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Adverse Perinatal Outcomes in Intrahepatic Cholestasis of Pregnancy in a Tertiary Care Teaching Hospital

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Abstract

Aim: To study adverse perinatal outcomes including preterm birth, meconium-stained liquor, NICU admissions, stillbirths in Intrahepatic Cholestasis of Pregnancy over a period of 5 years 6 months and compare it with controls.

Methods and methodology: This study was conducted in the Department of Obstetrics and Gynecology and Department of Biochemistry, of a tertiary care public hospital in New Delhi, India over a period of 5 years 6 months. It was a retrospective and prospective observational case-control study. Patients included were singleton pregnancies with pruritus without rash and a serum bile acid level >10micromol/L. Retrospective data of patients with Intrahepatic Cholestasis of Pregnancy who delivered in our Institute from Jan 2017 onwards was collected from the Medical Records Department. Patients of IHCP were enrolled prospectively from December 2021 to July 2022. 75 cases and controls were recruited. Cases were further divided into three groups on the basis of bile acid values, 10-39µmol/L- mild, 40-99µmol/L- moderate and ≥100µmol/L- severe IHCP. Treatment was provided as per hospital protocol and recorded. Follow up at 6 weeks postpartum was performed to look for the resolution of symptoms and normalization of LFT/SBAs. The patients not showing resolution of either symptoms or LFTS/SBA after 6 weeks were excluded from the analysis. The details of induced/spontaneous labor, gestational age at birth, mode of delivery and baby weight and centiles were observed in both groups. Adverse outcomes like preterm birth (<37 weeks), meconium-stained amniotic fluid, neonatal unit admission and stillbirth were recorded.

The transaminase levels did not show any correlation with bile acid levels. The primary outcome studied was preterm labor (<37 weeks) which was seen in 17 out of 75 cases (22.7%). Out of these 17, 12 (70%) had a spontaneous onset of labour whereas 5 (30%) had iatrogenic preterm birth (3 inductions and 2 preterm elective LSCS). When spontaneous births in both groups were compared the preterm births in the cases 12/75 (16%) were three times the number of preterm births in the controls 4/75 (5.3%). Regression analysis was performed after adjusting for confounders like age, BMI, parity, GDM and hypertension and OR for preterm birth in IHCP compared to controls was 3.371 (95% CI 1.247-9.108). There was also a significant difference in the number of births with meconium stained amniotic fluid in both groups, 21/75 (28%) in the cases compared to 10/75 (13.3%) in the controls. The p value between these two groups was 0.02. Regression analysis showed an odds ratio of 2.528 (95% 1.097-5.826). There were no cases of meconium aspiration syndrome. The babies that required NICU admission in both the groups were 10/75 (13.3%) in the cases vs 7/75 (9.3%) in the controls. This difference was not clinically significant. There were 3 stillbirths in the IHCP group whereas none in the control group. Two cases were mild IHCP and one moderate IHCP. Contributing factors in the occurrence of still births were SGA in one case and severe anaemia with GDM in the other.

Conclusions: The risk of adverse perinatal outcomes like preterm birth, meconium stained liqour and consequent neonatal morbidity is higher than control population and the risk depend on the level of bile acids. Serial bile acid monitoring is of utmost importance to balance the risk between late preterm delivery and occurrence of stillbirth. These women should be individualized for serial bile acid testing on the basis of their clinical picture like gestational age, previous bile acid levels and other coexistent conditions like GDM and preeclampsia to decide a suitable time for delivery. As fetal surveillance techniques like non stress tests, biophysical profiles and Dopplers are not useful in predicting adverse fetal outcome in IHCP, serial bile acid testing can serve as a tool to reduce stillbirths and neonatal morbidity in these women.

Results: Out of all cases mild, moderate and severe IHCP was seen in 80%, 17.3% and 2.7% cases respectively. The mean serum bile acids in these categories were 17 micromol/L, 58 micromol/L and 112 micromol/L respectively.

Keywords

Intrahepatic cholestasis of pregnancy; Meconium-stained liquor; Morbidity and mortality.

Introduction

Intrahepatic Cholestasis of Pregnancy (IHCP) is the most common liver disease during pregnancy. Its incidence varies greatly with geography and ethnicity. It has a very high incidence of about 15% in Chile and Bolivia but less than 1% in Europe [1]. Incidence ranges from 1.2-1.5% in India [2].

