Original Article

Foetal Outcome in Intrahepatic Cholestasis of Pregnancy Treated with Ursodeoxycholic Acid

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Abstract

Objective: To determine frequency of foetal outcome in patients with intrahepatic cholestasis of pregnancy treated with Ursodeoxycholic Acid (UDCA).

Methodology: The study was conducted at the Department of Gynaecology and Obstetrics, Jinnah Postgraduate Medical Center, Karachi, from 14-03-2017 to 13-03-2020. This interventional single-group cohort study included 139 pregnant women with ICP who received UDCA at a dose of 15 mg/kg orally for up to 6 weeks or until delivery/C-section. Weekly LFTs, urine analysis, and foetal ultrasounds were conducted. Weekly liver function tests (LFTs), urine analysis, and foetal ultrasounds were performed, and foetal outcomes were recorded. Descriptive statistics were used to analyze both qualitative and quantitative variables.

Results: The mean age of the participants was 27.3 ± 3.8 years, with a mean parity of 2.2 ± 1.4. The average family income was PKR 20,611.51 ± 7,057.23. Among the participants, 78 (56.1%) had a primary level of education, while 61 (43.9%) had a secondary level of education. The mean duration of UDCA treatment was 4.7 ± 1.8 weeks. The study revealed that 4 (2.9%) foetuses experienced intrauterine death (IUD), and 45 (32.4%) foetuses suffered from neonatal distress. However, 90 (64.7%) healthy babies were born. Additionally, 22 (15.8%) cases had meconium-stained amniotic fluid (MSAF), and 21 (15.1%) pregnancies resulted in preterm births. Significant correlations were found between parity and maternal age, MSAF and foetal outcome, anaemia and foetal outcome, and preterm delivery with maternal age. Gestational age was significantly correlated with all variables except parity.

Conclusion: The findings of this study support the use of UDCA in pregnant women with ICP, as it demonstrated beneficial effects on foetal outcomes.

Keywords: Ursodeoxycholic Acid, Intrahepatic Cholestasis of Pregnancy, foetal outcome, foetal distress, intrauterine death, hepatitis.

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Introduction

Intrahepatic cholestasis of pregnancy (ICP) is characterized by severe itching along with elevated serum concentrations of liver enzymes and bile acids (> 10 µmol/L) in previously healthy pregnant women. [1,2] The condition typically manifests during the second or third trimester of pregnancy, and its symptoms usually subside within 2 to 3 weeks after delivery. Although ICP resolves after delivery, it has been linked to a higher incidence of foetal complications, including foetal heart and lung dysfunction. [1,3,4] The prevalence of ICP varies across countries and ethnic groups.[5,6] The incidence of ICP has been found to vary among different regions of the world and different populations, underscoring the potential influence of environmental and genetic factors in the still unclear etiology and pathogenesis of the disorder.[7] The highest reported rates in Chile and Bolivia during the 1970s (11.8% to 27.6% according to ethnic origin), while other countries show prevalence rates between 0.5% and 1.5%.[6,8]

Pruritus is often a very unpleasant symptom, and cholestasis may have deleterious consequences, which may suddenly occurs at the end of pregnancy.[9] Although

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pruritus can be very disturbing, ICP typically remains a benign disease for mothers.[10] It increases the risk of preterm delivery, meconium excretion, respiratory distress syndrome and sudden intrauterine death.[11] The incidence of preterm delivery (ranging from 10% to 60%), foetal distress (ranging from 22% to 41%), and stillbirth (ranging from 1% to 4%) escalates when bile acid levels surpass 40 µmol/L.[2] Due to the augmented risk of neonatal complications beyond 38 weeks of gestation, a majority of women with ICP undergo induction of labor at 37 weeks. [2]

Prematurity-related complications pose risks to the foetus, such as neonatal respiratory distress syndrome (NRDS) or the need for neonatology hospitalization.[12] To address these concerns and improve pruritus while preventing foetal complications, pharmacological intervention is crucial. Ursodeoxycholic acid (UDCA) has emerged as a potential treatment option.[13-16] However, the use of UDCA remains contentious, with conflicting studies offering support or skepticism. Some studies, like Gurung et al, reported that UDCA significantly improves pruritus and reduces instances of foetal distress and asphyxial events, although the differences were not statistically significant.[17] Bacq et al[5] found UDCA have a several benefits for mothers, foetuses as well as for newborns. Conversely, a Cochrane review failed to find sufficient evidence to recommend UDCA for ICP treatment.[2]

