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Women successfully treated for severe intrahepatic cholestasis of pregnancy do not have increased risks for adverse perinatal outcomes

Jielian Yang, BS[a], Chong Chen, MS[b], Min Liu, MD[a,*], Shuye Zhang, MD[c]

Abstract

Intrahepatic cholestasis of pregnancy (ICP) increases adverse perinatal outcome (APO) incidence. Whether successful treatment of severe ICP reduces APO risk is unclear.

This retrospective, single-center study in China enrolled consecutive women with ICP who had term delivery (≥37 weeks, singleton) between August 2013 and June 2016. Patients were divided into the mild ICP (serum bile acids (SBA) ≤40 μmol/L throughout pregnancy) and severe ICP (SBA >40 μmol/L during pregnancy but fell after ursodeoxycholate therapy) groups. Baseline characteristics, laboratory investigations, and maternal and neonatal outcomes were assessed. Logistic regression was used to identify factors associated with meconium staining of amniotic fluid (MSAF) and APOs.

Seventy-three patients were included (mild ICP group, $n=47$; severe ICP group, $n=26$). Pruritus was more common in the severe ICP group (65.4% vs 40.4%; $P<.05$), but other baseline characteristics were similar. Compared with the mild ICP group, the severe ICP group had higher SBA at first visit and peak value, higher direct bilirubin before delivery and 4 days postpartum, and lower gamma-glutamyltransferase at peak value, before delivery and 4 days postpartum ($P<.05$). Other laboratory parameters, type of delivery, hemorrhage, and liver function abnormality were similar between groups, although the severe ICP group had longer duration of hepatic dysfunction ($P<.05$). Birth weight was lower in the mild ICP group ($P<.05$), but other fetal outcomes were similar between groups. Logistic regression identified no factors (including SBA group) associated with APOs or MSAF.

Women successfully treated for severe ICP do not have increased risks for APOs.

Abbreviations: ALB = albumin, ALT = alanine transaminase, APO = adverse perinatal outcome, AST = aspartate transaminase, CHE = cholinesterase, DBIL = direct bilirubin, GGT = gamma-glutamyltransferase, ICP = Intrahepatic cholestasis of pregnancy, MSAF = meconium staining of amniotic fluid, SAMe = S-adenosylmethionine, TBA = total bile acids, TBIL = total bilirubin, TP = total protein, UDCA = Ursodeoxycholate.

Keywords: adverse perinatal outcome, birth weight, intrahepatic cholestasis of pregnancy, serum bile acid, ursodeoxycholic acid

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1. Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-associated liver disease with an incidence of 0.25% to 1.5% in the USA and Europe[1–3] and as high as 5.2% in China.[4] ICP usually presents in late pregnancy with pruritus and abnormal liver function tests.[5] The symptoms of ICP resolve rapidly after labor but are likely to recur in subsequent pregnancies.[5] The clinical significance of ICP is associated with its increased risk for adverse pregnancy and perinatal outcomes, including preterm delivery, meconium staining of amniotic fluid (MSAF), low Apgar score, and stillbirth.[6] The increase in total bile acids (TBA) seen in ICP may involve the cholestatic effect of reproductive hormones, and it is thought that the accumulation of toxic bile acids in the fetal compartment may underlie the deleterious effects on pregnancy outcomes.[7] Ursodeoxycholate (UDCA) is now widely utilized for the treatment of ICP. UDCA decreases maternal symptoms and serum bile acid (SBA) levels, but whether it improves fetal outcomes is unclear.[8]

Currently, the American College of Obstetricians and Gynecologists does not have a guideline on the management of ICP, whereas the Royal College of Obstetricians and Gynecologists (RCOG)[9] and the Chinese Medical Association for Obstetrics and Gynecology[10] published guidelines for the management of ICP in 2011. Due to concerns regarding stillbirth later in pregnancy, the widely adopted practice in western

countries is to recommend delivery at 37 weeks or at diagnosis if this is made later than 37 weeks.[11–13] In contrast, the Chinese guideline recommends the induction of labor at 34 to 37 weeks of gestation in women with a SBA level >40 μmol/L and a continuation of pregnancy until the estimated due date in women with a SBA level <30 μmol/L; for women with a SBA level of 30 to 40 μmol/L, it is recommended that an individual decision be made carefully by the obstetrician.[10]

