Intrahepatic Cholestasis of Pregnancy: An Intriguing Pregnancy-Specific Disorder

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OBJECTIVE: *To review animal and human data available regarding the etiology, maternal and fetal impact, and treatment of intrahepatic cholestasis of pregnancy (ICP).*

METHODS: *Pertinent studies on human and animal models of ICP were selected through a MEDLINE database search, focusing on etiology and clinical impact of the disease. Analytic and descriptive studies were included, and the data were analyzed looking for crude numbers.*

RESULTS: *Intrahepatic cholestasis of pregnancy is a pregnancy-specific disorder. Its prevalence is higher in Chile and Sweden compared with any other population. Its etiology is largely unknown, although endocrine, genetic, and environmental factors have been postulated as responsible for the appearance of the disease. Maternal effects of ICP are mild; however, there is a clear association between ICP and poor perinatal outcome, including a higher frequency of fetal distress, preterm labor and delivery, and unexplained fetal death. The treatment is mainly symptomatic. Recent data suggest that oral use of ursodeoxycholic acid improves maternal condition and might prevent the fetal complications of ICP.*

CONCLUSIONS: *Intrahepatic cholestasis of pregnancy should be considered a high-risk condition, and careful fetal assessment and appropriate medical intervention might improve perinatal outcome. (J Soc Gynecol Investig 2002;9:10–4)*

KEY WORDS: Intrahepatic cholestasis of pregnancy, genetic basis of disease, preterm birth, fetal death.

Intrahepatic cholestasis of pregnancy (ICP) is associated with unexplained fetal death and premature labor and delivery. The present article summarizes the current knowledge regarding ICP and its complications, with emphasis on new information gathered on the genetic basis of the disease as well as its complications.

Intrahepatic cholestasis of pregnancy, also called obstetric cholestasis, is a pregnancy-specific disorder. The symptoms can be severe and incapacitating to the mother; however, the clinical course is usually benign. In the fetus, a high frequency of preterm labor and delivery and stillbirth of unknown etiology has been reported. Intrahepatic cholestasis of pregnancy was recently described as a puzzling disorder because of its clinical presentation and epidemiology, the absence of well-understood etiologic factors, and the unexplained fetal compromise.[1]

The present article summarizes the current knowledge of intrahepatic cholestasis of pregnancy. We review clinical features of the disease, its etiology, maternal and fetal risks, and treatment.

CLINICAL, PATHOLOGIC, AND EPIDEMIOLOGIC FEATURES

Intrahepatic cholestasis of pregnancy is characterized by generalized pruritus, most prevalent on the palms and soles and with a nocturnal predominance. The pruritus is not associated with skin lesions. It usually starts in the third trimester, remains until the end of gestation, and disappears a few days after delivery. In a subset of patients (one in six) mild jaundice and high plasma levels of conjugated bilirubin are observed. The diagnosis of ICP is established mainly on a clinical basis; liver function tests, including plasma bile acid levels, confirm the diagnosis.

The best-known biochemical marker of this condition is an increase (in the fed or fasting state) in the plasma concentration of primary bile acids, such as cholic or chenodeoxycholic acid. Their levels are 10–100 times that of healthy pregnant women.[2–4] Increases of plasma cholesterol, alkaline phosphatase, 5′ nucleotidase, and transaminases can also be found.[1,3,4] In addition, other laboratory tests are useful for differential diagnosis to exclude conditions such as viral hepatitis, autoimmune hepatitis, parasitic infections, skin allergies, cholesterol gallstone disease, or metabolic disorders.[5]

Histopathologic analysis of liver biopsy specimens revealed mild intrahepatic cholestasis characterized by accumulation of

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bile pigments in hepatocytes and bile duct tumefaction. Electron microscopy demonstrates widening of the bile canaliculi.[3]

Intrahepatic cholestasis of pregnancy has been described in almost all ethnic groups; however, its prevalence is high in Chile, particularly in the native Araucanean Indian population, and Sweden, whereas in North America and other countries it is infrequently reported. However, recently the frequency of diagnosis of ICP has decreased in both Chile and Sweden.[1] In Chile, before 1985 the incidence of ICP was as high as 15% of all pregnancies, whereas today it is less than 2%. At our own center (Pontificia Universidad Catolica de Chile) the prevalence of ICP between 1997 and 1999 was only 1.5% (unpublished data). The reported recurrence of ICP is around 40–60%. However, in a United Kingdom population the recurrence rate was approximately 90% (unpublished data, Williamson et al). In addition, the intensity of the clinical and laboratory findings may vary in subsequent pregnancies, as well as during the course of a given pregnancy, in an apparently random fashion.[5]

Etiology

Despite much research the precise etiology of ICP is still unknown. Endocrine, genetic, and environmental factors are thought to play a role. The condition is believed to result from a predisposition to the cholestatic effect of elevated serum estrogens.[6]

The Role of Estrogen in ICP

Although much epidemiologic, clinical, and basic data support an etiologic role for estrogens, the molecular mechanism of such association is not fully understood. Clinical evidence supporting the role of estrogen in ICP is based on the relationship between the temporal course of the disease and estrogen levels during gestation (higher in the third trimester when the estrogen production attains its maximum); the five times higher frequency of ICP in pregnancies with higher estrogen levels, such as twin pregnancies; and the observation that patients with ICP frequently develop similar clinical symptoms during subsequent use of combined oral contraceptives.

