Intrahepatic cholestasis of pregnancy

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Abstract

Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-specific disorder characterized by maternal pruritus and elevated liver enzymes. It usually begins in the third trimester of pregnancy and resolves spontaneously after delivery. ICP is considered benign for the pregnant woman, but it is associated with an increased risk for unexplained term stillbirth and preterm delivery.

ICP poses a risk for the fetus and is disadvantageous with respect to maternal wellbeing during pregnancy. Increased maternal blood levels of serum bile acids (BAs) are the most sensitive and specific biochemical marker of ICP and are widely used as a diagnostic tool, together with serum alanine aminotransferase (ALT). There are, however, no specific diagnostic laboratory parameters for the diagnosis of ICP.

There are ongoing controversies concerning treatment and management of ICP. Ursodeoxycholic acid (UDCA) is the most promising medical treatment. It is effective in reducing maternal pruritus and improving maternal liver function test values and that it also benefits fetal outcome. Women with ICP have still an increased rate of unexplained intrauterine fetal death at term, mostly between 37 and 39 gestational weeks. Active management, including fetal antenatal monitoring and labor induction, is usually recommended but also individually tailored management of ICP-affected pregnancies has been suggested.

Keywords: intrahepatic cholestasis, pregnancy, diagnosis, treatment, fetal surveillance, fetal complications

Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate transaminase; APTT: Activated partial thromboplastin time; BA: Bile acid; BMI: Body mass index; CTG: Cardiotocogram; FECG: Fetal electrocardiogram; FXR: Farnesoid X receptor; FIDD: Fibrinogen D-dimers; GA: Gestational age; GW: Gestational week; GSTA: Plasma glutathione S-transferase alpha; ICP: Intrahepatic cholestasis of pregnancy; IUFD: Intrauterine fetal death; HELLP: Hemolysis, elevated liver enzyme and low platelet count; MPR: Multidrug resistance associated protein; MSAF: Meconium staining of amniotic fluid; NICU: Neonatal intensive care unit; RCT: Randomized controlled trial; RDS: Respiratory distress syndrome; SAMe: S-Adenosyl-L-methione; TBA: Total bile acid; UA: Umbilical artery; UDCA: Ursodeoxycholic acid.

1. Terminology

Intrahepatic cholestasis of pregnancy (ICP), also known as obstetric cholestasis, is a liver disease of pregnancy associated with severe itching, which the patient senses especially in her palms and soles, combined with biochemical evidence of liver dysfunction. It typically arises in the third trimester of pregnancy and disappears spontaneously after delivery. A diagnosis of ICP requires that other pathological liver and skin diseases or conditions are excluded.

As an independent symptom, pruritus is fairly common among pregnant women; it affects as many as 20% of pregnancies. The main differential diagnosis of pruritus is skin diseases and allergic reactions. (Roger et al. 1994, Lammert et al. 2000, Pathak, Sheibani and Lee 2010)

2. Epidemiology

The incidence of ICP varies widely by geographical location and ethnicity (Geenes and Williamson 2009). The estimated prevalence of ICP in the United States is reported to vary from 0.001% to 0.32% and, in contrast, in Chile the number is as high as 6.5% (Berg et al. 1986, Laifer et al. 2001, Wilson and Haverkamp 1979, Glantz, Marschall and Mattsson 2004). In some ethnic groups the prevalence is much higher, e.g., in Araucanian, Chile, the prevalence is 27.6% and in Aimaras, Bolivia, 13.8% (Reyes et al. 1979). In Europe, it affects approximately 10 – 150 per 10,000 pregnancies; the incidence is highest in the Nordic countries (Finland 0.9%, Sweden 1.4%) and lowest in France (0.2%) (Lammert et al. 2000).

3. Etiology and pathogenesis

The etiology of ICP is still unknown, but among the risk factors are environmental factors, nutritional deficiencies, genetic variations and hormonal changes (Reyes et al. 1978).

Certain maternal physiological changes during pregnancy support fetal growth and development. Serum hormonal levels increase and affect metabolic, synthetic and excretory hepatic functions. There is evidence for a primary role of steroid hormones in ICP. The changes caused by genetic factors may increase the subject's sensitivity to normally produced steroid hormones, especially estrogens and progesterones. This is based on following three circumstances: Firstly, ICP usually starts in the last trimester, i.e., the time of the highest maternal estrogen and progesterone concentrations (Reyes 1997). Secondly, the incidence is higher in twin pregnancies than singletons (Rioseco et al. 1994, Koivurova et al. 2002, Gonzalez et al. 1989) and in pregnancies following in vitro fertilization than spontaneous conception (2.7% vs 0.7%) (Koivurova et al. 2002). Thirdly, ICP resolves promptly after delivery and also recurs in half of the patients during subsequent pregnancies (Heinonen and Kirkinen 1999, Reyes and Sjövall 2000).

