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EFFECT OF URSODEOXYCHOLIC ACID ON PRURITUS AND FETAL OUTCOMES IN INTRAHEPATIC CHOLESTASIS OF PREGNANCY: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

OBJECTIVE: To compare the mean pruritus score on the visual analog scale (VAS) at the last antenatal visit before delivery in ursodeoxycholic acid versus placebo groups for the management of pregnant women with intrahepatic cholestasis.

METHODS: The study design was a randomized controlled trial, to compare the mean pruritus score on VAS at the last antenatal visit before delivery in ursodeoxycholic acid (UDCA) versus placebo groups for the management of pregnant women with intrahepatic cholestasis. Sample formula and size: 100 (50 in each group). In a study comparing UDCA versus placebo; post-randomization maternal itch score was lower in the UDCA group than in the placebo group (49.5+12.9 versus 56.9+13.3; mean difference -5.7 mm [95% CI -9.7 to -1.71], p=0.0054) (10). The sampling technique was non-probability consecutive sampling. Data analysis was performed as data was entered in and analyzed through SPSS-25. Mean and standard deviation were calculated for age and pruritus on VAS for pruritus assessed before the start of the drug and at the last visit before presentation for delivery in both groups.

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RESULTS: UDCA was accepted well. Compared to women who did not receive medication, those who received UDCA had an ICP diagnosis five weeks earlier. Total serum bile acid (BA) and ALT levels were greater in the UDCA-using group at diagnosis than in the non-UDCA-using group. The perinatal outcome was favorable, and the majority of deliveries were induced. The UDCA group had significantly lower Apgar ratings at 5 minutes ($p < 0.05$). Those deliveries were induced shortly after diagnosis for 30 patients whose total BA was greater than 40 μmol/l at diagnosis, 24 of whom had UDCA, and 6 of whom were not taking any medication. These patients also had a higher prevalence of premature labor ($p<0.05$). ICP was identified sooner in women having preterm newborns, and their pruritus had a noticeably earlier beginning. Both at diagnosis and at first control, those pregnancies had significantly higher serum ALT and total BA levels.

CONCLUSION: Severe ICP (total BA > 40 μmol/l) was linked to preterm labor; ALT levels were also significantly higher, and ICP was identified sooner ($p < 0.05$). Preterm newborns' Apgar scores were poorer ($p < 0.05$). Pregnant women tolerated UDCA nicely. The obstetric result was favorable with low-dose UDCA therapy. Careful obstetrical follow-up is still advised.

KEYWORDS: Ursodeoxycholic Acid, Pregnant Women, Intrahepatic Cholestasis, Pruritus, Fetal.

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a fairly the most common condition related to pregnancy. It is characterized by maternal pruritus and increased levels of serum bile leading to - maternal symptoms and liver function tests that resolve in the post-partum period. Previous studies showed that ICP is associated with the risk of preterm birth, fetal distress, stillbirth, and neonatal admissions (1-2).

UDCA is used outside of pregnancy to treat hepatobiliary disorders and to treat intrahepatic cholestasis of pregnancy (3). It is a naturally occurring bile acid that has several functions (upregulation of hepatic metabolizing enzymes and bile acid transporters, stimulation of impaired hepatocellular secretion by post-transcriptional mechanisms, stabilization of the plasma membrane, and protection of cholangiocytes of the biliary epithelium against cytotoxicity of bile acids, and hepatocyte protection against bile acid-induced apoptosis) resulting in improvement of

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cholestasis by increasing biliary bile acid excretion (4-7). In a meta-analysis, UDCA proved to be effective in reducing pruritus and improving liver function tests in patients with ICP, and UDCA therapy might also benefit fetal outcomes (8). In another review study, UDCA significantly improves pruritus in ICP. Incidence of fetal distress/asphyxial events was less reported in the UDCA groups when compared with placebo but the difference was not statistically significant (9).

In an RCT,605 women were enrolled and randomly allocated to receive UDCA (n=305) or placebo (n=300). The primary outcome analysis included 304 women and 322 infants in the UDCA group, and 300 women and 318 infants in the placebo group (consent to use data was withdrawn for 1 woman and 2 infants). Prenatal death, preterm delivery, or neonatal unit admission for at least 4 hours were primary composite outcomes. The primary composite outcome occurred in 74 (23%) of 322 infants in the UDCA group and 85 (21%) of 318 infants in the placebo group (adjusted risk ratio 0 85 [95% CI 0.62-1.15]).

