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Intrahepatic cholestasis of pregnancy — prevalence and ethnic distribution in northern Israel

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ABSTRACT

Objectives: Intrahepatic cholestasis of pregnancy (ICP) is charachterized by pruritis and elevated serum bile acids (BA) and is associated with adverse obstetrical outcomes. ICP etiology is poorly understood and its incidence varies with ethnicity and geographical distribution.

Objectives: Explore the prevalence and characteristics of ICP in the different Northern Israeli ethnic groups and compare maternal and perinatal outcomes according to disease severity.

Material and methods: Single-center retrospective study. Women who were diagnosed with ICP based on clinical presentation and elevated fasting BA (≥ 10 μmol/L) were included. Disease incidence, maternal and neonatal complications were

explored according to ethnic subgroups analysis and obstetrical complications were examined according to disease severity.

Results: The incidence of ICP in the study population was 0.58%. Higher ICP incidence was found in our cohort compared with other reports arising from Central Israel ($p < 0.001$). The Christian patients had a higher incidence of ICP (1.1%) and preeclampsia (23.1%). A higher rate of neonatal intensive care unit (NICU) admissions was found in the Arab Muslim and Christian groups compared with the Jewish and Druze groups ($p = 0.007$).
A higher rate of preeclampsia was found in the severe (BA ≥ 40 μmol/L) ICP group ($p < 0.001$). Patients in the severe ICP group had earlier gestational age at delivery (37 versus 38.14 weeks, $p < 0.001$). Birth weight was significantly lower in the severe ICP group ($p = 0.018$).

Conclusions: The incidence of ICP at our institution was 0.58%, which is higher compared with previous reported Israeli incidence. Higher ICP and preeclampsia incidence were found among Arab Christian patients.

Keywords: intrapartum cholestasis of pregnancy; ethnicity; retrospective cohort review; maternal outcome; perinatal outcome

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a cholestatic disorder characterized by pruritus with increased serum bile acids (BA) and elevated serum aminotransferases. ICP manifests in the second half of pregnancy and rapidly resolves after delivery. It is associated with increased rates of fetal morbidity and mortality. It increases the risk of preterm delivery, meconium-stained amniotic fluid and fetal distress [1, 2]. Higher total serum bile acid levels are associated with higher rates of fetal complications, and severe cholestasis is defined as bile acids over 40 μmol/L [3].

There is significant geographical and ethnical variation in the incidence of ICP which suggest a genetic predisposition. For instance, in certain areas of Chile, rates have been reported up to 22% [4], while the rates from France and the United Kingdom are less than 1% [5]. Recent studies emerging from Central Israel have

reported an incidence of 0.1–0.36% for ICP, but ethnical charataristics have not been studied before [6, 7].

Compared with Central Israel, Northern Israel consists of a widely diverse population which includes several ethnic groups with unique genetic makeup. This study was conducted in the Galilee Medical Center in Nahariya, located in Northern Israel, which serves a population of over 600,000 comprising of Jews, as well as Christian and Muslim Arabs and Druze. Our study sought to investigate the prevalence and characteristics of ICP in the different Northern ethnic populations and to compare its incidence with Central Israel. Additionally, we aimed to compare maternal and perinatal outcomes between mild and severe disease.

MATERIAL AND METHODS

Study design

We conducted a historical cohort study of women diagnosed with ICP.

Study population

Women hospitalized between April 2013 and December 2017 in the Galilee Medical Center (Nahariya, Northern Israel) with a diagnosis of ICP were included in the study group.

We excluded women without a definitive diagnosis of ICP or missing information on pregnancy outcome.

Data collection

Demographic, clinical, obstetrical and laboratory data were collected from computerized medical records and the hospital's laboratory database.