The use of UDCA may have important implications in pregnancy outcomes. Although the maternal treatment with ursodeoxycholic acid (10-15 mg/kg/day given the twice daily regimen for 3 week) provides symptomatic relief of pruritus, and significant improvement in biochemical markers, the effect of UDCA on foetal outcome is currently an area of active research with recent studies showing that UDCA has no effect on foetal outcome.[11] In one recent observational study, 33% perinatal complication rate was found in patients with Intrahepatic Cholestasis of pregnancy.[11] Studies from other countries have shown that ICP has been associated with increased risk of preterm delivery (12-44%), meconium staining of amniotic fluid (MSAF) (16-58%), foetal distress (10-44%) and intrauterine foetal death (3.5-15%).[7] While one study conducted in Pakistan about neonatal outcome in obstetric cholestasis/ICP patients observed with following complications, intrapartum foetal distress (33.33%), Amniotic fluid meconium (20%), Spontaneous preterm delivery (10%), Intrauterine death (6.67%).[18] Although the underlying mechanisms associated with poor foetal outcomes are largely unknown, studies implicate high maternal serum bile acid (> 40umol/l) to play important if not central role in the causation of the adverse foetal outcome.[19]

The rationale behind this study is to examine the effects of Ursodeoxycholic Acid (UDCA) treatment on foetal outcomes in pregnant women diagnosed with intrahepatic cholestasis of pregnancy (ICP). By investigating the potential benefits of UDCA on foetal health, this research aims to advance the existing knowledge in the field and provide insights that can guide evidence-based clinical decisions for managing ICP in pregnant women.

Methodology

This interventional single-group cohort study was conducted in the Department of Gynaecology and Obstetrics, Jinnah Postgraduate Medical Center, Karachi, from 14-03-2017 till 13-03-2020. Informed consent was obtained from pregnant women aged 20-35 years with gestations of > 24 weeks who were suffering from ICP. Women with multiple pregnancies, HELLP syndrome, pre-eclampsia, pre-existing chronic liver disease (hepatitis B, hepatitis C, primary biliary cirrhosis, primary sclerosing cholangitis), and symptomatic cholecystitis were excluded from the study. Demographic data of the included women, including age, parity, family income, and educational status, were collected.

The calculated sample size for the study was 139, determined using the WHO sample size calculator. The calculation considered the least prevalence of preterm delivery at 10%[18], with 5% absolute precision and a confidence interval of 95%.

All selected women were given UDCA at a dose of 15 mg/kg in two divided oral doses for up to 6 weeks or until delivery/C-section, whichever occurred earlier. Liver function tests (LFT), urine analysis, and foetal ultrasound were repeated weekly. Foetal outcomes were recorded in the labour room, including foetal bradycardia, foetal distress, and meconium-stained amniotic fluid (MSAF).

Operational Definitions:

1. Foetal Outcome: Presence of any one of the following criteria was considered as a foetal outcome:

- Meconium-stained amniotic fluid (MSAF) observed at the time of delivery.

- Foetal distress identified during labour through CTG (cardiotocography) showing repetitive late decelerations requiring emergent delivery.
- Preterm delivery defined as delivery before 37th week of gestation.
- Anaemia defined as haemoglobin level less than 10 gm/dl.
- Compliance with treatment assessed as the degree to which a patient correctly follows medical advice for UDCA dosage given by her obstetrician.

2. Intrahepatic Cholestasis of Pregnancy (ICP): Pregnant women in their third trimester presenting after 36 weeks according to their ultrasound scans with known pruritus (itching for more than 2 weeks) and abnormal liver function test (LFT) results (ALT ≥ 40 U/L, AST > 35 U/L, ɣ-GT > 31 U/L, ALP > 300 U/L) will be diagnosed as having Intrahepatic Cholestasis of Pregnancy.

