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Ursodeoxycholic acid therapy in intrahepatic cholestasis of pregnancy: Results in real-world conditions and factors predictive of response to treatment

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ABSTRACT

Background: Ursodeoxycholic acid (UDCA) therapy is commonly used in intrahepatic cholestasis of pregnancy (ICP).
Aim: To evaluate the efficacy and tolerance of UDCA in real-world conditions and to search for factors predictive of response to treatment.
Methods: This observational study included 98 consecutive patients suffering from pruritus during pregnancy associated with increased ALT levels or total bile acid (TBA) concentrations, without other causes of cholestasis. The entire ABCB4 gene coding sequence was analyzed by DNA sequencing.
Results: UDCA was prescribed until delivery in all patients (mean dose 14.0 mg/kg/day; mean duration 30.4 days). Pruritus improved in 75/98 (76.5%) patients, and totally disappeared before delivery in 25/98 (25.5%). After 2–3 weeks of treatment, ALT levels decreased by more than 50% of base line in 67/86 (77.9%) patients and normalized in 34/86 (39.5%), and TBA concentrations decreased in 28/81 (34.6%). Only one patient stopped the treatment before delivery. On multivariate analysis, ALT >175 IU/l before treatment was associated with improvement of pruritus (OR 2.97, 95% CI 1.12–7.89, P = 0.029) and with decreased ALT (OR 18.61, 95% CI 3.94–87.99, P = 0.0002). ABCB4 gene mutation was not associated with response to treatment.
Conclusion: This study supports the use of UDCA as first line therapy in ICP.

1. Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a liver disorder which usually manifests during the second or third trimester of pregnancy, and then spontaneously improves after delivery [1]. ICP is characterized by generalized pruritus associated with an increase in serum aminotransferase activity and/or in serum bile acid concentration [2]. Pruritus may engender considerable discomfort, and the potential risks for pregnancy include premature delivery or sudden intrauterine fetal death (IUFD) [1,3]. ICP is a complex disease associated with hormonal and genetic factors [4,5]. Mutations in various genes encoding canalicular transporters have been found in patients with ICP, especially mutations in the ABCB4 (adenosine triphosphate-binding cassette, sub family B, member 4) gene encoding the canalicular transporter MDR3 [6,7]. The medical treatment of ICP is currently mainly based on ursodeoxycholic acid (UDCA) [8–10]. Based on a meta-analysis of nine randomized controlled trials (RCTs), and on the results of two recent RCTs not included in the metaanalysis, UDCA significantly reduces pruritus, and the levels of serum alanine aminotransferase activity and of bile acid concentration in patients suffering from ICP [11–13]. However data on the efficacy and tolerance of UDCA in real-world conditions are limited, and factors predictive of response to treatment with UDCA are unknown.

The aim of this study was to evaluate the efficacy and tolerance of UDCA in a real-world setting, and to search for factors predictive of response to treatment.

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2. Patients and methods

2.1. Design of the study

This was a single-center non-interventional study. All medical records of patients referred for hepatology consultation at the University Hospital Center of Tours (France) for liver disease during pregnancy and treated with UDCA between January 1999 and December 2013 were reviewed. All women were followed jointly by a single Hepatologist and the obstetric teams of several public or private hospitals. The patients were systematically examined after delivery for clinical evaluation and to check the results of liver function tests (LFTs). Patients with persistent abnormal LFTs were monitored in the longer term. The present study was approved by the Ethics Committee in Human Research of Tours, France (number 2014 027).

2.2. Inclusion and exclusion criteria

The criteria for inclusion in the analysis were: (1) occurrence of generalized pruritus during the current pregnancy, (2) fasting serum total bile acid (TBA) concentrations >10 μmol/l or alanine aminotransferase (ALT) levels >35 IU/l on at least two samples, (3) treatment by ursodeoxycholic acid, and (4) absence of intercurrent liver disease. The criteria for exclusion were: specific dermatosis of pregnancy, intercurrent acute or chronic viral hepatitis, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, benign recurrent intrahepatic cholestasis, intercurrent drug-induced liver injury, sepsis at diagnosis, treatment with UDCA before pregnancy, or loss to follow-up after delivery.

2.3. Data collection

The information researched in the medical records of the patients included: (1) past history, especially cholestasis during pregnancy, (2) characteristics of the current pregnancy, (3) evaluation of pruritus under UDCA therapy, (4) results of LFTs (see below), prothrombin time, serologic markers of viral hepatitis A, B, and C, and of cytomegalovirus and Epstein Barr Virus infections, and serologic markers of autoimmunity, (5) results of ultrasonography of liver and bile ducts, (6) modalities of treatment with UDCA, and other medications, (7) modalities of delivery, (8) characteristics of the newborn (birth weight, Apgar score at 5 min), and (9) maternal evolution after delivery. Whenever patients had been treated with UDCA for several episodes of ICP, only the first episode of ICP treated by UDCA was taken into account in the analysis.