Maternal data included: age, gravidity, parity, mode of conception, multiple pregnancy, ethnicity (Jews, Arab Christian, Arab Muslim, Druze), gestational age at diagnosis and at delivery, medications, comorbidities including pre-gestational diabetes mellitus, chronic hypertension, thrombophilia and any other renal, liver or cardiac disease. Data concerning current pregnancy complications included: rates of preeclampsia (PET), oligohydramnios, polyhydramnios, premature uterine

contractions and gestational diabetes. Laboratory parameters included serum levels of alanine aminotransferase (ALT) and fasting total BA.

Data concerning the course of labor was collected: onset of labor (spontaneous/iatrogenic), gestational age at delivery, mode of delivery, rate of preterm delivery (spontaneous or iatrogenic), postpartum hemorrhage (PPH), meconium-stained amniotic fluid, non-reassuring fetal monitoring.

Neonatal data included: gender, birthweight and birthweight percentile—which was calculated according to Dolberg fetal growth calculator [8], Apgar score at 1 and 5 min, arterial umbilical cord pH, neonatal intensive care (NICU) admission, respiratory complications (respiratory distress syndrome, transient tachypnea of newborn, ventilation, respiratory support), hypoglycemia, hyperbilirubinemia, anemia and perinatal mortality. In addition, pediatric emergency department (ED) visits during the neonatal period were examined

Definitions

ICP was defined as a combination of pruritus and an increased fasting serum BA ≥ 10 μmol/L, while other causes of itching and liver dysfunction were excluded. Severe ICP was defined by fasting serum BA ≥ 40 μmol/L.

PET was diagnosed by the combination of new-onset hypertension and proteinuria after 20 weeks of gestation. Elevated blood pressure was defined as systolic blood pressure of 140 mmHg or more or diastolic blood pressure of 90 mm Hg or more on two occasions at least four hours apart and proteinuria as 300 mg protein or more per 24-hour urine collection.

Postpartum hemorrhage was defined as estimated blood loss of ≥ 500 mL in the 24 h after vaginal delivery or ≥ 1000 ml after cesarean delivery.

Spontaneous delivery versus iatrogenic: according to our local management protocol of ICP and in line with accepted guidelines, iatrogenic induction of labor was performed at 37 weeks of gestation if spontaneous delivery has not occurred and ICP was diagnosed before term.

Preterm delivery was defined as delivery < 37 gestational weeks (either spontaneous or iatrogenic).

Three types of cesarean deliveries (CD) were defined: elective CD was done for maternal or neonatal indications, without evidence for compromise of either one of them, (e.g., repeated cesarean sections) and was performed at its scheduled time. Non-elective CD was carried out for maternal or fetal indications (e.g., ruptured membranes and breech presentation) and was not performed immediately. Emergency CD was performed immediately in cases of fetal or maternal compromise.
Small for gestational age (SGA) newborn was defined as birthweight below the 10^{th} percentile according to local growth curves (Dolberg fetal growth calculator) [8].

Ethics

Approval for this retrospective cohort study was given by the local Helsinki Committee prior to the initiation of data collection, reference no. 0042-18-NHR. All procedures were in accordance with the requirements of the Declaration of Helsinki.

Statistics

Statistical analysis was conducted by the statistical department at Galilee Medical Center using SPSS software (IBM SPSS Statistics version 25.0). Continuous variables are presented as the mean ± standard deviation or as median and range. Qualitative variables are presented as Frequencies and percentages. Comparisons of continuous variables between the groups were performed with an independent sample t-test or a Mann-Whitney test (according to the sample size of the groups and the variables' distribution shape). Categorical variables were analyzed using a Pearson's chi-square test or Fisher's exact test (if expectancy < 5). The prevalence of ICP was compared with findings of previous Israeli studies using Binomial Test. A two tailed p value < 0.05 was considered statistically significant.

RESULTS

Out of a total of 25,379 deliveries during the study period, there were 148 diagnosed cases of ICP. Another 128 cases were excluded due to non-definitive diagnosis of ICP or missing information regarding pregnancy outcome.

Of the 148 ICP cases, there were 20 (13.5%) twin pregnancies. Mean maternal age was 29.5 and mean gestational age at diagnosis was 35.5 weeks.

