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A study of clinical profile and immediate fetal and maternal Outcome in Intrahepatic Cholestasis in Pregnancy at Central Referral Hospital(CRH), Gangtok.

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A B S T R A C T

Context: The present study aims at the correlation of symptoms of Intrahepatic Cholestasis of Pregnancy(ICP) and subsidence of disease process by administration of Ursodeoxycholic acid and its outcome with the pregnant mother and newborn baby. There is a rising trend of cholestasis in pregnancy in the present era & especially affecting in the last trimester of pregnancy when hormonal influences are at the peak.

Aims:

1. To find out the frequency of Intrahepatic Cholestasis of pregnancy (ICP) among the pregnant woman attending at Central Referral Hospital.
2. To analyse the clinical profile of the patients attending CRH having intrahepatic cholestasis of the pregnancy(ICP).
3. To study the immediate maternal and fetal outcome of ICP patient

Settings and Designs: A Progressive observational study conducted between January 2019 to December 2019 at Department of Obstetrics & Gynaecology, Central Referral Hospital (CRH), Tadong, Gangtok, Sikkim.

Materials and Methods: 60 pregnant women with gestational age between 24 weeks to 42 weeks diagnosed as ICP were included.

Results: Theincidence of ICP is 60 (2.50 %) over a study period of one year. Majority diagnosed in the age group between 26-30 years, mostly were primigravida. Out of 27 multigravida ICP pregnancies, only 7 mothers (25%) had past history of ICP. ICP most commonly occurred (95%) in 32-36 weeks of gestation.35 pts (58.33%) had symptomatic response to UDCA, 25 pts (41.67%) did not have response. After 6 weeks of UDCA t/t, Bilirubin further came down to 0.67, median value 0.7 and std dev. 0.16, statistically significant. 5% (3 mothers) with IHCP had deranged coagulation profile along with increased level of AST, ALT and normalisation of LFT within 6 weeks of termination of pregnancy.
Statistical analysis was done by using descriptive and inferential statistics using Chi square test and Student's paired t test and software used in the analysis were SPSS 24.0 version and Graph Pad Prism 7.0 version and $p<0.05$ is considered as level of significance.

Conclusion: The incidence of ICP is 2.51% in our hospital, which is a Referral Centre in Sikkim. The Intrahepatic Cholestasis in Pregnancy has an adverse effect on the maternal health and fetal outcome, and hence, early diagnosis with careful clinical examination and biochemical assessment and follow-up are essential. UDCA provides symptomatic relief, improvement of Liver Functions and contribute to improvement of perinatal outcome. The obstetrics intervention rate is high in our study, so a protocol is made for active management of labour after 37 completed weeks to improve perinatal outcome.

Keywords:*Intrahepatic obstetric cholestasis, Alanine Amino-Transferase, Alkaline Phosphatase, Cardiotocography, Gamma Glutamyl Transferase, Induction of Labor, Intrauterine Fetal Death, Intra Uterine Growth Retardation,Non-Stress Test.*

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INTRODUCTION

Intrahepatic Cholestasis of Pregnancy (ICP), is a multifactorial condition of pregnancy characterised by jaundice, pruritus and abnormal liver function tests (either raised ALT or Bile acids or both) both resolving completely after delivery. Itching that involves the palms and soles of the feet, is particularly suggestive of obstetric cholestasis. It is the second most common cause of jaundice in pregnancy, more common in the last trimester of pregnancy when hormonal influences are at their peak[1].

The diagnosis of Intrahepatic Cholestasis of Pregnancy is based upon: (a) persistent pruritus of onset in pregnancy in the absence of rash other than excoriations, (b) abnormal Liver Function Tests (one or more of abnormal Gama glutamyl-transpeptidase, alanine aminotransferase, aspartate aminotransferase, total bile acids), (c) absence of other relevant liver

diseases, and (d) postnatal normalization of serum biochemistry and cessation of symptoms[2,3,4] . ICP is a reversible form of cholestasis appearing mainly in the late second or early third trimester of pregnancy and tends to resolve rapidly after delivery[5,6].

