Journal of Maternal-Fetal Medicine

ISSN: 1057-0802 (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ijmf19

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To cite this article: S. A. Laifer, R. J. Stiller, D. S. Siddiqui, G. Dunston-Boone & J. C. G. Whetham (2001) Ursodeoxycholic acid for the treatment of intrahepatic cholestasis of pregnancy, Journal of Maternal-Fetal Medicine, 10:2, 131-135

To link to this article: https://doi.org/10.1080/jmf.10.2.131.135

The Journal of Maternal-Fetal Medicine 2001;10:131–135

Ursodeoxycholic acid for the treatment of intrahepatic cholestasis of pregnancy

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Objective: To report our experience in managing intrahepatic cholestasis of pregnancy with ursodeoxycholic acid.

Methods: All cases of intrahepatic cholestasis of pregnancy that were diagnosed at Bridgeport Hospital from January 1997 to August 1999 were identified. Information was abstracted on demographics, medical and obstetric history, symptoms, laboratory data, therapy and pregnancy outcome. Statistical analysis was primarily descriptive; continuous variables were analyzed with *t* tests.

Results: A total of 20 cases of intrahepatic cholestasis of pregnancy were identified (0.32% of live births). All patients presented with pruritus. The mean gestational age at onset of symptoms was 31.1 weeks (range 13–38.4, median 32.4). Bile acids were measured in 18 cases and were elevated in all. The mean gestational age at delivery was 36.4 weeks (32.3–39.9). Eight patients were treated with ursodeoxycholic acid (600–1200 mg). All eight patients experienced subjective improvement in pruritus after initiation of treatment with ursodeoxycholic acid. Ursodeoxycholic acid was associated with a decrease in bile acids in most patients ($p = 0.16$) and with a significant decrease in serum transaminases ($p = 0.03$).

Conclusions: Ursodeoxycholic acid is an effective therapy for relief of pruritus and improvement of the liver dysfunction that occurs with intrahepatic cholestasis of pregnancy.

Key words: intrahepatic cholestasis of pregnancy; pruritus; ursodeoxycholic acid

INTRODUCTION

Intrahepatic cholestasis of pregnancy is a pregnancy-induced liver disorder that is characterized by severe generalized pruritus without skin lesions, in association with abnormal liver function (elevated levels of bile acids, transaminases and bilirubin). In addition to severe maternal discomfort, there is an increased risk of fetal compromise and fetal death in pregnancies complicated by intrahepatic cholestasis. Because conventional fetal monitoring may not be effective in predicting fetal compromise in this setting, early delivery after confirmation of fetal lung maturity has been advocated[1]. Until recently, treatment has been for the most part ineffective at providing adequate relief of pruritus and reversing liver dysfunction.

Ursodeoxycholic acid (ursodiol, Actigall) is a naturally occurring dihydroxy bile acid that is used for treating a variety of acute and chronic hepatic disorders, such as primary biliary cirrhosis, cholelithiasis and chronic hepatitis[2]. The principal mechanisms of action include displacement of toxic bile acids, cytoprotective effects on hepatocytes and bile duct epithelial cells, immunomodulatory effects and stimulation of bile secretion by hepatocytes and bile duct epithelial cells[3,4]. Recent reports from Europe and South America have described beneficial effects of ursodeoxycholic acid in the treatment of intrahepatic cholestasis of pregnancy[5–11]. The beneficial effects include improvement or resolution of pruritus, correction of laboratory abnormalities and decreased incidence of fetal compromise. On the basis of these reports, we have been offering ursodeoxycholic acid as a treatment option for intrahepatic cholestasis of pregnancy in selected patients. The purpose of this study was to review our experience with

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Received 16 May 2000; revised 22 November 2000; accepted 22 November 2000

the use of this agent in the management of intrahepatic cholestasis. Specifically, we sought to evaluate the effect of ursodeoxycholic acid on relieving symptoms of pruritus and to determine the effect of ursodeoxycholic acid on bile acids and liver injury tests.

MATERIALS AND METHODS

Through our antenatal testing unit database we identified all cases of intrahepatic cholestasis that were diagnosed at Bridgeport Hospital between January 1997 and August 1999. Patients were diagnosed with intrahepatic cholestasis if they presented with persistent pruritus, had no associated rash or skin lesions, had evidence of altered hepatic function (elevated bile acids and/or transaminases) and had no evidence of other pregnancy-induced hepatic disease. An additional criterion for inclusion in this study was resolution of the pruritus within several days after delivery.

