INTRAHEPATIC CHOLESTASIS OF PREGNANCY

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Intrahepatic cholestasis of pregnancy (ICP) is a well-defined liver disease that is unique to pregnancy. Signs of cholestasis, particularly pruritus, usually occur during the second or third trimester and, by definition, disappear spontaneously after delivery. ICP is a benign disease for the mother, but it carries a risk for the pregnancy because of the possibility of premature delivery and sudden fetal death. This risk for the baby requires the obstetric team and the hepatologists to be familiar with ICP, especially since active, timely obstetric intervention improves fetal prognosis.

EPIDEMIOLOGY

ICP has been identified all over the world, but its prevalence varies greatly according to country and to ethnic origin (Table 1). ICP is more common in Scandinavian countries, Bolivia, and Chile. In Chile, the prevalence, which in 1974 and 1975 was evaluated at 15.6% (i.e., 11.8%–27.7% according to ethnic origin), recently has decreased to between 4% and 6.5% for unknown reasons.[51,58,59]

Generally, ICP is more frequent in twin pregnancies,[26] which is not surprising considering the role of hormonal factors in ICP.[56]

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Table 1. PREVALENCE OF INTRAHEPATIC CHOLESTASIS OF PREGNANCY

Country (Ethnic Origin)	Prevalence (%)	Time of Survey	First Author (Reference)
Australia	1.5	1968–1970	Steel, 1973[67]
Australia	0.1	1965–1974	Fisk, 1988[18]
	0.2	1975–1984	Fisk, 1988[18]
Bolivia	9.2	1976	Reyes, 1979[52]
Whites	7.8		
Aimara Indians	13.8		
Quechua Indians	4.3		
Canada	0.1	1963–1976	Johnston, 1979[35]
Chile	15.6	1974–1975	Reyes, 1978[51]
Whites	15.1		
Araucanian Indians	27.6		
Aimara Indians	11.8		
Chile	4.0	not mentioned	Ribalta, 1991[58]
Chile	6.5	1988–1990	Rioseco, 1994[59]
China	0.1	1950	Zheng-Hui, 1986[74]
	0.3	1981–1983	Zheng-Hui, 1986[74]
Finland	1.1	1971–1972	Laatikainen, 1975[39]
Finland	1.1	1980–1981	Laatikainen, 1984[42]
France	0.2	1972–1973	Gagnaire, 1975[24]
France	0.5–0.7*	1988–1989	Roger, 1994[61]
Poland	0.8–1.2†	1964–1966	Roszkowski, 1968[63]
United States	<0.1	1932–1960	Cahill, 1962[11]
United States	0.7	1977	Wilson, 1979[71]
Sweden	1.5	1971–1974	Berg, 1986[8]
	1.0	1980–1982	Berg, 1986[8]
Switzerland	<0.1	1955–1965	Haemmerli, 1967[29]

*According to dermatologic or biochemical criteria of diagnosis.
†With or without urinary tract infection.

CLINICAL FINDINGS

As a rule, skin pruritus, which is the main symptom, appears in late pregnancy, although it can appear as early as the 10th week.[10] The pruritus, which initially is localized, often becomes generalized, but predominates on the palms and the soles of the feet. Pruritus may engender considerable discomfort, and generally is more severe at night and disturbs sleep. Pruritus declines a few hours after delivery and usually disappears in the few days following delivery. Clinical examination of the skin is normal except for evidence of scratching (i.e., excoriated papules and linear scratches).[61] When there is a skin eruption associated with pruritus, a disease of the skin should be suspected. In this case, the advice of a dermatologist is needed and a skin biopsy with direct immunofluorescence usually is performed to confirm the diagnosis.[61]

Approximately 10% of patients suffering from ICP experience jaundice.[59] The jaundice appears after the pruritus and usually disappears within the 2 weeks following delivery.[69] As a rule, the pruritus persists

longer than the jaundice.[69] ICP with jaundice but without pruritus is rare.[5,69] The conventional distinction between cholestatic jaundice of pregnancy, which corresponds to patients suffering from ICP with hyperbilirubinemia, and pruritus gravidarum, which corresponds to patients with pruritus and biologic signs of cholestasis except hyperbilirubinemia, is no longer necessary and is sometimes difficult.[53]

Patients do not experience abdominal pain or encephalopathy.

