Influence of severity of total bile acids and mode of delivery on the perinatal outcomes in intrahepatic cholestasis of pregnancy

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Abstract

To assess the associations between mode of delivery and pregnancy outcomes in patients with intrahepatic cholestasis of pregnancy (ICP) based on the severity of maternal hypercholanemia. A hospital-based retrospective cohort study was performed between January 1, 2015, and December 31, 2019. Among the 177 women with mild total bile acids, 123 (69.5%) had a vaginal delivery and 54 (30.5%) underwent a cesarean delivery, of which 42 (23.7%) were planned and 12 (6.8%) were unplanned. Among the 50 severe ICP women, 13 (26.0%) had a vaginal delivery and 37 (74.0%) underwent a cesarean delivery, of which 26 (52.0%) were planned and 11 (22.0%) were unplanned. Severe ICP was associated with an increased risk of preterm delivery ($P < 0.001$), low birthweight ($P = 0.001$), and neonatal intensive care unit admission ($P < 0.001$). Women with severe ICP (aOR, 5.017; 95% CI 1.848–13.622), planned cesarean delivery (aOR, 5.444; 95% CI 1.723–17.203), or unplanned cesarean delivery (aOR, 5.792; 95% CI 1.384–24.236) had increased risks of adverse fetal outcomes compared to controls. Both planned and unplanned cesarean delivery are associated with a higher incidence of adverse fetal outcomes and severe ICP than vaginal delivery.

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is characterized by unexplained maternal pruritus, raised serum bile acids and/or liver transaminases during the late second and third trimester of pregnancy¹. Currently, the etiology of ICP is not fully understood but may be affected by hormonal, genetic, and environmental factors².

Although ICP was thought to be a relatively benign condition, recent studies have indicated that ICP has adverse effects for both the mother and fetus, including a notably higher risk of developing preeclampsia and gestational diabetes mellitus (GDM)^{3–5}. Additionally, ICP is associated with increased risk for preterm delivery⁶, meconium staining of the amniotic fluid (MSAF)⁷, neonatal intensive care unit admission (NICU)⁸, and stillbirth⁹, especially in cases of severe ICP.

Glantz A, et al recently demonstrated that adverse pregnancy outcomes (AFOs) did not occur until maternal serum bile acids were $> 40 \mu\text{mol/L}$ ¹⁰; however, to date, no studies have been large enough to analyze the relationship between maternal serum bile acids and stillbirth. Fortunately, previous studies reported that stillbirth in ICP tended to happen after 37 weeks of pregnancy. Therefore, to prevent stillbirth, induction of labor has become common practice, especially in severe patients. Furthermore, a large retrospective cohort study demonstrated that the risks of emergency caesarean delivery (CD) or fetal asphyxia were not increased after induction of labor in women with ICP during gestational weeks 37–39¹¹. Compared with normal women, patients with ICP did not have increased risk of CD¹²; however, the relationship between the mode of delivery and maternal serum bile acids is not completely understood, and the risk for AFOs warrants further investigation.

The aim of this study was to analyze the delivery outcomes of women with severe ICP compared with mild ICP, to assess the risk for planned and unplanned CD, and to evaluate the association with risk factors and AFOs.

Results

Two hundred twenty-seven pregnancies (177 mild and 50 severe ICP) met the inclusion criteria. The demographic and obstetric characteristics of the patients in the mild group and severe group are presented in Table 1. Compared to women with mild ICP, women with severe ICP were more likely to have preterm delivery ($P < 0.001$), low birth weight ($P = 0.001$), and a higher incidence of NICU admission ($P < 0.001$) (Table 1). Women with severe ICP also had a significantly higher incidence of planned and unplanned CD compared with mild ICP subjects (52.0% vs 23.7% and 22.0% vs 6.8%, respectively; $P < 0.001$; Table 1 and Fig. 1).

