminases up to 12 $\mu\text{kat/l}$ (500 U/l), severe hypoglycemia, hepatic encephalopathy, and beginning disseminated intravascular coagulation. Pre-eclampsia is characterized by hypertension and proteinuria, and severe forms can be complicated by the HELLP-syndrome, which is defined by hemolysis, elevated liver enzymes, and low platelet count. The rise of transaminases is lower than

in viral hepatitis and bilirubin is usually normal. In patients with high transaminases and/or high bilirubin, acute viral hepatitis, choledocholithiasis and toxic hepatitis are to be excluded. A high and rapid increase of transaminases favors acute viral or toxic hepatitis. Bile duct obstruction causes an increase in γ -GT and ALP, and abdominal sonography confirms the diagnosis. If cholestasis and elevated transaminases persist for more than 4 weeks after delivery, chronic liver diseases like primary biliary cirrhosis have to be ruled out by testing for antimitochondrial antibodies (AMA) and liver biopsy.

Management

ICP is a fairly common disease with a high impact on fetal morbidity and mortality, and it is also a condition of great discomfort for the patients. Obstetric management of patients with ICP varies widely over the world. In spite of numerous reports of increased fetal risk (4,5,96) many obstetric clinics still choose to manage ICP pregnancies expectantly. Many different protocols for intensified surveillance have been proposed. It has been shown that a regimen including weekly fetal cardiotocographic (CTG) monitoring from the 34th week of gestation and induction of labor in the 38th week of gestation in mild cases, and in the 36th week of gestation in severe cases can reduce perinatal mortality to control levels (5). Another group (4) reported reduction of perinatal mortality by active management (including amnioscopy and generous induction of labor) to one third, compared to expectant management without fetal monitoring (4). The authors point out that the protocol still does not totally eliminate the risk of acute fetal death before onset of labor.

To date no randomized trials have been conducted to investigate the optimal surveillance level at a cost-benefit basis. Most authors agree that weekly CTG registrations are valuable, at least from the 34th week of gestation on. Weekly assessments of serum bile acids, transaminases, and bilirubin should be conducted. In severe cases or if the patient suffers from steatorrhea, control of prothrombin time should be considered. Obstetric management consists of weighing the risk of premature delivery against the risk of sudden death *in utero*. In addition, it has to be considered that induction of labor is associated with a higher frequency of complications such as operative deliveries compared to spontaneous labor. Since fetal prognosis correlates with disease severity (10,55,58), the aim of treatment should be reduction of bile acids in order to prolong the pregnancy and reduce both fetal risk and maternal symptoms.

Frequencies of abortions and malformations are not

TABLE 3

Differential diagnosis of intrahepatic cholestasis of pregnancy (ICP) with jaundice (95)

Etiology	Prevalence (%)
<i>Icterus e graviditate</i>	
ICP	21
Acute fatty liver of pregnancy	
HELLP syndrome	5
<i>Hyperemesis gravidarum</i>	6
<i>Icterus in graviditate</i>	
Viral hepatitis	42
Steatohepatitis	
Septic pyelonephritis	
Hyperbilirubinemia syndromes	
Drug icterus	
Bile duct obstruction	6
Hemolytic icterus	4
Metabolic diseases	

increased in ICP. Birthweights are adequate for gestational age. Breastfeeding is not contraindicated. Patients with a history of ICP may use low-dose oral contraceptives after normalization of liver function tests, provided they are instructed to stop medication if pruritus and cholestasis recur.

Pharmacological Treatment

Antihistamines, anion exchange resins and phenobarbital are given to remove putative peripheral pruritogens or to reverse their effects on empiric grounds (97). These therapeutic options have not received wide acceptance for treatment of ICP patients because of their ambiguous efficacy or side effects. Anion exchange resins such as colestipol or colestyramine bind bile acids and interrupt their enterohepatic circulation. They should therefore be given separately from ursodeoxycholic acid (UDCA, see below) (98). Since both ICP and colestyramine may independently lead to vitamin K deficiency, it is important that ICP patients who are treated with anion resins receive parenteral substitution of fat-soluble vitamins (A, D, and K). Because of the risks of antepartal fetal hemorrhage (99) and intra- and postpartal maternal bleedings, and the minor effect on pruritus, colestyramine is nowadays not considered first-line therapy for ICP.

S-adenosylmethionine (SAM) improves cholestasis in the ethinylestradiol-treated rat (14). It is a precursor of glutathione and, as a universal methyl group donor, involved in the hepatic synthesis of phosphatidylcholine. Thus, SAM has been proposed to influence not only the composition and fluidity of hepatocyte plasma membranes, but also methylation and biliary excretion of hormone metabolites. In two Italian ICP studies, daily intravenous application of 800 mg SAM for 20 days (100) or oral application of 1600 mg SAM (101) resulted in significant decreases of pruritus, bilirubin, and ALT. However, 900 mg SAM in daily intravenous infusions were without effect in a double-blind, placebo-controlled study in 9 Chilean patients with moderate or severe ICP (102). In conclusion, the role of SAM in ICP treatment is still a matter of debate.

Phenobarbital was once thought to be a therapeutic alternative for ICP, but it relieved pruritus in only 50% of the patients and showed no beneficial effects on liver parameters (103,104). Dexamethasone and UDCA are treatment options being currently evaluated. Dexamethasone inhibits the fetoplacental hormone synthesis, and a single study demonstrated significant improvement of pruritus, bile acids and ALT in 10 patients, who were treated with dexamethasone at an initial dose of 12 mg four times daily for 7 days with subsequent dose tapering over 3 days (105).

UDCA, a naturally occurring hydrophilic bile acid (106), improves clinical and biochemical indices in a variety of cholestatic liver diseases (107). It is nowadays considered as the first-line treatment option for patients with primary biliary cirrhosis (PBC), because the results from the combined analysis of the three largest randomized clinical trials of UDCA in PBC indicate that UDCA improves survival free of liver transplantation (108). These results are under intense discussion (109–111). The mechanisms of action of UDCA are still under debate. There is evidence that the hydrophilic UDCA protects against injury to bile ducts by hydrophobic bile acids and stimulates the excretion of these and other potentially hepatotoxic compounds (107).

Based on the positive experiences in PBC, UDCA has been used for the treatment for ICP as well. In a study with 20 ICP patients, UDCA at a dose of 450 mg/day was more effective in relieving itching and lowering serum bile acids than SAM at a dose of 1000 mg/day (112). The beneficial effects of UDCA have been confirmed in two small randomized double-blind placebo-controlled trials in 16 patients with ICP (113,114). At a dose of 600–1000 mg per day, significant improvements in pruritus, bilirubin and transaminases were observed.

In ICP patients, UDCA normalizes the increased CA/CDCA ratio (115,116) and reduces plasma concentrations as well as urinary excretion rates of sulfated steroid metabolites (115). Furthermore, administration of UDCA both restores the impaired bile acid transport across the trophoblast in ICP (68) and decreases the delivery of bile acids to the fetus (63,116–121), representing a valuable contribution to fetal well-being and outcome (114).

UDCA has virtually no side-effects except for mild diarrhea in rare cases. Up to now, no adverse effects on the fetus have been reported. Because the start of treatment with UDCA is usually delayed until the third trimester, the risk of teratogenicity is further minimized. Because UDCA has not yet been approved for ICP treatment, results of future larger randomized, controlled UDCA trials in ICP patients are eagerly awaited.

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