Management of Intrahepatıc Cholestasıs of Pregnancy: Revıew of Lıterature

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Abstract: *Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy specific liver disorder characterized by maternal pruritus in the latter half of the pregnancy, raised serum bile acids and increased rates of adverse fetal outcomes. Maternal effects of ICP are mild; however, there is a clear association between ICP and higher frequency of fetal distress, preterm delivery, and sudden intrauterin fetal death. The etiology of ICP is elusive but it is likely to result from the cholestatic effects of reproductive hormones and their metabolites in genetically susceptible women. The mechanisms by which fetal complications occur is also unclear. In this article we tried to review epidemiology, clinical features, etiology, diagnosis, pharmacologic treatment and obstetric management of ICP.*

Abbreviations: *Intrahepatic cholestasis of pregnancy (ICP), Familial intrahepatic cholestasis (PFIC), Benign Recurrent Cholestasis (BRIC), Cholic Acid (CA), Chenodeoxycholic Acid (CDCA), Ursodeoxycholic Acid (UDCA), Neonatal Respiratory Distress Syndrome (RDS), Meconium-Stained Amniotic Fluid (MSAF), Royal College of Obstetricians and Gynaecologists (RCOG), Progressive Familial İntrahepatic Cholestasis (PFIC), Contraceptive-İnduced Cholestasis (CIC), Adenosine Triphosphate-Binding Cassette, Subfamily B, Member 4 (ABCB4), Multidrug Resistance 3 (MDR3), Respiratory Distress Syndrome (RDS).*

Keywords: *Intrahepatıc Cholestasıs, Pregnancy, Bile Acids*

1. INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is characterized by skin pruritus and elevation of serum aminotransferase levels and bile acid concentration in maternal sera. It is one of the most common liver disorders in pregnancy [1].The condition is characterized by pruritus and jaundice with mild to moderate elevations in transaminases, bilirubin levels and bile acids in the absence of other pregnancy specific or non-specific diseases that can explain these findings. ICP usually manifests during the second or third trimester of pregnancy and spontaneously improves after delivery[2].The disease effects both mother and the fetus but the most deleterious harms are on fetus. The purpose of diagnosis and management is primarily better fetal and neonatal outcome[3].The pathophysiology, clinical features, diagnosis, complications and treatment of intrahepatic cholestasis of pregnancy is reviewed here. Recent advances in management is emphasized.

2. EPIDEMIOLOGY

ICP is a rare disease but there is a great variation in prevalance of the disease. Prevalence differs extremely in different areas, in different rates and also differs seasonally. The incidence differs ranging from 0.1 to 15.6 percent in literature[4].Scandinavia and Chile have the highest prevalence. In the past, 2% prevalence is reported in Sweden in 1950s and in Chile a prevalence up to 14% in 1960s. Curiously, prevalence in both regions has since fallen. ICP is less common in other regions of the world, although incidence has risen since the 1950s and 1960s in Europe, Asia, North America, Australia, and some other Latin American countries[5].The disease has a seasonal variability and is seen more commonly in winter in Chile and Scandinavia[6,7].A higher incidence is seen in twin pregnancies (20%-22%)[8,9].and following in vitro fertilization treatment (2.7% *vs* 0.7%)[10].The patients with ICP have drug sensivities hiher and have more prolonged emezis in the pregnancy[11].ICP is more common in Hepatitis C seropositive pregnant women and seems to be associated with early onset of the disease[12].Gallstones are identified more common at ICP patients and their families[13].

3. PATHOGENESIS

ICP is primarily associated with hormonal and genetic factors. Environmental factors may also influence the expression of the disease. Literature suggests a strong evidence of genetic factors in pathogenesis. Sister of a patient has a higher incidence than population. Familial intrahepatic cholestasis (PFIC) and benign recurrent cholestasis(BRIC) syndromes are defined. . These autosomal recessive syndromes are caused by homozygous mutations in the genes encoding biliary transport proteins, and case reports have described ICP in the heterozygous mothers of affected children[14].Bile formation is largely dependent upon the normal function of multiple hepatic and canalicular membrane transport proteins. Heterozygous mutations in gene ABCB4 (adenosine triphosphate-binding cassette, subfamily B, member 4), which encodes the hepatic phospholipid transporter MDR3 (multidrug resistance 3), have been found in patients with ICP[15]. ATP8B1, ABCB4 and ABCB11 represent three of the many known canalicular transport genes responsible for normal bile flow, and are found to be mutated in individuals with certain cholestatic diseases, such as progressive familial intrahepatic cholestasis (PFIC), benign recurrent intrahepatic cholestasis