Table 1
Obstetric and demographic characteristics of patients with mild and severe
intrahepatic cholestasis of pregnancy

	Mild ICP (n = 177)	Severe ICP (n = 50)	P value
Maternal age (years)	26.7 ± 3.1	26.9 ± 3.4	0.684
pBMI (Kg/m ²)	22 ± 3.6	21.1 ± 3.2	0.101
Gestational diabetes mellitus	18(10.2)	3(6)	0.534
Hypertension	8(4.5)	2(4)	1
Preeclampsia	20(11.3)	8(16)	0.372
Premature rupture of membranes	36(20.3)	6(12)	0.180
Meconium-stained amniotic fluid	29(16.4)	7(14)	0.684
Delivery gestational age			
≥ 37 weeks	162(91.5)	30(60)	0.000
34 to 37 weeks	10(5.7)	16(32)	
≤ 34 weeks	5(2.8)	4(8)	
Birth weight			
≤2500 g	12(6.8)	14(28)	0.001
2500 to 4000 g	155(87.6)	34(68)	
≥4000 g	10(5.7)	2(4)	
Fetal asphyxia	5(2.8)	5(10)	0.073 ^a
Stillbirth	2(1.1)	1(2)	0.528 ^a
NICU admission	15(8.5)	16(32)	0.000
Mode of delivery			
Vaginal delivery	123(69.5)	13(26)	0.000
Planned caesarean delivery	42(23.7)	26(52)	
Unplanned caesarean delivery	12(6.8)	11(22)	
^a Fisher's exact			
Abbreviations: pBMI, pregestational body mass index			

Based on mode of delivery, a total of 227 women with ICP were divided into vaginal delivery (60.0%) and CD (40%). Women with vaginal delivery were generally younger ($P=0.017$) and had a lower BMI ($P=0.017$) than women with CD (Table 2). Additionally, a significant increase in the incidence of preeclampsia ($P=0.001$) and decrease in PROM ($P=0.002$) was found in women with CD compared with control subjects (Table 2). Women with CD also had a significantly higher incidence of preterm delivery ($P<0.001$), low birth weight ($P<0.001$), and NICU admission ($P<0.001$) (Table 2).

Table 2
Obstetric and demographic characteristics of women undergoing vaginal delivery or caesarean delivery with intrahepatic cholestasis of pregnancy

	Vaginal delivery (n = 136)	Caesarean delivery (n = 91)	P value
Maternal age (years)	26.3 ± 2.7	27.3 ± 3.6	0.017
pBMI (Kg/m ²)	21.4 ± 3.0	22.5 ± 4.0	0.017
Gestational diabetes mellitus	10(7.4)	11(12.1)	0.228
Hypertension	7(5.1)	3(3.3)	0.737 ^a
Preeclampsia	9(6.6)	19(20.9)	0.001
Premature rupture of membranes	34(25)	8(8.8)	0.002
Meconium-stained amniotic fluid	25(18.4)	11(12.1)	0.203
Delivery gestational age			
≥ 37 weeks	129(94.9)	63(69.2)	0.000
34 to 37 weeks	4(2.9)	22(24.2)	
≤ 34 weeks	3(2.2)	6(6.6)	
Birth weight			
≤2500 g	5(3.7)	21(23.1)	0.000
2500 to 4000 g	124(91.2)	65(71.4)	
≥4000 g	7(5.1)	5(5.5)	
Fetal asphyxia	5(3.7)	5(5.5)	0.746 ^a
Stillbirth	3(2.2)	0(0)	-
NICU admission	7(5.1)	24(26.4)	0.000
^a Fisher's exact			

To better understand the differences between planned and unplanned CD, we performed a subgroup analysis. No significant differences in maternal age, pBMI, or the incidence of GDM, hypertension, preeclampsia, preterm delivery, low birth weight, and NICU admission were found (Table 3). Interestingly, compared with planned CD, women with unplanned CD were more likely to have PROM ($P=0.003$) and MSAF ($P=0.006$) (Table 3). Unexpectedly, the severity of ICP was not significantly different in planned compared to unplanned CD (aOR 2.184, 95% CI 0.632–7.545, $P=0.217$) (Table 4). Moreover, when compared to vaginal delivery, both women with planned and unplanned CD had a higher risk of severe ICP (aOR 6.374, 95% CI 2.751–14.767, $P<0.001$; aOR 14.333, 95% CI 4.634–44.330, $P<0.001$, respectively), and women with planned CD had a higher incidence of preeclampsia (aOR 3.767, 95% CI 1.299–10.921, $P=0.015$) (Table 4). Moreover, a significantly lower risk for premature rupture of membranes was found in planned CD compared to women with vaginal delivery (aOR 0.087, 95% CI 0.019–0.399, $P=0.002$) (Table 4).

