

Efficacy and Safety of Ursodeoxycholic Acid Versus Cholestyramine in Intrahepatic Cholestasis of Pregnancy

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Background & Aims: Treatment of intrahepatic cholestasis of pregnancy with ursodeoxycholic acid appears promising, but data are limited so far. The aim of this randomized study was to evaluate the efficacy and safety of ursodeoxycholic acid in comparison with cholestyramine. **Methods:** Eighty-four symptomatic patients with intrahepatic cholestasis of pregnancy were randomized to receive either ursodeoxycholic acid, 8–10 mg/kg body weight daily (n = 42), or cholestyramine, 8 g daily (n = 42), for 14 days. The primary end point was a reduction of pruritus by more than 50% after 14 days of treatment as evaluated by a pruritus score. Secondary end points were outcome of pregnancy, reduction of serum aminotransferase activities and serum bile acid levels, and drug safety. Intention-to-treat analysis was applied. **Results:** Pruritus was more effectively reduced by ursodeoxycholic acid than cholestyramine (66.6% vs 19.0%, respectively; $P < .005$). Babies were delivered significantly closer to term by patients treated with ursodeoxycholic acid than those treated with cholestyramine (38.7 ± 1.7 vs 37.4 ± 1.5 weeks, respectively, $P < .05$). Serum alanine and aspartate aminotransferase activities were markedly reduced by 78.5% and 73.8%, respectively, after ursodeoxycholic acid, but by only 21.4%, each, after cholestyramine therapy ($P < .01$ vs ursodeoxycholic acid). Endogenous serum bile acid levels decreased by 59.5% and 19.0%, respectively ($P < .02$). Ursodeoxycholic acid, but not cholestyramine was free of adverse effects. **Conclusions:** Ursodeoxycholic acid is safe and more effective than cholestyramine in intrahepatic cholestasis of pregnancy.

Intrahepatic cholestasis of pregnancy (ICP) is the most common pregnancy-related liver disorder. In many areas of the world, ICP is a rare disease occurring at a rate of 1 in 1000 to 10,000 pregnancies.¹ However, the incidence of ICP is markedly higher in Sweden and other Scandinavian countries (up to 2% of deliveries in 1950–1960) and even more in Chile (up to 14% of deliveries in 1960–1970).² In these countries, the incidence of ICP decreased more recently, whereas it increased in other parts of Europe, the United States, Asia, Australia, and some Latin American countries. The latter phenomenon

might be explained at least in part by a greater awareness for the disease.¹ In Lithuania, a retrospective analysis disclosed a rate of 0.4% of ICP in 16,252 pregnant women over a period of 5 years (1996–2000; Kondrackiene J, unpublished data, April 8, 2003).

ICP is characterized by pruritus associated with a mild or moderate increase in serum aminotransferases and serum bile acids starting in the second or third trimester of pregnancy and disappearing after delivery. Maternal prognosis is benign, but quality of life is impaired by intense, disturbing pruritus.³ In contrast, ICP may have serious consequences for the fetus. Clinical studies show that the disease is a strong risk factor for premature deliveries in 19% to 60%,⁴ stillbirths in 1% to 2%,^{5,6} and fetal distress in 22% to 33%.⁷ Despite the substantial risk, ICP remains widely disregarded as a serious clinical problem.

ICP has been described as a “puzzling disorder” because of its clinical presentation, unknown etiology, unexplained fetal prognosis, and intriguing geographic distribution.² The cause of ICP is still under discussion. The pathogenesis can be related to abnormalities in the metabolism and disposition of sex hormones and/or bile acids, determined by a genetic predisposition and environmental factors.^{1,8,9} There is increasing evidence that genetically determined dysfunction in the canalicular ABC transporters bile salt export pump (BSEP; ABCB11) and multidrug resistance protein 3 (MDR3; ABCB4) might be risk factors for development of ICP.^{10–12} Hormonal factors may trigger the transient decompensation of the heterozygous state for a MDR3 gene defect during pregnancy, leading to ICP.^{13–15}

Until now, optimal treatment of ICP is still under debate. Antihistamines, benzodiazepines, phenobarbital,

Abbreviations used in this paper: AP, alkaline phosphatase; CA, cholic acid; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; γ -GT, γ -glutamyltransferase; ICP, intrahepatic cholestasis of pregnancy; LCA, lithocholic acid; UDCA, ursodeoxycholic acid.

