

**ORIGINAL RESEARCH ARTICLE**

**A prospective observational study on foeto-maternal outcome in patients with intrahepatic cholestasis of pregnancy treated with ursodeoxycholic acid**

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**ABSTRACT**

**Background:** Intrahepatic cholestasis of pregnancy (ICP), characterised by elevated serum bile acid concentrations or elevated aminotransferase levels with pruritus, usually develops during the late second or third trimester and rapidly regresses after childbirth. The etiology of ICP is not yet completely understood, but it probably depends on the genetic predisposition, hormonal and environmental factors. IC is the most common liver disease specific to pregnancy. **Methods:** This study was a Prospective Observational Case Control Study conducted in the Department of Obstetrics & Gynaecology, Burdwan Medical College & Hospital, Burdwan, West Bengal, India from January 2019 to June 2020. 50 pregnant women with ICP cases treated with UDCA were included in the study. A suitable predesigned pretested Proforma for data collection was used. Template was generated in MS excel sheet and analysis was done on SPSS software.

**Results:** Among 50 ICP cases treated with UDCA 78% pruritis resolved, 28% of ICP not treated with UDCA pruritis resolved. among 50 cases 8 patients had preterm labour (16%), 4 patients had PPROM (8%), 9 patients had PROM (18%), 18 patients had oligohydramnios (36%), 2 patients had post dated pregnancy (4%), 1 patient had post term pregnancy (2%), 3 babies had IUGR (6%). 12 neonates required admission to SNCU (24%). There were 2 intrauterine foetal deaths (4%), 1 congenital anomaly (2%). There were 5 perinatal deaths among cases. Among these 50 babies, 1 baby was VLBW (2%), 17 babies were LBW (34%) and 32 babies had normal birth weight >2.5kgs (64%) and none was XLBW. Among 50 cases ICP treated with UDCA, 20 patients (40%) post-partum resolution happened at 2 weeks and 50 patients (100%) resolution happened at 4 weeks. **Conclusions:** Intrahepatic cholestasis of pregnancy has adverse maternal, foetal and neonatal outcome. There was significant resolution of the pruritus after 3 weeks of treatment with UDCA of ICP patient.

**Keywords:** Fetal outcome, Intrahepatic cholestasis of pregnancy, maternal outcome, ursodeoxycholic acid,

## INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP), also known as Obstetric Cholestasis, is a liver disease of pregnancy associated with severe itching, which the patient senses especially in her palms and soles, combined with abnormal LFT, typically arises in the third trimester of pregnancy and disappears spontaneously after delivery.<sup>1</sup> Other pathological liver and skin diseases must be excluded. ICP was first described in 1883 by Ahlfeld as recurrent jaundice during pregnancy that resolved after delivery (Ahlfeld 1883).<sup>2</sup>

The incidence of ICP varies widely by geographical location and ethnicity. It affects 1.5–2% women of Indian- Asian or Pakistani- Asian origin.<sup>3,4,5</sup>

The diagnosis of ICP is based on the clinical presentation, laboratory results and exclusion of other causes for the clinical and biochemical findings.

Risk factors for ICP are environmental factors, nutritional deficiencies, genetic variations and hormonal changes.<sup>6-10</sup> There is evidence for a primary role of steroid hormones in ICP<sup>11-13</sup> and is based on following three circumstances: ICP usually starts in the last trimester, higher in twin pregnancies than singletons and in pregnancies following IVF than spontaneous conception (2.7% vs. 0.7%).<sup>14</sup> It resolves promptly after delivery and also recurs in half of the patients during subsequent pregnancies<sup>5</sup>. Other reported risk factors for ICP are a family history of biliary disease.<sup>9, 15</sup>

Although severe maternal complications are rare in ICP, the fetus may be affected by spontaneous preterm labour and birth, foetal distress and bradycardia, MSAF (Meconium Stained Amniotic Fluids) and MAS (Meconium Aspiration Syndrome) and even sudden IUFD.<sup>16</sup> The foetal complications are believed to be related to the elevated maternal bile acid concentrations which stimulate the contractility of the myometrium which may result in spontaneous preterm labour and increase the motility of the large intestine of the foetus, which may be the reason for meconium expulsion.