Ursodeoxycholic acid was specifically recommended in cases of early presentation when pregnancy prolongation was desired and delivery was not considered an appropriate management option. It was used either as primary therapy or in place of other agents that had been initiated prior to perinatal consultation.

We collected data on maternal demographics, medical history, obstetric history, presenting symptoms, laboratory data, therapy and pregnancy outcome. We performed descriptive analyses on all variables. In patients who received ursodeoxycholic acid we compared concentrations of bile acids and transaminases before and after initiation of therapy. p Values of less than 0.05 were considered statistically significant. The study was conducted in accordance with the guidelines of the Bridgeport Hospital institutional review committee.

RESULTS

We identified 20 cases of intrahepatic cholestasis of pregnancy in 19 patients (0.32% of deliveries). One patient had successive pregnancies complicated by cholestasis. The ethnic profile included 12 Caucasians, four Hispanics, two African Americans and one Asian patient. There were 16 singleton gestations and four twin gestations.

All patients had evidence of altered hepatic function. Fasting bile acid concentrations were measured in 18 of the 20 pregnancies and were elevated in all 18 cases. Serum concentrations of aminotransferases were measured in all patients and were elevated in 15 patients. Although elevations in concentrations of aminotransferases are generally reported to be moderate (2–10 times normal)[12], four patients had peak alanine aminotransferase levels that exceeded 500 U/l (range 644–1668). Evaluation for other causes of hepatic injury (viral hepatitis) in these patients was negative and the concentrations of aminotransferases normalized in each patient after delivery. The highest total bilirubin level in the cohort of patients was 2.4 mg/dl. Three patients were found to be seropositive for hepatitis C, and two patients had a history of cholelithiasis.

Medical therapy was used in 13 cases. Cholestyramine was used in four patients and antihistamines in five patients (both were used in two patients). Eight patients were treated with ursodeoxycholic acid. Six patients received this agent as primary therapy and two patients received this agent after failing to respond to treatment with cholestyramine. The mean gestational age at onset of pruritus (31.1 weeks in the entire cohort) occurred earlier in the eight patients treated with ursodeoxycholic acid when compared with patients not treated with ursodeoxycholic acid (27.5 weeks vs. 33.5 weeks, $p = 0.005$). There was no difference in age, gravidity or severity of laboratory abnormalities between patients who received therapy with ursodeoxycholic acid and those who did not. The mean gestational age at initiation of ursodeoxycholic acid therapy was 30.9 weeks (range 22.4–35) and the mean duration of therapy was 5.4 weeks (range 2–13.1). There was no difference in the gestational age at delivery between patients who were treated with ursodeoxycholic acid and those who were not (36.5 ± 0.7 vs. 36.4 ± 2.4 weeks). The initial dose of ursodeoxycholic acid was 600 mg/day in two divided doses; all patients required dosage increases. At delivery five patients were taking 1200 mg/day and three patients were taking 900 mg/day (range of 12–17 mg/kg per day). After receiving ursodeoxycholic acid, six patients experienced a marked reduction in the severity of pruritus (symptom free for most of a 24-h period) and two patients experienced a modest improvement in the severity of their pruritus (less pruritus after initiation of therapy). Table 1 shows the values of the bile acid cholylglycine and aminotransferases in patients before and after initiation of treatment with ursodeoxycholic acid. Only the decreases in concentrations of aminotransferases achieved statistical significance. All patients tolerated the medication and did not report adverse effects.

All birth weights were appropriate for gestational age. One neonatal death occurred that was secondary to early-onset group B streptococcal sepsis. This baby was delivered at 36 weeks to a patient treated only with cholestyramine. There were no neonatal deaths or significant neonatal morbidities in the group treated with ursodeoxycholic acid.

