Intrahepatic Cholestasis of Pregnancy: A French Prospective Study

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The aim of this prospective study was to analyze the characteristics of intrahepatic cholestasis of pregnancy (ICP) in a French population. From 1989 to 1995 we studied 50 consecutive pregnant women with ICP (41 single, 7 twin, and 2 triplet pregnancies) referred for hepatologic consultation. All patients suffered from pruritus and/or jaundice associated with elevated fasting serum levels of total bile acids (mean 49 μmol/L, range 7-290). No patients had concomitant liver disease and all recovered normal liver function after delivery. Overall prematurity rate was 60%: 100% in multiple pregnancies and 41% in single pregnancies. Three of 61 babies died. Systematic clinical interviews revealed that 34 patients had been treated with oral micronized natural progesterone (200-1,000 mg/d) during the current pregnancy for risk of premature delivery, including at least 32 (64%) before the onset of pruritus. Onset of pruritus was statistically earlier in patients previously receiving progesterone than in patients not receiving progesterone (217 $\pm$ 21 vs. 240 $\pm$ 26 days, $P < .01$). This was also found in the single pregnancy subgroup of patients (222 $\pm$ 19 vs. 240 $\pm$ 26 days, $P < .05$). Pruritus disappeared before delivery in 10 of 50 patients, i.e., after withdrawal of progesterone in 7 patients (only one concurrently treated with cholestyramine), after decrease in dose of progesterone in 1 patient, and spontaneously in 2 patients. During the same period, the percentage of pregnant women without ICP who had been treated with progesterone during pregnancy was statistically lower than the percentage of patients treated with progesterone before the onset of pruritus in our group of patients with ICP (36% vs. 64%, $P < .01$, odds ratio 3.16, 95% CI:1.29-7.80). These results suggest that orally administered progesterone might be an exogenous factor which triggers ICP in predisposed women. (HEPATOLOGY 1997;26:358-364.)

Intrahepatic cholestasis of pregnancy (ICP) is a liver disease unique to pregnancy, which occurs in the second or third trimesters and disappears spontaneously after delivery. The occurrence of ICP carries a risk for the fetus and pruritus is a very uncomfortable symptom for the mother. Specific surveillance and treatment are recommended.[1,2]

Abbreviations: ICP, intrahepatic cholestasis of pregnancy; TBA, total bile acid; ALT, alanine aminotransferase; LFT, liver function test; AP, alkaline phosphatase; GGT, γ-glutamyl transpeptidase; AST, aspartate aminotransferase; UDCA, ursodeoxycholic acid.

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The prevalence of ICP varies greatly according to country. The prevalence is high in Scandinavian countries (1%-1.5%),[3,4] in Bolivia (9.2%),[5] and in Chile, with a prevalence of between 11.8% and 27.6% according to ethnic origin.[6] In Santiago the prevalence of ICP was recently evaluated at 4%.[7] In contrast, the prevalence is reported to be low in the United States,[8] Canada,[9] and Switzerland.[10] In France the prevalence has been assessed to be 0.2% to 0.5%[11,12] and ICP has not often been studied.

The aim of this prospective study was to analyze characteristics of ICP in France.

PATIENTS AND METHODS

Patients

Fifty consecutive patients with ICP referred for hepatologic consultation from 1989 to 1995 were studied. The criteria for diagnosis of ICP were: 1) pruritus and/or jaundice; 2) increased serum total bile acid (TBA) concentration and/or increased serum alanine aminotransferase (ALT) activity; 3) absence of current viral hepatitis and cytomegalovirus and Epstein-Barr virus infections; 4) absence of biliary tract dilatation on ultrasound examination; 5) absence of dermatological disease except lesions caused by scratching; and 6) normalization of routine liver function tests (LFTs) after delivery. Signs of pre-eclampsia, fever, and urinary or endocervical infection were exclusion criteria. In cases of recurrent ICP the first occurrence during the period under study was taken into account for the description of characteristics.

