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Intrahepatic Cholestasis and Adverse Perinatal Outcomes in the Third Trimester: A 10-year Case-control Study

Üçüncü Trimesterde İntrahepatik Kolestaz ve Olumsuz Perinatal Sonuçlar: 10 Yıllık Bir Olgu Kontrol Çalışması

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ABSTRACT

Background: To evaluate the perinatal outcomes in women whom developed intrahepatic cholestasis of pregnancy (ICP).

Materials and Methods: Medical records of 76 patients who were followed up in a tertiary center due to ICP between January 2010 and December 2019 were evaluated retrospectively. Women with ICP (n=76) and age matched controls (n=228) were included to our study. Bile acid (BA) values could be reached in 42 of 76 patients.

Results: There was no significant difference in terms of family history, fetal gender, or the presence of meconium in the amniotic fluid between the groups (p>0.05) except cesarean rates were significantly higher in ICP group (p<0.001). The median gestational weeks at delivery, fetal weight and Apgar scores at the 1st- and at the 5th-minutes in the ICP group were significantly lower than those in the controls (p<0.05). Gestational weeks at delivery was similar in women with BA values above or under 40 µmol/L (p>0.05).

Conclusion: ICP has important fetal implications. There is an increased risk for poor fetal outcomes, including preterm delivery and fetal demise. Therefore, close follow-up and meticulous observation is indispensable.

Keywords: Intrahepatic cholestasis, neonatal outcome, pregnancy, ursodesoxycholic acid

ÖZ

Amaç: Bu çalışmadaki amacımız gebeliğinde intrahepatik kolestaz (ICP) gelişen kadınlarda perinatal sonuçları değerlendirmektir.

Gereç ve Yöntemler: Ocak 2010 ile Aralık 2019 tarihleri arasında üçüncü basamak bir merkezde ICP nedeniyle izlenen 76 hastanın tıbbi kayıtları geriye dönük olarak değerlendirildi. ICP'si mevcut olan kadınlar (n=76) ve aynı yaştaki kontroller (n=228) çalışmaya dahil edildi. Safra asidi (SA) değerlerine 76 hastanın 42'sinde ulaşılabildi.

Bulgular: Gruplar arasında aile öyküsü, fetal cinsiyet ve amniyotik sıvıda mekonyum varlığı açısından anlamlı fark yoktu (p>0,05), ama sezaryen oranları ICP'li grupta anlamlı olarak yüksekti (p<0,001). ICP'li grubunda doğumdaki ortalama gebelik haftası, fetal ağırlık ve 1. ve 5. dakika Apgar skorları kontrollere göre anlamlı derecede düşüktü (p<0,05). SA değerleri 40 µmol/L'nin üzerinde veya altında olan kadınlarda doğumdaki gebelik haftaları benzerdi (p>0,05).

Sonuç: ICP'nin önemli fetal etkileri vardır. Erken doğum ve fetal ölüm dahil olmak üzere kötü fetal sonuçlar için artan risk mevcuttur. Bu nedenle yakın takip ve titiz gözlem vazgeçilmezdir.

Anahtar Kelimeler: İntrahepatik kolestaz, neonatal sonuç, gebelik, ursodeoksikolik asit

Introduction

Intrahepatic cholestasis of pregnancy (ICP) occurs due to the dysfunction of the membrane transport system of the hepatocyte and bile duct epithelium that provide bile excretion. It may occur due to genetic, autoimmune, metabolic, hormonal, environmental factors and as a result of some drugs or infections (1). Some mutations in the multidrug resistance 3 (MDR3/ABCB4) gene was observed, which is also found in progressive familial intrahepatic cholestasis (2).

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The worldwide incidence of ICP ranges from 0.1% to 1.5% (3,4), but is more common in multiple pregnancies and in Latin-American or Araucanian-Indian pregnant women (5,6). It is the most common liver disease in pregnant women, that is observed in the second and third trimesters of pregnancy, often after the 30th week (7).

