Scientific Research Publishing

Open Journal of Obstetrics and Gynecology, 2025, 15(8), 1243-1255
https://www.scirp.org/journal/ojog
ISSN Online: 2160-8806
ISSN Print: 2160-8792

Intrahepatic Cholestasis of Pregnancy: A Single-Center Retrospective Analysis of Obstetric and Neonatal Outcomes

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How to cite this paper: Gassó Perales, G., Sánchez Arco, C., González Blanco, I., Oribe Zarraga, L., Desantes Real, D., Carrasco Catena, M.A. and Valero Domínguez, F.J. (2025) Intrahepatic Cholestasis of Pregnancy: A Single-Center Retrospective Analysis of Obstetric and Neonatal Outcomes. *Open Journal of Obstetrics and Gynecology*, **15**, 1243-1255.
https://doi.org/10.4236/ojog.2025.158100

Received: July 5, 2025
Accepted: August 9, 2025
Published: August 12, 2025

Abstract

Introduction: Intrahepatic cholestasis of pregnancy (ICP) is an obstetric complication that occurs most frequently in the third trimester and endangers both the mother and fetus. **Objective**: To analyze the obstetric and neonatal outcomes of patients diagnosed with ICP at our center and compare these findings with current literature, while also reviewing clinical practice guidelines from various scientific societies. **Methods**: We conducted a retrospective observational descriptive study of all ICP cases at our center from 2013 to 2023. We analyzed maternal baseline characteristics, clinical and laboratory data, as well as maternal and neonatal complications in 273 cases that met the inclusion criteria. **Results**: Out of 949 initial patients, 273 met the inclusion and exclusion criteria (250 singleton and 23 twin pregnancies) with 94.1% diagnosed in the third trimester. Bile acid levels were not obtained in 41% of cases; 41% were <40 μmol/L, 13% were 40 - 100 μmol/L, and 4% were >100 μmol/L, with a mean diagnostic bile acid level of 29.32 μmol/L. The maternal complications included were hypertensive disorders (7.3%), gestational diabetes (8.7%), gestational hypothyroidism (4.7%), and preterm premature rupture of membranes (2.2%). Labor was medically induced in 77.3% of cases, while 22.7% started spontaneously. Vaginal delivery occurred in 64.1%, and cesarean section in 34.8%, all following institutional protocols. Neonatal complications included 20.5% preterm births and 9 NICU admissions, none due to ICP-related causes. **Conclusions**: These findings highlight the need for standardized care protocols and prospective studies to ensure early diagnosis and appropriate management to improve maternal and fetal outcomes.

Keywords

Intrahepatic Cholestasis, Pruritus, Pregnancy Disease, Liver, Bile Acids

1. Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-specific liver disorder that should be considered in patients presenting with generalized pruritus of new onset during pregnancy. Pathophysiologically, it is characterized by impaired bile acid flow, resulting in systemic accumulation that underlies both maternal symptoms and fetal risks. It affects approximately 0.1% - 2% of pregnancies, with significant variation according to geographic region [1].

The etiology of ICP is complex and multifactorial [2], involving the interaction of genetic, hormonal, and environmental factors. Mutations and polymorphisms have been identified in genes encoding hepatic bile acid transport proteins, such as *ABCB4* (MDR3) and *ABCB11* (BSEP) [3] [4]. In addition, pregnancy is associated with progressively increasing levels of estrogens and progestogens, particularly in the third trimester. These hormones exert a cholestatic effect [5], especially in genetically predisposed individuals.

Incidence varies substantially by geographic location and season, suggesting environmental influence. High rates have been reported in countries such as Chile, Bolivia, and Turkey, as well as in northern European regions (particularly Scandinavia) [6]. An increase in cases during winter months has also been observed, possibly linked to reduced sunlight exposure and vitamin D deficiency [7] [8].

The main pathophysiological factors contributing to fetal damage include maternal bile acid accumulation that crosses into fetal circulation and the lack of a feto-maternal gradient to eliminate bile acids of fetal origin. Another contributing factor is bile acid hydrophobicity. More hydrophobic bile acids (primarily unconjugated cholic and chenodeoxycholic acids) tend to accumulate and are more toxic [9] [10].

