Clinical Obstetrics, Gynecology and Reproductive Medicine

Research Article ISSN: 2059-4828

Asymptomatic intrahepatic cholestasis of pregnancy

Julia B Uspenskaya[1], Arkadiy A Sheptulin[2*], Irina V Kuznetsova[1], Evgeniy P Gitel[3], Andrey V Murashko[1], Natalja V Goncharenko[4], Andrey N Gerasimov[5], Elena V Melnik[6], Ekaterina A Korsunskaya[4], Galina V Tugarinova[6], Alla A Gindis[6] and Tatjana A Seredina[4]

[1]Chair of Obstetrics and Gynecology, №1, First Moscow State Medical I. M. Sechenov-University, Moscow, Russian Federation

[2]Chair of Internal Diseases Propedeutics, First Moscow State Medical I. M. Sechenov-University, Moscow, Russian Federation

[3]Central laboratory and diagnostic service, First Moscow State Medical I. M. Sechenov-University, Moscow, Russian Federation

[4]V. F. Snegirev-Clinic of Obstetrics and Gynecology, First Moscow State Medical I. M. Sechenov-University, Moscow, Russian Federation

[5]Chair of Medical Informatics and Statistics, First Moscow State Medical I. M. Sechenov-University, Moscow, Russian Federation

[6]Interclinical Biochemical Laboratory, First Moscow State Medical I. M. Sechenov-University, Moscow, Russian Federation

Abstract

Background and Aim: Pruritus is a varying symptom of cholestatic liver diseases. Previous studies suggested that latent intrahepatic cholestasis of pregnancy (ICP) affects a subset of pregnant women. The aim of this study was to assess the characteristics of asymptomatic ICP and its course following treatment.

Methods: We used total serum bile acids (BAs) as a laboratory marker of ICP. Patients were evaluated for history and clinical data, pregnancy outcome and laboratory biochemical parameters at baseline and 1 and 2 weeks after treatment with ursodeoxycholic acid (500 mg to 2 g per day).

Results: Among 97 pregnant women with laboratory-confirmed ICP, 70 (72.2%) had pruritus, while 27 (27.8%) did not. Among symptomatic and asymptomatic ICP patients, there was no significant difference in clinical and demographic parameters, pre-treatment biochemical parameters or pregnancy outcome. The rate of decrease of liver transaminases was significantly higher in symptomatic than in asymptomatic ICP patients ($p < 0.001$). By comparison, the therapy-associated changes of BAs levels were not significantly different in the two groups.

Conclusions: The lack of significant differences in clinical pattern, pregnancy outcome, and laboratory signs of liver damage suggests that asymptomatic ICP is not associated with pruritus. Since asymptomatic ICP and classical ICP carry the same risk to the fetus, it seems appropriate to perform BAs laboratory screening in pregnant women to detect subclinical ICP.

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is one of the most common liver diseases associated with pregnancy. The prevalence varies in different geographic regions and ethnic groups, but the average ranges from 1.5% to 2% [1-3]. ICP is due to the abnormal transport of bile from the hepatocytes to bile canaliculi and develops in predisposed women, mainly in the second half of pregnancy, due to high sex hormone levels [4]. The disease is benign and resolves spontaneously after delivery. However, ICP can cause multiple fetal complications during the perinatal period. The diagnostic work-up is based on pruritus as an essential symptom of ICP. The main cause of this symptom is transfer of bile acids (BAs), other components of bile, and pruritogens into the systemic blood circulation and peripheral tissues [5]. ICP traditionally presents as pruritus without primary skin lesions in the second or third trimester of pregnancy. Some substances have been associated with pruritus; there is strong evidence that BAs, autotaxin and lysophosphatidic acid, some sulfated progesterone metabolites, and high estrogen concentrations can activate serotonergic and opioid neurotransmission pathways [6-12].