Estrogens are cholestastic according to animal studies: they reduce the uptake of bile acids (BA) at the basolateral membrane of hepatocytes. Estrogen can

inhibit BA transport from hepatocytes into bile canaliculi by interfering with the bile salt export pump and the multidrug resistance-associated transporter 2 (Chen, Zhao and Liu 2013). Further, progesterone metabolites might play an even more important role in the ICP metabolism than estrogens (Reyes and Sjövall 2000). The levels of sulfated progesterone metabolites in the serum of women with ICP rise and the pattern of progesterone metabolites differs significantly from that in normal pregnancy (Sjövall and Sjövall 1970). The level of normal metabolism of progesterone in ICP is reduced, resulting in increased formation of metabolites and a larger fraction of sulfates (Meng et al. 1997). Women with ICP may also have a defect in the secretion of sulfated progesterone metabolites into bile (Reyes and Sjövall 2000), and the normal fetomaternal transfer of BAs across the placenta is impaired. The accumulated BAs are potentially toxic to the fetus (Fagan 1999).

The genetic etiology of ICP is largely unknown, but several investigators have studied potential genes associated with ICP (Müllenbach et al. 2003, Pauli-Magnus et al. 2004, Eloranta et al. 2003, Painter et al. 2005, Jacquemin 2012). Genetic predisposition may lead to changes in the membrane composition of the bile ducts and hepatocytes, and to dysfunctional transporters in the biliary canaliculi (Savander et al. 2003). Considerable evidence for a genetic predisposition to ICP comes from familiar clustering and an increased risk of ICP among first-degree relatives to affected individuals (Turunen et al. 2013).

Currently, the primary genes of interest are genes that encode biliary transport proteins (ABCB4, ATP8B1, and ABCB11). Mutations in these genes cause recessively inherited progressive familial intrahepatic cholestasis, which is a rare, early-onset condition associated with intrahepatic cholestasis in infancy or early childhood and resulting in death. Affected individuals benefit from transplantation. ABCB4 is a gene encoding for multidrug resistant protein 3 (MDR3) P-glycoprotein, and mutations in this gene may affect BA trafficking and lead to a rise in BA concentrations (Lammert et al. 2000, Wasmuth et al. 2007). ABCB4 gene variants have particularly been linked to a severe form of ICP (Wasmuth et al. 2007). Various single nucleotide polymorphisms (SNP) in ABCB11 and ABCB4 proteins are associated with ICP (Dixon et al. 2014). ATP8B1 is also a candidate gene for ICP, but not for ICP in Finnish ICP patients (Painter et al. 2005, Savander et al. 2003).

Seasonal variations affect the prevalence of ICP. ICP is most common in the winter months in Finland, Sweden, Chile and Portugal (Berg et al. 1986). Other reported risk factors for ICP are a family history of biliary disease, hepatitis C, prior ICP, multifetal gestation and maternal age greater than 35 years (Gonzalez et al. 1989, Heinonen and Kirkinen 1999). ICP patients have also often low concentrations of selenium in their serum (Reyes et al. 2000, Kauppila et al. 1987). Selenium deficiency may lead to

defective bile formation or secretion because selenium is a cofactor for several oxidative hepatic enzymes (Kauppila et al. 1987, Reyes et al. 2000).

4. Symptoms

The most common symptom of ICP is pruritus which typically appears in the third trimester and starts in the palms and soles. It often becomes generalized. The pathophysiology of the pruritus is still unknown. Bile salts are thought to be deposited on nerve endings of the skin causing itching. The pruritus is typically most severe at night and can cause insomnia and considerable discomfort for the patients. Other causes of itching must be excluded (atopic eczema, allergic reactions, urticarial or gestational pemphigoid and virus infections). Clinical examination of the skin is normal except for evidence of scratching. Usually 80% of patients have symptoms after 30 gestational weeks (GW) and the condition presents in the late second and third trimester of pregnancy, although ICP has been reported as early as at 6 – 10 weeks of gestation (Saleh and Abdo 2007, Kenyon et al. 2002, Brites et al. 1998).

The old term icterus gravidarum describes the old aggravated course of ICP. In rare cases ICP can cause steatorrhea with decreased absorption of fat-soluble vitamins and weight loss. Theoretically steatorrhea can increase the risk for postpartum hemorrhage as a result of malabsorption of vitamin K, although such cases have been reported only rarely (Reid et al. 1976). ICP resolves spontaneously in a few days following delivery.

5. Diagnosis

The diagnosis of ICP based on the clinical presentation, laboratory results and exclusion of other causes for the clinical and biochemical findings. The differential diagnosis includes other forms of hepatic disease. In patients with very high levels of serum alanine aminotransferase (ALT) and/or aspartate transaminase (AST), hepatitis A, B, C, severe pre-eclampsia, the HELLP syndrome, acute fatty liver of pregnancy, and drug toxicities should be excluded.

5.1. Biochemical features

The liver tests should be performed in every pregnant woman who complains of pruritus. ALT and TBA concentrations have been widely used to diagnose ICP. Minor elevations of liver enzymes are observed in up to 60% of ICP patients (Tan 2003).