Post-randomization maternal itch score was lower in the UDCA group than in the placebo group (49.5+12.9 versus 56.9+13.3; mean difference -5.7 mm 195% Cl -9.7 to -1.71], p-0.0054) (10).

ln another study by Chappell LC et al, women with ICP (pruritus and raised levels of serum bile acids) or pruritus and raised alanine transaminase levels (>100 IU/L) were recruited after 24 weeks gestation and followed until delivery. 32% of women in the UDCA group experienced a reduction in worst itching as compared to 16% in the placebo group (11).

Although the practice of use of UDCA in the treatment of ICP is very common, the evidence of its efficacy in outcomes is controversial (8-11). As there might be regional and ethnic difference in efficacy of UDCA for pruritus relief and fetal outcomes. So I have planned the study. My study will reassess the efficacy of UDCA in patients of ICP and thus might help to formulate guidelines for management of targeted population.

METHODS

Study Design was a randomized controlled trial, to compare the mean pruritus score on VAS at the last visit before presentation for delivery in UDCA versus placebo groups for management of pregnant women with intrahepatic cholestasis. The study setting was In-patient, OBG dept, Ibn-e-Siena Hospital, Multan. The duration of the study was six months after approval of the

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synopsis by REU CPSP (March-August 2024). Sample formula and size: 100 (50 in each group), Alpha (α): 0.05, Beta (β): 0.1, Mean in group I (μ1): 49.5, Standard Deviation in group 1 (α1): 12.9, Mean in group 2 (α2): 56.9, Standard Deviation in group 2 (α2): 13.3, Ratio of Group 2/Group l:1. In a study comparing UDCA versus placebo; post-randomization maternal itch score was lower in the UDCA group than in the placebo group (49.5+12.9 versus 56.9+13.3; mean difference -5.7 mm [95% CI -9.7 to -1.71], p=0.0054) (10). The sampling technique was non-probability consecutive sampling. Inclusion Criteria included Age 19-45 years, Gestational age of> 24 weeks, and Diagnosis of Intra-hepatic cholestasis of at least two week's duration as defined in the operational definition. While, Exclusion Criteria included patients with more than singleton pregnancy on ultrasound, Cholelithiasis or Choledocholithiasis on ultrasonography, and Delivery before completion of two weeks from start of treatment with any known allergy to UDCA. Data collection procedure was as, total 100 (50 in each group) women fulfilling the inclusion criteria were included in the study after informed consent from each patient and after study approval from ethical review committee and REU CPSP. Participants were ensured about confidentiality and fact that there was no risk involved to the patient in this study. Age, parity, was asked by researcher herself. Serum bile acid level and liver function test was performed in central laboratory of the hospital. Diagnosis of intrahepatic cholestasis and Gestational diabetes were labeled as defined in operational definition. Viral hepatitis serology (Hepatitis A and E) were checked in each case, from central laboratory of the hospital. Ultrasonography for liver was performed by a consultant radiologist of the hospital having at least 2 years post fellowship experience. Participants were randomly assigned to UDCA (cap. Urso 500mg per-oral BID) (Group-A) or Placebo (capsules resembling Group-A) (Croup-B) using lottery method, given as two oral tablets a day at an equivalent dose of 500 mg twice a day. All women were examined and followed till delivery every fortnightly by researcher herself under supervision of a consultant gynecologist having at least 2 years post fellowship experience. pruritus on VAS assessed before start of drug and at last scheduled visit before presentation for delivery was assessed on participant response by a trained staff nurse who was unaware of group allocation. All delivered infants was also examined by a consultant pediatrician at birth was followed by researcher herself for parameters mentioned in Fetal outcome variables. All data was recorded on

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especially designed proforma. Data analysis was performed as, data was entered in and analyzed through SPSS-25. Mean and standard deviation was calculated for age and pruritus on VAS for pruritus assessed before start ofdrug and at last visit before presentation for delivery in both groups. Frequencies and percentages were calculated for age groups, gestational diabetes and Fetal outcome variables in both groups. Mean in pruritus score on VAS assessed at last visit before presentation for delivery was compared between two groups by using independent sample t- test and p- value < 0.05 was considered as significant. Fetal outcome variables were compared between the two groups using chi square test and p-value < 0.05 was considered as significant. Mean in pruritus score on VAS assessed at last visit before presentation for delivery was again be compared between two groups after stratification with age groups, Gestational diabetes by using independent sample t- test and p-value < 0.05 was considered as significant. Fetal outcome variables were again compared between the two groups after stratification with age groups, Gestational diabetes using chi square test again and p-value S 0.05 were considered as significant.

