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Original Research Article

Foetal and neonatal outcomes in an era of active management of intrahepatic cholestasis of pregnancy

Bikram Bhardwaj[1]*, Vaibhaw Kumar[1], Damalapati Mounica[1], G. S. Dhillon[2], Sunil Kumar H.[1]

[1]Department of Obstetrics and Gynecology, [2]Department of Community Medicine, Armed Forces Medical College, Pune, Maharashtra, India

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***Correspondence:**
Dr. Bikram Bhardwaj,
E-mail: bikrambhardwaj@gmail.com

ABSTRACT

Background: Intrahepatic cholestasis of pregnancy is one kind of hepatic disorder which is unique to pregnancy. It is associated with many adverse pregnancy outcomes if not intervened at the right time. It requires adequate clinical and biochemical correlation during management.
Methods: A prospective observational study was conducted in a tertiary care hospital among 1397 patients who underwent delivery during the study period from 01 July 2021 to 30 Jun 2022. Among the study population, those suspected to be having IHCP were subjected to laboratory tests and confirmed cases were further analysed for incidence and pregnancy outcomes in form of several maternal and fetal factors by appropriate statistical test using IBM SPSS version 20.0
Results: During the study period a total of 1397 patients underwent delivery out of which 174 showed clinical signs suggestive of IHCP. On subjecting these 174 suspected cases to further testing 53 patients were diagnosed with IHCP. The incidence of IHCP was 3.7% of which 28.30% (16/53) were primigravida. There were 22.64% (12/53) IVF pregnancies, 11.3% (6/53) were twin pregnancies. Total 28.30% cases (15/53) of IHCP presented with preterm labour. Of the total, there was 7.5% (4 /53) with meconium-stained liquor. Total 54.71% (29/53) cases underwent normal vaginal delivery, one forceps and one VBAC delivery, 45.28% (24/53) cases were underwent LSCS delivery and of this 70.8% (17/24) were emergency caesarean and 29.2% (7/24) were elective caesarean deliveries, 75% (18/24) were primary caesarean delivery. There were 25.4% (15/59) NICU admissions among new born of cases and 28.8% (17/59) were low birth weight babies. 25.4% (15/59) of neonates were seen to have APGAR score of less than 7 at 5 minute There was no stillbirth noted in diagnosed case of IHCP.
Conclusions: IHCP causes significant maternal and neonatal morbidity and is major contributor of preterm delivery, caesarean delivery, meconium-stained liquor and NICU admission.

Keywords: Antenatal care, Intrahepatic cholestasis of pregnancy, Obstetric cholestasis

INTRODUCTION

Intrahepatic cholestasis of pregnancy (IHCP) is a common liver disease during pregnancy with reported incidence rates between 0.4 and 15% in different countries and populations.[1-3] Intrahepatic cholestasis of pregnancy has been described by Ahlfeld in 1883 as recurrent jaundice during pregnancy which gets resolved following delivery. It occurs predominantly during third trimester of pregnancy and gets relieved following delivery and is marked with pruritus without rash which might affect whole of the body but characteristically starts in the soles of the feet and palms of the hands and progresses to the trunk and face, and also causes biochemical disturbances

in liver tests. IHCP poses minimal risk to maternal health, but it has been found to be associated with poor fetal outcomes like increased risks of preterm delivery, meconium staining of amniotic fluid, fetal bradycardia, fetal distress and asphyxia.[3,4] IHCP has shown clustering in families and carries a substantial risk for recurrence.[2,5] Various findings on this subject over the last two decades has resulted in changes in management of IHCP like administration of urso-deoxycholic acid (UDCA) for pruritus relief and biochemically reduction of maternal bile acids and induction of delivery in gestational weeks 37-38, aiming to avoid stillbirth.[3,6-8] This study is done to observe fetal and neonatal outcomes in such pregnancies in an Indian population receiving modern obstetric care.

