

# Obstetric Cholestasis: Comparison of Maternal and Perinatal Outcome of Ursodeoxycholic Acid versus Placebo

Faiza Safdar<sup>1</sup>, Shabana Kalsoom<sup>2</sup>, Noreen Majeed<sup>3</sup>, Khairun Nisa<sup>4</sup>, Shazia Rafique<sup>5</sup>, Shamsa Tariq<sup>6</sup>, Mamoon Riaz<sup>7</sup>, Mehreen Mehdi<sup>8</sup>

<sup>1,4,5</sup> Assistant Professor, Department of Obstetrics & Gynaecology, Wah Medical College, Wah Cantt.

<sup>2,3</sup> Associate Professor, Department of Obstetrics & Gynaecology, Wah Medical College, Wah Cantt.

<sup>6,8</sup> Professor, Department of Obstetrics & Gynaecology, Wah Medical College, Wah Cantt.

<sup>7</sup> Senior Registrar, Department of Obstetrics & Gynaecology, Wah Medical College, Wah Cantt.

## Author's Contribution

<sup>1,6</sup> Conception of study

<sup>1,3,4,5,7,8</sup> Experimentation/Study conduction

<sup>1,2</sup> Analysis/Interpretation/Discussion

<sup>2</sup> Manuscript Writing

<sup>2,6</sup> Critical Review

## Corresponding Author

Dr. Faiza Safdar

Assistant Professor,

Department of Obstetrics & Gynaecology, Wah Medical College,

Wah Cantt.

Email: faizasafdar10@yahoo.com

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## Abstract

**Objectives:** To compare the maternal and perinatal outcomes of ursodeoxycholic acid with placebo in obstetric cholestasis.

**Materials and Methods:** It was an open randomized parallel-group study with convenient sampling, conducted at Pakistan ordinance factories hospital (POF Hospital) Wah Cantt, from 1<sup>st</sup> June 2016-30<sup>th</sup> May 2019. Patients with obstetric cholestasis of pregnancy, diagnosed between 24-34 weeks of gestation, were randomized to receive either ursodeoxycholic acid 500mg twice daily or placebo one capsule twice daily for 4 weeks. The data was collected on a pre-designed proforma. The data of 84 patients, who full fill the inclusion criteria were analyzed using SPSS vs 19. Maternal outcomes measured were a relief in pruritus and a decrease in hepatic alanine aminotransferase levels (ALT) at the end of 2 weeks and 4 weeks of treatment. The mode of delivery was noted. Fetal outcomes measured were meconium staining of amniotic fluid and the need for neonatal intensive care unit (NICU) admission.

**Results:** The results showed significant improvement in maternal itch score (P=0.001) and serum transaminases level (p=0.001) in patients using UDCA as compared to placebo. Although there were less number of caesarean sections (p=0.36), meconium-stained liquor (p=0.29) and NICU admissions (P=0.33) in the UDCA group the differences were not statistically significant.

**Conclusion:** Treatment with UDCA in obstetric cholestasis improved maternal complaint of itching and decreased raised transaminases levels but did not affect significantly the mode of delivery, incidence of meconium-stained liquor and NICU admissions.

**Keywords:** Obstetric cholestasis, Ursodeoxycholic acid, perinatal outcome, Pruritus.

## Introduction

Obstetric cholestasis also labelled as intrahepatic cholestasis of pregnancy is not an uncommon liver disorder that has adverse effects on both mother and fetus.<sup>1</sup> The disease Prevalence varies due to genetic and environmental differences in population from 0.7%-5%.<sup>2</sup> Women present, usually in the second and third trimester, with severe itching especially on palms and soles but there is no rash.<sup>3</sup> There is an elevation in serum transaminases and bile acid levels.<sup>4</sup> The diagnosis is made after excluding other causes of pruritus and deranged liver functions.<sup>5</sup> Complication increase if disease start before 33 weeks of gestation.<sup>6</sup>

In addition to maternal discomfort and sleep disturbance due to pruritus, the studies have shown increased fetal and perinatal risks which include prematurity, low birth weight, meconium staining of amniotic fluid, fetal distress, increased risk of NICU admission and stillbirth.<sup>7, 8, 9, 10, 11</sup>

While prescribing medications, the obstetrician has to take into consideration the maternal symptomatic relief as well as its effect on perinatal outcome. Many drugs have been tried to treat obstetric cholestasis with variable efficacy. These include activated Charcoal, Guar gum, Dexamethasone, S-adenosylmethionine (SAmE) and ursodeoxycholic acid (UDCA).<sup>12</sup>

Ursodeoxycholic acid (UDCA), a commonly used drug, is a secondary bile acid that is naturally occurring but can be chemically synthesized. UDCA may play a role in the liver in a variety of ways. These related pathways include changes in bile acid's Pool, choleresis, immune regulation, and cytoprotection mechanism.<sup>13,14</sup> it is available in the form of capsules for oral use.