There is no specific consensus regarding the effect of UDCA on fetomaternal outcome, True incidence & prevalence of ICP and its adverse effect on foetal and maternal wellbeing. In this study ICP treated with UDCA will be explored among pregnant women attending the Antenatal OPD, Department of G&O, BMC&H. Foeto- maternal wellbeing of both groups (Normal and ICP) was observed and evaluated

#### **Method and Materials:**

**Study design :** Prospective Observational Case Control Study.

**Study setting:** Department of Obstetrics & Gynaecology, Burdwan Medical College & Hospital, Burdwan, West Bengal, India.

**Period of study:** January 2019 to June 2020

**Study population :** Pregnant women presenting to Antenatal OPD of Burdwan Medical College and Hospital after fulfilling the requisite criteria.

**Inclusion Criteria:** All pregnant women presenting with pruritus and/or deranged liver function diagnosed first time during antenatal period.

**Exclusion criteria :** Causes of jaundice - biliary obstruction, acute cholecystitis, viral hepatitis, Different dermatological conditions with similar clinical presentation e.g. polymorphic eruption of pregnancy, pruritic folliculitis, prurigo, pemphigoid gestations, eczema, scabies etc., Drug reactions e.g. ATD (rifampicin, isoniazid), antihypertensive especially methyldopa etc, Congenital diseases e.g. Gilbert's, Dubin-Johnson, Rotor syndrome and Autoimmune liver diseases e.g. chronic active hepatitis, primary biliary cirrhosis, sclerosing cholangitis etc.

#### **Sample size :**

- a) Case -50 pregnant women with ICP case treated with UDCA were recruited
- b) ICP Cases who were diagnosed by routine blood test on admission and gave past history of symptoms (itching).

**Method of data collection:** All cases were recorded in printed performa and preserved.

**Statistical Analysis:** The data collected on the basis of the above mentioned parameters were analyzed methodically by standard statistical methods with the help of statistician. Categorical variables were expressed as number of patients and percentage of patients and compared across the groups using Pearson's Chi Square test. Continuous variables were expressed as Mean  $\pm$  Standard Deviation and compared across the 2 groups using unpaired t test.

**Ethical clearance:** The study was conducted only after obtaining written approval from the Institutional Ethics Committee. Written informed consent was taken from every study patient.

## Results

The present Prospective Observational Case Control Study was planned to study the incidence of intrahepatic cholestasis of pregnancy in the study population as well as to compare the fetomaternal outcome of pregnant women with ICP between subject group (treated with UDCA) and control group (not treated with UDCA).

Total 50 patients treated with UDCA and 50 patients not received with UDCA were included in the study. The time period for the study was from January 2018 to June 2020. In all the cases, thorough history taking and clinical examination was done after taking proper consent. Data thus obtained was noted in the Proforma. Results thus obtained were analysed and expressed in tables.

**Table 1: Distribution of ICP cases Treated with UDCA according to the severity of pruritis**

Grade of pruritis acc to the severity	No. of patient treated with UDCA	Percentage	No. of patientsnot received with UDCA	Percentage
Grade 0	15(50)	30%	0 (50)	0 %
Grade I (mild)	30(50)	60%	5 (50)	10%
Grade II (Moderate)	4(50)	8%	18(50)	36%
Grade III (Severe)	1(50)	2 %	23 (50)	46%
Grade IV (very severe)	0 (50)	0%	4 (50)	8 %

Grade 0= Absence of pruritis

Grade 1= mild pruritis without disturbance of daily activities or sleep

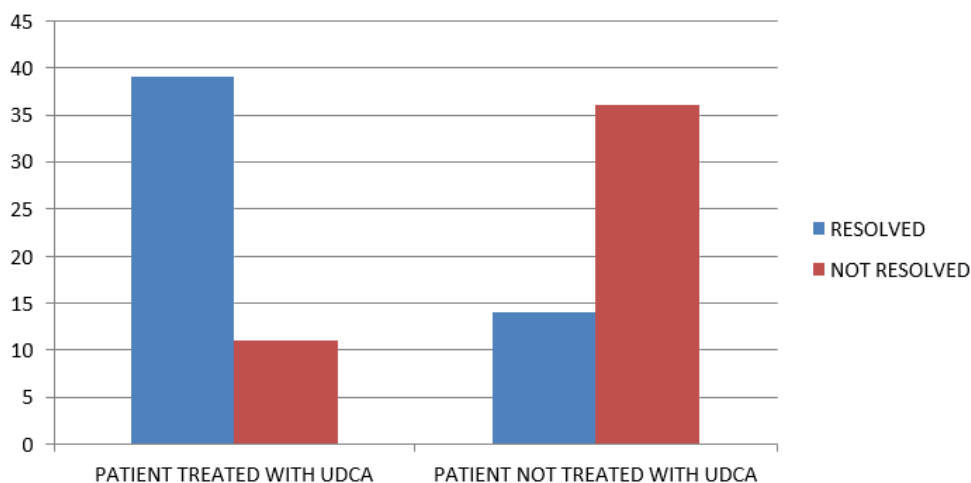
Grade 2= moderate pruritis intermittent during day prevailing asymptomatic lapses