Clinically, widespread peripheral itching is observed, especially in the palms and soles, increasing at night, so causing insomnia and mental distress. It is associated with increased serum liver transaminase and bile acid (BA) values. The clinical symptoms occur approximately 3 weeks before the laboratory findings, but usually regress within 48 hours after birth (8). Jaundice appears in 10% to 25% of patients. Some may also develop abdominal pain, diarrhea, and steatorrhea. Coagulopathies can develop due to a decrease in vitamin K absorption (9). Total BA concentration may increase up to 10 to 100 times. Cholesterol levels and usually serum alkaline phosphatase (ALP) levels increases. Hyperbilirubinemia occurs, but serum levels seldomly exceed 4-5 mg/dL. Serum transaminase levels may be normal or moderately increased, rarely exceeding 250 IU/L. Other dermatological diseases should be investigated, if liver enzymes are in normal limits. Abdominal ultrasonography may be necessary to detect gallstones and related obstructions. The absence of proteinuria and hypertension allows it to be differentiated from preeclampsia, or from acute viral hepatitis with low serum transaminase levels. Asymptomatic chronic hepatitis C increases the incidence of cholestasis (10). Even though, ICP has a benign character that regresses at the end of delivery without causing maternal serious morbidity and mortality, unlike the maternal condition, fetal morbidity and mortality increases. Maternal BA cross the placenta and may accumulate in the fetus and amniotic fluid, which carries notable risk for the fetus (11). Transplacental gradients facilitate fetal clearance of BA in normal pregnancies, albeit are reversed in this disease and this causes an accumulation of BA in the fetus and amniotic fluid (12). Hence, ICP may cause preterm birth, abnormal intrapartum fetal heart tracings and sudden intrapartum fetal death (13,14).

Our aim was to investigate the possible adverse fetal and maternal effects of ICP in our population in women that developed the disease in the 3rd trimester of pregnancy. In addition, our objective was to evaluate the likely relationship between increased BA levels and adverse outcomes.

Material and Methods

The medical histories of all pregnant women with ICP (n=76) that had given birth at the Perinatology Division of Trakya University Faculty of Medicine, between 1st of January 2010 and 31st of December 2019, and their neonatal outcomes were obtained from the hospital records and reviewed retrospectively with the approval of the Trakya University's Human Ethics Committee (no: 2020/230) in accordance with the Declaration of Helsinki.

We included patients meeting the following criteria in our study group.

- Generalized itching without a dermatological pathological condition.
- Laboratory findings supporting intrahepatic cholestasis [increased serum alanine transaminase (ALT) and aspartate transaminase (AST), and if available BA levels].
- Normal appearance of the liver and gallbladder by an ultrasonographic observation.
- Absence of active hepatitis, confirmed by HBsAg and Anti HCV testing.

Pregnant women having multiple pregnancies (n=13), congenital malformations (n=4), chromosomal abnormalities (n=1), systemic disease (n=5) and recurrence of cholestasis (each woman was included only one time) (n=4) were excluded from the study.

The control group was randomly selected from pregnant women who did not have any chronic disease and made their regular obstetric visits in our maternal and fetal unit, whom had uneventful pregnancies. Eligible control women (n=228) had a singleton pregnancy, the fetus in a cephalic presentation, without congenital malformations and no obstetric disorders requiring preterm induction. The control population was matched for maternal age (one year more or less), date of delivery (same calendar year), the same parity, the same mode of delivery history, did not have ICP and had normal liver transaminase levels. In order to increase our study power, three women with low-risk pregnancies were enrolled as controls for each ICP case.

After the diagnosis of ICP was made, all women were consulted and the systemic examinations were performed by a gastroenterologist. Topical emollients, antihistamines and ursodesoxycholic acid (Ursofalk®, Ali Raif İlaç San. A.Ş, İstanbul) at a dose of 300 mg three times a day were applied to all women having ICP.

Fetal and maternal outcomes and laboratory characteristics were compared in women with ICP and the controls. BA values could be reached in 42 patients. In a further analysis, women were divided into 2 groups according to values under (n=25) or above (n=17) 40 µmol/L, and the outcomes were also compared in these subgroups.

Statistical Analysis

K-S test was performed to examine the normality agreement of the distributions of the measurements of the patients.

After the test, it was determined that their distribution did not show normality. Descriptive statistics in the study

are given as median and IQR. Mann-Whitney U test was used to analyze the measurements according to patient groups. Logistic regression analysis was performed to determine the risk factors affecting the state of being sick. Risk levels (odds β) were determined according to the 95% confidence interval (Upper-Lower). Differences were defined as significant when p<0.05. SPSS 25 (Statistical Package for Social Science, Chicago, II, USA) Windows package program was used for statistical analysis.

Results

During the study period, 6.896 women were admitted for delivery. The incidence of ICP was 1.1%. The mean age of the pregnant women with ICP and controls was 27 (25-33).

