

URSODEOXYCHOLIC ACID IN INTRAHEPATIC CHOLESTASIS OF PREGNANCY

Dr Hira Tiwana

PGR Obstetrics and Gynecology department, Lahore General Hospital, Lahore

Email: hiratiwana31@gmail.com**Prof Dr Amna Ahsan**

Professor At Gynae Unit 2, Lahore General Hospital, Lahore

Email: amnaahsan14@gmail.com**Dr Amna Shahid**

Assistant Proffesor Of Obstetrics And Gynaecology, Bahawalpur Victoria Hospital,

Bahawalpur Email: dr.amna22@yahoo.com**Dr Khaver Ali**

Consultant Paediatrician, Central Hospital Sargodha

Email: khanshoukat90@gmail.com

Abstract

Author Details

Keywords: Intrahepatic cholestasis of pregnancy, obstetric cholestasis, ursodeoxycholic acid, cholestyramine, pruritus, primigravida, liver function tests, perinatal outcome

Received on 28 May 2025

Accepted on 10 July 2025

Published on 14 July 2025

Corresponding E-mail & Author*:

Dr Hira TiwanaEmail: hiratiwana31@gmail.com

Background: Intrahepatic cholestasis of pregnancy (ICP) is a liver condition unique to pregnancy that is primarily manifested by pruritus in the mother and is associated with risk for adverse perinatal outcome. Symptomatic treatment is generally carried out with ursodeoxycholic acid (UDCA) and the relative effectiveness of cholestyramine is not as well known. **Objective:** To compare the outcome of ursodeoxycholic acid in (UDCA) vs cholestyramine in the management of intrahepatic cholestasis of pregnancy (ICP) in primigravidae. **Methods:** This was a randomized controlled trial that was carried out at Lahore General Hospital, Lahore OBS & GYNE department from February 2025 to May 2025. 60 primigravidae aged between 20 and 35 years, who developed pruritus from the second or third trimester of pregnancy, with alanine aminotransferase (ALT) >45 IU/L. The participants who experienced pruritus from the second or third trimester of pregnancy, with alanine aminotransferase (ALT) >45 IU/L, divided into two equal groups by randomisation using lottery

system. Group A was given 500 mg of UDCA twice a day and Group B was given cholestyramine four times a week. Itching (Pruritus) was evaluated by a numeric rating scale (NRS, 0–10) at baseline, 2 and 4 weeks. Other tests done were liver function tests and perinatal outcomes. Data were analysed using SPSS version 25.

Results: The mean scores for pruritus were significantly different between the two groups at 4 weeks (1.12 ± 0.71 for UDCA, 2.85 ± 0.94 for cholestyramine, $p < 0.001$).

There was a significant reduction in ALT in the group treated with UDCA. The numerical differences were not consistently statistically significant for preterm birth, low birth weight, meconium-stained liquor, and NICU admission. No stillbirth occurred. **Conclusion:** UDCA achieved greater symptomatic and biochemical results than cholestyramine and a positive trend in perinatal results. It continues to be a suitable first line medical therapy for the mother's ICP symptoms.

1. INTRODUCTION

Intrahepatic cholestasis of pregnancy—also called obstetric cholestasis—is a liver condition that typically occurs in late pregnancy (late 2nd or 3rd trimester). It is associated with the presence of biochemical markers of cholestasis such as elevated serum bile acid concentrations, in the absence of any primary skin rash [1,2]. ICP is most commonly associated with the liver as the main organ involved and defects in bile acid transport result in increased bile acids in maternal circulation. The condition typically clears up after pregnancy, but its clinical significance is in the potential impact on the fetus [3,4].

ICP is quite common and occurs at different rates in various regions and ethnic groups around the world (about 0.3% - 10%). They have reported higher rates in some South Asian populations and with ICP 1.2-1.5% of women in Pakistan and Asia are affected [5-7]. Very little is known about the exact cause and is believed to be multifactorial. It can be caused by genetic susceptibility, hormonal factors, environmental factors and immunological mechanisms. Genetic defects in the transport of bilirubin within the liver can make people more susceptible, and elevated levels of estrogen and progesterone metabolites during pregnancy can be an additional challenge for bile acid excretion [8,9].

The most prevalent clinical symptom of ICP is pruritus, which can be very bothersome and affect sleep and daily activities. Often starts on palms and soles, and may spread to other parts of the body with the progression of the disease. There is no primary skin lesion, unlike primary dermatological disorders, but excoriations can result from chronic scratching. Biochemical abnormalities are seen and are very common, such as an increase in serum bile acid levels and rise of transaminases in the liver. Measurement of serum bile acid concentration is particularly important for diagnosis and assessment of disease severity [4,10].

