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Intrahepatic cholestasis of pregnancy: a narrative review of the management

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ABSTRACT

Intrahepatic cholestasis (ICP) is the most common liver disease in pregnancy. It is a multifactorial disease characterized by a supraphysiological rise in bile acid level associated with maternal symptoms. ICP is associated with increased incidence of some fetal complication, such as respiratory distress, premature delivery and stillbirth. For these reasons early recognition, a specific monitoring and appropriate treatment during pregnancy are necessary to improve fetal outcome. However, the optimum management and the best time of delivery still remain unclear. The purpose of this review is to evaluate and compare the most recent definitions and guidelines for intrahepatic cholestasis of pregnancy, trying to provide a global overview improving early diagnosis and adequate management.

SOMMARIO

La colestasi intraepatica (ICP) è la più comune malattia epatica in gravidanza. È una malattia a origine multifattoriale, caratterizzata da un incremento della concentrazione degli acidi biliari associato a sintomi materni. Inoltre, la colestasi gravidica si associa a un'aumentata incidenza di alcune complicanze fetali, come ad esempio la sindrome da distress respiratorio, il parto pretermine e la morte intrauterina. Per questo motivo, una diagnosi precoce, un monitoraggio specifico dei markers biochimici e sintomi caratteristici di questa patologia e un appropriata terapia durante la gravidanza, sono fondamentali per ridurre le complicanze fetali. Tuttavia, il management ottimale di questa malattia e il momento migliore in cui indurre o espletare il parto non sono ancora chiari. L'obiettivo di questa review è analizzare e confrontare tra loro gli studi clinici e linee guida più recenti presenti in letteratura sulla colestasi intraepatica in gravidanza, con l'intento di fornire informazioni più dettagliate per definire i criteri diagnostici utili per la diagnosi precoce e stabilire i più adeguati protocolli diagnostici per curare la colestasi gravidica e ridurre così le sue complicanze materno-fetali.

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Key words
Intrahepatic cholestasis of pregnancy (ICP); bile acid; intrauterine fetal death; Ursodeoxycholic acid; ICP management; pruritus.

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP), also called obstetric cholestasis, is a relevant and common liver disorder in pregnancy, usually occurring during the second or third trimester (1, 2) however, recent evidence showed that in rare situations ICP could be diagnosed as early as the first trimester. The gestational age at diagnosis does not differ significantly by severity, although severe ICP tended to be diagnosed around a week earlier. ICP is a pregnancy-specific condition with a multifactorial aetiology that includes environmental and hormonal contribution in genetically susceptible women. ICP is characterized by a supraphysiological rise in bile acid levels and pruritus, and requires careful monitoring during pregnancy because of the associated intrauterine fetal death. Fetal death is the worst complication of ICP; the cause of fetal death is not well understood; still, it possibly has a relationship to the toxic effects of bile acids on the fetal heart, causing arrhythmias and chorionic vasospasm causing deprivation of maternal oxygenated blood to the fetus causing asphyxia. For this reason, it is very important to have an active and apprehensive management.
However, clinical symptoms are variable and often unclear, with some patients paucisymptomatic and other symptomatic. Therefore, the early recognition and appropriate treatment of ICP should become a priority for obstetricians. In the last years, there were many attempts to find consensus about the management of ICP to provide an easier and earlier diagnosis and a consequent more accurate management of patients. The purpose of this review is to evaluate the most recent definitions and guidelines for ICP, to provide a global overview and improve early diagnosis and adequate management.