Methods

Biological Tests. Fasting blood samples were taken and serum TBA and total bilirubin and conjugated bilirubin concentrations, and serum ALT, alkaline phosphatase (AP), and γ-glutamyl transpeptidase (GGT) activity, were measured at least twice, for each patient. In fact, this was usually once or twice a week until delivery. Serum aspartate aminotransferase (AST) and 5′ nucleotidase activity was measured in 19 and 44 patients, respectively. Prothrombin time, creatininemia, and uricemia were also regularly monitored. For each patient, the most abnormal values, i.e., the highest values for LFTs, uricemia, creatininemia, and the lowest values for prothrombin time were retained for the calculation of the biological characteristics. Correlations were calculated between serum TBA concentrations and the other LFTs for the same blood sample. Serum ALT, AST, AP, and GGT activity and serum levels of total and conjugated bilirubin concentrations were measured by routine techniques. Serum 5′ nucleotidase activity was measured by Bertrand and Buret's method (Enzyline® 5′NU, Biomérieux, Marcy-L'etoile, France).[13] Serum values of TBA were measured by Mashige and Osuga's method (Enzabile®, NYCOMED AS, Oslo, Norway).[14] Enzyme activity values are expressed as IU/L at 30°C, with the exception of serum 5′ nucleotidase activity that is expressed as IU/L at 37°C. The upper limits of normal values in our laboratory for nonpregnant women were 90 IU/L for AP, 35 IU/L for ALT, 25 IU/L for AST, 15 IU/L for GGT, 17 μmol/L for total bilirubin, 9 IU/L for 5′nucleotidase, and 6 μmol/L for TBA, respectively.

TABLE 1. Liver Function Tests and Prothrombin Time in Patients With ICP

Test	N	Normal*	Mean	SD	Extremes
TBA	50	≤6 μmol/L	49	43	7-290
ALT	50	≤35 IU/L	322	216	24-839
AST	19	≤25 IU/L	196	123	25-522
Total bilirubin	50	≤17 μmol/L	25	18	4-78
GGT	50	≤15 IU/L	22	17	6-90
AP	50	≤90 IU/L	231	78	115-525
5′nucleotidase	44	≤9 IU/L	13	5	5-33
Prothrombin time	49	≥75%	94	11	58-100

NOTE. The most abnormal value, i.e., the highest values for LFTs and the lowest value for prothrombin time during pregnancy, were retained for each patient.

* Normal value in non-pregnant women.

Serological tests for viral hepatitis A, B, and C (hepatitis B surface antigen, anti-hepatitis B core, anti-hepatitis A virus immunoglobulin M, anti-hepatitis C virus) were performed for all patients and were negative except for one anti-HBc positive serum that was negative for anti-hepatitis B core immunoglobulin M and hepatitis B surface antigen. A second- or third-generation enzyme-linked immunoabsorbent assay (Ortho Diagnostic Systems, Raritan, NJ) was used for detection of anti-hepatitis C virus. Serological tests for cytomegalovirus and Epstein-Barr virus infections were performed with routine procedures. When appropriate these serological tests were performed on sera taken during the episode of ICP and conserved at −20°C.

Evaluation of Progesterone Intake in Pregnant Women Without ICP. In view of the results of the prospective study, we performed a retrospective study of intake of progesterone in a series of 50 pregnant women without ICP attending our Center during the same period. Each patient with ICP was matched with a control pregnant woman randomly selected for parity, single or multiple pregnancy, and year of delivery. Patients with pruritus or jaundice, dermatological disease, signs of pre-eclampsia, or infection were not included in this control group.

Statistical Analysis. Results are expressed as mean ± SD with extremes. The nonparametric Mann Whitney *U* test, and the χ^2 test or Fisher-Irwin exact test were used for comparison as appropriate. Correlations were calculated by Spearman's correlation coefficient. Differences with a P value $< .05$ were considered stastitically significant.

