New Insights on Intrahepatic Cholestasis of Pregnancy

Annarosa Floreani, MD[a,*], Maria Teresa Gervasi, MD[b]

KEYWORDS

• Intrahepatic cholestasis of pregnancy • Itching • Bile salts • Ursodeoxycholic acid • Cholelithiasis

KEY POINTS

- Intrahepatic cholestasis of pregnancy (ICP) is a disorder of pregnancy occurring in the third trimester, characterized by pruritus, elevated serum transaminases and serum bile acids.
- Fetal delivery results in the resolution of symptoms, but recurrence is common.
- The etiology is likely multifactorial, and includes genetic factors and the influence of several environmental factors.
- Elevated serum bile acids have been shown to be correlated with fetal complications, such as anoxia, prematurity, fetal distress, perinatal death, and stillbirth.
- Ursodeoxycholic acid is the current therapy for this condition, owing to its possible benefits on pruritus, liver function tests, safety, and decreased rates of prematurity and fetal adverse.

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a specific liver disease with onset during pregnancy. It classically presents in the third trimester with pruritus, increased levels of serum transaminases, and high total serum bile acids (BA).[1] The symptoms and biochemical abnormalities resolve rapidly after delivery, but may recur in subsequent pregnancies.

EPIDEMIOLOGY

The incidence of ICP varies worldwide between 0.2% and 25% with the greatest prevalence up to 25% in the Araucanic race in South America.[2] In Europe, the prevalence

The authors have nothing to disclose.

[a] Department of Surgery, Oncology and Gastroenterology, University of Padova, Via Giustiniani, 2, Padova 35128, Italy; [b] Department of Obstetrics and Gynecology, Azienda Ospedaliera, Via Giustiniani, 2, Padova 35128, Italy
* Corresponding author.
E-mail address: annarosa.floreani@unipd.it

Clin Liver Dis 20 (2016) 177–189
http://dx.doi.org/10.1016/j.cld.2015.08.010 **liver.theclinics.com**
1089-3261/16/$ – see front matter © 2016 Elsevier Inc. All rights reserved.

Downloaded for Anonymous User (n/a) at Michigan State University from ClinicalKey.com by Elsevier on November 10, 2019.
For personal use only. No other uses without permission. Copyright ©2019. Elsevier Inc. All rights reserved.

is 0.5% to 1.5% of all pregnancies, and the highest incidence has been reported in Sweden.[3] In China, ICP is considered to be common, with an incidence of 2.3% to 6.0%.[4]

RISK FACTORS

The most important risk factors are reported in **Table 1**. A risk for the development of ICP in hepatitis C virus (HCV)-positive mothers has been described. The first retrospective study reported a highly significant incidence of ICP in HCV-positive pregnant women compared with HCV-negative women.[5] Subsequently, another prospective Italian study confirmed these results and suggested the need to investigate the HCV status in women with ICP.[6] In a study population of 21,008 women with ICP identified from the Finnish Hospital Discharge Register from 1972 to 2000, the incidence of hepatitis C was significantly higher than in controls.[7] More recently, a study analyzing data of women with births between 1973 and 2009, registered in the Swedish Medical Birth Registry, confirmed a strong positive association between ICP and hepatitis C both before and after ICP diagnosis.[8] Moreover, women with HCV infection who developed ICP have been found to exhibit a higher HCV viral load compared with those without ICP.[9] The link between ICP and HCV has not been completely explained so far, although several hypotheses can be suggested, including a defect in the transport of sulphated pregnancy hormones in the liver. In fact, it has been suggested that HCV would downregulate the expression of the ABC transporter multidrug-resistance–protein 2 in the liver, thus inducing a failure in the transport of various toxic substances.[10] Furthermore, another link may be with a defect in ABCB11 gene encoding the bile salt export pump (BSEP).[11]

It was reported from Sweden, Finland, and Chile that the incidence of ICP is higher in the winter than in the summer.[12–14] It has also been suggested that other exogenous cofactors, such as low selenium levels, may act in alteration of oxidative metabolism in the liver.[15] A low vitamin D concentration has also been reported in women with ICP, although its role has yet to be defined.[16] It frequently recurs in multiparous women who previously experienced ICP and is more common in multiple gestations.[17–19] In particular, in the Finnish study[19] the incidence of ICP was 14% in twin pregnancies, and 43% in triplets. Moreover, a relatively advanced age (>35 years) has been shown to be a risk for ICP.[20]

GENETICS

Genetic defects in at least 6 canalicular transporters have been found to be associated with ICP (**Table 2**). Genetic variations may implicate heterozygous or homozygous

Table 1
Risk factors related to intrahepatic cholestasis of pregnancy

Risk Factor	References
HCV	5–8
Seasonal onset (winter)	12–14
Low selenium levels	15
Low vitamin D	16
Multiple gestations	17–19
Advanced age	20

Downloaded for Anonymous User (n/a) at Michigan State University from ClinicalKey.com by Elsevier on November 10, 2019.
For personal use only. No other uses without permission. Copyright ©2019. Elsevier Inc. All rights reserved.

