Jinekoloji - Obstetrik ve Neonatoloji Tıp Dergisi
The Journal of Gynecology-Obstetrics and Neonatology

ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

DOI: 10.38136/jgon.1419305

Comparison of composite adverse perinatal outcomes in early- and late-onset intrahepatic cholestasis of pregnancy

Erken ve geç başlangıçlı intra hepatic gebelik kolestazında kompozit olumsuz perinatal sonuçların karşılaştırılması

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ABSTRACT

Aim: To compare composite adverse perinatal outcomes (CAPO) in women with early- and late-onset intrahepatic cholestasis of pregnancy (ICP).

Materials and Methods: This study was designed as a single-center, retrospective study in a tertiary hospital and included a total of 198 patients with ICP, including 36 patients with early-onset ICP (EO-ICP) and 162 patients with late-onset ICP (LO-ICP). ICP that developed before the 28thweek of gestation was defined as EO-ICP, and ICP that occurred after the 28thweek of gestationwas defined as LO-ICP. The existence of at least one of the following criteria was defined as CAPO: umbilical cord arterial pH < 7.20, fifth-minute Apgar score < 5, andneonatal intensivecarestay of>24 hours.

Results: The rates of spontaneous preterm birth and neonatal intensive care admission were statistically significantly higher in the EO-ICP group (p<0.001). In the same group, a significantly higher number of neonates were born with meconium (p=0.040). The use of ursodeoxycholic acid was significantly greater in the EO-ICP group (p=0.007). The two groups did not show any significant differences in terms of neonatal umbilical cord arterial pH or base excess (p>0.05), however, the CAPO rate was significantly higher in the EO-ICP group(p=0.028). Receiver operator characteristic analysis revealed an optimal cut-off value of 33.5 µmol/L for the serum bile acid level, at which this parameter had 74% sensitivity and 68% specificity (area under the curve=0.759; p<0.001) in the prediction of CAPO.

Conclusion: We consider that the high CAPO rates in the fetuses of patients with EO-ICP are due to the effect of high serum bile acid levels on the fetus for a longer time than in the LO-ICP group. The differentiation of cases of EO-ICP and LO-ICP will serve as a guide for clinicians in predicting possible complications.

Keywords: Adverse perinatal outcomes; intrahepatic cholestasis of pregnancy, serum bile acid

ÖZ

Amaç: Bu çalışmanın amacı erken ve geç başlangıçlı intrahepatik gebelik kolestazı olan kadınlarda kompozit olumsuz perinatal sonuçları karşılaştırmaktı.

Gereç ve Yöntemler: Bu çalışma, üçüncü basamak bir hastanede tek merkezli, retrospektif bir çalışma olarak tasarlandıve 36 erken-başlangıçlı intrahepatik gebelik kolestazı (EB-IGK) ve 162 geç başlangıçlı intrahepatik gebelik kolestazı (GB-IGK) hastası olmak üzere toplam 198 IGK hastasını içeriyordu. Gebeliğin 28. Haftasından once gelişen IGK, EB-IGK olarak, 28. Gebelik haftasından sonra gelişen IGK ise GB-IGK olarak tanımlandı. Aşağıdaki kriterlerden en az birinin varlığı kompozit olumsuz perinatal sonuç olarak tanımlandı: umblikal kord arteriyel pH'ı<7,20, 5.dakika Apgar skoru<5 ve >24 saat yenidoğan yoğunbakımda kalış.

Bulgular: EB-IGK grubunda spontan erken doğum ve yenidoğan yoğun bakıma başvuru oranları istatistiksel olarak anlamlı derecede yüksekti (p<0,001). Aynı grupta anlamlı olarak daha yüksek sayıda mekonyumlu yenidoğan doğdu (p=0,040). Ursodeoksikolikasit kullanımı EB-IGK grubunda anlamlı olarak daha fazlaydı (p=0,007). Umbilikal kord arteriyel pH'I ve baz açığı açısından iki grup arasında anlamlı bir fark görülmezken, EB-IGK grubunda kompozit olumsuz perinatal sonuç oranı anlamlı olarak daha yüksekti (p=0,028). ROC analizinde, kompozit olumsuz perinatal sonuç öngörüsü için, serum safra asidi düzeyinin optimal kesme değeri %74 duyarlılık ve %68 özgüllük ile 33,5 µmol/L saptandı (Eğri altında kalan alan=0,759; p<0,001).