EPIDEMIOLOGY AND ETIOLOGY

The prevalence of ICP is influenced by genetic and environmental factors, varying between 0.7 and 5% in different population around the world (3). Risk factors include advanced maternal age, multiparity, history of oral contraceptive use, history of fertility treatment in women or twin pregnancies and a history of ICP during previous pregnancies (4-8). Interestingly, ICP is more common during colder months, for unknown reasons (4, 6, 9, 10-13). Seasonal variations in ICP have been assumed to be associated with dietary factors related to low maternal levels of selenium, zinc and vitamin D and high levels of copper (6, 14, 15).
The pathogenesis of ICP is poorly understood and is thought to be complex and multifactorial. Genetic susceptibility, hormonal, and environmental factors have been proposed as possible mechanisms. There appears to be a relation between cholestatic properties of reproductive hormones in genetically susceptible women and ICP. The supportive evidence for the genetic susceptibility hypothesis lies in the fact that the disease has been observed more in familiar clustering patterns, first-degree relative, and a higher risk of disease recurrence with subsequent pregnancies (16, 17). Recent studies showed mutations in gene (ABCB4) encoding for hepatobiliary canalicular translocator proteins called multidrug resistance 3 (MDR3) and pedigrees with the mode of inheritance being a sex-limited, dominant pattern (17-19). Other genes probably involved in the development of ICP are ATP8B1 (FIC1), ABCB11 (BSEP), ABCC2, and NR1H4 (FXR) (20-23).
The role of reproductive hormones in developing ICP has also been investigated in different studies. Many studies showed an association between high levels of estrogen conditions such as multiple pregnancy, ovarian hyper-stimulation effect and late second-trimester presentation of ICP (24).
In fact, ICP typically occurs in the late second trimester or in twin pregnancies, when the estrogen levels are the highest level and resolvers after delivery, when sex hormone levels fall down.
ICP shows similar characteristics seen in women taking contraceptive pills high in estrogen quantity. High circulating estrogen levels may induce cholestasis in genetically predisposed women in ICP (25). Physiopathologically, estrogen seems to reduce the expression of nuclear hepatic bile acid receptors and hepatic biliary canalicular transport proteins in genetically susceptible women causing impairment of hepatic bile acid homeostasis and subsequent increased level of bile acids (26). The role of progesterone is less understood; however, recent studies, including some animal model studies, have demonstrated that progesterone sulfated metabolites are partial agonists of farnesoid X receptor FXR (also called bile acid receptor) (26). The progesterone sulfate metabolites alter the hepatobiliary transport system by impairing the functioning of the main hepatic bile acid receptor (27, 28). A previous study showed that ICP may be associated with an increase in 3α-monosulfated and disulfat-

ed progesterone metabolites, compared with normal pregnancies. In fact, ICP symptom severity is correlated to sulfated progesterone metabolite levels in the urine of ICP women (29).
Finally, a number of studies have established that the gut microbiota changes during pregnancy, and this can be associated with the gestional metabolic alterations, including ICP, observed in late pregnancy (29-31).
Some Authors showed that imbalances in the maternal serum cytokine profile may be associated with ICP. In particular, the Authors showed that circulating proinflammatory cytokines are increased, including IL-6, IL-12, IL-17, and TNF-α, while anti-inflammatory cytokine IL-4 is decreased (32, 33). Work in obstructive cholestasis has suggested that bile acids levels associated with ICP cause the release of proinflammatory cytokines into the circulation that accumulate in the liver and can lead to hepatic injury (33).

CLINICAL PRESENTATION

The ICP is an exclusion diagnosis: elevated serum total bile acid levels (≥ 10 μmol/l) and normal or increased serum transaminases with pruritus are the typical characteristic findings of this pregnancy-specific disease (1, 2). ICP can be classified based on serum total bile acid levels in: mild cholestasis (10 < bile acids < 39 μmol/L), moderate cholestasis (40 < bile acids < 99 μmol/L) o severe cholestasis (bile acids > 100 μmol/L). The main symptom of this disease is generalized intense pruritus sine materia (without lesion, rash and other excoriation) that may precede biochemical abnormalities. It often develops after 25 weeks of gestation, with 80% of cases occurring after the 30th week of pregnancy (15).
Pruritus typically predominates on palms and soles of the feet and worsens at night, its location may be discriminatory for ICP diagnosis (4, 6). Other symptoms of cholestasis are nausea, anorexia, fatigue, right upper quadrant pain, dark urine, and pale stool, steatorrhea, malabsorption of fat-soluble vitamins and weight gain. Clinical jaundice is rare but may present in 14 to 25% of patients after 1 to 4 weeks from the onset of pruritus, with dark urine and pale feces (6, 9, 34). Some patients also complain of insomnia secondary to pruritus. Generally, the physical examination is unremarkable except for scratch marks on the skin from pruritus. Generally, ICP is a benign condition for the mother, in fact it has rapid postnatal resolution and pruritus often disappears in the first days following delivery. Symptoms, abnormal liver function and biochemical abnormalities, spontaneously and rapidly (within 6 weeks) revert to normal after delivery with good maternal prognosis. However, liver tests and bile acid concentrations controls are recommended to be performed during pregnancy and 6 to 8 weeks after delivery. According to recent data, ICP seems to be associated with an increased risk of developing other hepatobiliary diseases, such as hepatitis C, cirrhosis, and gallstones. In addition, patients with underlying chronic liver diseases (*e.g.*, hepatitis C or chronic hepatitis of different etiologies) have an increased risk of developing ICP (5, 13).
ICP is also associated with altered maternal lipid profiles: dyslipidaemia (35, 36), increased risk of gestational diabetes mellitus or impaired glucose tolerance (36, 37) and preeclampsia; therefore is important a strict follow-up for these diseases in women with ICP, especially among those with early presentation and twins' gestations. A large Swedish national cohort highlighted that patients with ICP had an OR of 2.62 (95% CI, 2.32-2.78) for preeclampsia (38). Raz at all showed that patients with total bile acid levels > 40 micromol/L have the highest risk of for eclampsia and preeclampsia. They also suggested that the diagnosis of preeclampsia occurs approximately 2-4 weeks after ICP diagnosis, and proteinuria preceded elevated blood pressure (39). Moreover, women with ICP are also at a higher risk for cardiovascular disease morbidity (40). Perhaps ICP is responsible for endothelial injury and atherosclerosis; therefore, blood lipid panel and cholesterol testing may be offered to higher risk women with ICP during the postpartum period, when pregnancy specific hormones lose their effect on plasma lipid profiles. In literature has been reported that postpartum hemorrhage risk is not increased among women with ICP (40).

