

# Neonatal Outcomes of Pregnancy with Intrahepatic Cholestasis

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## Abstract

**Objective:** Intrahepatic cholestasis of pregnancy is a clinical syndrome, characterized by maternal pruritus and biochemical cholestasis. Epidemiologic surveys show significant regional differences in the incidence of intrahepatic cholestasis of pregnancy. In this study, we evaluated the frequency of intrahepatic cholestasis of pregnancy and perinatal/neonatal outcomes in our hospital.

**Methods:** Twenty patients with intrahepatic cholestasis of pregnancy and their 22 newborn babies (3 twins), and one intrauterine exitus with unknown etiology were included in this retrospective analysis. Ursodeoxycholic acid was given to 50% of intrahepatic cholestasis of pregnancy patients. Fifteen (65.2%) of the newborn babies were  $\leq 37$  weeks. Eight (34.7%) of newborns had transient respiratory support, 2 with continuous positive airway pressure. None of the babies had diagnosed respiratory distress syndrome, thus none of them required surfactant. One case of intrauterine exitus has occurred with unknown etiology.

**Results:** We conducted a retrospective study about frequency and perinatal outcome of pregnancies complicated by intrahepatic cholestasis of pregnancy between June 2007-August 2010 at Baskent University Ankara Hospital. Perinatal/neonatal outcomes were retrospectively studied by medical chart review.

**Conclusion:** In our study intrahepatic cholestasis of pregnancy was present in 1.4% of pregnancies, that was similar to the European population. Increased risk of preterm delivery and respiratory distress syndrome were reported in literature, in our study group, none of the babies had RDS or other serious neonatal complications of preterm labor despite high rate of preterm birth rate and rather high levels of maternal serum bile acid levels.

**Keywords:** Intrahepatic cholestasis, newborn, pregnancy, perinatal outcomes.

## *Intrahepatik kolestazlı gebelerin neonatal sonuçları*

**Amaç:** Gebelik kolestazı, maternal kaşıntı ve biyokimyasal kolestaz ile karakterize klinik bir sendromdur. Epidemiyolojik çalışmalarda gebelik kolestazının insidansı bölgesel farklılıklar göstermektedir. Bu çalışmada gebelik kolestazlı hastalarımızın sıklığı ve perinatal/neonatal sonuçlarının belirlenmesi amaçlandı.

**Yöntem:** Çalışma Başkent Üniversitesi'nde Ankara Hastanesi Haziran 2007-Ağustos 2010 tarihleri arasında takip edilen kolestazlı gebelerin ve yenidoğanlarının dosyalarının retrospektif olarak taranması ile yapıldı.

**Bulgular:** Yirmi kolestazlı gebenin 22 bebeği (3'ü ikiz) çalışmaya dahil edildi. Ursodeoksikolik asit kolestazlı gebelerin yarısına verildi. On beş (%65.2) bebek  $\leq 37$  hafta altındaydı. Sekiz (%34.7) yenidoğana geçici solunum desteği sağlandı ( $FI O_2 < \%30$ ), bunlardan 2 bebeğe yenidoğanın geçici takipnesi nedeniyle sürekli pozitif basınç uygulaması yapıldı. Hiçbir yenidoğana respiratuvar distres sendromu tanısı konulmadı ve bu nedenle sürfaktan tedavisi verilmedi. Bir fetus intrauterin eksitus idi ancak ölüm nedeni belirlenemedi.

**Sonuç:** Çalışmamızda kolestazlı gebelerin sıklığı, Avrupa toplumuna benzer şekilde %1.4 olarak belirlendi. Literatürde prematüre doğum ve respiratuvar distres sendromunun kolestazlı gebelerde arttığı bildirilirse de bizim çalışmamızda hiçbir bebekte respiratuvar distres sendromunu görülmüdü. Yüksek maternal serum safra asitleri ve prematüre doğuma rağmen yenidoğanlarda diğer ciddi neonatal komplikasyonlar gözlenmedi.