RESULTS

Clinical Characteristics. Mean age was 29 years (18-39 years). Forty-seven patients were French, one was Portuguese, one Spanish, and one Algerian. Only one mother of a patient had suffered from pruritus during pregnancy.

During the episode of ICP under study, 49 patients experienced pruritus and of these, 5 had jaundice that appeared after onset of pruritus. Onset of pruritus was at 32 ± 4 weeks' gestation (24-39 weeks). Onset of pruritus occurred after 28 weeks' gestation (third trimester) in 37 patients (76%). For 38 patients pruritus disappeared after delivery (mean 3.5 days, 1-30 days) and for 10 patients pruritus disappeared before delivery (mean 10.8 days, 2-30 days). The time of disappearance of pruritus was not known for one patient. The relationship between the disappearance of pruritus before delivery and withdrawal of drugs, especially natural progesterone, is detailed below.

Only one patient had jaundice without pruritus. The patient was a 36-year-old Algerian, gravida III, para II, with a twin pregnancy and no history of pruritus during two previous pregnancies. At 30 weeks' gestation she was treated with salbutamol for risk of preterm delivery. Four weeks later she suffered from jaundice not preceded by pruritus. The LFT results were TBA, 97.5 μmol/L; ALT, 182 IU/L; GGT, 16 IU/L; AP, 236 IU/L; total bilirubin, 48 μmol/L; and prothrombin time, 100%. Ultrasound examination of the liver and biliary tract and liver computed tomography scan were normal. Cesarian section was performed at 34 weeks' gestation. The mother recovered normal liver function after delivery. Histological examination of the liver biopsy performed during the cesarian section revealed only cholestatic lesions. Two years later the patient and her twins were well.

Two patients experienced nausea without vomiting. No patients experienced abdominal pain or encephalopathy.

Biological Characteristics. Fasting serum TBA concentrations, routine LFTs, and prothrombin time are shown in Table 1. Serum TBA concentration was higher than the upper normal limit in all patients. Serum ALT activity remained in normal limits in three patients. ALT levels were greater than ten times the upper normal limit, i.e., 350 IU/L, in 20 patients (40%). TBA and/or ALT levels remained abnormal until delivery even when pruritus disappeared before delivery. Serum AST activity was measured in 17 patients on the day of maximum serum ALT activity and there was a good correlation between AST and ALT serum activities ($r = .75$, $P < .01$). This good correlation was also found when evaluated on the day of maximum serum TBA concentration ($r = .88$, $P < .001$). Serum GGT activity was increased in 28 patients (56%). It was equal to or lower than twice the upper normal limit in 42 patients (84%). Serum 5′ nucleotidase activity was increased in 36 of 44 patients (82%). No correlation or a poor correlation was observed between serum TBA concentrations and routine LFTs (Table 2). Prothrombin time was <75% in four patients with normal factor V. Prothrombin time normalized after parenteral administration of vitamin K. Creatininemia was 76 ± 21 μmol/L (47-193 μmol/L) and uricemia was 347 ± 96 μmol/L (203-712 μmol/L).

Ultrasound examination of the liver was normal in all patients. Two patients had small vesicular polyps, three patients had gallbladder stones, and biliary sludge was observed in two other patients. No patients had dilatation of the biliary tract.

Medical Treatment. Cholestasis was treated with cholestyramine (Questran®, Bristol-Meyers Squibb Laboratoires ALLARD, Paris-La Défense, France) in 27 patients. This treat-

TABLE 2. Correlation Between Fasting Serum TBA Concentrations and Other Liver Function Tests in 50 Patients With ICP

ALT	$r = .35$	$P < .05$
AST*	$r = .02$	P = NS
GGT	$r = .23$	P = NS
AP	$r = .02$	P = NS
5′nucleotidase†	$r = .25$	P = NS
Total bilirubin	$r = .32$	$P < .05$
Conjugated bilirubin	$r = .43$	$P < .05$

NOTE. Correlations were calculated between serum TBA concentrations and other LFTs for the same blood sample. The blood sample with the highest value for TBA concentrations was retained for each patient.