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dexamethasone, epomediol, *S*-adenosyl-L-methionine, and cholestyramine have been used without clear evidence of efficacy. Cholestyramine has been used for reducing pruritus. Observational studies suggest that cholestyramine may be associated with improved maternal morbidity without a documented improvement in fetal outcome.¹⁶⁻¹⁸ Cholestyramine may worsen the malabsorption of fat-soluble vitamins, especially vitamin K. A case report of severe fetal intracranial hemorrhage during treatment with cholestyramine for ICP has raised the possibility that severe maternal vitamin K deficiency may lead to fetal vitamin K deficiency and coagulopathy.¹⁸ Recently, ursodeoxycholic acid (UDCA) has been proposed for the treatment of ICP. Improvement in maternal and fetal morbidity was suggested in 8 clinical trials and several observational studies, although these studies were small and in some aspects inconsistent.^{16,17} However, data from large, randomized trials of treatment of ICP are lacking. Therefore, the aim of the present study was to evaluate the efficacy and safety of UDCA in patients with ICP in comparison with cholestyramine. UDCA and cholestyramine were administered at moderate doses to alleviate the risk of formation of potentially toxic bile acid metabolites and of malabsorption of fat-soluble vitamins, respectively.

Materials and Methods

Study Design

An open, randomized, parallel group study was performed comparing the efficacy and safety of UDCA and cholestyramine in intrahepatic cholestasis of pregnancy. The study was approved by the ethics committee of the Kaunas Medical University. The study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki.

Patients

Patients with a diagnosis of ICP as defined by the criteria below were prospectively evaluated for inclusion in this study between October 1999 and September 2002.

Inclusion criteria were as follows: skin pruritus starting in the second or third trimester of pregnancy and elevation of at least one of the following biochemical parameters above the upper limit of normal: alanine aminotransferase (ALT) >45 U/L, aspartate aminotransferase (AST) >40 U/L, and fasting serum bile acids >10 $\mu\text{mol/L}$. Exclusion criteria were as follows: chronic liver disease, hepatic viral infections (HAV, HBV, HCV, cytomegalovirus, Herpes simplex virus, Epstein-Barr virus), skin disease, allergic disease, and symptomatic cholelithiasis.

All patients gave written informed consent before inclusion into the study and were randomized to receive either UDCA, 8–10 mg/kg body weight per day (Ursofalk capsules; Dr. Falk, Pharma GmbH, Freiburg, Germany), or cholestyramine, 8

g/day (Ratiopharm GmbH & Co, Ulm, Germany), for 14 days. Randomization was performed by use of sealed envelopes.

Study End Points

The primary study end point was defined as a reduction of severity of pruritus by more than 50% after 14 days of treatment. Secondary end points were outcome of pregnancy (term of delivery, Apgar score, newborn status), reduction of serum aminotransferase activities and serum bile acids levels, and drug safety. Self-assessment of pruritus intensity was performed by the patients daily by use of a score from 0 to 4 (0, no pruritus; 1, occasional; 2, intermittent pruritus every day with asymptomatic periods prevailing; 3, intermittent pruritus every day with symptomatic periods prevailing; 4, constant pruritus day and night).

Serum liver tests, fasting serum bile acids and cholic (CA), chenodeoxycholic (CDCA), deoxycholic (DCA), lithocholic (LCA), and ursodeoxycholic (UDCA) acids were evaluated at entry and on the day after end of therapy. Abdominal ultrasonography and serologic tests (see inclusion and exclusion criteria) were performed before treatment. Serum liver tests were determined using routine laboratory techniques. Fasting serum levels of bile acids were determined as described previously.¹⁹ In brief, bile acids were extracted with Bond-Elut C18 cartridges (Analytichem International, San Diego, CA), solvolysis was performed to cleave sulfate groups, and enzymatic hydrolysis was performed to deconjugate bile acid amides. Deconjugated bile acids were isolated by extraction on Lipidex 1000 (Packard Instruments, Groningen, The Netherlands) and were then methylated and trimethylsilylated for gas chromatography. Capillary gas chromatography was performed using a Carlo Erba Fractovap 4160 gas-chromatograph (Carlo Erba Instruments, Hofheim, Germany). Bile acid derivatives were separated on a fused silica capillary CP Sil 19 CB column coated with chemically bonded OV-1701 (25 m \times 0.33 mm, Chrompack, Middelburg, The Netherlands). Hydrogen was the carrier gas ($P = .6 \text{ kg/cm}^2$). A temperature program from 140°C to 270°C with 8°/min was started after on-column injection. Eluting bile acid derivatives were detected by a flame ionization detector. Fasting serum samples were stored at -20°C until analyzed.