2.4. Liver function tests

LFTs were measured in fasting state and included routine LFTs i.e., ALT, aspartate aminotransferase (AST), alkaline phosphatase (AP), gamma-glutamyl transpeptidase (GGT), and total and conjugated bilirubin, and the determination of serum TBA concentrations by an enzymatic method (Enzabile NYCOMED AS, Oslo, or Biostat diagnosis system, Cheshire) when available. LFTs were performed before the initiation of treatment with UDCA, regularly (usually once a week) under UDCA therapy until delivery, and after delivery. The results of LFTs are given at 37 °C. According to the references used by our laboratory for non-pregnant women, the following values were considered as upper normal limits: 35 IU/l for ALT, 30 IU/l for AST, 120 IU/l for AP, 35 IU/l for GGT, 17 μmol/l for total bilirubin, and 10 μmol/l for TBA. The cut-offs for ALT and TBA were chosen according these values and our experience in pregnant women [14]. For TBA, most studies in ICP use a cut-off between 6 and 10 μmol/l in fasted women [9], and we chose the cut-off of 10 μmol/l for greatest specificity. Severe ICP was defined as TBA concentrations >40 μmol/l [15,16].

2.5. Detection of genomic variants of the ABCB4 gene

Mutations in the ABCB4 gene were investigated in all patients after obtaining their informed written consent. DNA was extracted from peripheral venous blood leukocytes by standard procedures. The search for genomic variants of ABCB4 was conducted by direct sequencing in all 27 coding exons of the ABCB4 gene, as already published [7].

2.6. Evaluation of the efficacy of UDCA on pruritus

The patients were divided into three groups according to the evolution of pruritus under treatment with UDCA: (1) disappearance of pruritus before delivery (whatever the time and definitively), (2) improvement of pruritus (with or without disappearance) before delivery, and (3) lack of improvement of pruritus before delivery. The evaluation was made by the patient without the use of a visual analog scale. The concomitant administration of hydroxyzine was recorded but was not taken into account in this assessment.

2.7. Evaluation of the efficacy of UDCA according to liver function tests

The changes in LFT results between the onset of treatment with UDCA and delivery were studied, with special emphasis on the changes during the first three weeks of treatment.

2.8. Search for factors predictive of response to UDCA

The three independent judgment criteria used to search for factors predictive of response to treatment were: (1) improvement of pruritus (with or without disappearance) before delivery, (2) decrease in serum ALT levels (more than 50% of baseline) after two or three weeks of treatment, (3) decrease in serum TBA concentrations (more than 50% of baseline) after two or three weeks of treatment. Patients with missing data after two and three weeks of treatment were not included in this analysis.

The following explanatory variables were assessed to search for factors predictive of response to UDCA: prior history of pruritus or cholestasis during pregnancy, parity, multiple pregnancy, presence of ABCB4 gene mutation, biliary lithiasis (history of cholecystectomy or presence of gallstones on ultrasonography), ALT levels, GGT levels, total bilirubin levels, TBA concentrations, period between onset of pruritus and initiation of UDCA, and dosage of UDCA.

2.9. Statistical analysis

Descriptive values are expressed as means with standard deviation (SD) or 95% confidence intervals (CI). Proportions are expressed as percentages. Comparison of proportions between groups was performed with a Chi-2 test or exact Fisher's test. Comparison of means between groups was performed with Student's *t*-test, and ANOVA or Kruskal–Wallis tests according the number of patients. The explanatory variables which could influence the judgment criteria (improvement of pruritus, decrease in serum ALT levels, and decrease in serum TBA concentrations) were tested in successive models of univariate logistic regression, and variables with a P value lower than or equal to 0.25 were introduced in a multivariate model. Multivariate analysis followed the procedure of Hosmer and Lemeshow which consists of successively eliminating the less significant variables, one by one, and keeping only independent significant variables ($P < 0.05$) at the end. The results of the univariate

Table 1
Characteristics of patients with ICP before initiating UDCA therapy according to the presence or absence of ABCB4 gene mutation.

