Body mass index implications in intrahepatic cholestasis of pregnancy and placental histopathological alterations

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Abstract

Introduction and objectives: Intrahepatic cholestasis is a frequent disease during pregnancy. It is unknown if liver function alterations produce specific placental lesions. The aim of this study was to evaluate placental histopathological changes in patients with intrahepatic cholestasis of pregnancy (ICP), and to explore correlations between the placental histopathology and hepatic function alteration or patient comorbidities, and body mass index.

Patients and methods: A retrospective cohort study included women with ICP, most of them showing comorbidities such as overweight/obesity, preeclampsia, and gestational diabetes. They were attended at the National Institute of Perinatology in Mexico City for three years. Placental histopathological alterations were evaluated according to the Amsterdam Placental Workshop Group Consensus Statement. Data was analyzed using Graph-Pad Prism 5.

Results: The results indicated that the placenta of ICP patients showed many histopathological alterations; however, no correlations were observed between the increase in bile acids or liver functional parameters and specific placental lesions. The most frequent comorbidities found in ICP patients were obesity, overweight, and preeclampsia. Surprisingly, high percentage of ICP patients did not respond to UDA treatment independently of the BMI group to which they belonged.

Conclusion: The data suggest that ICP contribute to placental lesions. In addition, in patients with normal weight, an increase of chorangiosis and a reduced accelerated villous maturation without syncytial knots were observed in comparison with overweight and obese patients. It is necessary to improve the medical strategies in the treatment and liver dysfunction surveillance of ICP patients.

1. Introduction

Intrahepatic Cholestasis (ICP) is one of the most frequent hepatopathies during pregnancy; it occurs in the second/third trimester and resolves for the mother after delivery. However, for the fetus it can lead to increased risks, such as respiratory distress syndrome, preterm delivery, stillbirth or even intrauterine death by asphyxia [1,2]. ICP is defined by the presence of nocturnal palmo-plantar pruritus, elevation of maternal serum total bile acids (TBA), >10 µmol/L, and could be accompanied by increased liver enzymes and bilirubin levels indicating liver dysfunction [3]. ICP has a prevalence of <1% to 27% of pregnancies around the world, its prevalence is high in Latin America.
being up to 5 - 27% in Chile [2,4]; however, in Mexico, it has not been
determined [1].

The main risk factors for ICP are maternal age >35 years, history of
biliary pathology, or ICP in previous pregnancies, diabetes mellitus,
viral hepatitis B or C, tobacco use, multiple pregnancies and use of
assisted reproductive technology [5,6]. Overweight and obesity are
well-known risk factors for several pregnancy-related complications
as gestational diabetes mellitus (GDM) or preeclampsia (PE) [7].
However, research about the implications of maternal body mass
index (BMI), in particular obesity, on the development of ICP is scarce,
and the reported data are inconclusive [7,8].

ICP is caused by an alteration of liver function due to the elevation
and accumulation of bile acids (BA), and as a consequence, their ele-
vation in maternal serum. They are inherently cytotoxic and thus
their metabolite is tightly regulated. In ICP the transport of bile salts
from the liver to gallbladder is dysregulated and there is a compensatory
transport of bile salts of the hepatocytes on to the blood [9].

The etiology of ICP is multifactorial, with the participation of genetic,
hormonal, immunological and environmental factors, such as genetic
variants of bile acids transporter proteins; an elevated estradiol and sul-
fated metabolites of progesterone that modifies the estradiol-bile acid
axis [4,10]. Immunological modifications are primary to cholestasis
because ICP is an inflammatory disorder. Impairment of immune function
may destroy the immune microenvironment of pregnant women, lead-
ing to various pathological reactions as a response of T helper cells with
an increase of cytokines as tumor necrosis factor alpha (TNF-α) [10,11].