Several risk factors have been described, including personal or family history of ICP [11], multiple pregnancy [5], conception via assisted reproductive technologies [5], pregestational or gestational diabetes [12], hepatitis C or other pre-existing liver diseases [13], high parity [5], advanced maternal age [14], and previous hormone-related cholestasis [5].

Clinical suspicion should arise based on findings such as palmoplantar pruritus progressing to generalized itching, absence of rash (though excoriations may be present), jaundice, and gastrointestinal symptoms [14]. Among diagnostic tests, bile acid levels (cholic and chenodeoxycholic acid) > 10 μmol/L are currently considered the most sensitive diagnostic marker [5], although normal levels do not rule out the disease.

Reported maternal complications include postpartum hemorrhage [4], persistent hepatic disease [15]-[17], preeclampsia [18], gestational diabetes [19],

dyslipidemia [20], chronic hepatitis (HR, 5.96; 95% CI, 3.4 - 10.3), cirrhosis (HR, 5.11; 95% CI, 3.3 - 7.9), and cholangitis (HR, 4.2; 95% CI, 3.1 - 5.7) [21].

Fetal complications are a major concern and are primarily attributed to bile acid toxicity crossing the placental barrier. A 2019 systematic review by Ovadia *et al.* published in *The Lancet* [22] identified the most frequent complications as preterm birth (OR 3.47; 95% CI, 3.06 - 3.95), fetal distress [23], meconium aspiration syndrome [24] [25], and intrauterine fetal death [26]-[28].

Treatment is recommended for all patients, following a stepwise approach depending on symptom severity and biochemical abnormalities [4]. Ursodeoxycholic acid, a hydrophilic bile acid, is the cornerstone of treatment. Its main mechanism involves displacing toxic hydrophobic bile acids from the bile pool, which it achieves in up to 60% of cases [29]-[31].

International guidelines differ regarding the optimal timing for delivery in ICP. The ACOG [4] suggests delivery between 36 and 39 weeks depending on severity, with earlier delivery for specific high-risk cases. The RCOG [2] recommends delivery at 40 weeks in mild cases, 38 - 39 weeks in moderate cases, and 35 - 36 weeks in severe cases, adjusting for comorbidities. The SOGC [5] proposes a more specific approach based on bile acid levels, recommending delivery between 36 and 39 weeks or earlier in special cases such as preeclampsia or multiple pregnancy. The Fetal Medicine Barcelona protocol [1] incorporates clinical criteria and recommends delivery at 40 weeks for mild cases, or at 37 weeks in the presence of severe symptoms or bile acids > 40 μmol/L, reserving earlier delivery for highly selected cases with bile acids > 100 μmol/L and evidence of severe disease.

Objectives

The primary objective of this study is to evaluate the perinatal adverse outcomes and maternal complications observed in the cohort of intrahepatic cholestasis of pregnancy (ICP) cases managed at Hospital Universitari i Politècnic La Fe, based on a retrospective review of clinical records from 2013 to 2023. The secondary objective is to compare the clinical presentation, progression, and management of ICP in our center with the recommendations provided by current international guidelines and scientific societies.

2. Methods

For data collection, an initial request was submitted to the Documentation Unit of our center, which provided a total of 949 patients whose medical records included the coded diagnoses of "Pruritus," "Suspected intrahepatic cholestasis of pregnancy" or "Intrahepatic cholestasis of pregnancy." These records were reviewed, and patients presenting with gestational pruritus attributable to alternative diagnoses were excluded, resulting in a cohort of 367 patients. Subsequently, patients from the years 2013 to 2015 (inclusive) were excluded due to missing analytical data (particularly bile acid measurements) and changes in outpatient follow-up protocols during that period, as well as those who did not deliver at Hospital Universitari i Politècnic La Fe, yielding a final sample of 273 patients. After

the compilation of patients, a thorough analysis was performed to mainly to evaluate perinatal adverse outcomes and maternal complications associated with ICP.

