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EFFICACY OF URSODEOXYCHOLIC ACID FOR MANAGEMENT OF INTRAHEPATIC CHOLESTASIS DURING PREGNANCY

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ABSTRACT

Background: Intrahepatic cholestasis of pregnancy is a pregnancy-specific liver disorder. This condition is characterized by symptoms of maternal pruritus in the third trimester of pregnancy. It is associated with raised serum bile acids and increased rates of adverse fetal outcomes. Ursodeoxycholic acid is currently the most effective treatment for intrahepatic cholestasis and is thought to reduce pruritus and neonatal complications. Ursodeoxycholic acid treatment should be recommended for women with intra hepatic cholestasis during Pregnancy to reduce adverse maternal and fetal outcomes. Rationale of this study is to assess the efficacy with UDCA for management of females presenting with intrahepatic cholestasis.

Methodology: A descriptive cross sectional study was conducted in the department of Obstetrics and Gynecology, services hospital, Lahore. The ethical approval was obtained from IRB of institute and study was done from 15th January 2022 to 15th June 2022. The 150 pregnant females with cholestasis were included in study through consecutive sampling. Demographic information (including name, age, gestational age, parity and contact) was also recorded. Females were given UDCA capsules (250 mg QID dose). Then females were followed-up in OPD for 20 days. If female report of absence of pruritus, then drug efficacy was labelled. Quantitative data like age and gestational age was presented as mean and standard deviation. Qualitative data like parity and efficacy was presented as frequency and percentage. Data was stratified for age, gestational age at presentation and parity. Post-stratification, chi-square test was applied with p-value≤0.05 as significant.

Results: In this study, the mean age of the women was 28.59 ± 6.84 years. Regarding parity, 35 women (23.3%) were primiparous, and 30 women (20%) had a parity of 1. The remaining 85 women (56.66%) were multiparous. The efficacy of ursodeoxycholic acid (UDCA) in treating intrahepatic cholestasis of pregnancy (ICP) was observed in 88 women (58.7%).

Conclusion: This study showed satisfactory treatment efficacy of UDCA for treating Intrahepatic Cholestasis in pregnancy by improving pruritus within 20 days of initiation of treatment.

Keywords: Ursodeoxycholic acid, Intrahepatic Cholestasis, Pregnancy, Efficacy.

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-specific liver disorder. This condition is characterized by symptoms of maternal pruritus in the third trimester of pregnancy. It is associated with raised serum bile acids and increased rates of adverse fetal outcomes. The causes of ICP are complex and not completely known, but it is likely to result from the cholestatic effects of reproductive hormones and their metabolites in genetically susceptible women. The prevalence of intrahepatic cholestasis is approximately 0.1% to 1.5% of pregnancies in Europe and the United States.(1)

ICP is more common in 3rd trimester when estrogen levels are at peak. This concept is further strengthened by another study in which cholestasis was more in twins than in singleton pregnancies. Actually the situation is different and needs particular attention to prevent maternal and fetal complications that could be life-threatening if not identified. It was being observed that pregnant women present with intense itching in the third trimester of pregnancy.(2)

Ursodeoxycholic acid (UDCA) is currently the most effective treatment for ICP and is thought to reduce pruritus and neonatal complications. UDCA treatment should be recommended for women with ICP to reduce adverse maternal and fetal outcomes.(3) A study showed a significant findings for improvement of maternal outcomes of pruritus and LFTs (ALT, bile acid, bilirubin), but no difference has been reported in terms of caesarean section. UDCA was also found in reducing fetal and neonatal adverse outcomes.(4)

Rationale of this study is to assess the efficacy with UDCA for management of females presenting with ICP. As previous literature has reported that UDCA is an effective in resolution of symptoms of ICP. But in developing country Pakistan, it is not practiced and female is followed till delivery of baby with expectant management. However, the lifestyle of females of local population and foreign countries is different. There is no local evidence observed regarding the effectiveness of UDCA among our population.

