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RAPID COMMUNICATION

Predictors of premature delivery in patients with intrahepatic cholestasis of pregnancy

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Abstract

AIM: To evaluate the predictive value of clinical symptoms and biochemical parameters for prematurity in intrahepatic cholestasis of pregnancy (ICP).

METHODS: Sixty symptomatic patients with ICP were included in this retrospective analysis. Preterm delivery was defined as delivery before 37 wk gestation. Predictors of preterm delivery were disclosed by binary multivariate logistic regression analysis.

RESULTS: Mean time of delivery was 38.1 ± 1.7 wk. No stillbirths occurred. Premature delivery was observed in eight (13.3%) patients. Total fasting serum bile acids were higher (47.8 ± 15.2 *vs* 41.0 ± 10.0 μmol/L, $P < 0.05$), and pruritus tended to start earlier (29.0 ± 3.9 *vs* 31.6 ± 3.3 wk, $P = 0.057$) in patients with premature delivery when compared to those with term delivery. Binary multivariate logistic regression analysis revealed that early onset of pruritus (OR 1.70, 95% CI 1.23-2.95, $P = 0.038$) and serum bile acid (OR 2.13, 95% CI 1.13-3.25, $P = 0.013$) were independent predictors of preterm delivery.

CONCLUSION: Early onset of pruritus and high levels of serum bile acids predict preterm delivery in ICP, and define a subgroup of patients at risk for poor neonatal outcome.

Key words: Intrahepatic cholestasis; Delivery; Pregnancy

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INTRODUCTION

Liver disorders during pregnancy range from benign nuisance to progressive and potentially lethal disorders for mothers and/or children. This is exemplified by intrahepatic cholestasis of pregnancy (ICP), which starts with modest itching and can end in intrauterine fetal demise[1]. ICP is a liver disorder unique to pregnancy and disappears after delivery. However, it frequently recurs in subsequent pregnancies or when women begin taking oral contraceptives.

The condition is very common in Chile and Bolivia (6%-27%), and in Sweden (1%-1.5%). The incidence of ICP is lower elsewhere in Europe (0.1%-1.5%) and the United States (0.7%)[2,3]. Genetic predisposition and hormonal factors have crucial roles in the pathogenesis[2]. There is increasing evidence that genetically determined dysfunction of canalicular transporters may be a risk factor for development of ICP[4-9]. ICP has been linked to adverse maternal and fetal outcomes. The main symptom is pruritus without evidence of skin lesions, which appears most typically in the third trimester of pregnancy. Laboratory tests demonstrate an increase in serum bile acids and aminotransferases[2,10,11]. ICP is essentially benign in mothers. The major consequences of this disease are premature delivery in 19%-60% of cases[12,13], stillbirths in 1%-2%[13,14] and fetal distress in 22%-33%[15,16]. The mechanisms by which ICP leads to poor fetal outcome are unclear. Recent clinical and biochemical studies have provided evidence for altered metabolism of bile acids and progesterone in ICP, although it remains unclear whether these changes are specific for ICP or are rather the consequence of cholestatic injury[17-20]. In a study from Sweden, a correlation between fetal complications and serum bile acids levels was demonstrated[3].

Various strategies have been proposed to improve obstetric outcome. Nevertheless, in several studies, the investigators have concluded that fetal death in ICP may not be predictable by traditional antepartum surveillance, and that delivery after establishment of fetal lung maturity may reduce fetal mortality rate[13-15]. Obstetric management consists of weighing the risk of premature delivery against the risk of sudden death *in utero*. As well, it has to be considered that induction of labor is associated with a higher frequency of complications such as surgical delivery compared to spontaneous labor[2]. To allow term delivery (≥ 37 wk) in patients with ICP, it appears essential to ascertain early prognostic markers for poor fetal outcome.

In our previous prospective therapeutic trial[21], we observed a significant effect of ursodeoxycholic acid (UDCA) in comparison to cholestyramine on pruritus, serum liver tests, and the duration of pregnancy in patients with ICP. However, the treatment groups did not differ significantly in the number of premature deliveries (< 37 wk gestation). Therefore, the aim of the current study was to re-evaluate clinical symptoms and biochemical parameters as potential predictors of spontaneous preterm births in patients with ICP.