Abbreviations: r, Spearman's correlation coefficient; NS, nonsignificant.

* Measured in 17 patients.

† Measured in 40 patients.

ment was discontinued in two patients because of diarrhea or abdominal pain. Mean maximum dose of cholestyramine was 13 ± 5 g/d (4-24 g/d). The pruritus disappeared before delivery in only one patient treated with cholestyramine, and in this patient progesterone treatment was concurrently withdrawn. None received ursodeoxycholic acid treatment. Twenty-one patients received a supplement of parenteral vitamin K, and 26 patients received hydroxyzine to reduce the discomfort of pruritus.

Obstetric and Fetal Characteristics. Forty-one patients had a single pregnancy, 7 a twin pregnancy, and 2 a triplet pregnancy. Twenty-five patients were primipara. Labor was induced in 22 cases and cesarean section was performed in 20 cases (33%). One patient, with a normal prothrombin time, suffered from hemorrhage during delivery without requiring blood transfusion.

Mean gestational age was 259 ± 14 days (210-284 days), i.e., 37 ± 2 weeks' gestation. Of the 60 live births, 36 babies (60%) were delivered before 37 weeks' gestation and 26 babies weighed < 2,500 g. The incidence of premature delivery in multiple pregnancies was 100% and in single pregnancies 41%.

Three of 61 babies died. One baby died at 7 days because of extreme prematurity (triplet pregnancy) and one baby was stillborn. This female infant was born of a 30-year-old woman, gravida II, para II, with a single pregnancy and without previous history of ICP. The patient had been treated with salbutamol without progesterone during her first pregnancy. The current pregnancy was uncomplicated until 22 weeks' gestation when natural progesterone was initiated for premature uterine contractions. At 35 weeks' gestation the patient was admitted with an 8-day history of pruritus, abnormal LFTs, and disappearance of fetal movement. On admission fetal heartbeat could not be detected. The LFT results were fasting TBA, 290 μmol/L; nonfasting TBA, 350 μmol/L; ALT, 194 IU/L; GGT, 36 IU/L; AP, 265 IU/L; total bilirubin, 34 μmol/L; and prothrombin time, 100%. Delivery was induced and the infant weighing 2,200 g was stillborn. Histological examination of the fetus and placenta showed no malformation. LFTs normalized after delivery. The patient became pregnant again 4 months later. The pregnancy was closely monitored and at 32 weeks' gestation there was a slight 48-hour increase in serum ALT activity (50 IU/L) with normal serum TBA concentration and no pruritus. Serum ALT activity normalized spontaneously. The patient delivered a normal female infant weighing 3,200 g spontaneously at 37 weeks. It was considered that ICP had not recurred in this patient. Thus the perinatal mortality was 32% (2/61). A third baby died at 15 days because of a streptococcal infection (single pregnancy).

Medication During Pregnancy Under Study. Drugs, especially natural progesterone and beta-mimetics, were explored systematically during hepatologic consultations.

