

Maternal and Fetal Outcomes in Pregnancies Complicated by Intrahepatic Cholestasis

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ABSTRACT

Objective: This study aimed to report the maternal and fetal outcomes in women with intrahepatic cholestasis of pregnancy (ICP).

Materials and Methods: The maternal and fetal outcomes in 70 consecutive women who gave birth at Atatürk University Hospital between January 2012 and December 2017 were assessed. The clinical diagnosis of ICP and diagnosis confirmed post-delivery when all the symptoms regressed and laboratory parameters returned to normal was utilized.

Results: Liver transaminases were elevated in 61 (87%) women. The median week of delivery was 37 (range, 26-42) and the preterm delivery rate was 40% (28 women delivered spontaneously at ≤ 36 weeks of gestation). Preeclampsia was noted in 8 (11%) women. There were no cases of stillbirth or neonatal death.

Conclusion: The rate of stillbirth does not increase in women with ICP. However, further investigations are needed to determine if this result is related to preterm birth.

Keywords: Intrahepatic cholestasis of pregnancy, serum transaminases, stillbirth, preeclampsia

Introduction

Intrahepatic cholestasis of pregnancy (ICP), characterised by elevated serum bile acid concentrations or elevated aminotransferase levels with pruritus, usually develops during the late second or third trimester and rapidly regresses after childbirth. The etiology of ICP is not yet completely understood, but it probably depends on the genetic predisposition, hormonal and environmental factors. IC is the most common liver disease specific to pregnancy [1]. The global incidence of IC is likely to vary from 1% to 27.6%, depending on the geographic variations, differences in sensitivity between ethnic groups and environmental factors [2-4].

The diagnosis of ICP involves the diagnosis of exclusion, and the diagnosis is confirmed by the regression of symptoms and changes in the laboratory parameters after birth. The classic maternal manifestation of pregnancy-induced IC is a generalised rash without itch. Itching is a common symptom in pregnancy. A diagnosis of ICP is made when serum bile acid or aminotransferase levels increases with pruritus. Pruritus of cholestasis is different from other diseases characterised by high transaminase levels, such as acute fatty liver of pregnancy and haemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome or severe preeclampsia. The absence of primary skin lesions together with itching helps distinguish pruritus of cholestasis from pruritic dermatoses specific to pregnancy and skin conditions not related to pregnancy. An infectious etiology is excluded through serological tests [4].

No strong evidence exists regarding the association between ICP and adverse pregnancy outcomes. Observational studies have reported a relationship between ICP and adverse pregnancy outcomes, such as spontaneous preterm labour, meconium passage, foetal distress and stillbirth [3, 4]. However, the frequency of adverse pregnancy outcomes reported in these studies is believed to vary widely depending on the criteria used in the definition of ICP, the limited number of patients included in these studies and changes in the management of cholestasis in recent years. In the last two decades, ursodeoxycholic acid has been widely used for ICP treatment and elective termination of pregnancy at 37 weeks of gestation is advised by internationally

Cite this article as: Cimilli Senocak GN, Topdagi Yilmaz EP. Maternal and Fetal Outcomes in Pregnancies Complicated by Intrahepatic Cholestasis. *Eurasian J Med* 2019; 51 (3): 270-2.

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Received: December 6, 2018
Accepted: December 6, 2018

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DOI 10.5152/eurasianjmed.2019.18447



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recognized organisations like American College of Obstetrics Gynecologists (ACOG), although it is not evident that it decreases perinatal mortality [4, 5].

Materials and Methods

The maternal and foetal outcomes in women diagnosed with ICP at our hospital between January 2012 and December 2017 were assessed. The diagnosis of ICP was based on clinical examinations. The study was approved by Ataturk University Clinical Investigations' Ethical Committee.

All women included in the study had generalised pruritus in the absence of any dermatological condition, viral hepatitis, hypertensive diseases of pregnancy and other hepatobiliary diseases and all symptoms related with ICP had regressed as clinically or laboratory at post-delivery period.