TNF-α is important in the growth of the fetus and placenta but can
be lethal when it is expressed in very high levels. In ICP, the significant
increase comes from placenta production. These changes are related
to down regulation of bile salt export pump and trophoblast apopto-

The placenta is an important and understudied organ in ICP, and
impairment of feto-maternal transport and lesions in the placental
structure have been reported, bile acids also induced vasoconstriction
[12] and increased cell apoptosis and intracellular edema due of
decreased cell surface death receptor ligand (FASL) expression and
increased of the receptor (FAS) in syncytiotrophoblast, induced by
TNF-α and interferon gamma (IFN-γ) [11]. Comparison of placental
lesions between patients with ICP and healthy patients has been per-
formed in previous studies, but no statistically significant differences
were found [12,13]. However, Geenes, et. al., identified small chori-
onic villi for gestational age, dense fibrotic stroma, congestion of the
villi and an increased number of syncytiot knots, which were repro-
duced in an in vitro model of liver cholestasis [14].

The aim of this study was to assess histopathological features of
placentas of women diagnosed with ICP, and to determine if specific
lesions are associated with liver function alterations or with the
comorbidities present in ICP women, particularly in relation to over-
weigh and obesity.

2. Material and methods

2.1. Study Design

A retrospective cohort study was performed that included 105
patients diagnosed with ICP at the Instituto Nacional de Perinatolo-
gia, Isidro Espinosa de los Reyes in Mexico City, in a period of three
years (2018-2021). Patients with diagnosis of ICP with single or
twin pregnancies were included. The electronic medical records of
the selected patients were consulted for the elaboration of a materi-

dal database. Since all patients with ICP seen in the period 2018-2021
were selected, patients with comorbidities such as obesity, pre-
eclampsia (PE), gestational diabetes (GD), among others, were not
excluded. The diagnosis of ICP was based on the following maternal
findings: palmar or plantar pruritus, serum total bile acids levels >10
µmol/L or altered liver function profile.

After delivery, placentas were collected and transferred to the
hospital Pathology service for macroscopic evaluation. Ten aleatory
samples were taken of each placenta for formalin fixation and para-
fin embedding or were frozen to obtain specimens for histopatholog-
ical analysis, according to the standard procedures established in our
institution. The specimens were analyzed in a double-blind study by
two expert pathologists and placental lesions were classified accord-
ing to the Amsterdam Placental Workshop Group Consensus State-
ment (APWGS) for sampling and definitions of placental lesions [15]
and the recommendations made by Slack and Parra Herran [16].

2.2. Statistical analysis

The data obtained were collected in Excel 2016 and Prism Graph-
Pad 5.0 statistical software (GraphPad Software, LLC, CA, USA.) was
used for the analysis.
All data were tested for normality. Normally distributed continuous
variables are presented as mean ± standard deviation (SD) and
categorical variables are presented as a percentage.

2.3. Ethical statement

This study was approved by the National Institute of Perinatology,
Institutional Review Board. The dataset was obtained from the Medi-

cal Records platform available for clinicians and researchers of the
institution.

3. Results

3.1. Study population characteristics

A total of 105 medical records were analyzed. The main clinical
data of the women with ICP are depicted in Table 1. All laboratory
parameters for liver functional evaluation, description of each patient
clinical data, including their comorbidities, and the placental histo-
pathological data are summarized in the supplementary material.
The length of pregnancies in women with ICP was 36.41±2.31
weeks. Out of all the patients 89.52% had a cesarean section delivery
and 10.47 % had vaginal delivery. However, 50.47 % of the pregnan-
cies resolved by cesarian delivery were premature (29-36.6 weeks of
gestation) (Table 1).

