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Role of serum organic solute transporter alpha/beta and sodium taurocholate cotransporting polypeptide in intrahepatic cholestasis of pregnancy

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ABSTRACT

Objectives: This study aimed to assess the role of OST-α, OST-β and NTCP in patients with ICP, with a view to determine patients with severe prognosis and to minimize adverse fetal outcomes.

Material and methods: Sixty-nine pregnant women diagnosed with ICP and 50 healthy women were included the study. Serum OST-α, OST-β and NTCP were measured using ELISA kits.

Results: The median OST-α levels were 176.3 pg/mL in women with ICP and 201 pg/mL in healthy subjects (p = 0.205). The median OST-β levels were found to be 51.17 pg/mL in patients with ICP and 40.9 pg/mL in controls (p = 0.033). Median NTCP levels were 519.7 ng/mL in the ICP group and 483.3 ng/mL in healthy women (p = 0.051).

Conclusions: This is the first study to evaluate serum levels of OST-α, OST-β and NTCP in patients with ICP. It is likely that OST-α, OST-β and NTCP contribute to the etiopathogenesis of ICP. Serum OST-α and OST-β levels can be used as diagnostic and monitoring markers of ICP, and the inhibition of these molecules could provide therapeutic benefit in ICP by reducing the circulation of enterohepatic bile acids.

Key words: bile acids; intrahepatic cholestasis of pregnancy; organic solute transporter alpha/beta; sodium taurocholate cotransporting polypeptide

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INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is the most common pregnancy-specific liver disease characterized by elevated serum bile acids, maternal pruritus in the second half of pregnancy, and an increased rate of adverse fetal outcomes, including intrapartum fetal distress, spontaneous preterm delivery, meconium staining of the amniotic fluid, and even stillbirths or intrauterine fetal death [1]. Although maternal prognosis is excellent, the risk of complications to the fetus and its development increases in parallel with maternal blood levels of total bile acids (TBA) [2]. After delivery, the symptoms and biochemical abnormalities usually resolve rapidly — almost spontaneously. The incidence of

ICP is estimated to range between 1% and 4%, but varies greatly depending on environmental factors, ethnic origin and genetic predisposition [3]. The etiopathogenesis of the disease is not fully understood, but is probably multifactorial with genetic, environmental, dietary and hormonal backgrounds that also effect its severity [4]. The impairment of the transport, excretion and function of bile acids may be associated with the development of ICP.

Organic solute transporter alpha/beta (OST-α/OST-β) are solute carrier proteins that were identified in the hepatocyte and intestinal epithelium. These heteromeric transporters, which are located in basolateral membranes, are critical in the reabsorption and enterohepatic circulation of ster-

oid-based molecules, particularly bile acids [5]. Furthermore, it was shown in a mice study that the functions of OST-α and OST-β include the protection of the ileal epithelium against the accumulation of bile acids [6]. The expression of OST-α and OST-β proteins were found to be altered in conditions that cause elevation in bile acids, including extrahepatic cholestasis, primary biliary cholangitis and nonalcoholic steatohepatitis [5]. However, to our knowledge, there are no studies that have investigated serum levels of OST-α/OST-β in patients with ICP.

Sodium taurocholate cotransporting polypeptide (NTCP) is another transport protein localized in the basolateral membrane of the hepatocyte. Its primary function is to collect conjugated bile salts from the circulation via cotransport of sodium [7]. NTCP has extremely high affinity and specificity for bile acids, and is reported to recover up to 90% from the circulation [3]. The gene encoding for NTCP (Solute Carrier Family 10 Member 1, SLC10A1) has been shown to have biallelic mutations that impair NTCP function; subsequently leading to increased serum levels of TBA [8]. In a recent case study including two women who had suffered from ICP, researchers found that homozygote mutations of SLC10A1 can lead to ICP development [7]. To date, the results of studies examining the role of NTCP in ICP patients remain rather limited. However, no studies have examined the serum levels of NTCP in ICP patients.

The aim of this study was to evaluate the serum levels of OST-α/OST-β and NCPT in patients with ICP with a view to identify whether they can be associated with disease development and/or severity.