	Whole population (n = 98)	Presence of mutation (n = 17)	Absence of mutation (n = 81)	P
Age, years	30.9 ± 4.9 (19.2–42.9)	29.2 ± 4.7 (22.4–39.4)	31.3 ± 4.9 (19.2–42.9)	0.124
Caucasian origin	88 (89.8%)	12 (70.6%)	66 (81.5%)	0.330
Familial history of ICP	9 (9.2%)	4 (23.5%)	5 (6.2%)	0.046
Primipara	35 (35.7%)	7 (41.2%)	28 (34.6%)	0.592
Mutiple pregnancy	16 (16.3%)	0 (0.0%)	16 (19.8%)	0.066
Prior history of ICP (among multipara)	41/63 (65.1%)	8/10 (80.0%)	33/53 (62.3%)	0.472
Prior history of IUFD	2 (2.0%)	1 (5.9%)	1 (1.2%)	0.318
Biliary lithiasis (past history or currently)	27 (27.6%)	5 (29.4%)	22 (27.2%)	1.000
Body weight, kg	72.7 ± 13.0 (51–111)	75.5 ± 15.7 (53–104)	72.1 ± 12.4 (51–111)	0.339
Gestational diabetes	15 (15.3%)	2 (11.8%)	13 (16.0%)	1.000
Onset of pruritus, weeks (+days of gestation)	30^{+1} (16^{+1}–36^{+6})	30^{+2} (19^{+4}–36^{+6})	33^{+2} (25^{+4}–36^{+5})	0.026
TBA concentration, μmol/l	27.5 ± 30.7 (2–140)	42.9 ± 36.7 (9–133)	24.3 ± 28.5 (2–140)	0.022
TBA concentration >40 μmol/l	17 (17.3%)	6 (35.3%)	11 (13.6%)	0.070
ALT level, IU/l	303.2 ± 273.9 (14–1443)	384.6 ± 302.9 (32–1049)	286.1 ± 266.3 (14–1443)	0.179
AST level, IU/l	168.3 ± 165.0 (16–985)	201.9 ± 169.6 (29–595)	161.3 ± 164.3 (16–985)	0.359
PAL level, IU/l	226.6 ± 76.3 (94–535)	203.6 ± 66.6 (113–340)	231.5 ± 77.7 (94–535)	0.173
Total bilirubin level, μmol/l	17.3 ± 11.5 (5–77)	23.7 ± 19.4 (5–77)	16.0 ± 8.6 (6–45)	0.011
Total bilirubin level >50 μmol/l	2 (2.0%)	2 (11.8%)	0 (0.0%)	0.029
GGT level, IU/l	36.9 ± 37.8 (5–170)	25.5 ± 13.3 (10–56)	36.2 ± 31.8 (5–170)	0.181
Prothrombin time, %	102.5 ± 7.4 (85–120)	100 ± 4.8 (90–111)	103.0 ± 7.8 (85–120)	0.134
Onset of UDCA, weeks (+days of gestation)	32^{+5} (19^{+4}–36^{+6})	30^{+3} (19^{+4}–36^{+6})	33^{+2} (25^{+6}–36^{+5})	0.026
Time between onset of pruritus and initiation of UDCA, days	18.9 ± 11.9 (3–67)	20.8 ± 134 (5–49)	18.2 ± 11.7 (2–67)	0.480
Dosage of UDCA, mg/kg	14.0 ± 2.4 (9.0–19.6)	13.6 ± 2.8 (9.6–18.9)	14.1 ± 2.3 (9–19.6)	0.433
Duration of treatment with UDCA, days	30.4 ± 19.4 (1–118)	44.8 ± 30.8 (12–118)	27.4 ± 14.5 (1–72)	0.036
Term of delivery, weeks (+days of gestation)	37^{+2} (30^{+6}–39^{+0})	36^{+6} (30^{+6}–38^{+4})	37^{+2} (33^{+0}–39^{+0})	0.330
Delivery by caesarean section	40 (40.8%)	4 (23.5%)	36 (44.4%)	0.174
Labor induced	66 (67.3%)	13 (76.5%)	53 (65.3%)	0.570
Prematurity (<37 weeks of gestation)	29 (25.4%)	7 (41.2%)	22 (27.2%)	0.257

ICP, intrahepatic cholestasis of pregnancy; UDCA, ursodeoxycholic acid; TBA, total bile acids; ABCB4 gene, adenosine triphosphate-binding cassette, sub-family B, member 4 gene; data are expressed as mean ± SD (with extremes) or number (with percentage).

and of the multivariate explicative analyses were expressed as odds ratios (OR) with their 95% CI. P values <0.05 were considered to be statistically significant.

3. Results

3.1. Population

Between January 1999 and December 2013, 129 outpatients were examined in hepatology consultation by one of the authors (YB) for liver disease during pregnancy and treated with UDCA. Of these 129 patients, 31 were excluded from the analysis for the following reasons: absence of pruritus during current episode of ICP (n = 9), chronic HCV (n = 2) or HBV (n = 2) infection, intercurrent cytomegalovirus (n = 4) or Parvovirus B19 (n = 1) infection, benign recurrent intrahepatic cholestasis (n = 1), suspected primary sclerosing cholangitis (n = 2), treatment with UDCA before pregnancy (n = 1), non-definitive diagnosis of ICP and/or loss to follow-up after delivery (n = 9).