Data was compiled and analysed using statistical package for social sciences version 26. Descriptive statistics was calculated for both qualitative and quantitative variables. The quantitative variables like age, gestational age, parity, family income, duration of UDCA treatment, and dose of UDCA was presented by mean ±SD. The qualitative variables like anaemia, compliance with treatment, educational status, foetal outcome including, foetal distress, MSAF and preterm delivery, was presented in-terms of frequency and percentage. Stratification was done on maternal age, gestational age, educational status & parity by using χ2-square test. Correlation of variables maternal age, parity, foetal outcome, MSAF & anaemia was tested by Kendall's Tau-b test. Significance was set at ≤ .05.

Results

One hundred thirty-nine women having ICP were inducted. Mean age was 27.3 ±3.8 years. Mean parity was 2.2 ±1.4 while mean family income was PKR 20,611.51 ±7,057.23. Seventy-eight (56.1%) were educated up to primary level while 61 (43.9%) were educated up to secondary level. Mean duration of UDCA treatment was 4.7 ±1.8 weeks. The weekly LFT are reported in Table showing progressive improvement in LFT.

Our study showed that in women with ICP, IUD occurred in 4 (2.9%) foetuses, neonatal distress in 45 (32.4%)

Table I: Weekly Mean LFT.

	W-0	W-1	W-2	W-3	W-4	W-5	W-6
Bilirubin (1.1 mg/dl)	15.3	14.4	12.2	8.3	6.1	3.9	3.3
ALT (35 IU/L)	881.3	721.5	534.3	311.8	221.4	183.2	89.9
Alk. Phos (117 IU/L)	1011.4	906.8	836.9	623.9	421.8	391.3	221.6
ɣ-GT (38 IU/L)	334.9	296.5	186.9	97.8	85.4	76.9	68.9

Table II: Stratification of foetal outcome, meconium staining & preterm delivery with parity, educational status, maternal age, gestational age & anaemia, and statistical significance by χ^2-test.

Variable		Foetal Outcome				MSAF (n=22)		Preterm Delivery (n=21)	
		IUD (n=4)	Neonatal Distress (n=45)	Healthy Baby (n=90)	Sig.				
		N (%)	N (%)	N (%)		N (%)	Sig.	N (%)	Sig.
Parity	Para 0	0	9 (56.3)	7 (43.8)	.351	1 (6.3)	.834	6 (37.5)	.169
	Para 1	1 (3.1)	10 (31.3)	21 (65.6)		5 (15.6)		4 (12.5)	
	Para 2	1 (2.9)	14 (41.2)	19 (55.9)		6 (17.6)		5 (14.7)	
	Para 3	1 (3.1)	5 (15.6)	26 (81.3)		6 (18.8)		4 (12.5)	
	Para 4	1 (5.9)	4 (23.5)	12 (70.6)		2 (11.8)		1 (5.9)	
	Para 5	0	3 (37.5)	5 (62.5)		2 (25.0)		1 (12.5)	
Educational Status	Primary	3 (3.8)	23 (29.5)	52 (66.7)	.566	15 19.2)	.214	13(16.7)	.562
	Secondary	1 (1.6)	22 (36.1)	38 (62.3)		7 (11.5)		8 (13.1)	
Maternal Age	20-25 years	2 (3.9)	18 (35.3)	31 (60.80)	.468	8 (15.7)	.967	15(29.4)	**.001***
	26-30 years	0	18 (34.0)	35 (66.0)		8 (15.1)		2 (3.8)	
	31-35 years	2 (5.7)	9 (25.7)	24 (68.6)		6 (17.1)		4 (11.4)	
Gestational Age	< 34 weeks	2 (16.7)	9 (75.00)	1 (8.3)	**<.001***	8 (66.7)	**<.001***	8 (57.1)	**<.001***
	34-36 weeks	1 (2.7)	14 (37.8)	22 (59.5)		6 (16.2)		10 27.8)	
	37 weeks or more	1 (1.1)	22 (24.4)	67 (64.7)		8 (8.9)		0	
Anaemia	Present	4 (22.2)	7 (38.9)	7 (38.9)	**<.001***	6 (33.3)	**.029***	3 (16.7)	.843

**** Significance ≤.05***

foetuses while healthy baby births occurred in 90 (64.7%). MSAF occurred in 22 (15.8%) and pre-term birth occurred in 21 (15.1%). Cross tabulation with statistical testing of parity with foetal outcome (p = .351), meconium staining (p = .834) & preterm delivery (p = .169) showed no significant difference. Similarly educational status was also not significant across all these parameters. Significantly high preterm births were observed in maternal age group of 20-25 years (p = .001). Gestational age showed significance with foetal outcome (p < .001), MSAF (p < .001) and preterm delivery (p < .001). Anaemia also showed significant difference in foetal outcome (p < .001) and MSAF (p = .029). Details are given in Table II.