**Anahtar Sözcükler:** Intrahepatik kolestazis, yenidoğan, gebelik, perinatal/neonatal sonuçlar.

## Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy specific liver disease characterized by maternal pruritus without any skin rash, and biochemical cholestasis with abnormal liver functions in the absence of other liver diseases, occurring in the late second trimester or third trimester and persisting until delivery. The etiology of ICP is complicated and poorly understood.<sup>[1-5]</sup> This syndrome may result in spontaneous preterm delivery, meconium-stained amniotic fluid, fetal distress and intrauterine fetal death, although thought to be benign for mothers.<sup>[6]</sup> Clinical studies clearly show that it may lead to preterm delivery in up to 19-60%, fetal distress in 27-33%, and fetal loss in 0.2-4.1% of patients.<sup>[1-3]</sup> Respiratory distress syndrome (RDS) was reported in some of the infants born from mothers with ICP.<sup>[7]</sup> Epidemiologic surveys show significant regional differences in the incidence of ICP; it varies from 0.1 to 1.5% of pregnancies in Europe and 1 to 5% in China.<sup>[4]</sup> There are also differences due to ethnicity. In comparison with the overall prevalence of ICP which is 0.7%, the white population has a low occurrence of 0.62%, while this number is 1.46% in the Pakistanian population and 1.24% in the Indian population.<sup>[8]</sup> It is found to be 5.6% in a primarily Latina Los Angeles population, much higher than the prevalence previously reported in the United States.<sup>[9]</sup> The frequency of ICP in Turkey has not been reported so far. In this study, we evaluated the frequency of ICP and perinatal/neonatal outcome in our hospital.

## Methods

The study was performed retrospectively on 20 pregnancies complicated by ICP between June 2007 and August 2010, at Baskent University Ankara Hospital, a tertiary care maternity center. The diagnosis of ICP is based on (i) development of pruritus and cholestasis during the second or third trimester of pregnancy, and (ii) elevated TBA  $\geq 11$   $\mu\text{mol/L}$  (and elevated serum transaminases but not necessarily). (iii) Spontaneous relief of signs and symptoms after delivery and (iv) absence of other diseases that cause pruritus and jaundice.<sup>[10,11]</sup> Ultrasonography of the abdomen and serological scan of viral hepatitis were performed to exclude other causes of liver diseases in all patients before enrollment. Liver biopsy is not necessary for the

diagnosis and histopathology is not diagnostic.<sup>[10,11]</sup> Patients with chronic liver diseases, skin diseases, allergic disorders, symptomatic cholelithiasis, and ongoing viral infections affecting the liver (hepatitis A, B and C virus, cytomegalovirus, herpes simplex virus, and epstein-barr virus) severe preeclampsia affecting liver functions and acute fatty liver of pregnancy, were excluded. Statistical analysis was performed with SPSS for Windows 17.0 (SPSS Inc., Chicago, IL, USA) and  $p < 0.05$  was considered statistically significant. The results are expressed as mean  $\pm$  SD. The difference between two samples was calculated using the Mann-Whitney U test and Chi-Square test.

## Results

Twenty patients with ICP and their 22 newborn babies (3 twins), and 1 intrauterine exitus with unknown etiology were included in this retrospective analysis. Thirteen of babies were female (56.5%) and 10 of them were male (43.5%). Mean age of mothers with ICP was  $31.4 \pm 4.5$  years. ICP was diagnosed at  $32.6 \pm 3.8$  weeks of gestation. The main symptom of patients was pruritus (96%). Abnormal liver function tests and epigastric pain were present in 5% of the cases. Initial serum bile acid levels were  $41.3 \pm 81.7$   $\mu\text{mol/L}$ . Liver and bile duct ultrasound findings were normal in 30% of patients. Bile stones, hemangioma of liver, intrahepatic minimal dilatation of bile ducts and inspissated bile were revealed in, 5, 2, 1 and 1 of the patients respectively. Ursodeoxycholic acid was been given to 50% of ICP patients. Cesarean section rate was 70% (Table 1). Antenatal corticosteroid was given to 15% of women with ICP for the prevention of RDS in preterm infants. Neonatal outcome: Mean gestational age at delivery was  $36.4 \pm 1.7$  (33-39) weeks, 15 (65.2%) of the newborn babies were  $\leq 37$ . Mean birth weight was  $2900 \pm 536$  g. Mean Apgar scores were  $8.3 \pm 0.7$  (7-9) and  $9.5 \pm 0.5$  (9-10) at 1 and 5 minutes respectively, excluding the case of intrauterine exitus. Eight (34.7%) of newborns had transient respiratory support [6 newborns with nasal high flow oxygen ( $\text{FiO}_2 < 30\%$ ), 2 with continuous positive airway pressure (CPAP) because of transient tachypnea of newborn (TTN)]. All of the newborns were fed with breast milk. Indirect hyperbilirubinemia, TTN, patent ductus arteriosus (PDA) and urinary tract infection were present in 9 (39.1%), 4