In normal volunteers (men and women) estrogens induce a reversible decrease in the hepatic clearance of bromosulpthalein.[7] The intensity of the cholestatic change induced by estrogens was higher in women with a history of ICP than controls. Moreover, women and men whose sisters or mothers had ICP had an exaggerated response to the estrogen challenge, suggesting a familial susceptibility to estrogen-induced cholestasis.[6] The exact nature of this association is presently unknown.

It has been suggested that estrogens, by acting in the basolateral side of the hepatocyte, may decrease membrane fluidity, alter protein function, or induce a disruption of the structural and functional integrity of the hepatocellular tight junction, generating dysfunction in the excretory pathways to the bile duct.[8,9] However our data do not show differences in estradiol or progesterone levels in the plasma of patients with ICP compared with normal pregnancies.[10] New evidence indicates that the maternal plasma levels of dehydro-3-epiandrosterone sulfate, the estriol precursor of fetal adrenal origin, is decreased in the plasma of patients with ICP, leading to decreased placental synthesis of estriol.[11] The exact nature and the consequence of decreased fetal adrenal endocrine function, coupled with a decrease in estriol production, remain to be determined.

It has also been suggested that progesterone or an associated metabolite may be causally related to ICP. Progesterone synthesis during ICP remains at a normal level, but increased plasma levels of sulfated progesterone metabolites have been found.[1,2,12] However, it is not known whether the changes in progesterone metabolism are the cause or consequence of the hepatic cholestasis.

The Role of Genetics in ICP

Support for a genetic basis to the etiology of ICP is based on population, pedigree, and molecular genetic studies. The incidence of ICP shows marked ethnic and geographic variation. The higher prevalence in Chile[13] and Scandinavia[14] suggests that there might be founder mutations in those populations. The condition is more common in women who have close relatives with a history of ICP,[5] and the small number of published pedigrees suggests autosomal-dominant, sex-limited inheritance.[15–17]

The clinical features of ICP are heterogeneous; therefore, the genetic etiology is likely to be complex. Clues to the genetic causes of the condition were given by studies of the childhood liver disease progressive familial intrahepatic cholestasis (PFIC), which is characterized by the onset of cholestasis in early childhood which can progress to cirrhosis and liver failure before adulthood.[18] It is divided into three subtypes (PFIC 1–3); children with PFIC1 and 2 have low concentrations of biliary bile acids and low to normal gamma glutamyltranspeptidase (γ-GT) in the serum. Patients with PFIC3 have high serum levels of γ-GT and bile that lacks phospholipid but has a normal biliary bile acid concentration,[19] together with distinctive liver histology that shows portal duct inflammation and ductular proliferation.[20] Homozygous mutations of the *MDR3* (multidrug resistance 3) gene have been described in three pedigrees with PFIC3.[17–19] The heterozygous mothers of two affected children with PFIC3 had symptoms consistent with ICP.[17–19] In one of those pedigrees in which a large consanguineous family had coexisting PFIC3 and ICP, three of the six mothers with ICP had pregnancies complicated by unexplained intrauterine death.[17] Four of the six women were shown to be heterozygous for the *MDR3* mutation, for which the proband was homozygous.[17] More frequently, however, ICP occurs in women with no family history of PFIC. We investigated a subgroup of women with ICP and elevated γ-GT and found a missense mutation in the *MDR3* gene in one such patient.[21] This mutation caused disruption of protein trafficking with a subsequent lack of functional protein at the cell surface.[21]

Studies on human leukocyte antigen (HLA) haplotype distribution failed to demonstrate a relationship between patients with a history of ICP and HLA.[22] Also a study on class II HLA

alleles found no differences between patients with ICP and controls.[23]

The Role of Environmental Factors in ICP

The participation of a still unidentified environmental factor(s) in ICP has been suggested. That suggestion is based on the following findings: (1) in Chile, only 60% of patients who develop ICP will have this condition in a subsequent pregnancy; (2) the intensity of the cholestasis changes during pregnancy; and (3) the prevalence of the disease has a geographic and seasonal distribution, with an increase in the number of cases during spring.[1,6] Several environmental factors have been proposed as causally related to ICP, including pollutants present in pesticides, erucic acid (a long-chain monounsaturated fatty acid) present in rape-seed oil,[1] and dietary deficiency of oligoelements such as selenium.[24] However, none of these has been confirmed to be the environmental factor related to the appearance of ICP.

In summary, ICP has a complex etiology with possible genetic, endocrine, and environmental factors. The information regarding the etiology of ICP is diverse and insufficient to generate a final conclusion. It appears that the disease has a genetic predisposition. Affected women have an abnormal hepatic reactivity to external factors, including estrogens. The presence of increased estrogen levels, as happens during the third trimester of pregnancy, may trigger the clinical manifestation of the disease.