Thirty-four patients (68%) had been treated with oral micronized natural progesterone (Utrogestan®, Laboratoires BESINS-ISCOVESCO, Paris, France) for risk of premature delivery, i.e., premature uterine contractions or cervical modifications. Mean maximum dose of natural progesterone was 548 ± 199 mg/d (200-1,000 mg/d) and mean duration of treatment was 68 ± 50 days (8-196 days). For at least 32 patients (64%) pruritus appeared after initiation of progesterone treatment, for one patient pruritus occurred before progesterone ingestion and for another the relationship between initiation of natural progesterone intake and onset of pruritus was not clearly established. Mean onset of pruritus after initiation of progesterone treatment was 55 ± 48 days (−7 to 193 days). In the most recent cases, natural progesterone was usually withdrawn when ICP was diagnosed. Of the 10 patients for whom the pruritus disappeared before delivery, eight had been treated with natural progesterone for risk of premature delivery. Pruritus disappeared after withdrawal of progesterone in seven patients (only one concurrently treated with cholestyramine) and 1 day before withdrawal of progesterone in one patient; indeed, in this patient pruritus disappeared after decreasing the dose of progesterone. In other words, natural progesterone was withdrawn before delivery in 13 patients not treated with cholestyramine. Pruritus disappeared after withdrawal of progesterone and before delivery in six of these patients, and 1 day before withdrawal of progesterone but after decreasing the dose of progesterone in another patient. Of these seven patients, serum TBA concentration and serum ALT activity decreased in four, and ALT serum activity decreased in two others. Treatment with natural progesterone was never reintroduced during the same pregnancy. Age, number of primipara, total bilirubin, and serum TBA concentrations and ALT serum activity were not statistically different between patients receiving progesterone before the onset of pruritus and patients not receiving progesterone (Table 3). Delivery was earlier and the number of multiple pregnancies was higher in patients receiving progesterone. Onset of pruritus was statistically earlier in patients receiving natural progesterone before onset of pruritus (217 ± 21 vs. 240 ± 26 days, $P < .01$) and this was also found in the subgroup of patients with single pregnancies (222 ± 19 vs. 240 ± 26 days, $P < .05$).

Twenty-three patients (46%) had been treated with salbutamol administered orally, intravenously or per rectum for premature labor. Only one patient received salbutamol without natural progesterone, i.e., the patient who suffered from jaundice without pruritus. For 19 patients pruritus appeared after initiation of salbutamol treatment. All these patients had also been treated with natural progesterone before the onset of pruritus. The onset of pruritus was not statistically different between patients receiving salbutamol before onset of pruritus and patients not receiving salbutamol (219 ± 22 vs. 229 ± 27 days). In contrast, delivery was earlier in the

TABLE 3. Characteristics of Patients Suffering From ICP With or Without Ingestion of Natural Progesterone Before Onset of Pruritus

	With (n = 32)	Without (n = 15)	*P*
Age (yr)	29 ± 5	29 ± 5	NS
Primipara	17/32	6/15	NS
TBA (μmol/L)	53 ± 18	37 ± 22	NS
ALT (IU/L)	344 ± 221	286 ± 226	NS
Total bilirubin (μmol/L)	24 ± 18	22 ± 16	NS
Multiple pregnancy	8/32	0/15	<.05
Term (d)	254 ± 13	271 ± 9	<.001
Onset of pruritus (d)	217 ± 21	240 ± 26	<.01

NOTE. Of 50 patients, one patient did not suffer from pruritus, for one patient pruritus occurred before progesterone ingestion, and for another the relationship between the initiation of progesterone ingestion, and onset of pruritus was not clearly established. Data are expressed as mean ± SD.

Abbreviation: NS, nonsignificant.

group of patients receiving salbutamol before onset of pruritus (250 ± 15 vs. 266 ± 10 days, $P < .001$). Of the 10 patients for whom pruritus disappeared before delivery, five were treated with salbutamol concurrently with progesterone; pruritus disappeared before withdrawal of salbutamol in three patients, on the day of withdrawal of salbutamol in one, and after withdrawal of salbutamol in one another.

One patient had been treated with dydrogesterone (Duphaston®, SOLVAY PHARMA Duphar, Suresnes, France), for 4 days, instead of natural progesterone, after onset of pruritus.

Recurrent ICP. Of the 25 multipara, 10 patients had suffered from pruritus during a previous pregnancy. Four of these 25 multipara gave birth after subsequent pregnancies and ICP recurred in two patients. At least 8 of 25 primipara became pregnant again and ICP recurred for five. Thus, 15 patients of 33 multipara suffered from recurrent ICP (45%). Six of 32 patients receiving progesterone before the onset of pruritus successfully gave birth after further pregnancies, each time without receiving progesterone, and ICP recurred in three patients.

