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Effect of Ursodeoxycholic Acid Alone Versus Ursodeoxycholic Acid and Rifampicin in Obstetric Cholestasis

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ABSTRACT

Background: Intrahepatic cholestasis of pregnancy (ICP) is a common liver disorder in pregnancy, associated with pruritus, elevated bile acids, and increased risk of adverse perinatal outcomes. While Ursodeoxycholic Acid (UDCA) is the first-line treatment, some patients respond inadequately. This study aimed to compare the effectiveness of UDCA alone versus UDCA combined with Rifampicin in reducing clinical symptoms and improving biochemical markers in women with ICP.

Methods: This quasi-experimental study was conducted at the Department of Obstetrics and Gynecology, Maternal and Child Health Hospital, Unit 1, PIMS Islamabad, from August 1, 2022, to January 31, 2023. A total of 122 pregnant women diagnosed with ICP were enrolled using non-probability consecutive sampling and divided into two groups. Group A received UDCA alone, and Group B received UDCA plus Rifampicin. Inclusion criteria were singleton pregnancy, gestational age 24–36 weeks, serum bile acids >10 µmol/L, and/or raised liver enzymes. Data were analyzed using SPSS version 21, with independent t-tests for continuous variables and chi-square tests for categorical data. A p-value < 0.05 was considered statistically significant.

Results: The combination therapy group showed significantly greater reductions in pruritus ($p = 0.023$), serum bile acids, liver enzymes, and bilirubin levels ($p < 0.0001$) at 2 and 4 weeks compared to UDCA alone.

Conclusion: Rifampicin combined with UDCA is more effective than UDCA monotherapy in improving both clinical and biochemical outcomes in ICP.

Keywords: Intrahepatic Cholestasis of Pregnancy, Ursodeoxycholic Acid, Rifampin, Pruritus, Liver Function Tests.

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INTRODUCTION

Obstetric cholestasis, also known as intrahepatic cholestasis of pregnancy (ICP), is the most common liver disorder occurring during pregnancy. It is particularly prevalent in Pakistani and Indian Asian women and is associated with increased risks of preterm delivery, fetal distress, and stillbirth[1]. The hallmark symptoms include intense pruritus without rash, elevated serum bile acids, and abnormal liver function tests[2]. The most sensitive biochemical marker for diagnosing and monitoring ICP is serum bile acid concentration[3].

Although the exact pathophysiology of ICP is not completely understood, several contributing factors have been identified, including genetic predisposition, hormonal influences, especially from estrogen and progesterone, and environmental triggers[4]. A familial tendency and high recurrence rate in subsequent pregnancies support the genetic component[5]. Progesterone sulfate metabolites are thought to influence the hepatobiliary transport system by acting on hepatic bile acid receptors[6].

Clinically, ICP usually manifests in the late second or third trimester. Apart from pruritus, patients may experience systemic symptoms such as vomiting, fatigue, anorexia, dark urine, and pale stools[7]. Histopathological findings show cholestasis with minimal inflammation, and liver biopsy is rarely required for diagnosis[8]. A serum bile acid level above 10 µmol/L is considered diagnostic[9]. Additionally, serum autotoxin activity has emerged as a specific and reliable marker to distinguish ICP from other pruritic disorders of pregnancy[10].

Management of ICP aims to alleviate maternal symptoms and reduce perinatal risks. Ursodeoxycholic acid (UDCA) is the first-line treatment, initiated at 300 mg twice daily and titrated based on clinical response and serum bile acid levels[11]. UDCA improves bile flow, reduces bile acid concentrations, and relieves pruritus. However, some patients experience suboptimal response or adverse effects such as nausea and diarrhea[12]. For such refractory cases, rifampicin has been used as an adjunct to UDCA. Although primarily a second-line agent, rifampicin has demonstrated effectiveness in reducing pruritus and bile acids in cholestasis unrelated to pregnancy, and in combination therapy for severe ICP[13].

