ORIGINAL ARTICLE

Diagnosis and Management of Intrahepatic Cholestasis of Pregnancy- A Retrospective Clinical Audit

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ABSTRACT

Introduction: Pregnant women presenting with pruritus, serum bile acid (SBA) ≥10 µmol/L and/or alanine transaminase (ALT) >30 U/l is diagnostic of intrahepatic cholestasis of pregnancy (ICP). A retrospective audit was performed to look at the diagnosis, management and outcomes of ICP patients in University Malaya Medical Center (UMMC). **Methods:** SBA requests from Obstetrics and Gynaecology Department from 1st January 2016 to 31st December 2020 were extracted from Laboratory Information System (LIS). The medical records (preexisting medical conditions, maternal and perinatal outcomes) of ICP were obtained. Mild and severe ICP were defined based on SBA 10-40µmol/L and SBA >40 µmol/L, respectively. **Results:** SBA was requested for 202 pregnant women. The prevalence of ICP in our cohort was 0.18% (47 out of 26,697 deliveries). The average gestation at diagnosis was 35 weeks. Both SBA and liver enzymes were elevated in 25 (53.2%) whereas only SBA was elevated in 20 (42.6%) women. In two women, the diagnosis was made based on clinical symptoms and elevated liver enzyme alone. All with ICP had a livebirth and 31.9% were preterm. Severe ICP was noted in eight (17%) and all had cesarean section, whereas, in mild ICP, only 17 (44%) had a caesarean section. In those with normal SBA (n=149) at initial presentation, a repeat SBA was performed only in 12 (8.1%). Postpartum follow-up of ICP patients was observed in only 10 (21.2%). **Conclusion:** Despite being an uncommon diagnosis in our population, early diagnosis and timely delivery is important to reduce the major perinatal adverse outcomes. In women with persistent pruritus but without the biochemical evidence of ICP at the time of presentation should have repeat SBA and LFT done.
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Keywords: Bile acid, Intrahepatic cholestasis of pregnancy, Prevalence, Pruritus, Retrospective audit

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INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP), also known as obstetric cholestasis, is the most common liver disease unique to pregnancy. It requires early recognition and prompt management. The guidelines on ICP by the Royal College of Obstetricians and Gynecologists (RCOG), 2011 state that the diagnosis is made when unexplained pruritus occurs in pregnancy, associated with raised serum bile acid (SBA) and/or abnormal liver function tests (LFT) and resolves after delivery (1). The onset of ICP is typically heralded by the development of pruritus, which generally starts and predominates on the palms and soles (2). ICP symptoms and signs occur mainly during the last trimester with spontaneous relief of clinical features within six weeks of delivery (3). The incidence of ICP varies according to geographical location and population (3). The combination of genetic susceptibility, hormonal, and environmental factors plays a role in ICP (4). Recent studies on epidemiology have reported a higher incidence in the South Asian population of 1.2% to 3.1% compared to 1.0% to 1.5% incidence in Europe (4,5).

ICP poses a significant risk to both maternal and foetal health. Complications seen in these women are essentially benign, however, they may lead to maternal morbidity due to postpartum haemorrhage and impair the quality of life due to pruritus, fat, and vitamin K malabsorption (6). The adverse foetal complications are increased foetal distress, premature delivery, meconium staining of amniotic fluid, and perinatal mortality (6). To prevent such complications and for a better maternal and foetal outcome, there is a need for early ICP diagnosis and treatment.

An increase in total SBA level is a key laboratory finding

and may be the first and only laboratory abnormality (5, 6). Total SBA measurement corresponds to the sum of more than 20 individual bile acids that are synthesised by the liver, modified by gut bacteria, and involved in complex enterohepatic circulation (7). Despite the lack of consensus in the diagnostic criteria, it is generally accepted that SBA ≥10 μmol/L is considered elevated (8). South Australia Maternal & Neonatal Community of Practice (SAMNCP) guidelines classify ICP as mild when the SBA measures 10-40 μmol/L and severe when the levels are >40 μmol/L, compatible with adverse pregnancy outcomes reported at this level (9). In a systematic review and meta-analysis report, it has been reported that the risk of stillbirth is increased only when SBA concentrations are ≥100 μmol/L (10). Apart from SBA, increased liver enzymes, particularly alanine aminotransferase (20% to 60%) and γ-glutamyl transferase (30%) are also seen in ICP (10). Since approximately one-third of patients have normal levels of liver enzymes, measurement of SBA is mandatory in suspected cases of ICP (11). It has been reported that there is an increased occurrence of several liver, biliary, pancreatic diseases in women with ICP compared to control. Hence follow-up measurements of SBA during the postpartum period are required (12). Since the prognosis remains unpredictable in some cases, regular monitoring of SBA (e.g. weekly) is needed to reassess the risk (13).