(BRIC) and contraceptive-induced cholestasis (CIC). More specifically, mutations in both ABCB4 and ABCB 11 genes have been associated with intrahepatic cholestasis of pregnancy[16,17].The prevalence of such *ABCB4* gene mutations in Caucasian patients suffering from ICP is 16 percent[18].There is strong evidence that hormones have a role in the etiology of ICP. The disease is more common in multiple than singleton pregnancies (20.9% *vs* 4.7% in one study) [19].Also, the disease is more common in the third trimester when the estrogens are highest. Because the disease can be recurred with oral contraceptive use when non-pregnant; this may be an evidence of role of reproductive hormones[15].In vitro studies have demonstrated that the cholestatic estrogen metabolite, 17-b-estradiol glucuronide, inhibits excretion of bile salt into the bile canaliculus[20].Altough estrogens are known to cause cholestasis in both experimental and clinical conditions, evidence suggests that progesterone has a role in pathogenesis of the disease. In one study of 50 women with ICP from France, 32 had been treated with oral natural progesterone to prevent premature delivery. During the same period, the percent of pregnant women without ICP who had been treated with natural progesterone during pregnancy was significantly lower[21].Although total progesterone levels does not change in ICP comparison to normal pregnancies, the profile of metabolites is different and this may reflect impaired excretion of these metabolites at the canalicular membrane, or abnormal synthesis[22].

4. CLINICAL FEATURES

Intrahepatic cholestasis of pregnancy is usually diagnosed in the third trimester and it is rarely seen before 25 weeks' gestation. Pruritus is usually the main complaint of patient and generally starts in the palms and soles, progresses to the arms and legs, and eventually involves the trunk and face. There is additional progression from occasional pruritus to constant pruritus, which can lead to sleep deprivation and irritability. Jaundice may be the initial complaint but not expected, it typically develops 1 to 4 weeks after the onset of pruritus[23].Pruritus may precede laboratory abnormalities. Abdominal pain is unexpected. Encephalopathy or other stigmata of liver failure are unusual, and their presence should initiate a search for other causes of liver disease[24].Pruritis typically resolves within 48 h of delivery. There are no associated dermatological features other than excoriation marks, which may be severe. Many women report that their pruritus worsens at night[22].The disease typically presents at late second trimester or third trimester but but ICP has been reported as early as 8 weeks gestation[25].Pruritis may be present either prior to or after abnormal liver function is detected. Constitutional symptoms of cholestasis may also be present, including anorexia, malaise and abdominal pain. Pale stools and dark urine have been reported and steatorrhea may occur[26].Co-existence of ICP with other pregnancy-related disorders including pre-eclampsia, acute fatty liver of pregnancy, and gestational diabetes are reported in literature[27,28].

Serum total bile acid concentrations increase in ICP and may be the first or only laboratory abnormality. The serum bile acid concentrations also are usually elevated, and the cutoff values chosen for diagnosis of ICP are usually values of more than 10 mmol/L. Normal bile acid concentrations do not exclude the diagnosis[29].In ICP, transaminases may rise before or after serum bile acids. ALT is thought to be a more sensitive marker of ICP; there is a 2-10-fold increase in serum levels that is generally more marked than the rise in AST[30].If hyperbilirubinemia is present, it tends

