

Intrahepatic Cholestasis of Pregnancy: Evaluation of Risk Factors and Predictive Factors.

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Abstract

Intrahepatic cholestasis of pregnancy (ICP) is a low prevalence pathology associated with premature delivery and fetal death. Objective: To determine risk factors, clinical course and predictive factors in a cohort of ICP patients. Methods: A retrospective cohort study was performed. There were studied fifty patients with ICP and 51 healthy women.

Results: ICP was more frequently found in multiparous, multiple pregnancies and ICP antecedent. Women with ICP had a greater incidence of premature delivery (76.0%, $p=0.001$). Meconium-stained amniotic fluid was more frequent in ICP women ($p=0.002$). The newborns showed differences in weight, size and gestational age, attributable to the difference in gestational age at birth. Conclusions: Advanced maternal age, multiparity, antecedent ICP and multiple pregnancies increase the risk of ICP. The consequences of ICP might be premature delivery and meconium-stained amniotic fluid at delivery

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is an illness exclusive to gestation and characterized by pruritus, elevated liver enzymes/bile salts with or without hyperbilirubinemia, without accompanying chronic hepatic damage. which resolves spontaneously at puerperium^{1, 2}. Clinically it is characterized as a cholestatic syndrome with pruritus of the palms and soles. There are some studies which associate it with adverse perinatal results such as chorioamnionitis, premature delivery and fetal death^{3,4,5}. It is not a common illness, and higher prevalence has been reported in Chile and in Scandinavian countries¹. The Latino population in Los Angeles, California in the United States⁶ has a reported prevalence of 5.6%; in Mexico, the prevalence is unknown.

The objectives of this study were to identify the principal risk factors associated with the development of ICP, to describe the clinical course and to describe the predictive factors for development of IPC.

MATERIAL AND METHODS

A retrospective cohort study was undertaken; the study was approved from Institutional Review Board. Fifty pregnant women with IPC treated at the National Institute of Perinatology ““Isidro Espinoza de los Reyes”” (INPerIER), Mexico in the period between January of 1999 to December of 2007 were included. The IPC diagnosis was made with

the appearance of pruritus, predominantly on the palms and soles, hyperbilirubinemia with or without elevated serum hepatic enzymes, and the elimination of other potential causes of cholestasis using abdominal ultrasonography, viral profile for hepatitis and cessation of the ingestion of hepatotoxic^{1,7} pharmaceuticals. A comparison cohort was selected, which included pregnant women with neither hepatobiliary nor hypertensive illness associated with pregnancy.

Demographic characteristics were analyzed, as well as the clinical course of women complicated with IPC. Variables were identified with the goal of determining risk factors for the development of IPC and the influence of IPC as a predictive factor for perinatal complications.

Descriptive statistics were used to characterize the population, the chi-squared test to compare the dichotomous variables and the Student's t-test for quantitative variables. Risk calculation and prediction were determined via relative risk, with a 95% confidence interval. Statistical analysis was performed using SPSS statistics 16.

RESULTS

During the study, 50 patients with ICP were treated at INPerIER, and an incidence of 1 case per 1000 pregnancies was observed. In the comparison cohort, 51 patients were included.

On average, the diagnosis of ICP was established at 29.2 ±6.3 weeks of gestation, and all of the patients had pruritus in palms and soles.

Significant differences were found in groups about antecedent of fetal death (p=0.05) and cholestasis during a previous pregnancy (p=0.01), even though the relative risk was not statistically significant.

Older ICP cohort patients more frequently had multiple pregnancies (p=0.002) and were multigravid (p=0.003) (Table I). Women with ICP had a greater incidence of premature delivery, 76.0% versus 3.9% (p=0.001), and greater presence of meconium-stained amniotic fluid. (Table II)

Figure 1

Table 1: Characteristics of study groups

	With ICP n=50		Without ICP n= 51		
	Average		Average		P
Age (Years old)	29.2±6.8		24.6±7.7		0.002*
BMI (kg/m)	26.3±3.2		26.5±4.1		0.755†
Start of ICP (Weeks)	18.2±8.3		21.5±11.5		0.103*
Resolution (weeks)	35±2.3		38.3±1.4		0.001*
	N	(%)	N	(%)	P
Fetal death antecedent	6	12	1	2	0.053‡
ICP's antecedent	6	12	0	0	0.013‡
Multiple pregnancy	7	14	1	2	0.028‡
Multiple gestation	37	74	13	44	0.003‡

ICP: Intrahepatic Cholestasis of Pregnancy. BMI: Body mass index.