MATERIAL AND METHODS

This was a prospective single center study that was carried out between July 2020 and September 2020 at the Maternal-Fetal Medicine Unit of Health Sciences University Kanuni Sultan Suleyman Research and Training Hospital, Istanbul, Turkey. A total of 69 pregnant women diagnosed with ICP and 50 healthy women with completely normal pregnancies (as the control group) in the third trimester were included in the study. The diagnosis of ICP was based on the following criteria: (i) presence of pruritus that cannot be explained with any other condition, (ii) elevated levels of serum aminotransferase (> 40 IU/L) and (iii) elevated levels of serum fasting TBA (> 10 μmol/L). ICP severity was defined according to TBA levels as: mild (10–40 μmol/L) and severe (> 40 μmol/L). Participants with a history of conditions that cause abnormalities in liver function tests, including hepatitis, gallstones or gallbladder diseases, acute fatty liver of pregnancy, hepatotoxic drug consumption, primary biliary cholangitis, primary sclerosing cholangitis, active infection and chronic inflammatory conditions, were excluded from the study. Additionally, patients with gestational diabetes,

preeclampsia, gestational thyroid disorders, malignancy, thrombophilia, those who had pruritus with normal bile acids, and those with skin lesions were excluded.

Gestational age was calculated according to last menstruation date and first trimester obstetric radiologic examination. Each ICP patient completed a questionnaire rating the severity of pruritus on a numerical scale from 1 to 10. Scores ranging from 1 to 4 were defined as 'mild', 4 to 7 as 'moderate', and a score of 8 or higher was defined as 'severe' pruritus. Patient characteristics, including maternal age, gravidity, parity, gestational age at the time of diagnosis, type of delivery, birth weight of neonates, and length of neonatal intensive care unit stay were recorded from patient files. The study protocol was approved by the Research Ethics Committee of Kanuni Sultan Suleyman Training and Research Hospital. All research procedures were conducted based on the ethical standards of the Declaration of Helsinki. Written and verbal informed consent was obtained from participating women prior to participation and sampling.

Blood samples were collected from all participants during the third trimester (at the time of initial admission) before the administration of medications or interventions. Hemogram (complete blood count) and routine blood biochemistry values were examined within one hour after sampling. For further analysis of OST-α, OST-β and NTCP, extracted serum samples (centrifuged at 4°C and 3000 RPM for 10 minutes) were frozen at –80°C until measurements. Hemogram parameters, including white blood cell count (WBC), neutrophil (NEU) and lymphocyte (LYM) counts, hemoglobin value (Hb), platelet count (PLT), mean platelet volume (MPV) were measured with a CELL-DYN 3700 System (Abbott Laboratories, IL, USA). Neutrophil to lymphocyte ratio (NLR) and Platelet to lymphocyte ratio (PLR) were calculated. Blood biochemistry parameters, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, direct bilirubin and TBA levels were determined with spectrophotometric methods using an Abbott Architect c8000 autoanalyzer (Abbott Laboratories, IL, USA). The serum OST-α and OST-β levels were measured using enzyme-linked immunosorbent assay (ELISA) kits (Elabscience Biotechnology, USA) as per the manufacturer's instructions. The serum NTCP concentrations were determined with a commercially available Human Sodium Bile Acid Cotransporter/NTCP ELISA Kit (Abbexa Ltd, Cambridge, UK). The measurement range was 0.78–50 ng/mL and the assay sensitivity was < 0.29 ng/mL. The intra-assay and inter-assay variations were < 10% and < 12%, respectively.

Statistical analysis

All analyses were performed on SPSS v21 (SPSS Inc., Chicago, IL, USA). For the normality check, the Kolmogorov-Smirnov test with Lilliefors correction was used. Data are

given as mean ± standard deviation or median (1st quartile––3rd quartile) for continuous variables according to normality of distribution, and as frequency (percentage) for categorical variables. Normally distributed variables were analyzed with the independent samples t test. Non-normally distributed variables were analyzed with the Mann Whitney U test. Categorical variable distributions were analyzed with Chi-square tests. Repeated (paired) measurements were analyzed with the Wilcoxon signed ranks test. Spearman correlation coefficients were calculated to evaluate relationships between continuous variables. Diagnostic performance of variables were evaluated by Receiver Operating Characteristic (ROC) curve analysis. $p < 0.05$ values were defined as statistically significant.