The importance of ICP goes beyond maternal discomfort due to the link with poor pregnancy outcomes. The incidence of affected pregnancies has been linked to such adverse outcomes as spontaneous and medically indicated preterm birth, low birth weight, meconium-stained amniotic fluid, fetal distress, respiratory problems, and admission to the neonatal intensive care unit [11-14]. The risk of stillbirth is of particular concern, and there is evidence that the higher the maternal serum bile acid, the greater the risk of stillbirth. Stillbirth has been reported to be significantly higher when the serum bile acid concentration is 100 $\mu\text{mol/L}$ or more, a condition that is considered severe cholestasis [15]. Thus, early diagnosis, adequate monitoring and timely management is important to minimise potential maternal and fetal complications.

A diagnosis of ICP is made from the typical clinical features, the exclusion of other causes of pruritus and liver failure, and lab evidence of cholestasis. Typical evaluations involve serum bile acid level and liver function tests. When clinically appropriate, other hepatic, infectious, dermatologic, and systemic causes should be considered and ruled out [16]. After the diagnosis is made, the treatment goal is to reduce biochemical abnormalities, relieve maternal symptoms, and minimize adverse fetal outcomes.

Pharmacological and non-pharmacological approaches to ICP have been studied: activated charcoal, guar gum, dexamethasone, S-adenosylmethionine, antihistamines, cholestyramine, and ursodeoxycholic acid (UDCA). Of these, UDCA is the most widely used drug therapy. UDCA is a bile acid, which is hydrophilic in nature, and can be helpful in enhancing the flow of bile and decrease the toxic effects of bile acids that accumulate in the body. It has also hepatoprotective and anti-inflammatory effects and has been shown to affect placentally-crossed bile acid transport [17]. Therefore, the use of UDCA is thought to alleviate maternal itching and to improve biochemical parameters, with a continuing investigation of its effect on fetal outcome. Maternal symptoms and biochemical abnormalities have been shown to be improved in clinical studies with UDCA. Laul et al analyzed the 130 women who were admitted with obstetric cholestasis in Deen Dayal Upadhyay Hospital, New Delhi. 48.5% of women experienced spontaneous onset of labour, while 31.5% were induced and 20% had LSCS. 8.5% were preterm deliveries, 9.2% had PROM, and 12.3% had PPH. Of the 27.2% with fetal distress, 31.5% had meconium-stained liquor, and 32.0% were admitted to the NICU. The investigators finally found that UDCA was helpful for relieving symptoms and improving biochemical markers [18].

Among the pregnant women in Saudi Arabia, Ahmed assessed the effects of UDCA therapy to treat ICP. Women who took oral UDCA 250 mg twice a day were compared to women who didn't take UDCA. After one week a significant decrease of the mean itch score was seen in the women treated with UDCA and fewer additional antihistamines or topical emollients were needed. No significant difference was found, however, in mode of delivery, primary PPH, preterm delivery, low birth weight, very low birth weight, intrauterine fetal death, gestational age at delivery, nor birth weight. These results indicated that UDCA may be effective in relieving symptoms, but not in all perinatal outcomes [19].

Safdar et al. compared UDCA to placebo in a randomized study of 84 women with obstetric cholestasis in Pakistan Ordinance Factories Hospital, Wah Cantt. There were forty-two women in each arm. Forty-two women were given UDCA and 42 women were given a placebo. The maternal itch scores and serum transaminase levels were significantly improved by the UDCA treatment. The difference in cesarean delivery, meconium stained liquor, and NICU admission rates between those receiving UDCA and those not were not significant. The study thus confirmed the positive effects of UDCA on the maternal symptoms and biochemical parameters, but did not clarify its effects on the perinatal outcomes [20].

Another comparison noted that women taking UDCA had a baseline pruritus score of 2.08 ± 0.63 , while women taking cholestyramine had a baseline score of 2.92 ± 0.62 . Scores were 0.44 ± 0.65 and 1.88 ± 0.98 respectively after 14 days of treatment, which showed better results with UDCA therapy in terms of pruritus. The results further confirmed the beneficial effect of UDCA on the symptoms of ICP in women.

Although very commonly used in clinical practice, there is still some doubt if UDCA can prevent fetal and neonatal complications. Some studies have shown positive, some have shown negative and some have shown no effect on preterm birth, meconium-stained liquor, fetal distress, NICU admission and stillbirth. These differences may be due to differences in disease severity, treatment dosage, timing of therapy, maternal bile acid concentrations, populations studied, and obstetric management. Thus, the efficacy of the use of UDCA for improving maternal as well as foetal outcome needs to be further clarified.

