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RESEARCH ARTICLE

Placental changes in pregnancies complicated by intrahepatic cholestasis: increased perivillous fibrin deposition and umbilical cord abnormalities

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Aim: To assess the frequency of pathohistological lesions in placentas from pregnancies complicated by intrahepatic cholestasis and compare them with placentas from uncomplicated term pregnancies.

Methods: This retrospective cross-sectional study included placentas collected at the University Hospital of Split from 1 January 2021 to 31 December 2022. The study group consisted of placentas from pregnancies with clinically diagnosed cholestasis, while the control group included placentas from uncomplicated term pregnancies. Demographic, clinical, and pathohistological data were obtained from hospital records and compared using appropriate statistical tests.

Results: We analyzed 28 placentas from pregnancies with cholestasis and 30 from uncomplicated pregnancies, including 16 twin pregnancies in the cholestasis group. Mothers in the cholestasis group were older (33 years, standard deviation (SD) = 3 *vs*. 31 years, SD = 4; $P = 0.012$) and had a lower gestational age at delivery (36 weeks, SD = 4.9 *vs*. 38 weeks, SD = 0.9; $P < 0.001$). Newborns had lower birth weight (2802 g ± 664 *vs*. 3388 g, SD = 362; $P = 0.0001$) and more frequent intrauterine growth restriction (14.3% *vs*. 0%, $P = 0.019$). Placentas had shorter umbilical cords (27 cm, SD = 10 *vs*. 44 cm, SD = 12; $P < 0.001$), a higher coiling index (0.28 *vs*. 0.20; $P = 0.027$), and more frequent perivillous fibrin deposition (14 cases *vs*. 1 case; $P < 0.001$). No significant differences were found in placental size, weight, thickness, umbilical cord diameter, or vascular or inflammatory lesions.

Conclusion: Cholestasis in pregnancy was associated with specific placental morphological changes and adverse neonatal outcomes. However, the intepretation of our findings is limited by our small sample size, the design of our study, and the inclusion of twin pregnancies in our sample. Further studies are needed to clarify these associations.

Keywords: histopathology; intrahepatic cholestasis of pregnancy; intrauterine growth restriction; placenta; perivillous fibrin; umbilical cord

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Introduction

Cholestasis is a condition characterized by a reduction or stoppage of bile flow, most commonly resulting from damage to adenosine triphosphate-dependent transporter mechanisms (*1*–*3*). Intrahepatic cholestasis of pregnancy (ICP) affects approximately 1–2 out of 1000 women (*1*, *2*). Identified risk factors include a history of ICP, chronic liver disease, chronic hepatitis C, multiple gestation, and advanced maternal age (*4*). The condition has been associated with adverse perinatal outcomes, including an increased risk of preterm birth and abnormal amniotic fluid findings (*2*). More severe cases, especially those with fasting serum bile acid levels greater than 40 μmol/L, are linked to higher rates of fetal complications such as meconium-stained amniotic fluid, fetal bradycardia, fetal distress, and fetal loss (*5*). If untreated, cholestasis may also cause progressive liver damage, including inflammation, fibrosis, and, in rare cases, cirrhosis and liver failure (*6*, *7*). Ursodeoxycholic acid is currently the first-line treatment for the condition, and delivery at 38 weeks is generally recommended once fetal lung maturity is confirmed (*5*).

Although the clinical outcomes of ICP have been widely studied, its impact on placental structure remains insufficiently explored. Most available studies focus on perinatal outcomes, with limited data on histopathological lesions in the placenta of affected pregnancies. Therefore, we aimed to determine the prevalence of histopathological lesions in placentas from pregnancies complicated by ICP and to compare these findings with placentas from uncomplicated pregnancies. We hypothesized that placentas from pregnancies complicated by ICP would show a higher frequency of histopathological lesions, particularly vascular and inflammatory changes, as well as differences in selected maternal and neonatal characteristics.

Methods

We conducted this observational retrospective cross-sectional study at the Clinical Department of Pathology, Forensic Medicine and Cytology and the Department of Obstetrics and Gynecology, University Hospital of Split. The Ethics Committee of the University Hospital of Split approved the study protocol (approval number 520-03/24-01/69, March 22, 2024; all procedures followed the Declaration of Helsinki and relevant national regulations on the protection of patients' rights and personal data.