The classic presentation of IHCP is unexplained pruritus and raised serum bile acids. Dark urine, pale stool, or jaundice may also be present, but these symptoms are uncommon (<5%). Cholestasis is diagnosed when serum bile acids are >10µmol/L, in the presence of unexplained itching [2]. IHCP is a diagnosis of exclusion and all conditions causing possible liver dysfunction like hepatitis (infective/autoimmune), obstructive gall stones, preeclampsia and HELLP need to be excluded.

The pathophysiology behind IHCP is hypothesized to be an inhibitory effect of excess estrogen and progesterone hormones, especially in the third trimester of pregnancy, on the hepatocellular secretion of bile acids into the common bile duct [1]. This causes an overflow of bile acids to the systemic circulation and leads to pruritus in these women, who may be inherently predisposed to developing this disorder.

The symptoms of IHCP resolve spontaneously post-partum along with transaminases and bile acids. But if these symptoms or abnormal biochemical parameters persist for more than 3months, an alternative diagnosis should be considered, and these women should be referred to a hepatologist. This subset of women is more likely to have affected family members due to higher prevalence of mutations in the bile acid transport genes.

Excess of bile acids make the myometrial smooth muscle cells more sensitive to oxytocin causing preterm labor (19-60%). There is evidence of increased spasticity of chorionic veins which may lead to acute anoxic events causing meconium staining of amniotic fluid and fetal heart decelerations (22-41%). Bile acids may cause arrhythmias and sudden fetal demise (0.75-7%) [3]. Ursodeoxycholic acid (UDCA) is being used in IHCP patients for improving the impaired hepatocellular secretion of bile acids, but studies have remained elusive regarding its role in preventing fetal adverse events.

The earlier practice was to deliver the fetus at 37-38 weeks due to the unpredictable risk of stillbirths at term4 but with newer emerging studies there is strong evidence that the risk of stillbirths is similar to the general population in cases with bile acid levels below 40micmol/L and birth can be planned at 40 weeks of gestation (with adequate bile acid monitoring depending upon the clinical situation) [5]. This risk remains the same in cases with moderate IHCP with bile acid levels between 40-99micmol/L upto 38-39 weeks, hence requiring delivery at this gestational age. The risk increases exponentially when the bile acids are >100µmol/L after 35-36 weeks (to up to 10%) and delivery should be planned early in these cases [6].

IHCP entails maternal hepatic impairment with fetal morbidity and mortality. It has a complex etiology, with endocrinological, genetic and environmental factors playing a role [7]. This condition is characterized by pruritus in the absence of a primary skin lesion (barring scratch marks due to intense itching) along with raised bile acid levels. Bile acids, namely cholic acid and chenodeoxycholic acid are the main solute constituents of bile secreted by hepatocytes. They are cholesterol breakdown products and are conjugated with taurine and glycine and secreted into the intestine to emulsify fat and help in its absorption. In the gut, bile salts are deconjugated to form secondary bile acids namely, deoxycholic acid and lithocholic acid. Most of these bile acids are absorbed by the enterocytes of the terminal intestine and transported back to the liver through the portal vein via enterohepatic circulation.

Recent studies have updated the pregnancy specific levels of non-fasting bile acid as 18micromol/L.8 Current RCOG green top guideline released in June 2022 has updated the definition of IHCP as pruritus with increased serum bile acid>19micromol/L. There has been no recent update in the SMFM (Society of Maternal and Fetal Medicine) guideline and level of bile acids to define IHCP remains at >10micromol/L which is the definition used for the study. LFTs including alanine and aspartate transaminases are also raised and may increase to 3-60 times the normal range for pregnancy but they are not necessary for

diagnosis. Alkaline phosphatase is physiologically raised in pregnancy due to the placental isoenzyme production and hence is not useful. Gamma glutamyl transpeptidase may be normal or elevated. Altered levels of GGT provide a clue towards genetic etiology of the condition like mutation in ABCB4 gene [2]. Serum bilirubin maybe increased upto 5mg/dl but in a few cases. Prothrombin time may be deranged in cases of fat malabsorption.

IHCP occurs commonly in the third trimester, but there can be an earlier onset in some women. It is necessary to differentiate this pregnancy dermatosis from preeclampsia and HELLP as these conditions commonly occur together. Diagnosis of IHCP can only be confirmed postnatally when the pruritus and LFTs/serum bile acids return to normal. If the LFTs/ bile acids persist to be high, possibility of additional comorbidities like nonalcoholic fatty liver, autoimmune hepatitis etc. may need to be considered. Higher incidence of recurrence of IHCP is seen in women with family history of IHCP (92% vs 42%) [9].