Sonuç: Erken başlangıçlı IGK hastalarının fetuslarında kompozit olumsuz perinatal sonuç oranlarının yüksek olmasını yüksek SBA düzeyinin geç başlangıçlı hasta grubuna kıyasla daha uzun sure fetus üzerine etkisinden kaynaklandığını savunmaktayız. EB-IGK ve GB-IGK vakalarının ayrımı, olası komplikasyonları öngörmede klinisyenlere yol gösterici olacaktır.

Anahtar Kelimeler: İntrahepatik gebelik kolestazı, olumsuz perinatal sonuç, serum safra asiti

Cite as: Agaoglu Z, Tanacan A, Ipek G, Peker A, Yıldız EG, Sahin D. Comparison of composite adverse perinatal outcomes inearly- and late-onset intrahepatic cholestasis of pregnancy. Jinekoloji-Obstetrik ve Neonatoloji Tıp Dergisi 2024;21(3):145–151.

Geliş/Received: 14.01.2024 • **Kabul/Accepted:** 28.04.2024

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Çevrimiçi Erişim/Available online at: https://dergipark.org.tr/tr/pub/jgon

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a disease that usually begins with pruritus of the palms and soles, accompanied by elevated serum bile acid (SBA) levels, and can have adverse perinatal outcomes (1). It occurs in the second or third trimester of pregnancy and continues with itching without lesions (2). Although the prevalence of ICP varies in the literature according to the country and population, the common consensus is that this rate ranges between 0.3 and 1.5% (3-5).

The diagnosis of ICP is made by taking a detailed history of the patient, including the duration of itching, evaluating the presence of skin lesions, and, if necessary, measuring the SBA value and determining whether it is above 10 µmol/L (6). Routine liver function tests and screening for viral hepatitis are not effective for diagnosis (1, 6). It has been proven that ICP causes fetal death due to sudden fetal arrhythmia and placental vasospasm resulting from increased bile acid and that there is an elevated sensitivity of oxytocin receptors in these patients, which contributes to an increased likelihood of spontaneous preterm birth and the presence of meconium in the amniotic fluid at term (7). It has been reported that adverse perinatal outcomes in ICP are associated with increased bile acid levelsrather than the deterioration of liver function (8, 9). Depending on the bile acid level, ICP is defined as mild (10-39 µmol/L), moderate (39-99 µmol/L), or severe (>100 µmol/L) (6). As the severity of ICP increases, the incidence of perinatal adverse outcomes also increases (10). This has been substantiated by several studies (11). As a result, it has been suggested that the management and birth weeks of patients diagnosed with ICP should be individualized (1, 12).

Patients diagnosed with ICP may be affected by the onset of the disease, which can potentially impact perinatal outcomes, and patient management should be evaluated by taking into consideration the possibility of this effect.To the best of our knowledge, there is only one study in the existing research that examines the impact of ICP on adverse prenatal outcomes based on the timing of disease onset (13). In the current study, our aim was to reveal the relationship between the week of onset of ICP and composite adverse perinatal outcomes (CAPO), as well as to determine whether early or late onset of the disease increasedthese negative outcomes.

MATERIAL AND METHOD

This study was designed as a retrospective, single-center study. Patients aged 18-45 who were followed up and treated with the diagnosis of ICP at the High-Risk Pregnancies Department of Ankara City Hospital from June 2019 to October 2023 were included in the study. The study obtained approval from the hospital's ethics committee (E2-23-5175). Every stage of the study adhered to the provisions of the Declaration of Helsinki.