Controversies still exist regarding the management of patients having obstetric cholestasis. Some obstetricians only advise simple emollients and anti-allergic for itch relief while others favour the use of UDCA. Studies done so far, comparing UDCA with other drugs or placebos, have shown variable results, especially concerning the perinatal outcome.<sup>15-23</sup>

Due to these debates in the management of patients having obstetric cholestasis we planned this study. We compared the UDCA with placebo and observed the effects on maternal symptoms of pruritus, biochemical marker i.e. serum transaminase level, caesarean section rate, meconium staining of liquor and NICU admission.

## Materials and Methods

An open, randomized, parallel-group study was performed comparing the efficacy and safety of ursodeoxycholic acid and placebo in obstetric cholestasis. The study was approved by the ethical committee of POF hospital Wah Cantt. The duration of study was 3 years from 1<sup>st</sup> June 2016 to 30<sup>th</sup> May 2019. Sampling Technique was convenient sampling.

Patients with a history of skin pruritus starting in the second and third trimester (between 24-34 weeks of gestation) characteristically involving palms and, soles with an elevation of alanine aminotransferase (ALT) above 45 IU /L, singleton pregnancy, no known lethal fetal anomaly and able to give written informed consent were included in the study. Exclusion criteria were patients having chronic liver disease, hepatic viral infections (HAV, HBV, HCV, cytomegalovirus, herpes simplex virus, and Epstein-Barr virus), skin diseases, allergic disorders, symptomatic cholelithiasis, history of previous caesarean section and multiple gestations.

All patients gave written informed consent before inclusion into the study and were randomized to receive either UDCA capsule 500mg twice daily (Group A) or placebo one capsule BD (Group B) for 4 weeks. Placebos were provided by the pharmaceutical company providing capsule Urso. They were of the same size, shape, and colour. Randomization was performed by using sealed envelopes by the doctor attending the patient. All the information were collected on a pre-designed proforma

Primary study outcomes were maternal symptomatic relief by measuring itch score and decline in hepatic alanine aminotransferase after 2 weeks and 4 weeks of treatment.

Secondary outcomes measured were the outcome of pregnancy (mode of delivery, meconium staining of liquor, and need for NICU admission). Self-assessment of pruritus intensity was performed two weekly by use of numeric rating scale (NRS) The NRS has only one item and has the numbers 0 ("no itch") to 10 ("worst imaginable itch"). Patients were requested to rate the intensity of their itch on an average in the past 1-3 days using this scale and it was noted on their proforma.

Liver function tests were done at the time of diagnosis and repeated after 2 weeks and 4 weeks by routine laboratory techniques. The decision to induce labour and carry out caesarean section was made by the managing obstetrician independently of this study. The mode of delivery, colour of liquor and need for

NICU admission were noted by the doctor present at delivery on the proforma.

Statistical analysis was performed using SPSS version 19. Numerical variables were analyzed using one way ANOVA test and descriptive variables were analyzed using the Chi-square test at 5 percent significant value.

## Results

Total of ninety patients aged 18-40 years between 24weeks and 34 weeks of gestation who fulfilled the inclusion criteria were enrolled in the study. Later on, six patients were excluded from the study because two were lost from follow up and four patients delivered before completion of 4 weeks of treatment. In the final analysis, 42 patients who received UDCA 500mg BD (Group A) and 42 patients who received placebos (Group B) for 4 weeks were included.

The mean age of patients in the study group was  $28.34 \pm 4.31$  years. The mean gestational age at the onset of treatment was  $31.68 \pm 1.71$  week. The mean parity of the study population was  $3.27 \pm 1.74$ .

The baseline variables of both groups didn't differ between the two groups as shown in Table 1.