It has been reported that severe ICP (defined as a SBA level >40 μmol/L) is associated with higher incidences of preterm delivery, MSAF and adverse neonatal outcomes than mild ICP (SBA level ≤40 μmol/L).[14–16] Furthermore, several studies have provided evidence that, compared with control populations, severe ICP is associated with adverse fetal and maternal outcomes (including spontaneous preterm delivery, fetal asphyxia, MSAF, and preeclampsia) whereas mild ICP is not.[3,17,18] Furthermore, for maternal SBA levels >40 μmol/L, significant relationships were identified between SBA level and preterm delivery, spontaneous preterm delivery, stillbirth, and MSAF.[19] However, it remains unknown whether the risk of adverse perinatal outcomes remains elevated in women who are initially diagnosed with severe ICP but whose SBA levels are subsequently maintained <40 μmol/L by treatment.

We hypothesized that women with severe ICP who are successfully treated (such that their SBA levels fall <40 μmol/L) would not have an increased risk of adverse perinatal outcomes. Therefore, we conducted a retrospective cohort study to determine whether successful treatment of severe ICP would reduce the risk of adverse perinatal outcomes.

2. Patients and methods

2.1. Patients

This retrospective study included consecutive patients diagnosed with ICP at the Shanghai Public Health Clinical Center of Gynecology and Obstetrics (August 2013–June 2016). Our Institutional Ethics Committee approved this study. Individual written informed consent was waived, as the study was retrospective, anonymous and used only existing data.

The inclusion criteria were:

1) a diagnosis of ICP[9] was made based on fasting SBA >10 μmol/L, elevated levels of liver transaminases and pruritus;
2) other causes of liver dysfunction were excluded, such as viral hepatitis, preeclampsia, HELLP (hemolysis, elevated liver enzymes and low platelet count) syndrome and autoimmune liver disease; and
3) ICP resolved within 4 weeks postpartum.

The exclusion criteria were:

1) multiple pregnancies;
2) women with a fasting SBA >40 μmol/L at any stage during their pregnancy whose SBA level did not respond sufficiently to treatment with UDCA with or without S-adenosylmethionine (SAMe), that is, their SBA levels after treatment did not fall below 40 μmol/L;
3) women who delivered preterm (i.e. at < 37 weeks of gestational age); and
4) data required for the analysis were missing from the medical records.

The patients were divided into 2 groups: women with SBA ≤40 μmol/L at all times during pregnancy (mild ICP group) and women with SBA >40 μmol/L at some stage during pregnancy but whose SBA fell to <40 μmol/L after treatment (severe ICP group).

2.2. Management of ICP

Patients were managed according to the guideline provided by the Chinese Medical Association for Obstetrics and Gynecology.[10] The patients were recommended a course of UDCA (10–15 mg/kg/d, taken orally and divided into 2–3 doses/day; Daewoong Pharmaceutical Co. Ltd, Seoul, South Korea) to decrease the SBA level. In addition, those with SBA >20 μmol/L were also administered SAMe (1000 mg/d, either by once-daily intravenous injection or by twice-daily oral administration; Abbott Laboratories, Lake Buff, IL). Liver function was monitored every week after diagnosis. The Chinese guideline recommends a continuation of pregnancy until term for women with SBA <30 μmol/L, individualized management (according to the wishes of the patient and/or concerns of the physician) for women with SBA of 30 to 40 μmol/L, and induction of labor at 34 to 37 weeks of gestation in women with SBA > 40 μmol/L.[10] However, in our institution, term delivery was achieved in some women with an initial SBA >40 μmol/L whose SBA level decreased to ≤40 μmol/L after pharmacologic therapy; thus, the present study was able to include only women with term delivery.