Grade 3= severe pruritis prevailing symptomatic lapse everyday

Grade 4=severe and constant itching day and night

In the present study total no. of ICP cases observed during study period was 50. Total no. of ICP cases treated with UDCA during study period was 50. Among 50 ICP cases treated with UDCA 15 patients showed grade 0 pruritis, 30 patient showed grade1 pruritis, 4 patient showed grade2 pruritis and 0 patient showed very severe pruritis. (table 1)

**Figure 1 : Distribution of ICP cases treated with UDCA**



From the above figure we conclude that among 50 ICP cases treated with UDCA 78% pruritis resolved, 28% of ICP not treated with UDCA pruritis resolved. P value-<0.0001. (Figure 1)

**Table 2 : Distribution of ICP cases treated with UDCA according to conjugated bilirubin**

Conjugated bilirubin	No. of pts with UDCA	Percentage	No. of pts not received with UDCA	Percentage
<0.8	48(50)	96%	31 (50)	62%
0.9-2.0	2(50)	4%	17 (50)	34%
2.1-3.0	0(50)	0%	2(50)	4%
>3	0(50)	0%	0 (50)	0%
<b>Mean ± SD</b>	<b>0.504±0.18</b>		<b>0.742±0.42</b>	

Table 2 shows distribution of ICP treated with UDCA in relation to the level of conjugated bilirubin levels. Total no. of ICP treated with UDCA observed during study period was 50. Among 50 patients of obstetric cholestasis cases diagnosed, 48 patients has total bilirubin leveln

<0.8mg/dl. 2 patients had total bilirubin level between 0.9-2.0mg/dl. 0 patient had total bilirubin level between 2.1-3mg/dl. 0 patient had total bilirubin level more than 3mg/dl. Thus most of the ICP patients treated with UDCA had total bilirubin level <0.8mg/dl(96%). Mean total bilirubin was  $0.504 \pm 0.188$ . p value- <0.0007.

**Table 3 :Relationship of ICP cases treated with UDCA according to the bile acid level**

Bile acid level (micromol/l)	ICP cases treated with UDCA	Percentage	ICP cases not received with UDCA	Percentage
<40	30(50)	60%	4(50)	8%
40-100	19(50)	38%	42(50)	84%
>100	1(50)	2%	4(50)	8%
Mean±SD	39.46±18.699			

Table 3 shows distribution of the ICP cases treated with UDCA according to the bile acid levels. No. of ICP cases treated with UDCA is 50. 30(60%) patients reported bile acid level <40. 19(38%) patients reported bile acid level 40-100. 1(2%) patient showed bile acid level >100micromol/l. Mean ±SD is  $21.08 \pm 12.8346$ . p<0.0001.

**Table 4 : Distribution of ICP cases treated with UDCA according to SGOT level**

SGOT(IU/L)	ICP cases treated with UDCA	Percentage	ICP cases not received with UDCA	Percentage
<30	5(50)	10%	6(50)	12%
<b>30-100</b>	33(50)	66%	32(50)	64%
<b>100-200</b>	12(50)	24%	6(50)	12%
>200	0(50)	0%	6(50)	12%
Mean±SD	70.048± <b>35.520</b>		90.468± <b>0.398</b>	

Table 4 shows distribution of ICP cases in relation to SGOT level. Total no. of ICP cases observed during study period was 50. Among 50 patients of obstetric cholestasis cases diagnosed, 33 patients had SGOT level in between 30-100 IU/L, 5 patients had SGOT level below 30 IU/L, 12 patients had SGOT level in between 100-200 IU/L and 0 patients had SGOT

level > 200 IU/L. Thus most of the ICP patients had SGOT level in the range 30-100 IU /L (66%). Mean SGOT level was  $70.048 \pm 35.520$  IU/L. P Value=0.0001.