**Table 1: Baseline characteristics of treatment groups**

Characteristics	UDCA Group (mean $\pm$ SD)	Placebo group (mean $\pm$ SD)	p-value
Age of patient (years)	$28.30 \pm 3.61$	$28.37 \pm 4.96$	0.945
Parity of patient	$3.26 \pm 1.69$	$3.28 \pm 1.81$	0.951
Gestational age at start of treatment (weeks)	$31.73 \pm 1.87$	$31.64 \pm 1.55$	0.820

The intensity of itch was similar in two groups at baseline  $8.42 \pm 0.88$  vs  $8.80 \pm 0.99$  ( $p=0.067$ ). Analysis of change in itch score between two groups at baseline and after 2 weeks showed significant improvement in the UDCA group compared with the placebo group and the difference was even more marked after 4 weeks of treatment (Table 2).

**Table 2: Comparison of itch score between groups**

Itch score	UDCA Group mean $\pm$ SD	Placebo Group mean $\pm$ SD	P-value
Before treatment	$8.80 \pm 0.99$	$8.42 \pm 0.88$	0.067
After 2 weeks	$4.69 \pm 1.15$	$7.23 \pm 0.75$	0.001
After 4 weeks	$2.19 \pm 0.94$	$6.23 \pm 1.07$	0.001

Table 3 shows mean ALT levels at the start of treatment, 2 weeks and 4 weeks after starting of treatment in the two groups.

**Table 3: Comparison of ALT levels in two groups**

Biochemical marker (ALT levels)	UDCA group (mean $\pm$ SD)	Placebo Group (mean $\pm$ SD)	p-value
At start of treatment	$191.45 \pm 61.42$	$166.85 \pm 41.00$	0.034
After 2 weeks	$93.73 \pm 35.08$	$152.50 \pm 38.39$	0.000
After 4 weeks	$58.16 \pm 15.71$	$149.00 \pm 32.79$	0.000

In the UDCA group, 5 patients underwent LSCS compared to 8 in the placebo group. The main indication was meconium-stained liquor causing fetal distress. Although their caesarean section rate was high and more babies had meconium-stained liquor in the placebo group as compared to the UDCA group but it was not statistically significant. (Table 4)

**Table 4: comparison of mode of delivery & perinatal outcome**

Parameters		UDCA Group N (%)	Placebo Group N (%)	p-value
Mode of delivery	SVD	37(88%)	34(81%)	0.365
	LSCS	5(12%)	8(19%)	
Meconium stained liquor	Yes	3(7.1%)	6(14.2%)	0.29
	No	39(92.9%)	36(85.7%)	
NICU Admissions	Yes	4(9.5%)	7(16.7%)	0.332
	No	38(90.5%)	35(83.3%)	

No stillbirths were observed in either group, and no significant difference between the two groups was observed concerning NICU admission.

## Discussion

The goal of the management of women having obstetric cholestasis is to decrease maternal discomfort caused by itching and to prevent the harmful effects of the disease on fetuses and neonates. These harmful fetal effects are at present unpredictable by fetal surveillance methods of CTG, biophysical profile, and Doppler studies. The management of obstetric cholestasis varies among different obstetric units and even among obstetricians in the same units. Some prescribe ursodeoxycholic acid while other obstetricians insist on the use of simple emollients or anti-allergic drugs for itch control.

This study which was a randomized controlled trial was an effort to resolve the issue of whether treatment with UDCA has a benefit for the mother and fetus.

The mean age of women in our study is 28.34±4.31 being 28.30±3.61 in the UDCA group and 28.37±4.96 in the placebo group. while a study by Medda S showed the mean age of 27.53±4.49 years with most patients between the age group 26-30 yrs.<sup>5</sup> In a local study conducted at CMH Kharian Pakistan mean age of women having obstetric cholestasis calculated was 29.8±4.76 years which is close to our observation.<sup>24</sup>

Mean parity was 3.27±1.74 and 17(20.2%) patients were primigravida (9 in UDCA Group and 8 in the

placebo group) and 67(79.8%) were multigravida (33 in UDCA group and 34 in the placebo group). Esitu M.C. in her study showed a prevalence of 35.6% in primigravida patients and 64.4% in multigravida patients.<sup>25</sup> A local study at Agha Khan hospital Karachi also showed a high prevalence of 57% among primigravidas.<sup>26</sup> The reason for this difference is not clear.