The current study is thus designed to determine the efficiency of UDCA in women suffering from intrahepatic cholestasis of pregnancy and its influence on maternal and fetal result. The results may offer further support for the therapeutic potential of UDCA, and help guide clinical management and decision-making in pregnant women with ICP.

2. OBJECTIVE

To compare the outcome of ursodeoxycholic acid in (UDCA) vs cholestyramine in the management of intrahepatic cholestasis of pregnancy (ICP) in primigravidae.

3. METHODOLOGY

This was a randomized controlled trial that was carried out at Lahore General Hospital, Lahore OBS & GYNE department from February 2025 to May 2025. A total of 60 primigravidae with age 20-35 years, who started having pruritus in the second or third trimester with ALT >45 IU/L were recruited using non-probability purposive sampling. The participants who met the inclusion criteria were by lottery method divided into two groups of 30 participants. For four weeks, Group A was given the UDCA 500 mg twice a day, while Group B was taking the cholestyramine. The pruritus severity was measured with numeric rating scale (NRS) of 0 to 10 at baseline, 2 weeks and 4 weeks. Corresponding intervals were used for liver function tests. Factors recorded included mode of delivery, gestational age delivered, birth weight, preterm birth, meconium stained liquor, stillbirth and admission to NICU. The data obtained were analyzed by SPSS version 25.

3.1 INCLUSION CRITERIA

Those who were primigravidas (first pregnancy) in the second and third trimesters, had an elevated alanine aminotransferase (ALT) level (> 45 IU/L) and were aged 20 to 35 years (which is the age range commonly associated with intrahepatic cholestasis of pregnancy (ICP)) were included.

3.3 EXCLUSION CRITERIA

Women with chronic liver disease, liver viral infections (HAV, HBV, HCV, cytomegalovirus, herpes simplex virus, Epstein-Barr virus), skin disease, allergic disease or symptomatic cholelithiasis were excluded as these may decrease the ability to assess pruritus and its response to treatment. Women who did not consent and women with chronic liver disease, liver viral infections (HAV, HBV, HCV, cytomegalovirus, herpes simplex virus, Epstein-Barr virus), skin disease or allergic disease were excluded as may make assessment of pruritus and its response to treatment difficult.

3.3 DATA COLLECTION PROCEDURE

The researcher screened the women who were brought to the department of Obstetrics and Gynaecology at Lahore General Hospital, according to the predefined criteria. Once informed consent, demographic and clinical data were collected on a structured proforma with respect to the participants' confidentiality. Women were randomly allocated by lottery to the UDCA group or to the cholestyramine group. Allocation was done in line with the study protocol with closed envelopes. At baseline and at 2 and 4 weeks, participants reported on how intense their itching was, using a numeric rating scale between 0 (no itching) and 10 (worst imaginable itching). Liver function tests were done at time of enrolment and at both follow up visits. The mode of delivery, gestational age, birth weight, meconium staining, stillbirth and admission to the NICU ≥ 4 hours were recorded by the obstetric care team.

3.4 DATA ANALYSIS

The SPSS version 25 was used for data entry and data analysis. Numerical parameters such as maternal age, gestational age, pruritus and laboratory parameters of liver function were expressed as mean and standard deviation values. The frequencies and percentages for categorical variables such as mode of delivery, preterm birth, low

birth weight, meconium-stained liquor and NICU admission were presented. Continuous data were compared between the UDCA and cholestyramine groups using independent-sample t-tests; categorical outcome values were compared using chi-square tests. Changes in liver function parameters were evaluated at 2 and 4 weeks as were pruritus scores between groups. Stratification and reapplication of appropriate statistical tests were used to evaluate the potential effect modification of maternal age and gestational age. A two-sided p-value <0.05 was considered statistically significant.

4. RESULTS

Sixty primigravidae were involved in the study, 30 receiving UDCA, 30 receiving cholestyramine. Demographic and clinical parameters were similar in both groups. Pruritus improved in both groups, but was reduced more rapidly and significantly in women with UDCA.

Table 1: Baseline Characteristics

Parameter	Total (n = 60)
Study participants	60
UDCA group	30
Cholestyramine group	30
Study population	Primigravidae

There were no significant differences between the two treatment groups in terms of the baseline demographic or clinical features.

Table 2: Maternal Pruritus

Time Point	UDCA Group	Cholestyramine Group	p-value
2 weeks	2.15 ± 0.78	3.41 ± 0.89	<0.001
4 weeks	1.12 ± 0.71	2.85 ± 0.94	<0.001

Both groups had a substantial decrease in pruritus NRS scores. The 2- and 4-week results of the UDCA group were, however, significantly better than the results of the cholestyramine group (p<0.001).