**Table 5 : Distribution of ICP cases treated with UDCA according to SGPT level**

SGPT(IU/L)	No. of Patients with UDCA	Percentage	No. of patients not received with UDCA	Percentage
<30	5(50)	10%	5(50)	10%
30-100	45(50)	90%	32(50)	64%
100-200	0(50)	0%	9(50)	18%
>200	0(50)	0%	4(50)	8%
<b>Mean <math>\pm</math>SD</b>	<b>45.308<math>\pm</math>16.221</b>		<b>95.038<math>\pm</math>78.221</b>	

Table 4 shows distribution of ICP cases in relation to SGPT level. Total no. of ICP cases observed during study period was 50. Among 50 patients of obstetric cholestasis cases diagnosed, 45 patients had SGPT level in between 30-100 IU/L, 5 patients had SGPT level below 30 IU/L, 0 patients had SGPT level in between 100-200 IU/L and 0 patients had SGPT level > 200 IU/L. Thus most of the ICP patients had SGPT level in the range 30-100 IU /L (70%). Mean SGPT level was  $45.308 \pm 16.221$  IU/L. P Value- <0.001.

**Table 6 : Incidence of foetal outcomes and neonatal morbidities (including perinatal death) among ICP cases treated with UDCA & not trated with UDCA**

Foetal/Neonatal complication	No. of cases with UDCA	No of cases not received with UDCA	P value
Preterm labour (PTL)	8(16%)	10(20%)	0.6045
PPROM	4(8%)	5(10%)	0.7281
PROM	9(18%)	8(16%)	0.7911
IUFD	2(4%)	2(4%)	1.0000
Oligohydramnios	18(36%)	20(40%)	0.6818
Post term (PT) pregnancy	1(2%)	1(2%)	1.0000
Post dated (PD)pregnancy	2(4%)	3(6%)	0.6480
IUGR	3(6%)	4(8%)	0.6966
Foetal Bradycardia (FB)	8(16%)	9(18%)	0.7911
Meconium stained liquor (MSL)	16(32%)	18(36%)	0.6744
Meconium aspiration syndrome (MAS)	9(18%)	10(20%)	0.7998
Abnormal CTG	10(20%)	12(24%)	0.6310
APGAR Score <7 at5min	12(24%)	13(26%)	0.8183

Congenital Anomaly	1(2%)	1(2%)	1.000
SNCU admission	12(24%)	14(28%)	0.6501
Perinatal Mortality Rate (PMR)	5(10%)	5(10%) 98.03 per 1000 total live births	1.000
None	10(20%)	8(16%)	0.6045

Table 6 shows among 50 cases included in my study 8 patients had preterm labour (16%), 4 patients had PPROM (8%), 9 patients had PROM (18%), 18 patients had oligohydramnios (36%), 2 patients had post-dated pregnancy (4%), 1 patient had post term pregnancy (2%), 3 babies had IUGR (6%), 8 patients had foetal bradycardia (16%), 16 patients had meconium stained liquor (32%), 9 babies suffered from meconium aspiration syndrome (18%), 10 patients had abnormal CTG findings (20%), 12 babies had APGAR score <7 at 5 min (24%), 12 neonates required admission to SNCU (24%). There were 2 intrauterine foetal deaths (4%), 1 congenital anomaly (2%). There were 5 perinatal deaths among cases (PMR - 98.03 per 1000 total births) while 10 patients had none of the above mentioned complications (20%). There is statistically significant difference (p value < 0.05) between ICP cases and controls regarding incidence of PTL, PPROM, PROM, oligohydramnios, foetal bradycardia, MSL, MAS, abnormal CTG, APGAR score <7 at 5 min, SNCU admission rate & pregnancies without any complications mentioned above. There is no statistically significant difference (p value > 0.05) between ICP cases and controls regarding incidence of IUFD, post term & post-dated pregnancy, IUGR, congenital anomaly & PMR.

**Table 7: Distribution of ICP cases & controls according to birth weight (kgs)**

Birth weight (Kgs)	No. of ICP case Treated with UDCA	Percentage	No. of ICP cases not received with UDCA	Percentage
Extremely low birth weight (XLBW) <1kgs	0(50)	0%	0(50)	0%
Very low birth weight (VLBW) <1.5kgs	1(50)	2%	2(50)	4%
Low birth weight (LBW) <2.5kgs	17(50)	34%	19(50)	38%
Normal birth weight >2.5kgs	32(50)	64%	29(50)	58%

Table 7 shows distribution of ICP cases according to birth weight (kgs) treated with UDCA. Total no. of ICP cases observed during study period was 50 and total



no of babies delivered were 50. Among these 50 babies, 1 baby was VLBW (2%), 17 babies were LBW (34%) and 32 babies had normal birth weight >2.5kgs (64%) and none was XLBW. There is no statistically significant difference between ICP cases treated with UDCA and ICP cases not treated with UDCA regarding the normal birth weight, LBW, VLBW and XLBW.

