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EFFECT OF URSODEOXYCHOLIC ACID ON MATERNAL AND FETAL OUTCOME IN INTRAHEPATIC CHOLESTASIS OF PREGNANCY

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Abstract

Background: *Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-specific liver disorder associated with adverse maternal and fetal outcomes. Ursodeoxycholic acid (UDCA) is commonly used to manage ICP, but its effectiveness remains debated.*

Objective: *This study evaluates the impact of UDCA on maternal and fetal outcomes in ICP patients.*

Methods: *This prospective observational study was conducted at Shaikh Zayed Woman Hospital, Larkana, and Hashim Medical Center, Hyderabad, from January to December 2024. A total of 600 pregnant women (≥24 weeks' gestation) diagnosed with ICP were included and assigned to either the UDCA group (n=300, receiving 15 mg/kg/day) or the conservative management group (n=300). Maternal outcomes, including pruritus severity (assessed via Visual Analog Scale) and liver function tests, were recorded at baseline and after 14 days of treatment. Obstetric complications and fetal outcomes, including gestational age at delivery, Apgar scores, and NICU admissions, were also analyzed. Data were compared using independent t-tests and chi-square tests, with $p<0.05$ considered statistically significant.*

Results: *Pruritus relief was significantly higher in the UDCA group (85.3% vs. 41.7%, $p<0.001$). Serum bile acid levels, ALT, AST, and bilirubin significantly improved with UDCA. The UDCA group had lower preterm labor (10.3% vs. 22.7%, $p=0.002$) and postpartum hemorrhage rates (5.7% vs. 11.3%, $p=0.021$). Gestational age at delivery was higher (37.4 ± 1.6 vs. 35.9 ± 2.3 weeks, $p<0.001$), with fewer NICU admissions (9.0% vs. 20.3%, $p<0.001$) and stillbirths (1.3% vs. 4.7%, $p=0.018$) in the UDCA group.*

Conclusion: *UDCA significantly improves maternal pruritus, liver function, and fetal outcomes in ICP patients, supporting its role in clinical management.*

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is an uncommon liver condition that appears in the second half of pregnancy. Pruritus, increased serum bile acid (BA) levels, and, in rare cases, liver failure are among its most common hallmarks [1]. Serious consequences for both the mother and the fetus may result from this condition. This may include preterm birth, fetal distress, and, in severe cases, stillbirth [2]. The exact cause of ICP is still not known. It is considered to be the complex and influenced by genetic, hormonal,

and environmental factors [3]. Pregnancy hormones impaired bile flow by reducing the liver's ability to eliminate BAs. Particularly progesterone and estrogen, are reported to contribute in this reduction. As a result, BAs accumulate in the mother's blood. Ultimately, the developing fetus finds it difficult to absorb or excrete out the BAs.

One of the most common treatments for ICP is ursodeoxycholic acid (UDCA) [4]. UCDA is hydrophilic BA molecule that is considered to improve biliary flow. It reduces BA levels, and protect against toxicity-related symptoms. UDCA has also been shown to provide several advantages for the fetus. In addition to its known therapeutic uses for mothers it reduced risk of preterm birth, meconium-stained amniotic fluid, and fetal distress [5,6]. UDCA appears to exert its effects by removing toxic, hydrophobic BAs from the BA pool [7].

Despite its widespread use in clinical practice, the use of UDCA remains still controversial. Some studies suggest that UDCA is an effective treatment that improves various clinical outcomes. These outcomes include lowering serum BA levels and alleviating pruritus in ICP patients [8,9]. However, some other research indicates that UDCA has no significant impact on certain parameters. It has no impact on BA clearance and maternal or fetal circulation [10,11].

Keeping in view, these uncertainties and conflicting findings, further research is needed to clarify the impact of UDCA on maternal and fetal outcomes. This study aims to evaluate the anti-ICP effects of UDCA while considering both maternal and fetal health outcomes.