Despite the increasing use of UDCA and rifampicin together, limited studies directly compare their efficacy in ICP management. Weekly biophysical profiles (BPP) are standard prenatal surveillance tools in affected pregnancies, though no antepartum test has been shown to predict stillbirth effectively[14]. Adjunctive treatments like cholestyramine, S-adenosyl-L-methionine, and antihistamines have been explored but lack consistent efficacy[15].

Despite the widespread use of Ursodeoxycholic acid (UDCA) as the first-line therapy for intrahepatic cholestasis of pregnancy (ICP), some patients show inadequate clinical or biochemical response. In such cases, adjunctive therapy with rifampicin has shown promise, but robust comparative data remain limited. Therefore, it is important to evaluate whether combining rifampicin with UDCA offers superior benefits compared to UDCA alone in the treatment of obstetric cholestasis. The objective of this study is to compare the effectiveness of UDCA alone versus UDCA combined with rifampicin in improving maternal symptoms and biochemical markers in patients with ICP.

METHODS

This quasi-experimental, interventional study was conducted at the Department of Obstetrics and Gynecology, Maternal and Child Health Hospital, Unit 1, Pakistan Institute of Medical Sciences (PIMS), Islamabad. The study was carried out over six months, from 1st August 2022 to 31st January 2023, following ethical approval from the Ethical Review Committee of Shaheed Zulfiqar Ali Bhutto Medical University (SZABMU), Islamabad (Approval No. 1-1/2015/ERB/SZABMU/1006, dated 20-07-2022).

The study targeted pregnant women admitted to PIMS with a confirmed diagnosis of intrahepatic cholestasis of pregnancy (ICP). ICP was diagnosed based on clinical symptoms, primarily pruritus without rash, along with elevated serum bile acid levels (>10 µmol/L) and/or abnormal liver function tests such as elevated ALT and AST. A total of 122 participants were included in the study. The sample size was calculated using OpenEpi, assuming a 20% clinically meaningful difference in treatment efficacy between the groups, with a 95% confidence level and 80% power. This assumption was informed by trials like the TURRIFIC study on ICP treatments[16].

A non-probability consecutive sampling technique was employed to enroll eligible participants. Group allocation was done using a quasi-random assignment method, wherein patients were alternately assigned to one of two treatment groups based on the order of their admission. Group A included 61 patients who received Ursodeoxycholic Acid (UDCA) alone, initiated at a dose of 300 mg twice daily, and adjusted up to three times daily depending on clinical response. Group B also included 61 patients and received a combination of UDCA (same dosage as Group A) with Rifampicin, starting at 150 mg once daily and increased to 150 mg twice daily if required. Both treatments were continued until delivery. Baseline investigations

included liver function tests (ALT, AST, ALP, and total bilirubin), serum bile acids, and assessment of pruritus severity using a visual analog scale (VAS). Follow-up assessments of these parameters were carried out two weeks after treatment initiation to evaluate therapeutic response.

Patients were monitored closely for symptom improvement, particularly reduction in pruritus, and for changes in biochemical markers such as serum bile acids and liver enzymes. Medication adherence and any adverse effects were documented. Exclusion criteria included women with pre-existing liver conditions such as hepatitis B or C, autoimmune hepatitis, gallstones, or acute fatty liver of pregnancy. Other exclusion criteria were multiple gestations, chronic co-morbidities (such as diabetes mellitus, hypertension, renal or thyroid disorders), known allergies to UDCA or Rifampicin, and unwillingness to participate.

All data were collected using a structured proforma and entered into SPSS version 21.0 for statistical analysis. Continuous variables, such as age, liver enzyme levels, and serum bile acids, were reported as mean ± standard deviation (SD), while categorical variables, such as parity and response to treatment, were presented as frequencies and percentages. Independent sample t-tests were used to compare the mean values of continuous variables between the two groups. Chi-square tests were employed for categorical outcomes. A p-value of less than 0.05 was considered statistically significant.

All participants provided written informed consent before enrollment. Confidentiality and anonymity were maintained throughout the study, and patients were assured that participation was voluntary and would not affect their care. No financial incentives were offered, and the study adhered to all institutional ethical guidelines.

