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Intrahepatic cholestasis of pregnancy: Correlation of preterm delivery with bile acids

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Background/aims: *The aim of this study was to determine the incidence, obstetrical and fetal complication rates of intrahepatic cholestasis of pregnancy in patients managed actively around 38 weeks and evaluate the correlation of these results with liver function tests and bile acids.* ***Material and Methods:*** *In this cohort study 3710 women were booked for delivery, of which 32 pregnant women were diagnosed as intrahepatic cholestasis of pregnancy. All data concerning obstetric- medical history, laboratory results, symptom onset time, pruritus degree, treatment response, and delivery time and infants information were recorded in the study protocol. Statistical analyses were conducted with SPSS 12.0 version and correlations were assessed by Spearman Rank correlation analysis.* ***Results:*** *The incidence of intrahepatic cholestasis of pregnancy was 0.86%. The symptoms appeared around 32 weeks. 16.6% multiparas had a previously affected pregnancy and 21.8% of intrahepatic cholestasis of pregnancy patients had family history of intrahepatic cholestasis of pregnancy. Symptom onset varied according to season ($p<0.05$). Most patients (69.5%) were diagnosed in winter and the beginning of spring. There were no reported cases of clinical maternal jaundice, bleeding tendency or stillbirth. Pruritus was decreased by ursodeoxycholic acid treatment. Total bile acids tended to be higher in patients with preterm delivery ($r=0.409$, $p=0.038$).* ***Conclusion:*** *Total bile acids are correlated with preterm delivery. An attempt to deliver at around 38 weeks may improve perinatal outcome.*

Key words: Intrahepatic cholestasis of pregnancy, bile acids, perinatal outcome, preterm delivery

Gebeliğin intrahepatik kolestazı: Safra asitleri ile preterm doğumun korelasyonu

Amaç: *Bu çalışmada, gebelikte gözlenen intrahepatik kolestaz olgularının insidansı, obstetrik ve fetal komplikasyonlarının tanımlanması ve ortaya konulan sonuçların karaciğer fonksiyon testleri ve safra asitleri ile korelasyonunun değerlendirilmesi amaçlandı.* ***Yöntem:*** *Kliniğimizde antenatal takibi yapılan ve doğumu gerçekleştirilen 3710 olgunun 32'sinde gebeliğin intrahepatik kolestazı tanısı konuldu. Olguların obstetrik-medikal hikâyeleri, laboratuvar sonuçları, belirtilerin başlama tarihi, kaşıntı dereceleri, tedaviye cevapları, doğum zamanlamaları, yenidoğan bebeklerin bilgileri çalışma protokolüne alındı. İstatistiki analizler SPSS 12.0 versiyon kullanılarak yapıldı. Korelasyonun ortaya konulmasında Spearman Rank Korelasyon Analizi kullanıldı.* ***Bulgular:*** *İntrahepatik kolestaz olgularının insidansı %0.86 olarak bulundu. Semptomlar 32. hafta civarında gözlendi. Multipar olguların %16,6'sında daha önceki gebelikte, gebeliğin intrahepatik kolestazının gözlendiği, tüm olguların ise %21,8'inde aile öyküsünün olduğu saptandı. Semptomların gözlenme zamanının mevsimlere göre değiştiği ve bunun istatistiki olarak anlamlı olduğu gözlendi ($p<0.05$). Olgularının büyük çoğunluğunun (%69.5) kış aylarında veya ilkbahar başlarında gözlendiği ortaya konuldu. Hiçbir olguda klinik olarak sarılık, kanamaya meyil veya fetal ölüm gözlenmedi. Ursadeoksikolik asit ile kaşıntı şiddeti azaldı. Erken doğum gözlenen olgularda ise serum safra asitlerinin daha yüksek olduğu ortaya konuldu ($r=0.409$, $p=0.038$).* ***Sonuç:*** *Total safra asitleri erken doğum ile koreledir. 38. haftalarda doğum planlaması ile perinatal outcome iyileştirilebilir.*

Anahtar kelimeler: Gebeliğin intrahepatik kolestazı, safra asitleri, perinatal outcome, preterm doğum

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a benign cholestatic liver disorder that is characterized by pruritus and elevated serum aminotransferases and serum bile acid levels (SBAs), with the

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onset in the second or third trimester of pregnancy. Signs and symptoms resolve spontaneously within two to three weeks after delivery. The prevalence of ICP differs depending on genetic make-up, geography and environmental factors. The estimated prevalence of ICP varies between countries, affecting 0.01-0.02% of births in North America, Asia and Australia and 2% of births in Sweden, with the highest risk in Chile, at 4% of births (1,2).

