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GESTATIONAL AGE AT DELIVERY AND MATERNAL AND PERINATAL OUTCOMES IN WOMEN WITH INTRAHEPATIC CHOLESTASIS OF PREGNANCY (IHCP)

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ABSTRACT
IHCP is a disease of exclusion with pruritis along with unexplained elevated levels of liver enzymes and/ or elevated serum bile acids which resolve after delivery. It is associated with increased rates of caesarean delivery, postpartum hemorrhage, spontaneous preterm labour, antepartum passage of meconium, fetal distress, fetal sphyxial events, fetal mortality and NICU admission. The objective was to study the gestational age at delivery and its association with maternal and perinatal outcomes in women with IHCP. Patients with IHCP beyond 28 weeks of gestation were evaluated clinically. Liver function tests (LFT) along with serum Bile acids were done every 2 weekly. They were managed according to hospital protocol. Decision for induction of labor or spontaneous delivery was taken according to department/unit protocol and trend of biochemical tests such as AST, ALT and serum bile acid. Patients were followed up till delivery and 2 weeks postpartum. Adverse maternal and perinatal outcomes were noted. LFT was done 2 weeks postpartum. A total of 150 cases of IHCP were recruited of which 77.3% were cases of mild IHCP and 22.7% were severe IHCP. Induction of labour was done in 87.3% of patients and 10% delivered spontaneously. Elective cesarean section was done in 2.7%. Maximum number of patients 74.7% (N=112) were induced between 37-38+6 weeks gestation. Preterm delivery occurred in 5.9% of patients. Cesarean rate observed was 34% and did not alter significantly with different gestational age at delivery. Major PPH was observed in 1.3% (2) of patients. There was one case of stillbirth. Low birth weight babies were 26% (39). There was one case of stillbirth and one case of asphyxia. Meconium stained liquor was seen in 9.3% (14) of patients. NICU admission and neonatal jaundice was seen in 9%(6) and 8.7% (13) patients respectively and was significantly higher in babies delivered at earlier gestational age. In conclusion, in patients with IHCP, termination of pregnancy can be considered after 37 completed weeks. In those patients who show a rising trend of serum bile acid >40 µmol/L or those who have values above 100 µmol/L, termination should be considered after 34 completed weeks due to risk of stillbirth keeping in mind the risks of prematurity. Therefore the decision for termination of pregnancy should be individualized taking into account the serum bile acid level of the patient.

KEYWORDS: IHCP, Obstetric cholestasis, Cholestasis in pregnancy.

INTRODUCTION
Intrahepatic Cholestasis of Pregnancy (IHCP) also known as Obstetric Cholestasis (OC) is the most common liver disease during pregnancy.[1] It is diagnosed when otherwise unexplained pruritus and abnormal liver function tests (LFTs) and/or raised bile acid, occur in the pregnant woman and both resolve after pregnancy. Pruritus involving the palms and soles are particularly suggestive of IHCP. Postnatal resolution of pruritus and abnormal LFTs is essential for confirmation of diagnosis.[2] IHCP usually presents in the late second and third trimester, which is 25-32 weeks of gestation.[1]

The pathogenesis of IHCP, although not well defined, is thought to be multifactorial, including an environmental, genetic and hormonal basis for the disease.[1] It is relatively benign to women but it has been reported to have important fetal implications. The condition is associated with increased rates of delivery by caesarean section, as high as 10-30%, postpartum hemorrhage, maternal morbidity associated with pruritus, spontaneous preterm labor, antepartum passage of meconium, fetal distress and asphyxial events.[1, 2] Its relation to perinatal mortality is uncertain; earlier studies reported an increased risk of stillbirth, but some recent studies have cast doubt on the magnitude of the increased risk. The

risk of stillbirth for singleton pregnancies increased above the population rate only when serum bile acid concentrations were 100 µmol or more according to a large systematic review and individual patient data meta-analysis of women with IHCP. The stillbirth rates of the countries contributing to this data varied from 0.18% to 0.72%.[2] Poor fetal outcomes have been shown to be associated with elevated maternal total serum bile acids (>40 micromole/L)/ liver enzymes in pregnancy.[1] Therefore it is prudent that women with IHCP should be booked under a consultant-led, team based care and give birth in a hospital unit.