Despite the associated adverse outcomes, there are differences in the guidelines regarding appropriate diagnostic criteria, maternal and foetal surveillance, treatment, and delivery timing (9, 14). The objectives of this study were to determine the prevalence of ICP in University Malaya Medical Centre (UMMC) Kuala Lumpur, Malaysia, the gestation at diagnosis and ascertain the gestation at delivery of those diagnosed, foetal outcome, as well as assess the extent of postnatal follow-up. The adherence to the existing guideline (RCOG) on the biochemical diagnosis of ICP was assessed.

MATERIALS AND METHODS

Subjects

SBA requests during the period of 1st January 2016 to 31st December 2020 were extracted from the Laboratory Information System (LIS) at University Malaya Medical Center (UMMC). Of these, 202 requests were from the Department of Obstetrics and Gynaecology for the possible diagnosis of ICP. Clinical details and biochemical investigations of each subject were extracted from the clinical notes and LIS respectively. Information on the patients' demographics, preexisting medical conditions, ICP complications, maternal and perinatal outcomes (mode of delivery, preterm birth, admission to neonatal unit and stillbirth) were obtained from the clinical notes. Based on the LFT and SBA results, the subjects were categorised into those with and without ICP. Pregnant women presenting with pruritus, serum bile acid (SBA) ≥10 μmol/L and/or alanine transaminase (ALT) >30 U/l were diagnosed as ICP (1,8). The maternal outcomes (delivery characteristics) were analysed according to mild (SBA 10-40 μmol/L) and severe (SBA > 40 μmol/L) ICP as it is a crucial feature used by the treating physician to decide on the mode and timing of delivery (8). The exclusion criteria was women in whom SBA was requested but the pregnancies ended before 24 weeks. The study protocol was approved by the Medical Ethics Committee, UMMC, conforming to the provisions of the Declaration of Helsinki.

Data analysis

Data of this study were collated onto a Microsoft Excel spreadsheet and were studied by descriptive statistics. The prevalence of each component studied in those with ICP, was represented in percentages and normally distributed data were presented as mean ± SD whilst non-normally distributed data were presented as median [interquartile range (IQR)].

RESULTS

A total of 26,697 deliveries were reported in UMMC over five-year period. The overall prevalence of ICP was 0.18% (n=47). Descriptive data of ICP pregnancies in our population are represented in Table I.

The mean maternal age at diagnosis in those with ICP was 31 years old. The average maternal body mass index (BMI) was 28 kg/m^2. Most ICP cases (95.7%) were diagnosed in the third trimester, with the median at 35 weeks of gestation, except for two women, who were diagnosed before 28 weeks. There were seven (14.9%) twin pregnancies. Three (6.4%) women had ICP in their previous pregnancies. Most of them presented with itchiness over the upper limbs. Comorbidities were noted in 14 (29.8%), out of which two (4.2%) had hypertension, one (2.1%) had T1DM, and 11 (23.4%) had gestational diabetes mellitus (GDM).