2.3. Collection of clinical data

The following information was extracted from the medical records and anonymized for analysis: baseline demographic and clinical characteristics, results of laboratory investigations, and maternal and neonatal outcomes. The laboratory investigations included measurements of alanine transaminase (ALT), aspartate transaminase (AST), TBA, total bilirubin (TBIL), direct bilirubin (DBIL), cholinesterase (CHE), total protein (TP), albumin (ALB), gamma-glutamyltransferase (GGT), leucocyte count, and lymphocyte count. The perinatal outcomes analyzed included gestational age at delivery, labor onset, mode of delivery, stillbirth, birth weight and centiles, and 1/5-minute Apgar scores. Adverse perinatal outcomes were defined as macrosomia, low birth weight infants (full-term fetus <2500 g), small for gestational age (SGA), large for gestational age (LGA), premature rupture of membranes, fetal distress, oligohydramnios, meconium contamination, neonatal asphyxia, and postpartum hemorrhage.

2.4. Statistical analysis

Statistical analyses were performed using SPSS 18.0 software (SPSS Inc., Chicago, IL). All data were tested for normality. Normally distributed continuous variables are presented as mean ± standard deviation (SD), non-normally distributed continuous variables are presented as median and interquartile range, and categorical variables are presented as n (%). Statistical comparisons between groups were made using Student t test (normally distributed continuous variables), the Wilcoxon rank-sum test (non-normally distributed continuous variables), or the Chi-squared test or Fisher exact test (categorical variables). Variables with $P <.1$ in these statistical analyses were subsequently entered into univariate logistic regression analyses to identify factors associated with adverse perinatal outcomes and with MSAF (separate analyses). Factors with $P <.1$ in the

univariate logistic regression analyses were then subjected to multivariate logistic regression analyses (using the enter method) to identify factors independently associated with adverse perinatal outcomes and MSAF (separate analyses). $P < .05$ was considered statistically significant.

3. Results

3.1. Baseline demographic and clinical characteristics

Among 126 patients screened for possible enrolment in the study, 3 were excluded due to twin pregnancy and a further 50 were excluded due to preterm delivery. Therefore, a total of 73 patients were included in the final analysis, with 47 in the mild ICP group (SBA ≤40 μmol/L at all times during pregnancy) and 26 in the severe ICP group (SBA >40 μmol/L at some stage during pregnancy, but SBA fell to ≤40 μmol/L before delivery in response to therapy) (Fig. 1).

The baseline demographic and clinical characteristics of the study participants are shown in Table 1. Pruritus was significantly more common in women in the severe ICP group than in women in the mild ICP group (65.4% vs 40.4%;

$P = .041$). However, there were no significant differences between the 2 groups in age, family history, gravidity, parity, or rates of gestational diabetes mellitus, anemia, thrombocytopenia, subclinical hypothyroidism, overt hypothyroidism, gallstones, or lipid metabolism disorders (Table 1).