The incidence of ICP in our study population was 0.58% (148 cases out of 25,379 deliveries).

We found a higher ICP incidence in our cohort compared with other reports arising from Central Israel (6) (0.58% compared with 0.36%, $p < 0.001$).

The clinical characteristics of our study population are presented in Table 1.

ICP incidence and outcomes according to ethnical groups

The incidence of ICP among Jewish and Druze patients was similar (0.69% and 0.62%, respectively). We found a lower ICP incidence among Muslim patients (0.4%). Compared with the other ethnic groups, the Christian patients had a higher incidence of ICP (1.1%, $p = 0.005$) (Tab. 2).

Maternal characteristics and outcomes of the different ethnical groups are shown in Table 3.

The mean maternal age at the time of diagnosis was similar in the Jewish, Christian and Muslim groups (30.37, 30.15 and 29.56 years, respectively). On the other hand, a lower maternal age of 26 years was found in the Druze group ($p = 0.012$). No difference was found in gravidity, parity, mode of conception or multiple pregnancy rates between the group. Mean fasting BA levels and ALT levels were comparable.

No difference in mean maternal age at diagnosis or at delivery was observed between the groups.

Higher incidence of PET (23.1%) was found in the Christian group compared with the other groups (3.2% Jews, 0% Arab Muslims, 3.8% Druze) ($p = 0.013$). No difference was observed in rates of oligohydramnios, polyhydramnios or gestational diabetes between the groups.

Mode of delivery and fetal gender were similar between the groups. Fetal weight was lower in the Christian group (2554.2 grams) ($p = 0.088$), but no difference was found in the SGA rates. No cases of 5-minutes Apgar less than 7 or perinatal death were found.

Higher rate of NICU admissions was found in the Arab Muslim and Christian groups (39.5% and 47.1%, respectively) compared with the Jewish and Druze groups (17.5% and 14.3%, respectively) ($p = 0.007$).

Preterm delivery (whether iatrogenic or spontaneous), PPH, meconium-stained amniotic fluid and non-reassuring fetal monitoring rates were not different between the four ethnic groups.

Obstetrical outcome according to the ICP severity

According to fasting BA levels (mild, fasting BA < 40 μmol/L and severe, BA ≥ 40 μmol/L) a subgroup analysis was performed. One hundred seven patients consisted the mild group, while 41 patients had severe ICP (Tab. 4).

Median ALT was significantly higher in the severe group compared with the mild group (79 versus 22 U/L, $p < 0.001$). A higher rate of PET was found in the severe group (14.6% versus 0%, $p < 0.001$). No difference was observed in rates of oligohydramnios, polyhydramnios or gestational diabetes between the groups.

Although not statistically significant, the median age at diagnosis was earlier in the severe ICP group (35.85 versus 36.85 weeks, $p = 0.095$). In addition, earlier gestational age at delivery was found in the severe group compared with the mild group (37 versus 38.14 weeks, $p < 0.001$). Although the mode of delivery was comparable between the two groups, a higher rate of induced vaginal delivery was found in the mild group (84.8% versus 64%, $p = 0.01$). Higher rates of iatrogenic preterm deliveries and meconium-stained amniotic fluid were found in the severe ICP group.

Birth weight was significantly lower in the severe ICP group (2689.72 versus 2945.2 grams, $p = 0.018$).

No correlation was found between ICP severity and neonatal emergency department (ED) visits during the neonatal period.

DISCUSSION

We found a higher ICP incidence in our cohort compared with other reports arising from the center of Israel (0.58% compared with 0.36%, $p < 0.001$) [6]. Furthermore, among our ethnically heterogenous study population, a higher ICP incidence was found in the Arab Christian group (1.11%) and a lower incidence in the Arab Muslim group (0.4%) compared with the Jewish (0.69%) and Druze (0.62%) groups.