Moreover, previous literature has shown variable results. So we want to conduct this study to confirm whether UDC is effective in preventing severe symptoms of ICP and can treat ICP cases effectively. This will help us to improve our practice as well as we will be able to implement the use of UDCA in future to treat ICP cases and prevent hazardous outcome of pregnancy and will also reduce burden of hospital by reducing maternal and fetal complications.

Literature Review

Intrahepatic Cholestasis of Pregnancy is a hepatic disorder, although less prevalent but of greater concern. It occurs in around one in 140 pregnancies in the UK, in this condition the normal flow of bile out of the liver is reduced. Chemicals in the bile called bile salts/bile acids, can then build up and ‘leak’ into the bloodstream. This results in increased levels of bile salts in the blood.(5)

This condition is also associated with itching, known as pruritus. It generally appears after the 24 weeks of pregnancy, but may also appear earlier. The severity of this condition varies and can be extremely distressing for the women. This condition subsides after the delivery and may not result in any complications later on in life.(6)

However, there can be an increased risk of preterm delivery and fetal distress. Some case studies have also revealed that stillbirth occurring in last trimester of pregnancy in women with this condition and therefore it is essential that the condition is identified and treated in time.(7)

At present, most obstetricians in the UK managing ICP pregnancies deliver babies early, at around 37 or 38 weeks. This is done because it is thought that it may help prevent the possibility of stillbirth. There have been no reports of any harmful effects to babies from ICP pregnancies once they have been delivered.(8)

The exact cause of the maternal disease and the fetal outcomes related to the condition are not completely understood. Instead, there are several evidence based studies showing that the adverse outcomes may be due to the harmful effects of bile acids. Other studies have determined a correlation between the serum bile acid level and the adverse fetal outcomes.(9) The most important

of these studies determined the incidence of of 45,000 women, of whom 690 women were diagnosed with ICP.(10)

The study indicates that for each 1 mmol/L increase in maternal serum bile acids, the risk of meconium staining of the amniotic fluid, green staining of the placenta and fetal membranes, asphyxial events, and preterm delivery rises by 1-2%. However, this increase was not statistically significant in women with mild to moderate elevations in fasting serum bile acids. It became significant only in cases of severe cholestasis, defined as fasting serum bile acid levels exceeding 40 mmol/L.(11)

ICP is more prevalent in regions like South Asia, South America, and Scandinavia, but its occurrence in the United States varies significantly due to the country's diverse population, with rates ranging from 0.32% to 5.6%.(12) ICP also tends to follow a seasonal pattern, being more common in the winter months. Additional risk factors include older maternal age, a personal or family history of cholestasis linked to oral contraceptive use, and having had multiple pregnancies. Furthermore, women expecting twins are five times more likely to develop ICP compared to those with a single pregnancy.(13)

Other studies provide evidence that reproductive hormones play a role in causing ICP. This condition is more common in multiple than singleton pregnancies (20.9% vs 4.7% in one study), and the symptoms may occur in a subgroup of affected women who are taking the oral contraceptive pill. In addition, most women present with symptoms of ICP in the third trimester when estrogen and progesterone levels are highest.(14) The itch associated with ICP is often the most irritable symptom for affected women. It has been studied that it is due to accumulation of bile acids in the interstitial fluid of the skin.(15) To reduce the risk of stillbirth women with ICP may be offered an early planned delivery once they reach their 37th week of pregnancy. UDCA is a naturally-occurring hydrophilic bile salt, which may increase the hydrophilic properties of the bile acid pool, thereby preventing damage to membranes by hydrophobic bile salts.

Methodology

A descriptive cross sectional study was conducted in department of Obstetrics and Gynecology, services hospital, Lahore. The ethical approval was obtained from IRB of institute and study was done from 15th January 2022 to 15th June 2022. The 150 pregnant females with cholestasis were included in study through consecutive sampling. Demographic information (including name, age, gestational age, parity and contact) was also recorded. Females were given UDCA capsules (250 mg QID dose). Then females were followed-up in OPD for 20 days. If female report of absence of pruritus, then drug efficacy was labelled. All the information was collected on a specially designed proforma. All the collected data was entered and analyzed through SPSS version 25. Quantitative data like age and gestational age was presented as mean and standard deviation. Qualitative data like parity and efficacy was presented as frequency and percentage. Data was stratified for age, gestational age at presentation and parity. Post-stratification, chi-square test was applied with p-value$\leq$0.05 as significant.