The fetal status was monitored in the same hospital every week. The outcome of pregnancy and the newborn status were assessed by routine investigations documented by the obstetricians and neonatologists. There was no specific protocol for assessing and managing the pregnancy of ICP patients participating in this trial. The decision to induce labor and carry out cesarean sections was made by the managing obstetricians independently of this study. Data recorded during delivery included term and mode of delivery, Apgar score at 1 and 5 minutes, and newborn weight.

Statistical Analysis

Efficacy and safety analyses were carried out on the intention-to-treat (ITT) population. The results are expressed as mean \pm standard deviation (SD). Comparisons of paramet-

ric, normally distributed data were performed by Student *t* test. Mann–Whitney *U* test was used for unpaired and Wilcoxon signed-rank test for paired nonparametric data. The χ^2 test was used to compare categorical variables. Comparison of the change of pruritus score every day of treatment was expressed as area under the curve (AUC). Statistical analysis was conducted with STATISTICA 5.0. (Statsoft, Tulsa, OK) A *P* < .05 was regarded as significant.

Results

Eighty-four patients, aged 18–41 years, between 25 and 39 weeks of gestation, who fulfilled the inclusion criteria were enrolled in the present study. After randomization, 42 patients received UDCA, 8–10 mg/kg body weight/day, and 42 patients received cholestyramine, 8 g/day, for 14 days. Median time of onset of treatment was 35.0 weeks (range, 22.0–39.0 weeks); delivery was at 37–38 weeks. Therefore, most of the patients were not offered continued medical treatment until delivery when the study was finished and pruritus had improved. Only those patients with early onset of pruritus (2 in the UDCA group and 2 in the cholestyramine group) were offered repeat treatment when pruritus exacerbated in the later course of pregnancy. Baseline clinical characteristics of both groups did not differ (Table 1). During 14 days of treatment, 10 patients in the UDCA group and 4 in the cholestyramine group withdrew or violated the study protocol prior to study completion: (1) 4 patients receiving UDCA discontinued treatment during the study period; (2) 6 patients in the UDCA group apparently took UDCA before inclusion in the trial as retrospectively disclosed by serum bile acid analysis that revealed markedly elevated serum UDCA levels (>15 $\mu\text{mol/L}$) in baseline samples; and (3) 4 patients treated with cholestyramine withdrew mainly because of adverse events (nausea and vomiting). Intention-to-treat (ITT) analysis included all 84 patients (Figure 1).

Table 1. Baseline Characteristics of Treatment Groups

Characteristic	UDCA group (n = 42)	Cholestyramine group (n = 42)	<i>P</i> value
Age (y)	28.9 \pm 5.9	27.5 \pm 5.3	NS
Multiparous	22	18	NS
Positive family history	5	6	NS
Recurrence	10	11	NS
Multiple pregnancy	3	2	NS
Onset of pruritus (wk)	31.7 \pm 3.1	31.0 \pm 3.8	NS
Onset of treatment (wk)	34.3 \pm 3.1	33.8 \pm 2.8	NS
Weight (kg)	69.2 \pm 5.8	70.8 \pm 7.1	NS

NOTE. Data are presented as means \pm SD.
NS, not significant.

The intensity of pruritus was similar in both treatment groups at baseline (2.88 \pm 0.40 vs 2.95 \pm 0.60) and improved after both treatments. However, analysis of the change in pruritus score between baseline and the end of the study revealed a significant difference between treatments. Relief of pruritus was observed after 3 to 4 days of treatment with UDCA, whereas intensity of pruritus usually diminished only after 7 to 10 days during treatment with cholestyramine (Figure 2). After 4 days, the pruritus score was significantly lower in patients receiving UDCA than in those receiving cholestyramine (pruritus score: 2.08 \pm 0.63 vs 2.92 \pm 0.62, respectively; *P* < .05), and the difference was even more pronounced after 14 days (pruritus score: 0.44 \pm 0.65 vs 1.88 \pm 0.98, respectively; *P* < .001) (Figure 2). Reduction of the pruritus score by more than 50% was observed in 67% (28 of 42) of patients treated with UDCA vs 19% (8 of 42) of patients treated with cholestyramine (*P* = .0021), indicating higher efficacy of UDCA regarding relief of pruritus.