It has been seen that about 25% of women develop itching in pregnancy but most of these are due to other dermatoses instead of IHCP, and unlike IHCP primary skin lesion is always present in these dermatoses like atopic eruption of pregnancy, pemphigoid gestationalis etc [10]. There is accumulating evidence to show that the adverse pregnancy outcomes in IHCP correlate with the levels of bile acids and other liver function tests perform poorly in reflecting the risk of stillbirths.

IHCP is considered a diagnosis of exclusion but according to newer emerging data, when not suspected on other clinical grounds, additional causes were not identified on virological, autoimmune and imaging investigations for itching and deranged liver function tests and bile acids, that would affect the pregnancy outcome [11].

As the peaks of serum estrogen and progesterone are higher in multiple as compared to singleton pregnancies, higher incidence of IHCP is seen in twin pregnancies. Higher incidence is also seen in pregnancies after in-vitro fertilization, advanced maternal age 35yrs and above, presence of hepatitis C infection and with a history of cholestasis in the previous pregnancy or a family history of intrahepatic cholestasis [1].

Literature supports that reproductive hormones and/or their metabolites influence the expression and function of hepatic bile acid transporters and bile acid metabolism, especially the glucuronide metabolite of 17β estradiol and mono and bisulphated progesterone metabolites [12].

Studies have shown that heterozygous mutations in the genes ABCB4 and ABCB11 involved in bile acid transport may be inherited and make women susceptible to the cholestatic effects of sex hormones. It may also lead to problems other than obstetric cholestasis like chronic hepatitis and cholangiocarcinoma [7].

In a subgroup of women, the rise in serum bile acids and transaminases can occur up to 15 weeks after the onset of pruritus, so it is advisable to review these women and to repeat the tests when persistent symptoms of IHCP are present even if the initial results are normal [13]. Progesterone sulfates14 and lysophosphatidic acid 15 have been proposed as pruritogenic candidates. Itching may range from being

mild and focal in some cases to severe and widespread, disrupting sleep and causing mental distress.

It has been seen that women with Hepatitis C have a higher prevalence of IHCP and hence this condition should be ruled out. These women have a higher risk of premature delivery.

In 2013, Wikström et al. were the first to systematically describe highly significant associations between ICP and both GDM and preeclampsia [16]. Subsequently various studies by Liu C. et al, Arafa et al, Martineau et al, Mor et al have demonstrated similar associations [17-20]. Bile acids cause disruption in glucose metabolism via the FXR (Farnesoid X Receptor) and TGR5 (Takeda G-Protein Coupled Receptor5) leading to GDM. Risk of preeclampsia is increased via endothelial damage and oxidative stress [21,22].

An increasing number of studies indicate that the level of the serum bile acids is related to the fetal complication rate [5]. Bile acids are known to cross the placenta and accumulate in the fetus and amniotic fluid due to reversed transplacental gradients in cholestatic pregnancies. A Swedish prospective cohort study examined the relationship between maternal serum bile acids and adverse fetal outcomes and found that with every 1micromol/L increase in bile acid concentration the risk of spontaneous preterm birth and meconium stained amniotic fluid increased by 1-2%, but this was only significant when the bile acid levels were >40micromol/L23 Myometrial smooth muscle cells have shown to be more sensitive to oxytocin in IHCP women, and cells from a normal women show increased response to oxytocin in the presence of bile acids1. In addition to spontaneous preterm births iatrogenic preterm deliveries are very common in the setting of IHCP but the risk of respiratory distress syndrome and NICU admissions in such late preterm births should not be taken lightly. Studies have shown that risk of RDS in late preterm IHCP infants are higher than late preterm infants born to mothers without IHCP. Bile acids may independently affect the lung surfactant production and cause neonatal respiratory distress. Meconium-stained amniotic fluid is explained by increased colonic motility secondary to bile acids. In a recent meta-analysis by Ovadia C. et al, bile acid level >100µmol/L has been shown to have a high risk of still birth in contrast to the previously held belief that the risk of stillbirth was increased for all women with IHCP [5]. Coexisting pregnancy complications, such as pre-eclampsia or gestational diabetes, might increase this risk [24]. The only intervention to affect adverse perinatal outcomes is likely to be appropriately planned delivery. In the group of women with bile acids >100µmol/L, delivery is recommended at 35-36 weeks to prevent stillbirths [25].

Stillborn infants born to IHCP mothers are appropriate for gestational age, and the intrauterine demise is not due to placental insufficiency. Intrauterine demise occurs suddenly in these fetuses despite of normal antenatal fetal surveillance [26]. Fetal cardiac arrhythmias and abnormal cardiac contractility are considered to be the cause of this sudden death [2]. Acute hypoxia due to chorionic vein spasm has also been postulated as a cause of sudden demise. Studies on cultured rat neonatal cardiomyocytes, have shown a decreased rate of contraction when exposed to bile acids and along with development of arrhythmogenic activity [28,29]. Stillbirths may occur despite normalization of bile acid levels [30].