Table 2
Genetic defects associated to ICP

Canalicular Transporter	Chromosomal Locus	Biochemical/Histologic Characteristics	Functional Defect	Clinical Spectrum
ATP8B1 (FIC1)	18q 21–22	High serum bile salts; low GGT/ bland cholestasis with coarse and granular bile	Abnormal excretion of aminophospholipids; downregulation of FXR	ICP, PFIC1, BRIC1, Byler disease
ABCB11 (BSEP)	2q24	High serum bile salts; low GGT/ portal tract fibrosis; bile duct proliferation	Abnormal bile acid secretion	ICP, Byler syndrome, PFIC2, BRIC2, drug-induced cholestasis, transient neonatal cholestasis
ABCB4 (MDR3)	7q21	High serum bile salts; elevated GGT/fibrosis, vanishing bile duct syndrome; low phospholipids in bile	Defect in phosphatidylcholine floppase	ICP, PFIC3, LPAC, neonatal cholestasis, drug-induced cholestasis
ABCC2 (MRP2)	10q24	High serum conjugated bilirubin/ black liver pigmentation	Alteration in canalicular transport of conjugated metabolites	ICP, Dubin–Johnson syndrome
NR1H4 (FXR)	12q23.1	High serum bile salts	Altered homeostasis of BSEP and MDR3	ICP, familial gallstone disease, idiopathic infantile cholestasis
FGF19	11q13.3	High serum bile salts	Abnormality in bile acid transport	ICP, Bile acid malabsorption

Abbreviations: BRIC, benign recurrent cholestasis; BSEP, bile salt export pump; FIC, familial intrahepatic cholestasis; FXR, farnesoid X receptor; GGT, gamma-glutamyl transferase; LPAC, low phospholipid cholestasis; MDR, multidrug resistance; MRP, multidrug resistance protein; PFIC, progressive familial intrahepatic cholestasis.

Downloaded for Anonymous User (n/a) at Michigan State University from ClinicalKey.com by Elsevier on November 10, 2019.
For personal use only. No other uses without permission. Copyright ©2019. Elsevier Inc. All rights reserved.

polymorphisms located in different points of the genes. ATP8B1 (or FIC1) gene, located in the chromosomal locus 18q21 to 22, encodes a P-type ATPase. Its functional defects have been identified in ICP, PFIC1, BRIC1, and Byler disease, depending on the localization and functional effect of the variation.[21,22] Mullenbach and colleagues[23] identified 2 ATP8B1 mutations that resulted in an amino acid exchange (D7ON and R867C) after DNA sequencing of 16 ICP cases in the UK. However, in an expanded study including 563 patients with ICP from Western Europe and 642 controls, no significant evidence for association with ATP8B1 was found.[24]

ABCB11 (BSEP, a member of the ABC transporter superfamily) is the high-affinity, liver-specific transporter responsible for the export of conjugated BA into the canaliculus.[25] The gene is located in the 2q24 chromosomal locus; its functional defect causes abnormal BA secretion and a clinical spectrum of diseases including ICP, Byler syndrome, PFIC2, BRIC2, drug-induced cholestasis, and transient neonatal cholestasis. The role of genetic variation at this locus in ICP has been explored in detail, with several recurrent mutations identified. In particular, the European study identified 6 SNIPs (single nucleotide polymorphisms) in ABCB11 significantly associated with risk for ICP.[24]

The ABCB4 (MDR3) is a transporter responsible for bile salt-dependent bile flow. Initial studies identified heterozygous mutations of this gene causing a defect in phosphatidylcholine (PC) floppase in familial and sporadic cases of ICP.[26,27] This susceptibility has been confirmed in large cohort studies.[24,28,29] The gene is located in the 7q21 chromosome and a defect in PC lipase causes low phospholipids in bile with a consequence of different clinical spectrum: ICP, progressive familial intrahepatic cholestasis type 3, juvenile cholelithiasis, neonatal cholestasis, and drug-induced cholestasis.

The ABCC2 (multidrug-resistance–protein 2) is a transporter of bilirubin and BA across the canalicular membrane located in the 10q24 chromosome. Involvement of genetic variants of multidrug-resistance–protein 2 have been reported in association with ICP in South American populations,[30] but not confirmed in the large European cohort study.[24]

The NR1H4 (farnesoid receptor X) is a major BA sensor that protects the liver from the BA toxicity by regulation the transcription genes involved in the BA homeostasis.[31] Genetic variations of farnesoid receptor X have been rarely identified in ICP.[32,33]

All the association studies with these candidate genes stress the complex variability of genotypes, the different penetrance, and the influence of several environmental factors. A recent study using microarray technology in 12 women with ICP and in 12 healthy controls, found that 20 genes were potentially correlated with ICP.[34] Among these, an upregulation of gamma-aminobutyric acid (GABA)2 receptor gene may indicate that GABA may play a role in the pathogenesis of pruritus in this condition.

The placentas of women with ICP displayed significant proteome differences compared with women with a normal pregnancy.[35] In particular, the proteins differentially expressed together with various enzymes comprised proteins in cytoskeleton activity, blood coagulation, platelet and chaperones activation, heat shock proteins, RNA-binding and calcium-binding proteins, and various enzymes. These results indicate that the pathogenic mechanism underlying ICP is rather complex and further verification and research are required to elucidate the exact role of proteins in ICP pathogenesis. Indeed placenta, connecting the developing fetus to the uterine wall allowing fetal and maternal exchanges of blood and nutrients, plays a crucial role in ICP pathogenesis. By a DNA microarray study, it has been found that placenta differentially express genes in mild ICP and severe ICP compared with healthy pregnancies.[36]

Downloaded for Anonymous User (n/a) at Michigan State University from ClinicalKey.com by Elsevier on November 10, 2019.
For personal use only. No other uses without permission. Copyright ©2019. Elsevier Inc. All rights reserved.