Urinary tract infection (UTI) may be associated with ICP,[28] and fever usually is caused by associated UTI.[33] In addition, bacterial infection may induce liver disease per se.[75] Consequently, UTI should be systematically sought and properly treated in patients suffering from cholestasis during pregnancy, even if the patient does not experience fever or clinical signs of UTI.

BIOLOGIC FINDINGS

Liver function tests are essential to confirm the diagnosis of cholestasis when a pregnant woman experiences pruritus. In such patients, an increase in serum transaminase activity or in serum bile acid concentration usually is enough to confirm the diagnosis of cholestasis.

Clinicians should bear in mind that serum transaminase activity remains within normal limits during normal pregnancy and that an increase should be taken into account whatever the level.[4] Both aspartate transaminase (AST) and alanine transaminase (ALT) serum activities increase in patients with ICP, but ALT seems to be more sensitive.[31] Indeed, measurement of serum ALT activity is a very sensitive test for the diagnosis of ICP when a pregnant woman experiences pruritus.[5,31] A good correlation has been found between AST and ALT serum activities, and we use mainly ALT levels routinely.[5] Some patients with ICP have a very high increase in serum transaminase activity.[72] Indeed, in a recent study, serum ALT activity levels were found to be more than 10 times the upper normal limits in 40% of cases.[5] This increase might be caused by an increase in membrane permeability, because liver histology usually does not reveal necrotic lesions; however, in these patients with marked increase in serum aminotransferase activity, acute viral hepatitis (especially hepatitis A and B), should be systematically ruled out with suitable serologic tests.[7]

The serum total and conjugated bilirubin levels are normal or increased according the severity of the cholestasis, but usually the serum total bilirubin level remains lower than 5 mg/dL.[53] Higher values may be caused by concomitant UTI[53] or to another liver disease (e.g., a viral hepatitis or a choledocholithiasis), which should be eliminated by appropriate investigations.

Serum bile acid concentrations are increased in patients with ICP.[30] Conjugated primary bile acids, especially cholic acid, are predominant.[3,9,66] Indeed, the most sensitive indicators of ICP in early diagnosis (i.e., before the onset of symptoms), are an increased serum cholic acid

level or a cholic acid to chenodeoxycholic acid ratio over 1.[31] In clinical practice, liver function tests usually are performed after the patient experiences symptoms (i.e., pruritus or jaundice). When measured with an enzymatic method, the fasting serum concentrations of total bile acids in normal pregnancy do not differ from the values found in nonpregnant women.[5] Thus, the measurement of fasting serum total bile acid concentration remains a specific test for the diagnosis of cholestasis during pregnancy.[4,55] This test is especially helpful for the diagnosis of ICP when a patient experiences pruritus with normal serum transaminase activity.

Serum gamma-glutamyl transpeptidase (GGT) activity remains in normal limits or is slightly increased in patients with ICP.[5] Women suffering from viral hepatitis in late pregnancy have lower serum GGT activity than women with viral hepatitis in early pregnancy. The same phenomenon has been observed in women receiving oral contraceptives.[12] The exact cause is unknown. The hepatic synthesis of GGT might be inhibited by hormone secretion during pregnancy, which is in agreement with the decrease in serum GGT activity found in normal pregnancy.[4] The slight increase in serum GGT activity, which may be detected immediately after delivery,[48] also is in agreement with this hypothesis. This explains why the measurement of serum GGT activity is not very useful for the assessment of cholestasis during pregnancy.

