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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 UDCA 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 disfunction surveillance of ICP patients.

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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,

Abbreviations: ALT, alanine aminotransferase; APWGCS, Amsterdam Placental Workshop Group Consensus Statement; ASP, aspartic aminotransferase; AVM, Acelerated Villous Maturation; BA, bile acids; BMI, body mass index; DA, Decidual Arteriopathy; DM2, Diabetes Mellitus type 2; DVM, Delayed Villous Maturation; ERS, Endoplasmic reticulum stress; FAS, cell surface death receptor; FASL, FAS ligand; GDM, Gestational Diabetes Mellitus; GGT, gammaglutamyl transferase; ICP, intrahepatic cholestasis of pregnancy; IF, Intervillous Fibrin; IFN-γ, Interferon gamma; ISK, Increased Syncytial Knots; PE, preeclampsia; TBA, total serum bile acids; TNF-α, tumor necrosis factor alfa; UDCA, ursodeoxycholic acid

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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 elevation in maternal serum. They are inherently cytotoxic and thus their metabolite is tightly regulated. In ICP, the flow of bile salts from the liver to gallbladder is disrupted and there is a compensatory transport of liver bile salts into the bloodstream [9].

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

TNF-α is important factor needed for the growth of the fetus and placenta but can be lethal when 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 apoptosis [11].

The placenta is an important and understudied organ in ICP, 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 an increased expression of the FAS receptor in the syncytiotrophoblast, induced by TNF-α and interferon gamma (IFN-γ) [11]. Comparison of placental lesions between patients with ICP and healthy patients has been performed in previous studies, but no statistically significant differences were found [12,13]. However, Geenes, et. al., identified small chorionic villi for gestational age, dense fibrotic stroma, congestion of the villi and an increased number of syncytial knots, which were reproduced in an *in vitro* model of liver cholestasis [14]

The aim of this study was to assess the histopathological features of the placenta 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 overweight 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 Perinatología, Isidro Espinosa de los Reyes in Mexico City, in a period of three years (2018-2021). Patients with diagnosis of ICP with singleton or twin pregnancies were included. The electronic medical records of the selected patients were consulted for the elaboration of a maternal database. Since all patients with ICP seen in the period 2018-2021 were selected, patients with comorbidities such as obesity, preeclampsia (PE), gestational diabetes mellitus (GDM), 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's pathology service for macroscopic evaluation. Ten aleatory samples were taken of each placenta for formalin fixation and paraffin embedding or were frozen to obtain specimens for histopathological analysis, according to the standard procedures stablished in our institution. The specimens were analyzed in a double-blind study by two expert pathologists and placental lesions were classified according to the Amsterdam Placental Workshop Group Consensus Statement (APWGCS) 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 GraphPad 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 Medical 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's clinical data, including their comorbidities, and the placental histopathological data are summarized in the Supplemental Table 1. 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 pregnancies 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
Characteristics of the cohort of women with intrahepatic cholestasis of pregnancy.

Characteristic	
Maternal age (years)	29.71 ± 6.4
Parity	
First	50 (47.61%)
Second	30 (28.57%)
Third or more	40 (38.09%)
Pregnancy and delivery	
Pregnancy length (weeks)	36.41 ± 2.31
Prematurity <37 weeks (29 -36.6 weeks)	53 (50.47%)
Singleton pregnancy	91 (86.66%)
Twin pregnancy	14 (13.33%)
Vaginal delivery	11 (10.47%)
Cesarian section	94 (89.52%)
Weeks of gestation at onset ICP symptoms	29.80 ± 5.6

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 found 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 syncytial 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 (UDCA), eleven patients with difficult control required treatment with UDCA 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 UDCA, independently of the BMI group to which they belonged (Table 3).

Table 2
Absolute and relative frequency distribution of placental histopathological lesions in women with intrahepatic cholestasis

	Placental lesions	Absolute frequency	Relative frequency
	Placental hypertrophy	37	36.27%
MVM	Placental hypoplasia	20	19.61 %
	Infarcts	18	15.12 %
	Retroplacental Hemorrhage	7	5.88 %
	Distal Villous Hypoplasia	15	12.60 %
	Accelerated Villous Maturation	11	9.24 %
	Accelerated Villous Maturation with Increased Syncytial Knots	44	36.97 %
	Increased Syncytial Knots	9	7.56%
	Decidual Arteriopathy	24	20.16 %
FVM	Villous Stromal-Vascular Karyorrhexis	0	0.00 %
	Stem Vessel Obliteration	17	14.28 %
	Intervillous Fibrinoid	31	26.05 %
	Thrombosis	2	1.68 %
	Avascular Villi	3	2.52 %
DVM	Delayed Villous Maturation	27	22.68 %
AII	Acute Subchorioamnioitis	1	0.84 %
	Acute Subchorionitis	2	1.68 %
	Chorioamnioitis	5	4.20 %
	Chronic Deciduitis	4	3.36 %
OL	Chorangiosis	31	26.05 %

AII. Ascending Intrauterine Infection, **DVM.** Delayed Villous Maturation, **FVM.** Fetal vascular malperfusion, **MVM.** Maternal Vascular Malperfusion**, OL.** Other lesions. **N=**119 studied placentas (including placentas of single and tween gestations).
The total number of alterations is higher as many placentas had several lesions
Note: Placental weight could be obtained in only 102 placentas.

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 syncytial knots in comparison with overweight and obese patients (Table 3).

4. Discussion

Preterm delivery and cesarian resolution of pregnancy have been previously associated with intrahepatic cholestasis, but not with overweight and obesity. The present study supports and extends these observations [7,8]. More than 50% of ICP women had preterm delivery, which could be explained by the therapeutical 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].

