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ORIGINAL ARTICLE

Serum Bile Acids in Intrahepatic Cholestasis of Pregnancy (ICP), Versus Pregnant and Nonpregnant Controls in Asian Indian Women and a Proposed Scoring to Optimize Management in ICP

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Abstract

Objectives This prospective clinical trial was conducted to assess serum bile acids (BA) levels in women with intrahepatic cholestasis of pregnancy (ICP) compared to both pregnant and non-pregnant controls; and evaluate perinatal outcome in relation to bile acid levels. A scoring is proposed based on biochemical markers to optimize management in ICP cases.

Materials and Methods Serum bile-acids(BA) were assessed in 71 intrahepatic-cholestasis of pregnancy(ICP) cases (group-I), versus 50 pregnant (group-II) and 35 non-pregnant (group-III) controls. Ursodeoxycholic acid (UDCA) was administered in ICP group. Baseline bilirubin (SB), aminotransferases (AT), alkaline-phosphatase were sent in groups I & II. Investigations were repeated in group-I after 4 weeks. Perinatal complications were noted.

Results Mean BA in group-I was 75.92 ± 39.9 µmol/L which reduced to 41.3 ± 15.4 µmol/L(45.6%, $p < 0.001$) with UDCA. Mean BA was 29.2 ± 5.7 and 5.9 ± 1.8 µmol/L in group-II and group-III. UDCA significantly reduced itching-score. Rate of fetal distress linearly increased with the increasing baseline levels of serum BA, AT and SB: from 2.5 to 100% at BA < 40 and ≥ 200 µmol/L, ($p = 0.008$); from 16.1 to 100% at AT < 100 and ≥ 500 IU/mL($p = 0.016$); and from 6.8 to 100% at SB < 0.8 and > 5 mg/dL ($p = 0.001$); respectively. Their baseline levels were divided into 5 groups in correlation to fetal distress. Serum BA < 40, 40–80, 80–120, 120–200, ≥ 200 µmol/L; AT < 100,100–200,200–500, ≥ 500 IU/mL; and SB < 0.8, 0.8–1.0, 1.1–2, 2.1–5 and > 5 mg/dL. Nutan ICP scoring was proposed with a score 0 to 4 given to each parameter and score-based management protocol was suggested for fetal surveillance and delivery.

Conclusions SBA are higher in Asian Indian pregnant women. Levels > 30 µmol/L can be taken as a cut off for diagnosing ICP in Asian-Indian women. Adopting higher cut-offs for this geographic part will avoid over-diagnosing ICP and iatrogenic early termination of pregnancy. Suggested scoring will help clinicians in optimizing the time of delivery on an individualized basis.

Keywords Intrahepatic cholestasis of pregnancy · Serum bile acid · Ursodeoxycholic acid · Scoring for ICP

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a reversible cholestatic disorder unique to pregnancy. It manifests as otherwise unexplained pruritus with altered liver function tests (LFTs) and/or raised bile acids (BA), which resolve after delivery [1]. While ICP poses minimal risk to the mother except for itching, it has been associated with increased fetal risks due to prematurity, fetal asphyxia, meconium stained liquor (MSL), fetal distress and unexplained still births. Spontaneous relief of signs and symptoms occurs within two to three weeks post-delivery. ICP may recur in subsequent pregnancies in upto 90% cases [2]. Diagnosis poses a challenge as pruritis and elevated serum aminotransferases

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may be associated with other dermatological and hepatic disorders. Serum bile acids (SBA) may be the only specific laboratory marker of ICP and are often the first or the only liver function to be affected [3].

Variation is reported in SBA according to geographic locality and genetic constitution; though in general, levels > 10 and < 40 μmol/L is taken as mild ICP and > 40 μmol/L as severe ICP which is associated with high rate of fetal complications [4]. However, overlapping of SBA is reported in women with ICP and healthy pregnant women [5]. SBA levels are slightly higher in healthy pregnant women compared to non-pregnant women [3].