Mean gestational age (weeks) in both groups at the time of diagnosis and start of the trial is 31.68±1.71 being 31.73±1.87 in the UDCA group and 31.64±1.55 in the placebo group. The range was 24-34 weeks. The finding in our study was similar to the study by Medda S who also showed the mean gestational age of patients at diagnosis 31.80±4.39 weeks.<sup>5</sup> Estiu MC showed mean gestational age at the time of diagnosis being 33.6±3.6 weeks with most cases diagnosed between 32 and 37 weeks.<sup>25</sup> The reason for the lower mean gestational age at diagnosis is that we excluded cases diagnosed after 34 weeks from our study.

There was no statistically significant difference in maternal itch score at the start of treatment (p=0.067) but a marked improvement in maternal symptoms was observed after 2 weeks in UDCA group compared with placebo (mean itch score: 4.69±1.15 vs 7.23±0.75) and there was further improvement after 4 weeks of treatment (mean itch score 2.19±0.94 vs 6.23±1.07). Kondrackiene J showed maternal pruritus was markedly improved with UDCA treatment compared to cholestyramine (pruritus score: 2.08±0.63 vs 2.92±0.62; p-value 0.05) and the difference was more pronounced after 14 days (pruritus score: 0.44±0.65 vs 1.88±0.98; p-value .001).<sup>15</sup> Rodrigo Z and Joutsiniemi T have also shown statistically significant improvement in maternal pruritus after UDCA treatment as compared to placebo.<sup>16,17</sup> Study by Glantz A showed more itch improvement in the placebo group compared to UDCA.<sup>20</sup> This may be because of a small sample size.

There was a significant improvement in biochemical marker i.e. ALT levels after treatment with UDCA as compared to placebo. The mean ALT levels fell from 191.45 IU/L to 58.14 IU/L after 4 weeks of UDCA treatment. Similar results have been shown by Palma in his study of 15 patients after 3 weeks of treatment.<sup>18</sup> Although the number of patients in studies by Diaferia and Nicastrì were small (16 in each study) but the results similar to our study were also observed by them.<sup>19, 20</sup>

Bile acids levels are also used to diagnose and assess the severity of disease but as they were costly and not

available at our hospital, we could not include them in our study.

Although more patients in the placebo group (19%) required delivery by caesarean section as compared to the UDCA group (12%), the main indication being fetal distress and meconium-stained liquor, but the difference did not reach the level of statistical significance ( $p=0.365$ ). A meta-analysis of 4 trials including 210 women had also shown similar results.<sup>12</sup> In our study meconium-stained liquor was observed in 14.2% patients on placebos and 7.1% patients on UDCA. The difference was not significant ( $p=0.29$ ). Chappell L in his analysis of 111 patients noted meconium-stained liquor in 23.6% (13/55) patients in the placebo group and 8.9% (5/56) in the UDCA group ( $p=0.04\%$ ).<sup>21</sup> The reasons for this difference in result may be the difference in gestational age at delivery because it included cases who had early-term delivery and late-term delivery both while we followed the policy of routine induction of labour at 38 weeks in patients diagnosed as obstetric cholestasis. Only 9.52% of babies (4/42) required admission in NICU in the UDCA group as compared to 16.6% (7/42) in the placebo group ( $p=0.332$ ). The same was observed by Chappell L where 8.3% (5/60) and 17.1% (11/64) babies in the UDCA group and placebo group required NICU admission respectively ( $p=0.15$ ).<sup>21</sup> Although this difference is not statistically significant it shows less need for NICU admission in the UDCA group.

This study showed clear maternal benefits of UDCA in improving maternal itch. The treatment also decreased pathologically raised serum ALT levels, showing improvement in biochemical markers. Although there was a reduction in caesarean section rate, meconium staining of liquor and NICU admission but the benefit was not significant statistically. The limitation of our study was that we only studied serum ALT levels due to the easy availability and cost-effectiveness of this test and did not include serum bile acid levels. Further multicenter studies with a large sample size are required to establish any fetal and neonatal benefits of UDCA treatment as well as its effect on birth weight.

## Conclusion

The results of our study recommend the use of UDCA for decreasing the severity of discomfort caused by itching and for improving liver function and recommend more studies to establish benefit for the perinatal outcome.

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