The main characteristics of the whole population are summarized in Table 1. Four patients were suffering from jaundice associated with pruritus. There were 16 multiple pregnancies (15 twin and one triplet pregnancy), and the 98 patients gave birth to 114 live children. Apgar score at 5 min was available for 92 babies, and no Apgar score was lower than 8. The mean weight of newborns for single pregnancies was 3160 mg (1790–4490 mg). One IUFD occurred at 33 weeks of gestation in a patient with a twin pregnancy, and the evolution of the second twin was favorable. This patient had no ABCB4 gene mutation. UDCA was prescribed at a dosage of 1000 mg per day, with the exception of three patients treated with 750 mg per day. The dosage of UDCA was increased progressively over a few days in 11 patients to the dosage of 750 or 1000 mg. Treatment with UDCA was well tolerated and taken until delivery by all patients, except for one. This patient had taken UDCA irregularly for 8 days and considered that the pruritus was a side effect of UDCA. She stopped the treatment definitively before delivery. Eight of the 98 patients received transitory treatment with cholestyramine. One patient received poorly tolerated cholestyramine four days before onset of treatment with UDCA. Seven patients received cholestyramine before and during the first days of treatment with UDCA. Pruritus did not disappear in these patients before onset of UDCA. Forty-one patients received treatment with hydroxyzine to alleviate the discomfort of the pruritus. The pruritus improved in 31/41 patients (75.6%) who received hydroxyzine, and in 44/57 patients (77.2%) who did not receive this treatment (OR 0.92, 95% CI 0.36–2.35, P = 0.86).

3.2. ABCB4 gene mutations

A mutation in the ABCB4 gene was found in 17 patients (17.3%). Nine different mutations were revealed in these 17 patients: 6 missense mutations (c.902T > C, c.959C > T, c.1769G > A, c.2144C > T, c.2210C > T, and c.2800G > A), two nonsense mutations (c.94insA and c.462C > T), and one splicing site mutation (c.3486 + 1G > T). Of these 17 patients, 16 had a mutation in the heterozygous state, and one patient had a c.959C > T mutation in the homozygous state. This patient with a homozygous mutation had a past history of biliary lithiasis treated by cholecystectomy and sphincterotomy, and presented with severe ICP during her first pregnancy. The pruritus began at the 18th week of gestation followed by jaundice. Serum ALT level was 919 IU/l, and bile acid concentration was 133 μmol/l. Pruritus improved under UDCA therapy, and disappeared 2 weeks after delivery. UDCA was continued until delivery and after 14 weeks of treatment (i.e., 3 days before delivery) her serum ALT level was 43 IU/l and serum bile acid concentration was 51 μmol/l. The patient gave birth by vaginal delivery at 36 weeks of gestation, and the evolution of the newborn has been favorable.

The clinical and biological characteristics of patients with and without a mutation in the ABCB4 gene are reported in Table 1. Eight of the 41 multipara with a prior history of ICP (19.5%) had an ABCB4 mutation.

Table 2
Evolution of liver function tests during treatment with UDCA in patients with ICP.

	Week 0	Week 1	Week 2	Week 3	W0–W1 P	W1–W2 P	W2–W3 P	W0–W2 P	W0–W3 P
ALT (IU/l)	303.2 ± 273.9 n = 98	192.4 ± 213.0 n = 90	106.6 ± 146.8 n = 84	88.8 ± 98.8 n = 65	0.002	0.002	0.379	<0.001	<0.001
AST (IU/l)	168.3 ± 165.0 n = 98	91.4 ± 100.3 n = 89	54.4 ± 58.4 n = 83	51.7 ± 41.2 n = 65	<0.001	0.003	0.744	<0.001	<0.001
GGT (IU/l)	36.9 ± 37.8 n = 98	24.9 ± 19.4 n = 90	22.1 ± 18.7 n = 83	21.4 ± 16.8 n = 64	0.006	0.294	0.785	<0.001	<0.001
AP (IU/l)	226.6 ± 76.3 n = 96	221.6 ± 71.0 n = 89	219.0 ± 69.3 n = 84	224.5 ± 74.4 n = 64	0.643	0.812	0.645	0.489	0.863
Total bilirubin (μmol/l)	17.3 ± 11.5 n = 97	11.2 ± 7.4 n = 89	10.5 ± 8.9 n = 81	10.7 ± 8.1 n = 60	<0.001	0.544	0.856	<0.001	<0.001
TBA (μmol/l)	27.5 ± 30.7 n = 97	22.0 ± 27.3 n = 80	17.0 ± 19.1 n = 76	15.1 ± 18.8 n = 59	0.211	0.185	0.570	0.006	0.002