Assessment of serum bile acids to decide the timing of birth stratified between 35 to 40 weeks gestation is being recommended by the Royal College of Obstetricians and Gynaecologists.[2] Timed delivery, when the obstetrician believes that the risks of early delivery are less than those of awaiting labor, has not been properly evaluated in IHCP.

IHCP is a challenging condition to treat as there is paucity of high quality studies. It remains a poorly understood and potentially dangerous condition with questions on diagnosis and management yet to be answered

MATERIALS AND METHODS

The prospective observational study titled 'Gestational age at delivery and maternal and perinatal outcomes in women with Intrahepatic Cholestasis of Pregnancy' was conducted from December 2018 to December 2019. Pregnant women attending the antenatal clinic after 28 weeks of gestation were recruited.

Inclusion criteria

Women with singleton pregnancy after 28 weeks of gestation with confirmed Intrahepatic Cholestasis of pregnancy.

- Pruritus in pregnancy with other causes excluded
- Raised serum bile acid level (> 10 µmol/L) or raised AST and ALT (>30 IU/L)

Exclusion criteria

1. Pregnant women <18 years of age
2. Laboratory confirmed Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis E, Cytomegalovirus, Ebstien-Barr virus
3. Preeclampsia
4. Acute fatty liver of pregnancy
5. Primary hepatic disorders
6. Known case of alpha 1 antitrypsin deficiency
7. Currently on drugs causing deranged liver enzymes
8. Lethal fetal anomaly

Sample size calculation

At 95% confidence level and taking the maternal outcome (mean gestation age at delivery) in study population to be 37.71±1.91 weeks (Chappell et al 2012)[3] and with error of 20%, the sample size comes out to be 354 using the formula.

$$n = \frac{Z^2_{1-\alpha/2}\sigma^2}{d^2}$$

Where n = sample size

Z_1-α/2 = 1.96 value of the standard normal variate corresponding to level of significance

Alpha 5%

Standard deviation (σ)

d = allowable error

In this study, we have taken a sample size of 150 for a period of one year.

METHODOLOGY

Women attending the antenatal OPD, who were beyond 28 weeks of gestation with singleton pregnancy, were screened for symptoms of IHCP, mainly itching in the palms and soles or the whole body after taking ethical clearance from Institutional Ethics Committee. Registration of this study was done under Clinical Trial Registry of India (CTRI) and CTRI number received was CTRI/2019/05/019410. History regarding other associated symptoms such as dark urine, pale stools and yellowish discoloration of the eyes and skin, past history of IHCP or hepatic and biliary disorders, family history of IHCP and relevant drug history were taken. Detailed general physical and systemic examination was done. Liver function tests and serum bile acid were done to confirm the diagnosis. Dermatology and gastroenterology consultation were taken, to rule out other primary skin, hepatic and biliary disorders. An ultrasound of the liver and hepatobiliary system was done to rule out other causes of raised liver enzymes. The exclusion criteria were applied and a written informed consent taken from the patients included in the study, after explaining to them the detailed methodology.

All the patients were managed according to their respective unit protocol. LFTs were repeated 1-2 weekly in the fasting state, regular antepartum fetal testing was done in the form of biweekly NST and weekly biophysical profile. Depending on the severity of IHCP and biochemical markers, UDCA (Ursodeoxycholic acid) was started and injection vitamin K given. Decision for induction of labor or spontaneous delivery was taken according to department/unit protocol and trend of biochemical tests such as AST, ALT and serum bile acid.

Timing of delivery, maternal and perinatal outcomes were observed. Patients and neonates were followed up for 2 weeks postpartum and observed for relief of symptoms and normalization of LFT, and development of complication in the neonate.

The patients were followed up and outcomes noted throughout the pregnancy and 2 weeks postpartum.