**Table 1.** Laboratory findings of pregnant women with ICP treated/untreated with ursodeoxycholic acid.

	Total (Mean $\pm$ SD, n=20)	Ursodeoxycholic acid treatment (+) (n=10)	Ursodeoxycholic acid treatment (-) (n=10)	P
Age (year)	31.45 $\pm$ 4.5 (22-38)	31.9 $\pm$ 4.2 (22-37)	30.3 $\pm$ 4.7 (25-38)	p>0.05
ICP diagnosis time (weeks)	32.6 $\pm$ 3.8 (22-38)	31.0 $\pm$ 3.7 (22-38)	34.2 $\pm$ 2.5 (28-37)	p>0.05
TBA ( $\mu$ mol/L)	41.3 $\pm$ 81.7 (11-366)	30.9 $\pm$ 4.0 (22-38)	34.5 $\pm$ 2.7 (28-37)	p>0.05
AST (U/L)	100.7 $\pm$ 142.1 (16-576)	141.7 $\pm$ 184.6 (16-576)	61.8 $\pm$ 68.4 (16-228)	p>0.05
ALT (U/L)	175.3 $\pm$ 293.8 (9-1065)	252.7 $\pm$ 387.8 (11-1065)	100.7 $\pm$ 144.1 (9-457)	p>0.05
ALP (U/L)	376.8 $\pm$ 206.5 (18-746)	429.1 $\pm$ 220.8 (95-745)	309.7 $\pm$ 180.3 (18-540)	p>0.05
Exposure time (day)	28.8 $\pm$ 28.8 (7-119)	37.6 $\pm$ 33.5 (7-119)	19.2 $\pm$ 20.3 (8-71)	p>0.05

TBA: Total fasting serum bile acids, ICP: Intrahepatic cholestasis of pregnancy, AST: Alanine aminotransferase, ALT: Aspartate aminotransferase, ALP: Alkaline phosphatase

(17.4 %), 2 (8.7%) and 1 (4.3%) of the newborns respectively. None of the babies had RDS, thus none of them required surfactant. Except one case of intrauterine death with unknown etiology, neonatal mortality or neonatal morbidity such as pneumonia, pulmonary hypertension, pneumothorax, necrotizing enterocolitis, meconium aspiration, sepsis, polycythemia, hypothyroidism, neonatal convulsion, meningitis, chronic lung disease, retinopathy of prematurity, congenital heart disease, intracranial hemorrhage, periventricular leukomalacia, congenital anomalies, metabolic diseases were not detected Tables 2 and 3.

## Discussion

Intrahepatic cholestasis of pregnancy is a clinical syndrome of unknown pathophysiology, characterized by abnormal liver biochemistry and generalized pruritus, occurring during the second half of pregnancy and persisting until delivery. This syndrome is associated with an increased risk of fetal distress, spontaneous preterm labor and unexplained stillbirth. The pathogenesis of the fetal complications is not fully understood,

although a role for increased bile acids or toxic metabolites of bile acids has been suggested.<sup>[12]</sup> The incidence of ICP varies widely with geographical location and ethnicity. This condition is very common in Chile and Bolivia (6%-27%) but not so frequent anywhere in Europe (0.1%-1.5%) and United States (0.7%).<sup>[4]</sup> In our study ICP was observed in 1.4% of pregnancies, that was similar to European population. Total serum bile acid levels appear to predict fetal outcome and this may be explained by the fact that high bile acid concentrations decrease the surfactant formation and impair fetal lung maturation.<sup>[7,13]</sup> Direct correlations between the intensity of elevation of bile acids and increased fetal risk have been observed and likewise fetal complications in ICP are rarely encountered in cases with TBA levels less than 40  $\mu$ mol/L.<sup>[14]</sup> The placenta plays a major role in protecting the fetus from the adverse effects of potentially toxic endogenous substances such as TBA.<sup>[15]</sup> Increased levels of TBA in maternal circulation, however, enhance placental transport and facilitate the generation of certain placental hormones which leads to significant constriction among chorionic vessels.<sup>[16]</sup> ICP may seriously impair the placental clear-

**Table 2.** Demographic and laboratory findings of newborn infants with respect to ursodeoxycholic acid treatment.

	Total (Mean $\pm$ SD)	Ursodeoxycholic acid treatment (+)	Ursodeoxycholic acid treatment (-)	P
Gender (female/male)	23	6/6	7/4	p>0.05
Mean gestational age (week)	36.4 $\pm$ 1.7 (33-39)	35.9 $\pm$ 2.1 (33-39)	37.0 $\pm$ 1.1 (35-38)	p>0.05
Mean birth weight (g)	2900 $\pm$ 536 (2000-3760)	2792.5 $\pm$ 653.6 (2000-3760)	2979.0 $\pm$ 360.9 (2260-3410)	p>0.05
Apgar score at 1 min	8.3 $\pm$ 0.7 (7-9)	8.1 $\pm$ 0.7 (7-9)	8.5 $\pm$ 0.7 (7-9)	p>0.05
Apgar score at 5 min	9.5 $\pm$ 0.5 (9-10)	9.5 $\pm$ 0.5 (9-10)	9.5 $\pm$ 0.5 (9-10)	p>0.05