There was lack of data from this part of the world, hence this pilot study was conducted to compare SBA levels in pregnancies affected with ICP in Asian Indian women compared to pregnant and non-pregnant controls; and to evaluate the role of biochemical parameters (SBA, aminotransferase, bilirubin) in assessing severity of ICP in terms of perinatal complications. A scoring is proposed which can be useful for optimizing time of delivery.

Materials and Methods

This prospective clinical trial was conducted as a pilot study in single unit of Obstetrics and Gynaecology Department, All India Institute of Medical Sciences, New Delhi, India as an intramural project. Ethical clearance was taken from institute's Ethics Committee. Funds were granted by the institute for the project and project was registered under Clinical Trials Registry of India (CTRI no2017/12/010797).

Seventy one pregnant patients diagnosed with ICP were included in group-I. Criteria for diagnosing ICP were presence of pruritis in absence of other hepatic and dermatological causes. Pruritus in pregnancy due to other causes, autoimmune liver diseases, gall bladder stone and viral hepatitis were excluded. Pruritis was graded on a 0–4 scoring system with 0 score for no itching, 1 for occasional pruritis, 2 for discontinuous pruritis with prevailing asymptomatic lapses, 3 for discontinuous pruritis every day with prevailing symptomatic lapses and 4 for continuous itching [6].

For the pregnant controls, 50 healthy matched pregnant women with no co-morbidity were enrolled during the same period (Group-II). Group-III included 35 non-pregnant controls. All participants were recruited after obtaining informed written consent.

Fasting serum BA and baseline liver function were assessed by serum bilirubin (SB), alanine aminotransferase (ALT), aspartate aminotransferase(AST), and alkaline phosphatase(ALP) at recruitment in group-I and II (between 20 and 24wks). In group-III, only BA were done to ascertain if the pregnancy per se affects BA in a population. BA were measured by kit available for bile acid determination from RANDOX company (CAT No. BI 1605).

All ICP patients were given oral ursodeoxycholic acid (UDCA) 300 mg thrice daily. Patients were evaluated 2 weekly for clinical improvement. Patients were evaluated after 4 weeks for clinical improvement, liver function tests and BA. Antepartum fetal monitoring was done by biweekly non stress test and biophysical profile from 34 weeks onward. All patients were induced at 38 completed weeks or earlier if indicated for obstetric complications. Complications such as preterm labour, premature preterm rupture of membranes (PPROM), fetal bradycardia, thick (MSL) were recorded in group-I and II. Data were analysed by using SPSS version 15; change over the period from baseline to 4 weeks was assessed by 2 way ANOVA test. A p value ≤ 0.05 was taken as significant.

Results

Seventy one cases were diagnosed as ICP among 1600 deliveries, showing an incidence of 4.4% in Asian Indian women. The mean age was 27.7 ± 3.8, 27.2 ± 3.5 and 29.9 ± 4.0 years in group1, II, and III respectively (p value 0.6). Mean gestational age when patients presented with ICP was 30.4 ± 4.7 (range 16–36) weeks; 42(59.2%) women presented after 30 weeks and 5(7%) presented even before 20 weeks. Mean gestational age in group-II was 31.2 ± 3.3 weeks (22–35) (p value 0.686).

Baseline BA, ALT, AST, ALP and bilirubin are shown in Table 1. Mean BA in ICP (group-I) was 75.9 ± 38.7 (23–213) μmol/L which is higher than other parts of world and same was observed with pregnant controls whose mean BA was 29.2 ± 5.6(18.9–35.6) μmol/L. All had BA > 10 μmol/L which is the diagnostic criteria for ICP, whereas in non-pregnant (group III) mean BA were 5.9 ± 1.8 (4.8–7.2) μmol/L.