Ursodeoxycholic acid (UDCA) has several actions that result in the improvement of cholestasis, including increasing biliary bile acid excretion through up-regulation of hepatic metabolizing enzymes and bile acid transporters, stabilization of the plasma membrane and hepatocyte protection against bile acid-induced

apoptosis [31,32]. UDCA is recommended in six national guidelines for management of intrahepatic cholestasis of pregnancy, [33] principally for the improvement of maternal symptoms and biochemical test results. A double-blind, randomized, placebo controlled trial studying the effect of UDCA in IHCP women (PITCHES) revealed that it had no effect on adverse perinatal outcomes [34].

A secondary analysis of the PITCHES trial by Felminger J. et al showed that there was no subgroup of women with IHCP, in whom a beneficial effect of treatment with UDCA on bile acid concentration or itch score could be identified [35]. A reduction in the risk of preterm birth by UDCA has been suggested in a systematic review by Ovadia C. et al, but the incidence of stillbirth was not seen to be reduced [36].

Vitamin K absorption may be affected due to steatorrhea leading to decreased synthesis of vitamin K dependent clotting factors in the liver, but this is not seen in the majority of cases with IHCP. This may be the cause of post-partum hemorrhage seen in these patients, although the causation due to, preterm birth, induction of labor and operative deliveries cannot be excluded. PPH is reported in 8-22% of cases following delivery [37]. Vitamin K should be supplemented when the prothrombin time is prolonged.

Other drugs which have been used in IHCP include cholestyramine, rifampicin, phenobarbitone, dexamethasone, s-adenosyl methionine, activated charcoal and epomediol. These medicines lack sufficient evidence to recommend their use in IHCP [38].

Aims & objectives

To study adverse perinatal outcomes in Intrahepatic Cholestasis of Pregnancy over a period of 5years 6months.

Methodology

The study took place in the Departments of Obstetrics and Gynecology and Biochemistry in a tertiary care public setup in New Delhi, India. The study duration was 5 years 6 months. It is a retrospective and prospective observational case-control study. Retrospective data of patients with intrahepatic cholestasis of pregnancy who delivered in our Institute from Jan 2017 onwards were collected. Patients of IHCP were enrolled prospectively from December 2021 to July 2022. Equal number of controls were enrolled. Patients with a singleton pregnancy, unexplained pruritus without rash and elevated serum bile acids (SBA) (>10µmol/L) were included. Any patient with a febrile illness with jaundice, acute hepatitis diagnosed by viral markers (Anti -HAV IgM, anti-HEV IgM, HBsAg, HBeAg), autoimmune hepatitis, extra hepatic obstructive jaundice, hepatotoxic drug intake, chronic liver disease, lethal anomalies on ultrasound, SARS-CoV2 RTPCR positive were excluded from the study. The primary outcome was to measure the incidence of preterm birth in Intrahepatic Cholestasis of Pregnancy and compare it with controls and the secondary outcomes were to measure the incidence of other adverse perinatal outcomes like meconium stained liquor, neonatal intensive care unit admissions and still birth in IHCP and compare it with controls Based on the study conducted by Arthuis C et al 39 the proportion of preterm delivery among those with IHCP was 15.7% and 4.8% among controls, by using these parameters a sample size of 75 was taken for both cases and controls.

Cases, who satisfied the aforementioned inclusion and exclusion criteria, were included in the study.

Details of the patients recruited retrospectively, were collected from the Medical Records Department.

Prospectively, cases were recruited at the time of their diagnosis. An informed consent was taken before recruitment of prospective cases. Patient's demographics, detailed history and examination, were noted as per the proforma attached. Hepatitis was excluded by doing viral markers HBsAg, anti HAV and anti HEV, wherever indicated. HCV cases were not excluded as the association of HCV with IHCP was studied. Chronic liver diseases like cirrhosis, alcoholic hepatitis, hemochromatosis, Wilsons disease, drug induced hepatitis and autoimmune hepatitis were excluded on the basis of history and examination, and investigations wherever indicated. Severity of pruritus was assessed by using the numerical rating score 40, taking the severity score as 0: no pruritus, < 3: mild pruritus, ≥ 3-<7: moderate pruritus, ≥ 7-<9: severe pruritus, ≥ 9: very severe pruritus. Liver function tests (LFT) and serum bile acids (SBA) were estimated. Estimation of liver transaminases was done by OCD Vitros-6500 equipment using dry chemistry. Abnormal LFTs were taken as more than double of the normal pregnancy ranges. Measurement of serum bile acids was done using colorimetric assay. Patients with serum bile acid more than 10µmol/L were diagnosed as IHCP and further divided into three groups on the basis of bile acid values, 10-39µmol/L- mild, 40-99µmol/L- moderate and ≥100µmol/L- severe.