Primary outcome
Maternal outcomes
1. Gestational age at delivery
2. Mode of onset of labor
3. Rates of cesarean section
4. Indication of cesarean section
5. Blood loss during delivery

Perinatal outcomes
1. Live birth
2. Birth weight
3. Meconium stained liquor
4. APGAR at 0, 1, 5 min
5. Admission and duration in neonatal unit
6. Need for and duration of ventilatory support
7. Convulsions
8. Jaundice

Secondary outcome
Other Maternal and perinatal morbidity/ mortality.

Statistical analysis
The collected data was entered in Microsoft Excel, analyzed and statistically evaluated using SPSS-PC-25 version. Quantitative data was expressed by mean, standard deviation and difference between comparable groups was tested by student's t-test (unpaired) or Mann Whitney 'U' test while for more than two groups, ANOVA test was used. Qualitative data was expressed in percentage. Difference between the proportions was tested by chi square test or Fisher's exact test. 'P' value less than 0.05 was considered statistically significant. Subgroup analysis was done based on gestational age at delivery and maternal and perinatal outcomes.

RESULTS
In the study a total of 150 cases, based on the inclusion criteria were included to study the gestational age at delivery and the maternal and perinatal outcomes in IHCP. Majority of the patients i.e. 87.3% (N=131) were between 20 to 30 years of age with a mean age of 26.35±3.76 years. Most of the patients, 82.7% (N=124) were within the normal weight category i.e. 18.5-24.9 kg/m^2 (Table 1) There were 116 (77.3%) patients with mild IHCP (serum bile acid 10- 40 µmol/L) and 34 (22.7 %) patients with severe IHCP (serum bile acid >40 µmol/L). None of the patients had serum bile acid values more than 100 µmol/L. Mean serum bile acid was 31.19±20.50 µmol/L (Table 2). Majority of them i.e. 42% (N=63) were induced and delivered at 37- 37+6 weeks of gestation. Out of the 9 cases of preterm births, 5 were spontaneous, 3 were induced in view of rising serum bile acid levels and 1 underwent elective cesarean for preterm labour with transverse lie. Out of 150 patients, 87.3% (N=131) were induced, 10% (N=15) went into spontaneous labor and 2.7% (N=4) were taken for elective cesarean section. Maximum inductions i.e. 96.9% (N=127) were done for IHCP. The cesarean rate was 34% (N=51) including those taken for elective cesarean section. The major indication for cesarean section was fetal distress, 39.2% (N=20) followed by failed induction in 29.4% (N=15) (Table 3)

In the group of patients who delivered between 37-37+6 weeks and 38-38+6 weeks of gestation, 98.4% (N=62) and 91.8% (M=45) were induced respectively. In the group who delivered at 40 weeks or beyond, 54.5% (N=6) were spontaneous and 45.5% (N=5) were induced. The p value was significant indicating that higher induction rates were seen with increasing gestational age, in patients with IHCP. In the group of patients who delivered between 37-37+6 weeks and 38-38+6 weeks of gestation, 63.5% (N=40) and 65.3% (N=32) delivered vaginally respectively. The cesarean rate in the 37-37+6 weeks, 38-38+6 weeks and 39-39+6 weeks group was 33.3% (N=21), 34.7% (N=17) and 50% (N=9) respectively. p value was non-significant indicating that gestational age at delivery did not significantly alter the cesarean rates. (Table 4)

Major PPH in this study was seen in 2 patients, both of whom delivered at or beyond 40 weeks. Both of these patients were postdated pregnancies and had normal blood counts and were delivered vaginally. One was induced for IHCP, had received injection vitamin K and had traumatic PPH. The other patient was a multigravida, went into spontaneous labor, did not receive injection vitamin K and had atonic PPH. Out of 150 patients 41.3% (N=62) had blood loss in the range of 500-1000 ml out of which 21 were vaginal deliveries including 2 instrumental deliveries and 41 were cesarean deliveries. Blood loss in the 37-37+6 weeks, 38-38+6 weeks and 39-39+6 weeks group was between 500-1000 ml in 41.3% (N=26), 38.8% (N=19) and 55.6% (N=10) respectively. P value was significant indicating that higher blood loss was seen at later gestational age at delivery. (Table 4)