**Table 8: Incidence of Postpartum Haemorrhage in ICP cases treated with UDCA and ICP cases not treated with UDCA**

Total no. of ICPcase	No. of ICP case treated with UDCA (50) %	No. of ICP case not receivedwith UDCA (50) %
ICP cases developing PPH	2(4%)	5(10%)
	P value 0.2420	

Table 8 shows that in present study among 50 ICP patients treated with UDCA, 2(4%) patients had postpartum haemorrhage during delivery and early puerperium making incidence of 4%. There is statistically significant difference regarding PPH incidence between ICP cases treated with UDCA and patient without UDCA (p value 0.2420).

**Table 9 : Postpartum resolution of symptoms and Liver Function Test**

Post partum resolution	No. of patient t Treated With UDCA	Percentage	No. of the patient not received with UDCA	Percentage
At 2 weeks	20(50)	40%	18(50)	36%
At 4 weeks	50(50)	100%	49(50)	98%

Table 9 shows that among 50 cases ICP treated with UDCA, 20 patients (40%) post-partum resolution happened at 2 weeks and 50 patients (100%) resolution happened at 4 weeks

## DISCUSSION

In the present study total no. of ICP cases observed during study period was 50. Total no. of ICP cases treated with UDCA during study period was 50. Among 50 ICP cases treated with UDCA 15 patients showed grade 0 pruritis, 30 patient showed grade1 pruritis, 4 patient showed grade2

pruritis and 0 patient showed very severe pruritis which is comparable to the previous study Zapata R et al (2005).<sup>17</sup> G Mazzella et al (2001)<sup>18</sup> showed UDCA had significant effect on pruritus.

In our study among 50 ICP cases treated with UDCA 78% pruritis resolved, 28% of ICP not treated with UDCA pruritis resolved. P value-<0.0001 which is compared to the previous study. Zapata R et al (2005)<sup>17</sup> p value-<0.05. Yannick Bacq et al (2012)<sup>19</sup> showed UDCA was associated with total resolution of the pruritis (odds ratio[OR], 0.23; 95% confidence interval. Monika Grymowicz et al (2006)<sup>20</sup> UDCA treatment attenuated pruritis (p<0.05). G Mazzella et al (2001)<sup>18</sup> showed UDCA had significant effect on pruritus.

In present study among 50 patients of obstetric cholestasis cases diagnosed 48 patients has total bilirubin level <0.8mg/dl. 2 patients had total bilirubin level between 0.9-2.0mg/dl. 0 patient had total bilirubin level between 2.1-3mg/dl. 0 patient had total bilirubin level more than 3mg/dl. Thus most of the ICP patients treated with UDCA had total bilirubin level <0.8mg/dl (96%). Mean total bilirubin was 0.504±0.188. p value- <0.0007. Zapata R et al (2005)<sup>17</sup> showed significant reduction of serum bilirubin(p<0.05).

In present study no. of ICP cases treated with UDCA is 50. 30(60%) patients reported bile acid level <40. 19(38%) patients reported bile acid level 40-100. 1 (2%) patient showed bile acid level >100micromol/l. Mean ± SD is 39.46±18.699. p<0.0001 which is compared to a previous study Xiang Kong et al. (2016)<sup>21</sup> reported that there were reduction of serum levels of bile acid (SMD, -0.68; 95%CI, -1.15 to -0.20; P<0.001).