The exact pathogenesis of ICP is not known, but likely involves genetic, hormonal, immunological and environmental factors. Previous Israeli studies on ICP were conducted in Rabin Medical Center in Petach-Tikva [6] and Sourasky Medical Center in Tel Aviv [7], both located in Central Israel and ethnical differences were not explored. We believe that unlike our cohort (which consisted of over 50% non-Jewish patients), and according to the demographics of Central Israel, the vast majority of Raz and Mor cohorts [6, 7] consisted of Jews. Our findings could be explained by the diverse genetic backgrounds of the different ethnic groups, although other factors such lifestyle factors may play a role and cannot be ruled out.

Inter-group comparison reveals a significantly lower maternal age at ICP diagnosis in the Druze group (mean age of 26 years) compared with the other groups. The Druze maternal average age at birth according to the Israeli Central Bureau of statistics is 28.5–29.5 years during the years 2013–2018 [9]. This finding raises the questions of whether Druze patients might suffer from ICP at an earlier maternal age and whether patient age affect ICP incidence. Others have reported that ICP is more prevalent in older women [10].

We found a significantly higher PET rate in the Arab Christian group (23.11%) compared with others, and a trend toward a lower gestational age at diagnosis and a lower birthweight. Previous studies have reported that ICP is associated with an increased risk for PET, and earlier diagnosis of ICP was associated with higher incidence of PET [6]. Recent study found that early-onset ICP is associated with a lower birth weight than late-onset ICP [11].

In line with earlier research [12], we found a higher GDM prevalence in our study cohort (14.9%) compared with a recent Israeli report of 3.9% [13]. In animal modality studies BA was demonstrated to take part in glucose and lipid metabolism

[14]. FXR, a primary BA receptor, has a regulatory role in both the glucose and cholesterol homeostasis [15].

More neonates in the Arab Christian and Muslim groups have been admitted to NICU which may be explained in part by the lower birth weight in the Arab Christian group and higher GDM rate in the Arab Muslim group.

In addition, a comparison was made between severe and mild ICP based on BA levels as mentioned earlier in the methods section. In the severe group, ICP diagnosis was made at an earlier gestational age. Previous study reported a trend for less severe BA levels when the ICP diagnosis was made closer to term [16]. Although it has been speculated that pruritis is a result of bile acids accumulation in the interstitial fluid of the skin and higher BA levels may lead to an earlier diagnosis, former studies have not found a correlation between pruritis and BA levels. Furthermore, some studies have reported that pruritus might precede the onset of biochemical abnormalities [17].

We found an elevated PET rate and meconium-stained amniotic fluid in the severe ICP group. In addition, the lower birthweight in this group might be attributed to the earlier gestational age at delivery; those findings are consistent with previous studies [6].

Strengths and limitations

To our knowledge, this is the first Israeli study exploring ICP incidence and characteristics in the different Israeli ethnical groups. Another strength of our study lies in it being a single-center study, with a uniform practice, treatment and clinical care. Furthermore, cases which were included followed strict criteria for ICP diagnosis, as only cases with pruritis and elevated fasting BA levels. Other etiologies had been excluded through carefully taken history and comprehensive physical examination while upper abdomen sonography was performed if needed. Despite the retrospective study nature, maternal and neonatal outcomes are well documented.

Our study is not without its limitations, foremost, due to its retrospective design and small cohort size, while confounding bias is impossible to eliminate. In addition, data on the Jewish ethnical subgroups (e.g., Ashkenazi, Northern Africa origins) was unavailable.

CONCLUSIONS

In conclusion, we found a higher ICP prevalence in our Northern Israeli cohort compared with previous reports from Central Israel, a higher ICP incidence among Arab Christian patients and a lower incidence in the Arab Muslim group. In line with previous studies, severe ICP is associated with certain pregnancy complications.

Further research is required to investigate reasons for the increased incidence of ICP in certain ethnical groups and to explore mechanisms responsible for the association between ICP, GDM and PET.