RESULTS

Table 1: Baseline Demographic and Clinical Characteristics

Variable	Group A (UDCA)	Group B (UDCA + Rifampicin)	p-value
Age (years)	28.18 ± 4.76	27.26 ± 4.67	0.285
Gestational age (weeks)	37.20 ± 1.85	36.98 ± 2.05	0.547
Primigravida	29 (47.5%)	30 (49.2%)	0.856
Multigravida	32 (52.5%)	31 (50.8%)	

A total of 122 pregnant women diagnosed with intrahepatic cholestasis were included in the study, with 61 participants each in Group A (UDCA only) and Group B (UDCA + Rifampicin). Baseline demographic and clinical variables, including age, gestational age, and parity, were statistically comparable between the two groups (**Table 1**).

Table 2: Comparison of Pruritus After 2 and 4 Weeks

Time Point	Group A (UDCA)	Group B (UDCA + Rifampicin)	p-value
After 2 weeks			0.031
Yes	19 (31.1%)	9 (14.8%)	
No	42 (68.9%)	52 (85.2%)	
After 4 weeks			0.023
Yes	11 (18.0%)	3 (4.9%)	
No	50 (82.0%)	58 (95.1%)	

Pruritus improved more significantly in the combination therapy group. After 2 weeks, only 14.8% of patients in Group B had persistent pruritus compared to 31.1% in Group A (p = 0.031). This difference further widened at 4 weeks, with 4.9% of Group B still symptomatic versus 18.0% in Group A (p = 0.023) (**Table 2**).

Table 3: Comparison of Biochemical Parameters at Baseline, 2 Weeks, and 4 Weeks

Parameter (units)	Time Point	Group A (UDCA)	Group B (UDCA + Rifampicin)	p-value
Serum Bile Acids (µmol/L)	**Baseline**	42.25 ± 9.61	44.13 ± 9.79	0.285
	After 2 weeks	29.52 ± 9.40	23.43 ± 9.39	0.0001
	After 4 weeks	25.54 ± 9.20	16.41 ± 8.20	0.0001

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AST (IU/L)	**Baseline**	69.69 ± 12.09	68.08 ± 11.81	0.459
	After 2 weeks	54.00 ± 11.75	42.46 ± 11.39	0.0001
	After 4 weeks	44.36 ± 11.88	26.08 ± 11.83	0.0001
ALT (IU/L)	**Baseline**	69.51 ± 8.68	69.90 ± 8.19	0.797
	After 2 weeks	53.20 ± 8.61	43.70 ± 8.06	0.0001
	After 4 weeks	44.31 ± 8.79	27.65 ± 8.18	0.0001
Total Bilirubin (mg/dL)	**Baseline**	0.99 ± 0.15	1.00 ± 0.16	0.609
	After 2 weeks	0.78 ± 0.16	0.56 ± 0.16	0.0001
	After 4 weeks	0.64 ± 0.15	0.25 ± 0.16	0.0001

Biochemical parameters, including serum bile acids, AST, ALT, and total bilirubin, were significantly lower in the combination therapy group at both 2 and 4 weeks of treatment. No significant differences were observed at baseline for any parameter (**Table 3**).

DISCUSSION

Intrahepatic cholestasis of pregnancy (ICP) remains a notable complication during gestation due to its association with maternal discomfort and adverse fetal outcomes. In this quasi-experimental study, combination therapy using Ursodeoxycholic Acid (UDCA) and Rifampicin was found to be significantly more effective than UDCA alone in reducing pruritus and improving biochemical parameters, including serum bile acids, ALT, AST, and total bilirubin. The reduction in pruritus was markedly more significant in the group receiving combined therapy, especially after four weeks, where only 4.9% of patients in the combination group reported persistent symptoms compared to 18.0% in the monotherapy group ($p = 0.023$). These findings are consistent with previous studies that have demonstrated enhanced symptomatic relief when rifampicin is added to UDCA in women with severe or refractory ICP[17,18].