DIAGNOSIS

The condition typically occurs during the third trimester of pregnancy with pruritus and increases in both bile salts and transaminases, with rapid resolution immediately after delivery. Some patients may have an early onset during the first trimester as early as in the seventh gestational week.[37,38] A marked increase in maternal serum estrogen levels, as in the case of ovarian hyperstimulation, might trigger ICP in the first trimester of pregnancy.[39] A recent study including 305 patients with ICP (subdivided in early onset [<28 weeks] and late onset [≥28 weeks]) showed that women presenting with early onset had a worse clinical course with a higher rate of preterm labor and fetal distress than women with late onset.[40]

Pruritus typically affects the palm of hands and soles, but can occur anywhere. As the disease progresses and generalizes, secondary skin changes develop from scratching and can range from minor excoriation to severe prurigo nodules. Skin lesions tend to concentrate on the extremities, although they may involve other sites such as buttocks and abdomen.[41] The relationship between the onset of pruritus and deranged liver function tests is unclear, but generally pruritus may precede or follow biochemical alteration.[42] Jaundice with dark urine and pale stools is exceptional.

SERUM BIOCHEMISTRY

Serum BA level is the most sensitive and specific marker for the diagnosis of ICP, after exclusion of other causes of cholestasis.[43] Higher BA levels (>40 mmol/L) have been found to be associated with higher rates of fetal complications in a large cohort series of 690 Swedish women diagnosed with ICP between 1999 and 2002.[44] This study reported an increased incidence of spontaneous preterm delivery, asphyxia events, meconium staining of the amniotic fluid, placenta, or amniotic fluid and placenta, and membranes. However, the increased risk became statistically significant only in 17% of women (having BA >40 μmol/L). Several studies have found that BA increase the sensitivity and expression of oxytocin receptors in the human myometrium, and this can explain the mechanism of preterm labor as a complication of ICP.[45,46] A Dutch group conducted a retrospective study that included women with ICP stratified according to the BA level into mild (10–39 μmol/L), moderate (40–99 μmol/L), and severe (≥100 μmol/L). Spontaneous preterm birth (19%), meconium-stained fluid (47.6%), and perinatal death (9.5%) occurred significantly more often in cases with severe ICP.[47] Moreover, BA levels correlated between mother and fetus, suggesting a causal relationship between levels of BA and fetal complications and adverse outcome.[47]

Despite the high levels of transaminases, gamma-glutamyl transferase (GGT) is commonly normal. GGT might be abnormal only in approximately 10% of cases and it is accompanied by a greater impairment of liver function tests.[48] Increased GGT serum levels suggested the involvement of ABCB4 mutations, whereas genetic BSEP dysfunction was postulated in the low GGT levels.[26] MDR3 is a flippase translocating PC from the cytosolic leaflet of the canalicular membrane to the leaflet facing the bile duct lumen. If MDR3 is not expressed, bile salts are pumped in the canaliculus unaccompanied by PC. Bile without PC is toxic to the bile ducts (bile salts are membranolytic); thus, damaged bile ducts proliferate and with the help of bile salts they shed large amounts of GGT into the circulation.[49] Otherwise, bile salts are pumped into the canaliculus by the BSEP and remove PC from the canalicular membrane to form mixed micelles containing bile salts, PC, and cholesterol. Bile, devoid of bile salts, cannot release GGT from the bile ducts.[49]

Downloaded for Anonymous User (n/a) at Michigan State University from ClinicalKey.com by Elsevier on November 10, 2019.
For personal use only. No other uses without permission. Copyright ©2019. Elsevier Inc. All rights reserved.

Serum autotaxin activity represents a highly sensitive, specific, and robust diagnostic marker distinguishing ICP from other pruritic disorders of pregnancy and pregnancy-related liver disease.[50] Bilirubin is increased only in exceptional cases.

Finally, a small case-control study demonstrated that ICP is characterized by glucose intolerance and dyslipidemia, consistent with the changes seen in the metabolic syndrome, in conjunction with enhanced fetal growth.[51] Further work, however, is required to understand whether these changes may have an influence on the pregnancy outcome and on the long-term morbidity of the offspring of the affected mothers.

Differential diagnosis of ICP include other cause of pruritus, specific or nonspecific to pregnancy, including pruritus gravidarum, atopic eruption of pregnancy, pemphigoid gestationis, atopic dermatitis, allergic or drug reactions, pregnancy-specific causes of hepatic impairment, liver disease preexisting, or coincidental to pregnancy.[1]