Hence, ICP is associated with increased risk of hazardous outcome in both the mother and fetus, neonates[7]. Identifications of such mothers with obstetric cholestasis and proper management adhering to guidelines will invariably reduce the maternal and perinatal mortality and morbidity. It is advisable to aim at delivering the foetus between 37-38 weeks of gestation or even earlier (as soon as fetal lung maturity is attained) if there is sufficient risk of maternal morbidity or fetal compromise is detected[8].

AIMS & OBJECTIVE OF THE STUDY

1. To find out the frequency of Intrahepatic Cholestasis of pregnancy among the pregnant woman attending Department of Obstetrics and Gynaecology at Central Referral Hospital (CRH).
2. To analyse the clinical profile of the patients attending CRH having intrahepatic cholestasis of the pregnancy.
3. To study the immediate maternal and fetal outcome of ICP patient.

MATERIALS AND METHODS

1. **Study Type:** Hospital based prospective observational study.
2. **Study Setting**: The study was conducted in the Department of Obstetrics and Gynaecology, Central Referral Hospital (CRH), Tadong, Sikkim.
3. **Place of Study:**Both the antenatal out-patient clinic and in-patient ward of the Department of Obstetrics & Gynaecology, Central Referral Hospital (CRH), Tadong, Sikkim.
4. **Study Duration**: The study was conducted over a period of one year (January 2019- December 2019). Period required for data collection: 1 year
5. **Study population**: All pregnant women diagnosed with ICP from 24- 42 weeks period of gestation
6. **Sample size:** All patients fulfilling the inclusion and exclusion criteria who will be admitted during the study period will be included in the study.60 pregnant women with pruritus who fulfilled the eligibility criteria during the study period in the Department of Obstetrics & Gynaecology, Central Referral Hospital (CRH), Tadong, Sikkim., were the study group after proper and detailed history taking.

Inclusion criteria: Pregnant mothers from 24 to 42 weeks diagnosed as IHCP
Exclusion criteria: Other known causes of jaundice like

- Haemolytic
- Hepatocellular: - Viral hepatitis - Acute fatty liver of pregnancy - Alcohol and drugs (e.g., halothane) - Autoimmune chronic active hepatitis
- Obstructive: - Cholelithiasis - Drugs (e.g., Chlorpromazine) - Primary biliary cirrhosis - Pancreatic carcinomaPatients/ Caregiver who refused to give consent to participate in this study.

7. **Parameters to be studied:**

- The incidence of obstetrics cholestasis among the mothers presenting with pruritus in the hospital, the period of gestation at which pruritus appears and the relationship of pruritus with and without obstetric cholestasis with maternal age and parity were studied. This distribution is determined in terms of percentage and also presented in figures where applicable
- Maternal outcomes were studied in reference to insomnia due to severe pruritus associated deranged coagulation profile (PT), mode of delivery: vaginal delivery, elective and emergency caesarean section, postpartum haemorrhage.
- Fetal outcomes were studied in reference to preterm labour, preterm prelabour rupture of membrane, abnormal CTG, fetal distress or hypoxia, meconium-stained liquor, low birth weight, NICU admission rate and perinatal death (IUFD/ Stillborn). Neonatal outcome were studied in reference to neonatal jaundice, respiratory distress and sepsis.
- Postpartum resolution was studied in reference to improvement of pruritus and abnormal liver function tests after six weeks of delivery.

The incidence of parameter is determined in terms of percentage and also presented in figures where applicable.

ETHICAL CLEARANCE

Approval of Institutional Ethical Committee (IEC) & Research Ethical Committee of Medical College was obtained.