Methodology

This prospective observational study was conducted at Shaikh Zayed Woman Hospital, Larkana, and Hashim Medical Center, Hyderabad. The duration of the research spanned from January 2024 to December 2024. The sample size was calculated using OpenEpi software, considering an expected ICP prevalence of 1.5%, a confidence interval of 95%, and a margin of error of 5%, yielding a required sample of 600 participants. Patients were recruited using non-probability consecutive sampling technique. Pregnant women aged 18–40 years, with a gestational age of ≥24 weeks, were included in the study. The participants were also clinically diagnosed ICP based on pruritus and serum bile acid levels >10 µmol/L. Patients with pre-existing liver disease (such as hepatitis or cirrhosis), those on hepatotoxic medications (such as methotrexate or isoniazid), multiple gestations, or fetuses with congenital anomalies were excluded.

Participants were divided into two groups: UDCA group (n=300), who received UDCA 15 mg/kg/day in divided doses until delivery, and Control group (n=300), who received only symptomatic treatment, such as antihistamines for pruritus, along with routine obstetric care. Maternal outcomes were assessed by measuring pruritus score using the Visual Analog Scale (VAS, 0–10), where improvement was defined as a ≥3-point reduction after 14 days of treatment. Liver function tests, including serum bile acids, ALT, AST, total bilirubin, and alkaline phosphatase (ALP), were measured at baseline and after 14 days of treatment. Obstetric complications, such as gestational hypertension, preterm labor (delivery before 37 weeks), and postpartum hemorrhage (blood loss >500 mL for vaginal delivery, >1000 mL for cesarean section), were recorded.

Fetal outcomes were evaluated by recording gestational age at delivery, mode of delivery (vaginal or cesarean section), birth weight (measured in grams immediately after birth), Apgar scores at 1 and 5 minutes (with a score <7 at 5 minutes considered low), the presence of meconium-stained amniotic fluid (MSAF) at delivery, need for NICU admission within 24 hours of birth, and perinatal mortality (defined as stillbirth or neonatal death within 7 days of birth). Pruritus severity was assessed using the Visual Analog Scale (VAS), a 10 cm linear scale where 0 represents "no itching" and 10 represents "worst possible itching." Participants were asked to mark the intensity of their pruritus on the scale at baseline and after 14 days of treatment. The difference between the two scores was calculated, and an improvement of ≥3 points was considered clinically significant.

For statistical analysis, data were analyzed using SPSS version 26. Continuous variables, such as pruritus score, liver function test values, gestational age, birth weight, and Apgar scores, were expressed as mean ± standard deviation (SD) and compared using an independent t-test. Categorical variables, including mode of delivery, MSAF, NICU admission, and perinatal mortality, were expressed as frequencies and percentages and analyzed using the chi-square test. A

p-value <0.05 was considered statistically significant. Ethical approval was obtained from the institutional review boards of both hospitals, and written informed consent was taken from all participants before inclusion in the study.

Results

A total of 600 pregnant women diagnosed with intrahepatic cholestasis of pregnancy (ICP) were included in the study, with 300 receiving UDCA treatment and 300 in the conservative management group. The mean age of participants was 29.4 ± 4.2 years. Table 1 presents the baseline characteristics of both groups. There was no significant difference in maternal age, gestational age at diagnosis, BMI, and parity, ensuring comparability between the groups.

Table 1: Baseline Characteristics of the Study Population

Parameter	UDCA Group (n=300)	Conservative Group (n=300)	p-value
Maternal age (years)	29.6 ± 4.3	29.2 ± 4.1	0.412
BMI (kg/m²)	27.8 ± 3.5	28.1 ± 3.3	0.502
Gestational age at diagnosis (weeks)	29.1 ± 2.7	28.8 ± 2.5	0.288
Parity (Nulliparous %)	40.3% (121/300)	42.0% (126/300)	0.68
Serum bile acid levels at diagnosis (µmol/L)	32.6 ± 7.4	32.1 ± 7.2	0.621
ALT (U/L) at diagnosis	85.4 ± 12.5	83.9 ± 11.8	0.430
AST (U/L) at diagnosis	79.2 ± 10.9	80.1 ± 11.2	0.518
Initial Serum Bile Acids (µmol/L)	34.8 ± 6.2	35.1 ± 5.9	0.72

Maternal Outcomes

Table 2 presents the comparison of maternal outcomes between the UDCA and conservative management groups. Pruritus relief was reported in **85.3%** of UDCA-treated patients compared to **41.7%** in the conservative group (**p < 0.001**). Serum bile acid levels significantly reduced in the UDCA group (**from 32.6 ± 7.4 to 14.2 ± 5.1 µmol/L**, p < 0.001), whereas no significant change was observed in the conservative group.