3.2. Comparison of laboratory parameters between groups

The results of laboratory investigations are summarized in Table 2. TBA was significantly higher in the severe ICP group than in the mild ICP group at first visit ($P < .001$) and at peak value ($P < .001$) but not before delivery ($P = .049$) and at 4 days postpartum. DBIL was significantly higher in the severe ICP group than in the mild ICP group before delivery ($P = .049$) and at 4 days postpartum ($P = .014$). Additionally, GGT was significantly lower in the severe ICP group than in the mild ICP group at peak value ($P = .029$), before delivery ($P = .002$) and at 4 days postpartum ($P = .003$). However, there were no significant differences between groups in ALT, AST, TBIL, CHE, TP, ALB, leucocyte count, or lymphocyte count (Table 2).
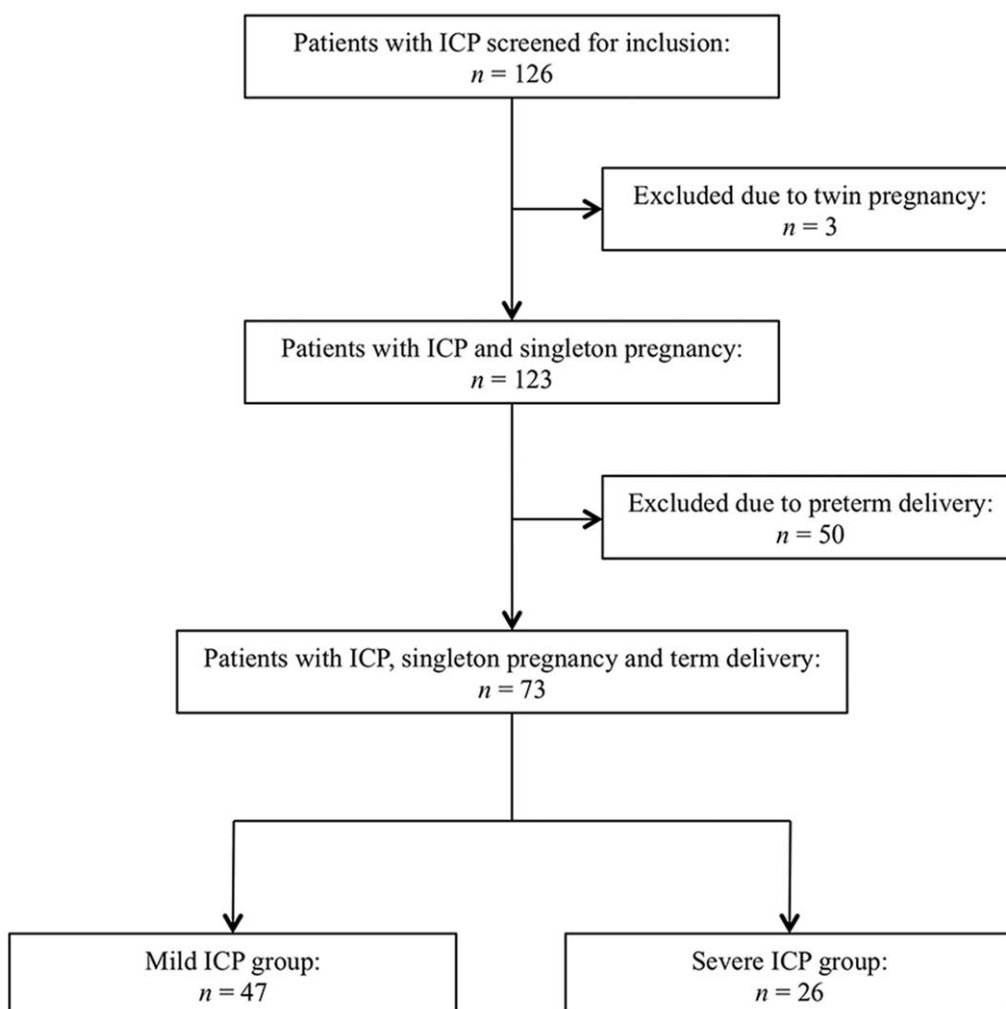

Figure 1. Enrolment of the study participants.

Baseline demographic and clinical characteristics of the study participants.

Characteristic		Mild ICP N = 47	Severe ICPN = 26	P value
Age		27.77±4.48	28.58±4.83	.548
Family history (first birth or mother)	No	46 (97.87%)	25 (96.15%)	1.0
	Yes	1 (2.13%)	1 (3.85%)	
Gravidity	1	31 (65.96%)	14 (53.85%)	.308
	>1	16 (34.04%)	12 (46.15%)	
Parity	0	31 (65.96%)	17 (65.38%)	.961
	>0	16 (34.04%)	9 (34.62%)	
Gestational diabetes mellitus	No	34 (72.34%)	23 (88.46%)	.111
	Yes	13 (27.66%)	3 (11.54%)	
Anemia	No	27 (57.45%)	14 (53.85%)	.767
	Yes	20 (42.55%)	12 (46.15%)	
Thrombocytopenia	No	34 (72.34%)	23 (88.46%)	.111
	Yes	13 (27.66%)	3 (11.54%)	
Subclinical hypothyroidism	No	44 (93.62%)	26 (100%)	.548
	Yes	3 (6.38%)	0 (0%)	
Hypothyroidism	No	47 (100%)	25 (96.15%)	.356
	Yes	0 (0%)	1 (3.85%)	
Gallstone	No	46 (97.87%)	24 (92.31%)	.287
	Yes	1 (2.13%)	2 (7.69%)	
Lipid metabolism disorder	No	3 (6.38%)	0 (0%)	.548
	Yes	44 (93.62%)	26 (100%)	
Pruritus	No	28 (59.57%)	9 (34.62%)	.041
	Yes	19 (40.43%)	17 (65.38%)	
Pruritus prior to TBA↑		11 (23.4%)	14 (53.85%)	
Pruritus following TBA↑		1 (2.13%)	0 (0%)	

The data are presented as mean±standard deviation or n (%). ICP=intrahepatic cholestasis of pregnancy; TBA=total bile acids. Anemia was defined as hemoglobin level <110 g/L.