FETAL RISKS

If on one side, generally, ICP is a benign condition for the mother, on the other side, it may be associated with a higher rate of adverse neonatal outcome (**table I**). ICP increases the risk of spontaneous and iatrogenic preterm labor, fetal distress, sudden intrauterine fetal death and admission to the neonatal unit (4, 9, 12, 41). Some studies have shown that adverse pregnancy outcomes were higher in patients diagnosed to have early onset

ICP compared to the late-onset ICP. The analysis revealed significantly higher rates of fetal distress, intrauterine growth restriction, preterm birth, and low birth weight in the early-onset ICP group (42). Many studies highlight the importance of regular monitoring of serum bile acid levels in women diagnosed with ICP and suggest that women with bile acid levels that do not exceed 40 micromoles/L may not be at an increased risk of fetal complications. In a prospective study in the United Kingdom of women with severe ICP (defined as bile acid levels ≥ 40 μmol/L), Geenes *et al*. (41) have found that women with ICP have an increased risk of preterm birth (25% *vs* 6.5%; aOR 5.39; 95% CI 4.17-6.98), neonatal unit admission (12% *vs* 5.6%; 95% CI 1.97-3.65), and stillbirth (1.5% *vs* 0.5%; aOR 2.58; 95% CI 1.03-6.49). They also found that meconium-stained amniotic fluid was associated with increasing levels of bile acids. Analysis with logistic regression by Otzas *et al*. have revealed that the probability of preterm delivery does not increase until (mean platelet volume) MPV levels exceeded 11.2 fL [odds ratio (OR) = 2.68, 95% confidence interval (CI) = 1.13-6.32, P = 0.025]. Total bilirubin levels exceeded 0.6 mg/dL (OR = 3.13, 95% CI = 1.21-8.09, P = 0.019) if we consider as outcome a low APGAR score, only increased postprandial total bile acid levels of ≥ 51 μmol/L are found to be significantly predictive (OR = 3.02) (43). Although the precise mechanism is not established, it is likely that elevated bile acids influence myometrial contraction leading to the increased pre-term labor rates. This is suggested by *in vivo* and *in vitro* data even if the laboratory findings were thousand times more concentrated than those, we observe in ICP affected women. Indeed, when bile acids are administered to pregnant ewes via an intravenous infusion pump, they have increased rates of preterm delivery, and different experiments demonstrated that the addition of bile acids to the culture medium of cultured uterine myocytes enhanced expression of the oxytocin receptor (1, 9). In addition, elevated bile acid concentrations impair cell membrane permeability and stimulate the release of prostaglandins, thus leading to enhanced uterine reactivity as well as increased sensitivity to oxytocin, which might cause preterm labor (44). Several experimental studies on animals showed that high bile acids levels have a harmful effect on cardiomyocytes (45). In rats, cardiomyocyte exposure to taurocholate provoked arrhythmias and impaired contractility. Therefore, it was hypothesized that the fetal deaths in ICP may be caused by an acute cardiac event caused by raised fetal serum taurocholate concentrations (16, 17). Finally, other recent studies showed that fetal cardiomyocytes express receptors for bile acids known as the nuclear bile acids receptor farnesoid-X receptor (FXR) that have been found to be involved in cardiac injury and cardiomyocyte apoptosis (46). It has been speculated that bile acid salts may also accumulate in the placenta, lead to edema, and accelerate placental cell apoptosis with subsequent alteration of the placental function. Moreover, a vasoconstrictive effect of bile acids on isolated human placental chorionic veins has also been shown, which may explain the occurrence of sudden fetal distress, asphyxia, or death in newborns.