A previous study showed that placentas of ICP patients present morphological alterations such as increased terminal villous and capillary surface area, and number of syncytial 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 reported for gestational diabetes or preeclampsia [7], and recently, an increased incidence of ICP was associated with a direct linear increment of 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/m^{2,} and the number of women who are expected to have obesity (BMI ≥ 30 kg/m^2) 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 reported 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 trophoblast 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,

Table 3
ICP cohort characteristics by body mass index

BMI	Obese 40 (38.1%)	Overweight 24 (22.85%)	Normal 33 (31.43%)	Underweight 8 (7.61%)	Total 105
Twin pregnancy	5 (12.5%)	6 (25%)	3 (9.09%)	0	14
Comorbidities					
Preeclampsia	11 (27.5%)	3 (12%)	3 (9.09%	1 (12.5%)	18 (17.14%)
GDM	6 (15%)	1 (4.17%)	1 (3.03%)	0	8 (7.61%)
DM2	3 (7.5%)	1 (4.17%	1 (3.03%)	0	5 (4.76%)
Hepatopathies	7 (17.5%)	8 (33.33%)	5 (15.15%)	0	20 (19.04%)
Total	27 (67.5%)	13 (54.17%)	10 (30.30%)	1 (12.5%)	51 (48.57%)
Treatment					
UDCA	33	21	28	5	87 (82.86%)
UDCA + rifampicin	2	3	4	2	11 (10.48%)
Treatment response	7	1	7	ND	15 (15.30%)
Without treatment	5	0	1	1	7 (6.67%)
Hepatic function alteration					
TBA	n=37	n=24	n=32	n=7	100
TBA < 40μmol/L	22 (59.46%)	15 (62.5%)	14 (43.75%)	5 (71.42%)	56
TBA 40-100μmol/L	12 (32.43%)	5 (20.83%)	11 (34.38%)	1 (14.29%)	29
TBA >100μmol/L	3 (8.1%)	4 (16.67%)	7 (21.86%)	1 (14.29%)	15
AST >30u/L	22/38 (57.89%)	11/24 (45.83%)	20/32 (62.5%)	3/8(37.5%)	56/102 (54.90%)
ALT >32u/L	28/38 (73.68%)	15/24 (62.5%)	24/32 (75%)	5/8 (62.5%)	72/102 (70.59%)
GGT >41u/L	11/14 (78.57%)	11/12 (91.66%)	9/10 (90%)	0/0	31/36 (86.11%)
Placental characteristics					
Weight	n=37	n=24	n=33	n=8	102
Hypoplasia	6 (16.22%)	6 (25%)	6 (17.64%)	2 (25%)	20
Normal	16 (43.24%)	12 (50%)	14 (42.24%)	3 (37.5%)	45
Hypertrophic	15 (40.54%)	6 (25%)	13 (39.39%)	3 (37.5%)	37
Histopathology	n=45	n=30	n=36	n=8	119
AVM +ISK	15 (33.33%)	13 (43.33%)	13 (36.11%)	3 (37.5%)	44
AVM without ISK	6 (13.33%)	3 (10%)	2 (5.56%)	0	11
ISK without AVM	4 (8.89%)	1 (3.33%)	3 (8.33%)	1 (12.5%)	9
DVM	10 (22.22%)	6 (20%)	7 (19.44%)	0	23
Intervillous fibrin	17 (37.78%)	5 (16.67%)	7 (19.44%)	2 (25%)	31
Decidual arteriopathy	10 (22.22%)	5 (16.67%)	7 (19.44%)	0	22
Chorangiosis	8 (17.17%)	4 (13.33%)	13 (36.11%)	2 (25%)	31

ALT: alanine aminotransferase; ASP; aspartic aminotransferase; AVM: Accelerated Villous Maturation; DM2;Diabetes Mellitus type 2; DVM: Delayed Villous Maturation; GDM: Gestational Diabetes Mellitus; GGT: gamma glutamyl-transferase; ISK: Increased Syncytial Knots; TBA: total bile acids; ND not determined.
Notes: TBA >40 μmol/L are considered moderate risk factors and >100 μmol/L for high fetal risk.
The cutoff values for AST, ALT and GGT corresponded to 3rd trimester of pregnancy [9].
In response to treatment only the patients with serial TBA determinations were considered.
In only 102/119 placentas could be obtained weight data.
For histopathology: Total placentas N=119, including tween pregnancies, % corresponds to relative frequency.

these lesions have not been associated previously with pregnancy hepatic alterations. DVM has been associated mainly with chronic hypoxia [22] and more frequently, with metabolic diseases such as GDM [23]. However, further studies are needed to determine whether DVM is a lesion associated with metabolic disturbances in ICP patients and liver dysfunction.

Interestingly, chorangiosis was found in 26.05% of the ICP studied placentas, this lesion is due to a marked increase in the number of vessels (>10 capillaries in more than 10 villi in several areas) from non-infarcted and non-ischemic placental areas [24,25]. It has been suggested that chorangiosis is a compensatory response to chronic hypoxia, associated with different comorbidities including GDM and PE, to allow vascular remodeling to adapt to low oxygen conditions [26]. Chorangiosis also has been reported as a hallmark of DVM in placentas from obese pregnancies due to insulin resistance and hypoxia [24]; DVM was present in 22.68% of the placentas in our study. However, chorangiosis has not been previously reported as characteristic of ICP. Interestingly, it was more frequent in the normal weight group, maybe do to a more efficient compensatory mechanism as has been reported for pregnancies with obesity, GDM, DM1 and those at high altitudes [25,27].

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 UDCA, additional therapeutic strategies should be considered, since it was observed that a reduced number of patients responded to UDCA 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.

Conflicts of interest

None.

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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.

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