3.3. Comparison of pregnancy outcomes between groups

As shown in Table 3, there were no significant differences between groups in type of delivery, estimated amount of hemorrhage, or prevalence of abnormal liver function (as detected by laboratory tests of liver function). However, the duration of the liver function abnormality was significantly longer in the severe ICP group than in the mild ICP group (P = .011).

3.4. Comparison of fetal outcomes between groups

Body weight at birth was significantly lower in the mild ICP group than in the severe ICP group. However, there were no significant differences between groups in any of the other fetal outcomes assessed (Table 4).

3.5. Logistic regression analysis of factors associated with adverse perinatal outcomes and MSAF

Variables with P <.1 in the above analyses were entered into a univariate logistic regression analysis to identify any associations with adverse perinatal outcomes or MSAF. No variables (including patient grouping based on SBA level) were identified as having significant associations with adverse perinatal outcomes or MSAF (Table 5). Therefore, multivariate logistic regression analyses were not performed.

4. Discussion

The objective of this retrospective study was to examine whether successful treatment of severe ICP (i.e. a reduction in SBA to below 40 μmol/L after therapy with UDCA) would decrease the risk of adverse perinatal outcomes. The main finding was that the incidence of adverse perinatal outcomes was similar between the mild ICP group and severe ICP group. This novel observation indicates that pregnancy in women with severe ICP who respond sufficiently to pharmacologic therapy can be managed in the same way as pregnancy in women with mild ICP. We envisage that our novel data will provide new and useful guidance that will facilitate future clinical practice.

In China, the current guidelines[10] recommend that women with mild ICP (i.e. SBA ≤40 μmol/L throughout pregnancy) be managed expectantly with a view to a term delivery, whereas delivery at 34 to 37 weeks is recommended for women with severe ICP (i.e. SBA >40 μmol/L at some stage during pregnancy). This guidance is based on previous research indicating that severe ICP is associated with adverse fetal and maternal outcomes. A study of women with dichorionic diamniotic twin pregnancies found that severe ICP increased the rates of preterm delivery (before 34 gestational weeks), MSAF and composite adverse neonatal outcome, as compared with mild ICP.[14] Moreover, another investigation found that women with severe ICP had higher rates of MSAF, admission to the neonatal intensive care unit and neonatal global morbidity than women with mild ICP.[15] Similarly, Qi et al observed that patients with severe ICP had higher incidences of MSAF, newborn asphyxia and admission to the neonatal intensive care unit than those with mild ICP.[16] Additionally, various reports have suggested that severe ICP but not mild ICP is associated with poorer perinatal outcomes when compared to control populations. For example, Furrer et al found that MSAF was observed more often in women with severe ICP than in women without ICP,[17] while Raz et al determined that severe ICP increased the risk of preeclampsia, as compared with controls.[18] Notably, Glantz et al reported that

Table 2

Comparison of laboratory parameters between groups.

