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Original Research Article

Pregnancy outcome in women with intrahepatic cholestasis of pregnancy

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ABSTRACT

Background: Intrahepatic cholestasis of pregnancy is a multifactorial condition of pregnancy diagnosed when otherwise unexplained pruritus with abnormal liver function test and neither of which has an alternative cause. The most appropriate gestational age for the delivery of women with ICP is yet to be determined. The present study is designed to determine whether with active intervention, pregnancy with ICP can be carried to a later gestation.
Methods: Fifty Women with diagnosed a case of ICP were recruited into the study. The diagnosis of ICP was based on the symptoms, clinical examination and lab investigations. Group I: 25 women planned for delivery at POG 37 - 37^{+6} weeks of pregnancy. Group II: 25 women Planned for delivery at POG ≥38 weeks of pregnancy.
Results: In group, one woman had preterm delivery at POG 36^{+2} weeks and rest of 24 women were delivered at POG 37-37^{+6} weeks. In group II, out of 25 women one woman had emergency LSCS at POG 35^{+3} weeks for MSL and induction of labour was done in 2nd for abnormal fetal well-being tests at POG 37 weeks. One woman had pre-term delivery at POG 36^{+1} weeks. Remaining 22 women in group II were delivered at POG ≥38 weeks. In the present study there was no significant difference in the gestational age at delivery between the two groups.
Conclusions: It can be concluded that pregnancies with obstetric cholestasis can be carried to later gestation of ≥38 weeks under surveillance with UDCA treatment.

Keywords: Intrahepatic cholestasis of pregnancy, Liver function test, Pre-term delivery

INTRODUCTION

Over the years, intrahepatic cholestasis of pregnancy (ICP) has also been described as jaundice in pregnancy, recurrent jaundice of pregnancy, idiopathic jaundice of pregnancy, obstetric hepatosis, hepatosis gestationalis or obstetric cholestasis, icterus gravidarum. ICP was originally described in 1883 by Ahlfeld as recurrent jaundice in pregnancy that resolved following delivery.

ICP is a multifactorial condition of pregnancy diagnosed when otherwise unexplained pruritus occurs in the absence of a skin rash with abnormal liver function test (LFT) and/or raised bile acids, neither of which has an alternative cause and both of which resolve after delivery.[1] The incidence of ICP varies widely with geographical location and ethnicity. It is most common in South America, particularly in Chile, where early reports described an overall incidence of 10%, with higher rates (24%) seen in women of Araucanian Indian descent.[2] More recently, this has fallen to approximately 1.5%-4%.[3] In UK suggested prevalence was found to be 0.7%, with 39-41% of women with ICP being of Asian descent.[4]

The pathogenesis of ICP, although not well defined, the etiology is thought to be multifactorial with genetic (ABCB4 gene), hormonal and exogenous environmental

factors involvement.[5] Animal studies have implicated bile acids in the pathophysiology of intrauterine death and (IUD) spontaneous prematurity Bile acids have been shown to have direct effect on fetal cardiomyocytes on placental chorionic veins and on gut motility.[6-9] Gorelik and colleagues (2006) suggest that bile acid may cause fetal cardiac arrest after entering cardiomyocytes in abnormal amount.[10] There have been some reports of the co-existence of ICP with other pregnancy related disorders including pre-eclampsia, acute fatty liver of pregnancy and gestational diabetes.[11,12]

There is wide range of definition of ICP and absence of any agreed diagnostic criteria. Although a wide variety of cut-off points have been used for defining abnormalities in LFT and bile salts, the upper limits of pregnancy specific ranges should be applied. Investigations to exclude other causes of pruritus and of abnormal LFT should be performed. Women with persistent pruritus and normal biochemistry should have LFT repeated weekly until delivery. Postnatal resolution of pruritus and abnormal LFT should be confirmed.[1]

But what makes this entity particularly deserving for a timely diagnosis and intervention are the dreaded fetal outcomes like pre-term delivery, meconium staining of amniotic fluid (MSL), fetal bradycardia, fetal distress and the most unfortunate, fetal loss. ICP is a condition with possible lethal outcome for the unborn child if not handled with care. Reported perinatal mortality fell from 11% to 3.5% in the more recent series, perhaps because most women were delivered by 38 weeks of gestation.[12,13]

The incidence of MSL in normal term pregnancies is approximately 15%. In ICP, MSL has been reported in 16%-58% of all cases and up to 100% of cases affected by IUD.[14] A recent series reported unexpected respiratory distress (RDS) in association with maternal cholestasis as a direct consequence of ICP.[15] Stillbirth is the major concern for those involved in the management of ICP. No specific traditional methods of antenatal fetal surveillance, biochemical result can predict IUD in ICP.[1]