Observations:

Table 1: Incidence of obstetric cholestasis in study population

Total Deliveries	TOTAL IHCP	Percentage
2398	60	2.50%

In my study, out of 2398 total number of deliveries, incidence of IHCP is 60 (2.50 %) over a study period of one year.

Table 2: Distribution of IHCP according to maternal age

Age Group (Years)	Number	Percentage
15-20	3	5%
21-25	4	6.67%
26-30	26	43.33%
31-35	21	35%
36-40	6	10%
Total	60	(100%)

Out of total 60 IHCP patients, 43.33% (26 mothers) of IHCP were in the age group of 26- 30 years, 31.67% (19 mothers) were in the age group of 31- 35 years, 6.67% (4 mothers) were in the age group of 21- 25 years.

Table 3: Incidence of IHCP according to gravida

Gravida	No. of cases (60)	Percentage
Primigravida	33	55%
Multigravida	27	45%
Total	60	100%

Majority (55%) were primigravida, while (45%) were multigravida

Table 4: Past history of IHCP only relevant in multigravida patients (27 patients)

Past history of IHCP	No of patients (27)	Percentage
Present	7	25%
Absent	20	75%
Total	27	100%

Out of 27 multigravida IHCP pregnancies, only 7 mothers (25%) had past history of IHCP.

Table 5: Frequency ofoccurrence of sleep disturbance in IHCP patients

Sleep Disturbance	No. of cases	Percentage
No	27	45%
Yes	33	55%
Total	60	100%

Majority of the patients 55% (33 pts) had sleep disturbance, 45% (27 pts) did not have sleep disturbance.

Table 6: Distribution according to the gestational age at diagnosis (in weeks)

Gestational age at onset of pruritis	No. of cases	Percentage
<28 weeks	0	0%
28-32 weeks	0	0%
32-36 weeks	57	95%
36-40 weeks	3	5%
Total	60	100%

In the studied population, ICP most commonly occurred (95%) in 32-36 wks of gestation.

Table 7: Distribution of ICP according to deranged coagulation profile

Deranged coagulation profile	Total	p-value	Significance
Absent	57(95%)	5.33 p=0.021	Significant
Present	3(5%)		
Total	60(100%)		

In my study 5% (3 mothers) with IHCP had deranged coagulation profile.

Table 8: Distribution of IHCP according to Mode of delivery

Mode of delivery	No. of IHCP cases	Percentage
VD	11	18.33%
LSCS	49	81.61%
Total	60	100%

In studied population, majority (81.61%) IHCP mothers had undergone LSCS and rest (18.33%) underwent vaginal delivery.

Table 9: Distribution according to the gestational age at delivery

Gestational age at delivery	No. Of IHCP cases	Percentage
34 - <36 weeks	6	10%
36-<38 weeks	16	26.67%
>38 weeks	38	63.33%
Total	60	100%

Majority (63.33%) IHCP patients delivered after 38 weeks, while 10% delivered between 34 – 36 weeks.

Table 10: Indication for caesarean section in IHCP patients

Indications for Cesarean section	No. of patients	Percentage
On request	**25**	**51%**
Previous lscs	**8**	**16.3%**
Pre-eclampsia	**4**	**8.2%**
Failed IOL	**2**	**4.1%**
Fetal distress	**2**	**4.1%**

PROM	**2**	**4.1%**
Polyhydramnios	**2**	**4.1%**
CPD in labor	**1**	**2%**
Oligohydramnios	**2**	**4.1%**
Floating head	**1**	**2%**

Maximum IHCP patients underwent LSCS on request (51%), second most common indication is previous lscs(8%)

Table 11: Distribution of IHCP according to Abnormal CTG

Abnormal CTG	No. of IHCP cases	p-value	Significance
No	55(91.67%)	9.26 p=0.0023	Significant
Yes	5(8.33%)		
Total	60(100%)		

Most patients (92%) had a normal CTG, while only 8.33% patients with IHCP (8.33%) had abnormal CTG which is significant.