Time point	Parameter	Mild ICP (N=47)	Severe ICP (N=26)	P value
First visit	ALT (U/L)	116 (6,443.4)	104 (3,1040)	.717
	AST (U/L)	74 (10,449)	57 (9,669)	.333
	TBA (μmol/L)	8 (3,34)	21.7 (5,158.4)	<.001
	TBIL (g/L)	10 (3,28.8)	10 (2,52.2)	.963
	DBIL (g/L)	4.1 (1.2,20.5)	4.1 (1,31.2)	.387
	CHE (U/L)	5202.8±826.7	4932.2±943.8	.207
	TP (g/L)	62.06±3.9	60.91±4.86	.274
	ALB (g/L)	35.36±2.78	34.67±3.37	.348
	GGT (U/L)	26 (3,340)	17.5 (3,83)	.117
Worst	ALT (U/L)	198 (7,611)	218.5 (4,1040)	.795
	AST (U/L)	143 (12,650)	139 (13,669)	.633
	TBA (μmol/L)	21.95±8.29	56.21±29.39	<.001
	TBIL (g/L)	12 (3.1,35.9)	10.9 (2.2,41.14)	.747
	DBIL (g/L)	6.5 (1.3,24.2)	8.2 (1,35.5)	.628
	CHE (U/L)	4927.3±927.2	4789.2±934.4	.545
	TP (g/L)	60.38±5.22	60.27±4.82	.929
	ALB (g/L)	34.47±3.1	34.01±3.21	.553
	GGT (U/L)	36 (3,199)	19 (5,90)	.029
Before delivery	ALT (U/L)	77 (6,411)	48.5 (3,400)	.515
	AST (U/L)	71 (10,449)	33.5 (10,400)	.471
	TBA (μmol/L)	11.3 (3.2,27.4)	8.3 (2,52.3)	.372
	TBIL (g/L)	5.6 (1.3,20.5)	3.7 (1,44.8)	.662
	DBIL (g/L)	14.4 (0.3,36)	16.1 (4,146)	.049
	CHE (U/L)	4975.9±985.1	4954.5±868.4	.926
	TP (g/L)	59.45±4.51	59.81±4.22	.742
	ALB (g/L)	33.73±2.52	33.7±2.54	.969
	GGT (U/L)	36 (3,190)	15 (4,71)	.002
Postpartum day 4	ALT (U/L)	46 (7,570)	38 (3,345)	.818
	AST (U/L)	32 (10,351)	30 (5,226)	.922
	TBA (μmol/L)	9.1 (2.7,54.6)	7.2 (2,30.8)	.394
	TBIL (g/L)	4.2 (1.1,14)	3.45 (1,25)	.553
	DBIL (g/L)	2.9 (0.6,20.5)	5.2 (0.6,58.6)	.014
	CHE (U/L)	4697.6±969.6	4551.3±1027.7	.547
	TP (g/L)	58.87±4.72	57.7±3.88	.285
	ALB (g/L)	32.54±2.73	31.62±3.16	.191
	GGT (U/L)	27 (4,115)	16.5 (3,67)	.003
	Leukocytes (×10^9/L)	7.52 (4.41,14.09)	7.96 (4.17,12.04)	.461
	Lymphocytes (×10^9/L)	1.53±0.43	1.48±0.48	.687
	Leukocytes/lymphocytes	4.72 (2.36,12.15)	5.375 (1.71,11.2)	.417

The data are presented as median (range) or mean±standard deviation. ALB=albumin, ALT=alanine transaminase, AST=aspartate transaminase, CHE=cholinesterase, DBIL=direct bilirubin, GGT=gamma-glutamyltransferase, ICP=intrahepatic cholestasis of pregnancy, TBA=total bile acids, TBIL=total bilirubin, TP=total protein.

Table 3

Comparison of pregnancy outcomes between groups.

Parameter		Mild ICP (N = 47)	Severe ICP (N = 26)	P value
Type of delivery	Vaginal delivery	6 (12.77%)	2 (7.69%)	.448
	Emergent Caesarean section	20 (42.55%)	15 (57.69%)	
	Elective Caesarean section	21 (44.68%)	9 (34.62%)	
Emergency delivery	No	21 (44.68%)	6 (23.08%)	.089
	Yes	20 (42.55%)	15 (57.69%)	
Hemorrhage	Median (Range)	300 (100,480)	300 (150,700)	.167
Abnormal liver function	No	17 (36.17%)	6 (23.08%)	.367
	Yes	29 (61.7%)	17 (65.38%)	
Duration of abnormal liver function (days)	Median (Range)	11 (4,18)	11 (11,42)	.011

The data are presented as median (range) or n (%). ICP=intrahepatic cholestasis of pregnancy, TBA=total bile acids.