The most appropriate gestational age for the delivery of women with ICP is yet to be determined. Elective delivery at 37 weeks is currently the widely adopted practice for prevention of IUD is not evidence based. While delivery at 37weeks of gestation will prevent IUD beyond that gestation, it is not known how much risk of such IUD might be. IUD in ICP has been reported across all gestations.[1] Conservative management of ICP of pregnancy was found to be associated with a high stillbirth rate despite monitoring of fetal well being.[16] Some studies have reported good outcomes with a policy of induction of labour at 37 or 38 wks gestation.[17]

In general obstetrics, elective early delivery results in increased respiratory complications as compared to later delivery. The risk of admission to neonatal intensive care unit (NICU) following elective caesarean section was reported to be 7-11% at 37 weeks of gestation, 6% at 38 weeks and 1.5% at 39 weeks1. Women delivering at or after 38 weeks had a lower incidence of caesarean section (LSSC), NICU and neonatal jaundice compared to those delivering at 37 weeks.[18] ICP consists of weighing the risk of early delivery against the risk of sudden IUD. Therefore decision regarding termination should be made after careful counseling and the iatrogenic consequences of elective delivery must be considered.

The present study is designed to study the pregnancy outcome with active management of ICP and to determine whether with active intervention, pregnancy with ICP can be carried to a later gestation under surveillance.

METHODS

A prospective randomized interventional study was conducted in the Department of Obstetrics and Gynaecology and Department of Hepatology, Dr. RPGMC Kangra at Tanda (HP) from 2014 to 2017 on the women diagnosed with ICP after taking approval of protocol review and institutional ethics committee.

Women with singleton pregnancy presented in the out door patient (OPD) / Labour room with complaint of generalized pruritus and diagnosed a case of ICP at or after 34 weeks of gestation were recruited into the study. The diagnosis of ICP was based on the symptoms of persistent pruritus, clinical examination and lab investigations after ruling out skin and liver disease. History of use of oral contraceptive pills was recorded. Clinical diagnosis was confirmed by raised AST and ALT (>40 IU/L). Serology to rule out Hepatitis A, B, and C was done. USG was done to rule out liver and gallbladder diseases. Pregnancy associated risk factors like hypertension, cardiovascular diseases, diabetes mellitus, renal diseases were ruled out.

Inclusion criteria

Women having singleton pregnancy with gestational age 34 weeks or more with cephalic presentation with complaint of generalized persistent pruritus having abnormal LFT (ALT/AST > 40 IU/L)

Exclusion criteria

- Pruritus due to skin disorders
- Gall bladder and biliary disorder
- Acute viral hepatitis
- Multiple pregnancy
- Pre-eclampsia / eclampsia

All the women meeting the inclusion criteria were explained in detail about the study. The women who were willing to participate, were included in the study and informed written and verbal consent was taken before participation.

Sample size

Assuming the relative risk of 3.0 and prevalence of NICU admission of 22.0% among women delivering at POG of 37-38 weeks of pregnancy, the sample size of a total of 50 women (25 women with delivery planned between POG 37 to 37^{+6} weeks and 25 who were planned to be delivered at POG ≥38 weeks) was calculated at 5.0% level of significance and 80.0% study power.

Sampling

Beforehand a hypothetical list of women of desired sample size (50) was prepared and based on that list, the women were assigned into two groups by computer generated randomization.

- Group I: Women planned for delivery at POG 37 - 37^{+6} weeks of pregnancy.
- Group II: Planned for delivery at POG ≥38 weeks of pregnancy.

The study was initiated with the recruitment of the pregnant women on actual line listing (serial number) maintained independently and managed as per the standard treatment protocol of the institution.

After enrolling the patient in the study, clinical details of the patient including name, age and other demographic data was recorded. Detailed history including present complaints, obstetric history, menstrual history, history of pruritus in previous pregnancy, previous pregnancy outcome and medical and surgical history was noted. History of liver and gall bladder disorders, skin disorders specially pruritus with rash, use of oral contraceptives were taken. Baseline investigations like haemoglobin, blood grouping and Rh typing, VDRL, HIV, OST, TSH, LFT and routine urine examination were recorded. Serology done for hepatitis A, B and C was recorded.

Blood testing for liver function were done at inclusion of study and repeated weekly till delivery. Fetal wellbeing monitoring was initiated from 34 weeks or later at diagnosis and it included daily fetal movement count, non stress test (NST), AFI, biophysical profile and doppler of umbilical artery and MCA. Fetal monitoring was conducted weekly till 36 weeks and biweekly or more frequently as required till delivery. All the patients received treatment with ursodeoxycholic acid 300 mg twice daily. The dose was increased up to maximum of 1500 mg per day. The women in both the groups were managed as per the treatment protocol of the hospital. Pregnancy was planned to be terminated at POG between 37-37^{+6} weeks in group I and at POG ≥38 in Group II under surveillance for fetal wellbeing. Mode of termination (induction of labour / elective caesarean section) was based on obstetric assessment, tests of fetal wellbeing, and bishop scoring.