METHODS

This prospective observational study was conducted at the department of obstetrics and gynecology, at tertiary care hospital in Pune, over a period of 1 year from July 2021 to June 2022. This study was approved by the institutional ethics and research review board. All the patients delivering in this hospital during the delivery period were observed for the outcome of interest and those showing clinical signs suggestive of IHCP were subjected to laboratory test. There were a total of 174 suspected cases out of which 53 were confirmed with the diagnosis of IHCP based on serum bile acid values of >10 micromol/l as per society of maternal-fetal medicine guidelines and were further analyzed.[9]

Inclusion criteria

Inclusion criterion for current study was all primigravidae or multigravida women attending antenatal clinic and registered at the hospital.

Exclusion criteria

Exclusion criteria for current study were; pregnant females with known liver disease, pregnant females with pregnancy induced hypertension and pregnant females with known skin condition.

RESULTS

There were 1397 patients who underwent delivery at this hospital out of which 53 patients were diagnosed with IHCP and were analysed for outcomes of interest. The incidence of IHCP in our study population was 3.7%. The mean age of the study population was 29.62±4.51 years and belonged to following age groups as per (Figure 1). Out of these patients, 16 (30.2%) were primigravida & 37 (69.8%) were multigravida, 37 (69.8%) gave birth at term and 16 (30.2%) had a pre-term delivery (Table 1). 47 of them had a singleton pregnancy while 6 gave birth to twins. Commonest mode of delivery among these IHCP patients was caesarean section (52.8%) which is way higher than national rate of 22.7% for government health facility in urban area as per NFHS-5 data. Out of these 28 caesareans, 19 were emergency caesarean and 9 were elective caesarean delivery.

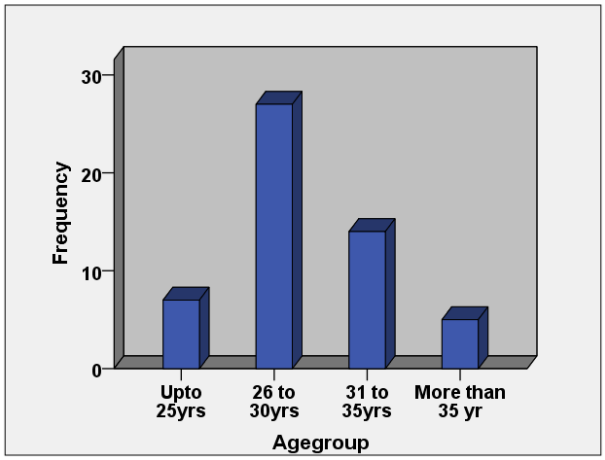

Figure 1: Distribution of study participants as per age.

Table 1: Distribution of participants based on various characteristics.

Characteristic	N	%
Gestational age at time of delivery		
Preterm	20	33.9
Term	39	66.1
Gravidity		
Primigravida	16	30.2
Multigravida	37	69.8
Mode of delivery		
Normal vaginal	24	45.2
Assisted vaginal	1	1.9
Caesarean section	28	52.8
Birth weight		
Low	17	28.8
Normal	42	71.2
Neonatal outcome		
NICU admission	15	25.4
No NICU admission	44	74.6

Fetal distress was most common indication followed by dysfunctional labor however previous caesarean delivery was most common indication for caesarean delivery in elective cases. There was no statistically significant association of mode of delivery with bile acid levels (Table 2) and neither with gravidity (Table 3). Antenatal progesterone support was given to 17 cases till variable period of gestation. Among the 59 new born, the median gestational age at delivery was 37 weeks 2 days (261 days) and mean gestational age at time of delivery was 257.17±15.5 days (approx. 36 weeks 05 days) with 95% CI from 259.63-261.61 days. 20 (33.9%) were pre-term, 17 (28.8%) had low birth weight and 15 (25.4%) required NICU admission (Table 1). Neither mean bile acid level of cases (Table 2) nor gravidity (Table 3) had any statistically

significant association with birth weight of new born and requirement of NICU admission.

Table 2: Bile acid levels.