The main clinical indication for the measurement of SBA was pruritus or skin rashes, which contributed to 90.6% (n=183). Other indications were deranged liver enzymes (n=12, 5.9%) intrauterine death (n= 4, 2%) and as part of cholelithiasis workup (n= 3, 1.5%). Forty-four (93.6%) women had elevated SBA >10μmol/L at the time of presentation, and among them, eight (17%) had SBA >40 μmol/L and were grouped as severe ICP. One woman who presented with skin rashes at 31 weeks had an initial SBA <10 μmol/L, however after 2 weeks, repeated SBA was >10 μmol/L. Hence the diagnosis of ICP was made and appropriate treatment was initiated. There were four twin pregnancies in the severe ICP group, with three having SBA ≥100 μmol/L. They were subjected to iatrogenic preterm deliveries at 34 to 35 weeks gestation. In two (4.3%) women who had elevated liver enzymes, SBA levels were noted to be

TABLE I: Characteristics of subjects with ICP (n=47)

Mother characteristics at diagnosis		ICP (n=47)
Age (years) (mean ±SD)		31 (0.651)
BMI(kg/m2) (mean± SD)		28 (0.715)
Gestation at diagnosis (weeks) (median & range)		35 (23-40)
Comorbidities (GDM, T1DM, hypertension) (n, %)		14, 29.8%
Twin pregnancy (n, %)		7, 14.9%
History of ICP in previous pregnancy (n, %)		3, 6.4%
Maternal outcome **Delivery characteristics**	**Mild ICP (n: 39)** **SBA≤40µmol/L**	**Severe ICP (n:8)** **SBA>40µmol/L**
Gestation of delivery		
≥37 weeks	30 (76.9%)	2(25%)
<37 weeks	9(23.1%)	6(75%)
Mode of delivery		
Vaginal	22(56.4%)	0
Caesarean	17(43.6%)	8(100%)
Neonatal Outcome		
Preterm delivery (spontaneous & iatrogenic)		15 (31.9%)
Neonatal intensive care (NICU)admission		4 (8.5%) †
Special care nursery (SCN)admission		10 (21.3%)
Meconium-stained liquor (MSL)		1 (2.1%)
Stillbirths		0

Values are presented as numbers (%). Abbreviations: SD, standard deviation, ICP, intrahepatic cholestasis of pregnancy, SBA, serum bile acid †All admissions are from mild ICP

normal. Based on the clinical presentation and elevated liver enzymes, they were diagnosed as ICP. However, in these individuals, SBA was not measured during their follow-up.

LFT was requested for 192 (95%) women. In those with ICP, 11 (23.4%) had elevated alkaline phosphatase (ALP) (>260 IU/L), whilst raised alanine transaminase (ALT) (>30 IU/L) was noted in 24 (51.1%) women. In 13 (27.7%) women, aspartate transaminase (AST) was >30 IU/L and gamma glutamyl transferase (GGT) >34 IU/L. Details of the laboratory investigations are shown in Table II. In 25 (53.2%) women, both SBA and liver enzymes were elevated. However, in 20 (42.6%) women, only SBA levels were elevated. Despite normal SBA levels in two women, the clinical diagnosis of ICP was made based on the clinical features and deranged liver enzymes.

Management

Medication

Tablet Urso-deoxycholic acid (UCDA) was commenced in 22 (46.8%) of ICP cases, except for those near-term gestations and those with immediate delivery including spontaneous preterm labour, as shown in Table III. We noted that UCDA was not prescribed for four (8.5%) confirmed ICP cases, probably due to mild and stable SBA levels with resolved pruritus after symptomatic management, indicating different clinical practices

TABLE II: Results of serum bile acid and liver function tests of subjects with ICP

Laboratory investigations	Mean ± SD / Median (IQR)	Deranged results† n (%)
SBA ≥10 µmol/l(mild ICP)	34 ±36	45 (95.7%)
SBA >40 µmol/l (severe ICP)	99.1 ± 49.2	8 (17%)
Severe ICP with SBA ≥100 µmol/l	150 ±42	3 (6.4%)
AST	50 (24-101)	13 (27.7%)
ALT	38 (15-120)	24 (51.1%)
ALP	173(137-261)	11(23.4%)
GGT	21(13-39)	13 (27.7%)

Abbreviations: ICP, intrahepatic cholestasis of pregnancy, SD, standard deviation, SBA, serum bile acid, AST, aspartate transaminase, ALT, alanine transaminase, ALP, alkaline phosphatase, GGT, gamma-glutamyl transferase.
† AST (>30 IU/L), ALT (>30 IU/L), ALP (>260 IU/L), GGT (34 IU/L)
All three subjects had twin pregnancies.