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Table 1. Clinical characteristics of the general study population

ICP cases (N = 148)			
Pregnancy complications, n (%)	Gestational diabetes		21 (14.1)
	Polyhydramnios		9 (6.1)
	Oligohydramnios		3 (2)
	Preeclampsia		6 (4.1)
Gestational age at delivery, weeks, mean (± SD)			37.5 ± 2.1
Mode of delivery, n (%)	Vaginal delivery (n= 84)	Spontaneous	16 (10.8)
		Induced	66 (44.6)
		Instrumental	2 (1.4)
	Cesarean delivery (n = 64)	Elective	11 (7.4)
		None-elective	15 (10.1)
		Emergency	38 (25.7)
Birthweight, grams, mean (± SD)			2873.7 ± 630.8
Labor related complications, n (%)	Iatrogenic preterm delivery		27 (18.2)
	Spontaneous preterm delivery		9 (6.0)
	Non-reassuring fetal monitoring		20 (1)

	Meconium-stained amniotic fluid	15 (10.1)
	PPH	8 (5.4)
Newborn related complications, n (%)	5-min Apgar < 7	0 (0)
	Cord around the neck	8 (4.8)
	True knot of cord	2 (1.2)
	Respiratory morbidity	16 (10.1)
	SGA	2 (1.2)
	NICU admission	42 (26.6)
	Hypoglycemia	1 (0.6)
	Hyperbilirubinemia	99 (62.7)
	Anemia	12 (7.6)

ICP — intrahepatic cholestasis of pregnancy; PPH — postpartum hemorrhage; SGA — small for gestational age; NICU — neonatal intensive care unit

Table 2. ICP incidence according to ethnical groups

	Pregnancies diagnosed with ICP	Total no. of deliveries in the Galilee Medical Center	Incidence of ICP (%)
Jew, n (%)	62 (41.9)	8890 (35.0)	0.69
Arab Muslims, n (%)	41 (27.7)	10,095 (39.7)	0.4
Arab Christians, n (%)	26 (17.6)	4175 (16.4)	1.11
Druze, n (%)	13 (8.8)	1167 (4.5)	0.62
Missing data on ethnicity	6 (4.0)	1052 (4.1)	0.57
Total	**148**	**25,379**	**0.58**

Table 3. Maternal characteristics, obstetrical and neonatal outcomes of the different ethnical groups

	Jews (N = 62)	Arab Muslims (N = 41)	Druze (N = 26)	Arab Christians (N = 13)	P value
Maternal age, years,	30.3 ± 5.6	29.5 ± 6.5	26 ± 4.2	30.1 ± 5.5	0.01

mean (± SD)					
Bile acids, mean (range)	16.3 (10.2–149.2)	17.6 (10–160.5)	21.8 (10.1–114.1)	23.2 (11–184.8)	0.54
ALT, mean (range)	24 (6–619)	48 (6–339)	34.5 (6–200.4)	121 (6–330)	0.16
GA at diagnosis, weeks, mean (range)	37 (27.8–40.2)	36.4 (25.2–40.2)	35.2 (25–41.2)	33.8 (30.2–40.1)	0.18
Preeclampsia	3.2 (2)	0 (0)	3.8 (1)	3 (23.1)	0.013
GA at delivery, weeks, mean (± SD)	37.7 (28.2–41.2)	37.7 (29.4–40.5)	38.4 (32.1–41.4)	37 (32.5–40.4)	0.17
Mode of delivery					
Vaginal delivery, % (n)	50 (31)	63.4 (26)	69.2 (18)	53.8 (7)	0.68
Spontaneous	19.4 (6)	15.4 (4)	27.8 (5)	14.3 (1)	
Induced	80.7 (25)	76.9 (20)	72.2 (13)	85.7 (6)	
Instrumental	0 (0)	7.7 (2)	0 (0)	0 (0)	
Cesarean delivery, % (n)	50 (31)	36.6 (15)	30.7 (8)	46.1 (6)	0.97
Elective	19.4 (6)	20 (3)	12.5 (1)	0 (0)	
Non-elective	25.8 (8)	20 (3)	25 (2)	33.3 (2)	
Emergency	54.8 (17)	60 (9)	62.5 (5)	66.7 (4)	
Birthweight, grams, mean (±SD)	2974.9 ± 576.6	2805.2 ± 727.3	2864.1 ± 637.0	2554.2 ± 476.7	0.08
Labor-related complications, % (n)					
Iatrogenic preterm delivery	16.1 (10)	14.6 (6)	19.2 (5)	38.5 (5)	0.27
Spontaneous preterm delivery	32. (2)	7.3 (3)	11.5 (3)	7.7 (1)	0.37
PPH	6.5 (4)	7.3 (3)	0 (0)	15.4 (2)	0.54
Meconium-stained amniotic fluid	4.8 (3)	14.6 (6)	19.2 (5)	5.9 (1)	0.11
Non-reassuring fetal monitoring	13.4 (9)	15.2 (7)	10 (3)	5.9 (1)	0.82
Newborn related complications, % (n)					
Respiratory morbidity	9.5 (6)	11.6 (5)	10.7 (3)	11.8 (2)	0.96
SGA	0 (0)	2.1 (1)	3.3 (1)	0 (0)	0.42
NICU admission	17.5 (11)	39.5 (17)	14.3 (4)	47.1 (8)	0.007
5-min Apgar < 7	0 (0)	0 (0)	0 (0)	0 (0)	
Perinatal death, % (n)	0 (0)	0 (0)	0 (0)	0 (0)	