RESULTS

Sixty-nine patients with ICP and 50 healthy women were included in the study. The mean age was 29.8 ± 5.8 years in the study group and 29 ± 5.7 years in the control group ($p = 0.468$). The serum levels of ALT, AST, total and direct bilirubin were higher in the patient group (all, $p < 0.05$). Elevated serum levels of hemoglobin, platelet count and PLR were found in patients with ICP compared to control subjects (all, $p < 0.05$). No differences were found between the two groups with regard to WBC, MPV, RDW, NLR, neutrophil and lymphocyte counts (all, $p > 0.05$). Demographic characteristics and laboratory values of the patient and the control groups are shown in Table 1.

The median OST-α levels were 176.32 pg/mL in women with ICP and 201.03 pg/mL in healthy subjects ($p = 0.205$). Median OST-β levels were found to be significantly higher (51.17 pg/mL) in patients with ICP compared to controls (40.90 pg/mL) ($p = 0.033$). The median NTCP values were 519.71 ng/mL in the ICP and 483.34 (ng/mL) in the healthy control group ($p = 0.051$) (Tab. 1). ROC analysis demonstrated that OST-β levels had 53.62% sensitivity, 73.47% specific-

Table 1. Participants' demographic characteristics and laboratory results

	Controls (n = 50)	Patients (n = 69)	p value
Age [years]	29.82 ± 5.81	29.04 ± 5.70	0.468
Gestational week	28 (24–35)	33 (31–35)	0.013
Numbers of pregnancy			
1	10 (20.00%)	21 (30.43%)	0.372
2	13 (26.00%)	21 (30.43%)	
3	14 (28.00%)	12 (17.39%)	
≥ 4	13 (26.00%)	15 (21.74%)	
ALT [IU/mL]	9 (8–13)	72 (48–152.5)	< 0.001
AST [IU/mL]	14.5 (13–17)	55 (35–91)	< 0.001
Total bilirubin [mg/dL]	0.22 (0.16–0.30)	0.49 (0.32–0.73)	< 0.001
Direct bilirubin [mg/dL]	0.11 (0.10–0.12)	0.27 (0.18–0.50)	< 0.001
WBC [× 10^3/mm^3]	9.09 ± 2.57	9.49 ± 1.89	0.327
Hemoglobin [g/dL]	11.15 ± 1.13	11.66 ± 1.31	0.030
MPV [μm^3]	10.85 (10.1–11.9)	11.15 (10.2–11.7)	0.618
RDW [%]	13.25 (13–13.7)	13.1 (12.6–13.8)	0.494
Neutrophil [× 10^3/mm^3]	7.79 (6.39–8.4)	7 (5.3–7.8)	0.054
Lymphocyte [× 10^3/mm^3]	1.9 (1.7–2.3)	1.8 (1.6–2)	0.051
Platelet [× 10^3/mm^3]	214.04 ± 47.58	245.87 ± 74.17	0.005
NLR	3.85 (3.18–4.51)	3.91 (2.83–4.68)	0.907
PLR	114.45 (91.58–131.30)	124.41 (108.23–176.03)	0.006
OST-alpha [pg/mL]	201.03 (167.01–238.36)	176.32 (145.76–212.27)	0.205
OST-beta [pg/mL]	40.90 (30.62–51.16)	51.17 (36.44–62.42)	0.033
NTCP [ng/mL]	483.34 (98.23–601.82)	519.71 (416.58–677.62)	0.051

ALT — Alanine aminotransferase; AST — Aspartate aminotransferase; WBC — White blood cell counts; MPV — Mean platelet volume; NLR — Neutrophil to lymphocyte ratio; PLR — Platelet to lymphocyte ratio; OST-alpha — Organic solute transporter alpha; OST-beta — Organic solute transporter beta; NTCP — Sodium taurocholate cotransporting polypeptide; Data are given as mean ± standard deviation or median (1st quartile–3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables

ity and 61.86% accuracy to determine presence of ICP with a cut-off point of 50.5 (AUC = 0.616, 95% CI: 0.513–0.718) (data not shown).