TABLE III: Management of subjects with ICP during antepartum (n=47)

Management			n (%)
Medication		UDCA	22 (46.8%)
Elective delivery	IOL booked	≥37 weeks	28 (59.6%)
		<37 weeks	2 (4.3%)
	ELLSCS	≥37 weeks	1 (2.1%)
		<37 weeks	3 (6.4%)
Non-elective delivery (EMLSCS/Delivery to progress)		≥37 weeks	4 (8.5%)
		<37 weeks	9 (19.1%)

Notes: Values are presented as numbers (%). Abbreviations: IOL, induction of labor, ELLSCS, Elective lower segment cesarean section, EMLSCS, Emergency lower segment cesarean section, UDCA, ursodeoxycholic acid.

among treating physicians. However, there were no clear reasons stated in the clinical notes. Pruritus improved in those patients who received UCDA. After commencing UCDA treatment, SBA was measured to monitor 18 (81.8%) of them, and improvement in SBA levels was observed in 14 (77.8%) women.

Maternal outcome

Gestation at delivery

The delivery characteristics were analysed according to mild and severe ICP as shown in Table I. The average gestation of delivery for mild cases was 37 weeks and 17 (43.6%) of them had a caesarean section (C-section). In women with severe ICP, the mode of delivery was a C-section, and 6 (75%) of them delivered before 37 weeks.

Mode of delivery

As shown in Table III, 28 (59.6%) women with ICP were booked for induction of labour at 37 weeks, whereas two (4.3%) women were booked prior to 37 weeks. Four (8.5%) women were planned for elective C-section due to other conditions other than ICP such as twin

pregnancies, breech presentation, pre-eclampsia, and intrauterine growth restriction. Thirteen women (27.7%) presented to the hospital during the labour phase and hence had spontaneous delivery or emergency C-section without prior booking for elective delivery. Nine (19.1%) of them had delivery prior to 37 weeks due to twin pregnancies in labour, footling breech in labour, and foetal distress.

Postpartum follow up

Postnatal biochemical testing is a part of the confirmatory diagnosis. Among the ICP cases, only eight (17.0%) women had SBA tested after two to six weeks postpartum. LFT was only performed in two (4.3%) women. There was no postpartum biochemical assessment in 37 (78.7%) women.

Neonatal outcome

All ICP cases had a livebirth. The preterm birth rate, both spontaneous and iatrogenic was 15 (31.9%) of which ten (66.7%) were due to other obstetric issues (preterm labour, preterm rupture of membranes, and twins with selective intrauterine growth restriction) whilst the remaining five (33.3%) were iatrogenic preterm deliveries primarily due to ICP. There was no stillbirth even in women who had SBA ≥100 μmol/L. There were four (8.5%) admissions to the neonatal intensive care unit (NICU). The indications for NICU admission were prematurity with respiratory distress syndrome, congenital pneumonia, and enterocolitis. The SBA levels of their mothers were < 40 μmol/L. Apart from this, 10 (21.3%) neonates were admitted to the special care nursery (SCN) for neonatal jaundice requiring phototherapy, presumed sepsis, transient tachypnoea of newborn, and congenital pneumonia.

Non-ICP pregnancies in whom SBA was measured

We also collected information on the follow-ups on women who had SBA levels measured and the diagnosis of ICP had been excluded (n=155). We divided this group into two categories as shown in Table IV. Six (3.9%) women had an initial SBA level ≥10 μmol/L but were diagnosed to have cholelithiasis. The second group is (n=149) in whom the initial SBA level was <10 μmol/L. Repeat measurement of SBA was only done in 12 (8.1%) individuals in the latter group.

DISCUSSION

TABLE IV: Serum bile acid levels in women with ICP diagnosis excluded (n=155)

Non-ICP pregnancies	n (%)
SBA >10μmol/L at first presentation - Diagnosed with other hepatobiliary pathology	6 (3.9%)
SBA≤ 10 μmol/L at first presentation	149 (96.1%) †

Abbreviations: ICP, intrahepatic cholestasis of pregnancy, SBA, serum bile acid.
† In 12 women (8.1%), repeat analyses were performed during the antenatal period and SBA was <10 μmol/L.