Treatment was provided as per hospital protocol and recorded. Trend of symptomatology and LFTs/SBAs was recorded. LFTS/serum bile acids were repeated weekly to fortnightly in patients depending on their severity and gestational age. Follow up at 6 weeks postpartum was performed to look for the resolution of symptoms and normalization of LFT/SBAs. The patients not showing resolution of either symptoms or LFTS/SBA after 6 weeks were excluded from the analysis.

Control group was formed by choosing the prior or next delivery to the case of cholestasis of pregnancy, excluding the subject only if the patient had cholestasis of pregnancy or the duration of pregnancy was less than 20 weeks. Informed consent was taken and demographic details, history, examination and investigations along with all the relevant information were noted as per the proforma attached.

The details of induced/spontaneous labor, gestational age at birth, mode of delivery and baby weight and centiles were observed in both groups. Adverse outcomes like preterm birth (<37 weeks), meconium-stained amniotic fluid, neonatal unit admission and stillbirth were recorded. Adverse outcomes in the mother, like PPH, were also recorded.

Data was entered in MS Excel and analysis was done using SPSS 21.0 version. Data was presented as mean and standard deviation for continuous variables and as percentages for categorical variables. Chi-square or Fisher exact tests were used to find out the association between the categorical variables. Unpaired t test or Mann Whitney U test were used to compare two group means. Risk measurements like relative risk were calculated to estimate the risk of IHCP for poor outcomes. Regression analysis was done to determine whether IHCP is an independent risk factor for poor outcomes. P value of less than 0.05 was considered significant.

Results

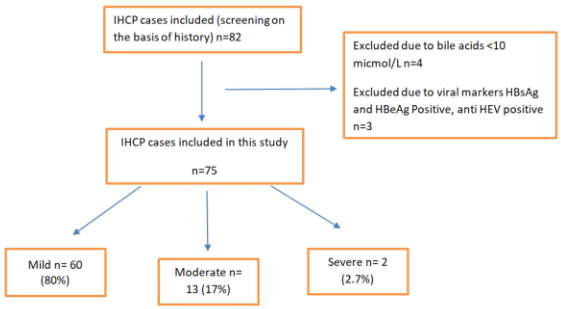

Figure 1: Flowchart of methodology.

A total of 75 cases and controls were included in this study. This was after screening these cases for symptoms and confirming diagnosis by serum bile acids and ruling out any other causes of liver dysfunction. 82 women had pruritus typical of IHCP, but 4 out of them had serum bile acid levels below 10micromol/L. Three out of these were positive for active Hepatitis B and E and were excluded from the study. The remainder of 75 cases were classified into mild, moderate and severe IHCP on the basis of bile acid levels. All these women showed postpartum resolution of symptoms and normalization of LFTs/ Bile acids. For each case recruited a corresponding control was also recruited at the time of delivery, which was either the prior or subsequent delivery.

The mean age ± SD of cases were 26.2 ± 4.9 years and those for controls were 26.4 ± 4.6 years. The mean gestational age at which the cases were recruited was 36 weeks and 4 days. The mean gestational age at birth in cases was 37 weeks and 39 weeks in controls. The mean± SD birthweight in cases was 2656.8g ± 475g and in controls was 2764g ± 417. The mean± SD BMI in both groups was 23.73 ±3.6 and 24.15 ±3.1 in both cases and controls respectively.

	IHCP (N=75)	Controls (N=75)	p value
Age (mean±SD)	26.2 ± 4.9	26.44 ± 4.6	0.732
Parity			
0	41/75 (54.7%)	30/75 (40%)	
1	24/75 (32%)	34/75 (45.3%)	0.471
≥2	10/75 (13.3%)	11/75 (14.7%)	
BMI (mean)			
<18.5	5/75 (6.7%)	0/75	
18.5-25	47/75 (62.7%)	51/75 (68%)	0.625
25-35	20/75 (26.6%)	24/75 (32%)	
>35	3/75 (4%)	0/75	
Current pregnancy complications			
Preeclampsia			
GDM	14/75 (18.4%)		0.493
	17/75 (22.6%)	5/75 (6.7%)	0.006
		5/75 (6.7%)	

Table 1: Demographic and obstetric histories of ihcp cases vs controls.