There was one case of stillbirth in the 37-37+6 weeks group who was born to a primigravida with serum bile acid of 96 µmol/L, and liver enzymes thrice the normal value which showed a decreasing trend. She had received UDCA 300 mg BD (total dose 600 mg/day) and 3 doses of injection vitamin K. She was induced for IHCP at 37+5 weeks, sudden IUFD (Intrauterine fetal demise) occurred and delivered a stillborn weighing 2930 g. Low birth weight babies of birth weight 1500-2500 g was seen in preterm deliveries (<37 weeks). Among babies born to mothers who delivered in the gestational age group of 37-37+6 weeks, 28.6% (N=18) were low birth weight. p value was significant indicating higher incidence of low birth weight babies in those who delivered at earlier gestational age. Meconium stained liquor was seen in 9.3% (N=14) of the patients. Among the patients who delivered in the gestational age group of 32-33+6 weeks, 34-35+6 weeks and 36-36+6 weeks, 100% (N=2), 60% (N=3) and 50% (N=1) of babies required NICU admission. p value is significant indicating that earlier gestational age at delivery had higher incidence of NICU admission in baby. Asphyxial event was seen in 0.7%

(N=1) of babies. No babies developed convulsions during the follow up period. Jaundice was seen in 100% (2) of the babies who were delivered at 32-33+6 weeks of gestation and 40% (2) of babies in the 34-35+6 weeks group. Incidence of jaundice decreased as the gestation age of delivery increased. p value was significant indicating higher incidence of neonatal jaundice in IHCP with preterm deliveries. (Table 5 and Table 6)

TABLES

Table 1: Demographic factors of patients with IHCP.

Age group (years)	**N**	**%**
20-25	66	44.0
25-30	65	43.3
30-35	16	10.7
>35	3	2.0
Total	150	100.0
Education		
Illiterate	6	4.0
Primary	44	29.3
Secondary	77	51.3
Higher secondary	23	15.3
Total	150	100.0
Parity		
Primigravida	80	53.3
Multigravida	70	46.7
Total	150	100.0
BMI (kg/m^2)		
<18.5	3	2.0
18.5-24.9	124	82.7
25-29.9	20	13.3
30-34.9	3	2.0
Total	150	100.0

Table 2: Serum bile acid levels in patients with IHCP.

Serum Bile acid at delivery (µmol/L)	**N**	**%**
10-40	116	77.3
41-100	34	22.7
Total	150	100.0

Table 3: Maternal outcomes and labour events in patients with IHCP.

Labor events		**N**	**%**
Gestational age at delivery	32-33+6	2	1.3
	34-35+6	5	3.3
	36-36+6	2	1.3
	37-37+6	63	42.0
	38-38+6	49	32.7
	39-39+6	18	12.0
	≥40	11	7.3
	Total	150	100.0
Onset of labor	Induced	131	87.3
	Spontaneous	15	10
	Elective LSCS	4	2.7
	Total	150	100
Indication for induction	IHCP	127	96.9
	Postdatism	2	1.5
	Type 2 DM + Gestational hypertension	1	0.8
	Decreased fetal movements	1	0.8
	Total induced	131	100
Mode of delivery	Vaginal	99	66
	Cesarean	51	34
	Total	150	100.0
Blood loss at delivery	<500	86	57.3
	500-1000	62	41.3
	≥1000	2	1.3
	Total	150	100.0
Febrile illness		0	0
Vaginal discharge		0	0
Paralytic ileus		1	0.7

Table 4: Comparison of gestational age at delivery and maternal outcomes.