No stillbirths were observed, and no significant differences of newborns' weight were found in both groups. The Apgar score at 1 minute was similar in both groups but was significantly higher at 5 minutes in the UDCA group than in the cholestyramine group: Apgar score: 9.4 \pm 0.5 vs 8.7 \pm 0.6, respectively; *P* < .05. In patients receiving UDCA, delivery occurred significantly closer to term than in patients who received cholestyramine (38.7 \pm 1.7 weeks vs 37.4 \pm 1.5 weeks, respectively; *P* < .05). Postnatal development has been normal in all babies. Pregnancy ended prematurely in 3 (7%) patients receiving UDCA and in 5 (12%) patients treated with cholestyramine. Seven (16.7%) patients of the UDCA group underwent cesarean section because of multiple pregnancies (3 cases), placenta praevia (1 case), cephalo-pelvic disproportion (1 case), fetal distress (1 case), and advanced maternal age (1 case), and 3 (7%) patients of the cholestyramine group underwent cesarian section because of fetal distress (1 case), twin pregnancy (1 case), and cephalo-pelvic disproportion (1 case).

Baseline serum levels of ALT, AST, bilirubin, γ -glutamyltransferase (γ -GT), alkaline phosphatase (AP), and endogenous bile acids were similar in both groups. UDCA significantly reduced serum aminotransferase activities and endogenous bile acids serum levels but did not affect serum bilirubin, γ -GT, and AP levels (Table 2). In contrast, cholestyramine did not significantly affect serum aminotransferases and endogenous bile acids levels, whereas serum levels of bilirubin and AP significantly increased (Table 2).

Comparison of treatment with UDCA and cholestyramine revealed that ALT, AST, and endogenous serum

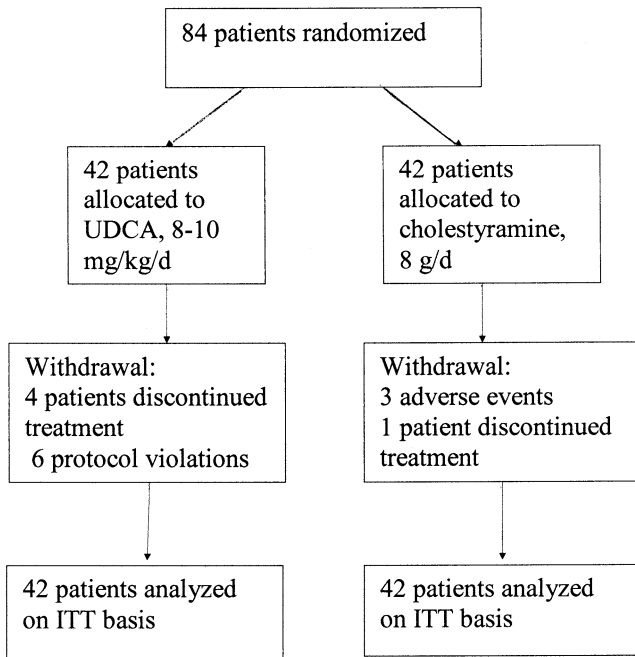


Figure 1. Randomization and allocation of patients. ITT, intention to treat.

bile acid levels were more effectively lowered by UDCA compared with those obtained in the cholestyramine group: ALT and AST activities were markedly reduced in 78.5% (33 of 42) and 73.8% (31 of 42), respectively, of the patients after ursodeoxycholic acid, but in only 21.4% (9 of 42) of the patients for both parameters after cholestyramine therapy ($P < .01$ vs ursodeoxycholic acid, each). Endogenous serum bile acid levels decreased in 59.5% (25 of 42) and 19.0% (8 of 42), respectively, of the patients ($P < .02$). No patient in the cholestyramine group but 16.7% (7 of 42) ($P < .02$) and 7.1% (3 of 42) ($P > .05$) of patients in the UDCA group displayed a normalization of their bilirubin and γ -GT serum levels. There was no significant difference in reduction of serum AP activity between the UDCA and cholestyramine groups: 7.1% (3 of 42) vs 4.8% (2 of 42), respectively, ($P > .05$) at the end of the treatment.