Participants

The study population consisted of women who delivered at the University Hospital of Split between January 1, 2021, and December 31, 2022, and whose placentas underwent histopathological analysis. The study group included pregnancies complicated by ICP, while the control group comprised uncomplicated pregnancies. Inclusion criteria were a confirmed diagnosis of ICP during pregnancy and the availability of placental histopathological analysis from the same pregnancy. In cases of multiple pregnancies, we included all placentas from the same pregnancy excluded repeated findings from the same participant within the study period.

Data collection and variables

We obtained retrieved data on maternal characteristics (age, gravidity, parity, comorbidities), pregnancy-related conditions (anemia, thrombocytopenia, gestational diabetes, hypothyroidism, gallstones, pruritus), and multiple pregnancies from electronic hospital records. Placental and fetal variables included placental weight, size, and thickness; umbilical cord length, diameter, insertion, number of vessels, and torsion index; fetal weight and fetoplacental weight ratio; and the presence of histopathological lesions, including maternal and fetal vascular malperfusion, inflammatory responses, villitis, and perivillous fibrin deposition.

Statistical analysis

We summarized continuous variables as means and standard deviations or medians and interquartile ranges (depending on the distribution of the data, as assessed by the Kolmogorov–Smirnov test), and categorical variables as frequencies and percentages. We compared groups using the unpaired Student's *t*-test or Mann–Whitney U test for continuous (depending on data distribution and the chi-squared test for categorical variables, with an α of 0.05 ($P<0.05$) set as the significance threshold. We performed the statistical analysis in MedCalc, version 19.1.2 (MedCalc Software, Ostend, Belgium).

Results

Mothers in the cholestasis group were significantly older and had a lower gestational age at delivery compared to the control group (**Table 1**). Newborns from pregnancies complicated by ICP had significantly lower birth weight and a higher incidence of intrauterine growth restriction (IUGR), while no such cases were observed in the control group. There was no significant difference in neonatal sex distribution between the groups. Twin pregnancies occurred only in the ICP group ($P<0.001$). Additional maternal clinical characteristics recorded in the ICP group included gestational diabetes, hypothyroidism, anemia, thrombocytopenia, pruritus, and gallstones, none of which were observed in the control group.

Table 1. Demographic and neonatal characteristics of the study groups*

		ICP group (n = 28)	Control group (n = 30)	*P*-value†
Maternal age (years), mean (SD)		33 (3)	31 (4)	0.012
Gestational age (weeks), mean (SD)		36 (4.9)	38 (0.9)	<0.001
Sex, n (%)	Male	17 (61)	13 (43)	0.189
	Female	11 (39)	17 (57)	
Birth weight (g), mean (SD)		2802 (664)	3388 (362)	0.0001
IUGR, n (%)		4 (14.3)	0	0.019

*Abbreviations: ICP – intrahepatic cholestasis of pregnancy, IUGR – intrauterine growth restriction, SD – standard deviation.
†Student's *t*-test or chi-squared test.