FETAL OUTCOME

Initial reports of adverse perinatal outcome associated with ICP focused on increased risk for prematurity, intrapartum fetal distress, and still births. The most alarming sequelae was a 3- to 5-fold increased risk of fetal death in utero.[52] However, a systematic review of a 53-year period found only 14 published cases of unexplained term stillbirths that were associated with ICP-affected pregnancies.[53] Given the relatively low frequency of stillbirths, 3 to 10 per 1000 birth in the general population, the risk of stillbirth in ICP is insignificant clinically without statistical proof. These data have been confirmed also by a cohort study in Australia between 2001 and 2011 including 975,240 births.[54] The adoption of routine active management of ICP has been also investigated.[53] No evidence has been found to support the use of active management of ICP-affected pregnancies; nevertheless, individual patient-centered management with informed decision making under the guidance of health care professionals, rather than routine implementation of an active management protocol, is recommended.[53] In selected cases Doppler investigation of the umbilical artery might be of some value in recognizing the specific risk of fetal compromise in pregnancies complicated by intrahepatic cholestasis.[55]

Numerous studies focused on predictors of fetal complications in ICP, but the majority are not large enough to assess the real risk. A summary of studies including at least 100 cases is presented in **Table 3**.[44,47,56–60] The percentage of fetal

Table 3
Risk factors associated with fetal complications (observational studies including ≥100 cases)

Author	No. of Cases	Period	Country	Fetal Complications (%)	Risk Factor
Brouwers et al,[47] 2015	215	2005–2012	Netherlands	64.1	High BA (>100 mmol/L)
Lee et al,[56] 2008	122	2000–2007	USA	34.4	Meconium passage
Glantz et al,[44] 2004	640	1999–2002	Sweden	25	High BA (>40 mmol/L)
Oztekin et al,[57] 2009	187	2004–2008	Turkey	19.2	High BA
Rook et al,[58] 2012	101	2005–2009	USA	33	None
Jin et al,[59] 2015	371	1993–2014	China	23.5	Early-onset ICP
Hu et al,[60] 2014	100	NA	China	43	HBV infection

Abbreviations: BA, bile acids; HBV, hepatitis B virus; ICP, intrahepatic cholestasis of pregnancy; NA, not available.

Downloaded for Anonymous User (n/a) at Michigan State University from ClinicalKey.com by Elsevier on November 10, 2019.
For personal use only. No other uses without permission. Copyright ©2019. Elsevier Inc. All rights reserved.

complications ranged between 19.2% and 64.1%. In a retrospective study including a Hispanic population with ICP, an association was found between meconium passage and moderate/severe ICP.[56] Three studies found that the main risk factor for fetal complications was the high BA concentration.[44,47,57] In a Chinese study early-onset ICP was associated with a greater frequency of adverse fetal outcomes than was in late-onset ICP, especially in severe disease.[59] In another Chinese study, it has been found that the rates of hepatitis B virus infection in the newborn, fetal distress, neonatal asphyxia, and birth defects in the newborns were higher in ICP pregnancies in whom the mother was infected with hepatitis B virus than in either healthy pregnancy or in mother with ICP not infected with hepatitis B virus.[60] Finally, a United States–based retrospective study of women with ICP, of whom 90% were of Hispanic origin, found a 33% rate of perinatal complications, but no risk factor was specifically correlated with fetal complications.[58]

A retrospective study carried out in Finland in 365 sons of mothers with ICP from 1969 to 1988 and 617 sons of mothers without ICP using a questionnaire found that in general a mother's ICP does not affect her son's health.[61]

MATERNAL OUTCOME

In general, fetal delivery results in the resolution of symptoms in mothers. Anecdotal cases have a persistence of symptoms of cholestasis and eventually develop a progressive cholestatic disease and/or cholelithiasis.[61] These cases may be related to MDR3 deficiency with altered bile composition and risk to develop progressive familial intrahepatic cholestasis type 3.[62] This condition should be suspected in young women with a history of cholestasis of unknown origin who develop a severe ICP.[62] Progressive familial intrahepatic cholestasis may have a progressive course with chronic icteric or anicteric cholestasis, portal hypertension, and liver failure. Women who experienced ICP can develop also the low phospholipids–associated cholelithiasis, either before or after pregnancy.[63] Biliary symptoms usually appear in young adults before the age of 40 years; a family history is often reported and the oversaturated bile can cause intrahepatic hyperechogenic foci, sludge, or microlithiasis.[64] Moreover, biliary pain and even pancreatitis may recur after cholecystectomy. Some rare familial cases may have a low phospholipid–associated cholelithiasis and induction of cholestasis by a reduced dosage of estrogens compared with pregnancy, that is, oral contraceptive-induced cholestasis.[65] A recent large Swedish study with more than 11,000 patients showed that the risk of later hepatobiliary cancer and autoimmune-mediated and cardiovascular diseases is greater in women with ICP than in women without this diagnosis.[66] Recurrence of ICP ranges between 45% and 70%.[67]

TREATMENT

A recent metaanalysis including 9 randomized clinical trials demonstrated that ursodeoxycholic acid (UDCA) is effective in reducing pruritus and improving liver test results in patients with ICP and improves fetal outcome.[68] This study shows that UDCA is safe, well-tolerated, and decreases the prematurity rate and consequently the number of hospitalizations in intensive care units. A number of mechanisms of action may explain these effects, including the hydrophilic properties of UDCA, the improvement of both transport and secretion of bile acids by the liver by increasing the activity of canalicular transporters, and improving the bile acid transport across the placenta, thus decreasing exposure of the fetus to toxic bile acids.[69] A novel mechanism of action of UDCA has been explored in an elegant study determining the concentrations of bile acids and sulphated progesterone metabolites in maternal

Downloaded for Anonymous User (n/a) at Michigan State University from ClinicalKey.com by Elsevier on November 10, 2019.
For personal use only. No other uses without permission. Copyright ©2019. Elsevier Inc. All rights reserved.

and fetal serum and placenta using high performance liquid chromatography–mass spectrometry/mass spectrometry.[70] The results of this study show that the ABCG2 export pump located at the apical membrane of trophoblast cells plays an important role in the placenta barrier for sulphated progesterone metabolites and bile acids, with the consequent protection of the fetus against the accumulation of these compounds in the maternal compartment.