The median TBA levels were 26 (16–48) µmol/L in the patient group. According to TBA levels, 45 patients had mild ICP and 24 patients had severe ICP. Forty patients received 4 doses of ursodeoxycholic acid (UDCA) treatment, while 26 patients were treated with 3 doses. Following the administration of UDCA, 45 patients had reduction in pruritus complaints and 34 patients showed decreased ALT and AST levels. After deliveries, 17 of the neonates were admitted to the neonatal ICU (Tab. 2).

Correlation analyses between patient characteristics and laboratory results are shown in Table 3. In correlation analyses, we found negative correlations between maternal age and the levels of OST-α and NTCP. A positive correlation was shown between NTCP and total bilirubin (Tab. 3).

Table 2. Patients' characteristics and laboratory results

Total Bile acid [µmol/L]	26 (16–48)
Patients with mild ICP [< 40]	45 (65.22%)
Patients with severe ICP [≥ 40]	24 (34.78%)
UDCA	4 (3–4)
0	1 (1.45%)
2	1 (1.45%)
3	26 (37.68%)
4	40 (57.97%)
6	1 (1.45%)
Pruritus	
Mild	25 (37.68%)
Moderate	19 (27.54%)
Severe	24 (34.78%)
Decrease in pruritus after UDCA	45 (77.59%)
Decrease in ALT after UDCA	34 (73.91%)
Decrease in AST after UDCA	34 (72.34%)
Alkaline phosphotase [IU/L]	199.27 ± 71.43
Gamma glutamyl transferase [IU/L]	17 (11–29)
Lactate dehydrogenase [IU/L]	227.22 ± 49.25
Gestational week at birth	37 (36–38)
Birth type	
Vaginal	22 (37.93%)
Cesarean	36 (62.07%)
Weight at birth [grams]	2793.17 ± 581.35
The number of patients requiring ICU admission	17 (29.31%)

ICP — INntrahepatic cholestasis of pregnancy; UDCA — Ursodeoxycholic acid; ICU — Intensive care unit; Data are given as mean ± standard deviation or median (1st quartile–3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables

DISCUSSION

This study was aimed at determining circulating levels of OST-α, OST-β and NTCP in patients with ICP order to identify whether these measures could be utilized to diagnose ICP, determine prognosis, or assess fetal outcomes. This was the first study to determine the serum levels of OST-α, OST-β and NTCP in patient with ICP. We demonstrated that serum OST-β levels were significantly higher in patients with ICP compared to healthy individuals. We also observed higher NTCP levels in patients, but statistical significance was not present with a p value of 0.051.

Intrahepatic cholestasis of pregnancy has a complex and multifaceted etiology, involving complex interactions between genetic features, endocrine and metabolic disturbances, and environmental factors [4]. Altered secretion and transport of bile acids and other biliary lipids play an important role on the etiology of ICP [9]. Bile salts are the most common organic solutes in the bile [1]. Bile acids (cholic acid and chenodeoxycholic acid) are synthesized from cholesterol in the liver, conjugated with either taurine or glycine to form bile salts, and are exported into the biliary canaliculi via specific transport proteins [10]. When the bile acids reach the gastrointestinal tract, they maintain their emulsifying functions as physiological detergents to break down and encapsulate lipids and fat-soluble vitamins for absorption and transport. Bile acids are also metabolic signaling molecules with systemic endocrine effects [11]. The specific nuclear receptors of bile acids include, farnesoid X receptor (FXR), vitamin D receptor, and the cell surface G protein-coupled bile acid receptor (GPBAR, TGR-5) [12]. After contributing to intestinal digestion and absorption, bile acids are actively transported into intestinal cells in the terminal ileum. The transporters involved in this function include OST-α and OST-β [12] which transport the bile acids across the basolateral membrane of the enterocytes, followed by secretion into the portal circulation. They are actively transported back to hepatocytes via NTCP and organic anion transporting polypeptides [10]. The mutations and variations in genes encoding hepatobiliary transport proteins have been shown to cause abnormal bile secretion and increased circulatory bile acids in patient with ICP [13].