Table 3
Obstetric and demographic characteristics of women undergoing planned or unplanned caesarean delivery with intrahepatic cholestasis of pregnancy

	Planned CD (n = 68)	Unplanned CD (n = 23)	P value
Maternal age (years)	27.3 ± 3.7	27.2 ± 3.7	0.892
pBMI (Kg/m ²)	22.2 ± 3.7	23.3 ± 4.9	0.281
Gestational diabetes mellitus	9(13.2)	2(8.7)	0.836 ^a
Hypertension	2(2.9)	1(4.3)	1
Preeclampsia	15(22.1)	4(17.4)	0.858
Premature rupture of membranes	2(2.9)	6(26.1)	0.003
Meconium-stained amniotic fluid	4(5.9)	7(30.4)	0.006 ^a
Delivery gestational age			
≥ 37 weeks	46(67.6)	17(73.9)	0.631
34 to 37 weeks	18(26.5)	4(17.4)	
≤ 34 weeks	4(5.9)	2(8.7)	
Birth weight			
≤2500 g	15(22.1)	6(26.1)	0.192
2500 to 4000 g	51(75)	14(60.9)	
≥4000 g	2(2.9)	3(13)	
Fetal asphyxia	2(2.9)	3(13.0)	0.100 ^a
Stillbirth	0(0)	0(0)	-
NICU admission	18(26.5)	6(26.0)	0.971
^a Fisher's exact			

Table 4

Adjusted ORs for pregnancy comorbidities in women undergoing planned caesarean delivery, unplanned caesarean delivery and vaginal delivery with intrahepatic cholestasis of pregnancy

Variables	Planned CD £		Unplanned CD £		Unplanned CD #	
	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Severe ICP ¹	6.374(2.751–14.767)	0.000	14.333(4.634–44.330)	0.000	2.184(0.632–7.545)	0.217
Gestational diabetes mellitus	2.748(0.792–9.529)	0.111	1.608(0.244–10.589)	0.621	0.497(0.069–3.581)	0.488
Hypertension	0.307(0.048–1.971)	0.213	0.518(0.046–5.880)	0.595	1.717(0.114–25.820)	0.696
Preeclampsia	3.767(1.299–10.921)	0.015	2.937(0.668–12.921)	0.154	0.750(0.162–3.479)	0.713
PROM	0.087(0.019–0.399)	0.002	1.484(0.461–4.773)	0.508	20.366(3.078–134.759)	0.002
MSAF	0.283(0.085–0.949)	0.041	2.361(0.736–7.571)	0.148	9.061(1.973–41.610)	0.005
Abbreviations: PROM, Premature rupture of membranes; MSAF, meconium staining of the amniotic fluid						
¹ Reference category is mild ICP						
£Controls are the Vaginal delivery						
# Controls are the planned Caesarean delivery						
ORs are adjusted for maternal age, pBMI, TBA level, Gestational diabetes mellitus, Hypertension, Preeclampsia, PROM, and MSAF.						

We discovered a strong association between severe ICP and AFOs (aOR 3.232, 95%CI 1.426–8.602, $P=0.021$) (Table 5). Compared to vaginal birth, patients who underwent both planned and unplanned CD had a higher risk of AFOs (aOR 4.429, 95%CI 1.654–12.301, $P=0.004$; aOR 4.762, 95%CI 1.295–18.374, $P=0.018$, respectively) (Table 5). Among GDM, hypertension, preeclampsia, MSAF, and PROM, only women with preeclampsia were significantly more likely to have AFOs (aOR 9.362, 95%CI 4.029–20.782, $P<0.001$) (Table 5).

