World Journal of Gastroenterology

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DOI: 10.3748/wjg.v21.i23.7134

World J Gastroenterol 2015 June 21; 21(23): 7134-7141
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

Review of a challenging clinical issue: Intrahepatic cholestasis of pregnancy

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Author contributions: Ozkan S and Ozkan OV designed and wrote the article; Ozkan S, Ceylan Y and Yildirim S reviewed and summarized the literature data, and wrote the paper; Ozkan OV helped to write the manuscript and performed final preparations before submitting the manuscript.

Conflict-of-interest: No potential conflicts-of-interest relevant to this article were reported.

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Received: January 27, 2015
Peer-review started: January 27, 2015
First decision: February 10, 2015
Revised: March 4, 2015
Accepted: April 17, 2015
Article in press: April 17, 2015
Published online: June 21, 2015

Abstract

Intrahepatic cholestasis of pregnancy (ICP) is a reversible pregnancy-specific cholestatic condition characterized by pruritus, elevated liver enzymes, and increased serum bile acids. It commences usually in the late second or third trimester, and quickly resolves after delivery. The incidence is higher in South American and Scandinavian countries (9.2%-15.6% and 1.5%, respectively) than in Europe (0.1%-0.2%). The etiology is multifactorial where genetic, endocrine, and environmental factors interact. Maternal outcome is usually benign, whereas fetal complications such as preterm labor, meconium staining, fetal distress, and sudden intrauterine fetal demise not infrequently lead to considerable perinatal morbidity and mortality. Ursodeoxycholic acid is shown to be the most efficient therapeutic agent with proven safety and efficacy. Management of ICP consists of careful monitoring of maternal hepatic function tests and serum bile acid levels in addition to the assessment of fetal well-being and timely delivery after completion of fetal pulmonary maturity. This review focuses on the current concepts about ICP based on recent literature data and presents an update regarding the diagnosis and management of this challenging issue.

Key words: Intrahepatic; Cholestasis; Pregnancy; Diagnosis; Management

Core tip: Intrahepatic cholestasis of pregnancy (ICP) is a unique hepatic disorder in pregnancy characterized by pruritus, elevated liver enzymes, and serum bile acids. It usually appears in the third trimester and dissolves rapidly after delivery. The incidence is variable between 0.1%-15.6% in different geographic regions of the world. Genetic, hormonal, and environmental factors interact in its etiopathogenesis. A considerable incidence of perinatal morbidity-mortality makes it one of the most concerning obstetric entities for obstetricians and critical care specialists. Timely diagnosis

and expert multidisciplinary management of pregnant women with ICP is mandatory to ensure a favorable maternal-fetal outcome.

Ozkan S, Ceylan Y, Ozkan OV, Yildirim S. Review of a challenging clinical issue: Intrahepatic cholestasis of pregnancy. *World J Gastroenterol* 2015; 21(23): 7134-7141 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i23/7134.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i23.7134

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a unique hepatic disorder in pregnancy characterized by mild to severe pruritus and disturbed liver function tests[1-6]. ICP is a reversible form of cholestasis (impaired bile flow) appearing mainly in the late second or third trimester of pregnancy, and tends to dissolve rapidly after delivery[3,7,8]. Incidence varies geographically between 0.1%-15.6%[3,9-11]. It is the second most frequent cause of jaundice in pregnancy following viral hepatitis[12]. Etiology seems to be multifactorial, with a combination of hormonal and environmental factors superimposing on a genetic predisposition[13]. Maternal prognosis is usually good, with intractable pruritus and a higher predisposition to postpartum bleeding being the leading causes of maternal morbidity. On the other hand, ICP is associated with increased fetal morbidity and mortality, particularly with regards to preterm delivery, fetal distress, and sudden intrauterine fetal death[12,14]. It appears to be of utmost importance to establish a clinical awareness with respect to the potential adverse fetal outcome in ICP and consider it as a high-risk pregnancy disorder. An early and accurate diagnosis with an appropriate medical intervention is mandatory for an improved fetal prognosis. The present article reviews the recent literature data and current concepts for ICP, and provides a 2014 update regarding the diagnosis and management of this challenging issue.