The etiology of ICP is unknown, although current investigations suggest a combination of hormonal, genetic and inflammatory factors that impair bile secretory function, which acts to increase maternal SBAs and elevate liver enzymes (2-5). According to several studies, although the maternal course is usually benign, the fetus faces an increase risk of spontaneous preterm delivery, fetal compromise, meconium-stained amniotic fluid, and intrauterine fetal demise (1,2,6). The pathogenesis of fetal complications is still poorly understood; however, a role for circulating bile acids or toxic metabolites of bile acids has been suggested (1,7,8).

In this cohort study, we evaluated the incidences of ICP and investigated whether fetal complications rates and other liver function tests (LFTs) correlated with the severity of disease measured by bile acid levels in the maternal serum.

MATERIALS AND METHODS

Between January 2006 and December 2010, all patients who were diagnosed as ICP were included in this study. In our clinic, the diagnosis of ICP was based on the clinical features and biochemical evidence of liver dysfunction in the absence of skin pathology (9,10). Clinical features were characterized as pruritus without a rash. Itching is classically on the palms and soles of the feet, although it may be more widespread, with nocturnal predominance, and women may exhibit skin excoriations from scratching. Patients with chronic liver diseases, skin diseases, allergic disorders, symptomatic cholelithiasis, or ongoing viral infections affecting the liver (hepatitis A, B and C virus, cytomegalovirus, herpes simplex virus and Epstein-Barr virus) were excluded. Pruritus intensity was assessed by patients using a subjective score (0-4 degree), which was previously described by Kondrackiene et al. (11).

After diagnosis with ICP, all women were treated with ursodeoxycholic acid (UDCA; 10-15 mg/kg/day). Fetal well–being was monitored by cardiotocography, modified biophysical profile or Doppler ultrasonography weekly or biweekly according to gestational status. LFTs were taken weekly if normal or biweekly if abnormal (12). After the birth, Apgar scores and weight and health status were evaluated by pediatricians and recorded in infant charts. All data concerning obstetric-medical history, laboratory results, pruritus degree, and infant characteristics were recorded in the study protocol. Spontaneous preterm birth was defined as delivery before 37 weeks' gestation after spontaneous onset of labor. If there were no other complications, delivery decision was carried out after 38 weeks.

Photometric, enzymatic and calorimetric methods were used to analyze total SBAs, aminotransferases and bilirubin measurements, respectively.

Statistical analysis was conducted with the Statistical Package for the Social Sciences (SPSS) version 12.0. Means, standard deviations, medians, and ranges were calculated for descriptive purposes. Correlation analysis was assessed by Spearman Rank correlation.

RESULTS

A total of 3710 women were booked for antenatal care and delivered in this period. Of those, 32 were diagnosed as ICP, with an incidence of 0.86%. Table 1 shows clinical characteristics of patients regarding age, gravidity, onset of pruritus, intensity of pruritus (score) before treatment and after treatment, gestational age at delivery, and the Apgar score at one minute and five minutes. Two of 12 multiparas (16.6%) had ICP in a previous pregnancy, and 7 of 32 patients (21.8%) had family history of ICP. Symptom onset varied according to season, with 33.3% in winter, 36.2% in spring, 13.3% in summer, and 16.7% in autumn. Most of the patients (69.5%) were diagnosed in the winter and beginning of spring, and this distribution was statistically significant ($p<0.05$). Table 2 shows the biochemical characteristics of the patients. In 3 of 32 patients (9.3%), gamma-glutamyl transpeptidase (GGT) was higher than the normal range.

During the follow-up of patients, no reported cases of clinical maternal jaundice or bleeding tendency or stillbirth were found. Pregnancy ended prematurely in 6 of 32 patients (18.7%). Postnatal development was normal in all babies.

Table 1. Clinical characteristics of patients

		Minimum-Maximum	Mean±SD
Age		27-37	31.5±2.9
Gravidity		1-5	1.5±0.6
Onset time of pruritus (weeks)		22-37	32.4±5.1
Intensity of pruritus	Before treatment	3-4	3.86±0.14
	After treatment	0-2	0.5±0.3
Gestational age at delivery (weeks)		33-41	37.6±1.5
Infant weight at delivery (grams)		1900-3910	3096.3±557.4
Apgar score	One minute	6-10	8.36±1.7
	Five minute	8-10	9.1±0.8 (8-10)

SD: Standard deviation

Table 2. Biochemical characteristics of patients

	Minimum	Maximum	Mean±Standard deviation
GGT (U/L)	5	161	23.07±32.5
ALT (U/L)	7	217	49.9±43.2
AST (U/L)	5	168	35.7±30.1
ALP (U/L)	60	468	152.5±67.5
Total bile acids umol/L	2.6	280	30.1±54

GGT: Gamma-glutamyl transpeptidase. ALT: Alanine aminotransferase. AST: Aspartate aminotransferase. ALP: Alkaline phosphatase.