Results

In this study, the mean age of the women was 28.59 ± 6.84 years, with a minimum age of 18 years and a maximum age of 40 years. The table 1 shows mean gestational age at the time of presentation was 29.35 ± 3.06 weeks, with a minimum gestational age of 25 weeks and a maximum of 35 weeks. Regarding parity, 35 women (23.3%) were primiparous, and 30 women (20%) had a parity of 1. The remaining 85 women (56.66%) were multiparous, with the following distribution: 31 women (20.7%) had parity 2, 22 women (14.7%) had parity 3, 15 women (10%) had parity 4, and 17 women (11.3%) had parity 5 as shown in figure 1.

The efficacy of ursodeoxycholic acid (UDCA) in treating intrahepatic cholestasis of pregnancy (ICP) was observed in 88 women (58.7%).

There was no statistically significant association between the age of the women and the efficacy of UDCA. The efficacy was 55.7% in women aged 18–30 years and 44.3% in those aged 31–40 years

(p = 0.72). Furthermore, neither gestational age at presentation nor parity had a statistically significant effect on the efficacy of UDCA in managing ICP.

Table: Sociodemographic characteristics of Women with intrahepatic cholestasis during pregnancy

Characteristic	Mean ± SD	Minimum	Maximum
Age (years)	28.59 ± 6.84	18	40
Gestational age(weeks)	29.35 ± 3.06	25	35

Table 2: Efficacy of Ursodeoxycholic Acid (UDCA) in Relation to Age, Gestational Age, and Parity (n=150)

Variable	Efficacy (Yes)	Efficacy (No)	Total	p-value
Age (years)				0.72
18–30	49 (55.7%)	36 (58.1%)	85	
31–40	39 (44.3%)	26 (41.9%)	65	
Gestational Age (weeks)				0.978
25–30	58 (65.9%)	41 (66.1%)	99	
31–35	30 (34.1%)	21 (33.9%)	51	
Parity				0.834
Primiparous	20 (22.7%)	15 (24.2%)	35	
Multiparous	68 (77.3%)	47 (75.8%)	115	

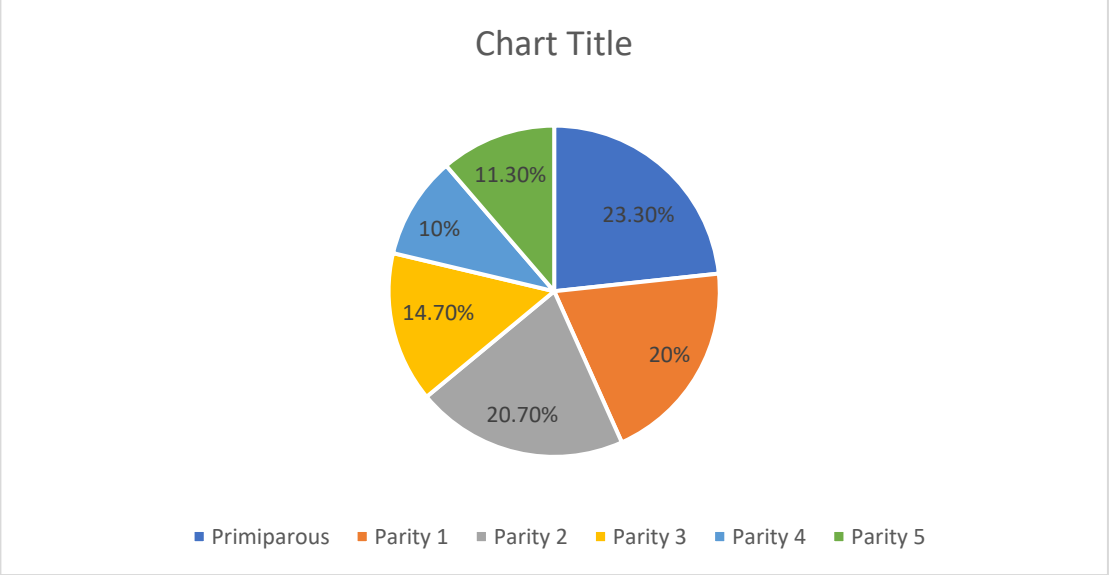

Figure 1: Distribution of parity among pregnant women with intrahepatic cholestasis.