Min: Minute

**Table 3.** Complications observed in newborn infants.

	Complications			
	Ursodeoxycholic acid treatment (+) (n=12)	Ursodeoxycholic acid treatment (-) (n=11)	Total (n=23)	%
Premature newborn	9	6	15	65.2
Transient respiratory support	7	1	8	34.7
Indirect Hyperbilirubinemia	4	5	9	39.1
TTN	3	1	4	17.4
PDA	1	1	2	8.7
Urinary tract infection	1	0	1	4.3
Intrauterine exitus	-	1	1	4.3

TTN: Transient tachypnea of newborn, PDA: Patent ductus arteriosus

ance of fetal bile acids (BAs), leading to a dangerous accumulation of these compounds within the fetus and the newborn.<sup>[17]</sup> Zecca et al.<sup>[7]</sup> reported that pregnant with ICP mean of bile acids was  $25.0 \pm 17.8$   $\mu\text{mol/L}$ . Neonatal outcomes in the ICP and control groups with preterm infants were reported. In the ICP and control groups median gestational age was 35.6 (33-37) and 35.1 (33-36) respectively. The percentage of infants delivered at <34 weeks' gestational age was 22.4% and 18.7% in the ICP and control group respectively. In the ICP and control groups RDS was observed in 28.6% and 14.1% of the cases and surfactant treatment was required in 24.6% and 12.2% of the cases respectively. Zecca et al.<sup>[7]</sup> reported that the incidence of RDS in late preterm infants from cholestatic pregnancies was almost double when compared with control infants, ICP was thought to be the main risk factor for neonatal RDS, together with gestational age.<sup>[7]</sup> In our study, although TBA levels were rather high, RDS was not observed in newborns. Oztekin et al.<sup>[18]</sup> investigated 187 pregnant patients with ICP. Asphyctic newborn and premature birth rates in their study were reported as 36 (19.2%) and 22 (11.7%) respectively. Laatikainen et al.<sup>[17]</sup> indicated that ICP could lead to premature births in up to 60%, fetal distress in up to 33%, and intrauterine death in 2% of patients. In our study, mean TBA level and rate of premature birth were found to be  $41.3 \pm 81.7$   $\mu\text{mol/L}$  and 65.2% respectively. Still-birth rate was 4.3% (1/23). There was no other perinatal mortality case. There was no perinatal asphyxia. Surfactant treatment was not given to any of the newborn babies. Eight (34.7%) of newborns needed transient respiratory support. Indirect hyperbilirubinemia was present

in 9 (39.1%), TTN in 4 (17.4%), PDA in 2 (8.7%) and urinary tract infection in 1 (4.3%) of the newborn infants of women with ICP. Ursodeoxycholic acid is safe for both mother and fetus and is the only treatment that can reduce the risk of premature delivery with perinatal morbidity.<sup>[19,20]</sup> Ambros-Rudolph CM et al.<sup>[21]</sup> investigated neonatal outcomes of pregnant with ICP who received ursodeoxycholic acid treatment. In their study, ursodeoxycholic acid was given to 10 of 13 cases. While preterm deliveries were 3/10 (30%) in treated patients, that was 3/3 (100%) in the others. In our study there was no statistically significant difference in neonatal outcomes between the treated and untreated patients with ICP. Ursodeoxycholic acid treatment group had higher levels of TBA ( $69.0 \pm 120.2$   $\mu\text{mol/L}$ ). TBA levels in the untreated group was  $20.0 \pm 12.5$   $\mu\text{mol/L}$ . Possible fetal-neonatal complications might be prevented by ursodeoxycholic acid treatment. According to the literature, neonatal complications are rare in cases with lower TBA levels. Our study had similar conclusions. But preterm birth rate among pregnant women with ICP who received and did not receive ursodeoxycholic acid treatment was 9 (75%) and 6 (55%) respectively. Treatment group included two twin pregnancies and severe cholestatic patients so preterm birth is more frequent in this group as expected because of potential fetal-maternal toxic effects of high TBA levels. In spite of the high TBA in this group, except preterm birth, there are no serious neonatal complications such as RDS, perinatal asphyxia, and this can be explained by the positive effect of ursodeoxycholic acid treatment. Only one fetal death observed in our study is in the untreated group.

## Conclusion

ICP carries risks for mothers and their newborn infants. But appropriate diagnosis, timely treatment and delivery of the pregnant women with ICP may eliminate the risks in the newborn infants during the perinatal and postnatal period.

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