Serum levels of primary bile acids decreased significantly during treatment with UDCA: CA from $20.7 \pm 26.4 \mu\text{mol/L}$ to $8.9 \pm 16.7 \mu\text{mol/L}$ ($P < .01$) and CDCA from $14.9 \pm 13.9 \mu\text{mol/L}$ to $7.0 \pm 8.3 \mu\text{mol/L}$ ($P < .01$). In parallel, UDCA increased from $1.4 \pm 2.8 \mu\text{mol/L}$ to $21.2 \pm 20.2 \mu\text{mol/L}$ ($P < .0001$). Serum levels of the secondary bile acids DCA and LCA were not significantly altered by UDCA administration (Figure 3A).

Serum levels of CDCA also decreased during treatment with cholestyramine from $13.0 \pm 14.6 \mu\text{mol/L}$ to $7.8 \pm 6.8 \mu\text{mol/L}$ ($P < .05$), whereas serum levels of all

other bile acids were unaltered during treatment with cholestyramine (Figure 3B). UDCA was well tolerated and did not cause any adverse effects. In the cholestyramine group, 12 patients (29%) reported treatment-related adverse effects (11 nausea, 5 vomiting, 1 diarrhea).

Discussion

The present study indicates that treatment of ICP with UDCA for 14 days is superior to treatment with cholestyramine regarding relief of pruritus, delivery near term, and improvement of maternal serum liver tests. Pruritus is frequently considered a concomitant to pregnancy and is often not recognized as a key symptom of ICP and treated expectantly. However, pruritus is not the major threat to mother and fetus, although its intensity may severely debilitate the mother. More seriously, ICP may have consequences for the fetus and can unexpectedly end with acute, lethal anoxia of the fetus.⁷ No treatment of ICP is as yet established. Cholestyramine has been used for reducing pruritus. Observational studies suggest that cholestyramine may be associated with improved maternal morbidity without a documented improvement in fetal outcome.^{17,18} Recently, UDCA has been increasingly used for the treatment of ICP. The present study is, to our knowledge, the first prospective, randomized trial comparing these 2 drugs directly for the treatment of ICP.

Experimental evidence suggests 3 major mechanisms of action of UDCA in cholestatic liver diseases: normalization of impaired hepatobiliary secretion, protection of cholangiocytes against cytotoxicity of hydrophobic bile acids, and protection of hepatocytes against bile acid-

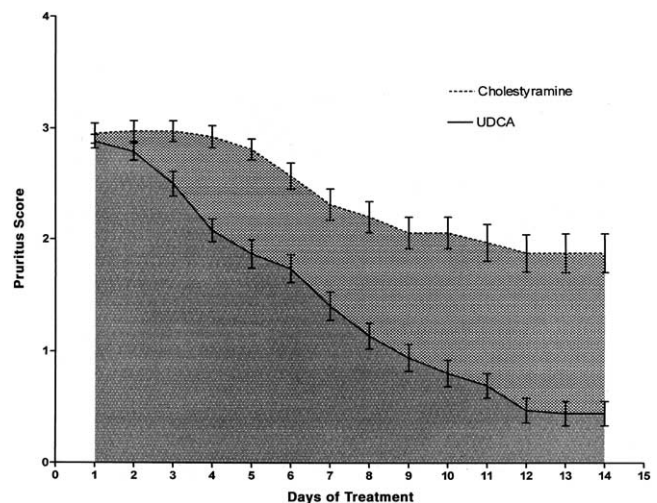


Figure 2. Change of pruritus intensity in patients with ICP treated with UDCA or cholestyramine as evaluated by a pruritus score. Data are presented as means \pm SD.

Table 2. Biochemical Parameters of Patients With ICP Before and After UDCA or Cholestyramine Treatment

Biochemical parameters	UDCA group (n = 42)		Cholestyramine group (n = 42)	
	$\bar{X} \pm SD$	P value	$\bar{X} \pm SD$	P value
ALT (U/L)				
Before	194.0 ± 155.4	<.0001	189.1 ± 115.5	NS
After	78.2 ± 57.4		222.4 ± 128.0	
AST (U/L)				
Before	125.0 ± 101.3	<.0001	139.4 ± 87.4	NS
After	48.8 ± 31.6		151.9 ± 85.2	
AP (U/L)				
Before	364.9 ± 124.3	NS	384.0 ± 145.7	<.05
After	369.4 ± 120.7		425.9 ± 155.9	
γ -GT (U/L)				
Before	27.4 ± 15.1	NS	24.1 ± 14.2	NS
After	25.1 ± 11.0		24.4 ± 15.1	
Endogenous bile acids (μ mol/L)				
Before	46.5 ± 41.3	<.01	38.8 ± 38.5	NS
After	24.4 ± 29.2		26.2 ± 23.3	
Bilirubin (μ mol/L)				
Before	17.2 ± 15.2	NS	13.3 ± 7.4	<.05
After	13.2 ± 8.5		15.9 ± 10.0	