All were spontaneous conceptions besides 3 (2 IVF and 1 ovulation induction), they received oral progesterone (micronized progesterone and dydrogesterone) in the first trimester till 12 weeks, and S. bile acids were in the mild category (10-39micromol/L) in all [3].

Mean gestational age for onset of symptoms was 33 weeks. Only 2 out of 75 cases (2.6%), reported early onset of itching at 12 weeks of gestation, the first had a serum bile acid level of 106micromol/L first done at 24 weeks of gestation and the second had bile acid concentration of 16micromol/L with associated cholelithiasis.

Thirteen out of 75 women reported sleep disturbance due to itching (17.3%) and psychiatric symptoms were observed in none.

Eight out of 75 (10.7%) women had history of IHCP in previous pregnancies. And only one of these showed association with gall stones.

Out of all cases mild, moderate and severe IHCP was seen in 80%, 17.3% and 2.7% cases respectively. The mean serum bile acids in these categories were 17micromol/L, 58micromol/L and 112micromol/L respectively. The transaminase levels did not show any correlation with bile acid levels.

The mean numerical rating score in mild, moderate and severe IHCP was 4.7, 5 and 7.5 respectively. After treatment with ursodeoxycholic acid the mean numerical rating score came down to 1.4, 2.3 and 4 in these groups. UDCA was used for all but 2 women in doses ranging from 600mg to 1200mg per day. Injection vitamin K was given to 69/75 cases.

The primary outcome studied was preterm labor (<37 weeks) which was seen in 17 out of 75 cases (22.7%). Out of these 17, 12 (70%) had a spontaneous onset of labour whereas 5 (30%) had iatrogenic preterm birth (3 inductions and 2 preterm elective LSCS). The of indications of preterm LSCS were previous LSCS with severe IHCP at 35 weeks and 6 days (bile acid 106) and severe preeclampsia with FGR with AEDF done at 34 weeks 6 days. The indications for induction were severe IHCP, preeclampsia and persistent reduced fetal movements. 20% of the mild IHCP cases were born preterm, similarly 23% of moderate and 50% of severe IHCP were preterm. Iatrogenic preterm births were 33% in mild, none in moderate and 50% in severe.

When spontaneous births in both groups were compared the preterm births in the cases 12/75 (16%) were three times the number of preterm births in the controls 4/75 (5.3%).

Regression analysis was performed after adjusting for confounders like age, BMI, parity, GDM and hypertension and OR for preterm birth in IHCP compared to controls was 3.371 (95% CI 1.247-9.108).

There was also a significant difference in the number of births with meconium stained amniotic fluid in both groups, 21/75 (28%) in the cases compared to 10/75 (13.3%) in the controls. The p value between these two groups was 0.02. Regression analysis showed an odds ratio of 2.528 (95% 1.097-5.826). There were no cases of meconium aspiration syndrome.

The babies that required NICU admission in both the groups were 10/75 (13.3%) in the cases vs 7/75 (9.3%) in the controls. This difference was not clinically significant.

	Outcomes				Chisquare test (p value)
	Cases (75)	%	**Controls (75)**	**%**	
Pre-Term	17	22.6%	6	8.0%	P=0.013
MSL	21	28%	10	13.3%	P=0.027
NICU	10	13.3%	7	9.3%	P=0.440
Still Birth	3	4.0%	0	0.0%	

Table 2: Adverse perinatal outcomes in cases vs controls.

There were 3 stillbirths in the IHCP group whereas none in the control group. Two cases were mild IHCP and one moderate IHCP. Contributing factors in the occurrence of still births were SGA in one case and severe anemia with GDM in the other.

The association of GDM with IHCP was seen in 17/75 cases (22.6%) as compared to 5/75 controls (6.7%) which was clinically significant (p= 0.006). Hypertension was associated in 14/75 cases (18.6%) and 5/75 controls (6.7%) which was not clinically significant.

There was one case that had coexisting inactive HCV affection. And 4 cases with associated symptomatic gall stones (5.3%).

The number of vaginal deliveries in the cases were 44/75 (58.6%) and 62/75 (82.6%) in the controls. 41.3% (31/75) were delivered by cesarean section in the cases vs 17.3% (13/75) in the controls. The most common indication for cesarean section was fetal decelerations in 11/31 (35.5%) of cases followed by meconium-stained liquor in 5/31 (16.1%) cases.

Out of 75 deliveries in the cases 48 (64%) were induced vs 33.3% in the controls. The number of inductions and cesarean sections were clinically significant (p<0.001) between both groups.