Table 4

Comparison of pregnancy outcomes between groups.

		Mild ICP (N = 47)	Severe ICP (N = 26)	P value
Sex of newborn	Male	25 (53.19%)	10 (38.46%)	.195
	Female	21 (44.68%)	16 (61.54%)	
Body weight (g)		3156.6 ± 315.0	3380.8 ± 393.6	.010
Apgar score	At 1 min	9 (3,10)	9 (3,9)	.437
	At 5 min	10 (8,10)	10 (9,10)	.630
	Score ≤7	4 (8.51%)	1 (3.85%)	
Adverse perinatal outcome	No	23 (48.94%)	12 (46.15%)	.820
	Yes	24 (51.06%)	14 (53.85%)	
Fetal macrosomia	No	38 (80.85%)	16 (61.54%)	.309
	Yes	0 (0%)	1 (3.85%)	
Low birth weight infant	No	37 (78.72%)	20 (76.92%)	1.000
	Yes	1 (2.13%)	1 (3.85%)	
Small for gestational age	No	45 (95.74%)	25 (96.15%)	1.000
	Yes	2 (4.26%)	1 (3.85%)	
Premature rupture of membranes	No	44 (93.62%)	24 (92.31%)	1.000
	Yes	3 (6.38%)	2 (7.69%)	
Fetal distress	No	36 (76.6%)	22 (84.62%)	.417
	Yes	11 (23.4%)	4 (15.38%)	
Oligohydramnios	No	42 (89.36%)	17 (65.38%)	.090
	Yes	5 (10.64%)	7 (26.92%)	
Meconium contamination	No	35 (74.47%)	19 (73.08%)	.897
	Yes	12 (25.53%)	7 (26.92%)	
Breech labor	No	35 (74.47%)	15 (57.69%)	1.000
	Yes	4 (8.51%)	2 (7.69%)	
Neonatal asphyxia	No	43 (91.49%)	25 (96.15%)	.649
	Yes	4 (8.51%)	1 (3.85%)	

The data are presented as n (%), median (range) or mean ± standard deviation. ICP = intrahepatic cholestasis of pregnancy.

Table 5

Univariate logistic regression analysis of factors associated with adverse perinatal outcomes or meconium staining of the amniotic fluid.

	Odds ratio	95% confidence interval	P value
Adverse perinatal outcomes			
Pruritus	1.059	0.423,2.653	.903
TBA group#	1.118	0.428,2.92	.820
TBA at first visit	1.007	0.987,1.027	.492
TBA at peak value	1.005	0.986,1.024	.596
GGT at peak value	1.002	0.992,1.012	.701
TBA before delivery	1.004	0.983,1.026	.704
GGT before delivery	0.999	0.987,1.011	.872
TBA at postpartum day 4	0.980	0.934,1.028	.413
GGT at postpartum day 4	0.992	0.974,1.011	.424
Duration of liver function abnormality	0.983	0.912,1.059	.648
Body weight	1.000	0.998,1.001	.634
Meconium staining of amniotic fluid			
Pruritus	2.143	0.731, 6.283	.165
TBA group#	1.075	0.362, 3.185	.897
TBA at first visit	1.006	0.987, 1.026	.510
TBA at peak value	0.994	0.972, 1.017	.609
GGT at peak value	1.006	0.995, 1.016	.301
TBA before delivery	1.012	0.990, 1.034	.285
GGT before delivery	1.007	0.994, 1.020	.300
TBA at postpartum day 4	1.01	0.963, 1.060	.676
GGT at postpartum day 4	1.004	0.984, 1.025	.687
Duration of liver function abnormality	0.921	0.801, 1.058	.243
Body weight	1.001	0.999, 1.002	.276

GGT = gamma-glutamyltransferase, TBA = total bile acids. # Grouping based on total bile acid.

the risk of fetal complications (spontaneous preterm delivery, asphyxia, and MSAF) increased by 1% to 2% per additional μmol/L of SBA above 40 μmol/L.[3] In agreement with this, Geenes et al observed significant relationships between SBA levels above 40 μmol/L and various adverse outcomes (preterm delivery, spontaneous preterm delivery, stillbirth, and MSAF).[19]