to be a conjugated hyperbilirubinemia. Alkaline phospatase has not a diagnostic value for the diagnosis due to placental isoform(30). Serum bile acid measurement is now considered to be the most suitable biochemical marker for both the diagnosis and monitoring of ICP, with the cholic acid(CA) level or the CA: chenodeoxycholic acid (CDCA) ratio proposed as being the most sensitive indicator for the early diagnosis of the condition[31].CA is the primary elevated bile acid, so this ratio increases. One study reported impaired glucose tolerance associated with ICP[32].Prolonged prothrombin time may be seen and is associated with vitamin K malabsorption and steatorrhea especially with the use of cholestyramine[33].In urine analysis elevated bile acids CA and CDCA are elevated[24]. On ultrasonography, the biliary ducts are not dilated, and hepatic parenchyma appears norma[34].Gallstones are more frequent with ICP. However, ICP has been described in women with previous cholecystectomy, suggesting that the presence of gallstones is not causative of ICP[35].Cholestasis recurs during subsequent pregnancies in 60 to 70 percent. Recurrent episodes change in severity. Affected women may be at increased risk for the development of gallstones[36].

5. TREATMENT

The primary purpose of treatment is to reduce the maternal symptoms and to prevent maternal and fetal complications. Several drugs have been studied, and most focus on relieving symptoms. Ursodeoxycholic acid (udca, ursodiol) has emerged as the most promising treatment. Ursodeoxycholic acid (UDCA) is currently the most effective treatment of pruritus in ICP[37].

5.1. Ursodeoxycholic Acid

UDCA is hydrophilic bile acid and used for the treatment of various cholestatic disorders. Currently, UDCA is the most promising treatment for ICP[38].First Palma et al. reported UDCA improved significantly serum biochemistry in patients with ICP at 1992[39].Initial pilot studies in ICP followed by controlled trials demonstrated that UDCA improved pruritus and liver tests and had no maternal or neonatal adverse effects[39,40].Since that time, there have been several studies and additional case series demonstrating that UDCA treatment results in clinical and biochemical improvement in ICP[41,42].Studies examining the bile acid pool composition have shown that, in addition to a reduction in the serum bile acid concentration, treatment with UDCA results in a normalization of the CA:CDCA ratios, and a reduction in urinary excretion that is associated with reduction in pruritus[43].The mechanism underlying the beneficial effect of UDCA is unclear. UDCA has been shown to correct the impaired bile acid transfer kinetics observed in ICP placentas and to reverse the morphological changes seen in the placentas of a rodent model of ICP. UDCA also protects cardiomyocytes from bile acid-induced arrhythmias in an in vitro model. A concern with UDCA therapy is that bile acids can cross the placenta, which might lead to fetal toxicity. However, one study found that treatment restored the serum bile acid composition to more closely resemble that seen in healthy, pregnant controls.

5.2. Cholestyramine

Cholestyramine, which decreases the ileal absorption and increases the fecal excretion of bile acids, has been used in ICP. Nevertheless, cholestyramine is less effective than ursodeoxycholic acid in improving pruritus and liver tests and is also associated with more side effects[44].There have been several studies suggesting that cholestyramine is effective at reducing pruritus in ICP. However, it has no effect on serum bile acid

levels or other biochemical markers of cholestasis[45].Furthermore, it may reduce the intestinal absorption of fat-soluble vitamins, thus depleting the levels of vitamin

K and increasing the risk of hemorrhage for the mother and fetus. Cholestyramine is therefore no longer considered a first-line therapy for ICP[46].

5.3. Dexamethasone

In a study from Finland, it is reported that dexametasone declined serum bile acid levels, improved liver biochemistry and improved symptoms. These benefits of dexamatosone is linked to its estrogen secretion inhibitor effects at placenta[47].But it is not preferred commonly, because it crosses placenta and may result adverse effects on the fetus at higher doses[48].

5.4. Other Drugs

Rifampicine recently being used commonly in the treatment of gallstones and primary biliary cirrhosis. But there is no published study for rifampicine monotherapy in ICP. Its combination with UDCA may be more effective for patients that are unresponsible to UDCA

monotheraphy[24].Although it is not supported in trials, many clinicians use oral vitamin K agents for vitamin K defficiency due to malabsorption[24].S-Adenosyl-L-methionine (SAM) is reported effective in a few trials, but this is not proved in more recent studies. SAM reversed estrogen induced impairment of bile flow in rats[49].Now it is advised as combined therapy with UDCA for unresponsible cases to monotherapy with UDCA[50].