Discussion

This study included IHCP cases according to the guidelines laid down by Society of Maternal and Fetal Medicine 2021 where there was pruritus with normal skin examination with elevated bile acids [41]. Serum bile acids were measured in non-fasting state in these women as the levels rise postprandially and better detection of peak bile acid levels is possible. Although currently RCOG Green Top Guidelines 2022 define mild IHCP as cases with serum bile acid >19micromol/L8, this study was initiated and executed before the cutoff for mild IHCP was redefined by these guidelines, hence bile acid level >10micromol/L has been used for mild disease. According to the newer RCOG criteria 31/75 patients fit into the new criteria. Eighty percent of the cases were mild, this corroborated with the prevalence of mild IHCP being

the highest in population data.

Elevated transaminase levels are not necessary for the diagnosis of IHCP and our study showed a wide variation if the transaminases in the case group.

In our study the intensity of itching was graded according to the numerical rating score [40] and was found to correlate with levels of bile acids. The score also improved in mostly all patients after the initiation of ursodeoxycholic acid therapy. This correlation has not been proved in various studies like the PITCHES trial by Fleminger et al [35], whereas Chappell et al found that there might be a minor improvement in the itch scale in the women taking UDCA [25].

Our study also shows a significant difference in the preterm births in the case vs control groups including both spontaneous and iatrogenic preterm births. A tripling in the incidence of spontaneous preterm birth in cases as compared to control group [OR 3.371 (95% CI 1.247-9.108]

This was in accordance with various studies conducted by Geenes et al, Glantz et al, Ovadia et al and Henderson et al. [5,23,24,42], showing an increased odds ratio for both spontaneous and iatrogenic preterm birth in women with IHCP. OR reported by Henderson et al being 3.47 [95% CI 3.06–3.95] for spontaneous preterm births and OR 3.65 [1.94–6.85] for iatrogenic preterm births [42]. The iatrogenic births were attributed to proactive management to prevent the risk of sudden stillbirths. 20% of the mild IHCP cases were born preterm, similarly 23% of moderate and 50% of severe IHCP were preterm, showing that the risk correlated with the bile acid levels. This has also been proven. Clinical trials and observational studies have shown that the risk of preterm birth increases with the serum bile acid concentration. Study by Ovadia et al also showed increase in occurrence of preterm births with increasing bile acid levels: 16.5% of women with bile acids below 40micromol/L (373/2264), 19.1% of women with bile acids 40–99micromol/L (261/1368), and 30.5% of women with bile acids 100micromol/L or more (157/514)5, [43]. They also showed that iatrogenic preterm birth remains high in all groups irrespective of serum bile acid concentration and is a major contributor of preterm birth in IHCP. Our study also showed correlation of preterm birth incidence with increasing levels of serum bile acid levels when the 3 groups mild, moderate and severe IHCP were compared. Also, in our study the number of iatrogenic preterm births were higher in the mild group (33%) as compared to the moderate group that had no iatrogenic births, laying stress on the unindicated preterm births, hence increasing the burden of short term and long-term problems of prematurity in these neonates and the health care system.

There was also a significant increase in the number of babies born with meconium-stained amniotic fluid which echoes the findings of a metanalysis of 23 studies, OR 2.60 (95% CI 1.62–4.16).5 Geenes at al showed the meconium staining (of any grade) was higher in IHCP when compared to women without IHCP and this occurred at lower gestational ages of 35-38 weeks. In utero MSL was reported in 85% of IHCP associated stillbirths [24].

Study by Ovadia et al also showed that the number of NICU admissions were higher in IHCP women but this difference was not significant when compared with those without IHCP [5].

Stillbirth in IHCP has been shown to be associated with bile acid levels. Recent individual and aggregate analysis have shown the risk of stillbirth increases when the serum bile acid levels are >100micromol/L and below this level the risk is the same as the background population, but this could be due to iatrogenic preterm births in many cases with bile acid levels <100micromol done to prevent stillbirths, as there is no reliable way for monitoring these fetuses. In our study we had three stillbirths [5].

The first one was a booked primigravida who developed IHCP at 33 weeks, serum OT/PT were 60/48 IU/L & serum bile acids were 32micromol/L. Her viral serology was negative and ultrasound of the liver/biliary system was normal. She was started on ursodeoxycholic acid at 34 weeks at the dose of 300mg BD, her symptoms were relieved and her transaminase levels were in the decreasing trend which were repeated twice. This patient had a stillbirth at 37 weeks and 4 days. She went into spontaneous labour 20 hours after the diagnosis and had a macerated stillbirth of 2300g which was at 4th centile for gestational age. SGA and the lack of adequate patient follow were contributing factors towards the stillbirth.