The OST-α and OST-β heteromeric transport proteins are present in ileal enterocytes, cholangiocytes and the renal proximal tubule [14]. FXR mechanisms have been associated with the key regulatory roles of OST-α and OST-β in maintaining homeostasis of bile acids [15]. As such, intestinal FXR induces the expression of OST-α and OST-β as an adaptive response to cholestasis [12]. Boyer et al. demonstrated that hepatic OST-α and OST-β mRNA levels were elevated by three-fold and 32-fold, respectively, in patients with primary biliary cirrhosis (PBC). They also demonstrated that OST-α and OST-β expression increased in the livers of rats and mice

Table 3. Correlations between clinical and laboratory characteristics in intrahepatic cholestasis of pregnancy patients

		OST-alpha	OST-beta	NTCP
Age	r	−0.278*	−0.169	−0.277*
	p	0.002	0.067	0.002
Gestational week	r	0.056	−0.105	0.065
	p	0.548	0.259	0.483
Total Bile acid	r	−0.177	−0.099	−0.107
	p	0.145	0.417	0.381
ALT	r	−0.150	0.144	0.133
	p	0.106	0.121	0.152
AST	r	−0.117	0.145	0.115
	p	0.213	0.120	0.218
Total bilirubin	r	−0.058	0.068	0.236*
	p	0.540	0.472	0.012
Direct bilirubin	r	−0.045	0.182	0.156
	p	0.632	0.052	0.098
Alkaline phosphatase	r	0.168	−0.056	0.028
	p	0.203	0.673	0.831
Gamma-glutamyl transferase	r	0.024	−0.020	−0.006
	p	0.858	0.878	0.961
Lactate Dehydrogenase	r	0.238	−0.100	0.053
	p	0.083	0.471	0.703
WBC	r	0.102	0.128	0.063
	p	0.274	0.169	0.503
Hemoglobin value	r	−0.033	0.130	0.150
	p	0.724	0.163	0.107
MPV	r	−0.107	−0.033	0.090
	p	0.250	0.728	0.332
RDW	r	0.010	−0.077	−0.011
	p	0.911	0.408	0.909
Neutrophil counts	r	−0.005	0.076	0.105
	p	0.957	0.418	0.261
Lymphocyte count	r	0.010	0.041	0.010
	p	0.916	0.659	0.918
Platelet count	r	−0.027	0.177	−0.059
	p	0.774	0.057	0.527
NLR	r	−0.012	0.044	0.125
	p	0.899	0.641	0.181
PLR	r	−0.018	0.124	−0.056
	p	0.845	0.181	0.547

ALT — Alanine aminotransferase; AST — Aspartate aminotransferase; WBC — White blood cell counts; MPV — Mean platelet volume; NLR — Neutrophil to lymphocyte ratio; PLR — Platelet to lymphocyte ratio; OST-alpha — Organic solute transporter alpha; OST-beta — Organic solute transporter beta; NTCP — Sodium taurocholate cotransporting polypeptid. r — Spearman correlation coefficient; *Correlation is significant at the 0.05 level

following common bile duct ligation [16]. In another study, Schaap et al. [17], showed increased OST-α and OST-β mRNA levels in the livers of patients with extrahepatic cholestasis. Malinen and colleagues [18] identified significantly in-

creased expression and protein levels of OST-β in livers from patients with nonalcoholic steatohepatitis (NASH) and PBC. They also observed unchanged OST-α mRNA expression and higher OST-α protein levels in patients with NASH and