Table 12: Distribution of IHCP according to colour of Liquor

Liquor colour	Total	Percentage
Clear	48	80%
Moderate MSL	6	10%
Thick MSL	6	10%
Total	60	100%

Maximum (80%) IHCP patients had clear liquor while an equal number(N=6,10%) had moderate and thick meconium-stained liquor
N.B.: Mild MSL is not included in our study

Table 13: Distribution of IHCP patients according to IUFD

IUFD	No.of IUFD	Total	p-value	Significance
No	57	(95%)	5.33 p=0.020	Significant
Yes	3	(5%)		
Total	60	(100%)		

In our studied population, 3 pts with IHCP (5%) had IUFD

Table 14: Distribution of IHCP according to PPH

PPH	Total	Percentage
No	56	93.33%
Yes	4	6.67%
Total	60	100%

4 patients (6.67%) developed PPH whereas 56 pts (93.33%) did not have PPH.

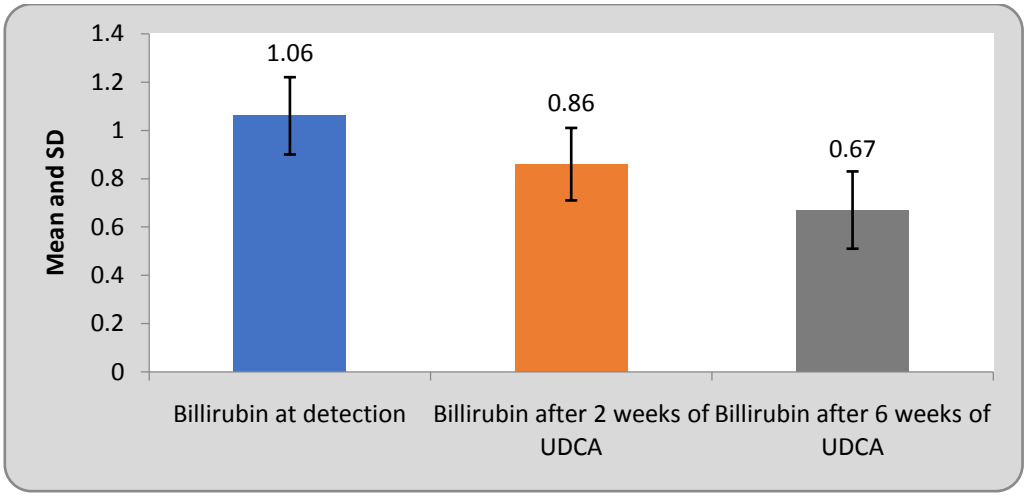

Fig 1: Change of bilirubin at detection after 2 weeks of UDCAtreatment and 6 weeks post-partum

Table 15: AST/SGOT at detection and changes after 2 weeks of UDCA treatment and 6 weeks post-partum

	AST at detection	AST after 2 weeks of UDCA	ASTafter 6 weeks of UDCA
Mean	109.60	60	35.85
Median	100	66	38
Std deviation	28.68	12.90	5.01
t-value	-	2.68 p=0.055, Not Significant	6.78 p=0.0001, Significant

Mean AST at detection was 109.60 with median of 100 and std. deviation of 28.68. twowks after UDCA t/t, AST came down to 60 with median of 66 and std deviation of 12.90. 6wks post-partum AST came further down to mean 35.85, median 38 and std deviation 5.01, p=0.0001, significant.

Table 16: Change of ALT/SGPT at detection after 2 weeks of UDCA treatment and 6 weeks post-partum

	ALT at detection	ALT after 2 weeks of UDCA	ALT after 6 weeks of UDCA
Mean	120.80	68.60	33.71
Median	120	67	31
Std deviation	18.45	7.33	4.44
t-value	-	5.66 p=0.005, Significant	10.61 p=0.0001, Significant

Mean value of AST at detection was 120.80 with median of 120 and std deviation of 18.45. Mean ALT value 2 wks after UDCA t/t was 68.60 with median 67 and std deviation 7.33 and t value 5.66. ALT value further came down to 33.71 with median of 31 and std deviation of 4.44 and t value of 10.61, p= 0.0001, significant.