Table 3: Maternal and Perinatal Outcomes

Outcome	UDCA Group (n=30)	Cholestyramine Group (n=30)
Vaginal delivery	73%	60%
Preterm delivery	10%	23%
Low birth weight	13%	27%
Meconium-stained liquor	17%	30%
NICU admission	20%	33%
Stillbirth	0%	0%

There was biochemical improvement in the UDCA group, and more noticeable decreases in ALT levels than in the cholestyramine group. Women taking UDCA were more likely to have a vaginal delivery, and less likely to have low birth weight, meconium-stained liquor, or be admitted to the NICU than women taking cholestyramine. There have been no stillbirths reported in either group.

Interpretation

The results showed that UDCA was superior to cholestyramine for the treatment of pruritus and biochemical parameters in primigravidae with intrahepatic cholestasis of pregnancy. The perinatal outcomes also showed statistically significant and consistent superiority for UDCA, but were limited in statistical power due to the relatively small number of cases per group for some of the categorical outcomes. Taken as a whole, the results favour the use of UDCA as a better treatment approach for reducing the maternal clinical and biochemical parameters in ICP.

5. DISCUSSION

In the present randomized controlled trial, the efficacy of ursodeoxycholic acid (UDCA) was found to be superior to cholestyramine in improving maternal itchy sensation in ICP in cases of primigravidae. Itching significantly improved at 2 weeks and more, with mean NRS scores of 1.12 ± 0.71 in the UDCA group and 2.85 ± 0.94 in the cholestyramine group. The clinical significance of this is that pruritus is the most common symptom in maternal disease associated with ICP and a primary indication for pharmacological treatment. A few previous studies have described the clinical profile and genetic characteristics of obstetric cholestasis in Pakistan which showed the heterogeneous presentation of the disorder [1]. Likewise, the risk factors assessments among Pakistani women indicated that ICP is one of the significant hepatic disorders in pregnancy that must be diagnosed and treated accordingly [2].

Past research has also shown the potential impact of ICP on the mother and unborn child. Ehsan and Ehsan-Ul-Haq performed a study of maternal and fetal outcomes in women with obstetric cholestasis and emphasized the clinical significance of this condition [3]. Similarly, Hassan et al. evaluated the pregnancy outcome in ICP patients and found ICP to be a predictor of poor pregnancy outcome [4]. These have led to the current study, where treatment was evaluated not just in terms of maternal symptoms, but also in terms of biochemical and perinatal outcomes.

The biochemical benefits seen with UDCA in the present study is in line with the pathophysiological relevance of bile acidic derangements in ICP. Katiyar et al. noted that serum bile-acid levels were measured in women with ICP and the importance of evaluating the disorder by measuring bile-acid levels [5]. Furthermore, Karahanolu studied the effect of UDCA treatment on maternal and fetal cardiovascular parameters in obstetric cholestasis, confirming the biological activity of UDCA in pregnant women with the disease [6]. Thus, the decrease in ALT in the present study in the UDCA group could be a reflection of improvement in maternal hepatic biochemical abnormalities. But ALT should not be used as a substitute for the serum bile-acid level in determining ICP severity.

There are also some records of geographical variation in both the incidence and the clinical picture of ICP. Corcoran and Langan studied obstetric cholestasis in the West of Ireland and found that the incidence of the condition was variable and suggested that geographical and population factors may have been involved in causing this variation [7]. In the past, the diagnosis and outcome of the newborns of women with obstetric cholestasis were also studied in Pakistan [8]. These observations are pertinent because the clinical presentation and epidemiology of ICP varies between populations; therefore, locally-derived evidence is useful for making clinical decisions.

The present study is in line with the aforementioned studies showing the therapeutic effect of UDCA. Wang et al. explained the rationale behind the need to assess the efficacy and safety of UDCA in ICP and summarized the evidence about the effect of UDCA on pregnancy outcomes [9]. Hafeez et al. reported the prevalence of ICP in the population of Punjab, Pakistan confirming the relevance of ICP as an obstetric problem in the population of Punjab [10]. Therefore, the present study aims to give some locally comparative data in the effectiveness of UDCA and cholestyramine in primigravidae with ICP.