MATERIALS AND METHODS

Sixty patients with ICP defined by (1) development of pruritus during the second or third trimester of pregnancy, and (2) total fasting serum bile acids (TBA) ≥ 11 μmol/L, were included in this retrospective analysis. All patients were seen at the Kaunas Medical University Hospital, Lithuania between October 1999 and September 2002. Patients with chronic liver diseases, skin diseases, allergic disorders, symptomatic cholelithiasis, and ongoing viral infections affecting the liver (hepatitis A, B and C virus, cytomegalovirus, herpes simplex virus, and Epstein-Barr virus) were excluded. All patients participated in a randomized parallel-group study as reported previously[21]. In contrast to the previous prospective trial, the actual retrospective analysis included patients with elevated TBA ≥ 11 μmol/L only.

Pruritus intensity was assessed daily by patients using a subjective score: 0, no pruritus; 1, mild pruritus, occasional; 2, moderate pruritus, intermittent during the day with asymptomatic periods prevailing; 3, severe pruritus every day with symptomatic periods prevailing; 4, severe, constant pruritus day and night. Serum liver tests and fasting serum bile acids were evaluated at the time of the first presentation. Serum liver tests were determined using routine laboratory techniques. Bile acids were analyzed by gas-liquid chromatography as described previously[21,22]. Fasting serum samples were stored at -20℃ until analyzed. Ultrasonography of the abdomen and serology of viral hepatitis were performed to exclude other causes of liver disease in every patient before enrollment.

The Obstetric and Gynecology Clinic of Kaunas Medical University Hospital is a tertiary care maternity center that provides all obstetric services for women with complicated pregnancies, for a stable and ethnically uniform population of 2 million inhabitants. Most of the high-risk deliveries in the area took place in this clinic. Fetal status was monitored in the same hospital every week. Pregnancy outcome and newborn status (term and mode of delivery, Apgar score at 1 and 5 min, asphyxial events, and newborn weight) were assessed by obstetricians and neonatologists, who were not given any specific instructions concerning date and form of delivery. Spontaneous preterm birth was defined as delivery before 37 wk gestation after the spontaneous onset of labor.

Statistical analysis

The results are expressed as means ± SD. Comparison of parametric, normally distributed data was performed by Student's *t* test. The difference between two samples was calculated using the Mann-Whitney test. Correlation analysis was assessed by Spearman's rank correlation. Multivariate analysis of significant prognostic factors of delivery before 37 wk gestation was based on binary multivariate logistic regression analysis. Factors found to be significant or having a trend towards significance (TBA concentrations, onset of pruritus) were selected for this model. Statistical analysis was conducted with SPSS 12.0. All reported *P* values were two-sided, and $P < 0.05$ was considered statistically significant.

RESULTS

Sixty patients who met the inclusion criteria were included in the study. Age ranged between 18 and 40 year (median 27.0), median gestational age was 35.0 wk (range, 22-39), median time of onset of pruritus was 32.0 wk (range, 20-37). Twenty-eight (46.6%) women were primiparous and 32 (53.4%) were multiparous. Recurrence of ICP was reported by 19 (31.6%) patients, 14 of these had a history of preterm delivery, and two of intrauterine fetal death. Ten (16.6%) patients had been users of oral contraceptives, of whom three women had experienced pruritus during use. Gallstone disease was diagnosed in seven (11.6%) cases. One (1.6%) patient had a urinary tract infection. No stillbirths were observed. The Apgar score at 1 min was 8.5 ± 0.7, and at 5 min, 9.0 ± 0.6. Delivery was after 38.1 ± 1.7 wk. Postnatal development was normal in all babies. Pregnancy ended prematurely in eight (13.3%) patients: in three receiving UDCA and in five treated with cholestyramine. Table 1 compares the clinical characteristics of patients who had deliveries before 37 wk and those who had delivery after 37 wk gestation. Significantly higher levels of TBA (47.8 ± 15.2 *vs* 41.0 ± 10.0 μmol/L, $P < 0.05$), and a tendency towards earlier onset of pruritus (29.0 ± 3.9 *vs* 31.6 ± 3.3 wk, $P = 0.057$) were found in cases of premature delivery when compared with term delivery. The correlation coefficient between TBA levels and pruritus scores tended to be higher in patients with preterm delivery (0.733) when compared to those with term delivery (0.523). In cases of preterm delivery (< 37 wk gestation), TBA concentration correlated positively with onset of pruritus ($r = 0.678$), bilirubin ($r = 0.538$), alanine aminotransferase ($r = 0.343$), and aspartate aminotransferase ($r = 0.308$), whereas correlation was weaker in term delivery.