Moreover, elevated maternal and amniotic fluid levels of bile acids can lead to umbilical vessels spasms with resultant reduction in the trans-placental nutrient exchange and fetal oxygenation. The hypothesis to explain increased neonatal morbidity also includes a direct effect of bile acids on neonatal lung, possibly leading to a "bile acid pneumonia" (47, 48). Since bile acids was found in the in bronchoalveolar lavage fluid of neonates affected by RDS, some authors have speculated that bile acids inhibit surfactant activity (48, 49).

The rate of malformations or abortions is not increased in ICP. The prevalence of in utero and perinatal mortality is estimated at 0.5%. Some studies showed that total bile acid concentrations are more highly predictive of stillbirth for singleton pregnancies than the other biomarkers, for example aminotransferase, aspartate aminotransferase and bilirubin. Indeed, a large systematic review demonstrated that the highest risk of stillbirth occurred in women with total bile acids greater than or equal to 100 micomol/L (50).

MANAGEMENT: DIAGNOSIS

The diagnosis of ICP relies on clinical symptoms and biochemical evidence of liver dysfunction, after excluding other causes of hepatobiliary diseases. Clinical symptoms are characterized by generalized itching, mainly localizing to the palms of the hands and the soles of the feet, with a nocturnal predominance (51, 52). It occurs during the second and the third trimester and rarely during the first trimester. There is not any rush over the skin and jaundice is rare and more likely associated with other hepatic disorders (42). The pruritus can precede the rise in serum bile acids by several weeks. Therefore, if symptoms persist and there is no other

explanation, it is necessary to repeat measurement of total bile acid concentration and serum transaminases if the previous values were normally (51).
The serum analysis is important to evaluate the elevated total bile acid concentration whit cut-off values ranging from 10 to 14 μmol/L as abnormal (42, 53, 54). We can consider mild cholestasis (10 < bile acids < 39 μmol/L), moderate cholestasis (40 < bile acids < 99 μmol/L) o severe cholestasis (bile acids > 100 μmol/L). Total bile acids are often reported including cholic, chenodeoxycholic, deoxycholic, ursodeoxy-cholic, lithocholic, and hyodeoxycholic acids. In healthy non-pregnant women, chenodeoxycholic acid levels in serum are higher than cholic acid levels (55). In women with ICP, cholic acid is greatly increased over chenodeoxycholic acid, often in a ratio of 3 to 1.
There are different types of assay available for bile acid test. Mass spectrometry and liquid chromatography can determine total and fractionated bile acid, while enzymatic assay provide only total bile acids. For ICP diagnosis, we usually analyze fasting bile acids; however, sometimes we could also use random bile acids because the differences between random and fasting results are small (56). Liver transaminases aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are also commonly elevated in ICP, possibly preceding the increase in bile acids by 1 to 2 weeks. However, elevated transaminases are not necessary for the diagnosis.
Once pregnant women have itching symptoms bile acid levels should be immediately measured. Regardless of the severity of the disease, total bile acid and liver function need to be checked every 1~2 weeks until delivery. For those with severe degree, the detection interval can be reduced moderately (42). It is important to note that ICP is an exclusion diagnosis: other liver diseases should be considered in case of atypical symptoms, such as abdominal pain, ascites, asterixis, jaundice or tremor. The differential diagnosis includes autoimmune hepatitis, viral hepatitis, acid fatty liver disease, preeclampsia, Hellp's syndrome, alcoholic liver disease, biliary obstruction and others rarest disorders (57). The clinician must evaluate risk factors for non-alcoholic fatty liver disease (such as obesity, type 2 diabetes, or dyslipidaemia), strong personal or familial history of autoimmune diseases, a family history of liver diseases, or exposure to medications or toxins that could cause liver damage. In these cases, alternative diagnosis and referral to a liver specialist should be considered. A suspicion for an alternative diagnosis based on atypical symptoms should suggest additional adjunctive tests such as liver ultrasound, the appearance of the liver on ultrasound should be normal with ICP (58). Other biochemical changes in serum analyses can be found, for instance Oztas E *et al*. have demonstrated that women with ICP have a significantly higher mean platelet volume (MPV) (mean 10.2 ± 1.0 *vs* 11.0 ± 1.3; P < 0.001) and platelet distribution width (PDW) (mean 13.1 ± 2.3 *vs* 14.7 ± 2.8; P < 0.001) values compared to controls (43).