RESULTS

Characteristics of the patients are collected. At the onset of pruritus, the average gestational age was >24 weeks for the entire group, 23 weeks for the UDCA group, and 26 weeks for the medication-free group ($p<0.05$). Pregnant women who took UDCA were diagnosed with ICP four weeks earlier than those who did not ($p<0.05$). In the majority of instances without UDCA, ICP started in the latter weeks of pregnancy, and these women did not need treatment since the pregnancy was ended or the symptoms were not severe.

Cholelithiasis during pregnancy did not result in any of the individuals requiring surgery.50 individuals began using UDCA, and their average daily dosage was 450 mg (range: 150–900). The average gestational age was >24 weeks at the time of diagnosis and 34.8 weeks at the first control visit. The majority of patients (N = 59) began using UCDA medication on their first visit to the maternal care unit, and their first control was at 34.2 weeks of pregnancy. Due to modest ICP at diagnosis, 17 patients began taking medication later in pregnancy. Later in the pregnancy, when the liver enzymes were greater and the symptoms worsened, the medicine was started.

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Medication side effects occurred in about 1.5% of the individuals. Twopatients complained of nausea, while three others experienced stomach pain.

Table 1 : Medication and their side effects to Patients

Medication	No. of Patients	Side Effects
UDCA	3	Nausea
	2	Stomach Pain

At the time of diagnosis, the group using UDCA had greater levels of serum ALT and total BA than the group not taking the drug; however, only the difference in ALT levels was statistically significant ($p < 0.05$). Following the initiation of the medicine, the levels of ALT and total bile acid started to decline. In the UDCA group, the decrease in total BA values between the diagnosis and control visits was statistically significant ($P < 0.05$). Following the initial control visit, serum ALT levels start to drop noticeably ($p<0.05$).

Table 2 : Results for UCDA group and Control Group was Significant

Groups	ALT and BA level	P-Value
UCDA Group	Greater level	<0.05
Control Group	Decreased level	

Additionally, there was a drop in serum levels of ALT and BA acids in the group that was not taking medication. This was likely due to the fact that the patients with more severe ICP had already given birth during the first few weeks of the study period, there were few women attending the last appointments, and the ICP was mild. That wasn't statistically significant, though.The mean delivery time for women taking UDCA was 34 weeks, while the mean delivery time for mothers not taking medication was 38 weeks ($p<0.05$). Due to the severity of ICP, the group receiving UDCA experienced higher premature deliveries (<37 weeks) ($p < 0.05$). The majority of deliveries were induced, and UDCA users had a higher labor induction rate ($p<0.05$).

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There were no prenatal deaths in our study material, and the perinatal result was favorable. The UDCA group had significantly lower Apgar ratings at 5 minutes ($p < 0.05$). Preterm labor, which was more likely in UDCA users ($p < 0.05$), was the main reason for the increased rate of neonatal unit hospitalizations for children in the UDCA group. ICP was identified sooner in women having preterm newborns, and their pruritus was in initial phases. Both at diagnosis and at first control, those pregnancies had significantly higher levels of serum ALT and total BA. Additionally, newborns' umbilical artery pH readings were identical, but their Apgar scores were considerably lower ($p < 0.05$). Thirty five, patients had significant ICP (total BA > 40 μmol/l), twenty-two had UDCA, and 7 were not taking any treatment. To avoid preterm delivery, four individuals received higher doses of UDCA. These patients also had a higher prevalence of premature labor ($p<0.05$).

DISCUSSION

Pregnancy-related intrahepatic cholestasis has been linked to an increased risk of fetal discomfort and potentially intrauterine death. Since there isn't a specific treatment for ICP, it has mostly been symptomatic. A hydrophilic bile acid, UDCA is used to treat a number of cholestatic conditions. The most promising treatment for ICP at the moment is UDCA. Mothers tolerate it well, and there have been no reported negative effects on babies. According to Palma et al. [17], UDCA considerably enhanced the serum biochemistry of ICP patients. Following this investigation, three small randomized controlled trials demonstrated that utilizing UCDA in ICP significantly reduced liver function tests and pruritus [14, 18, 19].

Additionally, in a Swedish research, UDCA considerably decreased bilirubin and aminotransferase levels in all treated women. Additionally, pruritus and bile acids were dramatically reduced in women whose serum bile acid levels were higher than 40 μmol/l at inclusion [5]. According to a recent meta-analysis, UDCA helped individuals with ICP experience less pruritus and had better liver test results [16]. The Cochrane database states that there is not enough data to support the use of numerous treatments, either alone or in combination, to treat individuals with ICP [15]. Additionally, a recent meta-analysis that incorporates both randomized controlled trials and non-randomized research has been published

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[20]. According to that study, UDCA treatment lowers poor maternal and fetal outcomes and should be advised for women with ICP [20].