Data are expressed as mean ± SD. Comparison of means between groups was performed with Student's *t*-test, and ANOVA or Kruskal–Wallis tests according to the number of patients. n: number of patients evaluated. UDCA, ursodeoxycholic acid; W0, week 0, (before onset of treatment with UDCA); W1, week 1 (after one week of treatment); W2, week 2 (after 2 weeks of treatment); W3, week 3 (after 3 weeks of treatment); W0–W1, W0–W2, W0–W3, comparison between W0 and 1 week, 2 weeks, and 3 weeks of treatment, respectively; W0–W2, W0–W3: comparison between W0 and 2 weeks, and 3 weeks of treatment, respectively. W1–W2, comparison between W1 and W2; W2–W3, comparison between W2 and W3. AP, alkaline phosphatase; TBA, total bile acids.

3.3. Effects of treatment with UDCA on pruritus

Pruritus improved in 75/98 (76.5%) patients, and disappeared before delivery in 25/98 (25.5%) patients. The remaining patients had no improvement in their pruritus before delivery. Pruritus disappeared after delivery in all patients.

3.4. Effects of treatment with UDCA on liver function test results

The results of routine LFTs and serum bile acid concentrations during the first three weeks of treatment with UDCA are given in Table 2. Between the onset of treatment with UDCA and the second or third week of treatment, serum ALT levels normalized in 34/86 (39.5%) patients and decreased (more than 50% of baseline) in 67/86 (77.9%) patients, and serum TBA concentrations decreased (more than 50% of baseline) in 28/81 (34.6%) patients. There was a significant correlation between serum ALT and AST levels before treatment ($r = 0.86$; $P < 0.0001$), after one week of treatment ($r = 0.89$; $P < 0.0001$), after two weeks of treatment ($r = 0.95$; $P < 0.0001$), and after three weeks of treatment ($r = 0.92$; $P < 0.0001$).

The weekly changes in serum ALT levels and TBA concentrations during prolonged UDCA treatment are reported in Fig. 1.

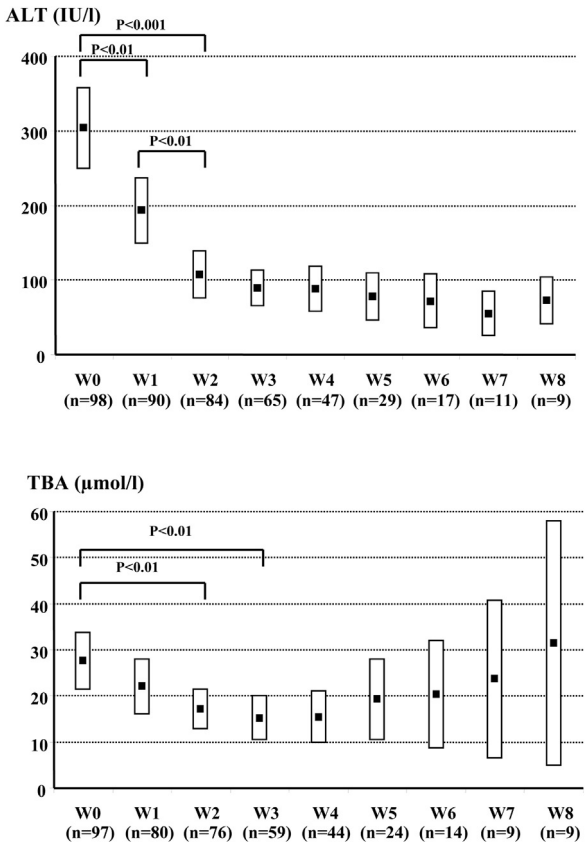

Fig. 1. Serial changes in serum alanine aminotransferase levels (ALT) and total bile acid concentrations (TBA) during UDCA therapy in patients with ICP. Data are expressed as means with 95% CI. W = weeks of treatment with UDCA, n = number of patients. There was no statistical difference between W3 and W8.

3.5. Factors predictive of response to UDCA

3.5.1. According to improvement of pruritus

On univariate analysis, multiple pregnancy and ALT >175 IU/l were associated with improvement of pruritus under UDCA therapy (Table 3). By contrast, improvement of pruritus was less frequent in patients with a prior history of ICP (Table 3). On multivariate analysis, ALT >175 IU/l was the only factor associated with improvement of pruritus (OR 2.97, 95% CI 1.12–7.89, P = 0.029).