MANAGEMENT: TREATMENT

Different medications have been proposed to treat ICP with the potential goal to reduce both maternal symptoms and the risk for adverse perinatal outcomes. First line treatment is represented by ursodeoxycholic acid (UDCA), with the mechanism of action not completely understood. Still, several studies demonstrated that treatment is associated with a reduction in total serum bile acids in both maternal and umbilical cord serum and a qualitative change in the serum bile acid pool (59, 60, 61). It has been hypothesized that UDCA acid concentrates in hepatocytes and bile, resulting in decreased hepatic cholesterol synthesis, hepatic cholesterol secretion, and intestinal cholesterol reabsorption. The symptoms improvement is usually observed within 1 to 2 weeks after initiation and a decrease in serum bile acids two weeks after. The standard starting dose for UCDA is 10-15 mg/kg/ day, which can be divided into twice ore three-times daily doses. UCDA can be titrated to a maximum dose of 21 mg/kg/day (~1500 mg for a 72 kg patient), usually split into multiple doses.
This therapy seems to improve symptoms and reduce liver dysfunction; however, its beneficial effects are still debated. For instance, the PITCHES trial has demonstrated that ursodeoxycholic acid is not effective in reducing a composite of adverse perinatal outcomes in women with ICP. Indeed, according to this study, although ursodeoxycholic acid appears to be safe, it has no clinically meaningful effect on maternal itch symptoms. In fact, it does not reduce maternal bile acid concentrations, and the reduction in alanine transaminase is of uncertain clinical significance, given that alanine transaminase is not known to be associated with the risk of stillbirth or preterm labor in ICP (62) (**table I**). The drug is usually well tolerated, although some patients report nausea and dizziness as adverse drug reaction.

Table I. *Comparative guidelines on intrahepatic cholestasis of pregnancy diagnosis and treatment.*

Guidelines	RCOG	SAMNCP	GWADOH	ACG
Clinical symptoms				
Pruritus	Yes	Yes	Yes	Yes
Ascites	No	No	No	No
Asterixis	No	No	No	No
Jaundice	Yes	Required	Yes	Yes
Steatorrhea	Yes	Yes	Yes	Not specific
Laboratory tests				
Bile acids	Yes	Yes	Yes	Yes
Transaminases	Diagnostic	Yes	Diagnostic	Yes
γGT	Yes	Yes	Optional	Optional
PT	Yes	Yes	Yes	Optional
Bilirubin	Yes	Yes	Yes	Yes
Liver ultrasound			Recommended	Recommended
Laboratory tests for differential diagnosis				
HCV	Yes	Yes	Yes	Not required
EBV	Yes	Yes	Yes	Not required
CMV	Yes	Yes	Yes	Not required
Primary biliary cirrhosis	Yes	Yes	Yes	Not required
Primary sclerosing cholangitis	Yes	Yes	Yes	Not required
Prenatal controls	Not specified	Not specified	Every two weeks	Not specified
Treatment				
UDCA	No dosing provided	Max 750 mg 3-4 times /day	10-15 mg/kg/ day	10-15 mg/kg/ day
S-adenosyl-L-methionine	No	No	No	No
Dexamethasone	Not first line	Not first line	Not first line	May be used for lung maturity
Rifampin		Consider if UDCA fails		
Delivery timing	Depending on laboratory abnormalities	38 wks or earlier If bile acids > 100 µmol/L	37-38 wks or earlier if maternal or fetal impairment	37 wks
Resolution after delivery	In 6 wks	In 6 wks	In a month	Not specified

Royal College of Obstetricians and Gynaecologists (RCOG) "Obstetric Cholestasis (2011)"; South Australia Maternal and Neonatal Community of Practice (SAMNCP) Clinical Guideline "Obstetric Cholestasis (2016)"; Government of Western Australia Department of Health (GWADOH) Clinical Guideline "Cholestasis in Pregnancy (2014)"; American College of Gastroenterology (ACG) "Liver Disease in Pregnancy (2016)".