Serum BA levels are sensitive indicators of hepatobiliary disease. Elevated serum BA levels have been used to screen for other cholestatic disorders than ICP, e.g., biliary atresia and bile acid synthesis defects (Mushtaq et al. 1999, Haas et al. 2012). A BA level ≥10 μmol/L during pregnancy was the diagnostic criteria for ICP in the study of Glantz et al. (Glantz et al. 2004). In Finnish studies the diagnostic laboratory criteria for ICP were BA ≥ 6 μmol/L or ALT > 40 U/L or AST > 35 U/L (Turunen et al. 2010). Earlier studies reported that 20 – 60% of women with pruritus during pregnancy and elevated serum BA levels have 2 – 10-fold levels of transaminases (Rioseco et al. 1994, Lunzer et al. 1986). Elevated serum

BA levels are the most sensitive indicator of ICP (Lammert et al. 2000), but serum ALT levels usually also rise in ICP, while other biochemical features remain normal (Lammert et al. 2000, Dann et al. 2004). The levels of both AST and ALT in the serum can rise in patients with ICP, but ALT seems to be the more sensitive indicator of the two (Bacq 1999). An earlier Finnish study reported no statistically significant correlation between TBA and ALT (Laatikainen 1975).

The levels of serum bilirubin are elevated in the most severe form of ICP, and the level of total bilirubin is associated with preterm delivery (Oztas et al. 2014). The activity of GGT is increased in about 10 – 15% of the women with ICP.

As the aminotransferases and GGT are located within the periportal hepatocytes, they are relatively poor markers of damage to the centrilobular hepatocytes (Beckett and Hayes 1993).

The glutathione S-transferase group of enzymes occurs in abundance in the liver. Cytosolic glutathione S-transferases are dimeric proteins which are divided into four classes: α, μ, π and θ (Mannervik et al. 1992). These enzymes are released in detectable amounts after only minor impairment of hepatocellular integrity (Beckett and Hayes 1993). Glutathione S-transferase alpha (GSTA) occurs in high concentrations in the liver and the levels in the plasma are known to rise exclusively in hepatic diseases (Beckett and Hayes 1993). Measurement of the activity of this enzyme in plasma samples may provide a fast and specific marker of acute hepatocellular damage (Beckett and Hayes 1993, Mannervik et al. 1992). Previously, elevated maternal concentrations of GSTA have been associated with obstetric complications, e.g., severe pre-eclampsia and the HELLP syndrome (Knapen et al. 1998, Steegers et al. 1995, Kumtepe et al. 2002). Dann et al. showed that high serum GSTA levels could be a useful indicator of liver dysfunction also in ICP and might help to distinguish ICP from pruritus gravidarum (Dann et al. 2004). GSTA may be a new, promising diagnostic tool for ICP. It has been found that the mean GSTA concentration in ICP patients was significantly higher than in the group of women with a normal pregnancy (Joutsiniemi et al. 2008).

In a recent study by Kremer et al., high serum autotaxin activity correlated with the onset of ICP-related pruritus (Kremer et al. 2014). Elevated autotaxin levels might be a highly sensitive and a specific diagnostic marker for ICP, not influenced by the circadian rhythm or food intake.

Also some routine laboratory parameters can predict an adverse perinatal outcome in ICP. An increased mean platelet volume is associated with preterm delivery in ICP patients (Oztas et al. 2014). The neutrophil-to-lymphocyte ratio is elevated in pregnancies complicated with ICP and may predict the severity of ICP (Kirbas et al. 2014).

5.2. Ultrasonography

Ultrasonography of the maternal liver and upper abdomen is an important

examination for ICP patients with puzzling laboratory test results, largely as a means to exclude some important liver disorders and to provide support to a working diagnosis of ICP. In ICP, it usually reveals no dilatation of the intrahepatic nor extrahepatic bile ducts (Krueger, Hoffman and Lee 1990), although the fasting and ejection volumes of the gallbladder seem to be higher than in healthy pregnancy (Krueger et al. 1990, Bacq 1999). ICP is associated with a predisposition for cholesterol gallstones and the incidence of ICP is higher among patients with gallstones (Leevy, Koneru and Klein 1997, Samsioe et al. 1975). Several liver and biliary diseases are significantly more common among patients with ICP than during healthy pregnancy (Ropponen et al. 2006). Some patients with ICP are at risk of liver cirrhosis or other severe chronic liver diseases (Ropponen et al. 2006).

5.3. Pathology

A liver biopsy is rarely needed in the diagnosis of ICP. If a biopsy is taken, pure cholestasis and sometimes bile plugs are seen in hepatocytes and canaliculi. Usually inflammation and necrosis are not present and the portal tracts are not affected (Rolfes and Ishak 1986, Bacq 1999). Untreated ICP patients present histopathologically with chorangiosis (increased number of capillaries in terminal villi), an increased surface volume of capillaries and terminal villi, and an increased number of syncytial knots (Wikström Shemer et al. 2012). In a recent histopathological case-control review of placentas from ICP patients and controls, there were no differences in placental histopathology between the groups (Patel et al. 2014). Placental histology usually shows nonspecific hypoxic changes, but it cannot be established whether these changes are primary or secondary (Costoya et al. 1980).