6. FETAL OUTCOME AND PROGNOSIS

Although ICP is commonly a benign disorder for the mother, it may have significant riks for the developing fetus. The main complications are prematurity, meconium-stained amniotic fluid(MSAF), intrauterine demise, and an increased risk for neonatal respiratory distress syndrome(RDS). All these complications are significantly correlated with elevated bile acid levels[51].Fetal complications seems to be results of bile acids in fetal circulation, fetal tissues and fetal airways. In vitro studies of isolated placental vesicles have shown that vectorial transfer of bile acids from fetus to mother is impaired in ICP, and that this is specifically the result of decreased efficiency of ATP independent transport[52].Bile acids are known to cause an increase in colonic motility and this is a possible explanation meconium-stained amniotic fluid. This is proved in a animal model[53].Alternatively, the bile acids may cause fetal distress and subsequent meconium passage. In ICP, MSAF has been reported in 16%-58% of all cases and up to 100% of cases affected by intrauterine death[54].The frequency of MSAF is greater in pregnancies with higher reported levels of maternal serum bile acids. Elevated bile acids in circulation of rat models resulted abnormal heart rate patterns. This may be responsable for cardiotocographical changes of fetus. Taurocholic acid treatment resulted decreased contractility at rat cardiomyocytes[55].

Recent studies report rates of preterm birth as 30%-40% in ICP cases without active management. Reid et al reported an overall incidence of 36%, but the incidence was 48% for the patients with hyperbillirubinemia[56].But recently majority of prematurity is related to increased active management and iatrogenic births arround 37 weeks. The rate of spontaneous birth is increased with elevated bile acid levels. The rate of this complication was significantly higher in ICP pregnancies with maternal fasting serum bile acids > 40 µmol/L in a large Swedish study[57].RDS was found to affect 28.6% of newborns from cholestatic pregnancies and high levels of bile acids were found in the bronchoalveolar fluid of 10 infants with RDS[58].This can a result of prematurity but it seems as an effcet of high bile acids on fetal lung and airways. The pathophysiology of fetal death in ICP is poorly understood, but may be related to the sudden development of a fetal arrhythmia or vasospasm of the placental chorionic surface vessels induced by high levels of bile acids[59].Intrauterine demise incidence is declined recently with active management of patients with ICP. Older studies using only biochemical abnormalities to diagnose ICP have reported a perinatal mortality rate of 10%-15% without active management[60].Active management consists of increased fetal monitoring, frequent biochemical testing, pharmacotherapy with ursodeoxycholic acid (UDCA) or delivery at 37-38 wk gestation. These management protocols are based on evidence showing that stillbirths in ICP tend to cluster around 37-39 wk. But there are a lot of reports of IUD before 37weeks in literature. No relation of ICP with fetal growth retardation reported in literature[24].

7. TIMING OF DELIVERY

The best treatment of ICP is delivery but the timing should be balanced with the risk of fetal death against the potential risks of prematurity. Active management has usually been recommended to prevent the risk of IUFD, and routine deliveries at 37 to 38 weeks of gestation are common place in maternity units. Royal College of Obstetricians and Gynaecologists (RCOG) recommends elective delivery after 37 weeks. But there is no consensus about the time of delivery[61].Timing of delivery should be individualized for each patient. The value of antepartum tests for fetal well-being are not proven. Several others reported intrauterine fetal demise occurring within a few days of a reactive NST. Non Stress tests and other tests for detection of the effects of chronic placental insufficiency on the fetus may not be useful in ICP because the mechanism of intrauterine fetal demise is thought to be a sudden event rather than the result of a chronic placental vascular process [62].But most obstetricians use NST for follow-up ICP patients. Moreover, the usefulness of a policy of the induction of labor has never been demonstrated by appropriate randomized controlled trials (RCTs). In the absence of evidence based recommendations, the timing of delivery should be discussed on an individual basis after weighing the risk related to prematurity, and the maternal morbidity related to

inducing labor, against the risk of sudden IUD, which thus far remains unpredictable[62].Indications for delivery prior to 36 weeks of gestation because of ICP include excruciating and unremitting maternal pruritus not relieved with pharmacotherapy, jaundice, or a prior history of fetal demise before 36 to 37 weeks due to ICP with recurring ICP in the current pregnancy. Based on limited data, total serum bile acid concentrations ≥100 micromol/L is another potential indication for delivery prior to 36 weeks of gestation[63,64].In these situations timing of delivery should be postponed and as long as possible after 34 weeks of gestation, depending on the individual's particular circumstances (severity of symptoms, gestational age of previous fetal demise) [64].ICP is not a contraindication to breastfeeding.

