The Importance of Serum Bile Acid Level Analysis and Treatment With Ursodeoxycholic Acid in Intrahepatic Cholestasis of Pregnancy

A Case Series From Central Europe

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Background: Intrahepatic cholestasis of pregnancy (ICP) is a severely pruritic form of reversible cholestasis that is associated with significant fetal risks. Because precise diagnostic and therapeutic guidelines are lacking, we performed a retrospective investigation of dermatologic and biochemical features, treatment, and neonatal outcome in patients with ICP seen from 2000 through 2005 at a university-based dermatologic hospital in central Europe.

Observations: The 13 observed cases of ICP (11 patients) represented 6% of all pregnancy-associated dermatoses at our department. Intrahepatic cholestasis of pregnancy started at a mean±SD of 30±4 weeks' gestation, with pruritus as the leading symptom, followed by secondary skin lesions in 11 cases (85%). Total serum bile acid levels were markedly elevated in all patients and correlated with impaired fetal prognosis. Only 10 cases (77%) had other liver function test result abnormalities. Fetal distress occurred in 3 pregnancies (23%). In the 10 cases treated with ursodeoxycholic acid, 3 (30%) involved preterm deliveries compared with a 100% preterm delivery rate in the cases not treated with ursodeoxycholic acid.

Conclusions: Severe pruritus with or without skin changes in the second half of pregnancy should alert the physician to the possibility of ICP. Elevated total serum bile acid levels are the clue to diagnosis, which should be established as early as possible. Close obstetric surveillance and prompt treatment with ursodeoxycholic acid are warranted.

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Intrahepatic cholestasis of pregnancy (ICP) or obstetric cholestasis is a rare form of reversible cholestasis occurring in the second half of pregnancy and is one of the specific dermatoses of pregnancy, along with pemphigoid gestationis, polymorphic eruption of pregnancy, and atopic eruption of pregnancy. Pruritus is typical for all 4 specific dermatoses of pregnancy, and their clinical presentation often overlaps. Intrahepatic cholestasis of pregnancy may be associated with significant fetal risks, including premature births in 19% to 60% of deliveries, intrapartal fetal distress in 22% to 33% of affected pregnancies, and stillbirths in 1% to 2%. Thus, prompt diagnosis and specific treatment are warranted to prevent fetal impairment. The difficult clinical diagnosis can be substantiated by the finding of elevated total serum bile acid levels. While various therapies have been applied, including antihistamines and cholestyramine resin, only ursodeoxycholic acid has been shown to improve fetal prognosis. Unfortunately, pruritus in pregnancy is often neglected. In the case of ICP, dermatologists may not have been alerted to the problem enough, since most of the pertinent literature has been published in hepatologic or obstetric journals. As a consequence, the dermatologic characterization of ICP is vague and precise diagnostic and therapeutic guidelines are lacking. This leads to delayed diagnosis and treatment and threatens fetal prognosis.

The purposes of this study were to report our experience with 13 recent cases of ICP seen at a university-based dermatologic hospital in central Europe with emphasis on clinical presentation, diagnostic clues, treatment, and fetal outcome and to review the literature.

Methods

Between 2000 and 2005, 228 pregnant patients with skin disorders were seen at the Department of Dermatology, Medical University of Graz, Graz, Austria, and entered into the database of our specialized dermatologic pregnancy clinic. Among these 228 patients, 13 cases of ICP could be identified and were retrospectively studied by medical chart review.
Table 1. Characteristics of 13 Cases (11 Patients) With Intrahepatic Cholestasis of Pregnancy

<table>
<thead>
<tr>
<th>Case No./Gravida/Para</th>
<th>Pruritus in Previous Pregnancies</th>
<th>Onset of Pruritus, wk</th>
<th>Skin Lesions</th>
<th>Time of Diagnosis, wk</th>
<th>Bile Acid Levels, µmol/L</th>
<th>Abnormal Routine LFT Findings</th>
<th>Treatment</th>
<th>Time of Delivery, wk</th>
<th>Mode of Delivery</th>
<th>Fetal Outcome</th>
<th>Neonatal Sex/Weight, g</th>
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Abbreviations: C, cesarean; Excor, excoriations; FD, fetal distress; IND, induction; LFT, liver function test; Prurigo, prurigo nodularis; SP, spontaneous; −, patient did not have a previous pregnancy.