SB was mildly raised (range 1.2–5.2 mg/dl) in 15 (21%) cases of ICP. Mean AST & ALT were sixfold higher, and ALP was fourfold higher in group-I than group-II (Table 1). Aminotransferases were normal in 7(9.8%) cases. Four weeks of UDCA therapy led to significant fall in BA and ALT/AST (Table 1) suggesting improved liver function.

A trend of higher mean baseline BA was found with increasing baseline itching score as depicted in Table 2. Itching score improved with UDCA therapy (Table 2). Initially 35.2% cases had itching score of 4 and none had score-0. After 4-weeks therapy, itching improved with total resolution (score-0) in 59.2% cases. This response in itching, however, did not correlate to the decline in BA.

Adverse perinatal outcomes were noticed more in group-I; preterm labour in 12.6% vs. 4%, PPROM in 4.2% vs. 0% and thick MSL in 21.1% vs. 6%, fetal bradycardia in 11.2% vs 4% in group-I vs. group-II, respectively.

Table 1 Bilirubin, ALT, AST, ALP and bile acid levels at baseline in Group I, II and III; and after 4 weeks UDCA treatment in group-I

Lab parameter	Baseline				After 4 weeks therapy	
	Group I(ICP) N = 71	Group IIPregnant controls N = 50	p value	Group III Non-pregnant controlsN = 35	Group IICPN = 71	% Reduction
SB (mg/dl) Mean ± SDRange	0.94 ± 0.79(0.2–5.2)	0.6 ± 0.08 (0.2–0.8)	0.067	–	0.66 ± .04	29.7%
AST (U/L) Mean ± SDRange	173.38 ± 139(17–566)	28.9 ± 8.2 (17–40)	0.001	–	76.8 ± 63.6 (20–311)	55.8%
ALT (U/L) Mean ± SDRange	177.7 ± 151.7(11–521)	27.1 ± 6.8(18–39)	0.001	–	73.58 ± 62.5 (15–253)	58.8%
ALP (U/L) Mean ± SDRange	475.85 ± 208 (90–1143)	103.3 ± 58.4 (38–234)	0.001	–	252.7 ± 210 (48–1025)	50.4%
Serum BA (µmol/L) Mean ± SDRange	75.9 ± 39.5 (23–213)	29.2 + 5.7(18.9–35.6)	0.001	5.9 ± 1.8 (4.8–7.2)	41.26 ± 15.4(23–108	45.6%

SB(Serum bilirubin), ALT (Alanine aminotransferase), AST (Aspartate aminotransferase), ALP (Alkaline phosphatase), BA (bile acids)

Table 2 Itching score and corresponding mean serum BA levels at baseline and after UDCA therapy

Itching Score	Baseline		After 2 weeks UDCA therapy	After 4 weeks UDCA therapy	
	No of patients (N = 71)	Mean SBA (in µmol/L)	No. of patients(N = 71)	No of patients(N = 71)	Mean SBA (in µmol/L)
0	0	_	21(29.6)	42 (59.2%)	38.5 ± 9.2
1	2 (2.8%)	27.0 ± 8.0	29 (40.8%)	17 (23.9%)	43.6 ± 6.4
2	17(23.9%)	50.6 ± 11.2	14 (19.7%)	7 (9.8%)	47.9 ± 5.5
3	27 (38.1%)	70.5 ± 23.2	5 (7.1%)	4 (5.6%)	49.6 ± 10.2
4	25 (35.2%)	102 ± 48.4	2 (2.8%)	1 (1.4%)	44.2 ± 8.9

Serun BA (bile acids), UDCA (Ursodeoxycholic acid)

Occurrence of complications correlated to the baseline serum BA levels but not to post-therapy levels. As the levels of BA and aminotransferase(AT) increased, the occurrence of complications (MSL, fetal bradycardia) also increased in linear fashion. However, bilirubin correlated only to MSL and ALP did not correlate to any of these complications. AST correlated better to perinatal complication than ALT. Pooled risk of fetal bradycardia and MSL according to range of biochemical parameters at baseline is shown in Table 3. As probability of complication rate increased proportionally to the higher range of levels. Nutan Scoring is proposed based on these results, where score of 0,1,2,3 or 4 is given to each of the three parameters (Table 3). Score can be written as $BA_xAT_xSB_x$; (subscript depicting individual score of bile acid, aminotransferase, and serum bilirubin respectively). Highest score of any of the three parameters is considered for management purposes; for example, score is taken as 3 for $BA_2AT_3SB_1$ rather than the sum-total (Table 4).

