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RESEARCH ARTICLE

INTRAHEPATIC CHOLESTASIS OF PREGNANCY: PERINATAL OUTCOMES FROM A TERTIARY REFERRAL HOSPITAL IN TURKEY

Neslihan Yerebasmaz., Deniz Esinler., Oya Aldemir., Hilal Ilgın., Omer Kandemir and Serdar Yalvac

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ABSTRACT

This retrospective cohort study included 56 women who were diagnosed with intrahepatic cholestasis of pregnancy (ICP) and 204 women in active labour who delivered in Etlik Zubeyde Hanım Women's Health Teaching and Research Hospital between 1st January, 2013 and 31st April, 2014. There was no significant difference between the groups according to maternal age, parity or birth weight. The most common complication was oligohydramnios in both groups (12.5% vs. 7.3, p=0.3). In the study group, 10.7% newborns had meconium-stained amniotic fluid whereas 2.9% had it in the control group (p=0.02). Rates of gestational diabetes mellitus and preeclampsia were significantly higher in the ICP group (p=0.02 and p=0.02, respectively). ICP was diagnosed at 31.4±1.35 weeks of gestation (min: 28-max: 34.4). The main symptom of the patients was pruritus (98.3%). The mean total bile acids (TBA) value was 38.97±37.49 µmol/L (min: 11.2-max: 244). There was no difference in complications according to TBA values (p=0.9). The ICP rate was 0.5% in this period.

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) occurs in the second and third trimesters of pregnancy. It is characterized by pruritus, an elevation in serum bile-acid concentrations and liver transaminases (Chen *et al*,2013). ICP is the most frequent cause of liver disease in pregnancy (Hay, 2008; Joshi *et al*, 2010). The prevalence of ICP varies from as high as 5% in Chile to 0.7% in the United Kingdom (Geenes *et al*, 2014). The frequency of ICP among Turkish pregnant women is 1.4% in total pregnancies (Kurt *et al*, 2010), which is similar to that of the European population, where the value varies from 0.1% to 1.5% of pregnancies (Arrese *et al*, 2006). The cause of ICP is unknown but genetic, hormonal and environmental factors are likely to be involved (Arrese *et al*, 2008).

Although the maternal prognosis in ICP is good, there is a significant increased risk for the foetus, such as prematurity, respiratory distress syndrome (RDS), meconium-stained amniotic fluid and stillbirth (Geenes *et al*, 2014; Williamson *et al*,2004; Zecca *et al*, 2006; Zecca*et al*, 2008). The incidence of prematurity varies greatly among studies (6%-60%). Pruritus appears to begin earlier in pregnancies that are complicated by spontaneous premature birth (Kondrackiene *et al*, 2007).

In this study, we aimed to investigate the maternal and foetal complications of ICP in our referral tertiary hospital in Turkey.

MATERIALS AND METHODS

All patients who were diagnosed with ICP among the 11,200 pregnant women between 1st January, 2013 and 31st April, 2014 at Etlik Zubeyde Hanim Women's Health Teaching and Research Hospital were included in the study. There were 56 patients (59 foetuses) with ICP in the study group. The control group comprised 204 women (206 foetuses) who were taken randomly from the pregnant women who delivered in our hospital in the same period. The study was designed as a retrospective cohort one. The maternal and foetal data were reviewed from patients' hospital medical records and a computerized database. The maternal and foetal outcomes of the groups were compared statistically.

The diagnosis of ICP was made by the presence of pruritus during the second or third trimester of pregnancy, elevated liver transaminases and total bile acids (TBA) (≥11µmol/L) in the serum.

Exclusion criteria of the study were as follows: 1) the presence of liver or gastrointestinal system disease, 2) the presence of systemic diseases, 3) a body mass index (BMI) < 18.5 kg /m^2, 4) the presence of chronic hypertension and 5) the presence of diabetes mellitus.

Stillbirth was defined as an intrauterine death after the pruritus complaints began. The diagnosis of gestational hypertension was confirmed when either two systolic blood pressure measurements were ≥ 140 mg Hg or two diastolic

blood measurements were ≥ 90 mm Hg, obtained at least six hours apart after 20 gestational weeks. Preeclampsia was diagnosed as hypertension with 300 mg/day of proteinuria after 20 gestational weeks. Gestational diabetes mellitus (GDM) was diagnosed by screening all patients using a 50g glucose challenge test at 24-28 gestational weeks, confirmed with a 100g oral glucose tolerance test. The study protocol was approved by the local ethics committee of our hospital (169-10).