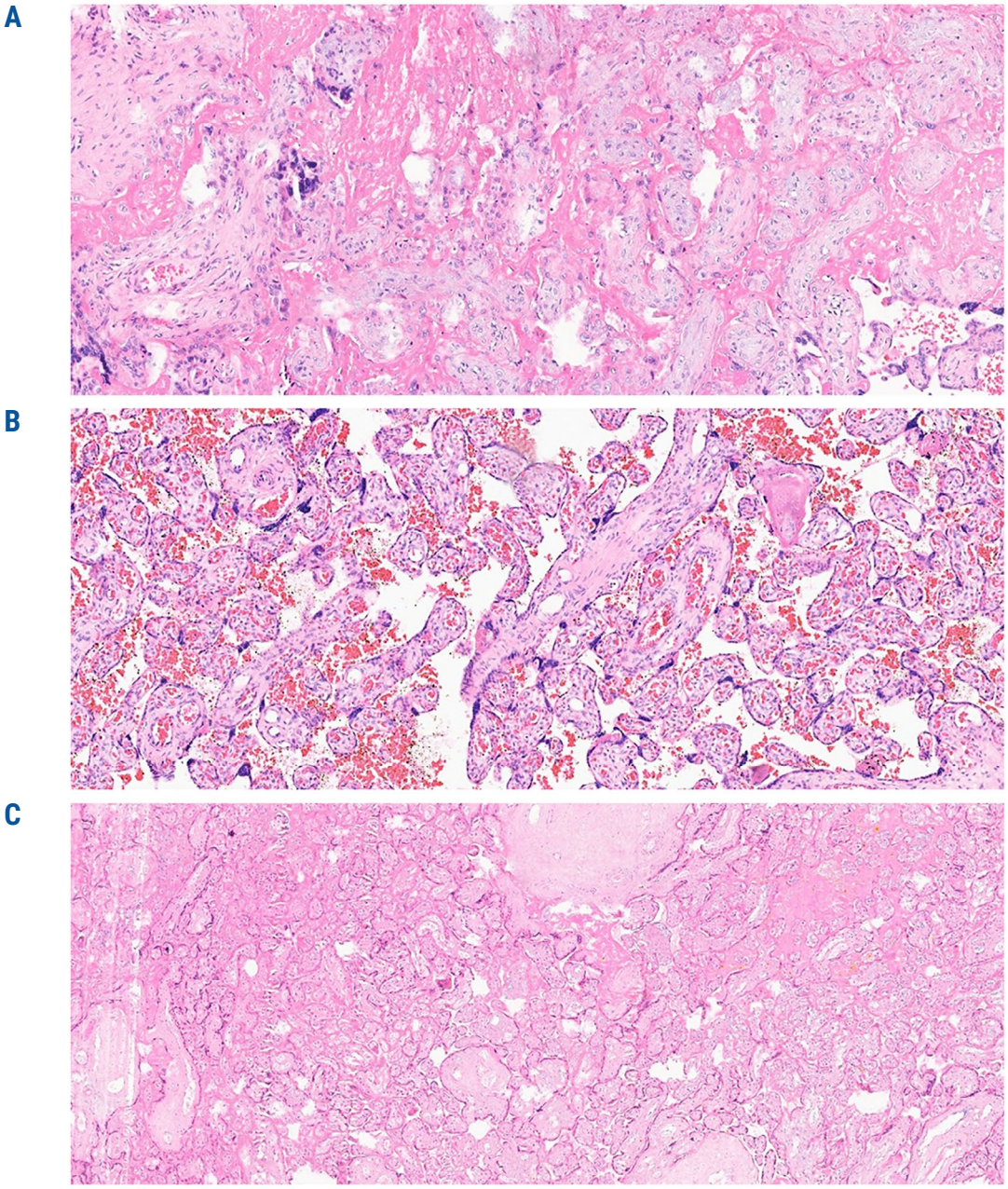

Figure 1. Histopathological features of placentas from pregnancies complicated by intrahepatic cholestasis of pregnancy and from uncomplicated pregnancies. **Panel A.** Increased perivillous fibrin deposition in a placenta from a pregnancy complicated by intrahepatic cholestasis of pregnancy. **Panel B.** normal chorionic villi in a term placenta from an uncomplicated pregnancy. **Panel C.** Chronic infarction of chorionic villi due to maternal vascular malperfusion. Hematoxylin and eosin staining, magnification × 200.

Placental histopathological findings

Placentas from pregnancies complicated by ICP had significantly shorter umbilical cords and a higher umbilical cord coiling index compared to controls (**Table 2**). Increased perivillous fibrin deposition was also significantly more frequent in the ICP group (**Figure 1**, Panel A) than in the control group (**Figure 1**, Panel B). There were no significant differences in placental weight, size, thickness, or umbilical cord diameter between the groups, or in the frequency of maternal and fetal vascular malperfusion, inflammatory responses, and chronic villitis (**Figure 1**, Panel C).

Table 2. Histopathological and morphological characteristics of placentas in pregnancies complicated by ICP and uncomplicated pregnancies*

Placental morphology		ICP group (n = 28)	Control group (n = 30)	*P*-value†
Weight (g), mean (SD)		461 (69)	497 (90)	0.091
Size (largest diameter, cm), mean (SD)		17.9 (2.9)	17.7 (2.3)	0.829
Thickness (cm), MD (IQR)		2.5 (1–3)	2.5 (1–4.5)	0.375
Umbilical cord characteristics	Length (cm), mean (SD)	27 (10)	44 (12)	<0.001
	Diameter (cm), MD (IQR)	1.2 (0.8–2.0)	1.2 (1.0–1.7)	0.352
	Coiling index, MD (IQR)	0.28 (0.1–4.6)	0.20 (0.06–0.5)	0.027
Coiling pattern, n (%)	Normal	18 (64)	24 (80)	
	Hyper	5 (18)	5 (17)	0.622
	Hypo	5 (18)	1 (3)	
Vascular lesions, n (%)		ICP group (n = 28)	Control group (n = 30)	*P*-value†
MVM		5 (18)	1 (3)	0.072
FVM		1 (4)	0 (0)	0.301
Inflammatory lesions, n (%)		ICP group (n = 28)	Control group (n = 30)	*P*-value†
Maternal inflammatory response		3 (11)	0 (0)	0.068
Fetal inflammatory response		1 (4)	0 (0)	0.301
Chronic villitis, n (%)	High	1 (4)	3 (10)	0.526
	Low	2 (7)	1 (3)	
Perivillous fibrin deposition, n (%)		14 (50)	1 (3)	<0.001