Another metaanalysis of the literature including both nonrandomized and randomized, controlled studies, including a total of 836 ICP showed that UDCA, had decreased pruritus in 73% of randomized, controlled studies and in 100% of NRSs with available data.[71] Liver function tests were improved in 82% and 100%, respectively. Moreover, the use of UDCA was associated with lower rates of prematurity and less frequent use of neonatal intensive care unit.[71]

More recently, the Cochrane Collaboration published an updated review of interventions for treating ICP after the first published in 2011.[72] This review included 21 trials with a total of 1197 women, and assessed 11 different interventions resulting in 15 different comparisons. Compared with placebo, UDCA showed improvement in pruritus in 5 (228 women) out of 7 trials. Two trials (48 women) reported lower pruritus scores for *S*-adenosylmethionine (SAMe) compared with placebo, whereas 2 other trials of 34 women reported no differences between groups. UDCA was more effective improving pruritus than either SAMe or cholestyramine, however, combined UDCA + SAMe was no more effective than UDCA alone with regard to pruritus improvement. Overall, there were no differences in instances of fetal distress in the UDCA groups compared with placebo, but the difference was not significant. On the basis of these data, the authors conclude that large trials of UDCA to determine fetal benefits or risks are needed. Moreover, there was insufficient evidence to indicate that SAMe, guar gum, activated charcoal, dexamethasone, cholestyramine, salvia, and even Chinese agents (yinchenghao decoction, danxioling and yiganling, or yiganling alone or in combination) are effective in treating women with cholestasis of pregnancy.

Rifampicin, which has been used in the treatment of pruritus in cholestatic liver diseases for its complementary mechanism of action to UDCA,[73] has been administered in 27 women with ICP (28 affected pregnancies). In 14 pregnancies (54%), serum bile acids decreased after the introduction of rifampicin.[74] In 10 pregnancies (38%), there was a 50% decrease in serum bile acids.[73,74] Although these data should be considered as preliminary, they suggest that rifampicin may be used as a useful adjunct to the treatment with UDCA in women with severe ICP.

Indeed, the crucial point in the management of ICP is to ascertain the optimal gestational age that would minimize the risk of overall perinatal mortality. In a large cohort of women with ICP (with 1,604,386 singleton, nonanomalous pregnancies evaluated between 34 and 40 weeks' gestation) it was found that the risk of fetal, neonatal, or infant mortality was minimized by delivery at 36 weeks of gestation for those diagnosed beyond the gestation; therefore, preterm delivery at this gestational age may be optimal.[75]

SUMMARY

ICP is a peculiar disorder of pregnancy whose etiology is likely multifactorial. In the last decade, genetic defects in at least 6 canalicular transporters have been found to be associated with ICP. All the association studies with these candidate genes stress the complex variability of genotypes, the different penetrance, and the influence of several environmental factors. In some way, ICP could be regarded as a phenotypic manifestation of a complex genetic condition involving bile secretion or its regulation.

Downloaded for Anonymous User (n/a) at Michigan State University from ClinicalKey.com by Elsevier on November 10, 2019.
For personal use only. No other uses without permission. Copyright ©2019. Elsevier Inc. All rights reserved.

Increased maternal bile acids have been shown to be correlated with fetal complications, such as anoxia, prematurity, perinatal death, fetal distress and stillbirth. ICP is generally a benign condition for mothers; long-term sequelae include the gallstone risk and chronic liver disease in some cases, suggesting a link between ICP and genetic conditions leading to an altered bile composition. Moreover, a positive association between ICP and hepatitis C before and after the diagnosis has been evidenced. The current medical treatment for ICP is UDCA; by examining all available evidence from the more recent literature, UDCA is recommended in the management of ICP owing the possible benefits on pruritus, liver function tests, safety, and decreased rates of prematurity and fetal adverse effects.