In our clinic, the women suspected of having ICP had a routine investigation and followup period. Initially, all of the women with ICP underwent liver function tests (LFTs), such as serum aspartate transferase (AST), serum alanine transferase (ALT), direct/indirect bilirubin, lactate dehydrogenase, alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase tests, 24-h urine collection for protein excretion, viral hepatitis serology and abdominal sonography. All women had normal ultrasonography of the liver and biliary tract. Thereafter, they biweekly underwent nonstress test (NST) and amniotic fluid (AF) volume assessment using the fourquadrant AF index and weekly underwent LFTs. All women were administered ursodeoxycholic acid (started at 1 g/day and increased up to 20 mg/kg/day as needed) and antihistamines if needed.

Statistical Analysis

The printed and electronic files of all women were reviewed, and demographic data and pregnancy outcome measures were collected retrospectively. Descriptive statistics were used to analyse data. The one-sample Kolmogorov-Smirnov test was used to test normal distribution. All analyses were performed using the Statistical Package for Social Sciences software (SPSS) version 23 (IBM Corp.; Armonk, NY, USA).

Results

The maternal and foetal outcomes in 70 consecutive women with ICP during the study period were assessed. Patient characteristics are shown in Table 1. There were 25 (26%) primipar women. In 63 (90%) women, the onset of symptoms was after 30 weeks of gestation. There were 19 (27 %) women at ≤ 32 gestational weeks and

27 (39%) at ≤ 34 gestational weeks. Four (6%) women had a history of ICP and three (4%) had a history of severe preeclampsia or the HELLP syndrome. At least one of the liver transaminases (ALT/AST) were elevated in 61 (87%) women, and both ALT and AST were elevated in 50 (71%) women. ALP was elevated in 28 (40%) women and total bilirubin levels were elevated in 51 (73%) women.

The follow-up and delivery outcomes are presented in Table 2. Despite ursodeoxycholic acid treatment, 10 (14%) women experienced severe pruritus and 8 (11%) women developed preeclampsia. The median week of delivery was 37, and the median period of diagnosis to delivery interval was 1 week. The number of women who delivered at ≤ 37 , ≤ 36 , ≤ 34 and ≤ 32 weeks' gestation was 47 (67%), 28 (40%), 11 (16%) and 5 (7%), respectively. Ten (14%) women delivered spontaneously at ≤ 36 weeks' gestation. The number of foetuses with birth weight under 2500 g and 1500 g was 20 (29%) and 3 (4%), respectively. There were 3 (4%) small-for-gestational-age (SGA) foetuses at birth. Four (6%) foetuses had a pH of < 7.2 , and there was no perinatal death. Three neonates were hospitalised for more than 24 h at a third-

level neonatal intensive care unit. None of the neonates had birth asphyxia. Also none of the women had eventful postpartum course.

Discussion

The maternal and foetal demographic data and outcomes in 70 women with ICP were assessed. Most of the women delivered at ≤ 37 weeks' gestation. The preterm delivery (≤ 36 weeks' gestation) and spontaneous preterm delivery rates were high. The incidence of foetuses with SGA was low; however, the number of foetuses with low birth weight was more, resembling the high preterm delivery rate. A high rate of preeclampsia was noted. No adverse maternal outcomes or perinatal deaths were observed.

Two recent large retrospective cohort studies conducted in Sweden and Australia reported favourable outcomes associated with ICP [3, 6]. The study conducted in Sweden reported an increased risk of preterm delivery, gestational diabetes and preeclampsia but not of stillbirth associated with ICP [3]. The study conducted in Australia reported on generally favourable outcomes associated with ICP, such as mild or severe outcomes with no stillbirths [6]. They reported a higher incidence of gestational diabetes, preeclampsia and/or spontaneous preterm labour in women with ICP compared to the general population [6]. These high rates of preterm delivery but not of stillbirths should be considered in the management of ICP. Authors of both cohort studies have argued that no increase in stillbirth rate was likely secondary to proactive medical management. The American College of Obstetricians and Gynaecologists endorses active management protocols for ICP [5]. However, several practitioners were against