The patients' data were accessed from the hospital database. For each patient included in the study, clinicodemographic information, age, parity, gravida, number of miscarriages, body mass index, week of gestation at which the disease started, pregnancy complications, any medication use, ICP severity, SBA value, routine liver function test results at diagnosis, gestational week at birth, newborn birth weight, first- and fifth-minute Apgar scores, newborn umbilical cord arterialpH and base excess (BE), and whether the newborn was admitted to the neonatal intensive care unit (NICU) were recorded.

The study included patients who experienced pruritus originating from the palms and soles of the feet and spreading throughout the body during pregnancy, accompanied by an SBA level above 10 µmol/L (1, 14). ICP that developed at or before the 28th week of gestation was considered early-onset ICP (EO-ICP), and ICP that occurred after the 28th week of gestation was considered late-onset ICP (LO-ICP). Patients with SBA levels of 10-40 µmol/L were considered to have mild ICP, and those with SBA levels above 40 µmol/L were considered to have severe ICP. The referenceranges of the measured laboratory values were as follows: SBA0–10 µmol/L; alanineaminotransferase, 0–35 U/L; aspartateaminotransferase, 0–35 U/L; alkalinephosphatase, 50–136 U/L; gamma-glutamyl transpeptidase, 0–38 U/L; total bilirubin, 5–21 µmol/L; and direct bilirubin, 0–7 µmol/L.

Multiple pregnancies, patients with organ transplants, those with immune deficiency, hypertensive patients, pregnant women with active or chronic viral hepatitis and autoimmune hepatitis, those with known major fetal chromosomal and structural anomalies, and those with missing or unavailable data were excluded from the study.

CAPO was determined by the presence of at least one of the following criteria: umbilical arterial pH below 7.20, fifth-minute Apgar score below 5, and a stay in NICU for more than 24 hours.

STATISTICAL ANALYSIS

SPSS version 22.0 (SPSS Inc., Chicago, IL, USA) statistical program was used for data analysis. The Kolmogorov–Smirnov and Shapiro–Wilk tests were conducted to analyze the suitability of the data for the normal distribution. The Student'st-test and the Mann-

Whitney U test were employed to compare normally and non-normally distributed variables, respectively. Descriptive analyses were presented using means and standard deviations for normally distributed variables and median and interquartile range values for non-normally distributed variables. The chi-square test was used to compare categorical variables. Areceiver operating characteristic (ROC)analysis was undertaken to determine the cut-off value of SBA in predicting CAPO. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The study included a total of 198 patients diagnosed with ICP, of whom 36 were in the EO-ICP group, and 162 were in the LO-ICP group. Table 1 presents the comparison of clinicodemographic data, gestational week at the time of ICP diagnosis, gestational week at birth, neonatal birth weight, neonatal first- and fifth-minute Apgar scores, maternal liver function test results, and SBA levels between the two groups. There were statistically significant differences between these groups in terms of gestational week atdiagnosis, neonatal birth weight, and neonatalfirst-minute Apgar score.

Table 2 shows the results related to disease severity, ursodeoxycholic acid (UCDA) use, pregnancy complications, the presence of meconium staining amnion, neonatal umbilical cord arterial pH and BE, NICU admission, and CAPO rates in both groups.The rates of spontaneous preterm birth, severe ICP, meconium-stained delivery, and NICU admission were statistically significantly higher in the group of EO-ICP. There were no significant differencesamong the two groups regarding neonatal umbilical cord arterialpH or BE. The rate of CAPO statistically significantly differed amongthe two groups (p=0.028). There was no intrauterine fetal loss in both groups during the antenatal period.

As a result of ROC analysis, the optimal cut-off value of the SBA level in predicting CAPO was determined to be 33.5 µmol/L, at which it had 74% sensitivity and 68% specificity (area under the curve =0.759; p<0.001) (Table 3) (Figure1).