REFERENCES

1. Williamson C, Geenes V. Intrahepatic cholestasis of pregnancy. Obstet Gynecol 2014;124:120–33.
2. Joshi D, James A, Quaglia A, et al. Liver disease in pregnancy. Lancet 2010;375:594–605.
3. Arrese M, Reyes H. Intrahepatic cholestasis of pregnancy: a past and present riddle. Ann Hepatol 2006;5:202–5.
4. Qi HB, Shao Y, Wu WX, et al. Grading of intrahepatic cholestasis of pregnancy. Zhonghua Fu Chan Ke Za Zhi 2004;39:14–7.
5. Locatelli A, Roncaglia N, Arreghini A, et al. Hepatitis C virus infection is associated with a higher incidence of cholestasis of pregnancy. Br J Obstet Gynaecol 1999;106:498–500.
6. Paternoster DM, Fabris F, Palù G, et al. Intra-hepatic cholestasis of pregnancy in hepatitis C virus infection. Acta Obstet Gynecol Scand 2002;81:99–103.
7. Ropponen A, Sund R, Riikonen S, et al. Intrahepatic cholestasis of pregnancy as an indicator of liver and biliary diseases: a population-based study. Hepatology 2006;43:723–8.
8. Marschall H-U, Shemer EW, Ludvigsson JF, et al. Intrahepatic cholestasis of pregnancy and associated hepatobiliary disease: a population based cohort study. Hepatology 2013;58:1385–91.
9. Belay T, Woldegiorgis H, Gress T, et al. Intrahepatic cholestasis of pregnancy with concomitant hepatitis C virus infection, Joan C. Edwards SOM, Marshall University. Eur J Gastroenterol Hepatol 2015;27:372–4.
10. Hinoshita E, Taguchi K, Inokuchi A, et al. Decreased expression of an ATP-binding cassette transporter, MRP2, in human livers with hepatitis C virus infection. J Hepatol 2001;35:765–73.
11. Iwata R, Baur K, Stigier B, et al. A common polymorphism in the ABCB11 gene is associated with advanced fibrosis in hepatitis C but not in non-alcoholic fatty liver disease. Clin Sci (Lond) 2011;120:287–96.
12. Berg B, Helm G, Petersohn L, et al. Cholestasis of pregnancy. Clinical and laboratory studies. Acta Obstet Gynecol 1996;175:957–60.
13. Laatikainen T, Ikonen E. Fetal prognosis in obstetric hepatosis. Ann Chir Gynaecol Fenn 1975;64:155–64.
14. Reis H, Baez ME, Gonzalez MC, et al. Selenium, zinc and copper plasma levels in intrahepatic cholestasis of pregnancy, in normal pregnancies and in healthy individuals in Chile. J Hepatol 2000;32:542–9.
15. Reis H, Kauppila A, Korpela H, et al. Low serum selenium concentration and glutathione peroxidase activity in intrahepatic cholestasis of pregnancy. Br Med J 1987;294:150–2.

Downloaded for Anonymous User (n/a) at Michigan State University from ClinicalKey.com by Elsevier on November 10, 2019.
For personal use only. No other uses without permission. Copyright ©2019. Elsevier Inc. All rights reserved.

16. Wilkstrom Shemer E, Marshall HU. Decreased 1,25 dihydroxy vitamin D levels in women with intrahepatic cholestasis of pregnancy. Acta Obstet Gynecol Scand 2010;89:1420–3.
17. Gonzales M, Reyes H, Arrese M, et al. Intrahepatic cholestasis of pregnancy in twin pregnancies. J Hepatol 1989;9:84–90.
18. Rioseco A, Ivankovic M, Manzur A, et al. Intrahepatic cholestasis of pregnancy: a retrospective case-control study of perinatal outcome. Am J Obstet Gynecol 1994;170:890–5.
19. Savander M, Ropponen A, Avela K, et al. Genetic evidence of heterogeneity in intrahepatic cholestasis of pregnancy. Gut 2003;52:1025–9.
20. Heinonen S, Kirkinen P. Pregnancy outcome with intrahepatic cholestasis. Obstet Gynecol 1999;94:189–93.
21. Bull LN, van Eijk MJ, Pawlikowska L, et al. A gene encoding a liver-specific ABC transporter is mutated in progressive familial intrahepatic cholestasis. Nat Genet 1998;20:233–8.
22. Klomp LW, Vargos JC, van Mil SW, et al. Characterization of mutations in ATP8B1 associated with hereditary cholestasis. Hepatology 2004;40:27–38.
23. Mullenbach R, Bennet A, Tetlow N, et al. ATP8B1 mutations in British cases with intrahepatic cholestasis of pregnancy. Gut 2005;54:829–34.
24. Dixon PH, Wadsworth A, Chambers J, et al. A comprehensive analysis of common genetic variation around six candidate loci for intrahepatic cholestasis of pregnancy. Am J Gastroenterol 2014;109:76–84.
25. Noe J, Stieger B, Meier PJ. Functional expression of the canalicular bile salt export pump of human liver. Gastroenterology 2002;123:1659–60.
26. Jacquemin E, Cresteil D, Manouvrier S, et al. Heterozygous non-sense mutation of the MDR3 gene in familial intrahepatic cholestasis of pregnancy. Lancet 1999;353:210–1.
27. Dixon PH, Weerasekera N, Linton KJ, et al. Heterozygous MDR3 missense mutation associated with intrahepatic cholestasis of pregnancy: evidence for a defect in protein trafficking. Hum Mol Genet 2009;9:1209–17.
28. Floreani A, Carderi I, Paternoster D, et al. Hepatobiliary phospholipid transporter ABCB4, MDR3 variants in a large cohort of Italian women with intrahepatic cholestasis of pregnancy. Dig Liver Dis 2008;40:366–70.
29. Schneider G, Paus TC, Kullak-Ublick GA, et al. Linkage between a new splicing site mutation in the MDR3 alias ABCB4 gene and intrahepatic cholestasis of pregnancy. Hepatology 2007;45:150–8.
30. Sookian S, Castano G, Burguen A, et al. Association of the multidrug-resistance-associated protein gene (ABCC2) variants with intrahepatic cholestasis of pregnancy. J Hepatol 2008;48:125–32.
31. Kim I, Ahn SH, Choi M, et al. Differential regulation of the bile acid homeostasis by the farnesoid X receptor in liver and intestine. J Lipid Res 2007;48:2664–72.
32. Van Mil SW, Milona A, Dixon PH, et al. Functional variants of the central bile acid sensor FXR identified in intrahepatic cholestasis of pregnancy. Gastroenterology 2007;133:507–16.
33. Davit-Spraul A, Gonzales E, Jacquemin E. NR1H4 analysis in patients with progressive familial intrahepatic cholestasis, drug-induced cholestasis or intrahepatic cholestasis of pregnancy unrelated to ATP8B1, ABCB11 and ABCB4 mutations. Clin Res Hepatol Gastroenterol 2012;36:569–73.
34. Floreani A, Caroli D, Lazzari R, et al. Intrahepatic cholestasis of pregnancy: new insights into its pathogenesis. J Matern Fetal Neonatal Med 2013;26:1410–5.
35. He P, Wang F, Jiang Y, et al. Placental proteome alterations in women with intrahepatic cholestasis of pregnancy. Int J Gynaecol Obstet 2014;126:256–9.