To unravel potential factors that may affect the time of delivery, we instituted a binary multivariate logistic

Table 1 Clinical characteristics at the time of first presentation of patients with ICP who had delivery before and after 37 wk gestation

Characteristics	Delivery before 37 wk *n* = 8	Delivery after 37 wk *n* = 52	*P*
Age (yr)	26.6 ± 7.2	28.3 ± 5.4	0.433
Onset of pruritus (wk)	29.0 ± 3.9	31.6 ± 3.3	0.057
Intensity of pruritus (score)	3.1 ± 0.4	2.9 ± 0.6	0.361
ALT (U/L)	187.3 ± 87.2	210.4 ± 149.3	0.721
AST (U/L)	126.6 ± 78.8	140.1 ± 101.4	0.855
AP (U/L)	386.9 ± 132.7	372.1 ± 136.2	0.707
γGT (U/L)	35.6 ± 23.2	24.4 ± 14.1	0.072
Bilirubin (μmol/L)	10.3 ± 4.0	15.5 ± 13.1	0.202
TBA before treatment (μmol/L)	47.8 ± 15.2	41.0 ± 10.0	0.041

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AP, alkaline phosphotase; γGT, γ-glutamyltransferase; TBA, total bile acids.

Table 2 Potential risk factors for preterm delivery: Predictive value as evaluated by binary multivariate logistic regression analysis

Factor	OR	95.0% CI	*P*
Onset of pruritus (wk)	1.703	1.227-2.947	0.038
Total bile acids before treatment (μmol/L)	2.128	1.126-3.252	0.013

regression model. The factors that were found to be significant or those that had a trend towards significance (TBA concentrations, onset of pruritus) were selected for this model. Binary multivariate logistic regression analysis demonstrated that serum bile acid concentration (OR 2.13, 95% CI 1.13-3.25, $P = 0.013$) and onset of pruritus (OR 1.70, 95% CI 1.23-2.95, $P = 0.038$) were the most important independent variables predicting preterm delivery (Table 2).

DISCUSSION

Although recent studies have improved our understanding of the underlying pathophysiological disturbances and their association with specific symptoms during ICP, the pathogenesis and prognosis of pregnancy have remained obscure. The current study aimed to unravel potential risk factors for fetal prematurity. We found that earlier onset of pruritus and higher TBA concentrations were associated with preterm delivery in our cohort of patients with ICP. The correlation between premature delivery and onset of pruritus is a new and interesting finding; although, high TBA levels have already been described as predictors of fetal outcome in other cohorts[3,23].

ICP is the most common liver disorder unique to pregnancy. In Lithuania, a retrospective analysis disclosed a rate of 0.4% of ICP in 16252 pregnant women over a period of 5 year (1996-2000; J. Kondrackiene, unpublished data). Although essentially benign in the mother, ICP may adversely affect the prognosis of the fetus. ICP has been reported to be associated with increased rates of spontaneous premature delivery[12,13]. According to the Lithuanian Medical Birth Register (2004), the total premature birth rate was 5.3%. Our study showed a 13.3% incidence of preterm delivery in patients with ICP.

The mechanism of preterm delivery remains unclear. Germain *et al*[24] have shown that during ICP, activation of the oxytocin receptor pathway is possibly caused by a cholic-acid-mediated increase in oxytocin-receptor expression. The placenta plays a crucial role in protecting the fetus from the adverse effects of potentially toxic endogenous substances, including TBA[25]. High levels of maternal TBA affect placental transport, placental hormone production, and chorionic vessel constriction[17]. In animal models, maternal hypercholanemia may affect the vectorial transfer of bile acids through the creation of inversely directed gradients, as compared with the physiological situation[26], and by impairing the ability of the trophoblast to transport bile acids[18]. A study from Argentina has shown that asymptomatic hypercholanemia of pregnancy, defined as TBA > 11 μmol/L in healthy pregnant women, does not necessarily lead to ICP[27]. Glantz *et al*[3] have demonstrated that no increase in fetal risk is detected in ICP patients with TBA levels < 40 μmol/L, and have proposed that these women can be managed expectantly. However, a recent case of fetal death at 39 wk and 3 d in a patient with ICP, who had low TBA concentrations at the time of diagnosis, has been reported[28]. This raises a crucial question: is the fasting TBA level sufficient to predict fetal outcome? Should testing be repeated on a weekly basis or discontinued once a less-than-critical level has been determined? What if concentrations increase dramatically over the following weeks, although levels are comparably low at the time of diagnosis for which the prognostic value has been evaluated[29]? Therefore, it is important to evaluate other clinical factors that are possibly associated with prematurity. We found significantly higher levels of TBA, and a tendency towards earlier onset of pruritus, although non-significant, in patients who had premature delivery, when compared with cases of term delivery. The binary multivariate regression analysis revealed that the TBA levels and early onset of pruritus were the most important independent factors predicting premature delivery.