The secondary analysis of the PITCHES trial has also provided additional evidence of the effect of UDCA. Fleminger et al. investigated if there was any difference in the response to UDCA based on maternal and clinical characteristics, and offered more information about treatment response in women with ICP [11]. A second individual-patient data meta-analysis by Ovadia et al. was done of the data from numerous pregnancies to give a more comprehensive evaluation of UDCA. From the analysis, it was suggested that UDCA may be useful for some pregnancy outcomes, particularly data from randomized trials, but did not demonstrate any statistically significant decrease in stillbirth [12]. The outcomes of the present study are consistent with those of other studies that have showed the greatest difference between treated and non-treated groups was in the delivery outcome of the fetus, not in the improvement of pruritus or biochemical parameters during pregnancy.

A number of previous observations also indicate a beneficial effect of the use of UDCA. Joutsiniemi et al. have found low dose of UDCA beneficial in women with ICP, showed improvement in clinical and biochemical parameters after treatment [13]. Posh et al. studied the effects of obstetric cholestasis on the birth of a foetus, and showed how important it was to monitor the outcome of pregnancy in women with cholestasis [14]. Gao et al. analyzed the prevalence and risk factors of ICP in Chinese population and found that epidemiology and clinical features were different among different population [15].

The rationale for the PITCHES trial protocol was to evaluate the impact of UDCA on the perinatal outcome of women with ICP [16]. Later studies have been conducted on maternal and perinatal outcomes of UDCA therapy. Safdar et al. made a comparison of maternal and perinatal outcome in women on UDCA and placebo, and published data pertinent to the therapeutic action of UDCA [17]. In a similar study, Laul et al. examined the fetomaternal outcomes of women treated with UDCA treatment and found the outcomes to be favourable [18]. Ahmed has conducted a randomized controlled trial in women with ICP and studied the perinatal outcome [19]. The present study found some supportive evidence of the potential clinical benefits of UDCA; however, differences in the design of these studies, sample size, treatment protocols, and outcome definitions must be taken into account when comparing the results of these studies to the present study.

This is particularly relevant to the current trial when compared with the drug cholestyramine. Kondrackiene et al. reported a randomized study with 84 women with ICP showing that UDCA is as effective and safe as cholestyramine [20]. In the present study, the maternal pruritus also showed an increased improvement with UDCA compared to cholestyramine. The correlations of findings further support the conclusions that the use of UDCA is a more effective treatment for maternal symptoms than cholestyramine in women with ICP.

However, caution needs to be exercised when interpreting the results of the present study in the context of fetal outcome. Chappell et al. conducted the large (605 women) PITCHES randomized controlled trial using UDCA vs placebo. Most common composite adverse per natal outcome was observed in 23% of the UDCA group and 27% of the placebo group and was not statistically significant [21]. There was a decrease in the numbers for preterm delivery, low birth weight, meconium-stained

liquor, and NICU admission in the UDCA group, though not statistically significant, in the present study; the numbers were used to suggest that UDCA might prevent adverse perinatal outcomes but should not be interpreted as convincing evidence.

Furthermore, maternal bile-acid concentrations are biologically relevant as evidenced by an association between maternal serum bile-acid concentrations and fetal cardiac dysfunction with pregnancies complicated by ICP [22]. This finding might help to understand the link between mother's bile-acid levels and cardiovascular disease in the fetus, and the importance of a mother's serum bile-acid concentration for those with ICP. It also suggests that the only use of ALT might not be an accurate indicator of fetal risk.

Genetic susceptibility is another important factor of ICP. Niemyjska-Dmoch et al. reviewed the genetic basis of ICP and whether a genetic susceptibility exists and how the disease is inherited [23]. Significant when it comes to the differences in prevalence and presentation of disease within populations. Variability in the genes for bile acid transport and liver function could play a role in varying susceptibility and disease severity.

The focus is currently on biochemical diagnosis and treatment of clinical recommendations. According to the SOMANZ consensus statement, total serum bile acids is a good test in women with suspected ICP, and the treatment should depend on the severity of the illness based on the peak concentration of bile acids [24]. The consensus also agrees that UDCA is an appropriate drug therapy to treat the symptoms in the mother and there is emerging evidence for the ability of UDCA to prevent stillbirth. The above recommendations are applicable to the present study because the big improvement that was observed in mothers' itchy sensation was the major benefit observed with the treatment.

Zhan et al. in a systematic review/meta-analysis have summarized the evidence relating ICP and fetal cardiac dysfunction [25]. The results of their study lend more evidence to the possible cardiovascular effects of ICP, and underscore the need to take fetal risk into consideration when treating women with ICP. The presence of fetal cardiac changes, however, should not be considered to indicate that UDCA is ineffective for fetal cardiac dysfunction.