Table 1. Comparison of clinicodemographic and obstetric data between the studygroups

Variables	EO-ICP group (n=36)	LO-ICP group (n=162)	*p*-value
Age (years)	28.9 (8)	28.8 (9)	0.854
Gravida (n)	1.8 (1)	2.3 (2)	0.434
Parity (n)	0.5 (1)	0.9 (2)	0.365
Miscarriage (n)	0.2 (0)	0.4 (1)	0.504
Body mass index (kg/m^2)	28.0 (4)	26.9 (4)	0.431
Gestational week at diagnosis	26.2 (2)	34.3 (3)	0.000
Gestational week at birth	36.3 (0)	36.5 (1)	0.953
Neonatal birth weight (gram)	2640.1 (320)	2856.2 (465)	0.000
First-minute Apgar score	7.1 (1)	7.4 (1)	0.002
Fifth-minute Apgar score	8.7 (1)	8.9 (0)	0.083
Bile acid level (µmol/L)	41.8 (31)	27.0 (12)	0.045
ALT (U/L)	76.3 ± 32.5	74.7 ± 34.5	0.687
AST (U/L)	67.8 ± 26.8	66.9 ± 29.6	0.569
GGT (U/L)	40.4 ± 13.8	39.3 ± 16.3	0.432
ALP (U/L)	186.3 ± 89.4	179.6 ± 88.2	0.278
Total bilirubin (mg/dL)	13.6 ± 3.7	12.9 ± 4.3	0.693
Direct bilirubin (mg/dL)	4.1 ± 1.7	3.9 ± 1.9	0.576

EO-ICP: early-onset intrahepatic cholestasis of pregnancy, LO-ICP: late-onset intrahepatic cholestasis of pregnancy, ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: gamma-glutamyl transpeptidase, ALP: alkaline phosphatase
Independent-samples *t*-test and Mann-Whitney *U*-test were used.
Data expressed as mean±SD; median interquartile range
p<0.05 was considered statistically significant.

Table 2. Comparison of CAPO between the study groups

Variables	EO-ICP group (n = 36)	LO-ICP group (n = 162)	*p*-value
UCDA use	32 (88.9%)	107 (66.0%)	0.007
Severe ICP	15 (41.7%)	28 (17.3%)	0.001
NICU admission	13 (36.1%)	22 (13.6%)	0.001
Cesarean delivery	27 (75.0%)	100 (61.7%)	0.290
CAPO	9 (25%)	18 (11.1%)	0.028
Preterm birth	12 (33.3%)	15 (9.3%)	0.000
FGR	4 (11.1%)	29 (17.9%)	0.323
Meconium-stained amnion	5 (13.9%)	8 (4.9%)	0.040
Umbilical cord arterial base excess (mmol/L)	-2.9(3)	-2.4(2)	0.311
Umbilical cord arterial pH	7.2(0.1)	7.3(0.2)	0.299

CAPO, composite adverse perinatal outcomes; EO-ICP, early-onset intrahepatic cholestasis of pregnancy; FGR, fetal growth restriction; LO-ICP, late-onset intrahepatic cholestasis of pregnancy; NICU, neonatal intensive care unit; UCDA,ursodeoxycholic acid
The chi-square test and Mann-Whitney U-test were used.
Data expressed as median interquartile range, number percentage
p<0.05 was considered statistically significant.

Table 3. Predictive performance of SBA in predicting CAPO

Variable	AUC	Std. error	Asymp. Sig	%95 CI		Cut-off value
				Lower	Upper	
SBA	0.759	0.058	0.000	0.646	0.872	33.5

AUC: Area under curve, CAPO: Composite adverse perinatal outcome; SBA, serum bile acid
p<0.05 statistically significant