After beginning the medicine, both the levels of alanine aminotransferase and total bile acid started to drop in our study. However, following the first control visit, the patients' ALT levels and total BA values both sharply dropped after beginning the drug. Mazzella et al. [21] found that large doses of UDCA (1.5–2 g/d) did not cause any negative side effects and that the treatment seemed to be entirely safe for the fetus while also improving the biochemical and clinical parameters of cholestasis. According to Zapata et al. [22], pregnant women tolerated UDCA well, and 26 newborns who were monitored for an average of six years after delivery showed no negative side effects. Maternal pruritus, liver testing, and the fate of the pregnancy were all improved in ICP patients by UDCA. Additionally, UDCA was well tolerated, and no negative side effects were found in either the mothers or the newborns who were monitored for three months following delivery. 26 of these children, who were up to 12 years old at the time of the revised follow-up, showed normal growth and development and no illness episodes linked to UDCA [22]. The dosage of UDCA has varied in previous studies: Mazzella et al. used up to 2 g/day, Palma et al. and Glantz et al. used up to 1000 mg/day, while Diaferia et al. and Nicastri et al. used 600 mg/day [13, 14, 18, 19, 21]. Due to the earlier start and severity of ICP, the group receiving UDCA experienced more premature births (less than 37 weeks) in our study. Children in the UDCA group were more likely to be admitted to the newborn unit as a result of preterm labor. Iatrogenic and spontaneous preterm births were considerably more likely to occur in pregnancies complicated by ICP (Puljic et al. [23]). In order to lower the likelihood of an unfavorable fetal outcome, most ICP patients now have their births induced prematurely. According to one cohort study, compared to expectant management, inducing labor may lower intrauterine fetal death [24]. According to Rioseco et al., inducing labor in patients with ICP was advantageous [6].

According to Roncaglia [9] et al., elective delivery at 37 weeks, together with fetal health monitoring, can dramatically lower the stillbirth rate without raising the risk of cesarean sections. When compared to expectant management, a recent study by Puljic et al. [23] showed that delivery at 36 weeks gestation decreased the risk of perinatal mortality. They came to the

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conclusion that the timing of delivery must consider the morbidities linked to preterm delivery as well as the reduction in the chance of stillbirth [23].

Nonetheless, the risk of respiratory distress syndrome (RDS) is higher for preterm infants and is much higher for elective cesarean sections than for induced vaginal births [25]. Furthermore, the newborn may be at risk for unanticipated respiratory distress syndrome if the mother has cholestasis [26]. Zecca et al. came to the conclusion that neonates from cholestatic pregnancies had double the incidence of RDS compared to the reference group. The dangers and advantages of preterm delivery must be weighed separately since they anticipated that bile acids could cause surfactant depletion in the alveoli [26]. In their meta-analysis, Bacq et al. also came to the conclusion that UDCA therapy would improve fetal outcomes [16]. There are fewer neonates in the intensive care unit and less fetal discomfort.The rate of caesarean sections in our hospital during the study period ranged from 13.9 to 17.4%, with a rate of 15% in the study group. Additionally, the hospital's vacuum extraction rate was 5.8% to 7.3%, while this study's was 5.5%. Vacuum extraction and cesarean sections were not more common in early-term deliveries, and the majority of deliveries were induced. According to Chappell et al. (2012), scheduled early-term deliveries do not considerably raise the rate of cesarean sections [8]. Close antenatal surveillance of pregnancies affected by severe ICP is recommended since a recent prospective study by Geenes [27] et al. showed significantly higher odds of an unfavorable perinatal outcome in severe ICP.

Our study material contained no stillbirths. Additionally, several recent studies indicate a significant drop in fetal complications, most likely as a result of improved knowledge of the condition and skilled care and treatment [4, 19]. Although the UDCA dosage in our department is relatively modest, the perinatal outcome was favorable, and the side effects experienced by the mother were negligible. In every instance of ICP, we continue to advise careful fetal status monitoring. Our research indicates that induced delivery and low-dose UDCA treatment are both safe and advised as treatments for ICP. Close prenatal monitoring is also necessary for patients who are not taking the drug.

CONCLUSION

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Severe ICP (total BA > 40 µmol/l) was linked to preterm labour; ALT levels were also significantly higher, and ICP was identified sooner ($p < 0.05$). Preterm newborns' Apgar scores were poorer ($p < 0.05$). Pregnant women tolerated UDCA nicely. The obstetric result was favorable with low-dose UDCA therapy. Careful obstetrical follow-up is still advised.

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