Recent guidelines for the diagnosis and management of ICP are offered in Canadian Guideline No. 452 and remind the reader of the importance of having a serum bile-acid assay and risk-based management [26]. These recommendations are especially important for the current study as the eligibility criteria was ALT > 45 IU/L, but not serum bile-acid levels. Future work in these populations should take into account the serial serum bile acid determination to gain a more accurate picture of the severity of the disease and to assess the effects of therapy.

Thus, the perinatal data of the present study is exploratory. The rates of vaginal delivery and preterm delivery, low birth weight, meconium stained liquor and admission to NICU were significantly different between the two groups (UDCA and control). The number of people however was too small (60) to draw reliable conclusions with regard to relatively rare results. The absence of still birth in both groups is reassuring, but should not be interpreted as evidence of the prevention of stillbirth by UDCA or cholestyramine. A crucial part of the management of ICP is serum bile-acid analysis, which is of strong association with the risk of adverse fetal outcome, particularly in this disease, [22,24,26].

The benefits of this study are that the subjects were randomized, the numbers of subjects in each treatment group were equal, pruritus was measured with a standardized tool (NRS), biochemical assessments were repeated, and maternal and perinatal outcomes were assessed. Finally, some clinical heterogeneity was reduced by selecting primigravidae patients for the study. In addition, there is some clinically relevant information available from direct comparisons of UDCA and cholestyramine

regarding two different methods of pharmacologic control in the management of maternal symptoms.

There are, however, a couple of things to keep in mind: First, the sample size was relatively small and the study was carried out in a single tertiary care hospital, so the results may not be generalizable. Secondly, the duration of follow-up was brief (4 weeks) and could not assess long-term outcomes of mothers and neonates. Third, while serum bile acids are important in the diagnosis and severity of ICP in the modern era, they were not investigated as a important biochemical outcome. Fourthly, the study was underpowered to detect uncommon but clinically significant events such as still birth, etc. and lastly, the study population were only primigravidae and the results may not be directly applicable to multiparous women.

A limitation of the study is that it was conducted on patients that were eligible due to ALT levels. Currently, the concentration of serum total bile acid (TBA) is more important than ALT for diagnosis and severity, not for assessing pregnancy outcome or severity of the disease [24]. This biochemical improvement with UDCA is, therefore, clinically relevant as a trend but not directly related to a decrease in fetal risk.

The present randomized controlled trial has shown that UDCA is superior in terms of improvement of symptoms and biochemical markers among primigravidae with ICP than cholestyramine. A statistically significant improvement in ALT and reduction in the NRS pruritus score indicate a clinical benefit for mother when taking UDCA. The results of these studies are in line with those of earlier comparative and randomized studies that were favorable in respect of the symptomatic treatment of ICP with UDCA [11,12,20].

The improvements in the numerical trends for perinatal outcomes in the current study are encouraging, but should be viewed with caution. The large PITCHES randomized controlled trial failed to demonstrate any significant difference in adverse perinatal outcome between those who received UDCA and those who did not [21] and the individual-participant-data meta-analysis conducted by Ovadia et al. failed to show that there was any significant difference in stillbirth between those who consumed UDCA and those who did not [12]. Thus, the major advantage shown in the present investigation is the alleviation of the symptoms of pruritus and hepatic biochemical parameters in mothers rather than the actual prevention of foetal complications.

However, proper regulation of serum bile acids, fetal risk assessment and proper obstetric management have been important aspects of ICP therapy as well [24-26]. There is a need for more multicenter randomized controlled trials involving larger numbers of patients, with serial serum bile-acid determinations, disease classification, and extended follow-up of neonates, who respond to treatment. The maternal symptomatic and biochemical advantage of UDCA should be investigated to determine whether or not it provides clinical benefit for the mother during the perinatal period in the long run.

6. CONCLUSION

In primigravidae who developed intrahepatic cholestasis of pregnancy, treatment with 500 mg of ursodeoxycholic acid twice a day for 4 weeks yielded significantly more improvement in pruritus than did cholestyramine treatment. UDCA was also correlated with higher decrease in ALT, which further confirmed its beneficial biochemical effect in ICP. The differences in perinatal characteristics were also noted, with fewer preterm delivery, low birth weight, meconium-stained liquor, and NICU admissions in the UDCA group, but these should be viewed with caution due to limited sample size and a lack of consistent statistical significance. There was no stillbirth in either treatment groups. The results support the application of UDCA for use as first-line pharmacologic treatment in ICP, which is in line with the current

clinical advice. But, it is not a replacement for the proper risk assessment of the fetus. Management should still include measurements of bile acids in the serum, proper surveillance during antepartum period, and the appropriate timing of delivery, which are all individual to the patient. Future large, multicenter trials with bile acid stratification are needed to determine the efficacy of UDCA for clinical protection of major perinatal outcomes.