The presence and severity of pruritus in chronic cholestatic liver diseases are not considered as predictive factors and in some cases do not reflect the severity of cholestasis [13,14]. This suggests that the pruritus in ICP, as well as in any other intrahepatic cholestatic liver disease is a complex symptom that not always correlates with the actual disease severity. Still, the diagnostic work-up to assess ICP focuses on the presence of pruritus or jaundice (in severe cases), bile pigments in the urine or steatorrhea and the incidental identification of laboratory signs of liver damage. The only anecdotal descriptions of ICP with no pruritus are case reports. No major studies on asymptomatic variants of ICP have been performed to date. The only retrospective study evaluated the outcome of pregnancy in patients with ICP and pregnant women who did not have pruritus but had elevated serum BAs [15]. In a comparative analysis of pregnancy outcomes, the risk of stillbirth in patients who did not have symptoms of ICP was similar or even higher than that in ICP patients with pruritus (3.5% and 0.5%, respectively; $p<0.001$). It is, therefore, important to identify asymptomatic variants of ICP and to describe their characteristics.

Conventional laboratory markers of cholestasis may be insufficient to diagnose ICP. For example, gamma-glutamyl transpeptidase (GGT) activity and bilirubin levels may be normal. Testing of alkaline

Correspondence to: Arkadiy Sheptulin, Professor, Chair of Internal Diseases Propedeutics, First Moscow State Medical I. M. Sechenov-University, Pogodinskaya Street, 1, Bld. 1, 119435, Moscow, Russian Federation, E-mail: arkalshep@gmail.com

Key words: *bile acids, liver enzymes, pruritus, pregnancy complications, pregnancy outcome, ursodeoxycholic acid treatment*

Received: February 20, 2020; **Accepted:** February 26, 2020; **Published:** February 28, 2020

phosphatase (ALP) as an indicator of cholestasis in pregnant women has low specificity as the placenta acts as an additional source of this enzyme, and its production linearly increases with gestational age. Liver transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) are universal markers of destruction of the hepatocytes of any cause. Thus, elevated liver transaminases only provide a reason to search for the cause of liver damage. During physiological gestation, 5-nucleotidase activity is moderately increased starting in the second trimester.

The most informative and sensitive marker of ICP is an elevated level of BAs. An increase of total BAs above 8-10 mM is considered diagnostically significant [3,16,17]. Deleterious effects of high concentrations of BAs on the electrophysiological conduction system of the fetal heart and lungs as well as on vessels of the placenta are associated with perinatal complications [1]. The aim of the study was to evaluate the natural course of asymptomatic variants of ICP and the effects of treatment with ursodeoxycholic acid (UDCA).

Methods

The study was performed at the V. F. Snegirev-Clinic of Obstetrics and Gynecology of First Moscow State Medical I.M. Sechenov-University. We included 97 pregnant women with laboratory-confirmed ICP. High levels of total BAs in serum (>8 mM) were used as main laboratory finding confirming ICP. In the first phase of the study, BAs were only measured in pregnant individuals presenting with pruritus. In the second phase, all pregnant women admitted for in-patient treatment were screened for BAs levels. Laboratory markers of infectious diseases, liver damage, and chronic autoimmune liver diseases (primary biliary cholangitis, autoimmune hepatitis) were also measured.

The standard laboratory parameters were determined by techniques routinely used in clinical chemistry. BAs were measured on biochemical analyzer Synchron CX5 and CX9 (Beckman Coulter, USA) with formation of formazan and application of reagent production TRYNITY BIOTECH (USA).

Pruritus severity was measured on a scale from 0 to 3 points using standard laboratory biochemical markers of liver damage (AST, ALT, GGT, alkaline phosphatase and bilirubin), and BAs at baseline and 1 and 2 weeks after the start of treatment with UCDA at a dose of 500 mg to 2 g per day. Exclusion criteria included infectious and autoimmune causes of cholestasis as well as mechanical jaundice.

Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics 21 statistical software. Confidence intervals (CIs) were calculated based on binomial distribution. The significance of differences was determined by chi-square test (2 x 2 contingency table, Fisher's exact test). The numerical indicators are expressed as arithmetic mean (M), standard deviation (SD), standard error of the mean (m), median (Me), and the other quartiles.