8. SIGNIFICANCE OF MATERNAL BILE ACID LEVELS

Maternal sera bile acid levels strongly associated with adverse fetal outcome and this is reported in a lot of different studies. The risk of fetal complications was statistically increased at bile acid levels ≥40 micromol/L. The risk for fetal demise also appears to be increased with higher bile acid levels, especially with bile acid levels ≥100 micromol/L. The rate of fetal demise at this level was 10 percent (2/21) in one study[63].and 15 percent (4/26) in another[65].In a large prospective cohort study of women with ICP with total bile acid concentrations ≥40 micromol/L, the incidence of IUD was 1.5 percent (10/669), which was higher than the control population incidence of 0.5 percent (11/2208). In this study, 6 of 10 stillbirths occurred before 37 weeks of gestation, with a median gestational age at delivery of 36±2 days and median total bile acid levels of 137 micromol/L[66].But it is not certain whether delivery timing should be altered once bile acids have reached a level below 40 micromol/L after the initiation of medical therapy.

9. CONCLUSION

Intrahepatic cholestasis of pregnancy can have devastating consequences for the fetus and mild complications for the mother. The etiology is unclear, but genetic, hormonal and environmental factors influence the prevalance of the disease. The best treatment is to reduce bile acid levels. Higher bile acid levels are related with more severe fetal complications. Recently, UDCA is the most efficient treatment for good fetal and maternal outcome. Timing of delivery should be individualized and balanced with prematurity and maternal-fetal complications.

REFERENCES

[1] Laatikainen T, Tulenheimo A (1984) Maternal serum bile acid levels and fetal distress in cholestasis of pregnancy. Int J Gynaecol Obstet 22: 91–94.

[2] Bacq Y, Sapey T, Brechot MC, Pierre F, Fignon A, Dubois F. Intrahepatic cholestasis of pregnancy: a French prospective study. Hepatology 1997;26:358-364.

[3] Davies MH, da Silva RCMA, Jones SR et al. Fetal mortality associated with cholestasis of pregnancy and the potential benefit of therapy with ursodeoxycholic acid. Gut 1995;37:580–584.

[4] Bacq Y. Intrahepatic cholestasis of pregnancy. Clin Liver Dis 1999; 3:1.

[5] Reyes H, Sjövall J. Bile acids and progesterone metabolites in intrahepatic cholestasis of pregnancy. Ann Med 2000;32;94– 106.

[6] Reyes H, Gonzalez MC, Ribalta J, et al. Prevalence of intrahepatic cholestasis of pregnancy in Chile. Ann Intern Med 1978; 88:487.

[7] Wikström Shemer E, Marschall HU, Ludvigsson JF, Stephansson O. Intrahepatic cholestasis of pregnancy and associated adverse pregnancy and fetal outcomes: a 12-year population-based cohort study. BJOG 2013; 120:717.

[8] Gonzalez MC, Reyes H, Arrese M, Figueroa D, Lorca B, Andresen M, Segovia N, Molina C, Arce S. Intrahepatic cholestasis of pregnancy in twin pregnancies. J Hepatol 1989;9: 84-90.

[9] Rioseco AJ, Ivankovic MB, Manzur A, Hamed F, Kato SR, Parer JT, Germain AM. Intrahepatic cholestasis of pregnancy: a retrospective case-control study of perinatal outcome. Am J Obstet Gynecol 1994; 170: 890-895.

[10] Koivurova S, Hartikainen AL, Karinen L, Gissler M, Hemminki E, Martikainen H, Tuomivaara L, Järvelin MR. The course of pregnancy and delivery and the use of maternal healthcare services after standard IVF in Northern Finland 1990-1995. Hum Reprod 2002; 17: 2897-2903.