Another treatment provides the use of Cholestyramine, an anion exchange resin, which binds to bile acids in the intestine, sequestering them from enterohepatic recycling and committing them to fecal excretion. However, according to Kondrackiene J and coll. (63), the use of 8 g daily for 14 days of this drug is less efficient to reduce serum alanine and aspartate aminotransferase activities and endogenous serum bile acid levels compared to UDCA ($P < .01$ and $P < .02$ *vs* ursodeoxycholic acid). Moreover, Cholestyramine is not considered a first-line treatment of ICP for its side effects, such as constipation, diarrhoea, abdominal pain, nausea, and concerns exists regarding the associated decrease in vitamin K levels.

S-adenosyl-L-methionine influences hepatic membrane composition and therefore biliary excretion of bile acids and other steroid hormones, and it is generally used in combination with UDCA. The combined therapy, according to Zhang L. *et al.* (64) significantly improves pruritus, levels of total bile acids, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin (TB). In their study, singleton pregnancies with ICP that have been randomized into three treatment groups: oral UDCA 4 × 250 mg daily (Group 1, n = 41), intravenous SAMe 1000 mg daily (Group 2, n = 38), and a combination of both drugs (Group 3, n = 41) until delivery. All therapies significantly and equally improved pruritus. The serum levels of total bile acid, alanine amino-

transferase (ALT), aspartate aminotransferase (AST) and total bilirubin (TB) in each group significantly decreased after treatment ($p < 0.05$). Group 1 was more effective than Group 2 in reducing total bile acids concentration ($p < 0.05$), Group 1 and Group 3 showed more effective than Group 2 in reducing AST and TB concentrations ($p < 0.05$), and Group 1 facilitated deliveries at term. No perinatal death or adverse drug reactions were observed.

Dexamethasone has also been proposed as a treatment for ICP given its effect on reducing circulating estriol levels whose levels are increased. Nevertheless, according to Giantz *et al.* (65) the administration of Dexamethasone (12 mg/day) does not improve pruritus or reduce ALT and it is less effective than UDCA at reducing bile acids and bilirubin (66, 67).

Rifampin is a semisynthetic derivative of one of the rifamycins, a group of macrocyclic antibiotics produced by Streptomyces mediterranei. Though not yet studied for use in ICP, there is evidence to suggest that rifampicin is an effective second-line treatment for primary biliary cirrhosis. Further studies are needed to fully establish the extent to which rifampicin may be useful in ICP and to investigate any potential effect on perinatal outcomes. The proposed mechanism of action for rifampicin in cholestasis is enhanced bile acid detoxification and excretion, an effect that is complementary to the upregulation of hepatic bile acid export by ursodeoxycholic acid (68).

Antihistamines such as chlorpheniramine are often used in ICP but there is no evidence of a histamine-mediated pruritus in this pathology thus their use is discouraged (69).

Since itching is generally widespread, topical antipruritic such as menthol is also of limited use. ICP is associated to an increased risk of preterm birth, fetal demise, fetal respiratory distress or meconium staining. For these reasons, it is important to adopt an active strategy to prevent any fetal problem and to program the right time to delivery. The timing of delivery should be approached using risk-stratification based on-specific factors, including total bile acid levels (70, 71).

The Society for Maternal Fetal Medicine (SMFM) recommends that patients with a diagnosis of ICP begin antenatal fetal surveillance at a gestational age when delivery is possible in response to abnormal fetal testing or at the time of diagnosis if it is made later in gestation. Since the optimal frequency of testing is unknown, it may be determined by bile acid levels and comorbidities.