* Mann-Whitney U test, † Student's t-test, ‡ chi-square.

Figure 2

Table 2: Comparison of perinatal outcomes. * chi-square

	With ICP n=50		Without ICP n=51		
	N	%	N	%	P*
APP	5	10	0	0	0.05
Chorio-amnionic	1	2	0	0	0.405
Fetal death	2	4	0	0	0.243
Meconium liquor.	8	16	0	0	0.002
Preeclampsia	1	2	1	1.96	0.748

In women with pregnancies complicated by ICP, the average gestational age at pregnancy resolution was 35 ± 2.3 weeks,

while in pregnant women without ICP pregnancy resolution occurred at 38.3 ±1.4 weeks gestational age (p=0.01). Caesarean section was used in 94% of the ICP patients and 50% of the pregnant patients in the control cohort (p=0.001).

Neonates of ICP mothers had an average weight of 2381±533 g, while children of mothers in the control cohort had an average weight of 3118±470 g (p>0.001). The gestational age and size were statistically lower in neonates born to women with pregnancies complicated by ICP. For the analysis of these three variables, multiple pregnancies were excluded (Table III). However, the minute and five minute Apgar scores did not differ between the cohorts. Of the children of ICP mothers, 18% had a Silverman-Anderson evaluation with a major score of 3, versus only 2% of the children born to the women in the comparison cohort (p=0.003).

Figure 3

Table 3: Characteristics of the neonates at birth. * Mann-Whitney U test, † chi-square.

	With ICP n=43		Without ICP n=50		
	Average		Average		P
Weight(g)	2381±533		3117±470		0.001*
Size (cm)	45.6±3.4		49.6±3.3		0.001*
Gestational age (weeks)	35.3±5.6		38.6±1.2		0.001*
	N	%	n	%	
Women (n)	18	41.9	25	58.1	0.532†

DISCUSSION

ICP is considered to be a pathology exclusive to gestation, associated with some adverse perinatal effects and with variable prevalence among different locations. We noted an incidence of 1 of 1000 newborns, which is considerably lower in comparison with figures reported in other countries;^{1,6}

For this study we selected the studied cases in such a way that we did not detect a difference in variables such as body mass index, the weeks when prenatal control began and the number of previous gestations. Important differences in age and in the presence of a multiple pregnancy, characteristics that had been already reported in the literature,⁶ must focus our attention on the multiple pregnancy group.

Patients with ICP presented more often with preterm labor, which correlates with previous studies reporting a higher frequency of preterm labor but lacking adequate empirical evidence to support the relationship. On average, patients

with ICP delivered at 35 weeks. For the analysis of this variable, multiple pregnancies were excluded. It is important to note that the majority of early deliveries were elective based on ICP's role as a risk factor for fetal death, which influenced the study variables linked with gestational age at delivery

Concerning the clinical presentation of ICP, 100% of the pregnant women with this complication showed the characteristic pruritus.

An official protocol for achieving resolution of ICP has not been established. There is currently no consensus regarding the optimal age to initiate delivery in pregnant women with ICP.^{6, 8, 9, 10, 11, 12, 13} In our population, there was a high frequency of elective cesarean sections, which limited our knowledge of the disease's evolution.

We did not find differences in the presence of chorioamnionitis and fetal death as reported by other groups.^{3,4} Nevertheless, the number of cases in our study was limited in comparison with other series. Both cases that presented with fetal death were singleton pregnancies. ICP diagnosis was established in the second trimester of pregnancy (26 weeks) and both patients received ursodeoxycholic acid treatment.

We found a higher frequency of meconium-stained amniotic fluid in patients with ICP, but this had no relationship with the average Apgar score or with complications at delivery. In concordance with the lower gestational age of children born to women with ICP, their weight, size and gestational age were below average. Nevertheless, in this study, it is not possible to conclude that there is a causal relationship between maternal illness and these variables. We conclude that conditions that should alert doctors to the possible presence of ICP in pregnant women include: age of 35 years old or older, having had multiple pregnancies, having had ICP during a previous pregnancy, and multiparity.

Our study also demonstrates that ICP is associated with the development of preterm labor and therefore with newborns who weigh less, are smaller and have a lower grade in Apgar test, Silverman-Anderson test and weight.

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