3.2. Placental histopathological analysis

The analysis showed several histomorphological abnormalities in
all placentas, except one, which were classified according to the

Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>29.71 ± 6.4</td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First</td>
<td>50 (47.61%)</td>
<td></td>
</tr>
<tr>
<td>Second</td>
<td>30 (28.57%)</td>
<td></td>
</tr>
<tr>
<td>Third or more</td>
<td>40 (38.00%)</td>
<td></td>
</tr>
<tr>
<td>Pregnancy and delivery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy length (weeks)</td>
<td>36.41 ± 2.31</td>
<td></td>
</tr>
<tr>
<td>Prematurity &lt;37 weeks (29-36.6 weeks)</td>
<td>53 (50.47%)</td>
<td></td>
</tr>
<tr>
<td>Singleton pregnancy</td>
<td>91 (86.66%)</td>
<td></td>
</tr>
<tr>
<td>Twin pregnancy</td>
<td>14 (13.33%)</td>
<td></td>
</tr>
<tr>
<td>Vaginal delivery</td>
<td>11 (10.47%)</td>
<td></td>
</tr>
<tr>
<td>Cesarian section</td>
<td>94 (89.52%)</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation or n (proportion).
N=105 pregnant women.
criteria established by the APWGCS and reported in Table 2, that summarizes the type of lesions founded and their frequencies. In regard to the general placental characteristics, 36.27% were hypertrophic and 19.61% had hypoplasia. The most frequent lesions observed in placentas of ICP patients were those related with maternal vascular malperfusion (MVM), including accelerated villous maturation (AVM) with increased syncytiotrophoblastic knots, and decidual arteriopathy (DA); related with fetal vascular malperfusion (FVM) intervillous fibrin (IF), and others as delayed villous maturation (DVM), and chorangiosis, all with frequencies upper than 20% (Table 2). We did not find any correlations between specific placental lesions and bile acid levels or altered liver function.

3.3. Analyses by body mass index

In Table 3, comorbidities, response to treatment, hepatic function alterations and placental characteristics are shown by groups based on BMI. Obesity was present in 38.1%, 22.85% had overweight, and 7.61% were underweight. Additionally, 48.57% of the patients had comorbidities, the most frequent were PE (17.14%), GDM (7.61%), T2 diabetes mellitus (DM2) (4.76%), and other hepatopathies (19.04%).

In all patients, the clinical diagnostic was performed by medical history and corroborated with determinations of maternal serum TBA and liver function tests including aspartic-aminotransferase (AST), alanine-aminotransferase (ALT) and gammaglutamyl-transferase (GGT) (Table 3 and supplementary material). In patients with ICP in whom GGT was evaluated, more than 80% had elevated values of this enzyme, regardless of the BMI group to which they belonged (Table 3).

Eighty-seven patients were treated with ursodeoxycholic acid (UDA), eleven patients with difficult control required treatment with UDA plus rifampicin and seven required emergency surgical resolution of the pregnancy. Analyzing the TBA values in serial determinations, a high percentage of patients did not respond to the treatment with UDA, independently of the BMI group to which they belonged (Table 3).

There was not association between comorbidities with placental lesions by BMI groups; however, patients with normal weight showed an increase of chorangiosis and a reduced AVM without syncytiotrophoblastic knots in comparison with overweight and obese patients (Table 3).

4. Discussion

Preterm delivery and cesarean resolution of pregnancy have been previously associated with intrahepatic cholestasis, but not with overweight and obesity. The present study support and extend these observations [7,8]. More than 50% of ICP women had preterm delivery, which could be explained by the therapeutic indication to avoid increased risk of stillbirth in ICP patients. Indeed, the induction of labor is often recommended at 37 weeks of gestation to balance the risk of iatrogenic preterm delivery against the risk of fetal mortality [3,4,18]. Besides, there is a markedly increased risk of stillbirth when bile acid levels are ≥100 μmol/L [3,17] and delivery in these cases may be considered at an earlier gestational age, such as 35 to 37 weeks; however, these decisions should be individualized with careful patient counseling [3,5,18].

Previous study showed that placentas of ICP patients present morphological alterations such as increased terminal villous and capillary surface area, and number of syncytiotrophoblastic knots [17]. In addition to the lesions reported in that study, we also found decidual arteriopathy, intervillous fibrin, delayed villous maturation and chorangiosis as the most frequent lesions in placentas of ICP patients, probably due to the different methodology employed for the analysis. Interestingly, chorangiosis was more frequent and AVM without ISK was reduced in ICP patients with normal weight (Table 3).