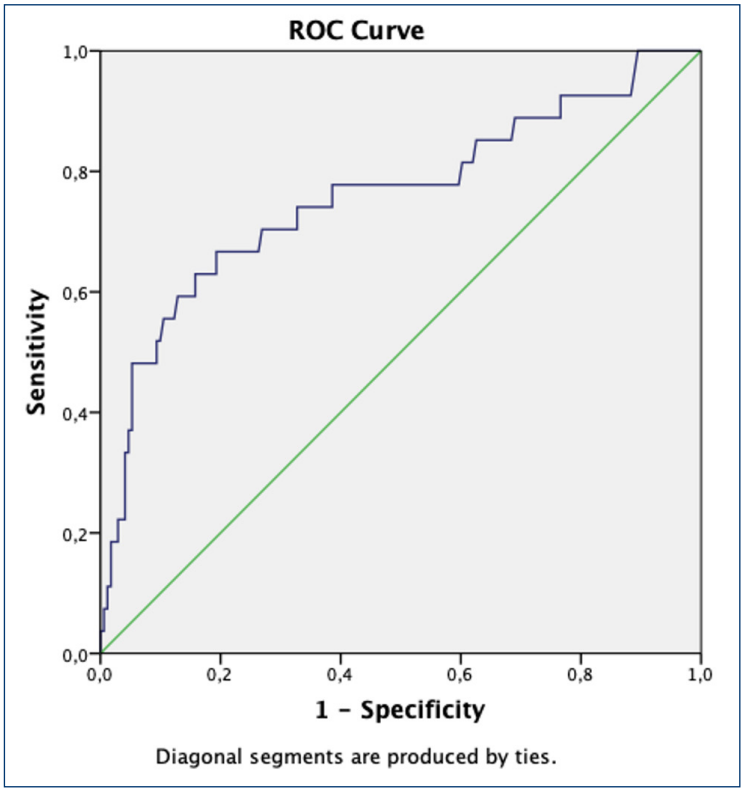

Figure 1. ROC analysis of the predictive ability serum bile acid for CAPO

DISCUSSION

This study examined the relationship between the week of onset of ICP and CAPO. We observed a statistically significant increase in the utilization of UCDA among patients in the EO-ICP group compared to the LO-ICP group, and the latter also presented with a higher number ofspontaneous preterm births and meconium-stained deliveries, lower first- and fifth-minute Apgar scores, and a higher rate of NICU admission. Consequently, the rate of CAPO was also higher in the EO-ICP group.

ICP is an obstetric complication with significant adverse perinatal consequences (15). Various theories and ideas have been proposed for the developmental mechanism of ICP and its effects on the fetus. However, it remains unclear which fetuses are at greater risk in the presence of ICP (7). Various blood markers, such as bile acid, transaminase, and other liver enzymes, have been used to predict adverse perinatal outcomes, but there is no consensus on this issue (12). There are many studies on this subject, and the prevailing idea is that the SBA mechanism is mostly likely to be responsible (8).

The pathophysiology of ICP is based on inflammatory mechanisms caused by high SBA levels (16). In a review, Majsterek et al. revealed that increased SBA levels were associated with adverse perinatal outcomes (8). In the same study, it was determined that as SBA elevation rates increased, adverse pregnancy outcomes increased proportionally (8). This idea is supported by the results of many studies conducted at different times (17).

This study found higher SBA values in the EO-ICP group than in the LO-ICP group. In proportion to the higher SBA values in the EO-ICP group, we also detected a higher rate of CAPO in this group, which is consistentwith the results of the abovementioned studies. Moreover, in the current study, at a cut-off value of 33.5 µmol/L, the SBA value had 74% sensitivity and 68% specificity in the prediction of CAPO.

Although staining of amniotic fluid with meconium is a condition that should not be observed during a normal pregnancy, it complicates 5-20% of women giving birth (18). The prevalence of this condition increases as the gestational age increases, and this rate reaches 27%, especially in post-term pregnant women (19). Amniotic fluid stained with meconium has been found to be associated with important problems in the neonatal period, including neonatal meconium aspiration syndrome, fetal acidemia, neonatal respiratory distress, and cerebral palsy (18). Grantz et al. reported that meconium staining increased up to 44% in patients with ICP, and this was in proportion to the elevation in the SBA level (20). This result was later confirmed by a meta-analysis by Ovadia et al. and a study by Çelik et al. (12, 21).