EPIDEMIOLOGY

ICP is significantly more frequent in South Asian (0.8%-1.46%) and South American populations (*e.g.*, Chile and Bolivia) (9.2%-15.6%)[8]. In Europe, the prevalence has been estimated to be 0.1% to 0.2%, with a higher incidence in Scandinavian countries (1.5% in Sweden)[9]. Advanced maternal age (> 35 years), multiparity, family clustering (*e.g.*, the higher prevalence in the Mapuche), ICP history in previous pregnancy, and a history of oral contraceptive use are found to be associated with an increased incidence of ICP[3,11,15]. The recurrence rate has been reported to be between 40%-60% and varying in intensity in subsequent pregnancies in a random manner[2,15,16].

ETIOLOGY AND PATHOGENESIS

The etiology of ICP is multifactorial, and involves genetic, hormonal, and environmental factors[3,4,14,16].

Estrogens and progesterone metabolites have been demonstrated to have role in the pathogenesis of ICP.

The disease usually appears in the third trimester of pregnancy when estrogen production reaches its maximum levels. The prevalence of ICP is five times greater in multiple pregnancies, which are associated with higher levels of estrogens in comparison with singleton pregnancies[5]. ICP is similar to the cholestatic situation which has been shown to occur in some women using oral contraceptives with high estrogen content. A high level of estrogen in genetically-predisposed individuals may be inducing intrahepatic cholestasis by impaired sulfation and the transport of bile acids[6].

The role of progesterone with respect to the pathogenesis of ICP seems to be still unclarified. Patients with ICP might have been presenting a selective defect in the secretion of sulfated progesterone metabolites into bile due to the genetic polymorphism of canalicular transporters for steroid sulfates or their regulation[17].

Family clustering, presence of ethnic and geographic variations, and recently demonstrated mutations in gene coding for hepatobiliary transport proteins indicate a genetic predisposition in ICP[5,18].

ICP-associated gene has been reported to be located in the p23 region of chromosome 2[19].

Genetic predisposition may lead to altered cell membrane composition of bile ducts and hepatocytes, as well as the subsequent dysfunction of biliary canalicular transporters[9]. Mutations in the hepatic phospholipid transporter (MDR3/ABCB4), aminophospholipid transporter (ATP8B1/FIC1), and bile salt export pump (BSEP/ABCB11) have been found in patients with ICP[2,5,6,8,9,18,20-24].

Class Ⅲ multidrug resistance P-glycoproteins (MDR3/ABCB4) are canalicular phospholipid translocators acting in biliary phosphatidylcholine excretion. ABCB4 mutations subsequent to loss of canalicular MDR3 protein are associated with low levels of phospholipids in bile and a high biliary cholesterol saturation index[24].

The bile salt export pump (BSEP/ABCB11) is a member of the ATP-binding cassette superfamily and the major transporter responsible for bile salt secretion from hepatocytes into bile in humans[24].

High GGT levels were shown in the majority of ICP subjects with MDR3 mutations, while BSEP mutations were postulated in low GGT cases[25]. Combined variants of MDR3 and BSEP mutations may be associated with severe phenotypic expression of ICP.

Genetic variation in ATP8B1 which encodes phosphatidylserine flippase FIC1 has been identified in a small number of ICP cases[5].

Placental expression of other bile acid transporters

(*e.g.*, OATP1A2, OATP1B1, and OATP1B3) were also found to be downregulated in ICP, indicating a potential role in the pathogenesis of ICP[26].

Placental gene expression profiles of ICP cases also revealed that the core regulatory genes were mainly included in immune response, the VEGF signaling pathway, and G-protein coupled receptor signaling, implying essential roles for immune response and angiogenesis in the pathophysiology of ICP[27].

Floreani *et al*[25] suggested that the GABA system had an active role in the pathophysiology of ICP upon finding GABRA2 gene upregulation in those cases. The same researchers demonstrated the downregulation of KIFC as a potentially protective mechanism to counteract increased bile salts[25].

ICP-associated single nucleotide polymorphisms in the xenobiotic receptor, pregnane X receptor (encoded by NR1I2), were identified in South American women[5]. Bile acid homeostasis and transport in hepatocytes are found to be tightly regulated by the nuclear hormone receptor, farnesoid X receptor, encoded by NR1H4. Four rare heterozygous variants in farnesoid X receptor have been described in ICP[5].