Discussion

The intrahepatic cholestasis in pregnancy is a benign condition, it is necessary for obstetricians to use efficient drugs to relieve the very uncomfortable symptom as pruritus affects the quality of life of the pregnant women. The gold standard for ICP treatment is drugs capable of reducing itching and liver function tests and improving the outcome of pregnancy with minimal side effects on the mothers and the fetuses.

Although UDCA appears as the most efficient treatment of ICP, the evidence of its benefit on pruritus is still debated, and the only previous meta-analysis failed to provide significant results. Moreover, the role of UDCA in preventing severe fetal outcome has never been demonstrated. In the previously published systematic review on this topic concluded that “inconsistent and inadequate reporting of results precluded pooling the results of small studies.”(16)

In this study UDCA was used for the management of females presenting with Intrahepatic Cholestasis of Pregnancy. Efficacy of UDCA was defined in terms of resolution of pruritus within 20 days of initiation of treatment. As per this criteria efficacy was observed in (58.7%) women. No statistically significant association was seen between efficacy of UDCA with age and gestational age of women. In another study no significant differences in maternal age, pregestational BMI and blood pressure were found between the ICP group getting the UDCA.(17)

This beneficial effect of UDCA on pruritus in patients with ICP supports its use as first line therapy in ICP is reported by various studies.(18, 19) In a previous meta-analysis, UDCA was effective in reducing pruritus and decreasing liver test results in patients with ICP.(20) Another recently published meta analysis reported that pooled analyses that compared UDCA with all controls, UDCA was associated with resolution of pruritus (risk ratio [RR], 1.68; 95% confidence interval [CI],1.12–2.52; P=0.01.(18)

A study showed that UDCA and SAMe are both effective and safe in the treatment of ICP. UDCA mono-therapy should be used as the first line therapy for ICP because it is more efficacious, cost-effective and convenient. Although efficacy of UDCA was not that much higher in this study but almost more than 50% of the patients had resolution of pruritus.(21)

According to the results of a study where the total resolution of pruritus occurred in 41.6% of cases and improvement in 61.3% of cases. A recent study by showed that pruritus had disappeared in 25.5% of cases and improved in 76.5% of cases under UDCA.(22) Efficacy of UDAC is quite higher as observed in this study. Efficacy of UDCA reported in this study is lower.

The improvement of fetal outcome could directly result in a decrease of maternal bile acid concentrations related to UDCA because a relationship has already been found between maternal bile acid concentrations and some fetal complications like fetal distress or RDS.92, 93 This improvement may also be, at least in part, secondary to the improvement of the maternal condition. Indeed, when the pruritus and liver test results improved under medical treatment, the obstetrical team may have chosen to delay the delivery, which may, in turn, contribute to the decrease of the rate of prematurity.(23)

Earlier the treatment of ICP has been mainly symptomatic as no specific treatment did exist. UDCA is a hydrophilic bile acid and is used for the treatment of various cholestatic disorders. The mechanisms of the beneficial effects of UCDA in cholestatic disorders are increasingly being unraveled. (24) Keeping in mind the results of this study it can be said that UDCA can be effectively used for treating women presenting with ICP. UDCA not only improves pruritus but it also has a significant effect on live function test, neonatal as well as fetal outcome.

Conclusion

Results of this study showed satisfactory treatment efficacy of UDCA for treating Intrahepatic Cholestasis in pregnancy by improving pruritus within 20 days of initiation of treatment. UDCA is considered a safe and widely accepted treatment option for ICP, helping to reduce maternal discomfort and potentially lowering the risk of adverse fetal outcomes. However, further research may be needed to fully understand its impact on long-term maternal and fetal health

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