[11] Johnson P, Samsioe G, Gustafson A. Studies in cholestasis of pregnancy. I. Clinical aspects and liver function tests. Acta Obstet Gynecol Scand 1975; 54: 77-84.

[12] Paternoster DM, Fabris F, Palù G, Santarossa C, Bracciante R, Snijders D, Floreani A. Intrahepatic cholestasis of pregnancy in hepatitis C virus infection. Acta Obstet Gynecol Scand 2002; 81: 99-103.

[13] Williamson C, Hems LM, Goulis DG, Walker I, Chambers J, Donaldson O, Swiet M, Johnston DG. Clinical outcome in a series of cases of obstetric cholestasis identified via a patient support group. BJOG 2004; 111: 676-681.

[14] Dixon PH, Williamson C. The molecular genetics of intrahepatic cholestasis of pregnancy. Obstet Med 2008; 1:65-71.

[15] Arrese M, Macias RI, Briz O, Perez MJ, Marin JJ. Molecular pathogenesis of intrahepatic cholestasis of pregnancy. Expert Rev Mol Med 2008;10:e9.

[16] Nicolaou M, Andress EJ, Zolnerciks JK, Dixon PH, Williamson C, Linton KJ. Canalicular ABC transporters and liver disease. J Pathol (Internet) 2012; 226(2):300–315.

[17] Anzivino C, Odoardi MR, Meschiari E, Baldelli E, Facchinetti F, Neri I et al. ABCB4 and ABCB11 mutations in intrahepatic cholestasis of pregnancy in an Italian population. Dig Liver Dis (Internet) 2013 (cited 29 Oct 2013) 45(3): 226–232.

[18] Bacq Y, Gendrot C, Perrotin F, et al. ABCB4 gene mutations and single-nucleotide polymorphisms in women with intrahepatic cholestasis of pregnancy. J Med Genet 2009;46:711.

[19] Gonzalez MC, Reyes H, Arrese M, Figueroa D, Lorca B, Andresen M, Segovia N, Molina C, Arce S. Intrahepatic cholestasis of pregnancy in twin pregnancies. J Hepatol 1989;9: 84-90.

[20] Stieger B, Fattinger K, Madon J, Kullak-Ublick GA, Meier PJ. Drug- and estrogen-induced cholestasis through inhibition of the hepatocellular bile salt export pump (Bsep) of rat liver. Gastroenterology 2000; 118: 422-430.

[21] Bacq Y, Sapey T, Bréchot MC, et al. Intrahepatic cholestasis of pregnancy: a French prospective study. Hepatology 1997; 26:358.

[22] Geenes V, Williamson C. Intrahepatic cholestasis of pregnancy. World J Gastroenterol 2009 May 7; 15(17): 2049-2066.

[23] Knox TA, Olans LB. Liver disease in pregnancy. N Engl J Med 1996;335:569–576.

[24] Kenyon AP, Piercy CN, Girling J, et al. Obstetric cholestasis, outcome with active management: a series of 70 cases. BJOG 2002; 109:282.

[25] Berg B, Helm G, Petersohn L, Tryding N. Cholestasis of pregnancy. Clinical and laboratory studies. Acta Obstet Gynecol Scand 1986; 65: 107-113.

[26] Reyes H, Radrigan ME, Gonzalez MC, Latorre R, Ribalta J, Segovia N, Alvarez C, Andresen M, Figueroa D, Lorca B. Steatorrhea in patients with intrahepatic cholestasis of pregnancy. Gastroenterology 1987; 93: 584-590.

[27] Shaw D, Frohlich J, Wittmann BA, Willms M. A prospective study of 18 patients with cholestasis of pregnancy. Am J Obstet Gynecol 1982; 142: 621-625.

[28] Goulis DG, Walker IA, de Swiet M, Redman CW, Williamson C. Preeclampsia with abnormal liver function tests is associated with cholestasis in a subgroup of cases. Hypertens Pregnancy 2004; 23: 19-27.