For the statistical analysis of this study, continuous variables were expressed as mean±standard deviation (SD), and categorical variables as numbers and percentages. The Kolmogorov-Smirnov test was used to assess normal data distribution. The Student t-test, Mann-Whitney U tests and the chi-square test were used. P values were considered significant at the 0.05 level. All of the statistical analyses were performed using SPSS Statistics version 21.0 software.

RESULTS

Basal characteristics of the patients and maternal complications are given in **Table 1.** No significant difference was found between the groups according to the patients' age, nulliparity or advanced maternal age. Preeclampsia and GDM rates were significantly higher in the study group (p=0.02 and p=0.02, respectively). In the ICP group, three patients had twins, whereas two patients had twins in the control group (p=0.04). The caesarean-section rate was significantly higher in the ICP group (55.4% vs. 42.4, p<0.001).

Table 1 The baseline characteristics of the patients

Characteristics of patients	Study Group (n=56)	Control Group (n=204)	p value
Maternal age (yr)	28.7± 5.1	27.5±5.8	NS
Advance maternal age ≥ 35 years (n, %)	10 (17.9)	30 (14.7)	NS
Rate of nulliparity (n, %)	25(44.6)	75 (36.8)	NS
Body mass index (kg/m2)	28.7 ±4.7	30.7±3.5	0.001
Gestational age at delivery (w)	38.1±1,2	38.9 ± 1.5	0.001
Premature delivery (<37 weeks) (n, %)	5 (8.5)	14 (6.9)	NS
Mode of delivery (n, %)			
Cesarean section	31 (55.4)	122 (59.8)	
Vaginal delivery	25 (44.6)	82 (40.2)	0.001
Birth weight (g)	3148.2± 427.2	3204.9± 608.7	NS
Gender of newborns			
Male	25 (42.4)	114 (55.9)	NS
Female	34 (57.6)	90 (44.1)	
Singleton (n, %)	53 (94.7)	202 (99)	NS
Twin (n, %)	3 (5.3)	2 (1)	0.04
Maternal Complications			
Preeclampsia (n, %)	7 (12.5)	9 (4.4)	0.02
Gestational Diabetes Mellitus (n, %)	9 (16.1)	13 (6.4)	0.02

NS: Non significant

The laboratory findings of the patients are given in **Table 2**. Meconium-stained amniotic fluid was significantly higher in the ICP group (p=0.002).

There was no significant difference in NICU admissions (p=0.6). In addition, in the ICP group, there were no stillbirths whereas there were two stillbirths in the control group. The rates of foetal complications and foetal Anomalies at birth are given in **Table 3.**

Table 2 Laboratory findings of the groups

Variable	ICP (n=56)	Control (n=204)	p value
AST (IU/L)	96.23±65,4	21.8±6.7	0.001
ALT (IU/L)	127.25 ± 93.68	27.2 ± 10.3	0.001
T.bilirubin (mg/dl)	0.89±0.43	0.58 ±0.24	0.0001
D. bilirubin (mg/dl)	0.41±0.12	0.22 ±0.13	NS
Hemoglobin (g/dl)	12.08 ± 1.33	11.6 ± 1.2	0.007
Platelets (Cells/µL)	2485350 ±72365	241207.5 ± 66879	NS

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase
NS: Non significant

Table 3 Fetal complications and fetal anomalies at birth

Fetal complications*	Study group (n=59)	Control group (n=206)	p value
Transient tachypnea of newborn	4 (6.8)	6 (2.9)	NS
Meconium stained amniotic fluid	6 (10.2)	6 (2.9)	0.02
Oligohydramnios	7 (11.9)	15 (7.3)	NS
Prematurity	5 (8.5)	14 (6.8)	NS
Intrauterine fetal demise	0	2	-
NICU[1]	2 (3.9)	10 (4.8)	NS
IUGR[2]/SGA[3]	-	3 (1.5)/6 (3)	-
Fetal anomalies*			
Single umbilical artery	1 (1.7)	0	-

*n %; [1] NICU neonatal intensive care unit; [2] IUGR intrauterine growth restriction; [3]SGA small for gestational age
NS: Non significant

There was no association between the distributions of the foetal complications according to total bile acid (TBA) values **(Table 4).**

Table 4 Cross table shows the distribution of the fetal complications according to total bile acid values

	11-40 µmol/L (n=37, 66.1%)	40-100 µmol/L (n=14, 25%)	>100 µmol/L (n=5, 8.9%)
Meconium stained amniotic fluid (n=6)	5	1	0
Transient tachypnea of the newborn (n=4)	2	2	0
Oligohydramnios (n=7)	4	2	1
Prematurity (n=5)	2	3	0

The main symptom of the patients was pruritus (92.9%). There were no perinatal complications in 34 women (60.7%) whereas 22 women (39.3%) had at least one complication. The median TBA value with no complications was 27.3µmol/L, and 28.6µmol/L had at least one complication (p=0.97). The gestational age at diagnosis of ICP was 31.4±1.35 weeks.

