INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP), a unique liver disease during pregnancy, is mostly described by pruritus connected with elevated serum bile acid or amino transferase levels. It occurs usually to the third trimester of pregnancy and improves itself after delivery. In 1970's the prevalence was reported highest in Bolivia and Chile, however, the prevalence in United States (US) ranges in between 0.3 to 5.6%, whereas, in Europe it is 0.5 to 1.5%. The awareness campaigns of the disease showed an increase in incidence in the high-incidence regions because of more reporting of the cases. Ursodeoxycholic acid (dose) is the treatment of choice for ICP. This treatment provides improved liver function and relief in pruritus and is considered safe during pregnancy. At the molecular level, it offers cytoprotection against hepatotoxic effects of hydrophobic bile acids, improves hepatobiliary bile acid transport, and decreases plasma bile acids. Moreover, to alleviate the pruritus; hydroxyzine or an aqueous cream with 1% methanol were used. ICP is a unique hepatic disorder in pregnancy with possibly an interaction of genetic, hormonal, and environmental factors in its etiopathogenesis, although the definite etiology still remains obscure.

DISCUSSION

Various animal studies have revealed that one of the actions of estrogens is cholestatic and is well established in ICP. On the other hand, a natural progesterone oral administration may increase the ICP risk. A genetic predisposition in ICP is an indication of code mutation of gene producing hepatobiliary transport proteins. "Studies show that heterozygous mutations in gene ABCB4, which encodes the hepatic phospholipid transporter multidrug resistance 3 (MDR3), have been detected in patients with ICP. This may also be due to family clustering and regional variations. Moreover, the genetic predisposition may cause an alteration in cell membrane composition of bile ducts and hepatocytes, and also the subsequent dysfunction of biliary canaliculartransporters. It is reported already that ICP-associated gene has been located in the 2p13 region of chromosome 2. In addition, environmental factors may be involved in the
expression of the disease.11

Clinical manifestations
The main symptom of ICP is pruritus which is painful and difficult for patients to tolerate. It appears approximately in 80% of women and presents itself after 30 weeks of gestation.21,22 The pruritus may be generalized but classically it appears on palmar and plantar aspects of hands and feet. Many women complain a variation in symptoms worsening at night and disturbance in sleep. Pruritus is usually relieved within 48h after delivery of the fetus, accompanied by normalization of serum bile acid concentrations and other liver enzyme levels. Its recurrence rate ranges between 40-70%. There would be of consideration for chronic liver diseases such as primary biliary cirrhosis, primary sclerosing cholangitis, or chronic hepatitis, liver enzymes if high and pruritus prolonged for a month after the delivery.18 In the presence of hormonal issues, the oral contraceptive use in women with ICP history is controversial even after biomedical tests normalization after delivery.24,25 Likewise Breastfeeding is not contraindicated. The women with risk or presence of gall bladder stones, pancreatitis, cirrhosis or any other related disorders and are more likely to be diagnosed require close clinical follow up if found with a history of ICP.26-28

Adverse Outcomes
ICP is linked with adverse outcomes including perinatal morbidity-mortality, preterm delivery, fetal distress, and meconium staining.29,30 It is difficult to calculate the real incidence of each adverse outcome due to the ICP diagnostic criteria differences, also to determine the precise nature of the risks for individual pregnancies. This might be due to the subject bias as almost all the published studies with these outcomes were studied retrospectively.

One of the studies conducted in Swedish women population showed a significant association between adverse perinatal outcomes and the maternal serum bile acid level in ICP.32 The incidences of spontaneous preterm birth, asphyxial events and meconium staining of the amniotic fluid, placenta or membranes, significantly increased in women with serum bile acids greater than 40 micromoles per liter at any time in pregnancy, compared with women with bile acids less than 40 micromoles per liter and women with pruritus gravidarum. Close monitoring of bile acid serum levels and liver enzymes does not definitely prevent acute fetal distress and sudden intrauterine fetal death.33 Other studies followed by this study conducted in different populations and support the increased meconium staining rates of amniotic fluid. Apgar scores at 5 minutes and preterm birth, the retrospective nature or small sample size in these studies make interpretation difficult. It is particularly difficult to assess the risk of stillbirth in ICP from these studies, as this is a rare event and reports of selected case series do not allow the calculation of true increased risks.34-40

Management of ICP
A twofold management of ICP suggested a) symptomatic therapy for the mother, and b) close surveillance and early delivery of the fetus.

Management of mother
Currently 10 to15 mg/kg/d of ursodeoxycholic acid (dose) is the treatment choice for ICP. Improved liver function, relief in pruritus is due to this treatment option and considered safe during pregnancy. At the molecular level, it offers cytoprotection against hepatotoxic effects of hydrophobic bile acids, improves hepatobiliary bile acid transport, and decreases plasma bile acid. Moreover, to alleviate the pruritus; hydroxyzine or an aqueous cream with 1% methanolwere used; it is observed that the treatment with chole- stamine and guar gum which are bile acid binders can also relieve the symptoms, but this therapy is worse in steatorrhea.41,42 The implication of different studies are that women with severe ICP need increased surveillance for adverse Para natal outcome and in most cases delivery has been recommended at 37-38 weeks of pregnancy.

Management of the fetus
The general conversation is that CTG and fetal kick count charting do not prevent IUD but may be a source of reassurance to mother with ICP and the obstetrician caring for her. Role of amniocentesis is considered as overly invasive by many obstetricians. With lack of evidences early delivery like in 37 weeks and fetal monitoring always remain a keystone in obstetric management. An even earlier delivery is advocated when cholestasis is severe.42 However, sudden IUFD cannot be avoided totally even with this approach.

Summary of pharmacological agents of ICP
The utmost purpose of any of the ICP pharmacologic treatment is not only to minimize the maternal symptoms but also to prevent fetal distress or sudden death. Pharmacologic treatment of ICP is summarized in Table 1.
Table 1: Pharmacologic Management of Intrahepatic Cholestasis of Pregnancy

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

An alternative therapeutic option for ICP was Phenobarbital, but could relieve pruritus in only 50% of the cases and did not show beneficial effects with respect to laboratory parameters.44 High-dose dexamethasone (12 mg/d) has been shown to be less effective in reducing bile acids and bilirubin. 32 This dosing is also a relief for pruritus.

**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. ICP is characterized by maternal pruritus with absence of skin rash, raised serum bile acids and abnormal liver function. It is a transient condition which resolves after birth but may cause hepatobiliary disorders in later life. Severe ICP is associated with meconium stained amniotic fluid, fetal asphyxia, neonatal unit admission, still birth and pre term delivery. The underlying mechanism of fetal complication are unclear but appear to relate with level of bile acids. The most effective pharmacological therapy to relieve maternal symptoms and improved biochemical abnormalities is UDCA(ursodeoxycholic acid). But definitive proof of its protective effect on fetus is unclear, in large trials undertaken. A common practices closed fetal surveillance antenataly and induction of labor at 37-38 weeks of gestation. Large randomized control trials are required to assess effective drug and implementation of best management to reduce adverse fetal outcome.

**REFERENCES**