There was no significant difference in terms of fetal gender, presence of meconium in the amniotic fluid, or family history of ICP (p<0.05). Women who had ICP in their previous pregnancies had a higher rate of ICP than those who did not experienced ICP previously (p<0.001). Cesarean rates were significantly higher in the ICP group (p<0.001). Indications for cesarean in ICP group was previous cesarean section (%56), scheduled cesarean delivery (33%) and non-reassuring fetal heart rate pattern/labor dystocia (13%). Induction of labor was performed to 44.7% (n=34) of women with ICP, compared to 11.8% (n=27) of the controls (p<0.001). Cesarean rates during labor were not observed significantly different between ICP group 13.3% (n=6) with the controls 12.1% (n=10) (p=0.557). Preterm delivery was significantly higher in the ICP group (39.4% vs. 3.9%, p<0.001) (Table 1).

Itching was the most common symptom in patients with ICP (100%). Medications relieved pruritus in 72 (94%) women. Other common symptoms were nausea (76%) and poor appetite (68%), respectively. Significantly lower gestational weeks at delivery, subsequently lower fetal birth weight, height, head circumference and additionally lower Apgar scores at the 1st-and at the 5th-minutes were observed in ICP group compared to the controls (p<0.001) (Table 2). There was no significant difference between the groups in terms of postpartum hemoglobin and hematocrit levels, postpartum hemorrhage or maternal transfusion need (p=0.299) (Table 2).

In terms of BA values, there was no statistically significant difference between the 2 groups, except for the high ALT levels observed in patients with BA ≥40 μmol/L (p=0.032) (Table 3).

Discussion

This retrospective case control study describes the feto-maternal outcome of obstetric cholestasis in a referral center of Thrace Region of Turkey. We found significantly lower gestational weeks at delivery, fetal weight and Apgar scores at the 1st-and at the 5th-minutes in the ICP group. No significant difference was observed between women with BA values above or below 40 μmol/L in terms of gestation weeks at birth, fetal weight and Apgar scores.

The incidence of ICP is between <1% and 27.6% worldwide. In the United States, incidence rates range from 0.32 percent to 5.6 percent. The incidence in Europe ranges from 0.5 to 1.5 percent, with the highest rates in Scandinavia. The incidence of ICP in our cohort was 1.1%, which is compatible with previous studies (1,2,3,4,5). The typical symptom of ICP is mild to unbearably itchy. It

Table 1. Maternal characteristics and obstetric outcomes of women with ICP and the controls

		Controls (n=228)	ICP (n=76)	p
Maternal age, years [median (IQR)]		27 (25-33)	27 (25-33)	1
Delivery weeks, n (%)	**>37 weeks**	219 (96.2%)	46 (60.6%)	**<0.001**
	<37 weeks	9 (3.9%)	30 (39.4%)	
Route of delivery, n (%)	**Vaginal**	139 (61%)	31 (49.7%)	**<0.001**
	Cesarean	89 (39%)	45 (51.3%)	
Induction of labor, n (%)	**Applied**	27 (11.8%)	34 (44.7%)	**<0.001**
Fetal gender, n (%)	**Female**	103 (45.2%)	35 (46%)	0.858
	Male	125 (54.8%)	41 (54%)	
Meconium-stained fluid, n (%)	**Positive**	29 (12.7%)	8 (10.5%)	0.687
Parity, n (%)	**Nulliparous**	99 (43.5%)	33 (43.4%)	0.989
	Multiparous	129 (56.5%)	43 (56.6%)	
Familial history of ICP, n (%)	**Positive**	2 (0.8%)	1 (1.3%)	0.169
Personal history of previous ICP, n (%)	**Positive**	0	10 (13.2%)	**<0.001**

ICP: Intrahepatic cholestasis of pregnancy, IQR: Interquartile range

usually starts on the palms and soles and worsens at night. Right upper quadrant pain, nausea, loss of appetite, sleep deprivation, or steatorrhea may occur. These symptoms usually develop in the late second or third trimester. In our study group itching was the most common symptom. Topical emollients, antihistamines and ursodesoxycholic acid (300 mg three times a day) are the treatments of choice in these patients. These medications relieved pruritus 72 out of 76 women in our population. However, there are opposing views in the literature. While, some believed

Table 2. Fetal and maternal outcomes and laboratory characteristics of women with ICP and the controls [values are presented as (median IQR)]