*Abbreviations: FVM – fetal vascular malperfusion, ICP – intrahepatic cholestasis of pregnancy, IQR – interquartile range, MD – median, MVM – maternal vascular malperfusion, SD – standard deviation.
*Student's *t*-test, Mann–Whitney U test, or chi-squared test, depending on data distribution.

Discussion

We examined the demographic, neonatal, and histopathological characteristics of placentas from pregnancies complicated by ICP compared with uncomplicated pregnancies. The findings suggest that ICP is associated with specific placental morphological changes, particularly shorter umbilical cord length, increased coiling index, and more frequent perivillous fibrin deposition. These findings may indicate alterations in placental structure and function in pregnancies complicated by ICP. Increased perivillous fibrin deposition has been associated with impaired maternal–fetal exchange and adverse fetal outcomes, including intrauterine growth restriction (*4*). It is assumed that IUGR in cholestasis is associated with bile-acid-induced endothelial damage, which promotes inflammatory reactions, hypoxia, and impaired maternofetal exchange (*4*, *8*). Similarly, abnormalities in umbilical cord length and coiling may reflect altered fetal circulation (*9*). Excessive coiling or reduced umbilical cord length may compromise nutrient and oxygen exchange between the

mother and fetus, potentially contributing to impaired fetal growth (*9*). However, given the observational design of the study, these interpretations remain speculative and require further investigation.

Our results are consistent with previous studies reporting increased rates of preterm birth and lower birth weight in pregnancies complicated by ICP (*6*, *10*). Kondrackiene *et al.* reported an association between maternal cholestasis and an increased incidence of fetal distress, intrauterine death, and preterm birth (*11*), which is consistent with our findings. Similarly, previous studies have shown that newborns from pregnancies complicated by cholestasis had significantly lower birth weight compared with controls, which may reflect more frequent maternal vascular malperfusion lesions and increased perivillous fibrin deposition in placentas from pregnancies complicated by ICP (*12*, *13*). Rook *et al.* also reported that labor was induced in as many as 87% of pregnancies complicated by maternal cholestasis to reduce the risk of fetal complications, particularly respiratory distress (*14*). Ovadia *et al.* reviewed and meta-analysed 109 studies evaluating the association between ICP and adverse perinatal outcomes and found that stillbirth occurred in 0.83% of pregnancies complicated by maternal cholestasis, compared with 0.32% of uncomplicated pregnancies (*15*). They further observed that higher maternal serum bile acid levels were associated with an increased risk of adverse fetal outcomes, including stillbirth (*15*). Other studies have also reported associations between elevated bile acid levels and IUGR (*4*, *16*), as well as inflammatory placental lesions such as villitis (*17*, *18*) and chorioamnionitis (*19*, *20*). Although most available studies on ICP have focused primarily on clinical and perinatal outcomes, data regarding histopathological placental changes remain limited. Given that ICP affects approximately 1–2 per 1000 pregnancies, studies specifically addressing placental pathology in these pregnancies are still relatively scarce (*1*, *2*). Therefore, our study contributes additional data to an area that remains insufficiently explored.

Several limitations of this study should be considered. First, the relatively small sample size limits the generalizability of our findings. The retrospective study design also restricted the availability of important clinical data, including serum bile acid levels and information on treatment during pregnancy. The inclusion of twin pregnancies exclusively in the ICP group represents a potential confounding factor that may have influenced both neonatal and placental findings. Therefore, our results should be interpreted with caution.

In conclusion, pregnancies complicated by ICP in our sample were associated with specific histopathological placental changes, particularly increased perivillous fibrin deposition and abnormalities of the umbilical cord, as well as adverse neonatal characteristics, including lower birth weight and a higher frequency of intrauterine growth restriction. In view of our study limitations, further research including larger cohorts and relevant biochemical and clinical parameters is needed to confirm these findings and to better clarify the relationship between ICP and placental pathology.

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Disclosure of interest: The authors completed the ICMJE Disclosure of Interest Form (available upon request from the corresponding author) and declare no conflicts of interest.

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