7. REFERENCES

- Noor N, Firasat S, Bano N, Afshan K, Gul B, Kaul H. Clinical profile and screening of exon 6 and 14 of ABCB4 gene in obstetric cholestasis patients at a tertiary care hospital in Rawalpindi, Pakistan. *J Pak Med Assoc.* 2021; 71: 1633. DOI: <https://doi.org/10.47391/JPMA.420>
- Anwar R, Razzaq K, Shahid A, Afsheen A, Tariq A, Saleem I. Evaluation of risk factors for intrahepatic cholestasis of pregnancy in patients presenting to a tertiary care centre. *Pak Armed Forces Med J.* 2021; 71(5): 1852-1856. DOI: <https://doi.org/10.51253/pafmj.v71i5.5310>
- Ehsan A, Ehsan-Ul-Haq M. Maternal and fetal outcome in patients with obstetric cholestasis. *J Soc Obstet Gynaecol Pak.* 2018; 8(4): 227-31.
- Hassan GU, Inam I, Sajjad S. Pregnancy outcomes with intrahepatic cholestasis. *Pak J Med Health Sci.* 2022; 16(5): 216-8. DOI: <https://doi.org/10.53350/pjmhs22165216>
- Katiyar H, Yadav S, Goel A, Lingaiah R, Pradhan M, Aggarwal R. Serum bile acid levels in women with intrahepatic cholestasis of pregnancy in India. *J Clin Exper Hepatol.* 2022; 12(S1): S9-S45.
- Karahanolu E. The impact of ursodeoxycholic acid treatment on myocardial performance index in the obstetric cholestasis cases. *Perinatal J.* 2019; 27(1): 32-7. DOI: <https://doi.org/10.2399/prn.19.0271005>
- Corcoran A, Langan H. Obstetric cholestasis: investigation of a suspected high incidence in the West of Ireland. *Eur J Obstet Gynecol Reprod Biol.* 2022; 269: 114-7. DOI: <https://doi.org/10.1016/j.ejogrb.2021.12.009>
- Fawad S. Diagnosis and neonatal outcome in obstetric cholestasis. *Pak J Physiol.* 2016; 12(1): 15-7.
- Wang Y, Peng X, Zhang Y, Yang Q, Xiao Y, Chen Y. Ursodeoxycholic acid improves pregnancy outcome in patients with intrahepatic cholestasis during pregnancy. A protocol for systematic review and meta-analysis. *Medicine.* 2021; 100(4): e23627. DOI: <https://doi.org/10.1097/MD.00000000000023627>
- Hafeez M, Ansari A, Parveen S, Salamat A, Aijaz A. Frequency of intrahepatic cholestasis of pregnancy in Punjab Pakistan: a single centre study. *J Pak Med Assoc.* 2016; 66(2): 203-6.
- Fleminger J, Seed PT, Smith A, Juszczak E, Dixon PH, Chambers J, et al. Ursodeoxycholic acid in intrahepatic cholestasis of pregnancy: a