	Controls (n=228)	ICP (n=76)	p
Gestational age at birth, weeks	38 (38-39)	36 (35-37)	**<0.001**
Fetal birth weight, grams	3.335 (3.070-3.650)	2.850 (2.577-3.132)	**<0.001**
Fetal height, cm	50 (49-52)	48 (46-50)	**<0.001**
Fetal head circumference	35 (33-35)	34 (33-35)	**<0.001**
Apgar score, 1st-min	9 (9-9)	8 (8-9)	**<0.001**
Apgar score, 5th-min	10 (10-10)	10 (9-10)	**<0.001**
Aspartate transaminase, IU/L	16 (14-21)	110 (64.5-162.5)	**<0.001**
Alanine transaminase, IU/L	10 (8-14)	95.5 (63-138)	**<0.001**
Platelet, 10^3/μL	202 (174-267)	214.5 (165-266)	0.932
Postpartum hematocrit, g/dL	35.1 (32.8-36.9)	34.9 (31.4-36.4)	0.708
Postpartum hemoglobin, g/dL	11.6 (10.7-12.6)	11.5 (10.5-12.05)	0.801
Prothrombin time, s	11.5 (11.2-12.1)	11.7 (11.6-13)	0.263
Activated partial thromboplastin time, s	23.6 (22.4-24.6)	23.8 (22.4-25.95)	0.326
Postpartum hemorrhage, n (%)	11 (4.8%)	4 (5.2%)	0.774
Maternal transfusion, n (%)	4 (1.7%)	1 (1.3%)	0.299

ICP: Intrahepatic cholestasis of pregnancy, IQR: Interquartile range

Table 3. Fetal outcomes and laboratory characteristics according to the bile acid levels [values are presented as (median IQR)]

	Bile acid value		p
	<40 μmol/L (n=25)	≥40 μmol/L (n=17)	
Maternal age, years	27 (21-35)	32 (23-35)	0.370
Gestation age at birth, weeks	37 (34-38)	37 (36-39)	0.368
Fetal birth weight, grams	2.700 (2.550-3.040)	2.870 (2.610-3.100)	0.290
Fetal height, cm	48 (45-50)	48 (46-50)	0.447
Fetal head circumference, cm	34 (33-35)	35 (34-35)	0.116
Apgar score, 1st-min	8 (8-9)	9 (7-9)	0.733
Apgar score, 5th-min	9 (9-10)	9 (9-10)	0.392
Aspartate transaminase, IU/L	82 (60-160)	146 (110-186)	0.105
Alanine transaminase, IU/L	78 (57-108)	132 (100-174)	**0.032**
Platelet, 10^3/μL	246 (176-268)	246 (126-290)	0.751
Hematocrit, g/dL	33.4 (29.8-36.4)	32.8 (30.6-35)	0.832
Hemoglobin, g/dL	11 (9.1-12.1)	10.6 (10.3-11.8)	0.944
Prothrombin time, s	12.4 (11.8-13.2)	13.1 (11.4-13.4)	0.832
Activated partial thromboplastin time, s	30.3 (25.2-33.6)	26.6 (25.8-29.7)	0.274
Postpartum aspartate transaminase, IU/L	26 (14-40)	46 (24-48)	0.097
Postpartum alanine transaminase, IU/L	18 (15-32)	36 (18-50)	0.162

IQR: Interquartile range

that this treatment improved the perinatal outcomes, some others thought it has no effect on adverse perinatal outcomes (15). PITCHES trial assessed perinatal outcome in ICP-affected pregnancies. The study evaluated the effect of ursodeoxycholic acid versus placebo and found that ursodeoxycholic acid treatment has no considerable effect on diminishing adverse perinatal outcomes (16). Since we administered ursodeoxycholic acid to all women with ICP in our cohort of patients, we could not comment on the effect of the treatment on perinatal outcomes, but we might even think that ICP per se have already some negative effects on some maternal and fetal outcomes such that despite lower gestational weeks at delivery, fetal weight or Apgar scores in women with ICP, not to commence any medication might have worsened these outcomes. Besides, a recent Cochrane review found the effectiveness of ursodeoxycholic acid to ameliorate pruritus, and also argued that the evidence for some adverse fetal outcomes like fetal distress and stillbirth were uncertain and unclear, due to serious limitations in study designs and imprecision (17). In our 10-year study period, no stillbirths occurred in the ICP group, but 3 patients who were previously diagnosed with ICP by another medical center admitted to our institute with stillbirth. Of those, two were at the 38th and the other was at the 39th weeks of pregnancy [BA level (68 µmol/L) could be reached in one out of three patients]. These patients were not under routine control after a diagnosis of ICP and were also not receiving ursodeoxycholic acid. All reported that they were asked to be hospitalized by their obstetricians. Nevertheless, they either denied to be hospitalized or use of ursodeoxycholic acid. We can consider using ursodeoxycholic acid, because, it is not only effective in reducing pruritus and improving maternal liver condition, but it might also bring some benefits for the fetal outcomes, since no fetal losses occurred in patients whom were hospitalized patients receiving ursodeoxycholic acid.