Oral Contraceptives. Forty-four patients had taken oral contraceptives before the ICP episode under study and none had suffered from pruritus during this period of contraception. After these episodes of ICP, at least 24 patients received oral contraceptives, 9 received progestogens without ethynilestradiol, and 15 an association of ethynilestradiol and progestogen. Only one patient suffered from pruritus with abnormal LFTs during this period of oral contraception (20 μg ethynilestradiol + 150 μg desogestrel). The oral contraceptive was withdrawn and LFTs normalized. This patient had had two previous episodes of ICP.

Progesterone Intake in Control Population of Pregnant Women Without ICP. In the 50 control patients, 18 (36%) had been treated with natural progesterone during pregnancy for premature uterine contractions or cervical modifications. The percentage of pregnant women in this control group who had been treated with progesterone during pregnancy was statistically lower than the percentage of patients treated with progesterone before the onset of pruritus in the group of patients with ICP (36% vs. 64%, $P < .01$, odds ratio 3.16, 95% CI:1.29-7.80).

DISCUSSION

This prospective study defines the clinical and biological characteristics of ICP in a French population and contributes to greater understanding of this disease. Patients with a potential cause of liver disease other than ICP, especially preeclampsia/eclampsia and urinary infection, were arbitrarily excluded from this study to obtain a homogeneous group of ICP patients. Indeed, liver lesions are common during preeclampsia/eclampsia[15] and bacterial infection can induce cholestasis.[16,17] It could therefore be considered that our 50 patients suffered from "pure" ICP.

Only six of our patients (12%) had jaundice, as in another study.[10] The greater frequency of jaundice in some studies could be caused by a concomitant urinary tract infection.[1] ICP with jaundice but without pruritus is rare[18] and we observed only one case.

Measurement of serum ALT activity is a sensitive test for the diagnosis of ICP.[19] In our study, serum ALT activity was increased in 94% and was particularly high in 40% of patients, as previously described in some case reports.[20] This high increase of serum ALT activity suggests current viral hepatitis that should be ruled out with suitable serological tests. The increase might be because of an increase in membrane permeability because liver histology does not usually reveal necrotic lesions, as we observed in two patients for whom liver biopsy was performed.

Serum GGT activity was increased in half of our patients but this increase was often slight. The values were not correlated with TBA serum concentrations, suggesting that serum GGT activity is not a good indicator of cholestasis during pregnancy.

Serum 5′ nucleotidase activity was also often slightly increased.

Increased bile acid serum concentration is a very sensitive marker of cholestasis during pregnancy.[21-23] Indeed, in our study fasting serum TBA concentration was always increased. However, it was sometimes very moderate whereas serum ALT activity was clearly increased. We believe that both tests should be performed for the diagnosis of cholestasis during pregnancy, especially when a pregnant woman suffers from pruritus. We therefore routinely perform these tests for the diagnosis of ICP, although at the present time evaluation of TBA concentration is not usually considered as a routine LFT in France, even during pregnancy. Evaluation of serum TBA concentration has been also suggested for fetal assessment in ICP. In fact, a relationship between maternal serum bile acid levels and fetal distress has been found in two studies.[19,24] The relationship between serum bile acid concentrations and other LFTs has previously been evaluated in only three studies. Serum transaminase activities were not correlated with serum cholic acid concentrations.[19] Similarly, in another study with 18 patients, no statistically significant correlation was found between serum bile acid concentrations and serum transaminase activity, serum PA activity, and bilirubinemia.[25] In a third study with 45 patients, there was a poor correlation between serum cholic acid or chenodesoxycholic acid and serum ALT, AST, PA activities, and bilirubinemia.[26] In our study there was little or no correlation between serum TBA concentrations and other LFTs, i.e., ALT, AST, GGT, AP, 5′ nucleotidase, and total bilirubin. This supports routine evaluation of serum TBA concentrations during pregnancy, not only to diagnose but also to monitor ICP.