ICP has been reported to affect 1.2% to 3.1% in the South Asian population, which is comparatively higher than the UK population (~0.7%) (4). Our retrospective audit identified ICP in 47 (0.18 %) pregnancies. The average maternal BMI at presentation was in the overweight category similar to findings in previous studies and suggesting a possible association between BMI and ICP risks (4,15). This further suggests that the actual prevalence of the community could be much higher, as Malaysia has been reported to have an increasing and the highest prevalence of obesity in the Southeast Asian population (16). This warrants the need for more awareness on ICP and to be able to recognise its characteristic features so that the diagnosis is not overlooked.

The aetiology of this condition remains obscure and is multifactorial as hypothesised by prior publications (12). Various observational and experimental data have proposed the potential link between the role of oestrogen and bile acid homeostasis (12). This clearly explains the occurrence rather exclusively in the third trimester in our study population. Along with oestrogen levels, insulin resistance which predominates in the third trimester and in those with higher BMI also supports the possible association for the development of ICP and DM (4,12). In our audit, one-quarter of patients with ICP also had concurrent GDM. Another important characteristic is twin pregnancies, which is also associated with higher oestrogen and insulin resistance. SBA levels >100 μmol/L was noted in twin pregnant women. This is similar to the findings of a large retrospective cohort study by Liu et al 2015 (13).

Pruritus or skin rash remains the most important indication with the highest contribution to SBA measurement in our center. In ICP, pruritus without rashes typically starts abruptly over palms and soles but may eventually become generalised (14). Despite it being a common occurrence in pregnancy, it is mandatory to discriminate the benign causes of pruritus from ICP, which carries a higher risk to both mother and foetus. Therefore, the presence of pruritus should raise the clinician's awareness of the possible diagnosis of ICP, and further investigation is mandatory. Currently, total SBA level is considered the most sensitive biochemical indicator for reliable diagnosis and monitoring of ICP. The acceptable and widely used upper limit normal of SBA, which is also adopted in our center, is 10 μmol/L. SBA level > 40 μmol/L is taken as highly abnormal and described as severe ICP (7). However, it should be noted that SBA level above the cut-off does not necessarily indicate that the woman is experiencing ICP and a lower level does not exclude the diagnosis (8). In our study, 95.7% of women were diagnosed with ICP based on initial SBA level of ≥10 μmol/L and 17 % were categorised as severe ICP as the SBA levels were >40 μmol/L. We noted that among the 149 pregnancies with normal SBA levels during the first visit, only 12 patients had

repeated biochemical assessments during the antenatal period. Kenyon et al reported that pregnant women who presented with classical pruritus on the palms and soles without biochemical evidence of ICP are likely to develop abnormal results and a diagnosis of ICP at a later gestation (17). Accordingly, they suggested that for women with persistent pruritus, biochemical evaluation should be repeated (17).

Along with the SBA levels, clinically significant changes were observed in liver enzymes in >50 % of ICP subjects, particularly ALP and ALT. It has been demonstrated in many previous studies that ALT serves as a more sensitive marker of ICP than AST, and it may rise before SBA and AST (1, 19). Since the upper limit of transaminases in pregnancy is 20% lower than non-pregnant levels, it is recommended to use pregnancy-specific ranges (1).

Establishing a diagnosis of ICP from clinical and laboratory findings allows the commencement of appropriate treatment for the best maternal and foetal outcomes. UCDA has been the main mode of medical management worldwide including in our center for all ICP patients. In the meta-analysis report by Kong et al, UCDA not only has the potential to reduce maternal pruritus but is also seen to improve overall foetal prognosis (20). In terms of delivery, majority of the ICP patients were delivered at 37 weeks with most of them being induced and only 15% of patients had preterm delivery. The proposed recommendations by RCOG (2011) are to offer induction of labour at 37 weeks (1) and South Australian Maternal and Neonatal Community of Practice Guideline (SAMNCP) added on earlier delivery in the presence of severe ICP with SBA levels ≥100 µmol/L (21). Due to elective delivery performed at 37 weeks, this may have reduced the complications like stillbirth. Small percentages of neonates were admitted to NICU, particularly among those delivered preterm, either spontaneous or iatrogenic.