There is no consensus regarding the obstetric management of patients diagnosed with ICP. In the study in which 70 cases were examined, they were interviewed weekly about their symptoms. All were actively managed according to a standard protocol of delivery before 38 weeks and obstetric outcomes were recorded. Based on these results, it was thought that active management policies might result in increased intervention and related complications, but this should be balanced against possible reductions in perinatal mortality (18). In our daily practice patients with ICP were hospitalized to diagnose and to identify possible conditions like preterm birth and fetal well-being. Modified biophysical profile (cardiotocographic examinations and amniotic fluid levels by ultrasound) was applied twice weekly. We discharge the patients if the fetal conditions are stable by a biophysical profile score $\geq$8, without and other accompanying problems like preterm labor or conditions such as uterine contractions. Thereafter, the patients were recommended close monitoring. Patients were observed weekly to check for the fetal status after the 32nd weeks, and twice weekly after the 36th weeks. At each visit modified biophysical profile was performed and if the ICP women having the deterioration of the symptoms like worsening of itching or clinically apparent jaundice then the serum ALT, AST and BA levels were reevaluated. We have planned delivery at 38 weeks or at diagnosis, if diagnosed later. The American College of Obstetricians and Gynecologists endorses active management protocols for ICP (19). In recently published committee opinion, delivery was suggested that if the levels are above 100 µmol/L at 36 0/7 weeks of gestation. If the BA levels are less than 100 µmol/L, it is recommended to deliver between 36 0/7-39 0/7 weeks. Likewise, in Australia and France, obstetricians support induction of labor for patients with ICP at 37-38 completed weeks of pregnancy (20,21). However, The Royal College of Obstetrics and Gynaecologists does not support routine active management of ICP-affected pregnancies (22). ICP carries the main risk for the fetus. Out of 352 pregnancies diagnosed with ICP, 23 (7%) were complicated by intrauterine death and preterm delivery occurred in 133 (38%) of them. Eighteen of the 20 individual intrauterine deaths occurred after 37 weeks. Itching begins earlier in pregnancies complicated by spontaneous prematurity (23). An activation of the oxytocin receptor pathway has been shown to occur during ICP. This event appears to be the result of a cholic acid-mediated increase in oxytocin receptor expression (24). As in some other previous studies, we found significant differences in gestational age at delivery in women with ICP and the controls (2,3,4,5,6,7,9). In addition, fetal birth weight and Apgar scores were observed significantly lower in ICP group. On the other hand, ICP does not adversely affect the mother as it severely does to the fetus. In our study, no significant difference was found in terms of postpartum hemorrhage and postpartum transfusion.

Whilst, there are studies which show the association of ICP with increased meconium-stained amniotic fluid, in present study we didn't observe statistically difference in terms of meconium-stained amniotic fluid between study groups (12,25). We hypothesized that this is due to our active management policy for ICP. Stillbirth occurred in 45 (0.83%) of 4936 ICP cases and 519 (0.32%) of 163 947 control pregnancies in a meta-analysis. In singleton pregnancies, stillbirth was associated with the maximum total bile acid concentration, but not with alanine aminotransferase. For singleton pregnancies, the prevalence of stillbirth was 3 in 2310 cases of ICP in women with serum total bile acids less than 40 µmol/L, 4 in 1412 cases with total bile acids of 40-99 µmol/L, and 524 for bile acids of 100 µmol/L or more 18 cases were detected (26). In our 10-year study period, no stillbirths occurred in ICP group. Therefore, after a diagnosis of ICP, close monitoring of the women should be warranted.

Due to the retrospective design, we could not find the BA levels of all patients. Di Mascio et al. (8) observed a

negative relationship between increasing levels of BA with birth weight and Apgar scores. However, we found similar gestational weeks at delivery, and fetal weights between in those having BA levels <40 μmol/L and ≥40 μmol/L.

Study Limitations

Our study limitations were firstly subgroup analysis was performed on small population and secondly our retrospective study design, as well potential bias about efficacy of ursodeoxycholic acid in reducing of stillbirth.

Conclusion

ICP is associated with adverse fetal outcomes. Hence, close follow-up and meticulous observation might have roles in the prevention of some serious outcomes like stillbirth.

Ethics

Ethics Committee Approval: Reviewed retrospectively with the approval of the Trakya University Human Ethics Committee (no: 2020/230) in accordance with the Declaration of Helsinki.

Informed Consent: The study was designed retrospectively.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: C.Y., C.S., F.V., Concept: C.S., Design: E.A.E., Data Collection or Processing: S.A., Analysis or Interpretation: C.Y., C.S., Literature Search: C.Y., Writing: C.Y.

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