Inclusion and exclusion criteria

Inclusion criteria comprised patients presenting with gestational pruritus without rash and without any other condition that could explain the symptomatology, such as urticaria, herpes gestationis, vulvovaginal pruritus, insect bites, erythema multiforme of pregnancy, or atopic dermatitis. Patients were included if they met at least one of the following criteria:

- A pruritus episode followed by outpatient obstetric follow-up
- Two emergency visits for pruritus
- Typical analytical findings consistent with ICP
- Persistent symptoms despite treatment
- Hospital admission due to pruritus
- Delivery induced due to gestational pruritus

In all cases, a thorough differential diagnosis was required to exclude other potential pruritic conditions under the above-mentioned scenarios. A subgroup of patients within the included cohort lacked bile acid measurements. In these cases, the diagnosis and follow-up were based on liver function test results and clinical assessment conducted on at least two separate occasions. Despite the absence of bile acid data, these patients were included due to the availability of sufficient clinical and biochemical information to support a presumptive diagnosis of ICP. All patients in the final cohort (regardless of bile acid availability) were evaluated for adverse perinatal and maternal outcomes.

Exclusion criteria included patients with a confirmed alternative diagnosis explaining pruritus. Also excluded were patients with a single isolated episode of pruritus during an emergency visit, no rash, normal laboratory results, and no subsequent visits to the Emergency department for pruritus during pregnancy or those whose follow-up showed symptom resolution without treatment. In these cases, labor induction had to be unrelated to pruritus. Additionally, patients diagnosed between 2013 and 2015 were excluded, as explained previously. During those years, the diagnosis of intrahepatic cholestasis of pregnancy (ICP) was often made based solely on clinical symptoms, without confirmation through laboratory testing. In addition, there was not a standarized follow-up of these patients along the pregnancy.

3. Results

A total of 273 cases of intrahepatic cholestasis of pregnancy (ICP) were identified at Hospital Universitari i Politècnic La Fe (Valencia) between 2016 and 2023. For subgroup analysis, ICP was classified as mild when bile acids were <40 μmol/L, moderate between 40 - 100 μmol/L, and severe when >100 μmol/L. Since this is a clinical diagnosis, bile acid levels were not obtained in 112 patients (41%). Among the patients with available bile acid quantification, 114 (70.8%) were classified as mild, 36 (13.2%) as moderate, and 11 (4%) as severe.

Focusing on clinical data, the mean gestational age at diagnosis was 34.45 weeks (SD ± 2.76), with only 16 cases diagnosed before 28 weeks, and 94.1% occurring in the third trimester. The mean number of previous pregnancies (parity) was 2.26. Of the cases, 250 involved singleton pregnancies and 23 were twin pregnancies (8.4%). Pruritus was the main presenting symptom in 268 patients (98.17%), and jaundice was recorded in 3 cases. The mean bile acid level at diagnosis was 29.32 μmol/L across all patients with at least one measurement. By subgroup, the means were: mild, 18.90 μmol/L; moderate, 59.18 μmol/L; and severe, 111.05 μmol/L.

Regarding hepatic enzyme values at diagnosis, mean AST (GOT) and ALT (GPT) levels were 68.79 U/L and 104.23 U/L, respectively. In the severe group, the means were 87.82 U/L and 124.55 U/L. The overall mean gamma-glutamyl transferase (GGT) was 31.98 U/L, and 79.8 U/L in the severe subgroup. For total bilirubin, the general mean was 0.59 mg/dL, rising to 0.99 mg/dL in severe cases.

In terms of treatment, 161 patients (59.4%) received ursodeoxycholic acid (UDCA) and symptomatic treatment; 64 (23.4%) received only symptomatic treatment (topical and/or systemic) and 47 (17.2%) did not receive any documented treatment.

Regarding pregnancy complications, 172 patients (63%) had no complications. Among those with complications, the most relevant findings were Table 1.