The significance of intergroup differences of means was determined using analysis of variance, while the significance of intergroup differences of the distributions were assessed with nonparametric Kolmogorov-Smirnov and Mann-Whitney U-tests, respectively. The Pearson correlation coefficient and nonparametric Spearman correlation coefficient were used to examine relationships between numeric parameters. $P < 0.05$ was considered statistically significant.

Results

Among the 97 pregnant women with laboratory-confirmed ICP, 70 (72.2%) had clinical signs (pruritus), while 27 (27.8%) did not. Tables 1 and 2 show the characteristics and baseline results of the laboratory tests.

A comparative evaluation of history and clinical data of women with or without pruritus showed no significant differences in age, gestational age at the time of ICP diagnosis, duration of ICP, number of previous pregnancies, biliary sludge, or the rate of cholestasis recurrence after therapy-associated resolution.

The comparative analysis of the rate of *in vitro* fertilization (IVF) to achieve pregnancy and of hormonal therapy during pregnancy revealed interesting results. IVF was used in 6 (22.2% CI: 11.1% to 38.1%) out of 27 women without pruritus and in 18 (25.7% CI: 17.2% to 36.0%) out of 70 women with pruritus ($p = 0.47$). Independent from the presence of pruritus, pregnant women with ICP had undergone IVF procedures much more frequently than women in the general population, in which pregnancy is based on IVF in only 1%-2% [18,19].

Notably, the use of sex hormones (progesterone, estrogen) during pregnancy was significantly more frequent in women with pruritus-associated ICP than in women with asymptomatic ICP. Among the 70 patients with pruritus, hormone therapy was performed in 52 cases (74.3% CI: 64.0% to 82.8%). Among the 27 patients without pruritus, sex hormone use was reported in only 9 cases (33.3% CI: 19.4% to 50.2%; $p < 0.001$).

The comparative analysis of baseline laboratory parameters showed no significant differences in BAs, AST, ALT, or direct bilirubin levels between women with symptomatic and asymptomatic ICP. However, women with pruritus had significantly higher levels of total bilirubin ($p_1 = 0.002$, $p_2 < 0.001$, $p_3 < 0.001$), and alkaline phosphatase ($p_1 = 0.02$, $p_2 = 0.001$, $p_3 = 0.012$) and lower levels of GGT ($p_1 \leq 0.001$, $p_2 < 0.001$, $p_3 < 0.001$) (Table 2). However, these differences can be considered clinically insignificant in view of the low reliability of single indicators to diagnose ICP.

Table 3 shows the comparative rate of pregnancy complications in our cohort. The rates of premature birth, intrauterine hypoxia, preeclampsia, intrauterine fetal death, and cesarean section were not significantly different between women with symptomatic and asymptomatic ICP. However, the differences in the rate of cesarean delivery are difficult to interpret because the decision for this mode of delivery is based also non-medical factors (personal decision of pregnant women and physicians). With respect to complications during previous pregnancies (i.e., intrauterine fetal death, preeclampsia, intrauterine fetal hypoxia, intrauterine growth restriction, preterm birth), there were no significant differences between women with symptomatic and asymptomatic ICP.

A comparative analysis of the time course of biochemical parameters (BA, ALT and AST levels) in women with symptomatic and asymptomatic ICP is presented in Table 4. In individuals with pruritus, the mean ALT level after 1 week of UDCA treatment was higher (53.44 U/l) than in women without pruritus (49.81 U/l, $p_3 = 0.043$) and was more significantly reduced at the end of the second week of treatment (38.84 and 42.19 U/l, respectively; $P_3 < 0.001$). Similar statistically significant differences were found for AST levels which decreased after 1 week to 40.41 and 38.15 U/l in women with symptomatic and asymptomatic ICP, respectively ($p_3 = 0.009$). After treatment for 2 weeks, these levels decreased to 30.58 and 33.44 U/l, respectively (p

Table 1. Baseline clinical and demographic parameters of ICP patients with or without pruritus