Serum alkaline phosphatase activity is increased in patients with ICP, but this increase is not specific of cholestasis because serum alkaline phosphatase activity is increased during late, normal pregnancy.[4] This physiologic increase mainly is caused by placental production of an isoenzyme, but also by an increase in the bone isoenzyme.[1,60,70]

Serum 5-nucleotidase activity usually is slightly increased in ICP.[5] The slight increase in serum 5-nucleotidase activity, which also is found during the second and third trimesters of normal pregnancy, decreases the specificity of this test and is a limitation of its use for the diagnosis of cholestasis during pregnancy.[4]

There is little or no correlation between serum total bile acid concentrations and other liver function tests (i.e., aminotransferase, GGT, alkaline phosphatase, 5-nucleotidase and total bilirubin).[5]

The prothrombin time usually is normal, although it may become abnormal in severe cholestasis with jaundice or when patients have been treated with cholestyramine. This is caused by vitamin K deficiency, which should be anticipated and treated before delivery to prevent hemorrhage. The parenteral administration of vitamin K results in a rapid return to normal.[69] The prothrombin time should be evaluated once or twice a week, especially in patients treated with cholestyramine, which increases malabsorption of fat-soluble vitamins.

Serum bile acid concentration and serum aminotransferase activity rapidly decrease after delivery and, as a rule, normalize in a few weeks. The persistence of laboratory abnormalities for more than 3 months after delivery necessitates ruling out chronic liver disease that pre-existed pregnancy, especially a primary biliary cirrhosis.[55]

ULTRASONOGRAPHY

Ultrasound examination of the liver in patients suffering from ICP reveals no dilatation of the intra- and extrahepatic bile ducts[36]; however, fasting and ejection volumes of the gallbladder have been found to be greater in patients with ICP than in normal pregnant women.[36] Gallstones may be identified in the gallbladder. A significant association has been found between ICP and gallstone disease in Sweden and Chile.[23, 25] In a case-control study, the frequency of gallstone disease was found to be higher in primiparae but not in multipara with ICP.[25] The incidence of ICP has been found to be higher in patients with gallstone disease, especially in patients who underwent cholecystectomy.[25] Therefore, although the pathogenesis of the association between the two diseases is unclear, gallstone disease seems to be a risk factor for ICP.

PATHOLOGY

Liver biopsy rarely is necessary for the diagnosis of ICP. Histopathology is characterized by pure cholestasis, sometimes with bile plugs in hepatocytes and canaliculi and predominantly in zone 3. Inflammation and necrosis usually are not observed, and portal tracts are unaffected.[62]

MATERNAL AND FETAL OUTCOME

Maternal prognosis is good, and ICP never leads to chronic liver disease. Cholestasis frequently recurs in subsequent pregnancies,[33,68] however the severity of the pruritus, the date of onset, and the intensity of the changes in liver function tests may differ in consecutive pregnancies.[55]

The administration of oral contraceptives to women with a history of ICP rarely results in cholestasis,[16] and ICP is not a contraindication for oral contraceptives.[5] Oral estroprogestogen contraception with a low dosage of estrogen could be initiated after normalization of liver function tests. The patient should be informed that there is a possibility of pruritus during such contraception.

ICP carries a risk for the fetus. Once the diagnosis is suspected, the patient should be considered as having a high-risk pregnancy.[56] The main complication of ICP is fetal prematurity, which is more frequent in patients with ICP than in the general population.[59] The rate of prematurity varies greatly according to the study (Table 2). The prematurity rate may be increased by the high rate of multiple pregnancies in patients with ICP.[5] The other complication of ICP is the risk of sudden fetal death. Its prevalence is about 1% to 2%, but also varies according to the study.[2,8,17,42,59,73] Sudden fetal death rarely occurs before 35 weeks gestation.

Table 2. PRETERM BIRTH IN INTRAHEPATIC CHOLESTASIS OF PREGNANCY

First Author (Reference)	Country (Ethnic Origin)	Time of Survey	Premature Rate (%)
Bacq, 1997[5]	France	1989–1995	60
Berg, 1986[8]	Sweden	1971–1974	<7
Fisk, 1988[17]	Australia	1975–1984	44
Rioseco, 1994[59]	Chile	1988–1990	19

PATHOPHYSIOLOGY

The cause of ICP is unknown; however, the results of epidemiologic and clinical studies suggest genetic, hormonal, and exogenous factors (Fig. 1).