Downloaded for Anonymous User (n/a) at Michigan State University from ClinicalKey.com by Elsevier on November 10, 2019.
For personal use only. No other uses without permission. Copyright ©2019. Elsevier Inc. All rights reserved.

36. Du Q, Pan Y, Zhang Y, et al. Placental gene-expression profiles of intrahepatic cholestasis of pregnancy reveal involvement of multiple molecular pathways in blood vessel formation and inflammation. BMC Med Genomics 2014;7:42–52.
37. Brites D, Rodrigues CMP, da Concejao Cardos M, et al. Unusual case of severe cholestasis of pregnancy with early onset, improved by ursodeoxycholic acid administration. Eur J Obstet Gynecol Reprod Biol 1998;76:165–8.
38. Chao TT, Sheffield JS. Primary dermatologic findings with early-onset intrahepatic cholestasis of pregnancy. Obstet Gynecol 2011;117:456–8.
39. Zamah AM, El-Sayed YY, Milki AA. Two cases of cholestasis in the first trimester of pregnancy after ovarian hyperstimulation. Fertil Steril 2008;90:1202.e7–10.
40. Zhou L, Qi H, Luo X. Analysis of clinical characteristics and perinatal outcome of early-onset intrahepatic cholestasis of pregnancy. Zhonghua Fu Chan Ke Za Zhi 2013;48:20–4.
41. Lehroff S, Pomeranz MK. Specific dermatoses of pregnancy and their treatment. Dermatol Ther 2013;26:274–84.
42. Kenyon AP, Piercy CN, Girling J, et al. Pruritus may precede abnormal liver function tests in pregnant women with obstetric cholestasis: a longitudinal analysis. BJOG 2001;108:1190–2.
43. Walker IA, Nelson-Piercy C, Williamson C. Role of bile acid measurement in pregnancy. Ann Clin Biochem 2002;39:105–13.
44. Glantz A, Marschall HU, Mattson LA. Intrahepatic cholestasis of pregnancy: relationships observed bile acid levels and fetal complication rates. Hepatology 2004;40:467–74.
45. German AM, Kato S, Carvajal JA, et al. Bile acids increase response and expression of human myometric receptor. Am J Obstet Gynecol 2003;189:577–82.
46. Israel EJ, Guzman ML, Campos GA. Maximal response to oxytocin of the isolated myometrium from pregnant patients with intrahepatic cholestasis. Acta Obstet Gynecol Scand 1986;65:581–2.
47. Brouwers L, Koster MP, Page-Christiaens GC, et al. Intrahepatic cholestasis of pregnancy: maternal and fetal outcomes associated with elevated bile acid levels. Am J Obstet Gynecol 2015;212:100.e1–7.
48. Milkiewicz P, Gallagher R, Chambers J, et al. Obstetric cholestasis with elevated gamma glutamyl transpeptidase: incidence, presentation and treatment. J Gastroenterol Hepatol 2003;18:1283–6.
49. Jansen PLM, Muller M. Genetic cholestasis: lessons from the molecular physiology of bile formation. Can J Gastroenterol 2000;14:233–8.
50. Kremer AE, Bolier R, Dixon PH, et al. Autotaxin activity has a high accuracy to diagnose intrahepatic cholestasis of pregnancy. J Hepatol 2015;62:897–904.
51. Martineau MG, Raker C, Dixon PH, et al. The metabolic profile of intrahepatic cholestasis of pregnancy is associated with impaired glucose tolerance, dyslipidemia, and increased fetal growth. Diabetes Care 2015;38:243–8.
52. Reid R, Ivery KJ, Rencoret RH, et al. Fetal complications of obstetric cholestasis. Br Med J 1976;1:870–2.
53. Henderson CE, Shah RR, Gottimukkala S, et al. Primum non nocere: how active management became modus operandi for intrahepatic cholestasis of pregnancy. Am J Obstet Gynecol 2014;124:189–96.
54. Bannister-Tyrrell M, Ford JB, Morris JM, et al. Intrahepatic cholestasis of pregnancy is not associated with stillbirth in an Australian maternity population. Eur J Obstet Gynecol Reprod Biol 2014;176:203–6.
55. Suri V, Jain R, Aggarwal N, et al. Useful of fetal monitoring in intrahepatic cholestasis of pregnancy: a prospective study. Arch Gynecol Obstet 2012;286:1419–24.