DISCUSSION

Prior to the use of ursodeoxycholic acid, the treatment options for patients with intrahepatic cholestasis were primarily directed at relief of pruritus. Agents such as antihistamines, phenobarbital and cholestyramine, however, provided only partial relief of symptoms. It is of concern that cholestyramine, the most commonly used agent, can

Table 1 Liver function tests of patients treated with ursodeoxycholic acid (UDCA)

Patient	CG before UDCA	CG during UDCA	AST before UDCA	AST during UDCA	ALT before UDCA	ALT during UDCA
1	3.44	3.81	108	64	192	109
2	6.21	1.38	normal	normal	normal	normal
3	2.41	1.81	95	57	116	65
4	41.26	3.46	97	30	154	35
5	15.16	1.16	97	22	139	16
6	3.42	0.19	142	20	233	12
7	2.39	3.14	normal	normal	normal	normal
8	3.33	5.55	301	94	566	118
Mean	9.981 ± 13.31	2.40 ± 1.46	140 ± 80.8	47.8 ± 29.1	233.3 ± 168.1	59.2 ± 46.2
Significance		$p = 0.16$		$p = 0.03$		$p = 0.03$

CG, cholylglycine (μmol/l, normal < 1.38 μmol/l); AST, aspartate aminotransferase (U/l, normal 14–36 U/l); ALT, alanine aminotransferase (U/l, normal 9–52 U/l)

also lead to coagulopathy by inhibiting the absorption of fat-soluble vitamin K[12]. None of these agents improved maternal liver dysfunction or decreased the risk of fetal compromise. The use of the intravenously administered medication, *S*-adenosylmethionine, which was initially thought to be effective for relieving pruritus and improving liver functions, has not been demonstrated to be effective in a randomized placebo-controlled study[13].

Ursodeoxycholic acid was first introduced as a medical therapy for dissolution of gallstones in Japan in 1957[4]. It is now used for treatment of a variety of hepatic disorders, including chronic hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis and autoimmune hepatitis[2,3]. In 1992, Palma and colleagues from the University of Chile[5] summarized their preliminary use of ursodeoxycholic acid for the treatment of intrahepatic cholestasis of pregnancy. In an open-label pilot trial of ursodeoxycholic acid given to eight pregnant patients with intrahepatic cholestasis, seven of the eight patients experienced a significant improvement in pruritus and a reduction in the concentrations of serum bile salts and aminotransferases. In 1997, the same group of investigators performed a small randomized, double-blind, placebo-controlled study of ursodeoxycholic acid for the treatment of intrahepatic cholestasis in patients who became symptomatic prior to 33 weeks' gestation[9]. After 3 weeks of therapy at a dose of 1 g/day (mean of 16 mg/kg per day), the eight patients who received ursodeoxycholic acid experienced significant improvement in pruritus, and significant decreases in serum levels of aminotransferases, compared with the seven patients who received the placebo. Furthermore, these investigators demonstrated an improvement in neonatal outcome. Patients who received ursodeoxycholic acid delivered closer to term (37.8 weeks) compared to patients who received placebo (33.8 weeks), of which one experienced a stillbirth and two experienced fetal distress[9]. In another small randomized, double-blind, placebo-controlled study, Diaferia and co-workers[8] treated eight patients with ursodeoxycholic acid and found significant decreases in levels of bile acids and transaminases and in pruritus score, when compared with patients treated with placebo. Because of improvements in liver function tests, these investigators also found that deliveries were performed at later gestational ages than in placebo-treated patients (38 vs. 34 weeks)[8].

In uncontrolled studies, Davies and colleagues[7], Brites and colleagues[10] and Meng and colleagues[14] also demonstrated reductions in bile acid concentrations in patients with intrahepatic cholestasis who were treated with ursodeoxycholic acid. The ability of ursodeoxycholic acid to promote bile acid secretion and decrease concentrations of serum bile acids probably explains its effectiveness at relieving the pruritus. Javitt[15] suggested that ursodeoxycholic acid lowers serum bile acids in the setting of intrahepatic cholestasis by restoration of bicarbonate secretion (choloresis) and promotion of normal bile acid flow. In addition to lowering bile acids, ursodeoxycholic acid was found by Meng and colleagues[14] also to stimulate biliary excretion of sulfated progesterone metabolites, which are increased in the serum of patients with intrahepatic cholestasis of pregnancy. These probably reflect the altered progesterone metabolism that may characterize this disorder. By lowering maternal concentrations of bile acids, ursodeoxycholic acid may provide additional protection to the fetus. In their trial, Diaferia and co-workers[8] also demonstrated a reduction in amniotic fluid bile acid concentrations in patients treated with ursodeoxycholic acid. Serrano and associates[16] studied bile acid transport in placental membranes taken from the placentas of patients who had intrahepatic cholestasis of pregnancy. These

investigators demonstrated that ursodeoxycholic acid had a beneficial effect on impaired placental bile acid transport systems.