SI Conversion factor: To convert bile acid to micrograms per milliliter, divide by 2.448.

*One patient presented with intrahepatic cholestasis of pregnancy in 3 successive pregnancies.

Approval from the Medical University of Graz ethics committee was obtained for this study. The diagnosis of ICP was based on the following criteria: (1) generalized pruritus with or without skin changes starting in the second half of pregnancy; (2) elevated total serum bile acid levels (>11 µmol/L)2 (to convert to micrograms per milliliter, divide by 2.448); and (3) exclusion of other dermatologic and/or internal conditions known to cause pruritus. The clinical parameters evaluated included age, ethnicity, and medical history (particularly, personal and/or family history of pregnancy-associated pruritus, time of disease onset, presenting signs and symptoms, disease duration, treatment, and maternal outcome). Laboratory results reviewed in all patients included levels of total serum bile acids, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transferase, total serum alkaline phosphatase, and total serum bilirubin. Scrutinized obstetric parameters were gestation, parity, time and mode of delivery, presence of fetal distress (pathological cardiotocogram and meconium-stained amniotic fluid), neonatal sex, and weight. Data for at least 1 follow-up visit after delivery were available in all patients.

CLINICAL CHARACTERISTICS AND THERAPY

The 13 observed cases of ICP (mean patient age, 30 years; range, 16–44 years) comprised 6% of the total 228 patients with pregnancy-associated dermatoses seen at our department (Table 1). Ten patients (91%) were central Europeans, and 1 patient (9%), who was seen for ICP in 3 successive pregnancies, was Egyptian. One patient (9%) had a family history of pregnancy-associated pruritus, and 7 (88%) of the 8 multiparous women reported pruritus and identical skin changes in previous pregnancies. Medical history was otherwise unremarkable. None of the patients had received progesterone treatment or antibiotics during pregnancy, and all had negative serologic findings for hepatitis B and C. The disease started during the second half of pregnancy in all patients (mean ± SD, 30 ± 4 weeks’ gestation; range, 24–35 weeks) with sudden severe, generalized pruritus, often pronounced on the palms and soles, but without primary skin lesions. In 2 cases (15%) that had the shortest disease duration until the time of diagnosis, pruritus remained the only symptom; all other cases developed secondary skin changes due to scratching over the next few weeks. Skin lesions varied from subtle excoriations (31%) to prurigo nodularis lesions (54%), and mostly involved the distal limbs (Figure). None of the patients presented with jaundice.

Diagnosis was established at a mean ± SD of 34 ± 3 weeks’ gestation (range, 29–39 weeks). At that time, oral therapy with ursodeoxycholic acid was started in 10 (77%) of 13 cases at a dose of 15 mg/kg per day after informed consent was obtained. Pruritus improved in all patients within 5 to 7 days, and treatment with ursodeoxycholic acid was continued until delivery (mean ± SD, 4 ± 3 weeks; range, 1–9 weeks). No adverse effects were observed except for very mild and transient diarrhea in 1 patient (10%). Two patients were treated with topical corticosteroids with only minimal effect. In 1 patient, neither administration of oral antihistamines for 14 days nor cholestyramine resin for 6 days proved beneficial. In these 3 patients, pruritus resolved completely only after delivery, within a maximum of 5 days.

LABORATORY FINDINGS

Total serum bile acid levels at the time of diagnosis were notably elevated in all patients (mean, 43.1 µmol/L; range, 11.3–138.0 µmol/L), whereas associated biochemical liver alterations were noted in only 10 cases (77%) (Table 1). These included elevated serum concentrations of aspartate aminotransferase (62%), alanine aminotransferase (46%), and γ-glutamyl transferase (23%). An increased total serum bilirubin level was observed in only 2 patients (15%), although clinically undetectable, with a highest value of 2.1 mg/dL (35.9 µmol/L) (normal range, 0.1–
1.2 mg/dL [1.7-20.5 µmol/L]). Total serum alkaline phosphatase levels were elevated in all patients, but alkaline phosphatase was most likely of placental origin, as usual in pregnancy, although isoenzymes were not determined.