3.5.2. According to decrease in serum ALT levels

On univariate analysis, serum ALT >175 IU/l was associated with a decrease in serum ALT levels under UDCA therapy (Table 4). By contrast, decrease in serum ALT levels was less frequent in patients with a prior history of ICP and multiparous, although the difference did not reach significance (Table 4). On multivariate analysis ALT >175 IU/l was the only factor associated with a decrease in serum ALT levels (OR 18.61, 95% CI 3.94–87.99, P = 0.0002).

3.5.3. According to decrease in serum TBA concentration

On univariate analysis, serum ALT levels >175 IU/l and serum TBA concentrations >40 μmol/l were associated with a decrease in serum bile acid concentration under UDCA therapy (Table 5). By contrast, a decrease in serum TBA concentrations was less frequent in patients with a prior history of ICP, although the difference did not reach significance (P = 0.06) (Table 5). On multivariate analysis, serum bile acid concentration >40 μmol/l was the only factor asso-

Table 3
Baseline factors predictive of improvement of pruritus under UDCA therapy in patients with ICP.

Variables	Improvement of pruritus	No improvement of pruritus	Univariate analysis	
	n = 75	n = 23	OR (95% CI)	P
Prior history of ICP (among 63 multipara)	27/48 (56.2%)	14/15 (93.3%)	0.09 (0.01–0.76)	0.01
Multiparous	48 (64%)	15 (65.2%)	0.95 (0.36–2.52)	0.92
Multiple pregnancy	16 (21.3%)	0 (0%)	13.03 (0.75–226.16)	0.02
Presence of ABCB4 mutation	12 (16%)	5 (21.7%)	0.69 (0.21–2.20)	0.52
Biliary lithiasis	10 (13.3%)	6 (26.1%)	1.10 (0.38–3.18)	0.85
ALT >175 IU/l	46 (61.3%)	8 (34.8%)	2.97 (1.12–7.89)	0.03
GGT >35 IU/l	26 (34.7%)	3 (13.0%)	3.54 (0.96–13.02)	0.07
Total bilirubin >17 μmol/l	27/74 (36.5%)	8 (34.8%)	1.08 (0.40–2.87)	0.88
Bile acids >40 μmol/l	12/73 (16.4%)	4 (17.4%)	1.01 (0.29–3.47)	1.00
Period between onset of pruritus and treatment >21 days	26 (34.7%)	7 (30.4%)	1.21 (0.40–3.75)	0.14
UDCA ≥15 mg/kg/day	27 (36%)	6 (26.1%)	1.59 (0.56–4.52)	0.37

OR, odds ratios; 95% CI, 95% confidence interval. In multivariate analysis ALT >175 IU/l was the only factor associated with improvement of pruritus under UDCA therapy (OR, 2.97, 95% CI 1.12–7.89, P = 0.029).

Table 4
Baseline factors predictive of decrease in serum ALT levels (more than 50% of baseline) after 2 or 3 weeks of UDCA therapy in patients with ICP.

Variables	Decrease of ALT >50%	No decrease ALT	Univariate analysis	
	n = 67	n = 19	OR (95% CI)	P
Prior history of ICP (among 56 multipara)	24/40 (60.0%)	14/16 (87.5%)	0.21 (0.04–1.07)	0.06
Multiparous	40 (59.7%)	16 (84.2%)	0.28 (0.07–1.05)	0.06
Multiple pregnancy	12 (17.9%)	0 (0.0%)	Indefinite	0.06
Presence of ABCB4 mutation	12 (17.9%)	3 (15.8%)	1.16 (0.40–4.70)	1.00
Biliary lithiasis	18 (26.9%)	4 (21.1%)	1.38 (0.84–1.36)	0.77
ALT >175 IU/l	46 (68.7%)	2 (10.5%)	18.62 (3.94–88.02)	<0.0001
GGT >35 IU/l	23 (34.3%)	4 (21.1%)	1.96 (0.58–6.59)	0.40
Total bilirubin >17 μmol/l	27/66 (40.9%)	4 (21.1%)	2.60 (0.78–8.68)	0.18
Bile acids >40 μmol/l	13 (19.4%)	1 (5.3%)	4.42 (0.54–36.16)	0.18
Period between onset of pruritus and treatment >21 days	23 (34.3%)	6 (31.6%)	1.13 (0.38–3.37)	0.82
UDCA ≥15 mg/kg/day	23 (34.3%)	6 (31.6%)	1.13 (0.38–3.37)	0.82

OR, odds ratios; 95% CI, 95% confidence interval. Patients with missing serum ALT activity measurements after 2 or 3 weeks of treatment with UDCA were not considered for analysis. In multivariate analysis ALT >175 IU/l before treatment was the only factor associated with decrease in serum ALT levels (OR 18.61, 95% CI 3.94–87.99, P = 0.0002).