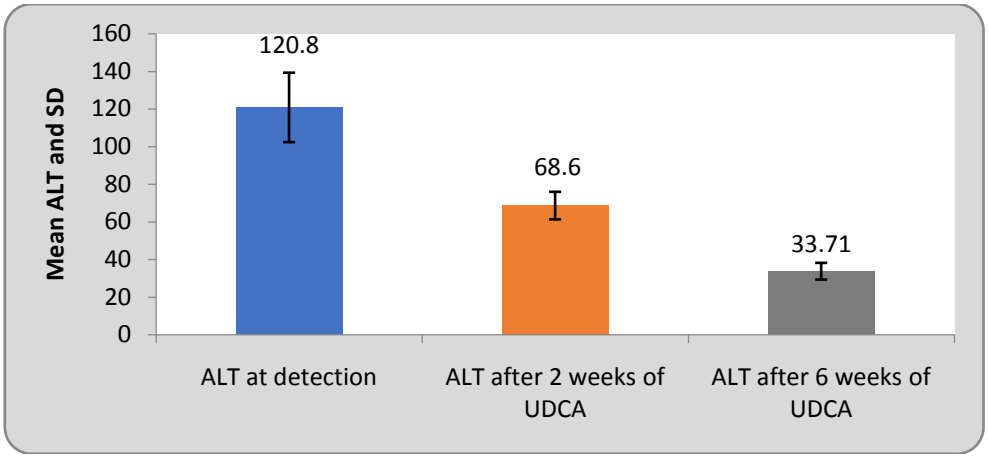

Fig 18: Bar diagramshowing ALT at detection, after 2 weeks of UDCA treatment and 6 weeks post-partum

Statistical analysis was done by using descriptive and inferential statistics using Chi square test and Student's paired t test and software used in the analysis were SPSS 24.0 version and Graph Pad Prism 7.0 version and $p<0.05$ is considered as level of significance.

Table 17: Symptomatic response to UDCA (ursodeoxycholic acid)

Symptomatic response to UDCA	No of patients	Percentage %
No	25	41.67
Yes	35	58.33
Total	60	100

35 pts (58.33%) had symptomatic response to UDCA, 25 pts (41.67%) did not have response.

Table 18: Change of bilirubin at detection after 2 weeks of UDCAtreatment and 6 weeks postpartum

	Bilirubin at detection	Bilirubin after 2 weeks of UDCA	Bilirubin after 6 weeks of UDCA
Mean	1.06	0.86	0.67
Median	1.1	0.8	0.7
Std deviation	0.16	0.15	0.16
t-value	-	1.53 p=0.20, Not Significant	4.99 p=0.002, Significant

Mean Bilirubin at detection is 1.06 with median value 1.1 and standard deviation 0.16. Bilirubin after 2 weeks of UDCA administration, value came down to mean 0.86, median 0.8 and std deviation 0.15, not significant. After 6 wks of UDCA t/t Bilirubin further came down to 0.67, median value 0.7 and std dev. 0.16, statistically significant.

DISCUSSION

The prevalence of ICP is influenced by metabolic, endocrinal, genetic and environmental factors and varies among populations. Intrahepatic obstetric cholestasis is a relatively common cause of hepatic impairment of pregnancy. The maternal cholestasis is transient with postnatal resolution, although affected women have adverse maternal and fetal-neonatal outcome. The incidence of ICP among Indian women has been reported as approx.3%. We found an incidence of 2.50% in our study. However, it is justified to mention that our hospital is a tertiary referral private Hospital and incidence of High-Risk Pregnancy is higher, hence the incidence is higher than expected. Mitra B et al[5]. did a prospective observational study in government hospital and found out incidence of IHCP to be 2.81%. Dodampahala S et al[9] showed that 1/3 of the mothers affected by ICPs were having pruritus.