- **20 cases of hypertensive disorders (7.3%)** distributed as follows: 13 in the mild group, 7 in patients without bile acid determination, and none in the moderate or severe groups.
- **24 cases of gestational diabetes (8.7%)**, of which 14 were in the mild group, 2 in the moderate group, and 8 in patients without bile acid measurement.
- **13 cases of gestational hypothyroidism (4.7%)**, including 1 in the severe group, 1 moderate, 8 mild, and 3 without bile acid data.
- **6 cases of preterm premature rupture of membranes (PPROM)** (2.2%), 2 in the mild group and 4 in patients without bile acid measurement.

Only two patients (0.73%) were found to have coexisting viral hepatitis (1 HCV and 1 HBV), and one patient had a personal history of autoimmune hepatitis. Other complications, such as intrauterine growth restriction (IUGR), preterm labor or oligohydramnios, were not observed in patients with severe ICP.

Table 1. Main maternal complications.

Severity ICP	Hypertensive disorders	Gestational Diabetes	Gestational Hypothiroidism	PPROM
Mild	13	14	8	2
Moderate	0	2	1	0
Severe	0	0	1	0
Non-classified	7	8	3	4
Total	20	24	13	6

This Table registers the exact number of cases of the main pregnancy complications.

Regarding labor and delivery, the mean gestational age at delivery was 37.46 weeks (SD ±1.49). 62 patients experienced spontaneous labor onset, while the remaining 211 cases (77.3%) were medically induced. As for delivery via, 95 patients underwent cesarean section and 175 had vaginal deliveries (64.1%). Among cesarean sections, 46 were elective based on institutional protocols, 32 were due to induction failure, arrested labor or cephalopelvic disproportion, and 17 were performed due to suspected fetal distress. Regarding to the indications for elective cesarean section, these were breech fetal presentation, a personal history of one or more cesarean deliveries, twin pregnancy not meeting criteria for vaginal delivery or placenta previa. This corresponds to an overall cesarean section rate of 34.8% in the cohort. In terms of labor induction, at our center it is performed using 10 mg vaginal dinoprostone or, when contraindicated, with a double-balloon catheter, followed by intravenous oxytocin administration according to the center's protocol.

Concerning gestational age at birth, 20.5% of neonates were born preterm, 28.5% at 37 weeks, 20.1% at 38 weeks, 15.3% at 39 weeks, 11.3% at 40 weeks, and 1.09% at 41 weeks. Nine newborns required admission to the neonatal intensive care unit (NICU). None of these admissions were associated with maternal severe cholestasis. The main reasons for NICU admission were related to prematurity and not directly linked to the severity of ICP.

4. Discussion

Intrahepatic cholestasis of pregnancy (ICP) is one of the most common liver disorders during gestation and represents a clinical challenge due to both maternal symptomatology and potential fetal implications. A retrospective analysis was conducted of the cases recorded at Hospital Universitari i Politècnic La Fe (Valencia) between 2016 and 2023, allowing a comparison with leading international guidelines (ACOG, SOGC, RCOG, and Fetal Medicine Barcelona).

As ICP is a diagnosis of exclusion, the inclusion and exclusion criteria applied in this study facilitated the accurate identification of patients with this condition. Patients whose pruritus could be attributed to other pathologies were excluded, and those who had persistent symptoms, follow-up in specialized consultations, abnormal laboratory values, hospital admission, or delivery due to this condition were included.

During the study period (2016-2023), a total of 273 cases of ICP were registered, with bile acid levels quantified in only 161 cases (59%). Of these, 114 patients (71%) were classified as mild, 36 (22%) as moderate, and only 11 (7%) as severe. These figures are consistent with current evidence [22] [32], which shows a higher incidence of mild cases (54%) compared to moderate (33%) and severe (12%) forms.

The mean gestational age at diagnosis in our center was 34.45 weeks (SD ± 2.76), with only 16 cases (5.9%) occurring before 28 weeks, and 94.1% being diagnosed in the third trimester. This finding aligns with existing evidence, which at-

tributes this pattern to the hormonal influence on the development of the disease [1] [2] [5] [14].