6. Impact on fetus

Although severe maternal complications are rare in ICP, the fetus may be affected by preterm labor and birth, meconium aspiration and even perinatal death (Reid et al. 1976, Alsulyman et al. 1996, Fisk and Storey 1988). The etiology of the fetal complications is poorly understood, but it is generally believed that the fetal complications are related to the elevated maternal BA concentrations. Intrauterine fetal death (IUFD) is thought to occur suddenly, as there is no evidence of preceding intrauterine growth restriction or uteroplacental insufficiency and the fetal autopsy is usually normal (Fisk and Storey 1988, Davies et al. 1995, Williamson et al. 2004).

High maternal serum BA levels are a significant predictor of preterm delivery, spontaneous preterm delivery, stillbirth and meconium staining of amniotic fluid (MSAF) (Geenes et al. 2014a). The doubling of the level of maternal serum BA increases the risk for preterm delivery by 68%, spontaneous preterm delivery by 66%, MSAF by 55% and IUFD by 200%. Maternal serum ALT and preterm delivery are also significantly, albeit more weakly, associated. In the study of Geenes et al. (2014), none of the other biochemical markers were significantly associated with

any perinatal complications (Geenes et al. 2014a). Brouwers and associates showed that in severe ICP (BA levels > 100μmol/L) sudden and unpredicted IUFD was even more common. A more aggressive approach to elective delivery may be justified when maternal BA levels are >100 μmol/L (Brouwers et al. 2015). In that study, the levels of BAs correlated between mother and fetus and this implies a causal relationship between the level of fetal exposure to BA and fetal complications and, ultimately, an adverse outcome (Brouwers et al. 2015).

It is estimated that the probability of fetal complications, such as spontaneous preterm deliveries, asphyxial events and MSAF, increase by 1 – 2% per additional μmol/L of serum BA (Glantz et al. 2004). When the BA levels are < 40 μmol/L, the fetal risk does not seem to be increased (Glantz et al. 2004).

The normal feto-maternal transfer of BA across the placenta is impaired in ICP patients. The fetus has no ability to excrete cholic acid, which remains elevated in the meconium in ICP, even after ursodeoxycholic acid (UDCA) treatment (Rodrigues, Marín and Brites 1999). Elevated BA may cause fetal arrhythmias. It is hypothesized that IUFD is caused by impaired fetal cardiomyocyte function, resulting in fetal cardiac arrest caused by raised fetal serum taurocholate concentrations (Williamson et al. 2001). Taurocholate also impairs the conduction in the fetal heart and ectopic electrical activity may arise (Miragoli, Gaudesius and Rohr 2006). The fetal PR interval is significantly increased in the ECG in ICP (Strehlow et al. 2010). Fetal atrial flutter and supraventricular tachycardia occur in pregnancy complicated by ICP (Al Inizi, Gupta and Gale 2006, Shand, Dickinson and D'Orsogna 2008) and BAs can cause vasoconstriction in isolated human placental chorionic veins (Sepúlveda et al. 1991).

Corticosteroid secretion is a part of the fetal stress response and in severe ICP it is suppressed. Elevated maternal TBA levels are associated with reduced fetal concentrations of cortisol, dehydroepiandrosterone sulfate and corticotropin-releasing hormone (Zhou et al. 2013, Wang et al. 2011). The impaired fetal stress control might contribute to the risk for IUFD. Corticotropin-releasing hormone is one of the most potent vasodilatory factors in the human fetoplacental circulation (Clifton et al. 1994). Downregulation of maternal serum and placental corticotropin-releasing hormone expression might result in poorer feto-placental vascular perfusion and adverse fetal outcomes (Zhou et al. 2013).

The cause of the spontaneous onset of preterm delivery in ICP is unknown. Increased levels of BA may affect the contractility of the myometrium (Rioseco et al. 1994). Also, myometrial contractility may be increased as a consequence of increased levels of cholic acid (Mullally and Hansen 2002); this activates the oxytocin receptor pathway (Germain et al. 2003) following a cholic acid-mediated increase in oxytocin-receptor expression (Germain et al. 2003).

There is an increased risk for meconium passage in ICP, but there is not sufficient evidence to suggest its role in fetal death (Kafkasli et al. 1997). The incidence of MSAF varies between 10% and 44% in ICP (Glantz et al. 2004, Lee et al. 2006, Bergasa 1995) and correlates positively with the severity of ICP (Glantz et al. 2004, Lee et al. 2008). The risk for meconium expulsion increases near term, similarly as in healthy pregnancies. BAs stimulate the motility of the large intestine of the fetus, which may be the reason for meconium expulsion (Kirwan et al. 1975), although Jain and associates did not establish an association between meconium passage and the severity of ICP (Jain et al. 2013).

Maternal ICP is also significantly associated with the occurrence of the respiratory distress syndrome (RDS) in the newborn (Zecca et al. 2008, Zecca et al. 2006). Zecca et al. concluded that the incidence of RDS in infants from mothers with ICP was almost double than that of infants born after healthy pregnancies. They hypothesized that the raised level of TBA in the feto-maternal unit could decrease fetal surfactant production. Another pathophysiological mechanism may consist of a direct toxic effect of BAs on type II pneumocytes (Oelberg, Downey and Flynn 1990). BAs are thought to be the direct causal factor for BA-induced pneumonia during early postnatal period (Zecca et al. 2004, Oelberg et al. 1990).