[29] Heikkinen J, Mäentausta O, Ylöstalo P, Jänne O. Changes in serum bile acid concentrations during normal pregnancy, in patients with intrahepatic cholestasis of pregnancy and in pregnant women with itching. Br J Obstet Gynaecol 1981; 88:240.

[30] Heikkinen J. Serum bile acids in the early diagnosis of intrahepatic cholestasis of pregnancy. Obstet Gynecol 1983; 61: 581-587.

[31] Walker IA, Nelson-Piercy C, Williamson C. Role of bile acid measurement in pregnancy. Ann Clin Biochem 2002; 39:105-113.

[32] Wójcicka-Jagodzińska J, Kuczyńska-Sicińska J, Czajkowski K, Smolarczyk R. Carbohydrate metabolism in the course of intrahepatic cholestasis in pregnancy. Am J Obstet Gynecol 1989; 161: 959-964.

[33] Jiang ZH, Qiu ZD, Liu WW, Liu YH, Wang QN, Miao HZ, Zhou ZC, Wu XL, Xu BY, Gu CH. Intrahepatic cholestasis of pregnancy and its complications. Analysis of 100 cases in Chongqing area. Chin Med J (Engl) 1986; 99: 957-960.

[34] Ylötalo P, Kirkinen P, Heikkinen J, Mäentausta O.Gallbladder volume in cholestasis of pregnancy. N Engl J Med 1981; 304: 359.

[35] Ikonen E. Jaundice in Late Pregnancy. Acta Obstet Gynecol Scand 1964; 43 Suppl 5: 1-130.

[36] Hirvioja ML, Kivinen S. Inheritance of intrahepatic cholestasis of pregnancy in one kindred. Clin Genet 1993; 43:315.

[37] EASL Clinical Practice Guidelines: management of cholestatic liver diseases. J Hepatol 2009;51:237-267.

[38] Joutsiniemi T, Timonen S, Linden M, Suvitie P, Ekblad U. Intrahepatic cholestasis of pregnancy: observational study of the treatment with low-dose ursodeoxycholic acid. BMC Gastroenterology (2015) 15:92. doi: 10.1186/s12876-015-0324-0.

[39] Palma J, Reyes H, Ribalta J, Iglesias J, Gonzalez M, Hernandez I et al. Effects of ursodeoxycholic acid in patients with intrahepatic cholestasis of pregnancy. Hepatology. 1992;15:1043–7.

[40] Meng LJ, Reyes H, Axelson M, et al. Progesterone metabolites and bile acids in serum of patients with intrahepatic cholestasis of pregnancy: effect of ursodeoxycholic acid therapy. Hepatology 1997; 26:1573.

[41] Floreani A, Paternoster D, Grella V, Sacco S, Gangemi M, Chiaramonte M. Ursodeoxycholic acid in intrahepatic cholestasis of pregnancy. Br J Obstet Gynaecol 1994; 101: 64-65.

[42] Berkane N, Cocheton JJ, Brehier D, Merviel P, Wolf C, Lefèvre G, Uzan S. Ursodeoxycholic acid in intrahepatic cholestasis of pregnancy. A retrospective study of 19 cases. Acta Obstet Gynecol Scand 2000; 79: 941-946.

[43] Glantz A, Reilly SJ, Benthin L, Lammert F, Mattsson LA, Marschall HU. Intrahepatic cholestasis of pregnancy: Amelioration of pruritus by UDCA is associated with decreased progesterone disulphates in urine. Hepatology 2008; 47: 544-551.

[44] Kondrackiene J, Beuers U, Kupcinskas L. Efficacy and safety of ursodeoxycholic acid versus cholestyramine in intrahepatic cholestasis of pregnancy. Gastroenterology 2005;129:894-901.

[45] Lutz EE, Margolis AJ. Obstetric hepatosis: treatment with cholestyramine and interim response to steroids. Obstet Gynecol 1969; 33: 64-71.

[46] Sadler LC, Lane M, North R. Severe fetal intracranial haemorrhage during treatment with cholestyramine for intrahepatic cholestasis of pregnancy. Br J Obstet Gynaecol 1995; 102: 169-170.