Regarding risk factors for ICP, the average number of previous pregnancies was 2.26, and 23 of the affected pregnancies (8.4%) were twin gestations. The mean maternal age at diagnosis was 33.09 years, with 13% of patients being over 40 years old. These results are consistent with current literature, which identifies all three as risk factors for the development of the condition [33]-[35].

Clinically, 268 patients (98.17%) presented with pruritus as the main symptom, in agreement with all analyzed clinical guidelines [1] [2] [5] [14], and only three cases of jaundice were recorded. Although jaundice is known to be rare in ICP [15], underreporting due to incomplete anamnesis may also represent a classification bias. The mean bile acid level at diagnosis was 29.32 μmol/L, supporting the predominance of mild cholestasis in our cohort. Regarding liver enzymes, the mean AST and ALT levels at diagnosis were 68.79 U/L and 104.23 U/L, respectively, with corresponding means in the severe cholestasis group of 87.82 U/L and 124.55 U/L. Although these values are elevated, the literature consistently shows that higher transaminase levels are not associated with poorer obstetric outcomes [22] [36]. Mean GGT was 31.98 U/L overall and 79.8 U/L in the severe subgroup. Total bilirubin levels had an overall mean of 0.59 mg/dL, increasing to 0.99 mg/dL in severe cases, findings that align with most studies, which report normal or only slightly elevated values for both parameters [5].

Only two patients presented with coexisting viral hepatitis (1 HCV, 1 HBV), and one patient had a personal history of autoimmune hepatitis. These findings suggest that such conditions were not relevant risk factors in our population, contrary to most existing studies [13]. Other known risk factors such as pregnancies achieved via assisted reproductive technology (ART), personal history of cholestasis associated with contraceptive use, or ICP in previous pregnancies were not analyzed in this study.

According to various studies, ICP has been associated with multiple maternal and fetal complications, including preeclampsia and gestational diabetes [18] [19]. In our cohort, hypertensive disorders were observed in 7.3%, gestational diabetes in 8.7%, gestational hypothyroidism in 4.7%, and there were 6 cases (2.2%) of preterm premature rupture of membranes (PPROM). Although these variables were analyzed, the literature also associates ICP with other relevant complications such as postpartum hemorrhage and persistent liver disease [1] [15] [37].

There are discrepancies in the reported rates of stillbirth. In the meta-analysis by Ovadia *et al*., the stillbirth rate was 0.91%, whereas in our center, it was 0% [22]. Other publications report a general rate of 1.2% [27] [28] [38]. This variation may be attributed to effective management strategies, particularly regarding to treatment and timely delivery.

With reference to therapeutic management, ursodeoxycholic acid (UDCA) remains the treatment of choice. However, there is no consensus on the optimal timing for initiation. The SOGC recommends initiating treatment when bile acids

exceed 100 μmol/L or in cases of severe pruritus [5]. Meanwhile, Hospital Clínic de Barcelona advises treatment for moderate to severe pruritus with laboratory findings compatible with ICP [1]. The Society for Maternal-Fetal Medicine (SMFM) considers UDCA first-line therapy when clinical symptoms arise [14], whereas the RCOG recommends offering it in symptomatic patients, although not specifically to improve laboratory parameters [2]. In our cohort, 59% of patients received UDCA. Nonetheless, current evidence does not support a significant reduction in fetal demise or acute fetal distress with this treatment [1] [2] [5] [14].

Regarding delivery outcomes, 77.3% of pregnancies were medically induced. As for delivery mode, 95 patients underwent cesarean section, and 175 delivered vaginally (64.1%). Among cesareans, 46 were elective and aligned with our institutional protocol, and only 17 (6.2%) were due to risk of fetal distress—a complication frequently cited in the literature [23]. For those who delivered vaginally, the reason for induction was not specified, making it difficult to determine whether the indication was directly related to ICP.

Finally, regarding gestational age at birth, 20.5% of newborns were preterm, while the remainder were delivered at term. It is well established that ICP is a risk factor for preterm delivery (OR 3.47) [3]. Nine newborns required admission to the NICU due to complications such as complex congenital heart disease, respiratory distress syndrome, hyaline membrane disease, transient tachypnea of the newborn, pneumothorax, and necrotizing enterocolitis. Some of these complications, particularly respiratory distress, have also been associated with ICP in previous studies [27].