Levels of total serum bile acids were correlated with fetal prognosis as determined by the t test; pregnancies complicated by fetal distress or prematurity exhibited significantly higher total bile acid levels than those with unimpaired fetal outcome (mean, 61.1 µmol/L vs mean, 21.8 µmol/L; P = .04). No statistically significant correlation was found for all other clinical, biochemical, or obstetric parameters investigated in this study.

**OBSTETRIC CHARACTERISTICS**

All 13 cases were single pregnancies. Premature delivery (before week 38 of pregnancy) occurred in 3 (30%) of the 10 patients treated with ursodeoxycholic acid (Table 1), at a mean of 36 weeks' gestation. In 2 of them (cases 11 and 12), fetal distress with pathological cardiotocogram led to induction of labor or cesarean delivery at 35 and 37 weeks' gestation, respectively. These 2 patients had the highest pretreatment levels of total serum bile acids measured within this series. The third patient experienced spontaneous delivery at 37 weeks' gestation. Interestingly, time of delivery was not correlated with the time of initiation of ursodeoxycholic acid. In contrast to this subgroup of patients, all 3 patients who were not treated with ursodeoxycholic acid experienced preterm delivery at a mean of 34 weeks' gestation. In 1 of these cases (case 7), labor had to be induced at 31 weeks' gestation because of severe fetal distress (pathological cardiotocogram and heavily meconium-stained amniotic fluid). In the other 2 patients, one experienced spontaneous delivery at 35 weeks' gestation and a mature fetus was induced at 37 weeks' gestation in the other. Of the babies born in this case series, 7 (54%) were male and 6 (46%) were female. Body weight was adequate for gestational age in all of them. No abnormalities were identified that could be associated with ICP or its treatment. Follow-up for up to 17 weeks postpartum showed normal growth and development in all infants.

**COMMENT**

We found a high frequency of ICP in this central European case series (6% of all pregnancy-associated dermatoses). In all 13 cases, ICP exclusively occurred in the...
second half of pregnancy, with sudden severe, generalized pruritus and then excoriations or prurigo nodularis developing with disease progression. Elevated total serum bile acid levels were diagnostic in all cases, whereas other liver function parameters were normal in one third or more of patients. The rate of preterm deliveries and fetal distress was significantly increased and correlated with levels of total serum bile acids. Therapy with ursodeoxycholic acid not only stopped maternal pruritus very effectively but also improved the rate of prematurity.

The frequency of ICP shows striking geographic and ethnic differences. While ICP is most common in South America, with the highest incidence rates observed in Chile (16%) (particularly among Araucanian Indian women [28%]) and Bolivia (9%), rates of only 0.1% to 1.5% have been described for Europe and North America, with “hot spots” in Scandinavia and the Baltic states (1%-2%).

Nevertheless, ICP represents an important dermatologic health issue, as reflected by the relatively high proportion of 6% of patients with ICP among all pregnancy-associated dermatoses in the present study.

The pathogenesis of ICP is multifactorial. A recurrence of ICP in 45% to 70% of subsequent pregnancies and a positive family history in up to 50% have been reported and may point to a genetic background of the disease.

In our series, recurrence was noted in 7 (88%) of 8 multiparous women, and 1 patient (9%) had a positive family history. Other postulated causes such as progesterone treatment, antibiotic treatment following urinary tract infection, or hepatitis C infection were not present in our patients. Historically, ICP has been associated with the cholestatic effect of estradiol metabolites, in particular 17-β-estradiol glucuronide. Progesterone metabolites, however, play an even more important role in its pathogenesis. The serum profile in ICP differs considerably from that seen in normal pregnancy. Excess of monosulfated or disulfated progesterone metabolites (in particular, the 3α- and 5α-isomers) in the urine of patients with ICP may be related to malfunction of biliary canalicular transporters normally responsible for their secretion from hepatocytes into bile. Several of these transporters have recently been characterized. Mutations in the ABCB4 gene, encoding a member of the ATP-binding cassette family of membrane transporters, and variants in the ATP8B1 gene have been identified in a small number of patients with ICP. Genetically linked mild dysfunction of canalicular transporters, which causes no problems in nonpregnant individuals or in the nonpregnant state, may lead to clinical symptoms of cholestasis when the transporters’ capacity to secrete substrates is exceeded, as occurs with the high levels of sex hormones produced in pregnancy. Environmental factors may also play a role, as suggested by the peak incidence of ICP in winter or the decreased prevalence in Sweden and Chile in association with improved selenium supply over the past decades. Only recently, an increased intestinal permeability (“leaky gut”), which has been demonstrated in several liver diseases, was also detected in patients with ICP. Reyes and coworkers postulated that a leaky gut may play a role in the pathogenesis of ICP by enhancing the absorption of bacterial endotoxins and the enterohepatic circulation of cholestatic metabolites of sex hormones and bile salts.