Prothrombin time may be reduced in prolonged cholestasis, especially when patients have been treated with cholestyramine. Vitamin K deficiency should be anticipated and treated before delivery to prevent hemorrhage. This contributes to good maternal prognosis.

ICP carries a high risk for the pregnancy because of risks of premature delivery and stillbirth.[27] The main complication of ICP is fetal prematurity. The overall prematurity rate in our study was 60% compared with 8% for all births in our Hospital in 1994. This was higher than that observed in other countries where the prematurity rate was 33% to 36%.[28,29] This might have been related to the high rate of multiple pregnancies in our series (18%). Indeed the multiple pregnancy rate in our series was much higher than that generally observed in France (1%). This is not surprising because it has been shown that ICP is more frequent in twin pregnancies.[30] The rate of prematurity for single pregnancies (41%) in our study was similar to studies performed in other countries and was also much higher than the prematurity rate

observed in France in 1988-89 (4%).[31] In a recent study performed in Chile the overall prematurity rate was 19% in patients with ICP compared with 6.8% in the control group.[32] The other complication of ICP is the risk of sudden fetal death. The case of sudden fetal death in our study occurred at 35 weeks' gestation. The maternal serum TBA concentration was particularly high, indeed the highest that we observed. This emphasizes that very high serum bile acid levels should be considered as a high risk for sudden fetal death. The rates of pre- and perinatal mortality were approximately similar to previous studies.[4,24,25,32,33] Perinatal mortality for all births in our Center was 15.6% in 1994. The fact that delivery was earlier in patients receiving progesterone or salbutamol before the onset of pruritus than in patients not receiving these drugs is not surprising because these drugs were prescribed for a risk of premature delivery.

The administration of oral contraceptives to women with a history of ICP could result in cholestasis.[18] However, ICP is not an absolute contraindication for oral contraceptives.[34] We consider that oral estroprogestogen contraception with a low dosage of estrogen (i.e., 20 or 30 μg ethynilestradiol) could be initiated after normalization of LFTs but the patient should be informed that there is a possibility of pruritus during such contraception. Only one of our patients suffered from pruritus with abnormal LFTs during oral contraception.

The cause of ICP is unknown. However, the results of previous epidemiological and clinical studies suggest genetic, hormonal, and exogenous factors. The genetic factors could explain familial cases and the higher incidence in some ethnic groups such as the Araucanos Indians of Chile.[6] Only one of our patients had a family history of pruritus during pregnancy. The role of estrogens has been clearly established in ICP.[27,35,36] Animal studies have shown that estrogens, in particular ethynilestradiol, are cholestatic. Genetically determined anomalies might lead to particular hepatic reactions to estrogens and/or estrogen metabolism dysfunction.[27] The role of progesterone is less clear. One hypothesis, based on the abnormalities of progesterone metabolism found in ICP, has been suggested as an alternative to the role of estrogens in the development of ICP.[37] Meng et al. have hypothesized that the formation of large amounts of sulfated progesterone metabolites, possibly related to an increased relative importance of 5-alpha and 3-alpha reductions, may in some genetically predisposed women, result in a saturation of the hepatic transport system(s) used for biliary excretion of these compounds.[37] Our results are in agreement with this hypothesis. The dosage of progesterone prescribed in our patients is similar to the synthesis of progesterone during normal pregnancy (250-500 mg/d).[37] Oral natural progesterone may impose an additional load on the transport system of sulfated metabolites. Further studies at a molecular level of the system involved in the transport and secretion of the sulfated progesterone metabolites and the connection with bile acid transport and bile secretion are necessary to confirm this hypothesis.[37] Some characteristics of ICP suggest that exogenous factors might be associated with the genetic factors[1]: 1) ICP is recurrent in only 60% to 70% of pregnancies in multiparous women.[1] In our study, ICP recurred in only 45% of multiparous patients and the patient with a stillbirth suffered from ICP during only one of her three pregnancies, in fact the pregnancy during which she received progesterone. 2) The reported seasonal variability is difficult to explain with genetic factors alone.[3,4,38] 3) Changes of prevalence of ICP in Sweden[4] and Chile[38] also suggest exogenous factors. However, until now no particular exogenous factor has been clearly established in the phenotypic variability of ICP.[1]