However, pregnant women with severe ICP and subsequent successful treatment represent a relatively uncharacterized subpopulation that has not received attention in previous studies.[20,21] In particular, it is important to understand whether this population should be managed in a similar manner to patients with persistently mild ICP. The guidelines in China and elsewhere do not take into account the response of severe ICP to therapy, hence decisions regarding the management of pregnant women with currently mild but previously severe ICP are challenging. The present observational study has yielded novel data indicating that women with severe ICP that are treated successfully do not carry increased risks for adverse maternal and neonatal outcomes. If subsequent studies confirm these findings, we would suggest that revisions to the guidelines be made recommending that women with severe ICP whose SBA falls to below 40 μmol/L after treatment should be managed along the same lines as women with mild ICP.

UDCA has been widely used in the treatment of ICP and shown to improve maternal biochemical parameters, alleviate pruritus and lower SBA levels.[5] However, the impact of UDCA treatment on fetal and neonatal outcomes has not been confirmed by adequately powered studies.[22] Although meta-analyses of trials comparing UDCA with other therapies found that its utilization reduced the likelihood of adverse perinatal outcomes, these

analyses were limited by a lack of direct comparisons of UDCA with placebo.[23,24] Here, our study has added novel evidence to support the effectiveness of UDCA therapy. Since a study comparing UDCA-treated women with UDCA-untreated women would raise ethical concerns,[8] we utilized a unique study design to focus on patients with previously severe ICP who were then successfully treated with UDCA. All the women in our severe ICP group responded well to UDCA, and their liver function tests showed significant improvement following therapy. Indeed, the serum level of GGT at the time of delivery was lower than that of women with persistently mild ICP. Importantly, the risk of adverse perinatal outcomes was comparable between the severe ICP and low ICP groups, strongly indicating that UDCA therapy is effective in reducing the incidence of adverse perinatal outcomes in women with severe ICP who respond well to treatment. However, patients with severe ICP do not respond equally to UDCA, and this study excluded those defined to have an insufficient response (these cases were managed mainly by preterm delivery, in accordance with the guidelines). The causes for the varying response to treatment are currently unknown but may include differences in UDCA dosage, time of diagnosis (early vs late), genetic factors and environmental factors.[25] This is a question that warrants future investigation.

Another interesting observation in our study was the significantly higher birth weight of infants born to mothers in the severe ICP group. Previous studies have shown that women with ICP are more likely to develop gestational diabetes mellitus and dyslipidemia and have proportionately larger babies.[26] Elevated maternal glucose may induce hyperinsulinemia, while elevated serum triglycerides can promote fetal growth independent of glucose levels; both mechanisms may contribute to increased fetal growth in women with ICP.[26] This particular finding of our study is a reminder that metabolic changes induced by ICP can have important consequences, and the impact of severe ICP on fetal growth can be detected even after successful treatment with UDCA. Whether or not the metabolic changes induced by ICP are permanent or only temporary remains unclear, although there is recent evidence for a long-lasting effect. For example, children of women with ICP have been reported to have a higher body mass index and higher rates of dyslipidemia, obesity and metabolic syndrome in later life.[27] Therefore, the long-term effects of ICP on both the mother and child should be further addressed.

This study has some limitations. First, this was a retrospective study, so it may have been prone to selection bias and/or information bias. Especially, serial SBA measurements in time and in relation to treatment were not available for the mild ICP group. Second, as this was a single-center study, the generalizability of the results remains unknown. Third, the sample size was quite small, so the study may have been underpowered to detect some real differences between groups. Fourth, a control group of women without ICP was not included because pregnancy was terminated before full-term in women with ICP and SBA >40 μmol/L, as per the Chinese guidelines.[10] Fifth, long-term outcomes were not assessed. Additional research is needed to confirm and extend our findings.

5. Conclusions

In conclusion, women with severe ICP do not have increased risks for major adverse perinatal outcomes if they are successfully treated. Therefore, pregnant women with severe ICP who respond well to pharmacologic therapy can be managed in the same way as women with mild ICP. We envisage that our novel data will provide useful guidance to obstetricians treating women with ICP.

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