Recent advancements in the detection of fetal DNA in maternal plasma uncovered emerging evidence regarding the correlation of this fetal DNA in maternal blood with a number of obstetric complications. Yi *et al*[28] demonstrated that elevated circulating hypermethylated RAS-association domain family 1, isoform A (RASSF1A) gene sequences might be used as a diagnostic marker for ICP[28].

Environmental factors, such as geographic and seasonal conditions, may induce ICP in genetically-susceptible individuals[6]. A higher number of cases in January may suggest a higher incidence of ICP in winter[6,7]. Seasonal variations of the disease have been attributed to dietary factors related with high maternal levels of copper and low levels of selenium and zinc[17]. In spite of some data pointing out a potential role of long chain monounsaturated fatty acid erucic acid and low selenium levels regarding the etiopathogenesis of ICP, as well as selenium acting as a co-factor of a number of enzymes in oxidative metabolism in the liver, the definite role of selenium in bile secretion has yet to be elucidated, thus further research is required[15,17,29,30].

ICP is shown to be associated with poor perinatal outcome and increased risk of preterm labor, fetal distress, and sudden intrauterine fetal death. Although the pathophysiology of fetal risk has yet to be clarified, an elevation in maternal-fetal bile acid flow and a reduced fetal capacity to eliminate bile acids through the immature fetal liver, in addition to altered placental function, appear to be responsible for impaired fetal-maternal bile acid transport in ICP[5]. Those phenomena contribute to an excess accumulation of hydrophobic bile acids that are hepatotoxic in the fetal compartment. Impaired fetal-maternal transport of bile acids across the placenta and the inability of the fetus to excrete cholic acid leads to an accumulation of bile acids and fetal cardiotoxicity, thus causing fetal dysrhythmia and sudden intrauterine fetal demise[31].

Transplacental passage of excess bile acids in ICP may be related with intrauterine fetal death in terms of inducing oxidative stress in the placenta and impaired fetal cardiomyocyte function[32]. Autopsy findings of fetuses lost in ICP cases have been found to be consistent with acute anoxia, but with no signs of chronic anoxia. A major increase in meconium staining of the amniotic fluid is an additional finding of acute anoxia. Cholic acid infusion in sheep has been shown to stimulate meconium passage, which is subsequently associated with acute umbilical vein constriction[7]. Bile acids, especially cholic acid, have been found to induce vasoconstriction in human placental chorionic veins *in vitro* and umbilical vein constriction. Those findings related with meconium passage and vasoconstriction of umbilical veins might explain fetal hypoxia, meconium inhalation, and even neonatal death in those cases[5-7]. Adequate birthweights and normal Doppler findings of those fetuses in ICP suggest that fetal death is not the consequence of chronic placental insufficiency. Additionally, taurocholic acid has been shown to decrease rat cardiomyocyte contractions, thus causing loss of synchronous beating. These acquired data may be indicating a direct effect of bile acids with respect to sudden intrauterine fetal demise in ICP[5-7]. It appears to be a satisfactory conclusion that acute fetal hypoxia subsequent to a placental ischemic event or umbilical vasoconstriction is mediated by pathophysiological phenomena induced by bile acids.

The etiopathogenetic mechanism of premature labor in ICP still remains to be elucidated[1]. Elevated levels of bile acids have been suggested to stimulate myometrial contractions and increase oxytocin bioactivity triggering preterm labor[11,33]. Additionally, increased prostaglandin secretion and modified synthesis (transformation of 16α-hydroxylate dehydroepiandrosterone into estradiol) may be related with labor induction.

Hemorrhagic complications due to vitamin K deficiency may contribute to fetal mortality.

Since it is difficult to predict fetal outcome via standard fetal cardiac monitoring tests, it is best to deliver the fetus as soon as fetal pulmonary maturity is confirmed.

CLINICAL FEATURES

ICP is characterized by mild to severe pruritus starting after the 30th week of gestation, which usually dissolves within 48 h following the delivery of the fetus[12]. It is frequently generalized on the palms and soles, and gets worse at night. Skin rash is characteristically lacking, with the exception of excoriations due to scratching[5-7]. Jaundice is uncommon in ICP, but may develop 1-4 wk after the onset of pruritus, with an incidence of 14%-25%[1]. Insomnia, fatigue, anorexia,

malaise, weight loss, epigastric discomfort, steatorrhea due to malabsorption of fat, and dark urine are the other symptoms and signs associated with ICP[15,29,34].