Our findings suggest that oral natural progesterone prescribed for risk of premature delivery could be such an exogenous factor. Micronized natural progesterone is used orally in the treatment of premature labor.[39] This hormone has been reported to increase the tocolytic effect of beta-mimetics and could permit reduction of the dosage of beta-mimetics.[40] Nevertheless, the effectiveness of this treatment in decreasing perinatal mortality and morbidity has not yet been clearly established.[41] Progesterone is usually well tolerated.[39] However, in a previous study of 13 patients with ICP we noted that most patients had been treated with natural progesterone before the onset of pruritus.[42] Elevated serum transaminase activity was also recently reported in four pregnant women treated with micronized natural progesterone (Utrogestan®).[43] In our prospective study pruritus occurred earlier in patients who had received progesterone. This was not found with salbutamol, another treatment for premature labor. Moreover, withdrawal of progesterone led to disappearance of pruritus with improved LFTs in half the patients, without specific concurrent treatment of cholestasis. However, serum ALT activity and/or serum TBA concentration did not normalize before delivery. This suggests that progesterone is an additional factor and not the only cause of the disease. Finally, in our Center we observed a statistical difference in progesterone intake during pregnancy between patients with and without ICP.

The role of salbutamol in the development of ICP in our patients appears to be unlikely, although interaction with natural progesterone cannot be entirely ruled out in some patients. Salbutamol is not considered as hepatotoxic and in our study pruritus did not occur earlier in patients who had or had not received salbutamol during pregnancy.

Ursodeoxycholic acid (UDCA) has been used successfully in various chronic cholestatic liver diseases.[44,45] UDCA was reported to be effective in ICP in some case reports[46,47] and in an open pilot study comprising eight patients with severe ICP.[48] In these patients UDCA improved pruritus and LFTs. No side effects were reported for mothers or babies. However, because the safety of UDCA for the baby has not yet been clearly established[49] UDCA is currently contraindicated during pregnancy in France. We therefore did not use UDCA for the treament of ICP in the patients of this study. Recently the efficacy and safety of UDCA was confirmed in three controlled studies. In a double-blind placebo-controlled study comprising 15 patients with severe ICP, i.e., onset of disease before week 32 of pregnancy, UDCA (mean daily dose 14 mg/kg) attenuated pruritus and appeared to improve the outcome of pregnancy and fetal prognosis.[50,51] In the second controlled trial comparing the efficacy of *S*-adenosylmethionine (100 mg/d, intramuscularly) and UDCA (450 mg/d) in 20 patients with ICP, UDCA was more effective than *S*-adenosylmethionine in controlling pruritus and serum total bile acid levels.[52] In the third study comprising 19 patients treated for at least 2 weeks with UDCA (10 mg/kg/d up to 1 g/d) or placebo, UDCA improved pruritus but not biochemical tests.[53] Again, no side effects were reported for the offspring. Although the number of patients treated is still small, all these findings suggest that UDCA seems to be safe during

pregnancy and may be useful in improving cholestasis and fetal prognosis in patients with severe ICP. In the more frequent milder cases of ICP and with the current state of our knowledge, it is probably not advisable to add the potential theoretical risk of UDCA.[50]

In conclusion, our results suggest that orally administered progesterone might be an exogenous factor that triggers ICP in predisposed women. The possibility of improving cholestasis after withdrawal of progesterone should be considered in future studies of ICP. We also consider that natural progesterone should be avoided in patients with a previous history of ICP and that such treatment should be immediately withdrawn when cholestasis occurs during pregnancy.

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