POG at delivery (weeks)	Labour onset							Mode of delivery							Blood loss(ml)						
	Induced		Spontaneous		Elective LSCS		P value	Vaginal		Cesarean		Instrumental		P value	<500		500-100		>1000		P value
	N	%	N	%	N	%		N	%	N	%	N	%		N	%	N	%	N	%	
32-33+6	1	50.0%	1	50.0%	0	.0%		1	50.0%	1	50.0%	0	.0%		1	50.0%	1	50.0%	0	.0%	
34-35+6	2	40.0%	2	40.0%	1	20.0%		3	60.0%	2	40.0%	0	.0%		3	60.0%	2	40.0%	0	.0%	
36-36+6	0	.0%	2	100.0%	0	.0%		1	50.0%	1	50.0%	0	.0%		1	50.0%	1	50.0%	0	.0%	
37-37+6	62	98.4%	1	1.6%	0	.0%	<0.001	40	63.5%	21	33.3%	2	3.2%	0.519	37	58.7%	26	41.3%	0	.0%	0.006
38-38+6	45	91.8%	2	4.1%	2	4.1%		32	65.3%	17	34.7%	0	.0%		30	61.2%	19	38.8%	0	.0%	
39-39+6	16	88.9%	1	5.6%	1	5.6%		9	50.0%	9	50.0%	0	.0%		8	44.4%	10	55.6%	0	.0%	
≥40	5	45.5%	6	54.5%	0	.0%		11	100.0%	0	.0%	0	.0%		6	54.5%	3	27.3%	2	18.2%	

Table 5: Perinatal outcomes in babies born to mothers with IHCP.

Neonatal Outcomes	N	%
Gender		
1.Male	79	52.7
2.Female	71	47.3
Birth weight		
1.1500-2500 g	39	26.0
2.2500-4000 g	111	74.0
Stillbirth	1	0.7
MSL (meconium stained liquor)	14	9.3
1.Grade I	2	1.3
2.Grade II	7	4.7
3.Grade III	5	3.3
Asphyxial event	1	0.7
NICU admission	9	6
Ventilatory support	4	2.7
Convulsions	0	0
Jaundice	13	8.7

Table 6: Comparison of Gestational age at delivery and perinatal outcomes.

POG at delivery (weeks)	Live birth			Birth weight (g)			MSL					Admission and duration in NICU			Ventilatory support			Jaundice		
	Yes	No	P value	1500-2500	2500-4000	P value	No MSL	MSL I	MSL II	MSL III	P value	No	Yes	P value	No	Yes	P value	No	Yes	P value
	N (%)	N (%)		N (%)	N (%)		N (%)	N (%)	N (%)	N (%)		N (%)	N (%)		N (%)	N (%)		N (%)	N (%)	
32-33+6	2 (100)	0 (.0)		2(100.0)	0(.0)		2(100.0)	0(.0)	0(.0)	0(.0)		0(.0)	2(100.0)		1(50.0)	1(50.0)		0(.0)	2(100.0)	
34-35+6	5 (100)	0 (.0)		4(80.0)	1(20.0)		5(100.0)	0(.0)	0(.0)	0(.0)		2(40.0)	3(60.0)		4(80.0)	1(20.0)		3(60.0)	2(40.0)	
36-36+6	2 (100)	0 (.0)		1(50.0)	1(50.0)		1(50.0)	0(.0)	0(.0)	1(50.0)		1(50.0)	1(50.0)		1(50.0)	1(50.0)		2(100.0)	0(.0)	
37-37+6	62 (98.4)	1 (1.6)	0.966	18(28.6)	45(71.4)	0.004	55(87.3)	1(1.6)	6(9.5)	1(1.6)	0.081	61(96.8)	2(3.2)	<0.001	63(100.0)	0(.0)	<0.001	56(88.9)	7(11.1)	<0.001
38-38+6	49 (100)	0 (.0)		10(20.4)	39(79.6)		46(93.9)	0(.0)	1(2.0)	2(4.1)		48(98.0)	1(2.0)		48(98.0)	1(2.0)		48(98.0)	1(2.0)	
39-39+6	18 (100)	0 (.0)		4(22.2)	14(77.8)		17(94.4)	0(.0)	0(.0)	1(5.6)		18(100.0)	0(.0)		18(100.0)	0(.0)		17(94.4)	1(5.6)	
≥40	11 (100)	0 (.0)		0(.0)	11(100.0)		10990.9)	1(9.1)	0(.0)	0(.0)		119100.0)	0(.0)		11(100.0)	0(.0)		11(100.0)	0(.0)	
≥40	5	45.5%	6	54.5%	0	.0%		11	100.0%	0	.0%	0	.0%		6	54.5%	3	27.3%	2	18.2%	