Intrahepatic cholestasis of pregnancy typically appears in the late second or third trimester of pregnancy, as it did in our patients. The usual scenario is the sudden onset of incapacitating pruritus, which often starts on the palms and soles but then becomes generalized. Of our cases, 2 (15%) that were presented shortly after the onset of pruritus had no further signs; the others all presented with secondary skin changes due to scratching, which varied from excoriations to prurigo nodularis lesions. Although jaundice has often been believed to be a common finding in ICP, it did not occur in any of our patients. Also Rioseco and colleagues noted jaundice in only 10% of patients with ICP, complicating the most severe and prolonged episodes. If present, jaundice may be associated with steatorrhea and subsequent vitamin K deficiency with increased risk for intrapartum and postpartum hemorrhage.

The differential diagnoses of ICP include primarily the other specific dermatoses of pregnancy. The categorization of these dermatoses has been controversial for decades. For instance, ICP has not been considered in this list until 1998. Also, the classification of prurigo of pregnancy and pruritic folliculitis of pregnancy was not defined because of a lack of a clear clinical and etiopathogenetic definition. In a large study of more than 500 pregnant patients with pruritus, we recently demonstrated significant overlap between these skin changes and eczema in pregnancy both clinically and histopathologically. We therefore introduced the term atopic eruption of pregnancy (AEP) to cover these dermatoses. Atopic eruption of pregnancy is defined as exacerbation of or the first occurrence of eczematous or papular skin changes during pregnancy in atopic individuals and is not associated with impaired fetal outcome.

The distinction between ICP and AEP, in particular its prurigo type, can be challenging. The most important diagnostic clue to discriminate ICP from AEP is gestational age. While ICP manifests in late pregnancy, the onset of AEP is considerably earlier, with 75% of cases occurring before the third trimester. Additional atopic skin features and frequently elevated IgE levels further support the diagnosis of AEP. The differentiation from pemphigoid gestationis and polymorphic eruption of pregnancy is usually straightforward because they always present with characteristic morphologic primary skin change. Other diagnostic considerations include drug reactions, scabies, and viral rashes, for which history, associated symptoms, and/or blood cell count can be helpful clues to the correct diagnosis. Intrahepatic cholestasis of pregnancy with jaundice should be distinguished from acute liver of pregnancy, pre-eclampsia complicated by increased levels of liver enzymes, hyperemesis gravidarum, viral hepatitis, hyperbilirubinemic states, drug-induced jaundice, and obstructive biliary disease, as well as hemolytic and metabolic diseases.

Most important for the diagnosis of ICP is a notable (>11-µmol/L) elevation of total serum bile acid levels. Total serum bile acid levels are slightly higher in pregnant than in nonpregnant women (mean±SD, 6.6±0.3 µmol/L vs 5.7±0.4 µmol/L), and levels up to 11.0 µmol/L.
are accepted as normal in late gestation. We and others could demonstrate elevated liver enzymes (20%-60%), in particular alanine aminotransferase, and γ-glutamyl transpeptidase levels (30%) in ICP. Because serum transaminase levels are normal or even lower and γ-glutamyl transpeptidase is usually lower in healthy pregnancies, any rise should lead to further tests. Since at least one third of patients have normal liver function test results, serum bile acid level analysis is mandatory when ICP is suspected. An upper abdominal ultrasound may be considered in patients with ICP with abdominal symptoms to exclude concomitant cholelithiasis, whereas liver or skin biopsies are unnecessary.