Data was analysed using statistical packages. Maternal and fetal outcome was done with chi-square test or students t-test as appropriate. p value less than 0.05 was considered significant statistically.

RESULTS

Mode of delivery

Out of 25 women in each group, 16 women (64%) in group I and 18 women (72%) in group II had normal vaginal delivery. Instrumental delivery was done in 8% and 12% of women in group I and group II respectively. Emergency cesarean section was done in 7 women (28%) in group I and 4 women (16%) in group II. Though more number of women were delivered by cesarean section in group-1 as compared to group II but the difference in the caesarean section rate between the two groups was not statistically significant (p value >0.05). Table 1 show the mode of delivery amongst two groups.

Table 1: Mode of delivery.

Mode of delivery	Group I (37 Weeks)		Group II (38 Weeks)		p value	Significance
	N=25	Percentage	N=25	Percentage		
Normal vaginal deliveries	16	64	18	72	0.544	NS
Instrumental deliveries	2	8	3	12	0.637	NS
Emergency cesarean section	7	28	4	16	0.306	NS

Table 2: Intra- partum complications.

Intra- partum complications			Group I (37 Weeks)		Group II (38 Weeks)		p value	Significance
			N=25	Percentage	N=25	Percentage		
Fetal	MSL	Ante-Partum	0	0	1	4	0.312	NS
		Intra- Partum	5	20	2	8	0.221	NS
	Fetal cardiac abnormalities	Ante-Partum	2	8	2	8	1.000	NS
		Intra-Partum	5	20	2	8	0.221	NS
Maternal	APH		2	8	1	4	0.551	NS
	PPH		3	12	2	8	0.637	NS

Table 3: Perinatal characteristics.

Perinatal characteristics		Group I (37 Weeks)		Group II (38 Weeks)		p value	Significance
		N=25	Percentage	N=25	Percentage		
Live births		25	100	25	100	1.000	NS
Still births		0	0	0	0	--	--
Term births		24	96	23	92	0.551	NS
Preterm births		1	4	2	8	0.552	NS
Birth weight (kg)	>2.5	16	64	20	80	0.2077	NS
	1.5-2.5	9	36	5	20	0.2077	NS
	<1.5	0	0	0	0	--	--
Average Birth Weight (kg)		2.63±0.24		2.85±0.30		>0.05	NS

Table 4: Perinatal complications.

Perinatal complications		Group I (37 Weeks)		Group II (38 Weeks)		p value	Significance
		N=25	Percentage	N=25	Percentage		
Ante/intra Partum fetal distress		7	28	4	16	0.712	NS
APGAR<7 at 5 min.		7	28	4	16	0.712	NS
NICU Admission for <24 hours		1	4	1	4	1.000	NS
NICU Admission for 24-72 hours		4	16	3	12	0.683	NS
NICU Admission for>72 hours		2	8	0	0	0.149	NS
Mean APGAR Score	At 1 min	6.44±0.71		7.50±0.82		>0.05	NS
	At 5 min	7.92±0.57		8.68±0.63		>0.05	NS
Mean hospital stay of new born		3.66±2.58		2.33±0.58		>0.05	NS

Intra- partum complications

In group I, 5 out of 25 women (20%) had MSL during labour. In group II, out of 25 women, 1 woman had MSL during antenatal period and 2 women (8%) had MSL during labour. Fetal cardiac abnormalities occurred in 7 women in group I (2 ante partum and 5 during labour) and 4 women in group II (2 ante partum and 2 during labour).

Ante-partum haemorrhage (APH) occurred in 2 women (8%) in group I and 1 woman (4%) in group II. Three women (12%) and 2 women (8%) had PPH in group I and II respectively.

Though more no of women had intrapartum complications in group I as compared to group II like MSL (5 / 3), fetal cardiac abnormalities (7/4), APH (2/1) and PPH (3/2) but the difference was not statistically significant. The intra partum complications in the two groups are given in Table 2.

Perinatal characteristics

All 25 women in each group had live births. Also there was no early neonatal death within 7 days of birth in both the groups. The difference in the perinatal outcome of neonates in two groups was not statistically significant (p- value >0.05). In group I, 1 woman (4%) had preterm delivery and 2 women (8%) in group II had preterm delivery. The average birth weight of neonates in group-I was 2.63±0.24 kg and 2.85±0.30 kg in group II. This difference in birth weight of neonates in two groups was not statistically significant (p- value >0.05). The perinatal characteristics of the new borns in the two groups are given in Table 3.