Characteristic	Bile acid level		
	Mean	SD	P value
Mode of delivery			
Vaginal	21.10	10.0	0.951
Caesarean section	20.94	9.61	
Birthweight of new born			
Normal	21.50	10.75	0.543
Low	19.78	6.50	
Neonatal outcome			
No NICU admission	20.14	8.18	0.246
NICU admission	23.53	13.22	
Gestational age at delivery			
Term	20.53	9.38	0.801
Pre-term	21.27	11.12	

Taking APGAR score as a marker for neonatal outcome, 25.4% (15/59) of neonates were seen to have APGAR score of less than 7 at 5 minutes. In further sub group analysis, we found that the caesarean delivery rate in preterm and term delivery was 11/17 (64.7%) and 17/36 (47.2%) respectively. The vaginal delivery in term and preterm pregnancy group was 19/36 (52.78%) and 6/17 (35.30%) respectively. There was no statistically significant association between mode of delivery and period of gestation among these cases (Table 3). Meconium-stained liquor (MSL) was noted in 4 cases (7.5%) of delivery. Preterm delivery group has approx. 16% more MSL compare to term delivery group. (42.86% versus 26.61%). NICU admissions following delivery was 5/36 (13.9%) in term delivery group and 7/17 (41.2%) in preterm delivery group, which was found to have statistically significant association (Table 3). There was no case of intrauterine fetal demise noted among cases.

Table 3: Comparison of various parameters in varied gravidity stages.

Variables	Parameters			P value
Gravidity total	**Mode of delivery**		Total	
	Normal vaginal	**C-section**		
Primigravida	8	8	16	0.786
Multigravida	17	20	37	
Total	25	28	53	
Gravidity total	**NICU admission**		Total	1.000
	Yes	**No**		
Primigravida	4	12	16	
Multigravida	8	29	37	
Total	41	12	53	
Gravidity total	**Birth weight**		Total	0.150
	Normal	**Low**		
Primigravida	10	6	16	
Multigravida	31	6	37	
Total	41	12	53	
Gestational age at delivery	**Mode of delivery**		Total	0.234
	Normal vaginal	**Caesarean**		
Term	19	17	36	
Pre-term	6	11	17	
Total	25	28	53	
Gestational age at delivery	**NICU admission**		Total	0.270
	Not required	**Required**		
Term	31	05	36	
Pre-term	10	07	17	
Total	41	12	53	

DISCUSSION

Intrahepatic cholestasis of pregnancy, a reversible cholestasis of pregnancy, having complex etiology with endocrine environmental and genetic factor involved, occurs in late second and third trimester of pregnancy, which complicates maternal as well as fetal outcome.[1,2] The overall incidence among pregnant women in India is 1.2-1.5% however the incidence of IHCP shows greater variation between different countries or population highest incidence is found in Chile (4%) our study we found the incidence of IHCP is 3.7% which is higher than the national average.[12] However it is prudent to mention that, our centre is a tertiary care hospital providing ART facility available for eligible couple. Majority of the studies conducted have reached to conclusion that IHCP is more

common in primigravida with advanced maternal age however our study showed that IHCP is more common in multigravida (69.8%) with no significant relation to age, this finding was in contrast to study conducted by Kant et al[3]. Preterm delivery rate was higher among IHCP patients. All preterm birth were spontaneous in onset in our study and it was (28.30%) of patients. The study reported by Dang et al reported 19.14% of preterm delivery in IHCP patients.[13] In present study incidence of preterm birth is much higher than the above study. IHCP also contributes to iatrogenic preterm birth due its severity in third trimester. However, in contrary to present believe, we found the mean gestational age of delivery was 37 week 2 days (260.58±5.50 days). Shobaili et al reported the mean gestational age of their study population was in late preterm range (36.63±2.57 weeks).[11]