Genetic factors could explain familial cases and the higher incidence in some ethnic groups, such as the Araucanian Indians of Chile.[51] Regarding the markers of genetic susceptibility of the human leukocyte antigen (HLA) system, no statistically significant association of ICP with HLA-A,-B, and -C antigens[54] or with HLA-DPB1 alleles have been demonstrated to date.[44]

ICP clearly is an estrogen-related disease, but the exact mechanism leading to cholestasis remains unknown.[56] Genetically determined abnormalities might lead to particular hepatic reactions to estrogens or estrogen metabolism dysfunction. Experimental studies have shown that estrogens, particularly ethinylestradiol, are cholestatic, and estrogen administration may induce signs of cholestasis in nonpregnant women

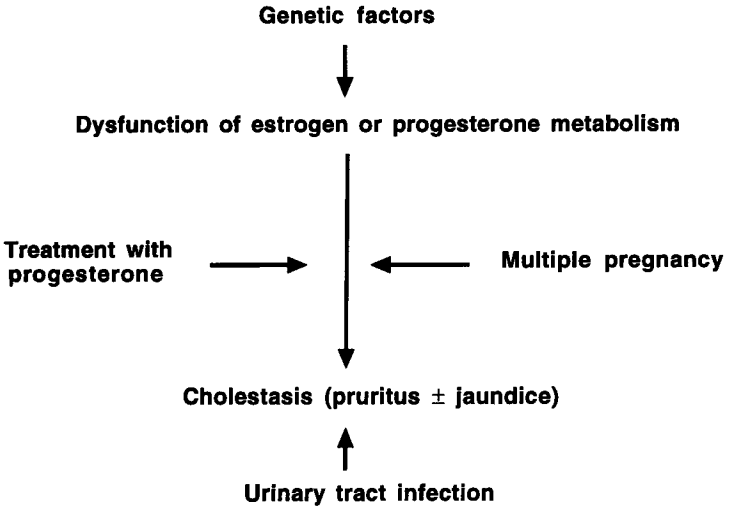

Figure 1. Pathogenesis of intrahepatic cholestasis of pregnancy.

who have suffered previously from ICP.[33,38] Cholestasis may be the result of the production of an abnormal estrogen metabolite or the result of an increase in the hepatic susceptibility to the cholestatic effect of normal estrogen metabolites. An impairment in sulfation, which is an important metabolic pathway in the detoxification of endogenous and exogenous compounds, has been found in patients with ICP and in women taking contraceptive pills.[14] The imbalance of sulfation and glucuronidation associated with high levels of circulating estrogen might play a role in the pathogenesis of ICP.[14]

Progesterone metabolism also is involved in the pathophysiology of ICP. Abnormalities of progesterone metabolism, especially elevated levels of serum sulfated metabolites, have been found in patients with ICP. It is not clear whether these abnormalities are primary or secondary to the cholestasis. These abnormalities have led to one hypothesis as an alternative to the role of estrogens in the development of ICP.[45,46] The formation of large amounts of sulfated progesterone metabolites, possibly related to greater 5-α reduction and 3-α reduction, might, in some genetically predisposed women, result in saturation of the hepatic transport systems used for biliary excretion of these compounds.[45] Indeed, recent studies have suggested that oral, natural progesterone prescribed for risk of premature delivery could trigger ICP in predisposed women.[5,6] In a prospective study of patients with ICP referred for hepatologic consultation, we found that 62% of patients had been treated with oral micronized natural progesterone (200-1000 mg/d, mean dosage, 548 mg/d) for risk of premature delivery before the onset of pruritus during the current pregnancy.[5] In this study, onset of pruritus was statistically earlier in patients previously receiving progesterone than in patients who had not received progesterone. Withdrawal of progesterone led to disappearance of pruritus with improved liver function tests in about one-half of the patients. Moreover, in our center we observed a statistical difference in progesterone intake during pregnancy between patients with and without ICP.[5] In a controlled, double-blind study versus placebo, orally administered micronized progesterone (900-1200 mg/d) during the third trimester was associated with greater frequency of elevation of serum bile acid concentrations and serum ALT activity.[6] In these studies, the dosage of natural progesterone prescribed in pregnancy was similar to or higher than the synthesis of progesterone during normal pregnancy (250-500 mg/d).[45] This intake of progesterone may impose an additional load on the transport system of sulfated metabolites. Therefore, in our clinical practice, we consider that progesterone treatment should be avoided in pregnant women with a previous history of ICP and immediately withdrawn when cholestasis occurs during pregnancy.