Table 5

Adjusted ORs for predictors of poor neonatal outcome in intrahepatic cholestasis of pregnancy

Variables	Adjusted OR £ (95% CI)	P value
Severe ICP ¹	3.232(1.426–8.602)	0.021
Gestational diabetes mellitus	1.425(0.347–5.239)	0.636
Hypertension	2.946(0.578–11.042)	0.257
Preeclampsia	9.362(4.029–20.782)	0.000
Premature rupture of membranes	1.643(0.594–6.093)	0.534
MSAF	0.792(0.234–2.285)	0.834
Planned caesarean delivery ²	4.429(1.654–12.301)	0.004
Unplanned caesarean delivery ²	4.762(1.295–18.374)	0.018
Planned caesarean delivery ³	1.973(0.659–5.382)	0.694
¹ Reference category is mild ICP		
² Reference category is vaginal delivery		
³ Reference category is unplanned caesarean delivery		
£Controls are the women without poor neonatal outcome		
ORs are adjusted for maternal age, pBMI, TBA level, Gestational diabetes mellitus, Hypertension, Preeclampsia, PROM, mode of delivery and MSAF.		

The indications for planned/unplanned CD in women with mild or severe ICP are shown in Table 6. Of the 42 women with mild ICP who underwent CD, 10 (23.8%) had severe preeclampsia, 9 (21.4%) malpresentation, 15 (35.7%) were elective. Most planned CD for patients with severe ICP were due to Fetal risk factors (69.2%). Of the 12 unplanned CD among women with mild ICP, 5 (41.7%) were due to arrest of descent/dilation, 3 (25%) were due to abnormal fetal heart rate. Among unplanned CD women with severe ICP, 3 (27.3%) had an arrest of descent/dilation, 4 (36.4%) had abnormal fetal heart rate, 3 (27.3%) had PROM + MSAF.

Table 6
Indications for planned or unplanned caesarean delivery

	Mild ICP	Severe ICP
Planned caesarean delivery	n = 42	n = 26
Severe preeclampsia	10(23.8)	2(7.7)
malpresentation	9(21.4)	1(3.8)
Fetal risk factors	8(19.0)	18(69.2)
Elective	15(35.7)	5(19.2)
Unplanned caesarean delivery	n = 12	n = 11
Arrest of descent/dilation	5(41.7)	3(27.3)
abnormal fetal heart rate	3(25)	4(36.4)
PROM + malpresentation	1(8.3)	1(9.0)
PROM + MSAF	3(25)	3(27.3)
Abbreviations: PROM, premature rupture of membranes; MSAF, meconium staining of the amniotic fluid.		

Discussion

The present data indicate that women with severe ICP have an increased risk of CD, including planned and unplanned CD, and a higher incidence of AFOs, compared to women with mild ICP. CD, especially planned CD, was associated with an increased risk of severe ICP, preeclampsia, and AFOs compared to vaginal delivery. Except for PROM and MSAF, no differences in the main obstetric complications and fetal outcomes were found between planned and unplanned CD.

Tetsuya Kawakita et al. reported that the rate of CD in women with mild or severe ICP was less than 40%⁹. In our study, almost 70% of patients with mild ICP underwent vaginal delivery, while only 26% of patients with severe ICP underwent vaginal delivery. Given that patient preference to choose CD to avoid stillbirth while with severe ICP, the increased incidence of CD in women with a TBA level $\geq 40 \mu\text{mol/L}$ is not unexpected. Moreover, another study revealed that women with ICP during gestational weeks 37–39 had no increased risk of emergency CD compared to women without ICP; however, this study was limited to gestational weeks 37–39 and lacked data regarding preterm birth¹¹. As many authors have advocated the implementation of elective early delivery for ICP, especially for severe ICP^{13, 14}, the rates of planned and unplanned CD in our patients with severe ICP were higher than patients with mild ICP.