Present evidence supports either the induction of labour or spontaneous onset of labour doesn't increase the incidence of emergency caesarean delivery in pregnancy complicated by IHCP.[8] In our study we found overall caesarean rate was 52.8% with slight increase in caesarean delivery rate among preterm delivery group and most common indications were fetal distress/abnormal CTG trace. Therefore, it needs to be diagnosed at an early stage to prevent complications. This condition being a diagnosis of exclusion, involves both physical examination and certain pre-defined lab parameters. For the diagnosis of IHCP, the most important liver functions to be considered are serum transaminases (SGOT, SGPT).[16,17] High serum Bile acid levels (>10 micromole/l) are the most characteristic lab abnormality based on which the severity of the condition is determined. At a level of > 40 micromole/l, the condition is considered to be severe and risk of adverse fetal increases significantly. Management involves relief of pruritis and reducing the perinatal risks and safe delivery, for which local application of calamine lotion plus UDCA is given.[10] Urso-deoxycholic acid is the most effective treatment for IHCP. Inj. Vit K is also given to reduce the risk of PPH and fetal or neonatal bleeding. Till date there is no specific test for fetal monitoring to prevent stillbirth in these patients.[1,4] Therefore, continuous fetal monitoring in labor is done and most obstetricians in order to avoid adverse outcomes of pregnancy, opt to go for an elective delivery at 37-38 weeks of gestation. Even though Serum Bile acids is the gold standard test for detection of IHCP, it being a costly and a not so readily available test in different types of health set-ups make Liver function tests the investigation of choice for early detection of IHCP as these are relatively a lot cheaper and more readily available. The same has been found in studies by Davis et al and Palma et al.[16,17]

In the present study, 53 pregnant females, attending the antenatal clinic, satisfying the inclusion and the exclusion criteria underwent a set of lab investigations and accordingly were diagnosed to be having Intrahepatic cholestasis of pregnancy. The study population included pregnant females with no pre- defined age group. Mostly patients fell into age group between 26-30 years. In the present study, study population included both primigravida and multigravida patients. Primigravida patients were 16 of the total study group, these patients were started on urso-deoxycholic acid, dosage of which was adjusted according to the weekly LFT's and two weekly SBA. There was significant improvement in symptoms and in lab parameters with timely and judicious usage of urso-deoxycholic acid, and the fetal and neonatal outcomes were also better. This was in accordance with the studies of Bacq et al, Benjaminov et al, Kondrackiene et al and Glantz et al.[14,15,17] Zhonghua et al conducted a prospective cohort study to evaluate the relationship between IHCP and neonatal outcomes and observed that IHCP was associated with low-birth-weight babies and adverse neonatal outcomes.[4]

In the present study, even with timely diagnosis and intervention, 28.8% of the neonates had low birth weight, which in itself suggests effects of raised bile acid on fetal weight. In a retrospective case control study by Turkmen et al case and controls were categorized based on diagnosis on IHCP and it was found that mean birth weight of newborn born to cases had mean birth weight significantly lesser compared to those born to females in control group.[5] In a prospective observational study by Garcia-Flores et al conducted in 145 pregnant patients with persistent pruritis, it was found that newborns of IHCP patients had a higher rate of overall neonatal morbidity and NICU admission.[6] Brouwers et al study concluded the same.[7] The mode of delivery and the neonatal outcomes significantly improved in present study group due to timely diagnosis and treatment of patients and therefore, no significant statistical difference was observed for liver function parameters and serum bile acids with respect to mode of delivery or neonatal outcome.

MSL and fetal distress during labour are the known complications in patient with IHCP. IHCP is also associated with higher rate of sudden intrauterine fetal demise. Present study also showed overall 7.5% delivery complicated by MSL with approx. 50% of MSL is associated with preterm birth. Asulum et al also reported that IHCP was associated with 44.3% rate of MSL in their study.[19] The probable cause of such high MSL was mainly due to fetal distress and bile acid induced increase in gut motility of fetus. Overall there were 25.4% (15/59) NICU admissions among new born of cases and 28.8% (17/59) were low birth weight babies admissions and no still birth in present study. Study reported by Mahajan et al also reported the NICU admission rate of 16%.[18] Majority of the NICU admissions were due low birthweight baby with respiratory distress in our study. Shemer et al conducted a population-based cohort study, in which he concluded that patients with IHCP were more likely to have a neonate with less than 7 APGAR score at 5 minutes. In the present study, APGAR at 1min and APGAR at 5min were observed as a marker for neonatal outcome, and it was observed that only 25.4% of neonates had APGAR of less than 7 at 5 minutes.

CONCLUSION

The study concluded that patients with IHCP should be taken with utmost care and for the good fetal and neonatal outcome, timely and early intervention should be done.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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