MATERNAL AND FETAL IMPACT OF ICP

Maternal Consequences of ICP

Clinical features of ICP include minor effects on maternal health but greater risks for the fetus. Elevation of plasma prolactin concentration, changes in carbohydrate metabolism, and alteration of renal and intestinal function associated with ICP have been reported.[25–27] Steatorrhea and a decrease in vitamin K–dependent clotting factors have also been reported, and these are thought to cause the increased risk of postpartum hemorrhage in ICP patients. These alterations are uncommon, mild, and transient. Severe or persistent liver failure has not been reported after an episode of ICP.

Uterine and Placental Consequences of ICP

A significant increase in uterine contractile activity has been shown during the course of the disease, an event that has been related to the high incidence of spontaneous preterm labor.[28] A reduction in the activity of steroids and xenobiotic metabolizing enzymes has been shown in human placentas obtained from ICP patients.[29,30]

Perinatal Consequences of ICP

There is a well-known but inadequately understood association between ICP and poor perinatal outcome. Higher incidence of clinical markers of intrauterine asphyxia, such as meconium staining of amniotic fluid (25–45%) and fetal distress (12–22%),[31,32] have been described.

Since the first report of ICP in 1851 describing a woman with a history of recurrent ICP and preterm delivery,[33] many publications have shown the association between ICP and spontaneous preterm labor.[2,31,32,34,35] The reported risk of preterm birth from descriptive and noncontrolled studies is as high as 44%. We reported a fourfold increase in the risk of spontaneous preterm delivery during ICP compared with controls (odds ratio [95% confidence interval], 3.98 [1.96, 8.22], $P < .05$).[32] Intrahepatic cholestasis of pregnancy is therefore a potent risk factor for preterm delivery. This risk of preterm delivery is associated with the precocity of ICP presentation, duration of disease, degree of hepatic dysfunction, and presence of jaundice in the mother, suggesting that longer evolution or greater severity of disease increases the risk of prematurity.[2] The molecular mechanisms responsible for ICP-associated preterm delivery are still poorly understood, although a role for bile acids by way of increased oxytocin bioaction has been suggested.[36–38]

A higher incidence of unexplained, third-trimester fetal death has been described in association with severe ICP in almost all large series. The reported frequency of ICP-related stillbirth is as high as 35%, which is double that of the normal population.[31] No studies of ICP to date have provided an etiologic explanation of the fetal death. The fetuses show no evidence of growth restriction and have normal surveillance tests 1 week or less before the fetal death.[39] Meconium-stained amniotic fluid is the single clinical sign that has been reported to assist in the prediction of the at-risk fetus.

Bile acids in high concentration were shown to induce contraction of the chorionic vessels in vitro,[40] which supports the hypothesis that bile acids present in very high concentration in meconium may induce chorionic vessel spasm and therefore acute fetal asphyxia by decreasing fetoplacental blood flow. In addition, a direct toxic effect of meconium on the umbilical cord vessels has also been reported.[41,42] However, umbilical artery Doppler studies failed to show any abnormalities in patients with ICP.[43,44] At this time there is no convincing evidence available to postulate a role for meconium or any other mechanism for the unpredictable fetal death.

TREATMENT

Several drugs have been tested in clinical studies, including cholestyramine, phenobarbital, s-adenosyl methionine, epomediol, and dexamethasone.[6,45,46] They produced only slight symptomatic relief, minor improvement in hepatic function, and no changes in fetal outcome. However, the populations involved in such trials were not large enough to be able to detect changes in fetal outcome.[6] Dexamethasone was originally advocated to treat pruritus, but later its benefit was unproved; currently it is not recommended.[45,46] Recent and encouraging studies suggest that oral use of ursodeoxycholic acid improves maternal clinical and biochemical features and may prevent the fetal effects of ICP.[47–53] The mechanism of action of ursodeoxycholic acid is not completely understood; however, it has been postulated that it may exert its beneficial effects by direct hepatoprotective effect, by influencing the enterohepatic circulation of endogenous bile salts, by enhanc-

ing bile flow through a cholehepatic shunt mechanism, or by immune modulation.[54,55] Of those studies, only one was concerned with fetal outcome and found a decrease in prematurity and perinatal mortality; however, the limited number of patients enrolled in the study precluded a significant conclusion.[53] We believe the treatment efficacy needs to be further evaluated in large controlled clinical trials. Currently, there is no known treatment for ICP, with the exception of delivery by 38 weeks' gestation.

Even in the absence of a specific treatment for this condition, careful fetal assessment and appropriate medical intervention have improved the perinatal outcome.[32] It has been reported that biophysical profile and nonstress test are not good enough for predicting fetal risk in the setting of ICP[35,39]; however, we have reported perinatal outcomes similar to those of the general population using nonstress testing to evaluate fetal condition.[32] Thus in our center (Pontificia Universidad Catolica de Chile) we recommend maternal monitoring of fetal activity and weekly nonstress test starting at ICP diagnosis. Labor is induced, unless contraindicated, at 38 weeks' gestation. In patients with jaundice the interruption will be planned from 36 weeks onwards, after evaluation of lung maturity by amniotic fluid analysis. Fetal monitoring during labor and delivery is a matter of standard care.[32]

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