Management based on Nutan ICP scoring may aid the clinicians in planning time of delivery for optimum pregnancy outcome. All ICP women need antenatal fetal surveillance and termination by 38 weeks as even with score 0, risk of adverse outcomes is more than normal pregnancy. Score-wise gestational age for initiation of fetal surveillance and delivery is shown in Table 4.

Discussion

Incidence of ICP varies from 0.7 to 5%; as ethnic and geographic difference exists [7, 8]. Reported incidence in South Asian women is 1.2–3.1% which is approximately twice compared with white European women [9, 10]. There appears a predilection for higher risk of ICP in Asian Indian women as incidence in present study was 4.4%. Approximately 60% patients in our study presented after 30 weeks in contrast to reported 80% [11]. So gestational age at onset might also have some genetic predisposition.

Pruritis and raised serum BA clinches the diagnosis of ICP and some patients may have deranged liver enzymes. Since, upto one third of ICP may have normal LFT [12], increased aminotransferases may be due to hepatitis and ALP is non-specifically increased during pregnancy; hence

Table 3 Rate of pooled risk of fetal bradycardia and meconium stained liquor (MSL) in different ranges of biochemical parameters; and proposed Nutan scoring for ICP

Parameter	Range	Range-wise distribution of patients(n = 71)	Occurrence of MSL/fetal bradycardia(Range-wise details of 23* patients)n (%)	*P* value	Proposed ICP Scoring	Documentation
Bile acids(BA)(In µmol/L)	< 40	8	1/8 (12.5%)		0	BA_0
	40- < 80	32	7/32 (21.8%)	$p = 0.008$	1	BA_1
	80- < 120	21	7/21 (33.3%)		2	BA_2
	120- < 200	8	6/8 (75%)		3	BA_3
	≥ 200	2	2/2 (100)		4	BA_4
Aminotransferase (AT) (In IU/mL)	< 100	31	5/31 (16.1)%	$p = 0.016$	0	AT_0
	100- < 200	17	5/17 (29.4%)		1	AT_1
	200- < 400	15	7/15 (46.6)%		2	AT_2
	400- < 500	7	5/7 (71.4)		3	AT_3
	≥ 500	1	1/1 (100%)		4	AT_4
Serum bilirubin** (SB) (In mg/dL)	< 0.8	29	2/29 (6.8%)	p = 0.001	0	SB_0
	0.8 −1.0	22	3/22 (13.6%)		1	SB_1
	1.1- < 2.0	16	7/16(43.75%)		2	SB_2
	2.0- < 5	3	2/3 (66.6%)		3	SB_3
	≥ 5.0	1	1/1 (100%)		4	SB_4

* Total 23 patients in group-1 had thick MSL or fetal bradycardia

**Serum bilirubin is related only to thick MSL(15 cases) and not to fetal bradycardia(8 cases)

Baseline levels of Bile acids, Aminotransferase and Serum bilirubin would be matched with the range of levels and score would be noted