The findings of our study revealed a significantly higher incidence of meconium-stained amnion in the EO-ICP cohort than the LO-ICP cohort, which is consistent with the literature. Although the mechanism of prenatal meconium discharge in ICP remains unknown, the higher prevalence of thiscondition in patients with EO-ICP can be attributed to the fetal distress environment that occurs as a result of the toxic effect of increased SBA on the fetus for a relatively longer time compared to cases of LO-ICP, as well as the direct stimulating effect of bile acids on the intestinal muscles.

Preterm birth is an obstetric complication with adverse perinatal outcomes (22). It complicates approximately 10% of all pregnancies. It is also associated with many complications, such as increased visits to the NICU in the neonatal period, neonatal sepsis, hyperbilirubinemia, apnea, bradycardia, hypoglycemia, anemia, and necrotizing enterocolitis (23, 24).Shemer et al. found high preterm birth rates compared to the normal pregnancy group(24). In a later study, Chen et al. confirmed this result by detecting a preterm birth rate of 18.6%(11).

In this study, the rate of preterm birth was found to be three times higher in theEO-ICP group compared to theLO-ICP group(33.3% vs. 9.3%). This result supports the hypothesis that the bile acids that rise more in patients with EO-ICP compared to those with LO-ICP take longer to act and that the bile acids increasing withpreterm birth increase oxytocin receptors.

One of the cornerstones of ICP treatment is the use of UCDA (25). It is considered safe for both the fetus and the mother and has been shown to improve perinatal outcomes in many studies (25, 26). In a research conducted by Jin et al., no significant difference was seen in the use of UCDA among the EO-ICP and LO-ICP groups, the rate of patients using UCDA was significantly higher in the former (13). This was attributed to the more apparent and distressingclinical manifestation of the diseaseand the higher SBA level in the EO-ICP group.

It is common for newborns to be admitted to the NICU in the presence of ICP (27). This is considered to be due to the presence of meconium-containing amniotic fluid, spontaneous or iatrogenic premature birth, which is common in patients with ICP, and the fetal hypoxic and asphyxial environment created by placental vasospasm caused by elevated SBA levels, which negatively affect the fetus starting from the intrauterine period (28). In studies conducted with ICP cases, the average rate of NICU admission is reported to range from 17 to 38%, depending on the gestational week at birth. There are studies showing that the NICU rate can reach 60% in untreated patients or in patient groups presenting with high SBA levels (29). In this study, we found that the rate of

NICU admission was higher in the EO-ICP group compared to the LO-ICP group, which was related to various factors, including a higher rate of preterm births and meconium staining and higher maternal SBA values in this group.

In this study, CAPO rates were investigated for the first time in patients with ICP according to the onset of the disease. The rate of CAPO was shown to be significantly higher in the EO-ICP group, which is similar to the results of the only study in the literature that investigated the adverse perinatal outcomes of patients (but did not evaluate the outcomes as a composite) with ICP according to the week of disease onset(13).

In this study, CAPO was investigated according to the onset time of ICP, and, to our knowledge, it is the first studyof this nature in the literature. We consider this a strong aspect of our study. The limitations of the current study include its single-center and retrospective design and the limited number of patients in the EO-ICP group. Future multicenter and prospective studies that will include a large number of patients can elucidatethe detailed risk factors and outcomes of ICP according to the onset of the disease.

In conclusion, careful perinatal follow-up should be undertaken in patients with ICP due to the frequency of adverse perinatal outcomes. We consider that the high CAPO rates in the fetuses of patients with EO-ICP are due to the effect of high serum bile acid levels on the fetus for a longer time than in the LO-ICP group. Therefore, if ICP develops early, the patient should be informed in detail about possible complications and should be closely followed up.The differentiation of cases of EO-ICP and LO-ICP will serve as a guide for clinicians in predicting possible complications.

Conflict of interest statement
None

Funding
None

Author contribution
ZA: methodology, data collection, writing, editing, AT: methodology, writing, editing, analysis, GI: technical assistance, data collection, correction, analysis, AP: technical assistance, data collection, correction, analysis, EGY: technical assistance, writing, editing, analysis, DS: methodology, design, correction, analysis

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