Parameter	Patients with asymptomatic ICP (n = 27)		Patients with pruritus-associated ICP (n = 70)		P
	Abs.	Rel.	Abs.	Rel.	
Multiple pregnancy	6	22.2% (CI: 11.1%- 38.1%)	14	20.0% (CI: 12.5% - 29.7%)	0.505
IVF-induced pregnancy	6	22.2% (CI: 11.1% - 38.1%)	18	25.7% (CI: 17.2% - 36.0%)	0.47
Hormonal therapy use during pregnancy	9	33.3% (CI: 19.4% - 50.2%)	52	74.3% (CI: 64.0% - 82.8%)	<0.001
Cholestasis recurrence after resolution	8	29.6% (CI: 16.5% - 46.3%)	26	37.1% (CI: 27.2% - 48.1%)	0.327
Biliary sludge	16	59.3% (CI: 42.4% - 74.5%)	52	74.3% (CI: 64.0% - 82.8%)	0.116

Abs. = absolute; CI = confidence interval; ICP = intrahepatic cholestasis of pregnancy; IVF = in vitro fertilization; Rel. = relative.

Table 2. Baseline clinical and biochemical parameters in ICP patients with or without pruritus

Parameter	Patients with asymptomatic ICP (n = 27)			Patients with pruritus-associated ICP (n = 70)			Significance values		
	M	σ	m	M	σ	M	p_1	p_2	p_3
Age, years old	30.44	4.41	0.85	29.39	5.47	0.65	0.371	0.31	0.49
Gestational age at the time of ICP diagnosis, weeks	29.48	9.61	1.85	29.71	7.75	0.93	0.902	0.301	0.195
BAs, µmol/l, baseline	32.74	16.18	3.11	32.94	28.99	3.47	0.973	0.64	0.807
ALT, U/l, baseline	56.59	19.43	3.74	72.27	50.40	6.02	0.12	0.803	0.113
AST, U/l, baseline	43.19	12.44	2.39	50.67	29.00	3.47	0.199	0.885	0.1
-GTP, U/l, baseline	63.11	16.79	3.23	42.80	25.25	3.02	<0.001	<0.001	<0.001
ALP, U/l, baseline	136.26	59.39	11.43	214.51	167.41	20.01	0.02	0.001	0.012
Total bilirubin, µmol/l, baseline	9.91	2.16	0.42	15.33	8.54	1.02	0.002	<0.001	<0.001
Direct bilirubin, µmol/l, baseline	3.42	0.77	0.15	3.76	2.26	0.27	0.45	0.476	0.235

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BAs = bile acids; GGT = gamma-glutamyl transpeptidase; ICP = intrahepatic cholestasis of pregnancy; p_1 = significance of differences of mean values (analysis of variance); p_2 = Mann-Whitney U-test; p_3 = Kolmogorov-Smirnov test.

Table 3. Complication rates in ICP patients with or without pruritus

Types of complications	Complications of pregnancy in patients with asymptomatic ICP (n = 27)		Complications of pregnancy in patients with pruritus-associated ICP (n = 27)		p
	Abs.	Rel.	Abs.	Rel.	
Premature delivery	5	18.52%	26	37.14%	0.061
Intrauterine hypoxia	9	33.33%	20	28.57%	0.411
Preeclampsia	9	33.33%	14	20.00%	0.133
Cesarean section	13	48.15%	27	38.57%	0.264
Intrauterine fetal death	0	0.0%	1	1.4%	0.722

Abs. = absolute; CI = confidence interval; ICP = intrahepatic cholestasis of pregnancy; Rel. = relative.

Table 4. Time course of biochemical parameters in symptomatic and asymptomatic ICP patients during UDCA therapy

Parameter	Patients with asymptomatic ICP			Patients with symptomatic ICP			p_1	p_2	p_3
	M	σ	m	M	σ	M			
BAs, µmol/l, baseline	32.74	16.18	3.11	32.94	28.99	3.47	0.973	0.640	0.807
BAs, µmol/l after 1 week of treatment	26.04	16.19	3.12	24.57	27.52	3.29	0.796	0.567	0.558
BAs, µmol/l after 2 week of treatment	21.70	18.48	3.56	19.10	28.61	3.42	0.662	0.361	0.404
ALT, U/l, baseline	56.59	19.43	3.74	72.27	50.39	6.02	0.12	0.803	0.113
ALT, U/l after 1 week of treatment	49.81	14.92	2.87	53.44	34.43	4.12	0.599	0.210	0.043
ALT, U/l after 2 week of treatment	42.19	8.04	1.55	38.84	21.32	2.57	0.431	0.000	0.000
AST, U/l, baseline	43.19	12.43	2.39	50.67	29.00	3.47	0.199	0.885	0.100
AST, U/l after 1 week of treatment	38.15	8.99	1.73	40.41	21.68	2.59	0.601	0.287	0.009
AST, U/l after 2 week of treatment	33.44	5.09	0.98	30.58	9.87	1.19	0.155	0.001	0.000