In addition, with the increase in maternal age as well as pregestational BMI, the incidence of CD increased^{15–17}. In our study, the maternal age and pregestational BMI in the CD group were significantly

higher than the vaginal birth group; however, no statistically significant differences in maternal age and pregestational BMI between planned CD and unplanned CD were found. These data may indicate that women suffering from ICP with advancing age and increasing pregestational BMI may contribute to CD, including planned and unplanned CD.

Recent studies have reported that an elevated TBA level may cause preeclampsia or GDM^{3, 5}. Although our study did not find a higher incidence of preeclampsia in women with severe ICP compared to mild ICP, which occurs most often 2–4 weeks after the diagnosis of ICP, and still occurred even though TBA levels decreased toward the normal range according to a recent study from Raz et al.³, we revealed that CD was associated with preeclampsia. Moreover, compared to vaginal delivery, CD in cases of ICP was associated with an increased risk of preeclampsia even after adjusting for maternal age, BMI and other confounders; however, after adjusting for confounders, preeclampsia was not associated with the mode of CD. Unexpectedly, our study did not find that GDM was concomitant with ICP severity at initial diagnosis, which is similar to that reported by Dan Shan, et al.¹⁸. Additionally, no statistically significant difference was found in the incidence of GDM between CD and vaginal delivery, or between planned and unplanned CD. Advanced age and increased pregestational BMI may contribute more to the pathogenesis of GDM, in addition to the known effects on bile acid homeostasis.

Previous studies have reported that high bile acid levels could cause MSAF^{7, 18}. Moreover, previous reports have indicated that MSAF is more likely to occur during later compared to earlier gestation, which may be due to the higher bile acid concentrations in amniotic fluid and a more advanced maturation of the gastrointestinal tract⁷. Women with severe ICP might reduce the incidence of MSAF by choosing to deliver before week 37. Interestingly, women undergoing CD did not suffer from higher MSAF than those who underwent vaginal delivery; however, after CD was further divided into planned and unplanned CD, unplanned CD was associated with a higher risk of MSAF than planned CD in our study. Although our study did not find MSAF to be associated with an increased risk of AFOs, obstetricians usually make decisions by considering the MSAF and the time to delivery to prevent newborns from developing meconium aspiration syndrome, which can be fatal.

Although there are no randomized studies investigating the optimal timing of delivery for women with ICP, a majority of researchers have advocated the implementation of elective early delivery for ICP, especially for those patients with TBA levels $\geq 40 \mu\text{mol/L}$ ¹³. Most spontaneous or induced onset of early term labor did not increase the incidence of CD; however, many women with ICP in need of induction of labor underwent CD directly, which may have increased the incidence of CD in our study. Furthermore, to find the potential risk factors associated with CD, we analyzed the indication for these CD cases, which might diverge from current guidelines, containing planned and unplanned CD with different ICP severity. More than half of planned CD with severe ICP occurred due to fetal risk factors, while most unplanned CD with severe ICP occurred for abnormal fetal heart rate, arrest of descent/dilation, and PROM + MSAF. Although the mechanism for the high rate of these events in severe ICP undergoing CD remains unclear, these

indications were the reason the obstetrician chose planned or unplanned CD to prevent poor prognosis, especially stillbirth.

As reported in previous studies, severe ICP as well as preeclampsia are risk factors of AFOs^{19,20}, including preterm delivery, low birth weight, NICU admission, and stillbirth^{12,21}. This study found that both planned and unplanned CD cases had increased fetal complications compared to vaginal delivery in ICP patients. Later birth might increase the rate of stillbirth, and CD was associated with AFOs do make sense. Further research is needed to identify the ideal time of birth with regard to neonatal outcomes and to reduce the rates of CD if possible.

The present retrospective study has several limitations. Although the patients in our study were treated with UDCA, except for those who delivered before ICP diagnosis, the lack of data regarding the specific time and dose of UDCA use limited our ability to analyze the effect of UDCA on TBA levels. A previous study indicated that UDCA treatment appeared to improve the prognosis of both women with ICP and the fetus²². However, Tetsuya Kawakita, et al. concluded that UDCA was not associated with a reduction in the risk of AFOs⁹. Additionally, since the study presented here was retrospective, we could not evaluate any rare outcomes such as intracranial hemorrhage, and sepsis.