Perinatal complications

Out of 25 women in each group, 7 (28%) women in group I and 4 (16%) women in group II had ante/intra-partum fetal distress. The APGAR score was <7 at 5 minutes in these newborns and they were admitted to NICU. Out of these 1 neonates in each group was admitted in NICU for <24 hours. In group I, 4 new born and 2 in group II were admitted in NICU for 48-72 hours and 1 neonates in group I required NICU admission for >72 hours.

Though all the perinatal complication including fetal distress, APGAR score <7 at 5 minutes, NICU admission and duration of stay in NICU was observed more in group I of women as compared to group II but the difference was not statistically significant (p value >0.05). The mean hospital stay of new borns in group I and group II was 3.66±2.58 and 2.33±0.58 days respectively. The perinatal complications in the two groups are given in Table 4.

Table 5: Fetal outcome in relation of POG at delivery.

Fetal Outcome		<35 weeks	35-35^{+6}	36-36^{+6}	37-37^{+6}	≥38 weeks
Abnormal BPP		0	1	0	3	0
MSL	Ante-Partum	0	1	0	0	0
	Intra-Partum	0	0	0	5	2
Intrapartum Distress (NRFHR)	Instrumental deliveries	0	0	0	4	1
	LSCS	0	1	0	8	2
Still Birth		0	0	0	0	0
APGAR< 7 at 5 min		0	1	1	7	2
Birth Weight <2.5 kg		0	1	1	8	4

Table 6: Neonatal complications in relation to POG at delivery.

Neonatal complication		<35 weeks	35-35+6	36-36+6	37-37+6	≥38 weeks
NICU admission	<24	0	1	0	1	0
	24-72	0	0	1	4	2
	>72	0	0	0	2	0
Neonatal jaundice		0	1	1	3	1
Neonatal sepsis		0	0	0	1	0
Meconium aspiration syndrome		0	1	0	1	0

Fetal outcome in relation of POG at delivery

Table 5 shows (group I and group II) over all fetal outcome in relation of POG at delivery. In group II MSL appeared in 1 case at POG 35 weeks 3 days during antenatal period. During Intra-partum period, 5 women at 37-37^{+6} weeks and 2 women at POG >38 weeks had MSL. Majority of LSCS were done for non-reassuring FHR and MSL (8 women between 37-37^{+6}, 2 women after ≥38, 1 at 35^{+3} weeks) and majority of these women were induced for term ICP. None of the women included in our study had still birth. Seven newborns delivered at 37-37^{+6}, 2 at ≥38weeks, 1 at 35-35^{+6} and 1 at 36-36^{+6} weeks had APGAR <7 at 5 minutes of birth. Eight neonates delivered at 37-37^{+6} weeks and 4 neonates delivered at ≥38 weeks had weight less than 2.5 kg.

Neonatal complications

In the present study 2 neonates were admitted to NICU for <24 hours, 7 neonates required NICU admission between 24 -72 hours and 2 neonates delivered at 37-37^{+6} weeks were admitted to NICU for more than 72 hours. Six neonates had jaundice after delivery one had neonatal sepsis and two neonates had meconium aspiration syndrome. Table 6 shows the combined over all (group I and group II) neonatal complications in relation to POG at delivery.

DISCUSSION

In the present study there was no significant difference in the preterm deliveries in both the groups as 4% women had preterm delivery in group I and in group II, 8% women had preterm delivery. Similar preterm delivery rates were reported in the studies conducted by Sharma et al (4.16%), Neslihan et al (8.5%), and Jain R et al 10.4%.[18-20] In our study women had spontaneous preterm labour or PPROM except one case in group II in which LSCS was done at 35 weeks for fetal distress. However a much higher incidence of preterm deliveries was observed in the studies conducted by S.H Dodampahala et al (76.4%), Bacq et al (60%).[21,22] They observed that all ICP diagnosed women were actively managed according to standardised protocol, which included increased intervention and early delivery resulting in complication of iatrogenic prematurity.

There was no intrauterine death of fetus or stillbirth in the present study. Similarly, Jain R et al and PATA et al also observed no case of IUD of fetus or stillbirth.[18,23] This may be because of better antenatal care and meticulous monitoring of fetal wellbeing in these studies. Dodampahala et al also had no IUD inspite of a very high rate of prematurity (76%).[21] As compared to the present study of no case of IUD, there was a higher incidence of IUD in the study by Sultana et al (6.6%) and Elisabeth et al (9-12.5%).[19,24]

CONCLUSION

Therefore it can be concluded from the present study that pregnancies with obstetric cholestasis can be carried to later gestation of ≥38 weeks under surveillance with UDCA treatment without adversely affecting the perinatal outcome and with the benefit of a lower LSCS rate and improved obstetric outcome. However our study sample size was limited and further randomization controlled trials are needed for most appropriate

gestational age for delivery with active management in ICP to avoid unnecessary early intervention just after 37 weeks.

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