Some characteristics of ICP suggest that exogenous factors might be associated with the genetic factors to modulate the expression of the disease: ICP recurs in only 45% to 70% of pregnancies in multiparous women[5,55]; seasonal variability has been observed in Finland[39] and Sweden[8]; and the prevalence of ICP has decreased in Sweden[8] and Chile.[55]

Currently, no exogenous or environmental factor, except the treatment with natural progesterone, has been identified clearly.

The exact cause of sudden fetal death in ICP is unknown. Morphologic study of placental terminal villi obtained from women with ICP have shown a reduction in the intervillous space with syncytial and cytotrophoblastic hyperplasia.[13] Experimentally, high concentrations of bile acids, especially cholic acid, have a dose-dependant vasoconstrictive effect on isolated human placental chorionic veins.[64] This suggests that bile acids could exert a deleterious effect on the fetus by increasing the resistance in chorionic veins through vasospasm of the placental chorionic surface. The reduction in the oxygenated blood flow in the placental chorionic plate may impair fetal perfusion and oxygenation, resulting in fetal asphyxia.[64] The results of a recent study suggest that some placental bile acid transport systems are impaired in ICP and that such impairment could be restored by the use of ursodeoxycholic acid.[65]

MEDICAL TREATMENT

Hydroxyzine (25–50 mg/d) may alleviate the discomfort of pruritus.

Cholestyramine (8–16 g/d) decreases ileal absorption of bile salts and increases their fecal excretion, but its effect on pruritus is limited.[41] This treatment should be initiated progressively to improve the digestive tolerance.

The efficacy of S-adenosylmethionine is a matter of debate.[21,22,58] In two Italian, placebo-controlled studies, intravenous administration of S-adenosylmethionine (800 mg/d) induced a significant amelioration of the pruritus and improved serum bile acid concentrations, conjugated bilirubin levels and serum transaminase activities[21,22]; however, efficacy of S-adenosylmethionine was not found in Chilean patients with moderate or severe ICP (i.e., with onset of pruritus before 32 weeks' pregnancy).[58] In these patients, intravenous administration of S-adenosylmethionine (900 mg/d) for 20 days failed to improve pruritus and liver function tests.[58]

In a Finnish study including 10 patients with ICP, high doses of dexamethasone (12 mg/d for 7 days and then tapering over 3 days) reduced the pruritus, serum bile acid concentrations, and serum ALT activities.[32] These results remain to be confirmed in a controlled study.

In an open study, epomediol reduced pruritus without improvement in bile acid concentrations.[27]

Ursodeoxycholic acid (UDCA) is a tertiary bile acid that is used widely in the treatment of chronic cholestasis.[50] UDCA improved ethynyl estradiol-induced cholestasis in the rat.[34] In open studies and some case reports, UDCA was effective in patients with ICP, and it improved pruritus and liver function tests in such patients.[10,15,19,43,48] No side effects have been reported in mothers or babies following UDCA treatment. The efficacy of UDCA was confirmed recently in case-control studies.[20,49] In a randomized, double-blind, placebo-controlled study consisting of