The diagnosis of ICP requires the exclusion of other clinical entities which are included in the differential diagnosis of cholestasis and hepatic disease. Viral hepatitis, autoimmune liver disease, gall bladder stones, tumors of the hepatobiliary tract, and a number of causes with elevated hepatic enzymes specified to pregnancy (*e.g.*, namely preeclampsia, HELLP syndrome, and acute fatty liver) should be considered in the differential diagnosis[15,29,35].

ICP is associated with elevated total bile acid levels of up to 10- to 25-fold, which may be the first, or indeed only, laboratory abnormality observed[3,13,15,35]. A significant rise in cholic acid and a decline in chenodeoxycholic acid levels leading to a marked elevation in the cholic/chenodeoxycholic acid ratio may be detected. A reduced glycine/taurine ratio may also be present[4,36]. A serum bile acid profile presenting increased total bile acids (> 11 μmol/L), enhanced cholic acid percentage (> 42%), and decreased glycine/taurine bile acid ratio to < 1 are used in the differential diagnosis[5-7]. A mild elevation in liver enzymes may be detected in up to 60% of the subjects[1]. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels rarely exceed two times the upper limits of normal pregnancy[8,11]. GGT levels are found to be increased in less than 1/3 of the cases, indicating a greater impairment of hepatic function[20]. Hyperbilirubinemia, which rarely reaches 6 mg/dL, may be another laboratory finding with an incidence of 25%[3,11]. Serum alkaline phosphatase (AP) levels may be elevated up to 4-fold, but does not contribute much to the diagnosis, as AP increase in pregnancy is already expected physiologically[8]. A liver biopsy, although not recommended for the diagnosis, would just show a normal hepatic parenchyma with widening of the bile canaliculi, pure centrilobular cholestasis without inflammation, bile plugs in the hepatocytes, and canaliculi predominantly present in ZONE 3[3,15,35,36]. Liver biopsy is indicated in cases of jaundice with no pruritus, the beginning of symptoms before 20 wk of gestation, and sustained abnormal laboratory findings beyond 8 wk after delivery[36].

MANAGEMENT OF ICP

The mainstays of managing ICP cases appear to be reducing the maternal symptoms and offering satisfactory obstetric care in order to avoid fetal distress and sudden intrauterine fetal demise.

MATERNAL OUTCOME

Maternal outcome is usually benign. In addition to pruritus treatment, proper attention should be provided for fatigue, anxiety, and malabsorption of fat and fat-soluble vitamins. Malabsorption due to persistent cholestasis may result in vitamin K deficiency, leading to intrapartum and postpartum hemorrhage[36]. Thus rest, mild sedation, and a low fat diet may be recommended alongside parenteral administration of vitamin K[37].

Pruritus is usually relieved within 48 h after delivery of the fetus, accompanied by normalization of serum bile acid concentrations and other liver enzyme levels. The recurrence rate is high (45%-70%), but not inevitable. If pruritus and elevated liver enzymes continue beyond a month after the delivery, chronic liver diseases such as primary biliary cirrhosis, primary sclerosing cholangitis, or chronic hepatitis should be considered[35]. In spite of the presence of hormonal issues in the pathogenesis, the use of combined oral contraceptives in women with a past history of ICP is not contraindicated after the normalization of biochemical tests following the delivery[6,12,35]. Breastfeeding is not contraindicated[35].

Those women with a history of ICP deserve a close clinical follow-up, since they are found to be significantly more likely to be diagnosed with gall bladder stones, pancreatitis, cirrhosis, or another disorder of the hepatobiliary tract in the future[15,37,38].

FETAL OUTCOME

ICP poses a significant risk for the fetus in terms of perinatal morbidity-mortality, preterm delivery, fetal distress, and meconium staining[11,35,39]. The rates of fetal malformations and abortions are not shown to be increased, and fetal birthweight for gestational age appears to be adequate in ICP[11].