DISCUSSION

In the present study there were 77.3% (N=116) of patients with serum bile acid in the range 10-40 µmol/L and 22.7% (N=34) with serum bile acid 41-100 µmol/L who were labeled mild and severe IHCP respectively. Out of the 150 patients, 87.3% (131) were induced, 10% (15) delivered spontaneously and 2.7% (4) underwent elective cesarean. A comparable outcome was seen in the

study by Chappell LC et al 2012, where 83.3% (25) were induced and 3.3% (1) delivered spontaneously.[3] Similarly Friberg AK et al in 2016 also found inductions done in 62% (70) of patients and spontaneous delivery in 14.1% (16).[4] In the present study the cesarean rate was found to be 34% (51) which was similar to a rate of 34.5% (39) seen in a study by Friberg AK et al in 2016.[4] A slightly higher percentage of patients with IHCP underwent cesarean section in the studies conducted by Estiu MC et al (2017), Celik S et al (2019), and Senocak GNC et al (2019) which were 58.6% (224), 58% (214) and 67% (47) respectively.[5,6,7] The percentage of preterm deliveries were only 5.9% (9), which was very less compared to 58.9% (225) and 40% (28) in the previous studies conducted by Estui MC et al (2017) and Senocak GNC (2019) et al respectively.[5,7] When the gestational age at delivery was compared with the various maternal outcomes, more inductions were seen beyond 37 weeks of gestation, with a significant p value=0.001. However the gestational age at delivery did not affect the cesarean rates (p value=0.519). Blood loss was slightly higher in those patients who were delivered at a later gestational age (p value= 0.006). The present study showed 9.3% (14) cases with meconium stained amniotic fluid which was comparable to 10% (3) in the study by Chappell LC et al in 2012.[3] But in a study by Celik S et al 2019 meconium stained amniotic fluid was seen in staggering 25% of patients with severe IHCP.[6] Babies requiring NICU admission was 6%(9) in the present study similar to 6% (2) seen in the study by Chappell LC et 2012.[3] As seen in the case of MSAF, nursery admissions were also as high as 33% (41) in severe IHCP group in the study by Celik S et al 2019.[6] Babies affected by neonatal jaundice was 8.7% (13) similar to 7% (2) seen in the study by Chappell LC et al 2012.[3] In the present study, there was only one case of stillbirth and the patient had a high serum bile acid level of 98 µmol/L. According to literature, the stillbirth rates in IHCP were 1.5-7%, reported in various studies.[8,9,10] When gestational age was compared to the rates of adverse perinatal outcomes, it was seen that earlier the gestational age at delivery, higher were the rates of NICU (Neonatal intensive care unit) admission and ventilator support with significant p value <0.001 and p value <0.001 respectively. Also higher rates of neonatal jaundice was seen in those who were delivered at earlier gestational age (p value <0.001). In the study by Chappell LC et al 2012, when early term delivery was compared to expectant management in patients with IHCP, no significant difference was seen in any of the perinatal outcomes.[3]

CONCLUSION

This was a prospective observational study, done to observe gestational age at delivery and the maternal and perinatal outcomes of women with IHCP. In the present study, 94% (N=141) of the patients delivered after 37 weeks and both maternal and perinatal outcomes were good. There was one case of stillbirth at gestational age of 37+5 weeks who was diagnosed at 34+2 weeks gestation with IHCP, and had serum bile acid level of 98 µmol/L at delivery. Therefore, in patients with IHCP, termination of pregnancy can be considered after 37 completed weeks. But in those patients who show a rising trend of serum bile acid >40 µmol/L or those who have values above 100 µmol/L, termination should be considered after 34 completed weeks due to risk of stillbirth. Termination before 37 weeks can lead to prematurity and higher incidence of low birth weight babies, NICU admissions, ventilator support and neonatal jaundice. Therefore the decision for termination of pregnancy should be individualized taking into account the serum bile acid level of the patient. However delivery beyond 37 weeks of pregnancy did not significantly increase cesarean section rates.

The strength of this study was that it was a prospective study. The limitations were the small sample size and that it was an observational study.

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