There was no significant difference between those patients who had had ICP in previous pregnancies and those who had not, according to the mean gestational age, the mean age of the patients, the gestational week at diagnosis, TBA values and complications. The mean TBA value was (µmol/L)38.97±37.49 in the ICP group. In the ICP group, the total bilirubin (mg/dl) level was 0.89±0.43 and the direct bilirubin (mg/dl) level was 0.41±0.12.

Ursodeoxycholic acid (UDCA) was given to 48 (85.7%) out of 56 patients. The mean TBA values in these patients were 43.3 µmol/L and 23.1 µmol/L, respectively (p=0.04).

DISCUSSION

We have demonstrated that rates of meconium-stained amniotic fluid, preeclampsia and GDM in the ICP group were higher than those of the control group. In addition, we noted

that the incidence of ICP was found to be 0.5% (56/11,200) in our study population.

The pathogenesis and prognosis of pregnancy in a state of ICP remains uncertain. Although ICP is usually relatively benign to the mother, the risk of foetal complications is increased in pregnancies affected by ICP. These complications are preterm delivery, meconium-stained amniotic fluid, RDS, foetal distress and IUFD. The risk of foetal morbidity and mortality in ICP is higher than in the general population (Glantz *et al*, 2004). In our study, 39.3% of the births had an associated perinatal complication, including meconium staining of the amniotic fluid, preterm delivery, foetal distress, oligohydramnios and transient tachypnoea of the newborns in the ICP group, whereas this rate was 27.1% in the control group.

Geenes *et al*. demonstrated that TBA values were significantly elevated in both maternal and foetal serums in ICP pregnancies (Geenes *et al*, 2014). In addition, it was demonstrated that the risk of adverse pregnancy outcomes was significantly increased when maternal serum bile-acid levels rose above 40 mmol/L (Geenes *et al*, 2014; Glantz *et al*, 2004). Brouwers *et al*. showed that severe ICP (TBA >100 µmol/L) was associated with adverse pregnancy outcomes (Brouwers *et al*, 2015). The optimal cut-off for the TBA level was 69 mmol/L for an adverse composite neonatal outcome (Kawakita *et al*, 2015). In our study, there was no significant correlationbetween the maternal TBA values and foetal complications (p=0.911 for foetal distress and p=0.480 for oligohydramnios).

The incidence of RDS in the neonates of mothers with ICP is twice that of the normal population. It was hypothesized that bile acids can cause surfactant depletion in the alveoli (Zecca *et al*, 2006; Zecca *et al*,2008). In our cases, there were four cases of (7.1%) transient tachypnoea of the newborns in the ICP group and in six (2.9%) newborns in the control group (p=0.2).

The incidence of meconium-stained amniotic fluid at full term in a normal pregnant population varies between 12-15% (Sriram *et al*, 2003; Oyelese *et al*, 2006). We observed that meconium staining of amniotic fluid was significantly higher in the study group (p=0.02). As a result of an elevation in bile acids in maternal serum, TBA will cross the placenta and affect the foetus, and the risk of meconium passage will increase. Roncaglia *et al*. reported that the TBA content of meconium increased in cases of ICP (Roncaglia *et al*,2002).

Previous studies have reported different rates of intrauterine foetal demise (IUFD) in ICP cohorts. Foetal demise usually occurs in the last month of pregnancy (Puljic *et al*, 2015). In the literature, unexpected IUFD cases have been described by Lee *et al*. (Lee *et al*,2009) and Brouwers *et al*. (Brouwers *et al*,2015). They mentioned an increase in perinatal deaths correlating with TBA levels, but the mechanism is not clear. Geenes *et al*. found the incidence of stillbirths to be 1.5% in ICP women whereas it was only 0.5% in the control group (Geenes *et al*, 2014). In addition, Henderson *et al*. found the incidence of stillbirth after 37 weeks of gestation to be approximately 1.2% in their study (Henderson *et al*, 2014). In a series including 20 cases of IUFD associated with ICP, the median gestational age at foetal death was 38 weeks, and only two foetal deaths occurred before 37 weeks (Williamson *et al*, 2004). A bile acid level of 100 mmol/L was associated with an increased risk of stillbirth (Kawakita *et al*, 2015). The ideal method for the improvement of foetal well-being in cases of ICP is controversial. Different studies reported IUFD occurring within a few days of a reactive nonstress test (NST). It is thought that the mechanism of IUFD is a sudden event rather than a chorionic placental vascular process (Sentilhes *et al*, 2006;Lee *et al*, 2009). It is possible that bile acids cause the vasoconstriction of the placental chorionic vessels (Geenes *et al*, 2009).