Although our study was uncontrolled, our findings corroborate the effectiveness of ursodeoxycholic acid for treatment of the pruritus and liver dysfunction associated with intrahepatic cholestasis of pregnancy. All patients showed improvement in the severity of their pruritus, all patients with elevated levels of aminotransferases showed decreases and five of the eight patients had reductions in levels of the bile acid cholylglycine. Cholylglycine is an accurate marker for bile acid elevation in the setting of intrahepatic cholestasis[17,18], and the one most readily available for measurement by our hospital laboratory. It is possible that, if other bile acids had been measured, a reduction with ursodeoxycholic acid therapy may have been identified in all patients. We did not demonstrate a difference in fetal/neonatal outcome or gestational age at delivery in our cohort of patients with intrahepatic cholestasis who were treated with ursodeoxycholic acid, but this was probably because our patients were not randomized and because of the later gestational age at diagnosis of those patients who were not treated.

Based on the small series from Europe and South America and our own experience, our conclusion is that ursodeoxycholic acid is an effective treatment for the pruritus and liver dysfunction associated with intrahepatic cholestasis of pregnancy. There have been no short-term or long-term adverse fetal or neonatal effects reported with its use, and first-trimester use of ursodeoxycholic acid does not occur with this disorder. Additionally, animal studies have not demonstrated a teratogenic effect[19]. Although individualized treatment is recommended, Table 2 shows our current management approach to the diagnosis of intrahepatic cholestasis of pregnancy. If a patient presents at or beyond 36 weeks and the cervix is favorable, we consider assessment of fetal lung maturity and delivery rather than initiating a medical treatment regimen at that time. If a patient presents prior to 36 weeks, we consider initiating therapy with ursodeoxycholic acid. Ursodeoxycholic acid is generally available in 300-mg tablets and our initial dose is 600 mg/day in two divided doses. All patients in our series required an increased dose (900–1200 mg/day) for more effective relief of pruritus and our next step would be to increase the evening dose to 600 mg because the pruritus is generally worse at night. In our cohort of patients, a daily dose of 900–1200 mg (12–17 mg/kg per day) was roughly equivalent to the effective doses of 14–16 mg/kg per day reported by others[5,9]. We serially monitor liver function and, if normalization of liver function occurs, we consider continued expectant management and close fetal surveillance with the goal of spontaneous labor and delivery.

It is of interest that an association between hepatitis C seropositivity and intrahepatic cholestasis has been identified. Locatelli and co-workers[20] showed that intrahepatic cholestasis occurred more frequently and at an earlier gestational age in pregnant women who were hepatitis C virus-positive. These authors suggested that modifications in hepatocytes and biliary epithelial cells induced by the hepatitis C virus may facilitate the development of cholestasis, although the mechanism is unclear. The patient in our current series who presented at 13 weeks of gestation with intrahepatic cholestasis was found to be serologically positive for hepatitis C. It would seem prudent, therefore, to consider screening patients for hepatitis C if they present with pruritus and intrahepatic cholestasis prior to the third trimester.

Table 2 Management of intrahepatic cholestasis of pregnancy

Gestational age ≥ 36 weeks
Initiate fetal surveillance
Consider amniocentesis and delivery
Gestational age ≤ 36 weeks
Initiate fetal surveillance
Consider therapy with ursodeoxycholic acid
initial dose 300 mg twice a day
if symptoms persist after 1 week, increase evening dose to 600 mg
if symptoms persist after a further week, increase dose to 600 mg twice a day
Monitor serial liver functions and bile acids (every 2–4 weeks)
Deliver at 36–37 weeks with fetal maturity, or continue surveillance if liver function improves

ACKNOWLEDGEMENT

This paper was presented in part at the 47th Annual Clinical Meeting of the American College of Obstetricians and Gynecologists, May 1999.

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