In present study distribution of ICP cases in relation to SGOT level. Total no. of ICP cases observed during study period was 50. Among 50 patients of obstetric cholestasis cases diagnosed, 33 patients had SGOT level in between 30-100 IU/L, 5 patients had SGOT level below 30 IU/L, 12 patients had SGOT level in between 100-200 IU/L and 0 patients had SGOT level > 200 IU/L. Thus most of the ICP patients had SGOT level in the range 30-100 IU /L (66%). Mean SGOT level was 70.048±35.520IU/L. Distribution of ICP cases in relation to SGPT level. Total no. of ICP cases observed during study period was 50. Among 50 patients of obstetric cholestasis cases diagnosed, 45 patients had SGPT level in between 30-100 IU/L, 5 patients had SGPT level below 30 IU/L, 0 patients had SGPT level in between 100-200 IU/L and

0 patients had SGPT level > 200 IU/L. Thus most of the ICP patients had SGPT level in the range 30-100 IU /L (70%). Mean SGPT level was  $45.308 \pm 16.221$  IU/L. P Value- <0.001. Zapata R et al (2005)<sup>17</sup>, Xiang Kong et al (2016)<sup>21</sup> reported that decrease of serum alanine amino transferase (ALT) (standardized mean diff (SMD), -1.36; 95% CI, -2.08 to -0.63; P<0.001.

In present study among 50 cases of ICP treated with UDCA included in my study 8 patients had preterm labour (16%) (p value- 0.6045), fetal bradycardia (16%) (p value-0.7911), SNCU (24%) (p value-0.6501). Yannick Bacq et al (2012)<sup>19</sup> reported that there were no statistically significant difference of ICP patient treated with UDCA. 4 patients had PPRM (8%), 9 patients had PROM (18%), 18 patients had oligohydramnios (36%), 2 patients had post dated pregnancy (4%), 1 patient had post term pregnancy (2%). 3 babies had IUGR (6%) (p value-0.6966), 8 patients had foetal bradycardia (16%), SNCU (24%)(p value-0.6501) 16 patients had meconium stained liquor (32%)(pvalue-0.6744), 9 babies suffered from meconium aspiration syndrome (18%)(p value- 0.7998) which is compared to previous study medicine (Baltimore) (2017) reported that there were no significant diff in MSL, MAS and IUGR between the groups(p>0.05). There is no statistically significant difference (p value > 0.05) between ICP cases and controls regarding incidence of IUFD, post term & post-dated pregnancy, IUGR, congenital anomaly & PMR. Ana Glantz et al (2005)<sup>22</sup> reported that there is no significant difference on fetal outcome. Zapata R et al (2005)<sup>17</sup> reported that spontaneous preterm delivery (33- 44%), MSL (20-30%), FB (22%), abnormal CTG (20-30%) and perinatal morbidity (10-15%).

In present study Distribution of ICP cases according to birth weight (kgs) treated with UDCA. Total no. of ICP cases observed during study period was 50 and total no of babies delivered were 50. Among these 50 babies, 1 baby was VLBW (2%), 17 babies were LBW (34%) and 32 babies had normal birth weight >2.5kgs (64%) and none was XLBW. There is no statistically significant difference between ICP cases treated with UDCA and ICP cases not treated with UDCA regarding the normal birth weight, LBW, VLBW and XLBW. Zapata R et al (2005)<sup>17</sup> showed no significant increase in fetal birth weight.

In present study the incidence of PPH was 2 (4%). There was no significant reduction of PPH of patient treated with UDCA. In a patient with ICP cases not treated with UDCA, incidence of PPH

was 5 (10%). Zapata R et al (2005)<sup>17</sup> reported that there was no significant improvement on maternal complications(PPH).

In present study all patients showed postpartum resolution of symptoms and deranged liver function test after 4 weeks. Sultana R et al (2009)<sup>23</sup> reported that in majority of cases liver function test started coming to normal within 48 hrs and complete resolution occurred by 10th day of puerperium. According to Rasheed S et al (2009)<sup>24</sup> postnatal resolution of pruritus and liver function test occurred within 5-14 days with a mean of 8 days  $\pm$  2.52

### CONCLUSIONS

There was significant reduction of total bilirubin; conjugated and unconjugated bilirubin, bile acid SGOT & SGPT level Caesarean section rates are not that decreased in obstetric cholestatic patient treated with UDCA. Incidence of PPH was not significantly decreased in obstetric cholestasis treated with UDCA. Neonatal morbidity is mainly due to prematurity, low birth weight, oligohydramnios and meconium staining of amniotic fluid. Neonatal outcome is not significantly improved when treated with UDCA. Present study was done with small sample size and over shorter duration of time in a single centre at the OPD. Multicentre study should be required for better results. Due to unavailability of adequate resources, biochemical tests such as fasting serum bile acid level which give a more accurate assessment could not be done

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**Ethical approval:** The study was approved by the institutional ethics committee

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