In cases of ICP, total bile acid (TBA) concentration was correlated positively with GGT (r=0.473, p=0.008) and aspartate aminotransferase (AST) (r=0.488, p=0.006). TBA levels tended to be higher in patients with preterm delivery (r=-0.409, p=0.038). On the other hand, there was no correlation between TBA and birth weight (p=0.507), the onset of symptom time and symptom intensity, or response to UDCA treatment. Pruritus intensity was decreased after UDCA treatment. Only 8 cases (25%) had residual pruritus after treatment, although intensity was reduced. In all patients, pruritus resolved within 1-2 weeks postpartum.

DISCUSSION

This study measured the incidence of ICP, evaluated obstetrical and fetal outcome in patients with ICP, and analyzed the correlation of these results with LFTs and bile acids. The prevalence of ICP in our study was 0.86%, while the average incidence varies from 0.001% to 4% in the literature (1). It was reported that there is a wide geographic and ethnic variation of ICP in many studies worldwide. Interestingly, in the following years, the prevalence of disease has markedly decreased in some regions (13,14). The incidence found in the current study was comparable to the others conducted in the United States and Europe.

Despite intense research, the causes of ICP remain unknown. However, the pathophysiology of the disease is thought to be multifactorial, with higher estrogen levels being the main implicating factor (15). Genetic factors are also likely, as many women have a family history and recurrence is common. In our study, 21.8% had family history, and 16.6% of multiparas had ICP in previous pregnancies. Several lines of evidence suggest the role of estrogens, i.e. the disease appears in the third trimester, the prevalence of ICP is five times greater in twin pregnancies, which are characterized by higher estrogens levels, and finally, ICP closely resembles the clinical picture developed in some women using oral contraceptives with high estrogen contents (14,16). Furthermore, it was reported that the prevalence of ICP may have seasonal cycles, with greater prevalence in winter. This suggests that some environmental factors may play a role in the pathogenesis of ICP. In this study, ICP cases were seen as more prevalent in winter and in the beginning of spring.

Intrahepatic cholestasis of pregnancy (ICP) is essentially benign in mothers, and clinically resolves approximately two weeks after delivery. Clinically apparent jaundice rarely develops. Although essentially benign in the mother, ICP may adversely affect the prognosis of the fetus. The major consequences of the disease are premature delivery, found in 19% - 60% of cases (11, 17), stillbirths in 1% - 2% of cases (11,18) and fetal distress in 22% - 33% of cases (11,19). Even though there are multiple reports of adverse outcome associated with

ICP, this study reported no stillbirth or meconium staining of amniotic fluid. This may be the result of increased antenatal surveillance and our policy of early delivery at around 38 weeks. Furthermore, when we diagnosed ICP, we started UDCA treatment in all of the cases. Although there are conflicting data regarding the effects of UDCA treatment on the perinatal outcome, several clinical trials and observational studies showed that UDCA treatment improved maternal and fetal morbidities (20,21). On the other hand, some studies emphasized that, while pruritus and serum levels of total bile salts and ALT improved, perinatal outcomes with respect to the effect of UDCA are less clear (1). We cannot, however, comment on this subject, as we administered UDCA treatment to all our patients. Randomized controlled studies on this subject are therefore required to determine whether UDCA decreases the rates of fetal asphyxia and meconium staining of the amniotic fluid.

Exactly how ICP causes preterm births is uncertain; however, *in vitro* studies showed an increased response of myometrial strips from healthy woman to oxytocin and an increased oxytocin receptor expression after being incubated with cholic acid (22). High TBA levels have already been described as predictors of fetal outcome in some cohort studies (11,23). In one study, the author reported increased adverse outcomes if bile acid was ≥40 μ mol/L (24). Furthermore, Kondrackiene et al. (11) demonstrated that early onset of pruritus and high levels of SBA were associated with preterm delivery. In the current study, comparable to the other studies, high levels of SBAs were negatively correlated with delivery weeks; however, the onset time of pruritus or response to UDCA treatment was not found to be correlated with preterm delivery. Due to the fact that only a small number of cases were found with early-onset pruritus, we could not clearly demonstrate the correlation between early-onset pruritus and preterm delivery.

In conclusion, TBAs are correlated with preterm delivery. An attempt to deliver at around 38 weeks may improve the perinatal outcome.

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