Table 5
Baseline factors predictive of decrease in serum bile acid concentrations (more than 50% of baseline) after 2 or 3 weeks of UDCA therapy in patients with ICP.

Variables	Decrease in serum bile acids	No decrease in serum bile acids	Univariate analysis	
	n = 28	n = 53	OR (95% CI)	P
Prior history of ICP (among 52 multipara)	11/20 (55.0%)	26/32 (81.3%)	0.28 (0.08–0.99)	0.06
Multiparous	20 (71.4%)	32 (60.4%)	1.64 (0.61–4.40)	0.32
Multiple pregnancy	2 (71.4%)	8 (15.1%)	0.43 (0.04–2.42)	0.48
Presence of ABCB4 mutation	5 (17.9%)	9 (17.0%)	1.06 (0.32–3.54)	1.00
Biliary lithiasis	8 (28.6%)	12 (22.6%)	1.37 (0.48–3.87)	0.56
ALT >175 IU/l	20 (71.4%)	24 (45.3%)	3.02 (1.13–8.07)	0.03
GGT >35 IU/l	7 (25.0%)	16 (30.1%)	0.77 (0.27–2.17)	0.62
Total bilirubin >17 μmol/l	12 (42.9%)	18 (34.0%)	1.46 (0.57–3.73)	0.43
Bile acids >40 μmol/l	9 (32.1%)	4 (7.5%)	5.80 (1.60–21.11)	0.01
Period between onset of pruritus and treatment >21 days	11 (39.2%)	16 (30.2%)	1.50 (0.57–3.90)	0.40
UDCA ≥15 mg/kg/day	9 (32.1%)	17 (32.1%)	1.00 (0.38–2.67)	1.00

Patients with missing serum bile acid concentrations after 2 or 3 weeks of treatment with UDCA were not considered for analysis. OR, odds ratios; 95% CI, 95% confidence interval. In multivariate analysis bile acids >40 μmol/l was the only factor significantly associated with decrease in serum bile acid concentrations under UDCA therapy (OR, 5.80, 95% CI 1.60–21.11, P = 0.0076).

ciated with a decrease in serum TBA concentration (OR 5.80, 95% CI 1.60–21.11, P = 0.0076).

4. Discussion

In this study, patients with ICP were managed by collaboration between a Hepatologist and obstetric teams. Such collaboration is not the rule, and a recent survey in France showed that about 20% of obstetric teams collaborate with Hepatologists in the management of ICP [17]. A definitive diagnosis of ICP was accepted after careful review of medical records. Patients without pruritus during the current episode of ICP were excluded from the analysis, since one aim of the study was to evaluate the efficacy of UDCA on this symptom. Patients with intercurrent causes of cholestasis were excluded, although in some cases there was a possible association with ICP. The presence of abnormal LFT results after delivery was not considered in itself to be an exclusion criterion in the present study, provided that specific chronic liver disease (especially hepatitis C) had been excluded. Indeed, although ICP usually is considered to be a liver disease unique to pregnancy, an association between ICP and chronic liver abnormalities has been reported [18,19]. All patients in the present study were followed up after delivery, and no included patient continued to suffer from persistent pruritus or an increase in serum bile acid concentration after delivery. Whenever a patient had persistent routine LFT abnormalities after delivery, appropriate complementary tests

were systematically performed to search for specific chronic liver disease.

The relationship between ICP and cholelithiasis has been demonstrated by the results of long term longitudinal studies [18,19]. The prevalence of gallstones was relatively high in our study (27.6%), compared to the study of Glantz et al. (2.9%) [16]. The difference might be related to our criteria for cholelithiasis (prior cholecystectomy for gallstones or current presence of gallstones) and overall to our method of diagnosis of gallstones, i.e., systematic investigation by ultrasound performed in fasting state. It was surprising that in our study cholelithiasis was not associated with the presence of mutation in the ABCB4 gene, which is involved in the formation of gallstones [20]. We can speculate that, in patients with ABCB4 gene mutations, gallstones and biliary complications appear later in life, after women have completed pregnancies. Indeed, long term longitudinal studies have demonstrated biliary complications after ICP [18,19].

Seven of the nine mutations demonstrated in this study had previously been described in the literature, some by our team [7,21]. Mutations c.94insA and c.3486 + 1G > T are novel mutations in ICP. Patients with an ABCB4 mutation had more severe cholestasis characterized by earlier onset of pruritus and higher levels of total bile acids, as already reported [22]. The results of this study confirmed that elevated GGT levels are not a factor predictive of an ABCB4 mutation in patients suffering from ICP [7,21].