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BAs = bile acids; ICP = intrahepatic cholestasis of pregnancy; p_1 = significance of differences of mean values (analysis of variance); p_2 = Mann-Whitney U-test; p_3 = Kolmogorov-Smirnov test; UDCA = ursodeoxycholic acid.

<0.001). Taken together, reductions in ALT and AST levels were more pronounced in women with pruritus-associated ICP than in women with asymptomatic ICP.

There were no significant differences with respect to treatment-associated changes of BAs levels between patients with asymptomatic and symptomatic variants of ICP, indicating that this parameter does not influence of clinical presentation of ICP during treatment. It should be noted that there was no correlation between changes of BAs levels and of other laboratory parameters during treatment (Table 5), suggesting that the change in BAs levels is not associated with other biochemical markers of liver damage. Therefore, the effectiveness of ICP treatment should be monitored with BAs serum level measurement during treatment.

There were highly significant correlations between BAs, AST and ALT levels and the severity of pruritus (Tables 6-8). Baseline BAs levels strongly correlated with the severity of pruritus at baseline and after 1 and 2 weeks of treatment, respectively ($p = 0.03$, $p < 0.001$, and $p < 0.001$, respectively). Thus, the reduction of the severity of pruritus during treatment may reflect the effective reduction of BAs and transaminase, levels. The effectiveness of treatment in patients with asymptomatic ICP can therefore be determined the reduction of BAs and transaminase levels during treatment.

Discussion

The lack of significant differences in pregnancy complication rates and baseline biochemical measurements in pregnant women with ICP

Table 5. Correlations between changes in biochemical parameters in ICP patients during treatment

Biochemical parameters		Pearson's correlation coefficient *r*	p	Spearman rank correlation coefficient *ρ*	p
BAs level	ALT activity	0.212	0.037	0.161	0.115
BAs level	AST activity	0.206	0.044	0.12	0.245
BAs level	Total bilirubin	0.085	0.413	0.105	0.313

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BAs = bile acids; ICP = intrahepatic cholestasis of pregnancy.

Table 6. Correlations between BAs levels and severity of pruritus in symptomatic ICP patients

BAs level	Pruritus severity	Correlation coefficient	p	Rank correlation coefficient	p
Baseline	Baseline	0.121	0.239	0.22	0.03
Baseline	After 1 week of treatment	0.224	0.028	0.363	<0.001
Baseline	After 2 weeks of treatment	0.143	0.162	0.336	0.001
After 1 week of treatment	After 1 week of treatment	0.216	0.033	0.345	0.001
After 1 week of treatment	After 2 weeks of treatment	0.134	0.191	0.337	0.001
After 2 weeks of treatment	After 1 week of treatment	0.244	0.016	0.287	0.004
After 2 weeks of treatment	After 2 weeks of treatment	0.196	0.054	0.382	<0.001

BAs = bile acids; ICP = intrahepatic cholestasis of pregnancy.

Table 7. Correlations between ALT levels and severity of pruritus in patients with symptomatic ICP

On-treatment ALT levels	On-treatment pruritus severity	Correlation coefficient	p	Rank correlation coefficient	p
Baseline	Baseline	0.23	0.023	0.121	0.239
Baseline	After 1 week of treatment	0.38	<0.001	0.273	0.007
Baseline	After 2 weeks of treatment	0.371	<0.001	0.277	0.006
After 1 week of treatment	Baseline	0.138	0.178	-0.017	0.869
After 1 week of treatment	After 1 week of treatment	0.342	0.001	0.165	0.107
After 1 week of treatment	After 2 weeks of treatment	0.364	<0.001	0.234	0.021
After 2 weeks of treatment	Baseline	-0.013	0.897	-0.297	0.003
After 2 weeks of treatment	After 1 week of treatment	0.266	0.009	0.033	0.748
After 2 weeks of treatment	After 2 weeks of treatment	0.288	0.004	0.167	0.104

ALT = alanine aminotransferase; ICP = intrahepatic cholestasis of pregnancy.