Maternal age at onset

Some authors have reported that women of relatively higher age (>35 yrs) are at increased risk of development of ICPs but in our study the mean age was 28.7 years (range 20 -37 yrs) and there was no significant difference between the two groups in maternal age and parity.

Aloknanda and Rashne[10] their study found age of 24.7 yrs in their study. About two-third of the patients were primigravida 55%, consistent with the study by Padmaja et al[11], as ICP present mostly in primigravida (71.8%). In the present study the recurrence rate was 25% among multiparous women.

Rasheed et al[7] reported that mean age of women affected by OCs was 28 years +_ 5. Sosa SY et al[63]also reported mean age of ICP cases was 29.2 + 6.8 years. Heinonen S et al[13] reported that women of relatively advanced age (> 35 years) were at increased risk of developing intrahepatic cholestasis.

Gestational age at Diagnosis

In 60.0% women, ICP were diagnosed in the third trimester which is similar to that seen in other studies, Kenyon AP et al.[14]. In our study, ICP most commonly diagnosed (95%) at 32-36 weeks. It has been reported severe pruritus of the soles of the feet may be particularly suggestive of this condition, Kenyon AP et al.[2] However it has been reported in up to 10% women, Rioseco AJ et al.[15].

Altered biochemical Changes

In our study 55.0% pruritus mother with ICP had sleep disturbances. Most common site of pruritus was on the palms and soles (64.85%). Abnormalities in one or more of the transaminases, GGT, bilirubin/or bile salts are consistent with diagnosis of ICP. The most commonly elevated LFTs have been our Transaminases and Bile acids and the Transaminases were raised in 97.8% of the women and the maximum value found in our study was five times the normal value in pregnancy. Various studies have reported that elevated levels of Bilirubin have been noted up to 50% and 22 to 56% patients respectively but evidence of clinical jaundice was rare. In our study we have found raised levels of hyperbilirubinemia in 18.4% women. There was no case of clinical jaundice. As bile salt assessment was not available in our set-up, we could not determine in our patients.

In a study by Meng et al[16], 84 women with ICP elevation of GGT from 2-fold to 15-fold were noticed in 85 % of patients, bilirubin concentration in 2-fold to 4-fold in 14%, and alkaline phosphatase up to3-fold in 60 % of patients. 3 mothers (5%) with ICP had deranged coagulation profile.

In a study of Mahajan et al[17] 2017, 29.34% had elevated bilirubin and LFT was mildly deranged in most of the patients and these findings were consistent with that of that of Rashid and Mazhar[7]. Out of 60 ICP mothers, 35 mothers (58.33%) had symptomatic improvement to UDCA.

Improvement of Symptoms

The efficacy of topical emollients like calamine lotion and oral antihistaminics like Cholpheniramine has not been tested in clinical trials but their use is safe in pregnancy and for some women may provide mild temporary relief of symptoms (RCOG guideline, 2006). Several studies demonstrate that in addition to providing safe and effective relief of pruritus and improving LFTs, UDCA may improve prenatal outcome[18] by preventing the accumulation of biliary constituents of maternal origin in the fetus, which may contribute to the risk of fetaldistress and even stillbirth. In our study UDCA was prescribed in all women and there was complete relief of pruritus in all with biochemical improvement in 58.3% women.

Kenyon et al[14] found a high incidence of PPH in women with ICP who did not receive Vitamin K compared to those who did (45% vs 12%), but we found 4 cases of PPH though all ICP women(N=60) in our study received vitamin K.