[47] Hirvioja ML, Tuimala R, Vuori J. The treatment of intrahepatic cholestasis of pregnancy by dexamethasone. Br J Obstet Gynaecol 1992; 99: 109-111.

[48] Bloom SL, Sheffield JS, McIntire DD, Leveno KJ. Antenatal dexamethasone and decreased birth weight. Obstet Gynecol 2001; 97: 485-490.

[49] Stramentinoli G, Di Padova C, Gualano M, Rovagnati P, Galli-Kienle M. Ethynylestradiol-induced impairment of bile secretion in the rat: protective effects of S-adenosyl-L-methionine and its implication in estrogen metabolism. Gastroenterology 1981; 80: 154-158.

[50] Nicastri PL, Diaferia A, Tartagni M, Loizzi P, Fanelli M. A randomised placebo-controlled trial of ursodeoxycholic acid and S-adenosylmethionine in the treatment of intrahepatic cholestasis of pregnancy. Br J Obstet Gynaecol 1998; 105:1205-1207.

[51] Glantz A, Marschall HU, Mattsson LA. Intrahepatic cholestasis of pregnancy: Relationships between bile acid levels and fetal complication rates. Hepatology 2004; 40:467.

[52] Marin JJ, Serrano MA, el-Mir MY, Eleno N, Boyd CA. Bile acid transport by basal membrane vesicles of human term placental trophoblast. Gastroenterology 1990; 99: 1431-1438.

[53] Falconer JD, Smith AN, Eastwood MA. The effects of bile acids on colonic motility in the rabbit. Q J Exp Physiol Cogn Med Sci 1980; 65: 135-144.

[54] Shaw D, Frohlich J, Wittmann BA, Willms M. A prospective study of 18 patients with cholestasis of pregnancy. Am J Obstet Gynecol 1982; 142: 621-625.

[55] Williamson C, Gorelik J, Eaton BM, Lab M, de Swiet M, Korchev Y. The bile acid taurocholate impairs rat cardiomyocyte function: a proposed mechanism for intrauterine fetal death in obstetric cholestasis. Clin Sci (Lond) 2001; 100: 363-369.

[56] Reid R, Ivey KJ, Rencoret RH, Storey B. Fetal complications of obstetric cholestasis. Br Med J 1976; 1: 870-872.

[57] Glantz A, Marschall HU, Mattsson LA. Intrahepatic cholestasis of pregnancy: Relationships between bile acid levels and fetal complication rates. Hepatology 2004; 40:467-474.

[58] Zecca E, De Luca D, Marras M, Caruso A, Bernardini T, Romagnoli C. Intrahepatic cholestasis of pregnancy and neonatal respiratory distress syndrome. Pediatrics 2006; 117: 1669-1672.

[59] Williamson C, Miragoli M, Sheikh Abdul Kadir S, et al. Bile acid signaling in fetal tissues: implications for intrahepatic cholestasis of pregnancy. Dig Dis 2011; 29:58.

[60] Reid R, Ivey KJ, Rencoret RH, Storey B. Fetal complicationsof obstetric cholestasis. Br Med J 1976; 1: 870-872.

[61] Royal College of Obstetricians and Gynaecologists. Obstetric cholestasis. RCOG guidelines 2011;N_43:Available at: www.rcog.org.uk.

[62] Saleh MM, Abdo KR. Consensus on the management of obstetric cholestasis: National UK survey. BJOG 2007; 114:99.

[63] 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.

[64] Rook M, Vargas J, Caughey A, et al. Fetal outcomes in pregnancies complicated by intrahepatic cholestasis of pregnancy in a Northern California cohort. PLoS One 2012; 7:e28343.

[65] Kawakita T, Parikh LI, Ramsey PS, et al. Predictors of adverse neonatal outcomes in intrahepatic cholestasis of pregnancy. Am J Obstet Gynecol 2015; 213:570.e1.

[66] Geenes V, Chappell LC, Seed PT, et al. Association of severe intrahepatic cholestasis of pregnancy with adverse pregnancy outcomes: a prospective population-based case-control study. Hepatology 2014; 59:1482.