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Table 2: Comparison of Maternal Outcomes Between UDCA and Conservative Groups

Parameter	UDCA Group (n=300)	Conservative Group (n=300)	p-value
Pruritus relief (%)	85.3% (256)	41.7% (125)	<0.001
Bile acid levels at delivery (µmol/L)	14.2 ± 5.1	30.8 ± 6.9	<0.001
ALT at delivery (U/L)	46.3 ± 10.2	78.5 ± 14.6	<0.001
AST at delivery (U/L)	40.1 ± 9.8	72.4 ± 13.2	<0.001
Total bilirubin (mg/dL)	0.9 ± 0.3	1.6 ± 0.5	<0.001
Direct bilirubin (mg/dL)	0.4 ± 0.2	0.9 ± 0.3	<0.001
Preterm labor (%)	10.3% (31)	22.7% (68)	0.002
Postpartum hemorrhage (%)	5.7% (17)	11.3% (34)	0.021
ICU admission (%)	2.0% (6)	5.0% (15)	0.045

Fetal Outcomes

Table 3 summarizes the fetal outcomes. The mean gestational age at delivery was significantly higher in the UDCA group (**37.4 ± 1.6 weeks vs. 35.9 ± 2.3 weeks, p < 0.001**). NICU admissions and stillbirth rates were significantly lower in the UDCA group (**p < 0.05**).

Table 3: Comparison of Fetal Outcomes Between UDCA and Conservative Groups

Parameter	UDCA Group (n=300)	Conservative Group (n=300)	p-value
Gestational age (weeks)	37.4 ± 1.6	35.9 ± 2.3	<0.001

Birth weight (kg)	2.9 ± 0.5	2.5 ± 0.6	<0.001
Apgar score (1 min)	7.9 ± 1.1	6.5 ± 1.3	<0.001
Apgar score (5 min)	9.1 ± 0.9	7.8 ± 1.2	<0.001
Meconium-stained amniotic fluid (%)	6.3% (19)	15.7% (47)	0.001
NICU admission (%)	9.0% (27)	20.3% (61)	<0.001
Stillbirth (%)	1.3% (4)	4.7% (14)	0.018

Discussion

Intrahepatic cholestasis of pregnancy (ICP) is a rare condition of liver, characterized by the accumulation of bile acids (BAs) in the blood and liver. This can result in maternal pruritus and increased risks of fetal complications, including preterm birth and stillbirth [12,13]. This condition is typically observed in the second or, sometimes, the third trimester. UDCA has become the standard treatment for ICP [14]. The findings of our study indicate that mothers reported improvements in their symptoms after UDCA administration. They showed improvements in pruritus, and their serum BA levels were also stabilized. Additionally, the medication was associated with positive fetal outcomes. It resulted in decreased rates of NICU admissions, preterm delivery, and fetal distress.

One of the clearest findings of this study was the significant reduction in pruritus severity among women who received UDCA. Pruritus relief was reported in 85.3% of UDCA-treated patients compared to only 41.7% in the conservative management group ($p < 0.001$). This improvement supports previous clinical trials indicating that UDCA reduces pruritus and BA levels in ICP patients [15,16]. Reducing pruritus is very important, as it can enhance the overall quality of life for pregnant women with ICP.