Sudden IUFD occurs in 0.4% – 1.5% of pregnancies complicated with ICP (Geenes et al. 2013, Glantz et al. 2004). The cause of the IUFD seems to be multifactorial and is still unknown. BAs are thought to play a key role in its pathogenesis, although IUFD can occur at virtually physiological TBA levels (Sentilhes et al. 2006). There is currently no effective way of identifying the fetuses at risk for IUFD.

7. Management

Treatment of the mother

The treatment of ICP has mainly been symptomatic. Several medications during pregnancy, e.g., phenobarbital, cholestyramine, S-Adenosyl-L-methionine (SAMe), dexamethasone and ursodeoxycholic acid (UDCA), have been evaluated in the treatment of ICP (Heikkinen et al. 1982, Ribalta et al. 1991, Roncaglia et al. 2004, Glantz et al. 2005). These therapies aim at altering the enterohepatic circulation of BA and in this way at reducing the concentration of BA in the maternal serum (Pathak et al. 2010). The goal of these treatments is to improve perinatal outcome with continued pregnancy (if safe) and relief of maternal symptoms.

Currently, UDCA is the most promising treatment for ICP. It is a naturally occurring hydrophilic BA that replaces more cytotoxic BAs and constitutes less than 3% of the physiological BA pool in humans. It is clinically used for the treatment of various cholestatic disorders, e.g., primary biliary cirrhosis (Lazaridis, Gores and Lindor 2001). The main modes of action of UDCA are protection of cholangiocytes against the cytotoxicity of hydrophobic BAs, stimulation of hepatobiliary secretion

and protection of hepatocytes against BA induced apoptosis (Paumgartner and Beuers 2002). It might also improve BA transport and detoxification (Marschall et al. 2005).

UDCA lowers the levels of cholestatic estrogen metabolites in the serum. Overall, however, the mechanisms of these beneficial effects are not fully understood. Serum levels of cholesterol, HDL-cholesterol and triglycerides, APTT, FIDD and estradiol, progesterone, prolactin and platelet count were not modified by UDCA administration (Joutsiniemi et al. 2014). In a study by Dann et al. ICP was associated with an abnormal lipid profile but UDCA did not affect plasma lipid concentrations (Dann et al. 2006).

Corelik and associates showed in vitro study in rats that dexamethasone and UDCA protect against the arrhythmogenic effect of taurocholate (Gorelik et al. 2003). Most patients in our study with ICP had UDCA therapy and this may have decreased the fetal risk for arrhythmia by stabilizing the QTc-interval which was close to normal. Several experimental models have shown that UDCA may have a direct protective effect on the fetal compartment (Geenes et al. 2011). Treatment with UDCA reduces the levels of BA in the maternal and fetal compartments (Geenes et al. 2014b) and there is no significant fetal metabolism of the increased exposure of BA of maternal origin in obstetric cholestasis (Dixon et al. 2014).

The dose of UDCA has varied between different randomized controlled trials. In most trials, the dose of UDCA has been between 600 and 900 mg/d (Diaferia et al. 1996, Nicastri et al. 1998, Roncaglia et al. 2004, Kondrackiene, Beuers and Kupcinskas 2005, Binder et al. 2006, Liu et al. 2006). In the studies of Palma el al. (1997) and Glantz et al. (2005) the UDCA dose was quite high, 1000 mg/d (Palma et al. 1997, Glantz et al. 2005). Floreani (1996) and associates used the dosing 450 mg/d (Floreani et al. 1996). According to our results, low-dose UDCA treatment (450 mg/d) was effective in ICP patients. The perinatal outcome was good, liver enzyme levels decreased during treatment and maternal side effects were minimal (Joutsiniemi et al. 2015). Also Bacq et al. concluded in their meta-analysis that UDCA therapy might benefit fetal outcomes (Bacq et al. 2012). It might reduce fetal distress, and the need for NICU treatment might decrease.

UDCA has also a beneficial effect on the BA transport mechanisms in human placentas (Serrano et al. 1998) by the following mechanism: ICP induces impairment of the placental antioxidant system, which causes oxidative damage. These alterations are accompanied by enhanced activation of the mitochondrial pathway of apoptosis (Perez, Macias and Marin 2006). Treatment with UDCA prevented partly these placental changes in a rat model (Perez et al. 2006).

Treatment with UDCA reduces serum BA in the maternal compartment and reduces the transplacental gradient between fetus and placenta. There are no

major differences between the level of BA in the umbilical cord artery and vein serum samples, which implies that there is no significant fetal metabolism of BA of maternal origin in ICP (Geenes et al. 2014a, Geenes et al. 2014b). UDCA treatment decreases urinary excretion of disulfated progesterone metabolites. This suggests that the amelioration of the pruritus of ICP is connected to enhanced hepatobiliary excretion of progesterone disulfates (Glantz et al. 2008).

Maternal serum and placental corticotropin-releasing hormone expression in ICP patients are up-regulated during UDCA treatment, which may be important for our understanding of the therapeutic mechanisms of UDCA treatment. UDCA may reduce fetal distress through the up-regulation of placental and maternal serum corticotropin-releasing hormone levels (Zhou et al. 2014b).