Score can be documented as explained in table-4

Table 4 Management protocol for delivery on basis of scoring

Score (Cut-offs given in Table-3)	Score assigned*	Initiation of fetal surveillance	Time for planning delivery
$BA_0AT_0SB_0$	Score 0	Outpatient, from 36 weeks onward	38 weeks
$BA_1AT_xSB_x$ or$BA_xAT_1SB_x$ or $BA_xAT_xSB_1$ (x can be 0 or 1)	Score 1	Outpatient, From 34 weeks onward	$37–37^{+6}$ weeks
$BA_2AT_xSB_x$ or$BA_xAT_2SB_x$ or $BA_xAT_xSB_2$(x can be 0 or 1 or 2)	Score 2	Outpatient, From 32 weeks onward	$36–36^{+6}$ weeks
$BA_3AT_0SB_0$ or$BA_0AT_3SB_0$ or $BA_0AT_0SB_3$(x can be 0 to 3)	Score 3	Outpatient, From 32 weeks onward	$35–35^{+6}$ weeks
$BA_4AT_0SB_0$ or$BA_0AT_4SB_0$ or $BA_0AT_0SB_4$(x can be 0 to 4)	Score 4	In-patient, From 32 weeks onward	$34–34^{+6}$ weeks

Baseline levels of Bile acids (BA), Aminotransferase (AT) and Serum bilirubin (SB) would be matched with the range described in Table 3 and score would be noted

Score would be documented as $BA_xAT_xSB_x$ (Subscript x represent score number 0–4)

*Highest number for any of the three parameters would be the referring score and should be considered for management

BA remain the most specific investigation. BA > 10 µmol/L diagnoses ICP [4] but in present study markedly higher levels were observed even in normal pregnant women whereas in non-pregnant the levels were comparable to other parts of the world. In the present study only 6% ICP cases had SBA < 30 µmol/L. Besides, the mean BA in normal pregnant controls was high (29.2 µmol/L); with 24% having levels between 30-35 µmol/L, and none with > 35 µmol/L. Hence higher cut-off can be considered for Asian (Indian) pregnant women, and based on our results, we suggest the BA cut-off of 30 µmol/L for diagnosing ICP in this population.

Most studies have graded ICP as mild and severe taking an arbitrarily BA cut-off of > 40 µmol/L as it was shown that fetal complications do not occur until BA exceed 40 µmol/L [4, 13]. However, recent studies almost similarly graded ICP as mild, moderate and severe if SBA were 10–39.9; 40–99.9 and ≥ 100 µmol/L [14–16] with increased risk of stillbirth at BA > 100 µmol/L [16]. Present study suggests ICP in Asian Indian women can be graded little differently as baseline

SBA itself was higher almost approaching 40 µmol/L and even pregnant controls had mean BA of 30 µmol/L compared to 5.9 µmol/L in non-pregnant women. For this geographic area, based on our results, ICP can be graded as very mild if BA < 40 µmol/L, mild 40- < 80 µmol/L, moderate 80- < 120, severe 120- < 200 µmol/L very severe if BA levels ≥ 200 µmol/L. Intensive monitoring as in-patient maybe required for BA > 200 µmol/L as risk of preterm, MSL and fetal bradycardia increases exponentially.

Gestational age at onset and other parameters are also incorporated for classifying severity. Gestational age ≥ 28 weeks at onset, BA upto 40 µmol/L, SB upto 25 µmol/L, ALT and AST up to 300 U/L and no/mild fetal complication; is categorized as mild ICP [13]. ICP is severe if at least one of the above lab parameters is more or gestational age is < 28 weeks at the disease onset [13]. In ICP, jaundice is reported in upto 20% cases but in present study, increased bilirubin was seen in only 10% cases which might be due to ethnic and geographic variation.

UDCA therapy in ICP improves pruritus in 60% with complete resolution in approximately 40% cases [17]. A meta-analysis of 12 RCTs involving 662 patients indicated efficacy of UDCA in resolving pruritis [18]. We observed complete resolution of pruritis in 59% cases after 4 weeks therapy.