ALT — alanine aminotransferase; GA — gestational age; PPH — postpartum hemorrhage; SGA — small for gestational age; NICU — neonatal intensive care unit

Table 4. Maternal characteristics, obstetrical and neonatal outcomes of the mild and severe ICP groups

	Mild ICP (N = 107)	Severe ICP (N = 41)	P value

Maternal age, years, mean (± SD)	29.4 ± 5.6	29.8 ± 6.3	0.69
Ethnicity, % (n)			
Jews	79 (49)	21 (13)	0.21
Arab Muslims	63.4 (26)	36.6 (15)	
Druze	73.1 (19)	26.9 (7)	
Arab Christians	61.5 (8)	38.5 (5)	
Bile acids, mean (range)	14.8 (10–36)	71.9 (41–184.8)	–
ALT, mean (range)	22 (6–313)	79 (6–619)	< 0.001
GA at diagnosis, weeks, mean (range)	36.8 (25–41.2)	35.8 (29.4–39.7)	0.09
Preeclampsia	0 (0)	14.6 (6)	< 0.001
GA at delivery, weeks, mean (± SD)	38.1 (28.2–41.4)	37 (32.1–40.1)	< 0.001
Mode of delivery			
Vaginal delivery, % (n)	55.1 (59)	60.9 (25)	0.01
Spontaneous	13.6 (8)	32 (8)	
Induced	84.8 (50)	64 (16)	
Instrumental	1.7 (1)	4 (1)	
Cesarean delivery, % (n)	44.8 (48)	39.0 (16)	0.71
Elective	18.8 (9)	12.5 (2)	
Non-elective	20.8 (10)	31.3 (5)	
Emergency	60.4 (29)	56.3 (9)	
Birthweight, grams, mean (± SD)	2945.2 ± 657	2689 ± 520.4	0.018
Labor-related complications, % (n)			
Iatrogenic preterm delivery	15.9 (17)	24.4 (10)	0.24
Spontaneous preterm delivery	3.7 (4)	12.2 (5)	0.11
PPH	4.7 (5)	7.3 (3)	0.68
Meconium-stained amniotic fluid	7.5 (8)	19.5 (8)	0.07
Non-reassuring fetal monitoring	11.7 (14)	12.8 (6)	1.0
Newborn related complications, % (n)			
Respiratory morbidity	12.5 (14)	4.3 (2)	0.15
SGA	0.8 (1)	2.1 (1)	0.48
NICU admission	24.1 (27)	32.6 (15)	0.32

ALT — alanine aminotransferase; GA — gestational age; PPH — postpartum hemorrhage; SGA — small for gestational age; NICU — neonatal intensive care unit