The second stillbirth was a booked G3P2L2 at 38 weeks at 6 days of gestation, she developed IHCP at 34 weeks, her serum transaminases were 133/88 at the time of diagnosis and serum bile acids were 15micromol/L, she was worked up and viral markers and ANA were negative. Her ultrasound showed presence of multiple galls stones. She was started on UDCA at 300 BD dose, after which her symptoms resolved partially, serum OT/PT reduced to 85/80 IU/L. Serum bile acids were not repeated. She was induced after the intrauterine demise and delivered a macerated stillbirth of 3255g (72nd centile). Her symptoms resolved postpartum and transaminases also came to the normal ranges. There was no other contributing factor in this case. Repeat bile acid levels and a stricter fetal surveillance and early delivery could possibly have prevented this outcome.

The third case was a 20 year old G2P1L1 who was unbooked and was referred to us at 37 weeks and 2 days for severe anemia. She was in labour and already had an intrauterine demise when she presented to us. She was transfused 1 unit of packed cell concentrate. On further evaluation she had symptoms of itching and mild jaundice. Her bile acid levels were 41micromol/L. She was also found to have deranged fasting and post prandial blood sugar levels. She birthed a macerated stillbirth of 2560g and had PPH which was medically managed.

It is well known that IHCP increases the risk of stillbirth, and this risk is proportional to the level of bile acids. Rate of stillbirths in expectantly managed IHCP pregnancies is 2-11%44 Risk of stillbirths is highest when serum bile acid concentration is more than 100micromol/liter and increase in still birth rate is exponential when compared to control population beyond 36 weeks. Therefore, it is recommended to deliver these women by 36 weeks [8,41].

Due to a small number of stillbirths and the lack of repeat serum bile acid testing the association with bile acid levels could not be derived. The presence of confounding factors like SGA and GDM also hindered this association.

Four patients out of 75 (5.3%) in the case group vs 3/75 (4%) in the control group had postpartum hemorrhage. The difference was not clinically significant.

Study by Webster et al, Furrer et al and Yang et al also showed no increased risk of PPH in these women [45,46]. A study by Arthius et al of 140 IHCP cases demonstrated significant increase in PPH but this could be due to the higher rate of prelabor cesarean sections and oxytocin inductions in these women as compared to controls [39].

The number of GDM and hypertension cases were higher in the case group as compared to the control. The association was clinically significant for GDM. Liu et al also found a higher prevalence of GDM and preeclampsia with IHCP [17]. This association was also observed in an aggregate meta- analysis performed by Ovadia et al, the OR being 2.4 [95% CI 2.1–2.8] for GDM and 3.7 [95% CI 3.2–4.3] for preeclampsia when compared with controls.5 This has been postulated due to the effect of bile acids on the Farnesoid X receptor (FXR) and Takeda G protein coupled receptor (TGR5) which can alter the glucolipid metabolism and predispose the woman to glucose intolerance and dyslipidemia. Preeclampsia is also thought to occur due to the vasoconstrictive action of bile acids on chorionic plate vessels, leading to oxidative stress and release of vasoactive mediators like endoglin and sFlt [1].

Higher rate of inductions for these women ranging to 82% were reported by Arthius et al. But there was no increase in the cesarean sections performed in labor as compared to controls [39].

Unlike our study, a population-based case-control study and a retrospective study showed no significant increase in the cesarean section rate between cases and controls [24,47]. Study by Liu et al showed increased rate of scheduled cesarean sections and cesarean sections in labour in their cohort of 911 IHCP pregnancies [17].

Strengths

Use of bile acids to define the cases of IHCP, including postnatal follow up.

Limitations

Small sample size and inability to perform serial bile acid levels, inability to determine the association of stillbirth with serum bile acid concentration, lack of adjustment for confounders like preeclampsia and GDM.

Conclusions

The risk of adverse perinatal outcomes like preterm birth, meconium stained liqour and consequent neonatal morbidity is higher than control population and the risk depends on the level of bile acids. Hence serial bile acid monitoring is of utmost importance to balance the risk between late preterm delivery and occurrence of stillbirth. These women should be individualized for serial bile acid testing on the basis of their clinical picture like gestational age, previous bile acid levels and other coexistent conditions like GDM and preeclampsia to decide a suitable time for delivery. As fetal surveillance techniques like non stress tests, biophysical profiles and Dopplers are not useful in predicting adverse fetal outcome in IHCP, serial bile acid testing can serve as a tool to reduce stillbirths and neonatal morbidity in these women.

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