The use of UDCA was first reported as a treatment for ICP in 1992 by Palma et al. (1992). Later they reported a significant reduction in pruritus and a decrease in serum bilirubin, AST and ALT concentrations after 3 weeks treatment at a dose of UDCA of 1 g daily (Palma et al. 1997). Also Diaferia et al. reported that pruritus abated and biochemical parameters improved in ICP when the dose of UDCA was 600 mg/day (Diaferia et al. 1996).

Later Glantz et al. reported that 3 weeks of UDCA treatment improved the values of some of the biochemical markers of ICP irrespective of disease severity, whereas significant relief from pruritus and a marked reduction of serum BA took only place in patients with severe ICP and BA levels $\geq$ 40 μmol/L (Glantz et al. 2005). More recently, a meta-analysis showed that UDCA therapy is effective for reducing pruritus and improving liver test values in women with ICP (Bacq et al. 2012). Chappell et al. found that UDCA reduces pruritus, but that the benefit may be modest (Chappell et al. 2012). According to a meta-analysis including both non-randomized and randomized controlled trials, UDCA-treatment reduces pruritus and improves the biochemical features of patients with ICP (Grand'Maison, Durand and Mahone 2014).

UDCA therapy during ICP benefits also fetal outcomes. Bacq et al. (2012) reported that this treatment reduces the occurrence of neonatal RDS and that fewer neonates need NICU treatment for RDS. There were fewer cases of fetal distress or asphyxia events in the groups on UDCA compared to placebo, but the difference was not statistically significant (Chappell et al. 2012). There were also significantly fewer total preterm births among the patients treated with UDCA (Chappell et al. 2012). UDCA treatment did not increase the rate of Cesarean sections, but it was associated with less prematurity, a reduced need for treatment at the NICU and there was also a trend favoring increased birth weight and decreased meconium staining (Grand'Maison et al. 2014). Zapata et al. reported that UDCA treatment during pregnancy had no adverse effects on 26 infants followed up for a mean of 6 years after delivery (Zapata et al. 2005).

On the basis of a meta-analysis, which included both non-randomized and randomized controlled trials, UDCA was recommended for women with ICP to reduce adverse maternal and fetal outcomes (Grand'Maison et al. 2014).

Dexamethasone therapy reduces circulating estriol levels which are thought to be increased in ICP. Dexamethasone relieves pruritus and normalizes serum levels of ALT and BA but suppresses fetoplacental estrogen production (Hirvioja, Tuimala and Vuori 1992). Also clinical and biochemical improvement in ICP patients has been reported in another small study and no maternal or fetal adverse effects were recorded (Diac et al. 2006). In a larger randomized study on the effects of dexamethasone, UDCA and placebo were compared with dexamethasone in the treatment of ICP (Glantz et al. 2005). Dexamethasone provided no alleviation of pruritus or reduction of ALT levels and was less effective than UDCA at reducing BA and bilirubin (Glantz et al. 2005). Worsening of ICP following treatment with dexamethasone has been documented (Kretowicz and McIntyre 1994). In conclusion, dexamethasone is not an optimal treatment of ICP and is no longer used (Pathak et al. 2010).

S-Adenosyl-L-methionine (SAMe) alters hepatic surface membrane function in a way that improves impaired bile flow due to increased levels of ethinyl estradiol (Boelsterli, Rakhit and Balazs 1983). According to a randomized study, a high daily dose of SAMe (800 mg intravenously daily) is associated with significantly decreased levels of serum transaminases, conjugated bilirubin and TBA (Frezza et al. 1984). Pruritus was also decreased (Frezza et al. 1984). In contrast, Ribalta and associates showed no similar advantages, not even at a higher dosage of SAMe (900 mg intravenously daily) compared to placebo (Ribalta et al. 1991). Roncaglia et al. compared UDCA with SAMe and reported that UDCA was more effective than SAMe in improving maternal liver tests, although both therapies were equally effective in reducing maternal pruritus (Roncaglia et al. 2004). Floreani et al. showed that UDCA is more effective in controlling pruritus and reducing TBA-levels than SAMe (Floreani et al. 1996). Combination studies of UDCA and SAMe imply a synergistic effect (Binder et al. 2006, Zhou et al. 2014a). SAMe is usually given intravenously or intramuscularly and the therapeutic effect is not predictable and thus SAMe has not become primary medication in the treatment of ICP.

Two Finnish study groups studied phenobarbital as a treatment for ICP years back (Laatikainen 1978, Heikkinen et al. 1982). These studies showed inconsistent reduction in maternal itching and only a negligible effect or no effect at all on serum biomarkers (Laatikainen 1978, Heikkinen et al. 1982).

Geenes et al. reported recently on the effect of rifampicin in the treatment of ICP (Geenes et al. 2015). Rifampicin has been used in primary biliary cirrhosis and it reduces bilirubin, enhances hepatic efflux of organic anions including BA and reduces pruritus. Combined treatment with

UDCA and rifampicin was effective in treating women with severe ICP who had not responded to treatment with UDCA monotherapy (Geenes et al. 2015).