Serum bile acid levels, which are considered the most sensitive biomarker for diagnosis and monitoring of ICP, showed significantly greater reduction in the combination group. This aligns with studies reporting that rifampicin, through its effect on hepatic bile acid transporters and nuclear receptors like PXR, improves bile acid metabolism and excretion[19,20]. The rapid decline in bile acid levels is clinically important as elevated bile acids have been directly associated with increased risks of fetal complications, including stillbirth and preterm delivery[21]. Improvement in liver function tests was also more pronounced in the combination group. AST and ALT levels, which were initially comparable, decreased significantly in the rifampicin group by the second and fourth weeks of therapy. Similar trends have been observed in other studies, particularly in patients with severe hepatic dysfunction where UDCA monotherapy was insufficient[22,23].

Total bilirubin levels also declined significantly in the combination group compared to UDCA alone. This observation supports earlier findings that demonstrated improved cholestasis resolution with adjunct rifampicin therapy[22]. While our study focused primarily on maternal biochemical and symptomatic outcomes, previous literature has linked reductions in bile acid and liver enzyme levels with improved perinatal outcomes, including lower risks of respiratory distress syndrome and neonatal intensive care unit admission[23]. Although perinatal endpoints were not measured in our study, the favorable biochemical profile observed suggests potential fetal benefits. Overall, the findings of this study reinforce the utility of combining rifampicin with UDCA in patients with moderate to severe ICP or those unresponsive to standard therapy. However, despite its apparent effectiveness, rifampicin should be used cautiously and under strict clinical supervision due to limited safety data in pregnancy, particularly during early gestation.

The findings of this study suggest that combining Rifampicin with Ursodeoxycholic Acid (UDCA) offers superior clinical and biochemical outcomes in patients with intrahepatic cholestasis of pregnancy (ICP), particularly in those who do not respond adequately to UDCA alone. The combination therapy led to faster and more significant reductions in pruritus and bile acid levels, which may lower the risk of adverse fetal outcomes. These results support the integration of rifampicin as a second-line agent in treatment protocols for moderate to severe ICP, under careful clinical monitoring. This study has several limitations. Being a quasi-experimental design, it lacked randomization and blinding, which may introduce selection bias. The sample size, although adequate for detecting differences in primary outcomes, limits the generalizability of findings. Additionally, fetal and neonatal outcomes such as preterm birth, meconium-stained liquor, or NICU admission were not assessed. Long-term safety data for rifampicin use in pregnancy also remain limited. Further randomized controlled trials with larger populations and inclusion of obstetric outcomes are recommended.

CONCLUSION

This study demonstrates that the combination of Ursodeoxycholic Acid and Rifampicin is significantly more effective than UDCA alone in improving clinical symptoms and biochemical parameters in patients with intrahepatic cholestasis of pregnancy. The addition of Rifampicin resulted in faster and greater reductions in pruritus, serum bile acids, liver enzymes, and bilirubin levels. These findings support the use of combination therapy as a valuable option, particularly in moderate to severe cases or in patients who show inadequate response to UDCA alone. However, given the limited data on fetal outcomes and long-term safety of Rifampicin in pregnancy, further large-scale randomized trials are warranted to confirm its efficacy and safety profile.

LIST OF ABBREVIATIONS

ICP: Intrahepatic Cholestasis of Pregnancy
UDCA: Ursodeoxycholic Acid
PXR: Pregnane X Receptor
ALT: Alanine Aminotransferase
AST: Aspartate Aminotransferase
NICU: Neonatal Intensive Care Unit
SD: Standard Deviation

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CONFLICT OF INTEREST

None

ETHICAL APPROVAL

This study was approved by the Ethical Review Committee of Shaheed Zulfiqar Ali Bhutto Medical University (SZABMU), Islamabad, under approval number 1-1/2015/ERB/SZABMU/1006, dated 20-07-2022.

AUTHORS' CONTRIBUTION

All authors equally contributed as per ICMJE Policy.

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