The incidence of meconium staining of amniotic fluid is 25% to 45%, whereas acute fetal distress, preterm delivery, and intrauterine fetal death have been demonstrated to occur in 22%, 44%, and 2% of the patients, respectively[2,12].

Fetal prognosis was not shown to be correlated with the severity of maternal signs and symptoms[27]. However, some studies have suggested that higher serum levels of bile acids might be related with increased fetal mortality. Glantz *et al*[10] have reported a significant correlation between higher serum bile acid levels (≥ 40 μmol/L) and adverse fetal outcome. Since they determined no increase in fetal complications in cases of serum bile acid levels < 40 μmol/L, they proposed expectant management for those cases[10]. Although essential, close monitoring of bile acid serum levels and liver enzymes does not definitely prevent acute fetal distress and sudden intrauterine fetal death[12].

Fagan[34] suggested a weekly non-stress test, estimation of amniotic fluid volume, and umbilical artery Doppler ultrasonographic examination, together with regular growth scans from 30 wk of gestation to delivery in ICP cases. Maternal liver tests (bile acids and liver enzymes) and blood clotting tests should be studied weekly[34].

Table 1 Pharmacologic treatment of intrahepatic cholestasis of pregnancy is summarized

Pharmacologic agent	Mechanism of action	Dosing	Clinical effects	Pregnancy risk
Ursodeoxycholic acid	Hydrophilic bile acid that replaces more cytotoxic bile acids Protects bile ducts by detoxifying hydrophobic bile acids	15 mg/kg per day or 500 mg twice a day	Improves pruritus, decreases elevated liver enzymes and bile acid levels, improves fetal outcome Safe use in pregnancy, no side effects	C
Cholestyramine	Binds bile salts and cuts off their enterohepatic circulation and increases their fecal excretion	8-16 g/d	Decreases pruritus with no effect on biochemical parameters and fetal outcome Non-palatable, constipation Fat-soluble vitamin deficiency	C
S-adenosyl methionine	Affects the composition and fluidity of hepatocyte membranes Increases methylation and biliary excretion of hormone metabolites	1000 mg/d	Treats pruritus variably	C
Dexamethasone	Suppresses fetal production of estrogen reducing bile acid levels	12 mg/d	Less effective in decreasing pruritus and bile acid levels	B
Phenobarbital	Induces hepatic enzymes to reduce the bile acids	2-5 mg/kg per day orally	Decreases pruritus 50%, no beneficial effects regarding the laboratory tests, no change in fetal outcome	C
Anti-histaminics	Manages pruritus by antihistaminic effects	25-50 mg/d	Decreases pruritus, no effect on liver enzymes and fetal outcome	C

The general agreement suggests that delivery should not be delayed after 37-38 wk of gestation in patients with ICP[8,11,12,19,29,40-45]. In spite of widespread acceptance of active management of ICP in terms of delivering the fetus < 39 wk of gestation, not all obstetric professionals agree with the concept of active management in ICP[41]. Unfortunately, randomized clinical trials to support active management with labor induction to prevent intrauterine fetal demise and consensus for obstetric management in ICP are lacking[29,46,47]. Due to the absence of evidence-based recommendations, the decision to induce labor should be established individually after comparing the risk of prematurity and morbidity with that of intrauterine fetal demise. The Royal College of Obstetricians and Gynecologists does not endorse routine active management in ICP, since they have reported that there has been no evidence to support or refute the practice of active management, and instead suggested individualized management for those women in 2006[48]. On the other hand, the American College of Obstetricians and Gynecologists supports active management protocols in ICP[49]. Henderson *et al*[48] conducted a systematic review involving 16 articles published between 1986 and 2011 regarding this obstetric controversy, and were unable to find evidence supporting the practice of active management of ICP. They have recommended individualized management that provides informed decision-making guidance for the patient, rather than the routine implementation of an active management protocol. Scientific evidence, including the risks and benefits of the available management options, should be presented to the patient in a clear manner by the health care providers.

PHARMACOLOGIC TREATMENT

The aim of the pharmacologic treatment in ICP is to reduce the maternal symptoms and prevent fetal distress or sudden fetal death. Pharmacologic treatment of ICP is summarized in Table 1.