Cholestyramine is an anion exchange resin that binds to BA and decreases their absorption in the ileum. In women with ICP cholestyramine did not show adequate benefits. Itching was not well or consistently controlled and serum BAs did not decrease consistently (Laatikainen 1978, Heikkinen et al. 1982). UDCA was more effective than cholestyramine and did not cause any adverse effects in a larger randomized study comparing those two preparations (Kondrackiene et al. 2005). Cholestyramine reduces the absorption of fat-soluble vitamin K and may thus increase the risk for hemorrhage for the mother as well as for the fetus (Sadler, Lane and North 1995). Given the poor performance of cholestyramine in ameliorating maternal pruritus, improving maternal liver tests or newborn outcomes, its use as a treatment in ICP has not gained acceptance (Pathak et al. 2010).

Activated charcoal absorbs BA and decreases the levels of TBA in the serum, but has no influence on liver enzyme activities nor on pruritus symptoms (Kaaja et al. 1994). Guar gum is a dietary fiber binding to BA and provides some relief of pruritus (Riikonen et al. 2000, Gylling et al. 1998). However, neither activated charcoal nor guar gum has proven to be clinically effective for ICP.

A recent study by Wu et al. demonstrated a regulatory effect of the farnesoid X receptor (FXR) agonist. A highly selective and potent FXR agonist protected against placental oxidative stress in an ICP mouse model (Wu et al. 2015). The data demonstrated that the FXR agonist is a promising group of specific drugs for treating ICP (Wu et al. 2015).

To relief pruritus, antihistamines are widely used. Hydroxyzine (25 – 50 mg/d) may alleviate the discomfort of pruritus.

Generally, UDCA is the most promising maternal treatment for ICP. According to a recent Cochrane review, there is insufficient evidence to introduce other medications (for example SAMe, guar gum, activated charcoal, dexamethasone, cholestyramine alone or in combination) to the treatment of obstetric cholestasis (Gurung et al. 2013).

8. Prenatal surveillance

There is no ideal method of fetal surveillance in ICP and antenatal testing has thus far had only limited predictability with regard to fetal outcome. Monitoring of fetal wellbeing during pregnancy is mandatory for all women with ICP and it is pleasing to learn that no less than 95% of maternity units in Europe have some policy for antenatal routine monitoring of women with ICP (Saleh and Abdo 2007).

Fetal surveillance has included various kinds of follow-up protocols, but usually daily maternal recording of fetal movements and regular (at intervals of 1 – 2 weeks) nonstress cardiotocogram (CTG) test as of 34 GW until delivery are performed (Rioseco et al. 1994). However, earlier studies have not clearly established the value of weekly non-stress CTG-testing

in the antepartum management of ICP (Rioseco et al. 1994). Also non-stress testing just before the onset of delivery did not predict fetal asphyxia in a group of ICP patients (Oztekin et al. 2009). Usually, then, antenatal CTG has been reported in ICP (Rioseco et al. 1994, Glantz et al. 2004).

Most fetal deaths in ICP occur towards the end of pregnancy. Roncaglia et al. used a protocol including search for meconium with amnioscopy, amniocentesis, semi-weekly non-stress CTG-testing and amnionic fluid volume determinations. Labor was induced at 37 weeks or earlier if there was meconium, nonreassuring fetal testing or severe maternal symptoms. They suggested that their protocol might significantly reduce the stillbirth rate without increasing the cesarean delivery rate (Roncaglia et al. 2002). Doppler umbilical artery (UA) velocimetry is only of little value to evaluate the risk for fetal distress in ICP (Zimmermann et al. 1991). However, Doppler ultrasonography might have some value in recognition of the risk for fetal compromise in ICP (Suri et al. 2012). Suri and associates reported that UA Doppler velocity waveform indices in pregnancies complicated by ICP usually exceeded the reference range (Suri et al. 2012). However, abnormal UA Doppler results were not associated with the severity of ICP or abnormal fetal outcome (Suri et al. 2012).

Various strategies have been tested to predict the fetal outcome and to improve the obstetric outcome in ICP. Thus, many studies have evaluated specific active management protocols, e.g., various GW limits (37-38 GWs) when elective delivery should be induced. The hypothesis is that active management improves fetal outcome (Fisk and Storey 1988). In contrast to this, Kenyon and associates showed that a policy of active management in ICP may result in increased intervention and labor-associated complications. This must be balanced against the gain of a possible reduction in perinatal mortality. Kenyon et al. therefore concluded that appropriate consideration and advice should accompany active management of ICP, not forgetting the iatrogenic risks of labor associated complications (Kenyon et al. 2002).

Ataalla et al. reported recently on a study of fetal electrocardiogram and a tissue Doppler imaging. They observed significant differences in myocardial tissue velocities of both the mitral and the tricuspid valve between a study group of fetuses to mothers with ICP and TBA levels of < 40 μmol/L and a control group, versus a study group of fetuses to mothers with ICP and TBA levels > 40 μmol/L (Ataalla et al. 2016). There was a positive correlation between maternal TBA levels and fetal myocardial tissue velocities at the mitral and tricuspid annuli and, on the other hand, between maternal TBA and fetal diastolic myocardial tissue Doppler velocities. They analyzed the motion velocities at both the mitral and the tricuspid annuli during systole and early and late diastole (Ataalla et al. 2016).