Fetal complications like preterm labour, PPROM, thick MSL, intrapartum fetal distress and sudden fetal demise are directly related to BA levels. No difference was noted in MSL with UDCA, though reduced premature births (RR, 0.56), fetal distress (RR, 0.68), and NICU admissions (RR, 0.55) were observed in a meta-analysis [18]. Another meta-analysis reported significantly increased risk of adverse fetal outcomes (pooled RR, 1.96) and unexplained fetal demise in 1–3% cases at BA ≥ 40 µmol/L with RR of 2.23 for preterm birth, 2.27 for MSL and 1.67 for neonatal asphyxia [19]. Present study found RR of 3.1 for preterm, 3.5 for MSL and 2.8 for fetal bradycardia. In relation to BA, pooled risk of MSL and fetal bradycardia was nearly twofold at 40- < 80, threefold at 80- < 120, fivefold at 120 < 200 and eightfold at BA ≥ 200 µmol/L in comparison to risk of 12.5% at BA < 40 µmol/L (Table 3) and 10% in controls. As there was no correlation to declining BA with UDCA hence probably therapy does not have beneficial effect on perinatal outcome. A review of 1280 patients reported 6.8% perinatal death in 118(9.2%) patients with BA > 100 µmol/L [20]. Meta-analysis of 27 studies ($n = 5557$) also suggested that peak BA correlates to fetal outcome irrespective of treatment [21]. Although earlier meta-analysis showed benefit of UDCA on maternal/fetal outcomes [22], (but recent evidence shows no such benefit [23]. In present study BA, AT and SB at baseline correlated to perinatal outcomes, but not to the levels after UDCA therapy. The higher the baseline BA, AT, SB; the higher were the occurrence of complications. Based on baseline biochemical parameters, Nutan scoring system is suggested to score and grade ICP (Table 3) where each parameter is to be considered independently. In present study, 18.3% patients had BA > 100 µmol/L and 14.1% had SBA > 120 µmol/; but none had perinatal loss which may be due to intensive monitoring at tertiary centre. But 70% of these patients with BA > 120 µmol/L had MSL or fetal bradycardia. Baseline BA > 200 µmol/L were associated with more severe adverse fetal complications.

The reason for increase in fetal complications despite declining BA after therapy is not known. Presumably, fetal ability to remove BA decreases and accumulated BA leads to impaired fetal cardiomyocyte function and sudden fetal anoxia or vasoconstriction of placental vasculature [24].

The incidence of fetal complications has been reported to increase by 1–2% for each µmol/L of BA over 40 µmol/L [4]. About 1–3% can have sudden intrauterine death, elective termination of pregnancy is recommended at 37–38 completed weeks. Some forums recommend delivery at 37 weeks gestation to reduce stillbirths if BA ≥ 40 mmol/L [11]. Some have suggested induction at 36 weeks [25]. It is an issue of debate when to terminate ICP pregnancy, hence we propose a scoring to plan monitoring, admission and delivery based on grading ICP severity. Management based on Nutan ICP scoring can avoid iatrogenic prematurity while balancing the risk of perinatal complications.

However, there is need for population-specific or geographic locality-specific cut-offs as BA variations are reported in different populations. BA in non-pregnant women were same as reported in other parts of world, but probably pregnant Asian Indian women have higher BA levels. Regular antenatal fetal surveillance is crucial in ICP management. Elective induction should be considered as per the scoring.

Conclusion

ICP is a disease which though benign for mother, is associated with higher perinatal complications. In pregnant Asian Indian population, BA levels are higher even without ICP, compared to world literature. Hence a higher BA cut-off of 30 rather than 10 µmol/L is suggested for diagnosing ICP in this population. Also, Nutan ICP score based on baseline BA, AT and SB may help clinicians in optimizing the time for delivery and preventing complications and prematurity.

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Author contributions All authors contributed in the patient management and follow-up. NA conceptualized the study. RM and VS were

responsible for the acquisition of clinical data, and obtaining informed consent. NA, VK and RM were responsible for manuscript writing. NA, AK and AS had overall supervision. NA and VK were responsible for manuscript's critical editing.

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Declarations

Conflict of interest None of the authors have any potential conflict of interest.

Ethical statement Study was conducted after obtaining approval from the Institute's Ethics Committee.

Human Participants and/or Animals All parts of Declaration of Helsinki have been applied.

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