In our cohort study 70% of the patient presented body weight alterations and 48.47% had other comorbidities as PE, GDM or hepatic alterations (Table 3). Overweight and obesity have not been directly associated with intrahepatic cholestasis [7]; however, we could not exclude a direct effect of metabolic changes generating ICP as has been reported for gestational diabetes or preeclampsia [7], and recently, with a ICP direct linear increment with BMI [8,19]. The obesity prevalence in Mexican women has increased dramatically by 30.6%, from 2000 to 2018; thus presently, more than 75% of women on reproductive age have a BMI above 25 kg/m², and the number of women who are expected to have obesity (BMI ≥ 30 kg/m²) when they become pregnant is unknown, but near 36% of women between 20 to 50 years old exhibit obesity [20]. However, in the present study patients with obesity (38.1%) correspond to the expect frequency of the obese women, and whether obesity may contribute directly to the development of ICP deserves to be further explored. Nevertheless, its effect in the development of PE, GDM and other hepatopathies is clearly appreciated in the group of the obese women as 67.5% showed comorbidities (Table 3).

Previous studies performed with placental explants from ICP patients and in rodent models, have shown that the excess of BA produces vasoconstriction with a consequently decreasing volume of blood flow, generating a hypoxic environment that directly affects the structure of the placenta, being AVM with ISK the most representative lesions [14]. In our study, we did not find any association between BA increased levels and placental lesions; however, AVM with ISK was the most frequent lesion in our ICP cohort, although more studies are needed to correlate these findings with TBA levels.

It has been reported that in ICP the activation of endoplasmic reticulum stress (ERS), enhanced apoptosis of the trophoblasts in the placenta and deoxycholic acid can induce a significant increase in the expressions of ERS markers, thus leading to trophoblasts apoptosis, suggesting that this ERS-induced phenomena may play a key role in the development of ICP [21].

Many other histopathological alterations in the placenta were observed in patients with ICP, as is depicted in Table 2. However,
and more frequently, with metabolic diseases such as GDM and those at high altitudes. These lesions have not been associated previously with pregnancy weight gain, maybe due to a more efficient compensatory mechanism as has been reported for pregnancies with obesity, GDM, DM1 and DM2. However, chorangiosis has not been previously reported as characterizing ICP patients. In this study reported a relation of ICP with placental lesions. Here, we demonstrated that other type of lesions might be present in placentas of patients with ICP. In this study, increased levels of bile acids and liver enzymes did not correlate with specific placental damage. Interestingly, chorangiosis and AVM without ISK were increased and reduced respectively in ICP patients with normal weight in contrast with obese and overweight patients. Thus, this study supports and extends the idea that ICP might be related to placental lesions, although further studies are needed to determine if there is an association between ICP and specific placental lesions. Regarding the treatment of ICP with UDA, additional therapeutic strategies should be considered, since it was observed that a reduced number of patients responded to UDA treatment.

6. Author contributions

All authors have made substantial contributions as follows: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) all authors gave their approval for the final submitted version.

5. Conclusions

Studies related to placental histopathology during ICP, are scarce, and to the best of our knowledge, only one previous, non-recent study reported a relation of ICP with placental lesions. Here, we demonstrated that other type of lesions might be present in placentas of patients with ICP. In this study, increased levels of bile acids and liver enzymes did not correlate with specific placental damage. Interestingly, chorangiosis and AVM without ISK were increased and reduced respectively in ICP patients with normal weight in contrast with obese and overweight patients. Thus, this study supports and extends the idea that ICP might be related to placental lesions, although further studies are needed to determine if there is an association between ICP and specific placental lesions. Regarding the treatment of ICP with UDA, additional therapeutic strategies should be considered, since it was observed that a reduced number of patients responded to UDA treatment.
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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.aohep.2022.100879.

References