NOTE. Data are presented as means \pm SD.

induced apoptosis.^{20–24} In ICP, hepatocellular cholestasis and retention of endogenous bile acids and sex hormone metabolites are predominant features, suggesting that improvement of hepatocellular secretion may be a key mechanism of action of UDCA in ICP. Effects of UDCA in ICP resemble the effects observed in other cholestatic diseases, although, in ICP, the clinical and biochemical effects are obtained faster, and they fade quickly when the drug is discontinued.^{25,26}

Recent studies have confirmed that patients with ICP have evident changes in the metabolism of bile acids and sex hormones. The cholestatic potential of some D-ring estrogens, in particular glucuronides such as estradiol-17 β -D-glucuronide, and mono- or disulfated progesterone metabolites, mainly 3 α , 5 α -isomers, is supported by experimental and clinical data.^{1,8,9} The mechanism by which metabolites of sex hormones may induce cholestasis in ICP is still under debate, and mutations in genes coding for biliary transport proteins of physiologically occurring metabolites in pregnancy as well as abnormal metabolites inhibiting hepatobiliary transport proteins have been considered to contribute to ICP. In ICP, the relief of cholestasis by UDCA has been suggested to be due to stimulation of vesicular exocytosis resulting in mobilization of an increased number of transport proteins to the canalicular membrane and, thereby, stimulation of transport systems involved in the biliary secretion of steroid mono- and disulfates.^{1,3,4,21–24,26,27}

Following oral administration, approximately 30% to 60% of UDCA is absorbed in the gut.²⁸ The degree of UDCA enrichment in biliary bile following chronic

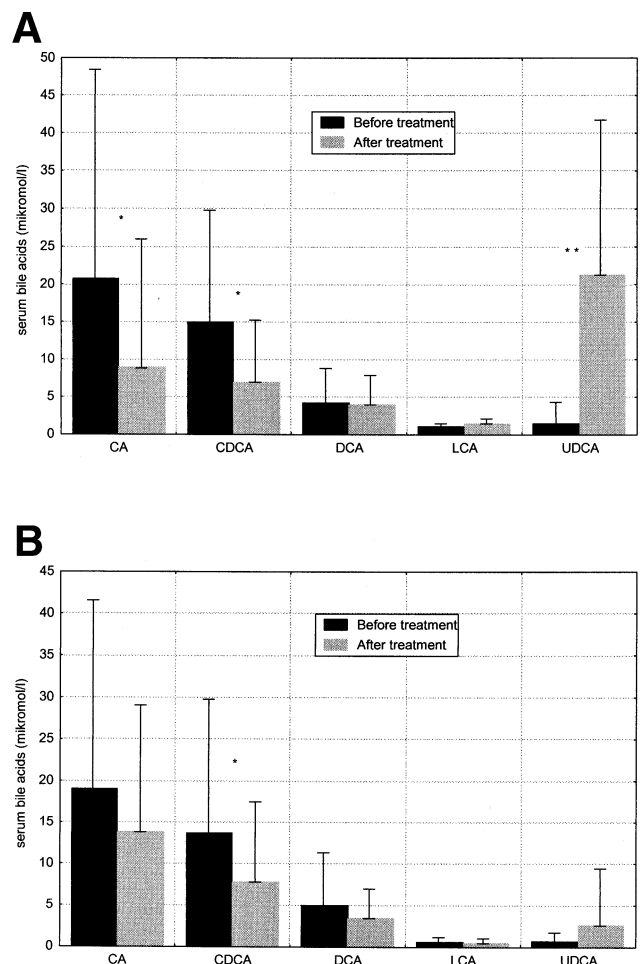


Figure 3. Serum bile acids before and after (A) UDCA therapy and (B) cholestyramine therapy. Data are means \pm SD; * P < .05, ** P < .0001.