In summary, the present retrospective study demonstrates a significantly increased incidence of CD, including planned and unplanned, in women with severe ICP. Severe ICP with planned or unplanned CD was associated with AFOs, suggesting that further prospective studies are warranted to identify the proper delivery mode to improve fetal outcome and prevent stillbirth.

Methods

The data for the retrospective cohort study were obtained from January 1, 2015, to December 31, 2019 at the Changzhou Maternal and Child Health Care Hospital in Jiangsu (China), where 10,000-12,000 deliveries per year are performed. All methods were carried out in accordance with relevant guidelines and regulations. Women with fasting serum bile acid levels of more than 10 $\mu\text{mol/L}$ and pruritus of unexplained cause were included in the study. Since multiparas and women with twin pregnancies might influence the mode of delivery directly, only nulliparous women with a singleton fetus were invited to participate in the study. Women were excluded if they had viral or autoimmune hepatitis, liver or biliary disease, and fetal chromosomal abnormalities or fetal malformation. The study protocol was approved by the Ethical Committee of the University and the Hospital. All recruited participants provided their written informed consent.

The patients were diagnosed according to the relevant ICD-10 code (O26.6). The women received ursodeoxycholic acid (UDCA) therapy, and fetal monitoring was performed more than once per day before delivery, except in cases where delivery occurred before ICP diagnosis. For the primary analysis, ICP severity was defined according to TBA levels as mild (10-39.9 $\mu\text{mol/L}$) or severe (≥ 40 $\mu\text{mol/L}$). Women

with ICP were grouped based on vaginal delivery or CD (planned CD and unplanned CD). Information on maternal demographics, medical comorbidities, and AFOs was collected for evaluation.

The AFOs assessed included an Apgar score of less than 7 at 5 minutes, meconium aspiration, neonatal unit admission, and stillbirth. Preterm birth was defined as a gestational age before 37 completed gestational weeks. Information regarding the occurrence of GDM, gestational hypertension, preeclampsia, premature rupture of membranes (PROM), and other pathologies was also retrieved from the medical records.

Planned CD was defined as the intended mode of delivery, whereas all other CD were classified as unplanned. The indications for planned CD were severe preeclampsia, malpresentation, fetal risk factors (estimated macrosomia, fetal intrauterine growth restriction, oligohydramnios and other cases of fetal intolerance of labor), and elective. The indications for unplanned CD were arrest of descent/dilation, abnormal fetal heart rate, PROM + malpresentation, and PROM+MSAF.

A two-tailed t-test was used to analyze continuous variables, and the χ^2 or Fisher's exact test was used to analyze qualitative variables. Univariate and multivariate logistic regression analyses were also performed. Statistical significance was defined as p-values<0.05, and the data were analyzed using the statistical software package SPSS 17.0.

Abbreviations

ICP: intrahepatic cholestasis of pregnancy; AFOs: adverse fetal outcomes; TBA: total bile acids; CD: cesarean delivery; NICU: neonatal intensive care unit; pBMI: pregestational body mass index; GDM: gestational diabetes mellitus; MSAF: meconium staining of the amniotic fluid; UDCA: ursodeoxycholic acid; PROM: premature rupture of membranes.

Declarations

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Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Author contribution

C.C. Kong and F.L. Mei contributed equally to this work. C.C. Kong was responsible for the conception and design of the study. F.L. Mei, P.P. Xue, and J.Y. Cao were responsible for the acquisition of data. Y. Li performed the Formal analysis. F.L. Mei, Y.S. Dong and C.C. Kong drafted the manuscript. C.C. Kong revised and commented on the draft, and all authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

This study was approved by the Human Research Ethics Committee, Nanjing Medical University. Permission was sought from Medical Record Office on use of patient files. All recruited participants provided their written informed consent.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

Mode of delivery in cases of mild and severe intrahepatic cholestasis of pregnancy