Downloaded for Anonymous User (n/a) at Michigan State University from ClinicalKey.com by Elsevier on November 10, 2019.
For personal use only. No other uses without permission. Copyright ©2019. Elsevier Inc. All rights reserved.

56. Lee RH, Kwok KM, Ingles S, et al. Pregnancy outcomes during an era of aggressive management for intrahepatic cholestasis of pregnancy. Am J Perinatol 2008; 25:341–5.
57. Oztekin D, Aydal I, Oztekin O, et al. Predicting fetal asphyxia in intrahepatic cholestasis of pregnancy. Arch Gynecol Obstet 2009;280:975–9.
58. Rook M, Vargas J, Caughey A, et al. Fetal outcomes in pregnancies complicated by intrahepatic cholestasis of pregnancy in Northern California cohort. PLoS One 2012;7:1–6.
59. Jin J, Pan S, Huang L, et al. Risk factors for adverse fetal outcomes among women with early-versus late-onset intrahepatic cholestasis of pregnancy. Int J Gynaecol Obstet 2015;128(3):236–40.
60. Hu Y, Ding Y-L, Yu L. The impact of intrahepatic cholestasis of pregnancy with hepatitis B virus infection on perinatal outcomes. Ther Clin Risk Manag 2014; 10:381–5.
61. Hamalainen ST, Turunen K, Kosunen E, et al. Men's health is not affected by their mothers' intrahepatic cholestasis of pregnancy. Am J Mens Health 2015. [Epub ahead of print].
62. Lucena J-F, Herrero JI, Quiroga G, et al. A multidrug resistance 3 gene mutation causing cholelithiasis, cholestasis of pregnancy, and adult biliary cirrhosis. Gastroenterology 2003;124:1037–42.
63. Davit-Spraul A, Gonzales E, Baussan C, et al. The spectrum of liver diseases related to ABCB4 gene mutations: pathophysiology and clinical aspects. Semin Liver Dis 2010;30:134–46.
64. Poupon R, Rosmorduc O, Boelle PY, et al. Genotype-phenotype relationships in the low-phospholipids-associated cholelithiasis syndrome: a study of 156 consecutive patients. Hepatology 2013;58:1105–10.
65. Pasmant E, Goussard P, Baranes L, et al. First description of ABCB4 gene deletions in familial low phospholipid-associated cholelithiasis and oral contraceptives-induced cholestasis. Eur J Hum Genet 2012;20:277–82.
66. Wilkstromer Shemer EA, Stephansson O, Thuresson M, et al. Intrahepatic cholestasis of pregnancy and cancer, immune-mediated and cardiovascular diseases: a population-based cohort study. J Hepatol 2015;63(2):456–61.
67. Hay JE. Liver disease in pregnancy. Hepatology 2008;47:1067–76.
68. Bacq Y, Sentilhes L, Reyes HB, et al. Efficacy of ursodeoxycholic acid in treating intrahepatic cholestasis of pregnancy: a meta-analysis. Gastroenterology 2012; 143:1492–501.
69. Erlinger S. Ursodeoxycholic acid in intrahepatic cholestasis of pregnancy: good, but can do better. Clin Res Hepatol Gastroenterol 2013;37:117–8.
70. Estiù MC, Monte MJ, Rivas L, et al. Effects of ursodeoxycholic acid treatment on the altered progesterone and bile acid homeostasis in the mother-placenta-foetus trio during cholestasis of pregnancy. Br J Clin Pharmacol 2014;79: 316–29.
71. Grand'Maison S, Durand M, Mahone M. The effect of ursodeoxycholic acid treatment for intrahepatic cholestasis of pregnancy on maternal and fetal outcomes: a meta-analysis including non-randomized studies. J Obstet Gynaecol Can 2014; 36:632–41.
72. Gurung V, Stokes M, Middleton P, et al. Interventions for treating cholestasis in pregnancy [review]. Cochrane Database Syst Rev 2013;(6):CD000493.
73. Marshall HU, Wagner M, Zollner G, et al. Complementary stimulation of hepatobiliary transport and detoxification systems by rifampicin and ursodeoxycholic acid in humans. Gastroenterology 2005;129:476–85.

Downloaded for Anonymous User (n/a) at Michigan State University from ClinicalKey.com by Elsevier on November 10, 2019.
For personal use only. No other uses without permission. Copyright ©2019. Elsevier Inc. All rights reserved.

74. Geenes V, Chambers J, Khurana R, et al. Rifampicin in the treatment of severe intrahepatic cholestasis of pregnancy. Eur J Obstet Gynecol Reprod Biol 2015; 189:59–63.
75. Puljic A, Kim E, Page J, et al. The risk of infant and fetal death by each additional week of expectant management in intrahepatic cholestasis of pregnancy by gestational age. Am J Obstet Gynecol 2015;212:667.e1–5.

Downloaded for Anonymous User (n/a) at Michigan State University from ClinicalKey.com by Elsevier on November 10, 2019.
For personal use only. No other uses without permission. Copyright ©2019. Elsevier Inc. All rights reserved.