PBC when compared to healthy subjects (but statistical significance was not present). Chai et al. [19], revealed in 22 liver samples from cholestatic patients with biliary obstruction (due to gallstones) that mRNA and protein levels of OST-β protein levels was significantly increased (10.4 fold), while OST-α protein levels were decreased while transcription was unchanged compared to control livers. Soroka and colleagues [20] demonstrated in mice with genetically deficient OST-α that loss of OST-α prevents liver damage in obstructive cholestasis through adaptive responses in both the kidney and liver. In agreement with these studies, we found significantly elevated serum OST-β levels and somewhat decreased OST-α level (no statistical significance) in patients with ICP. Our results may suggest that OST-α and OST-β are induced in ICP, possibly due their association with the re-uptake of bile acids. The increase in OST-β levels may be related to the elevation of intrahepatic bile acid and TBA concentrations during cholestasis. Further studies are necessary to determine whether serum levels of OST-β can be used as a marker for the diagnosis and prognostic assessment of ICP. We demonstrated a cut-off point of > 50.5 for the identification of ICP with OST-β levels. Our results suggest that OST-α and OST-β could be contributing factors in the pathogenesis of ICP. However, there is still uncertainty about the contribution of OST-α and OST-β to bile acid efflux and attenuation of cholestasis in literature [21].

NTCP is a sodium-dependent primary transporter that transports conjugated bile salts from the plasma to the hepatocyte. NTCP is highly expressed in the basolateral membrane of hepatocytes and plays an important role in the maintenance of enterohepatic circulation of bile salts [7]. Vaz et al. [22], demonstrated mild hypotonia, growth retardation, and elevated total bile acid levels (> 1500 μM) without signs of cholestatic jaundice, pruritus, or liver dysfunction in a patient with NTCP deficiency caused by a point mutation in the SLC10A1 gene. Kojima et al. [23], showed no change in NTCP expression in patients with chronic hepatitis C or primary biliary cirrhosis stage I and II, while they identified downregulation in stage III. A case reported by Van Herpe et al. [24], described a woman with ICP who had lost her fetus at 38 weeks of pregnancy due to spontaneous rupture of membranes with meconium-stained fluids. They revealed persistently elevated TBA levels and NTCP deficiency in the post-partum period. In another clinical study, Chen et al. [7], demonstrated elevated TBA levels in five patients with NTCP deficiency diagnosed with SLC10A1 gene analysis. They also showed that two of these individuals had suffered from ICP without intense pruritus in the third trimester of pregnancy — leading to caesarean section delivery in one. In our study, we found higher NTCP levels in the ICP group compared to controls, a result which was only marginally insignificant (p = 0.051). This indicates that elevated NTCP levels may be associated with increased bile acid uptake into the liver in ICP disease. Furthermore, NTCP was correlated with age and total bilirubin levels. Consistent with our findings, Sargiacomo et al. [25], found that NTCP protein levels were modulated in an age-dependent manner in the hepatocyte membrane. In addition, Shneider et al. [26], demonstrated that NTCP mRNA levels correlated inversely with serum bilirubin in patients with pre- and postportoenterostomy biliary atresia. A mild increase in bilirubin levels in ICP patients can lead to increased levels of transport protein for hepatic uptake, and thus the excretion of bile salts and bilirubin.

Several limitations of the current work should be mentioned. First, the study had a relatively small sample size which may have reduced statistical strength; thus future studies will benefit from utilizing the results of this study in their power analyses. Secondly, the study was limited to Turkish ICP patients; considering the known genetic and environmental variations in the characteristics of patients with ICP, our results may not be generalized for women in other geographic regions. Thirdly, we were not able to evaluate fetal cord levels or placental levels of these biomarkers. Lastly, the lack of mRNA expression measurements may also be considered as a limitation.

CONSLUSIONS

In conclusion, this is the first study to evaluate serum levels of OST-α, OST-β and NTCP in patients with ICP. We demonstrated significantly elevated OST-β levels in patients with ICP. We believe that OST-β and NTCP could contribute to the etiopathogenesis of ICP. Early identification and management of ICP prevents adverse outcomes, especially for the fetus. It is crucial to determine whether serum levels of OST-α, OST-β or NTCP can be used as diagnostic or monitoring markers. Furthermore, considering their role in bile acid turnover, it may be interesting to evaluate the inhibition of these transporters as a possible therapeutic option in ICP.

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