Systematic delivery at 37-38 weeks of gestation, or even before when cholestasis is severe, has been recommended to prevent IUFD (Roncaglia *et al* 2002; Henderson *et al*, 2014). Puljic *et al*. reported that delivery at 36 weeks of gestation would reduce the perinatal mortality risk as compared to expectant management (Puljic *et al*, 2015). In addition, Lo *et al*. reported that the optimal time of delivery was 36 weeks of gestation to reduce maternal and foetal morbidities and mortalities (Lo *et al*, 2014). Even though there were no cases of IUFD in our study, the overall complication rate was high.

The incidence of GDM is higher in women predisposed to developing ICP. Women with ICP were more likely to have gestational diabetes (OR 2.8) and give birth to large infants for their gestational age (Wikström *et al*, 2013). There are different studies that suggest a correlation between pregnancies complicated by ICP and GDM, which becomes increasingly significant following the onset of cholestasis (Wikström *et al*, 2013; Martineau *et al*, 2014). Alternatively, it is possible that once cholestasis has occurred, performing glucose tolerance testing during late pregnancy should be offered. GDM complicates about 3%-14% of all pregnancies (World Health Organization, 2013). In our study, GDM rates were significantly higher than in the control group (16.1% vs. 6.4%, p=0.02). However, these patients developed ICP after being diagnosed with GDM. The result was higher than in normal pregnancies that were not complicated by ICP, but we cannot generalize this result because of our limited number of patients.

In the current study, the rate of preeclampsia was found to be significantly higher than in the control group (12.5% vs. 4.4%, p=0.02). Raz *et al*. showed in their study an increased incidence of preeclampsia among women with ICP compared with the control group (7.4% vs. 1.5%, p<0.05). They claimed that high levels of TBA might precipitate preeclampsia (Raz *et al*, 2015). The high levels of TBA may cause endothelial injury, resulting in oxidative stress. Furthermore, the accumulation of TBA in placentas leads to oxidative damage of those placentas (Perz *et al*, 2009). Wikström *et al*. demonstrated an increased incidence of preeclampsia in ICP with an adjusted OR 2.62 (Wikström *et al*, 2013).

The reasons of poor foetal outcomes in ICP are unclear; the toxic metabolites of bile acids could play a role in these problems. Currently, the hydrophilic bile acid UDCA is the most effective treatment for ICP. The other treatment modalities are S-adenosyl-L-methionine, dexamethasone and

cholestyramine. Geenes *et al*. demonstrated that total serum bile-acids were reduced by UDCA treatment. UDCA treatment resulted in significantly higher levels of unconjugated UDCA in umbilical cord vein samples when compared with umbilical cord artery samples (Geenes *et al*, 2014). In our study, we used UDCA for the treatment of maternal pruritus and improving TBA and serum transaminases. The correction in TBA and serum transaminases was seen at approximately two weeks.

It was reported that ICP frequently recurred in up to 90% of subsequent pregnancies (Williamson *et al*, 2004; Geenes *et al*, 2009).Wang *et al*. reported the recurrence rate of ICP as being 30.2% in their studies (Wang *et al*, 2007). In our study, only three (5.6%) patients had a history of ICP in their previous pregnancies. These patients had no significant differences in TBA values and gestational age from those who did not have ICP in their previous pregnancies.

The current management of ICP is induction of labour at 36-38 weeks' gestational age. In our study, we followed patients with symptoms, measured TBA and conducted NST for foetal well-being and ultrasound examination. At term, after the therapy of UDCA, the symptoms of patients, TBA and serum transaminase values were within normal ranges. All of our preterm labours occurred spontaneously. We decided to deliver according to the foetal well-being tests between 37-39 gestational weeks. The mean gestational age at delivery was 38.2±1.9 weeks in our study. After 39 gestational weeks, we did not follow up pregnancies further or enforce delivery.

Our study had several limitations. The major limitation of our study is its retrospective nature. In our clinic, we could not test routinely for TBA. If we could measure TBA values of the control group, the results would be more reliable. Furthermore, our cohort was too small as a result of the incidence of ICP.

Although there are no common criteria for diagnosing ICP, we used elevated TBA or serum transaminase levels, combined with pruritus. ICP carries an increased risk of prenatal complications. Meconium-stained amniotic fluid and oligohydramnios were the most common complications, occurring in 39.3% of the pregnancies in our study. Contrary to the reported data, we had no cases of IUFD in our study and saw no difference in preterm delivery; the mean birth was at 38.2 weeks. The incidence of ICP was found to be 0.5% in our region.

Declaration of Interest

The authors report no conflict of interest.

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