A continuous fetal monitoring in labor is necessary for the higher risk of stillbirth in patients with ICP (72). In Puljic *et al.* (73) retrospective cohort study of over 1.6 million pregnancies, they assess the risk of fetal demise, the risk of infant death and the composite risk of expectant management for every additional week of gestation from 34 to 40 weeks. They found that the balance between the risk of perinatal mortality associated with liver damage and the risk of fetal demise associated with expectant management begin to shift at 36 weeks gestation. A recent metanalyses (74) compares the elevated serum bile acids level above 100 μmol/L to levels below 40 μmol/L. Only women with bile acids above 100 μmol/L have fetal demise rates and an increased risk of stillbirth that are significantly higher than the pooled national rate.

Early term induction is discussed in all guidelines and there are conflicting opinions because there are not published randomized controlled clinical trials sufficiently powered to compare delivery outcomes at different gestational ages, regardless of disease severity, prevention of perinatal morbidity or mortality (**table II**).

Indeed, ACG society recommends delivery at 37 weeks (75). RCOG advises discussing with patients the option of early term delivery *versus* expectant management (76). RCOG notes that induction may be preferential in pregnancies with more severe laboratory abnormalities. SAMNCP advises delivery at 38 weeks for severe disease and to consider earlier induction of labor if bile acid concentrations are > 100 mmol/L (77).

SMFM recommends delivery between 36 and 39 weeks of gestation if total bile acid leves are < 100 mmol/L.

SMSF also recommends delivery at 36 weeks of gestation if total bile acid leves are > 100 mmol/L because the risk for stillbirth is increased substantially around this gestational age, and suggests antenatal administration of corticosteroids for fetal lung maturity for patients delivered before 37 weeks if not previously treated (72). Delivery between 34 and 36 weeks of gestation can be considered if total bile acid leves are > 100 mmol/L, and any of the following: intense and unremitting maternal pruritus unresponsive to drugs, a prior history of stillbirth before 36 weeks of gestation for ICP, a clinical or laboratory evidence of worsening hepatic function in ICP patients with preexisting or acute hepatic disease. GWADOH (Government of western Australia department of health) recommends delivery between 37 and 38 weeks unless

Table II. *Maternal and neonatal outcomes after treatment with UDCA.*

Authors	Study design	Sample size	Therapy	Maternal outcomes	Neonatal outcomes
C M P Rodrigues *et al.* (73)	Longitudinal prospective study	9 patients	UDCA	Symptoms improved bile acids decreased (3-fold)	Apgar: no differences Birth weight: no differences
D Brites *et al.* (74)	Longitudinal prospective study	15 patients	UDCA	Symptoms improved cholic acid decreased (3-fold)	Apgar: no differences Birth weight: no differences
LB Manna *et al.* (75)	Longitudinal prospective study	51 patients	UDCA	Symptoms not valuated cholic acid decreased (4-fold) CDCA decreased (5-fold) UDCA increased (97-fold)	Not evaluated
Joutsiniemi *et al.* (76)	Observational retrospective study	208 patients	UDCA	Total bile acids decreased Pruritus improved Liver function tests improved	Apgar: lower in UDCA users umbilical ph values: no differences Birth weight: not evaluated
Mazzella *et al.* (77)	Longitudinal prospective study	20 patients	UDCA	Pruritus improved Liver function tests improved	Apgar: no differences Birth weight: not evaluated

maternal or fetal compromise dictates earlier induction. Moreover, the majority of early deliveries are induced and there is no evidence that this results in higher rates of emergency cesarean delivery. Indeed, it has been shown in two retrospective cohorts and one prospective study that rates of operative and instrumental delivery are not increased in women with ICP after labor induction (78-80).

CONCLUSIONS

ICP is a relative common disorder of pregnancy, especially of the second and third trimester, occurring in up to 5% of pregnancies. The diagnosis is suspected on clinical symptoms (mainly palm and soles pruritus) and is confirmed by the detection of elevated total bile acids. Maternal risks are often negligible while fetal risks may be considerable, including fetal death, preterm birth, meconium staining, neonatal asphyxia. Its treatment and management remains debated in literature.
Often UDCA is used as first line treatment for its beneficial effects both on pruritus and biochemical abnormalities, but on the reduction on fetal risks has not been definitely proven. Other medications revealed to be inferior compared to UDCA. Management of ICP pregnancy often includes early labor induction between 37 and 39 weeks depending on the severity of total bile acids levels.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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