Maternal outcome

11.67% of mothers with ICP had PPROM. The overall Caesarean section (CS) rate was higher than vaginal delivery (VD) (81.67% vs 18.33%). 41.67% had elective CS, 40.0% had emergency CS. In our study, most of the mothers with ICP delivered between 36 – 38 weeks of gestation. In our study mothers with ICP, 18,33% had fetal distress, 8.33% had abnormal CTG, 10.00% had meconium-stained liquor. In our study only 3(5%) IUFD occurred among 60 ICP mothers. 16 babies (26.67%) of ICP mothers required NICU admission. The median value of bilirubin at detection was 1.1, after 4 weeks of UDCA treatment was 0.80 and at 6 weeks post-partum it was 0.70. For AST the median value was 100.0 at detection, 66.0 after 4 weeks of UDCA treatment and 38.0 at 6 weeks post-partum period. For ALT the median value was 120.0 at detection, 67.0 after 4weeks of UDCA treatment and 31.60 at 6 weeks post-partum period. The obstetric

intervention rate was higher in our study as we adopted a policy of active management with close antenatal surveillance and elective delivery after 37 completed weeks to improve perinatal outcome.

Fetal outcome

The disease has been related to a high incidence of perinatal complications including an increase in perinatal mortality rate (35/1000), a high incidence of meconium-stained amniotic fluid up to 45%, preterm labourup to 44% and fetal distress upto 22%. Our study shows an incidence of 11.67% of PPROM and **Maximum (80%) IHCP patients had clear liquor while an equal number (N=6,10%) had moderate and thick meconium-stained liquor**.

Hani et al[19] found increased incidence of fetal asphyxia in women with IHCP. It has been suggested that both fetal distress and increased stimulation of gut motility by bile acids is the cause of increased incidence of meconium-stained liquor in OCs. Poor neonatal outcome was seen in nearly one-third of neonate i.e., 38.67% consistent with the study of Rook et al. who reported fetal complication in 33% of pts with ICP, whereas Padmaja et al[8] found meconium staining in 17.8% of pts.

IUFD

There was one intrauterine death in our study group, were unbooked cases the one who came in at 39 weeks gestation with complaints of loss of fetal movements and urgent USG confirmed fetal demise. Two neonatal deaths were due to extreme prematurity and IUGR.

As the pathophysiological basis of the fetal risks in ICPs is not clear, conventional fetal surveillance is not always helpful in determining the risk of fetal compromise. Increased perinatal mortality rate (1.3 -3.5%) and increased stillbirth rate ranging from (2.5 – 11%) has been reported. Intrauterine fetal demise appears to be an acute anoxic event and the high concentration fetal bile acids may contribute to this acute event. The risk of fetal death increases near term and most deaths occur after 37 – 38 weeks. To avoid the risk many hospitals, adopt a policy of active management with antenatal surveillance and early elective delivery after completed 37 weeks. In our study active management with fetal surveillance during delivery between 37 -38 weeks was practiced.

CONCLUSION

The incidence of ICP is high in our Central Referral Hospital, located in Gangtok. Larger studies are required to assess the correct incidence in the general population. Intrahepatic Cholestasis in Pregnancy has an adverse effect on the fetal outcome and hence, early diagnosis with careful clinical examination and biochemical assessment is essential. Affected women should be offered treatment with UDCA. This provides symptomatic relief, improvement of Liver Function and contributes to improvement of the perinatal outcome. To conclude, the following points are noted:

1) The incidence of ICP is 2.51% in our hospital, which is a Referral Centre in Sikkim.
2) Intrahepatic Cholestasis in Pregnancy has an adverse effect on the maternal health and fetal outcome, and hence, early diagnosis with careful clinical examination and biochemical assessment and follow-up are essential.
3) Affected women should be offered treatment with UDCA. This provides symptomatic relief, improvement of Liver Functions and contribute to improvement of perinatal outcome.
4) The obstetrics intervention rate is high in our study, so a protocol is made for active management of labour after 37 completed weeks to improve perinatal outcome.

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Conflict of Interest: There are no conflict of interest.

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