Table 1. Patient characteristics. Data are presented as n (%), mean \pm standard deviation and median (minimum–maximum) wherever appropriate

Variable	Results
Age, years	29 \pm 5
Gravida	2 (1-5)
Parity	1 (0-4)
Primipara	25 (36)
Gestational week at diagnosis	35 (19-40)
Previous ICP	4 (6)
Previous HELLP/severe preeclampsia	3 (4)
Previous caesarean delivery	12 (17)
Haemoglobin, g/dL	13 (10-16)
% of women with elevated LFT at diagnosis	
ALT	58 (83)
AST	53 (76)
Total bilirubin	51 (73)
LDH	5 (7)
ALP	28 (40)
Severe pruritus	10 (14)

ICP: intrahepatic cholestasis of pregnancy; HELLP: haemolysis, elevated liver enzymes and low platelet count; LFT: liver function tests; ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDH: lactate dehydrogenase, ALP: alkaline phosphatase
Cut-offs for ALT, AST, total bilirubin, LDH, ALP: 40 IU/dL, 40 IU/dL, 1.2 mg/dL, 525 U/L, 250 U/L, respectively

Table 2. Follow-up and delivery outcomes. Data are presented as n (%), mean \pm standard deviation and median (minimum–maximum) where appropriate

Variable	Results
Preeclampsia	8 (11)
Gestational week at delivery	37 (26-42)
Diagnosis-delivery interval, weeks	1 (0-4)
Caesarean delivery	47 (67)
Spontaneous onset of preterm delivery	10 (14)
Foetal weight	2820 \pm 604
Foetal weight < 10 centile	3 (4)
Umbilical vein pH < 7.20	4 (6)
Third level ICU admission > 24 hours	5
Stillbirth	-
Neonatal death	-

ICU: intensive care unit

proactive management [7, 8]. They proposed that given the relatively low frequency of stillbirths, the historically reported stillbirth rate in pregnancy with ICP does not have sufficient power to accept that stillbirth rate increased in ICP [7, 8]. The Royal College of Obstetrics and Gynaecologists does not support routine active management of ICP-affected pregnancies [8].

The onset of symptoms occurred in the third trimester in 90% of the women presenting after 30 weeks of gestation, which is similar to that reported in other studies [9, 10]. A vast majority of women had elevated AST or ALT. In addition to symptoms, elevated serum bile acid levels are considered in the diagnosis of ICP in a majority of studies [3, 4, 6]. However, the onset of pruritus in ICP precedes the elevation of bile acids by 3 weeks on an average [9]. The levels of ALT and AST also increase in a majority of women with ICP, and the elevation may precede an increase in bile acid levels by 1-2 weeks [9]. The relative levels of serum bile acids and serum transaminases for the diagnosis of ICP is debatable because it is not yet established which of the two is the best prognostic indicator [11].

The sample size and retrospective nature of our study limited the results. However, these concerns are generally valid for all the available literature on ICP. The incidence of ICP is low; this is the limiting factor for conducting prospective studies. We believe that it is necessary to clarify whether ICP-related prematurity is due to spontaneous or iatrogenic preterm birth. We

recommend individual management of ICP-affected pregnancies rather than routine early delivery, given that there is no substantial evidence indicating that ICP increases the rate of stillbirth.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Ataturk University.

Informed Consent: Informed consent was obtained from the patients.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – G.N.C.S., E.P.T.Y.; Design – G.N.C.S., E.P.T.Y.; Supervision – G.N.C.S., E.P.T.Y.; Resources – G.N.C.S., E.P.T.Y.; Materials – G.N.C.S., E.P.T.Y.; Data Collection and/or Processing – G.N.C.S., E.P.T.Y.; Analysis and/or Interpretation – G.N.C.S., E.P.T.Y.; Literature Search – G.N.C.S., E. P. T.Y.; M.A.A.; Writing Manuscript – G.N.C.S., E.P.T.Y.; Critical Review – G.N.C.S., E.P.T.Y.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: Only routine patient examinations were used for our study.

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