ingestion correlates with the administered dose. Most clinical trials have used UDCA at a dose of 13–15 mg/kg/day.^{29–32} Recently, Mazzella et al reported positive results and no adverse reactions of high-dose UDCA (1.5–2 g/day).^{33,34} Little is known about the efficacy of a moderate dose of UDCA (8–10 mg/kg day) in patients with ICP. We aimed to determine the efficacy of this moderate dose to limit formation of the monohydroxy bile acid LCA, a potentially toxic bacterial product of UDCA in the human colon. UDCA given at 8–10 mg/kg per day causes an enrichment of approximately 40% in biliary bile acids.³⁵ The results of our study demonstrate a beneficial effect of a moderate dose of UDCA on relief of pruritus when compared with cholestyramine (>50% relief in 67% vs 19% of those treated with cholestyramine). The present study confirmed rapid relief of pruritus in patients receiving UDCA, and most of them experienced a clear relief of pruritus after 3–4 days, whereas during treatment with cholestyramine, pruritus usually attenuated only after 7–10 days. In agreement with the literature, elevation of aminotransferase activities from 2- to 15-fold was noticed in 85% of patients, bilirubin from 2- to 4-fold in 14% of patients, and fasting serum bile acids from 1.5- to 20-fold in 78% of patients.^{3,36} Sensitive serum markers for cholestasis such as γ -GT and AP were usually normal or slightly elevated: γ -GT was elevated up to 3-fold in 11% of patients, and AP was elevated 2- to 3-fold in 60% of patients. When γ -GT levels are high, a mutation of the gene encoding the canalicular phosphatidylcholine translocase (multidrug resistance gene 3; MDR3) is suspected.^{13–15,37} Aminotransferase activities and fasting serum bile acids levels were significantly reduced after treatment with UDCA, whereas cholestyramine did not affect these parameters. Serum bilirubin and γ -GT levels were normal in 86% and 89% of patients, respectively, before treatment and were not significantly affected by UDCA or cholestyramine. Serum alkaline phosphatase activity, which is mainly of placental origin in the third trimester of pregnancy, was not altered by medical treatment.

Our results also confirm earlier findings demonstrating that an increase of serum bile acids and especially of CA appears to be a sensitive indicator of ICP.^{1,3,8,38–44} The measurement of serum bile acids is particularly helpful in patients with pruritus but normal transaminase activities. CA predominated in the spectrum of serum bile acids during ICP when compared with healthy pregnant women. In a prospective cohort study from Sweden, Glantz et al demonstrated

a correlation between fetal complications and serum bile acids levels.⁴⁴ Elevated CA levels in maternal serum have been found to correlate with stronger uterine muscle contractions and placental chorionic vein vasoconstriction, which may cause fetal distress.^{41–46} A significant reduction of the concentrations of CA and CDCA was detected after treatment with UDCA, whereas, under treatment with cholestyramine, the serum concentrations of bile acids were not significantly changed, with the exception of CDCA. One possible explanation for this decrease of CDCA could be the binding of bile acids by cholestyramine and the interruption of their enterohepatic circulation.¹⁸ In the colon, unabsorbed UDCA is partially converted by intestinal bacteria into LCA, known to be embryotoxic in rats.^{1,41} Our data have shown that LCA is not significantly increased during the treatment with UDCA at moderate doses. The decrease of CA may be clinically relevant because it has been reported to cause fetal distress.^{41–46} No stillbirths or significant differences of newborn weight were found in both groups, whereas the Apgar score at 5 minutes was significantly higher in the UDCA group, and the delivery occurred significantly closer to term than in patients who received cholestyramine.

The present data confirm an excellent safety profile of UDCA: No adverse effects were observed. By contrast, 12 patients (29%) did not tolerate cholestyramine because of nausea and vomiting. Both ICP and cholestyramine treatment may independently lead to vitamin K deficiency. Therefore, prolonged high-dose cholestyramine treatment of pruritus in ICP can increase the risk of coagulopathy.¹⁸ However, no cases of coagulopathy were noticed in our study. This might be due to the short duration of treatment.

In conclusion, the results of our study showed a significant improvement of pruritus severity, aminotransferase activities, and serum bile acid concentrations and a more favorable outcome of pregnancy and absence of adverse events after treatment with a moderate dose of UDCA. In contrast, cholestyramine alleviated pruritus only mildly and caused adverse effects. These promising results obtained in the present and previous studies confirm the use of UDCA as first-line therapy for ICP.

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