UDCA also led to a marked reduction in serum BA levels, with levels decreasing from 32.6 ± 7.4 to 14.2 ± 5.1 μmol/L ($p < 0.001$), whereas no significant change was observed in the conservative group. Since elevated BA levels are a key pathogenic factor in ICP, their reduction through UDCA treatment is critical in minimizing maternal and fetal risks. Nicholas et al. [17] previously reported similar findings, suggesting that UDCA enhances bile acid excretion and reduces hepatocellular injury.

ALT and AST levels at delivery were significantly lower in the UDCA group compared to the conservative group ($p < 0.001$), indicating improved hepatic function. Elevated transaminase levels are indicative of liver stress in ICP, and their reduction following UDCA administration further supports its hepatoprotective role [18].

Furthermore, UDCA significantly reduced the incidence of preterm labor (10.3% vs. 22.7%, $p = 0.002$) and postpartum hemorrhage (5.7% vs. 11.3%, $p = 0.021$). These findings suggest that UDCA stabilizes hepatic function and mitigates inflammatory responses. As a result, early labor is induced and coagulation abnormalities are also corrected [19]. The decreased need for ICU admission in the UDCA group (2.0% vs. 5.0%, $p = 0.045$) further supports its beneficial effects in reducing severe maternal complications.

The study also found that UDCA treatment of ICP women was linked with improved fetal outcomes, significantly. Gestational age at delivery was higher in the UDCA group (37.4 ± 1.6 weeks vs. 35.9 ± 2.3 weeks, $p < 0.001$), reducing the risk of preterm birth. This finding supports previous reports indicating that UDCA stabilizes bile acid levels and reduces fetal distress [20].

Birth weight was also significantly higher in the UDCA group (2.9 ± 0.5 kg vs. 2.5 ± 0.6 kg, $p < 0.001$). This might be because of improved placental function and reduced fetal exposure to toxic bile acids [21]. The Apgar scores at both 1 and 5 minutes were significantly better in the UDCA group ($p < 0.001$), suggesting improved neonatal health and reduced perinatal distress.

Additionally, UDCA treatment resulted in a lower incidence of meconium-stained amniotic fluid (6.3% vs. 15.7%, $p = 0.001$), NICU admissions (9.0% vs. 20.3%, $p < 0.001$), and stillbirths (1.3% vs. 4.7%, $p = 0.018$). Meconium-stained amniotic fluid is a marker of fetal distress, which is commonly observed in ICP due to increased BA levels. The significant reduction in this parameter further supports the protective effects of UDCA on fetal well-being. Previous studies have also demonstrated similar reductions in NICU

admissions and stillbirths among UDCA-treated ICP patients, emphasizing its role in improving perinatal outcomes [22,23].

A key finding of this study was the association between bile acid normalization and improved outcomes. Among UDCA-treated patients, 46.7% achieved bile acid normalization (<10 μmol/L at delivery), compared to only 10.7% in the conservative group. This suggests that bile acid normalization should be a critical therapeutic goal in ICP management. Studies have shown that persistent elevation of bile acids beyond 40 μmol/L is strongly correlated with increased fetal mortality [24]. Therefore, effective bile acid reduction through UDCA may significantly lower the risk of adverse pregnancy outcomes.

The results of this study reinforce the role of UDCA as the first-line treatment for ICP, emphasizing its efficacy in improving both maternal and fetal outcomes. The ability of UDCA to lower bile acid levels, improve liver function, and reduce perinatal complications highlights its importance in obstetric practice. However, some studies have questioned the universal benefits of UDCA, suggesting that its impact on stillbirth rates and overall neonatal mortality may not be as pronounced [25]. Nevertheless, early detection and management of ICP, as demonstrated in this study, appear to enhance the efficacy of UDCA treatment.

A limitation of this study is that long-term neonatal outcomes were not assessed. Future studies should also investigate the potential combination of UDCA with emerging therapeutics for more comprehensive ICP management.

Conclusion

This study demonstrates that UDCA significantly improves maternal and fetal outcomes in ICP patients by reducing pruritus, bile acid levels, and liver dysfunction while also lowering the incidence of preterm labor, NICU admissions, and stillbirths. The findings highlight bile acid normalization as a crucial therapeutic target in ICP management.

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