Recently, ursodeoxycholic acid (UDCA) (500 mg twice a day or 15 mg/kg per day) has been suggested to be the most efficient treatment for ICP[10,35,50,51]. UDCA is a naturally hydrophilic bile acid. It stimulates the detoxification of hydrophobic bile acids and protects the bile ducts. UDCA decreases high cholic acid levels while increasing chenodeoxycholic acid levels, restoring the reduced glycine/taurine ratio[9,10]. UDCA reduces cholic acid and chenodeoxycholic acid levels in the amniotic fluid by repairing maternal-placental bile acid transport. It displays a protective role for hepatocytes and cholangiocytes against the toxic effects of bile acids[22], and is shown to be cardioprotective for the fetus against the toxic effects of bile acids[8]. No maternal or fetal adverse effects have been reported regarding the use of UDCA in ICP, thus indicating its safe use in the third trimester[34,52]. Protection against injury of bile ducts by hydrophobic bile acids, replacement of hepatotoxic bile acids, immune modulation, cytoprotection by preventing apoptosis, choleretic activity, and stimulated secretion of potentially hepatotoxic compounds by the liver (thereby inhibiting the absorption of more cytotoxic bile acids) have been suggested as the mechanisms of action that UDCA presents[5-7,22].

Cholestyramine binds bile salts, cuts off their enterohepatic circulation, and increases their fecal excretion. Clinical data from a variable number of

studies have pointed out that, in spite of an improved maternal morbidity rate, cholestyramine does not correct the impaired biochemical parameters and provide a better fetal outcome[53]. It is not palatable, requires frequent dosing (8-16 g/d), and causes constipation. Cholestyramine may cause malabsorption of dietary lipids and fat-soluble vitamins, especially vitamin K, thus leading to a potential risk of antepartum and postpartum maternal bleeding[53]. Vitamin K (10 mg/d) should be used throughout pregnancy in order to avoid those hemorrhagic complications[36].

S-Adenosyl-L-methionine is the principal glutathione precursor and methyl group donor involved in the synthesis of phosphatidylcholine. It not only influences the composition and fluidity of hepatocyte plasma membranes, but also increases the methylation and biliary excretion of hormone metabolites. It has been shown variably treating pruritus (1000 mg/d), with a drop-off for jaundice[35,54].

Phenobarbital was once considered to be an alternative therapeutic option for ICP, but could relieve pruritus in only 50% of the cases and did not show beneficial effects with respect to laboratory parameters[9].

High-dose dexamethasone (12 mg/d) has been demonstrated to act in the correction of cholestatic symptoms and laboratory findings[55]. It has been shown to be less effective in reducing bile acids and bilirubin, and is ineffective in relieving pruritus[55].

Antihistamines (*e.g.*, hydroxyzine, 25-50 mg/d, promethazine, chlorpheniramine, and terfenadine) may be used to relieve pruritus through their sedating effects, especially in case of nocturnal itching[36].

Aqueous cream with 1% menthol may help alleviating pruritus[14].

Rifampin has been shown as an effective agent in alleviating pruritus in 77% of cases in a recent meta-analysis[56].

Plasmapheresis has been suggested to be useful in treating severe cholestasis, but was unresponsive to medical treatment in a few case reports[15,57].

CONCLUSION

ICP is a unique hepatic disorder in pregnancy. Genetic, hormonal, and environmental factors seem to interact in its etiopathogenesis, although the definite etiology still remains obscure. It is presented as a diagnosis of exclusion based on suspected clinical and laboratory data indicating a hepatic disorder specified to pregnancy. Alleviating the devastating symptoms of maternal itching, preventing antenatal and intrapartum hemorrhagic complications, providing close maternal-fetal surveillance in order to avoid fetal complications (*i.e.*, namely fetal distress, sudden intrauterine fetal demise, and preterm delivery) are the mainstays of managing ICP. UDCA is the best available therapeutic agent, with proven safety and efficacy in alleviating pruritus and restoring abnormal levels of serum bile acids and hepatic function tests. Prompt and correct diagnosis with appropriate medical intervention is mandatory for improved fetal prognosis. Further large-scale clinical trials with rigorous scientific design are required to raise a comprehensive evidence-based approach to establishing management strategies for ICP.

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ISSN 1007-9327