9. Timing of delivery

Because most unexplained fetal deaths in ICP occur after 37 GW, guidelines generally recommend delivery in ICP at 37-38 GW (Geenes and Williamson 2009). There is a general agreement from previous years that all women with ICP should deliver no later than 37-38 GW (Tan 2003, Heinonen and Kirkinen 1999, Mullally and Hansen 2002, Rioseco et al. 1994, Roncaglia et al. 2002). Delivering at 37 GW is associated with a low risk for an adverse perinatal outcome due to ICP among ICP patients with a total serum BA concentration ≥ 40 μmol/L (Lee et al. 2008).

A more aggressive approach to elective delivery may be justified in severe ICP (BA > 100 μmol/L) (Brouwers et al. 2015). In a recent, prospective population-based case-control study there was a significantly increased risk for adverse perinatal outcomes including IUFD among patients with severe ICP (Geenes et al. 2014a). The risks for preterm delivery, neonatal unit admission and stillbirth were higher in ICP than controls. The authors suggest close antenatal monitoring of pregnancies affected by severe ICP (Geenes et al. 2014a).

Henderson et al. analyzed the evidence in support of ICP as a medical indication for early term delivery. They reviewed sixteen studies with respect to IUFD that had occurred at the end of a term pregnancy (Henderson et al. 2014). They claim that empiric, active management of ICP is inappropriate. Rather, they recommend individual management of ICP-affected pregnancies in favor of routine active management.

In a recent large retrospective cohort study on fetal, neonatal and infant mortality in ICP, mortality was minimized by delivery at 36 GWs if ICP had been diagnosed at 36 GWs or earlier (Puljic et al. 2015). Immediate delivery minimized perinatal mortality at 36 GWs, after which mortality increased. Timing of delivery must take into account both the reduction in risk for stillbirth and the morbidities associated with preterm delivery.

ICP patients delivering after 38 GWs had a higher incidence of MSAF, abnormal cardiotocography and need for NICU treatment compared to those delivering between 35-38 GWs, regardless of maternal laboratory values (Simják et al. 2014). The rate of cesarean sections was not increased by early induction of labor (Chappell et al. 2012, Roncaglia et al. 2002) and active management was associated with a low incidence of maternal and neonatal complications (Lee et al. 2008). Also a large recent cohort of twin pregnancies showed that there is a significantly increased risk for adverse perinatal outcomes, including stillbirth and preterm birth, in twin pregnancies with ICP (Liu et al. 2015). ICP and stillbirth also occurred at an earlier GA in twin pregnancies, suggesting that the policy of delivery at 37 GW in singletons may not be optimal for twin gestations (Liu et al. 2015).

The obstetrical decision to proceed with early delivery is influenced by several factors. The first is the duration of GWs,

since the risk for fetal death is increased near term. The second is the severity of cholestasis. There is a relationship between maternal serum BA levels and signs of the fetal distress. Thirdly, the signs of fetal distress are an indication for delivery.

10. Health risks for offspring and mother

Although the symptoms of ICP resolve spontaneously after delivery, there are potential risks for both the mother and the newborn later in life. The intrauterine exposure to environmental stimuli including maternal disease can predispose to alterations in gene expressions (Barnes and Ozanne 2011). Papacleovoulou et al. have studied adolescent offspring of mothers who have had ICP during pregnancy in Northern Finland. They found that males had a higher BMI than the average population and females had an increased waist and hip girth compared with the offspring of uncomplicated pregnancies (Papacleovoulou et al. 2013). Women with ICP are at an increased risk for hepatobiliary disease, hepatitis C, cirrhosis and gallstones (Ropponen et al. 2006, Marschall et al. 2013). ICP also increases the risk for perinatal complications, like gestational diabetes and pre-eclampsia (Wikström Shemer et al. 2013, Martineau et al. 2014). A recent population-based study reported that women with ICP have an increased risk for hepatobiliary cancer, immunomediated disease (specially diabetes mellitus and thyroid disease) and cardiovascular disease later in life (Wikström Shemer et al. 2015). The study gave rise to the suggestion that women with ICP should have a follow-up of biochemical evidence of liver dysfunction 6-12 weeks after delivery and if the liver enzymes are elevated, further evaluation by a hepatologist is recommended (Wikström Shemer et al. 2015).

Summary

The etiology of ICP is unclear, although it seems to result from a combination of genetic and hormonal factors. ICP poses a risk for fetal wellbeing. The disorder is associated with an increased risk for preterm birth, meconium passage and even fetal death. The risk for spontaneous preterm delivery, fetal asphyxia and MSAF is the greater in pregnancies with the higher the maternal BA concentration. There is no specific laboratory test for ICP. The diagnosis of ICP is important and fetal wellbeing must be followed up regularly after maternal diagnosis. The most effective pharmacological treatment is UDCA which reduces maternal pruritus, the concentrations of serum BA and the levels of liver enzymes. UDCA also improves fetal outcome. Maybe the future will witness gene tests for identifying high-risk patients before ICP becomes evident.

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