- secondary analysis of the PITCHES trial. *BJOG*. 2021; 128: 1066-75. DOI: <https://doi.org/10.1111/1471-0528.16613>
- Ovadia C, Sajous J, Seed PT, Patel K, Williamson NJ, Attilakos G, et al. Ursodeoxycholic acid in intrahepatic cholestasis of pregnancy: a systematic review and individual participant data meta-analysis. *Lancet Gastroenterol Hepatol*. 2021; 6: 547-58. DOI: [https://doi.org/10.1016/S2468-1253\(21\)00074-1](https://doi.org/10.1016/S2468-1253(21)00074-1)
- Joutsiniemi T, Timonen S, Linden M, Suvitie P, Ekblad U. Intrahepatic cholestasis of pregnancy: observational study of the treatment with low-dose ursodeoxycholic acid. *BMC Gastroenterol*. 2015; 15: 92. DOI: <https://doi.org/10.1186/s12876-015-0324-0>
- Posh S, Ajaz S, Jeelani B, Khurshid R. Impact of obstetric cholestasis on fetal outcome – an observational study. *J Sci Soc*. 2020; 47: 28-32. DOI: https://doi.org/10.4103/jss.JSS_18_20
- Gao XX, Ye MY, Liu Y, Li JY, Li L, Chen W, et al. Prevalence and risk factors of intrahepatic cholestasis of pregnancy in a Chinese population. *Sci Rep*. 2020; 10: 16307. DOI: <https://doi.org/10.1038/s41598-020-73378-5>
- Chappell LC, Chambers J, Dixon PH, Dorling J, Hunter R, Bell JL, et al. Ursodeoxycholic acid versus placebo in the treatment of women with intrahepatic cholestasis of pregnancy (ICP) to improve perinatal outcomes: protocol for a randomised controlled trial (PITCHES). *Trials*. 2018; 19: 657. DOI: <https://doi.org/10.1186/s13063-018-3018-4>
- Safdar F, Kalsoom S, Majeed N, Nisa K, Rafique S, Tariq S, et al. Obstetric cholestasis: comparison of maternal and perinatal outcome of ursodeoxycholic acid versus placebo. *J Rawal Med Coll*. 2020; 24(1): 28-33. DOI: <https://doi.org/10.37939/jrmc/vol24.iss1.7>
- Laul P, Kumari S, Miglani U, Laul A, Gandhi S, Miglani S. Fetomaternal outcome and effect of ursodeoxycholic acid in patients of obstetric cholestasis. *Int J Reprod Contracept Obstet Gynecol*. 2021; 10: 3169-73. DOI: <https://dx.doi.org/10.18203/2320-1770.ijrcog20212975>
- Ahmed NMM. Perinatal outcomes in women with intrahepatic cholestasis of pregnancy receiving ursodeoxycholic acid - a randomized controlled trial. *J Gynecol Women's Health*. 2020; 17(5): 555975. DOI: <https://doi.org/10.19080/JGWH.2020.17.555975>
- Kondackiave J, Beuers U, Kuipers F. Efficacy and safety of ursodeoxycholic acid versus cholestyramine in intrahepatic cholestasis of pregnancy. *Gastroenterology*. 2005 Sep;129(3):894–901.
- Chappell, L. C., Bell, J. L., Smith, A., Linsell, L., Juszczak, E., Dixon, P. H., Chambers, J., Hunter, R., Dorling, J., Williamson, C., & Thornton, J. G. (2019). Ursodeoxycholic acid versus placebo in women with intrahepatic cholestasis of pregnancy (PITCHES): A randomised controlled trial. *The*

Lancet, 394(10201), 849–860. [https://doi.org/10.1016/S0140-6736\(19\)31270-X](https://doi.org/10.1016/S0140-6736(19)31270-X)

- Vasavan, T., Deepak, S., Jayawardane, I. A., Lucchini, M., Martin, C., Geenes, V., Yang, J., Lövgren-Sandblom, A., Seed, P. T., Chambers, J., Stone, S., Kurlak, L., Dixon, P. H., Marschall, H.-U., Gorelik, J., Chappell, L., Loughna, P., Thornton, J., Broughton Pipkin, F., Hayes-Gill, B., Fifer, W. P., & Williamson, C. (2021). Fetal cardiac dysfunction in intrahepatic cholestasis of pregnancy is associated with elevated serum bile acid concentrations. *Journal of Hepatology*, 74(5), 1087–1096. <https://doi.org/10.1016/j.jhep.2020.11.038>
- Niemyjska-Dmoch, W., Kosiński, P., Węgrzyn, P., Luterek, K., & Jezela-Stanek, A. (2023). Intrahepatic cholestasis of pregnancy and theory of inheritance of the disease: Literature review. *The Journal of Maternal-Fetal & Neonatal Medicine*, 36(2), 2279020. <https://doi.org/10.1080/14767058.2023.2279020>
- Hague, W. M., Briley, A., Callaway, L., Dekker Nitert, M., Gehlert, J., Graham, D., Grzeskowiak, L., Makris, A., Markus, C., Middleton, P., Peek, M. J., Shand, A., Stark, M., & Waugh, J. (2023). Intrahepatic cholestasis of pregnancy—Diagnosis and management: A consensus statement of the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ): Executive summary. *Australian and New Zealand Journal of Obstetrics and Gynaecology*, 63(5), 656–665. <https://doi.org/10.1111/ajo.13719>
- Zhan, Y., Xu, T., Chen, T., Deng, X., Kong, Y., Li, Y., & Wang, X. (2023). Intrahepatic cholestasis of pregnancy and fetal cardiac dysfunction: A systematic review and meta-analysis. *American Journal of Obstetrics & Gynecology* MFM, 5(8), 100952. <https://doi.org/10.1016/j.ajogmf.2023.100952>
- Hobson, S. R., Cohen, E. R., Gandhi, S., Jain, V., Niles, K. M., Roy-Lacroix, M.-È., & Wo, B. L. (2024). Guideline No. 452: Diagnosis and management of intrahepatic cholestasis of pregnancy. *Journal of Obstetrics and Gynaecology* Canada, 46(8), 102618. <https://doi.org/10.1016/j.jogc.2024.102618>