Based on the recommendations on active management options, frequent maternal bile acid, and foetal surveillance have vital roles in directing clinical management decisions. Scanty information is available on the frequency of SBA measurements so far, however, SAMNCP has recommended measuring SBA weekly in severe ICP cases and every two weeks for mild cases (21,22). In terms of LFT, most of the available guidelines including RCOG (2011) have stated that it is reasonable to evaluate LFTs weekly until delivery (1) and to defer testing at least 10 days postpartum (21). Based on the available guidelines for ICP, we recommend following Table V for diagnosis and management of ICP.

Regarding postpartum biochemical follow-ups, our audit revealed a rather unsatisfactory finding. Less than 30% of ICP patients had either SBA or LFT evaluated at 6 weeks postpartum. It is important to reinforce the benefits of re-evaluation postpartum as it has been shown in a large population-based cohort study that ICP diagnosis is associated with a risk of developing hepatobiliary disease later at approximately 1% increase per year and there is also the possibility of these women being misclassified as suffering from ICP alone (23). In addition, a few other conditions namely hepatitis C, hepatic fibrosis, and cholangitis are reported to be more common in patients with a history of ICP (23, 24). Hence, it is important to identify patients with persistently elevated levels of liver enzymes and SBAs postpartum and detect them early for further management.

Our retrospective audit has a few weaknesses. We encountered limitations in acquiring adequate information for patients in the year 2016 as the electronic medical record (EMR) system was newly introduced. The delivery findings and neonatal progress were also not recorded in maternal notes. The prevalence calculated may not represent the actual prevalence of the community in Malaysia, as the cases were in a single healthcare facility.

CONCLUSION

Despite being an uncommon diagnosis in our population,

TABLE V: Recommendations for diagnosis and management of ICP

Groups	Initial biochemical findings	Further evaluation	Findings & management
Group A	SBA normal ALT/AST normal	† If pruritus persists, repeat SBA & LFT every 2–3 weeks < 34/40 gestation, weekly thereafter until delivery.	SBA normal, ALT/AST normal, continue as †
			SBA normal, ALT/AST raised, manage as Group B
			SBA raised, ALT/AST raised, manage as Group C
Group B	SBA normal ALT/AST raised	‡ Exclude other causes of hepatic impairment: hepatitis (HCV serology), autoimmune hepatitis (AMA, SMA), and extrahepatic biliary obstruction (liver USS). Consider PET, AFLP, HELLP. If pruritus persists, repeat SBA & LFT every 2 weeks < 34/40 gestation & weekly thereafter until delivery.	SBA normal, ALT/AST raised, continue as
			SBA raised, ALT/AST raised, manage as Group C
Group C	SBA raised ALT/AST raised/normal	Exclude other causes of hepatic impairment: hepatitis (HCV serology), autoimmune hepatitis (AMA, SMA), & extrahepatic biliary obstruction (liver USS). Consider PET, AFLP, HELLP. If the above is negative – diagnose ICP. Consider drug treatment	SBA <100 µmol/L and < 34/40,weekly SBA & LFT, consider induction by 39 weeks.
			SBA > 100 µmol/L and/or > 34/40, consider twice weekly SBA & LFT. Recommend delivery from 34–35 weeks.

Abbreviations: SBA, serum bile acid, AMA, antimitochondrial antibody, SMA, smooth muscle antibody, ALT, alanine transaminase, AST, aspartate transaminase, HCV, hepatitis C virus, USS, ultrasonography, LFT, liver function test, ICP, intrahepatic cholestasis of pregnancy, PET, preeclampsia, AFLP, Acute fatty liver in pregnancy, HELLP, hemolysis, elevated liver enzymes, low platelet. Adapted from ICP Support 2021.

early diagnosis and timely delivery is important to reduce the major perinatal adverse outcomes. In women with persistent pruritus but without the biochemical evidence of ICP at the time of presentation should have repeat SBA and LFT done every two to three weeks. We also suggest that future studies include more national maternal healthcare facilities to enable a broader research approach in ICP with regards to the associations of biochemical testing, medical management, and perinatal outcome.

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