15 patients with severe ICP (i.e., onset before 33 weeks), UDCA (14 mg/kg/d for 3 weeks) improved pruritus and fetal prognosis.[49] In another controlled study consisting of 20 patients in the last trimester, UDCA (450 mg/d) was more effective than S-adenosylmethionine (1000 mg/d intramuscularly) in controlling pruritus and serum total bile acid concentrations.[20] UDCA administration improves the maternal serum bile acid profile, and the percentage of cholic acid, which is increased in ICP, significantly decreases after UDCA administration.[9,47] UDCA also improves the abnormalities of progesterone metabolism and markedly decreases the serum levels and the urine excretion of sulfated steroids.[47] Finally, although the number of patients treated so far is still small, the current findings strongly suggest that UDCA is not toxic for the fetus and may be useful in patients with severe ICP or in patients with a history of sudden fetal death. Clinicians should remain prudent about the routine use of UDCA, as with all new drugs during pregnancy. In the less severe forms of ICP and with our current knowledge, the use of UDCA is probably not yet justified.

In patients with jaundice or who are treated with cholestyramine, vitamin K deficiency may be avoided by regular injection of vitamin K (e.g., 10 mg/wk).

OBSTETRIC MANAGEMENT

The obstetric team has the responsibility of deciding whether early delivery is necessary. This decision may be influenced by several factors. The first is the number of weeks gestation because the risk of death in utero is increased during the last month of pregnancy. The second concerns the severity of the cholestasis, which can be evaluated by the serum bilirubin concentration and possibly by serum bile acid concentrations. It has been suggested that serum bile acid concentration levels could be used for fetal assessment in ICP. A relationship between maternal serum bile acid levels and signs of fetal distress has been observed[40,42]; however, the usefulness of the evaluation of serum bile acid concentrations in the obstetric management of patients with ICP has not clearly been established to date. The third factor is signs of fetal distress, which usually are an indication for delivery. Sudden fetal death, however, may not be predicted by conventional fetal surveillance (i.e., weekly nonstress tests and amniotic fluid assessment), probably because sudden fetal death in ICP is caused by an acute fetal hypoxia.[2]

Finally, the obstetric decision to terminate the pregnancy should be taken after weighing the risks related to extreme prematurity caused by early, active delivery against the risk of sudden death in utero. Rioseco et al[59] recently proposed systematic delivery at 38 weeks' gestation in patients without jaundice and at 36 weeks in patients with jaundice (or total serum bilirubin >1.8 mg/dL) if pulmonary maturity has been achieved. Such active intervention provided perinatal outcome equal to that of controls and better than previously reported.[59] In this study, the

management of patients with ICP also included weekly prenatal visits from the time of diagnosis, and fetal surveillance included daily maternal recording of fetal movements and a weekly nonstress test beginning at 34 weeks' gestation until delivery.[59] The value of the weekly nonstress test in the antepartum management of ICP has not been clearly established.[59] Doppler investigation of the umbilical artery seems to be of little value to evaluate the risk of fetal distress because even high serum bile acid levels do not influence the umbilical circulation.[76]

Systematic early delivery may be indicated as soon as pulmonary maturity is achieved in the case of a patient with recurrent ICP and a history of sudden fetal death during a previous pregnancy, whatever the severity of cholestasis.

Breast-feeding is not contraindicated in patients with ICP.[57]

CONCLUSION

When a pregnant woman experiences pruritus, cholestasis can be diagnosed easily by serum liver function tests; however, the cholestasis may be caused by a disease other than ICP per se, (e.g., UTI or viral hepatitis). These diseases should be systematically ruled out, especially in countries where the prevalence of ICP is low or when there are atypical features, such as abdominal pains or fever. By contrast, with the lack of risk for the mother, ICP carries a risk for the baby because of the possibility of premature delivery or sudden fetal death. Regarding obstetric management, the risks related to extreme prematurity caused by early active delivery should be weighed against the risk of sudden death in utero.

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