In the current retrospective study, we did not analyze the effect of treatment on preterm delivery. Indeed, among the women who had births before 37 wk gestation, three of eight patients had received UDCA, and five were treated with cholestyramine. The size of the cohort may have been too small to detect any difference in the rate of preterm delivery between patients treated with UDCA and those treated with cholestyramine, although the timepoint of delivery was significantly earlier in patients treated with cholestyramine than in those treated with UDCA in our previous analysis. As well, the rate of preterm delivery in the present cohort was lower than that reported in other studies. This could in part be due to increased attention devoted to ICP during the study[3].

The current analysis indicated that early onset of pruritus, along with markedly elevation of TBA levels, may predict premature delivery, which represents a potential risk factor for the fetus in women with ICP. Because the

prognosis remains unpredictable in some cases[28], our current strategy is to begin pharmacological treatment after confirmation of diagnosis in all ICP patients. The treatment of choice is UDCA, which has improved maternal and fetal morbidity in several clinical trials and observational studies[21,31-34]. When lung maturity is achieved for those patients with risk factors of prematurity, delivery should be considered.

In conclusion, the present study indicated that early onset of pruritus and high levels of TBA were the most important factors associated with preterm delivery in a well-defined cohort of patients with ICP; thereby, defining a group at risk of poor neonatal outcome and so requiring active management.

COMMENTS

Background

Intrahepatic cholestasis of pregnancy (ICP) is characterized by pruritus and an elevation in serum bile acid concentrations. The major consequences of this disease are premature delivery, stillbirth and fetal distress. The mechanisms by which ICP leads to poor fetal outcome are unclear, although a role for bile acids or toxic metabolites of bile acids has been suggested. Currently, the hydrophilic bile acid ursodeoxycholic acid (UDCA) is the most effective treatment for ICP. Various strategies have been proposed to improve obstetric outcome. In several studies, the investigators have concluded that fetal death in ICP may not be predictable by traditional antepartum surveillance, and that delivery after establishment of fetal lung maturity may reduce fetal mortality rate. To allow for term delivery ($\geqslant$ 37 wk) in patients with ICP, it appears essential to disclose early prognostic markers for a poor fetal prognosis.

Research frontiers

There is increasing evidence that genetically determined dysfunction in the canalicular ABC transporters might be risk factors for development of ICP. Heterozygous mutations in the MDR3 gene (encoding for a canalicular phospholipid translocator involved in the biliary secretion of phospholipids) have been found. Recent clinical and biochemical studies provided evidence of abnormal metabolites impairing hepatobiliary carriers for an altered metabolism of bile acids and progesterone in ICP although it remains unclear whether these changes are specific for ICP or are rather the consequence of cholestatic injury in ICP.

Innovations and breakthroughs

We found that earlier onset of pruritus and higher fasting serum bile acid concentrations were associated with preterm delivery in our cohort of patients with ICP. The correlation between premature delivery and onset of pruritus is a new and interesting finding; although, high serum bile acid levels have been described as predictors of fetal outcome in other cohorts.

Applications

The present study indicates that early onset of pruritus and high levels of serum bile acid are the most important factors associated with preterm delivery in patients with ICP; thereby, defining a group at risk of poor neonatal outcome and so requiring active management.

Peer review

This is a well-written manuscript reporting on a cohort of 60 patients with symptomatic ICP. Early onset of pruritus and high levels of serum bile acids predict preterm delivery in intrahepatic cholestasis of pregnancy and define a subgroup of patients at risk of poor neonatal outcome.

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