Significant positive correlation was found between parity & maternal age (r = .328, p <.001), MSAF & foetal outcome (r = .254, p =.003), anaemia with foetal outcome (r = .253, p =.003) & MSAF (r = .185, p =.03), preterm delivery was significantly correlated with maternal age (r = .239, p = .001), gestational age correlated significantly with all variables except parity while parity didn't correlated significantly with any variable but it did negatively correlated in non-significant manner with MSAF & anaemia. Details are given in correlation matrix in Table III.

Discussion

In this study, we examined the effect of UDCA on foetal outcomes in pregnant women with ICP and found that its use has beneficial effects on foetal outcomes. Our study showed a significant positive impact of UDCA on foetal outcome in women with ICP, with only four cases of IUD and 21 preterm deliveries out of the 139 women included in the study. A study by Noor N et al. reported that about 10% of women with ICP experienced miscarriages or stillbirths.[20] In our study, the occurrence of IUD was only four cases, which accounts for 2.88% of the total women included. Another study from Pakistan by Hafeez M et al. reported a frequency of 3.1% of ICP in women presenting in their setup.[21] It appears that ICP is underreported in our country, whereas it is reported internationally in 6-29% of pregnancies.[2] Although ICP typically follows a benign course in pregnant women, its effects on foetal outcomes can be hazardous.[10, 22] The frequency of preterm deliveries has been reported to range from 10% to 60%, foetal distress from 22% to 41%, and stillbirths from 1% to 4% of cases.[23-25]

In a meta-analysis by Grand'Maison S et al that included 17 studies on the subject reported in forest plot that UDCA has beneficial effect adverse effects, prematurity & presence of meconium.[2] In our study gestational age correlated significantly with maternal age, anaemia, foetal outcome, MASF & preterm delivery showing that the outcome of ICP is strongly correlated with its onset in relation to gestational age.

It is reported that in women with ICP, total bile acid (TBA) synthesis is over active while steroids are decreased in placenta, urine and serum of affected women.[26] Among the risk factors it is reported that use of vaginal progesterone in first and second trimester is associated with high frequency of ICP.[27] The role of gut microbiomes is also under study in one study it is shown that the patients of ICP harbour Bacteroides fragilis which stimulate ICP by altering modulation of bile acid metabolism causing excessive synthesis, and interrupting hepatic excretion of bile.[28]

Conclusion

Our study supports the use of UDCA in pregnant women with ICP and it has shown beneficial effects on foetal outcome. However, further research is needed to resolve the ongoing debate on the effectiveness of UDCA in managing ICP. Rigorous studies investigating the impact of UDCA on foetal outcomes are crucial to

Table III: Correlation by Kendall's Tau-b test among parity, foetal outcome, MSAF, anaemia, preterm delivery, maternal age & gestational age.

		Maternal Age	Parity	Foetal Outcome	MSAF	Anaemia	Preterm Delivery
Parity	r	**.328****					
	Sig.	**<.001**					
Foetal Outcome	r	0.052	0.126				
	Sig.	0.462	0.093				
MSAF	r	0.010	-0.059	**.254****			
	Sig.	0.887	0.436	**0.003**			
Anaemia	r	0.022	-0.077	**.253****	**.185***		
	Sig.	0.755	0.311	**0.003**	**0.03**		
Preterm Delivery	r	**.239****	0.141	0.164	0.147	0.017	
	Sig.	**0.001**	0.063	0.051	0.084	0.844	
Gestational Age	r	**.158***	0.003	**.318****	**.309****	**.453****	**.475****
	Sig.	**0.024**	0.965	**<.001**	**<.001**	**<.001**	**<.001**

*** Significance ≤.05, ** Significance ≤.01**

establish evidence-based guidelines for treating pregnant women with ICP.

Limitations: Study has limitation of being a single centre study. No comparative group was present to compare the results with placebo due to the ethical considerations as UDCA is now standard recommendation for ICP patients.

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