In the present study most of the patients received 1000 mg UDCA per day, which corresponds to the dosage currently recommended in France where UDCA has recently been licensed for use in symptomatic ICP (licensed dose in France: 15 mg/kg UDCA per day with a maximum of 1000 mg per day). In RCTs selected in a metaanalysis the dosage of UDCA was the same or was lower (450–1000 mg per day) [11]. Reports with higher dosages (up to 2000 mg par day) are limited [12,23]. In our study, UDCA was introduced gradually for some women, as sometimes recommended in chronic liver disease, because there have been anecdotal reports of worsening of pruritus following introduction of UDCA [8].

Pruritus is a common symptom of cholestasis that is difficult to treat [8]. In our study, pruritus had disappeared in 25.5% of cases and improved in 76.5% of cases under UDCA. These results observed in real-world conditions are somewhat different from those of a meta-analysis of RCTs where the total resolution of pruritus occurred in 41.6% of cases and improvement in 61.3% of cases [11]. These differences may be due to the method we used for evaluation of pruritus improvement under UDCA therapy. Indeed, by contrast with assessment of pruritus in RCTs, there is no standardized method to assess this subjective symptom in routine practice [24]. In our study, the evaluation of pruritus improvement was assessed globally, regardless of the time of improvement before delivery, whereas in RCTs evaluation was usually made 2 or 3 weeks after treatment by UDCA [11]. This beneficial effect of UDCA on pruritus in patients with ICP supports its use as first line therapy in ICP [8,9,11].

In our study, there was a significant decrease in all LFT results under UDCA therapy, except for serum AP levels. Indeed, the serum level of AP increases during normal late pregnancy, mainly because of placental synthesis, and it is not a helpful in the diagnosis or monitoring of cholestasis during pregnancy [9]. The results of this study confirmed a significant decrease in serum TBA levels under UDCA therapy, which is particularly relevant for fetal prognosis [9]. Our results demonstrated that improvements in routine LFTs were observed as early as the first week of treatment and were maximal after 2 or 3 weeks of treatment. Serum ALT levels remained stable thereafter, even after two months of treatment. By contrast, a decrease in serum TBA concentrations was observed only after two weeks of treatment, and was followed by a tendency to increase thereafter. This increase was not statistically significant, possibly because of the number of patients. However, since a high serum bile acid concentration is considered to be a risk factor for fetal prognosis [9,16], these results suggest that such concentrations should be regularly monitored until delivery in patients with ICP treated with UDCA.

In our study UDCA was prescribed until delivery. In some published RCTs UDCA was prescribed for a limited duration (usually 2 or 3 weeks) and stopped several days or weeks before delivery [11,13]. This practice could lead to a rebound in serum bile acid concentrations in late pregnancy secondary to the withdrawal of UDCA, and thus may carry a risk of IUFD [25].

Only one patient in our study stopped UDCA treatment prior to delivery because of intermittent pruritus considered by the patient herself to be a side effect. No other undesirable side effect of UDCA was reported, and our results confirmed the good tolerance of UDCA during late pregnancy [11–13,26].

This study is the first that aimed to characterize factors predictive of response to treatment with UDCA in ICP. Taking the 50% decrease in ALT levels as a criterion of response to treatment, having a prior history of ICP appears to be a factor predictive of poor response to UDCA. By contrast, serum ALT levels $\geq$175 IU/l and serum bile acid concentrations $\geq$40 μmol/l appeared to be factors predictive of good response to UDCA. Finally, it was recently suggested that ABCB4 mutations may have an effect on treatment response in ICP [5]. In this study the presence of an ABCB4 mutation did not appear to be a factor predictive of response to UDCA.

IUFD remains the most feared complication of ICP, and one case occurred in this study. Because this risk of IUFD usually occurs late in pregnancy, most obstetricians advocate active obstetric management with induction before the 38th week of gestation, especially in patients with high serum TBA concentrations, although this practice is not evidence-based [3,8,9,12,17]. No controlled studies have demonstrated the value of UDCA to prevent this rare complication (about 1% of pregnancies with ICP) [11,12].

This study has some limitations, one of which might have been the selection of patients via a hepatology consultation as this may have been a cause of bias. However, some characteristics of the patients in our series were similar to those reported in literature series. Just over 40% of women had a history of ICP, compared with recurrence rates of 40–60% reported in the literature. The prevalence of severe cholestasis, defined by serum bile acid concentrations $\geq$40 μmol/l, was the same in our study (17%) as the prevalence found in other studies (15–19%) [15,16]. One other limitation of this single-center study was the number of patients included which limited the statistical power of tests to search for factors predictive of response to treatment with UDCA. However, our results can be used to guide future research in the field.

In conclusion, this study in real-world conditions confirms the beneficial effect of UDCA on pruritus and LFTs in patients with ICP, with good tolerance.

Conflict of interest

Dr. Yannick Bacq has served as speaker for Aptalis Pharma (October 2013).

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