Table 8. Correlation between AST levels and severity of pruritus in patients with symptomatic ICP

On-treatment AST level	On-treatment pruritus severity	Correlation coefficient	p	Rank correlation coefficient	p
Baseline	Baseline	0.187	0.067	0.076	0.457
Baseline	After 1 week of treatment	0.345	0.001	0.198	0.052
Baseline	After 2 weeks of treatment	0.255	0.012	0.278	0.006
After 1 week of treatment	Baseline	0.116	0.256	-0.018	0.86
After 1 week of treatment	After 1 week of treatment	0.351	<0.001	0.154	0.133
After 1 week of treatment	After 2 weeks of treatment	0.275	0.006	0.272	0.007
After 2 weeks of treatment	Baseline	-0.083	0.423	-0.242	0.018
After 2 weeks of treatment	After 1 week of treatment	0.164	0.11	0.027	0.795
After 2 weeks of treatment	After 2 weeks of treatment	0.247	0.015	0.231	0.023

AST = aspartate aminotransferase; ICP = intrahepatic cholestasis of pregnancy.

with or without pruritus suggests that asymptomatic ICP is a distinct subclinical variant of ICP.

Due to the subclinical latent course, the diagnosis of asymptomatic ICP which carries a high risk of pregnancy complications may be missed. In our study, screening of pregnant women with or without pruritus revealed a high prevalence of asymptomatic ICP that may be similar to the prevalence of 'classical' ICP Therefore, the determination BAs serum levels may be appropriate not only in patients with clinical symptoms of ICP, but also in patients without pruritus who have increased levels of transaminases or cholestatic liver enzymes or a family history of ICP. In some cases, the cause of pregnancy complications in women with undiagnosed asymptomatic ICP remains elusive because obstetrical management and treatment of patients do not consider ICP as the etiology.

With the early recognition of a subclinical ICP variant, the appropriate treatment can be instituted to prevent the development of severe perinatal complications. In view of similar rates of pregnancy complications after previous pregnancies with or without pruritus, some complications may be a recurrence of an undiagnosed latent ICP. In this context, it is well known that ICP recurrence rates in subsequent pregnancies reach 45%-70% [20]. Therefore, we recommend searching for ICP in women with a history of gestational complications, such as premature birth, intrauterine hypoxia, intrauterine fetal death, preeclampsia or placental insufficiency, as well as in women with such complications in the current pregnancy.

The results from our study indicate a slower therapy-associated reduction of liver transaminase levels in women with asymptomatic ICP as compared to women with symptomatic ICP. The variations in the severity of the pruritus correlated with lower BAs serum levels and may reflect the effectiveness of UDCA treatment. The repeated measurement of laboratory parameters is required to clarify this issue.

The results from our study are limited by the fact that the women in whom the BAs serum levels were determined had different obstetric complications or abnormal liver enzymes In order to assess the real prevalence of ICP including the asymptomatic variants one would have to analyze all pregnant women.

Conclusions

Apart from patients with the classic symptomatic variant of ICP associated with pruritus, some pregnant women have abnormal findings consistent with a asymptomatic/ latent/ subclinical form of ICP without pruritus. Since there are no significant differences in the clinical presentation, the rate of pregnancy complications and the severity of laboratory abnormality in ICP patients with or without pruritus, ICP not associated with pruritus may suggest the existence an asymptomatic (subclinical) ICP variant.

The repeated BA determination is an appropriate option to monitor the effectiveness of treatment in asymptomatic ICP women. In view of the increased risk of fetal complications in women with ICP, pregnant women should undergo BAs screening to detect asymptomatic/ subclinical cases.

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