4.1. Strengths and Limitations of the Study

Among the main strengths of this study is the sample size, comprising 273 pregnant women diagnosed with intrahepatic cholestasis of pregnancy (ICP) at our center between 2016 and 2023, whose progression was monitored from diagnosis until delivery. This feature allowed for a detailed longitudinal evaluation of disease progression and per-inatal outcomes.

Additionally, the data were obtained exclusively through the electronic health record system of the Valencian Community (Orion Clinic), ensuring greater accuracy in the collection of clinical data, which contributes to reinforcing the internal validity of the study and the reliability of the results obtained.

Furthermore, for the analysis of the clinical cases as well as the interpretation of the data and its comparison with the available evidence, several updated international clinical guidelines were employed, allowing the findings to be contextualized within the framework of current recommendations.

Although this study provides relevant findings, it is not without limitations. Firstly, the lack of analytical data for patients attended between 2013 and 2015 prevented their inclusion in the analysis, which may have potentially compromised the overall representativeness of the study sample.

Another major limitation lies in the absence of bile acid measurements in 41.2%

of patients, making precise stratification of ICP severity difficult in these cases. This factor is likely influenced by the lack of homogeneity in the management of these patients, due to variability in current clinical guidelines and the absence of standardized treatment criteria. These criteria may have introduced a potential misclassification bias, as some clinically diagnosed cases of ICP without laboratory confirmation were not included.

An additional concern of the present study is the lack of specific consideration of maternal risk factors such as obesity, use of in vitro fertilization (IVF), smoking habits, or a history of previous intrahepatic cholestasis of pregnancy.

4.2. Proposals and Future Research Directions

On the one hand, it is fundamental to conduct epidemiological studies to estimate the incidence of intrahepatic cholestasis of pregnancy more accurately in our healthcare area, which would allow for better resource planning and early case identification. Also, it would be important to evaluate maternal risk factors.

On the other hand, relevant research avenues may include the investigation of predictive biomarkers. It would be valuable to study how transaminase levels and other analytical parameters might serve as predictive tools in the development and progression of ICP, aiding earlier detection and more precise risk stratification.

Moreover, exploring the development of new treatment lines that not only focus on symptom control but also aim to address the underlying etiology of the disease would be pertinent, with the goal of reducing perinatal complications.

Finally, the implementation of standardized clinical protocols is crucial to enable more homogeneous management of this condition.

5. Conclusions

Intrahepatic cholestasis of pregnancy (ICP) represents a clinically significant obstetric condition due to its maternal and perinatal implications. Through a representative clinical case and a retrospective analysis of 273 pregnant women diagnosed at our center between 2016 and 2023, we have studied the clinical, biochemical, and evolutionary profile of this pathology in our population, as well as compared its management with leading international guidelines.

This study highlights the high prevalence of mild forms, the frequent onset of symptoms in the third trimester, and the association with risk factors such as advanced maternal age, multiparity, and multiple pregnancies. Furthermore, pruritus is confirmed as the cardinal symptom, and the hepatic profile proves useful in diagnosis. However, the absence of systematic bile acid measurements in a significant proportion of patients limits precise disease stratification, underscoring the need to unify diagnostic and therapeutic criteria.

Although ursodeoxycholic acid remains the treatment of choice, no conclusive impact has been demonstrated on severe perinatal outcomes such as fetal death. This emphasizes the importance of continued research into alternative therapies that more effectively address the underlying pathophysiology.

In conclusion, this work underscores the necessity of developing standardized care protocols and prospective studies in order to optimize early diagnosis, monitoring, and treatment of ICP, aiming to improve maternal-fetal outcomes in this clinical context.

Fundings

This observational study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics Approval

As this is a retrospective observational study using anonymized data, it was exempt from formal ethical approval according to institutional and national regulations.

Consent to Participate

Since this study is retrospective and based on anonymized data, individual patient consent for participation was not required in accordance with applicable ethical guidelines and regulations.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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