Fetal risks in ICP include spontaneous preterm delivery, meconium staining of amniotic fluid, and abnormal intrapartum heart rate in more than one third of cases. Perinatal morbidity attributable to prematurity has been detected in 10% to 15% of neonates. The most concerning consequence is the 3- to 5-fold increased risk for fetal death in utero. The cause of fetal distress and stillbirth in ICP is not fully understood, but acute placental anoxia due to abnormal uterine contractility and vasoconstriction of chorionic veins as well as impaired fetal cardiomyocyte function because of elevated bile acid levels seem to play a central role. An increased flux of bile acids from the mother to the fetus and a reduced ability of the fetus to eliminate bile acids across the placenta have been observed, and high bile acid levels have been found to be associated with more frequent occurrence of fetal distress, in particular with levels exceeding 40 µmol/L. Also among our patients, fetal risk increased with higher levels of total serum bile acids. We observed no stillbirths, but the rate of preterm delivery was 46% and of fetal distress, 23%. An association between early onset of pruritus and prematurity, as noted by others, was not observed among our patients. Neonatal weight was adequate for gestational age in all of our cases, irrespective of ursodeoxycholic acid treatment, arguing against a role for chronic placental insufficiency. Thus, neither growth nor development of the infants appear to be influenced by the disease or its treatment. Obstetric management of patients with ICP should include weekly cardiotocogram examination, starting at least at 34 weeks’ gestation. Because most intrauterine deaths occur after 37 weeks’ gestation, elective delivery at 37 weeks has been discussed to prevent intrauterine deaths. The obstetric challenge is to weigh the risk of such a premature delivery against the risk of sudden death in utero.

Treatment of ICP should ideally decrease maternal bile acid levels to prolong the pregnancy and reduce both fetal risk and maternal symptoms. Systemic treatment with antihistamines, epomediol, silymarin, phenobarbital, or activated charcoal have had only limited success. The role of S-adenosylmethionine is unclear, while suppression of fetoplacental estrogen production with dexamethasone was effective in a small uncontrolled trial. Anion exchange resins, such as cholestyramine resin, have only a minor effect on pruritus and may lead to vitamin K deficiency with the risk of antepartal fetal hemorrhage and intrapartum and postpartum maternal bleedings and should therefore not be considered as first-line therapy. Although not licensed for this indication in most countries, ursodeoxycholic acid, a naturally occurring hydrophilic nontoxic bile acid, is the treatment of choice for patients with ICP, and has been successfully used to improve clinical and liver function abnormalities in a variety of cholestatic liver diseases. It stimulates the excretion of hydrophobic bile acids, other potentially hepatotoxic compounds, and sulfated progesterone metabolites. Although the exact mechanism of action in ICP is still not fully understood, there is evidence that it corrects the maternal serum bile acid profile, decreases the passage of maternal bile acids to the fetoplacental unit, and improves the function of the bile acid transport system across the trophoblast, thus representing a valuable contribution to fetal well-being and outcome.

Ursodeoxycholic acid is safe for both mother and fetus and is the only treatment that can reduce the risk of premature delivery with perinatal morbidity. In the present study, ursodeoxycholic acid was used to treat 10 of 13 cases. Of these 10 cases, 3 (30%) involved preterm deliveries compared with a 100% preterm delivery rate in the 3 cases not treated with ursodeoxycholic acid. With the exception of 1 patient who experienced transient, mild diarrhea, ursodeoxycholic acid was tolerated without adverse effects in all our patients.

In conclusion, pruritus in pregnancy, particularly in the last trimester, must never be neglected, and its workup should always include laboratory assessment of total serum bile acid levels to exclude or confirm ICP. Because ICP may be associated with severe fetal risks, including premature birth, intrapartal fetal distress, and stillbirth, early diagnosis, close obstetric surveillance, and prompt treatment with ursodeoxycholic acid are essential. Dermatologists have an important role in detecting and treating ICP and therefore need to be familiar with its diagnostic criteria and therapeutic options.

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REFERENCES