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MONITORING OF ADRS FOR DRUG USES IN MANAGEMENT OF ELEVATED LIVER MARKERS DURING PREGNANCY

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Abstract :

The physiological changes in liver function in pregnancy are commonly transient, rarely permanent. Disorders arising in pregnancy, such as pre-eclampsia and eclampsia, acute fatty liver of pregnancy (AFLP), hemolysis, elevated liver enzyme and low platelets (HELLP) syndrome, cholestasis, hyperemesis gravidarum and isolated cases of raised liver enzymes canhave serious implications. Proper interpretation of liver function tests (LFTs) at an early stage can lead to timemanagement and may reduce complications in both mother and fetus. Normal LFTs do not always mean that the liver isnormal. A number of pitfalls can be encountered in the interpretation of basic blood LFTs. The commonly used LFTsprimarily assess liver injury rather than hepatic function. Abnormal LFTs may indicate that something is wrong with theliver, and they can provide clues to the nature of the problem but this is not always the case. The various biochemical tests,their pathophysiology, and an approach to the interpretation of abnormal LFTs are discussed in this review. Commonlyavailable tests includealanine transaminase, aspartate transaminase, alkaline phosphatase, bile acid, serum bilirubin, serumalbumin and prothrombin time. Keywords:Liver function tests, pregnancy, delivery, obstetric

IndexTerms **- Component,formatting,style,styling,insert.**

INTRODUCTION

Changes in liver biochemical profile are normal during pregnancy. However, severe liver disease, although rare, can occur and must be recognized at an early stage to reduce morbidity and mortality for mother and infant. Here we provide an overview of the liver conditions that are primarily associated with pregnancy and the effect of pre existing liver disease in pregnancy. Normal Liver Function In Pregnancy: Although the increase in the cardiac output peaks at 32 weeks, the blood flow in the liver remains the Same or in some studies decreases.In a prospective analysis of aspartate transaminase (AST), alanine transaminase (ALT), bilirubin and Gamma-glutamyl transferase (GGT) in 430 pregnant Women it was found that these tests were about 20%Lower in pregnant women when compared with Laboratory reference ranges [4].Liver disease in pregnancy should be considered in Three categories:Pre-existing disease, disease specific to pregnancy And coincidental acute liver or biliary tree disease. Serum albumin concentration falls in normal pregnancy And is thought to relate to the increase in total plasma volume. This may persist for several months after delivery.Serum alkaline phosphatase (ALP) increases and may reach 2 to 4 times baseline level. This relates to placental production. In general, alanine aminotransferase (ALT), aspartate Aminotransferase (AST), bilirubin, and gamma-glutamyl Transpeptidase (GGT) concentrations remain normal, but Elevations require further investigation.

NEED OF THE STUDY.

According to this study, there is insufficient evidence to support the routine use of ursodeoxycholic acid in pregnant women with intrahepatic cholestasis in order to clinically usefully improve mother symptoms or lessen poor perinatal outcomes. It's feasible that there are certain subgroups that aren't now recognised that might gain from ursodeoxycholic acid therapy. There are currently no other medications that are widely used for the prevention of the negative perinatal outcomes linked to the

condition since ursodeoxycholic acid has been the only medication continuously recommended in guidelines as a disease-modifying agent.

Variable ICP incidence has been seen in the Indian community, however there is a lack of information comparing different foetal risks with healthy pregnant women.16,17 Data linking several IHCP risk variables to maternal and foetal outcomes in the north Indian population are lacking.

Therefore, in this study, increased liver markers during pregnancy in the north Indian population were evaluated in relation to mother and fetal outcomes

RESEARCH METHODOLOGY

Study type: Prospective Study
Study duration: 3 -5 Months
Sample size: 120 Patients

Calculated with the formula used for sample size is as mentioned:

$$n = \frac{(Z\alpha_{/2} + Z_\beta)^2 \times 2\sigma^2}{(\mu_1 - \mu_2)^2}$$

n = sample size per group before dropout

$Z_{\alpha_{/2}}$ = standard normal z-value for a significance level α = 0.05, which is 1.96

Z_β = standard normal z-value for the power of 80%, which is 0.84.

INCLUSION CRITERIA:

- Age > 19 years
- Gestational age of ≥ 28 weeks at the time of study enrolment but less than orequal to 33 weeks
- Body weight between 40 kg and 90 kg (both inclusive)
- Consistent pruritus associated with elevated levels of serum transaminases(ALT > 40 U/L or AST > 37 U/L) and raised serum bile acids (≥ 10 µmol/L)
- Patients on standard therapy of at least one drug UDCA or cholestyramine.

EXCLUSION CRITERIA:

- History or present hepatic viral infections (liver disorders caused by the hepatitis A, B, C, and E viruses)
- existing allergies or sensitivities to the study medicine or its excipients in the past that may be relevant
- Obstetric ultrasonography suggestive of fetal growth restriction/ abnormalities

METHOD AND DATA COLLECTION:

The condition of the patient and the inclusion requirements for the research will be taken into consideration. A thorough history, physical, vitals, and obstetrics examination were completed.

Information on the therapy, such as the drug names, daily dosages, time frame, previous therapies, and other treatments.

In the two weeks leading up to delivery, the Visual Analogue Scale (VAS) scale was used to quantify the location and severity score of pruritis. (Annexure 1)

During the course of therapy, the liver function test (LFT), which includes ALT, AST, BILIRUBIN, and serum bile acid level, was examined every two weeks.

Regular investigation was done in the two weeks leading up to delivery and in the four weeks after birth.

Drug safety was assessed in both the mother and the foetus during therapy and after birth.

The data collected in CRF was entered in database and further statisticallyanalysis will be performed using t test.

IV. RESULTS AND DISCUSSION

Patients were screened and 84 were diagnosed as having Elevated Liver Markers, the incidence being 8.4% in duration of 4 month, aged 19–41 years, between 28 and 39 weeks of gestation, who fulfilled the inclusion criteria were enrolled in the present study.

6.0 : Baseline characteristics of Group

Following randomization, 42 patients were given cholestyramine (8 g/day) for 14 days and UDCA (8-10 mg/kg body weight/day) for 42 patients. Delivery occurred between 37 and 38 weeks after the median time of therapy beginning (35.0 weeks; range, 22.0-39.0 weeks). Because of this, the majority of the participants were not provided additional medical care until after delivery, when the trial was over and the pruritus had subsided.

Table 6.1: Baseline Characteristics of Treatment Groups

Characteristic	**UDCA group(n = 42)**	**Cholestyramine group (n = 42)**	***P* value**
Age (*y*)	28.9 ± 5.9	28.5 ± 5.3	NS
Multiparous	22	18	NS
Positive family history	5	6	NS
Recurrence	10	11	NS
Multiple pregnancy	3	2	NS
Onset of pruritus (*wk*)	31.7 ± 3.1	31.0 ± 3.8	NS
Onset of treatment (*wk*)	34.3 ± 3.1	33.8 ± 2.8	NS
Weight (*kg*)	69.2 ± 5.8	70.8 ± 7.1	NS

Data are presented as means ± SD.NS, not significant

only those individuals with pruritus that started early When pruritus worsened in the latter stages of pregnancy, 2 patients in the UDCA group and 2 patients in the cholestyramine group received repeat therapy. Both groups' baseline clinical features were the same. (Table 6.1).

6.1 Change in Pruritis Intensity

To measured the pruritis the Pruritis Visual Analog Scale was used.

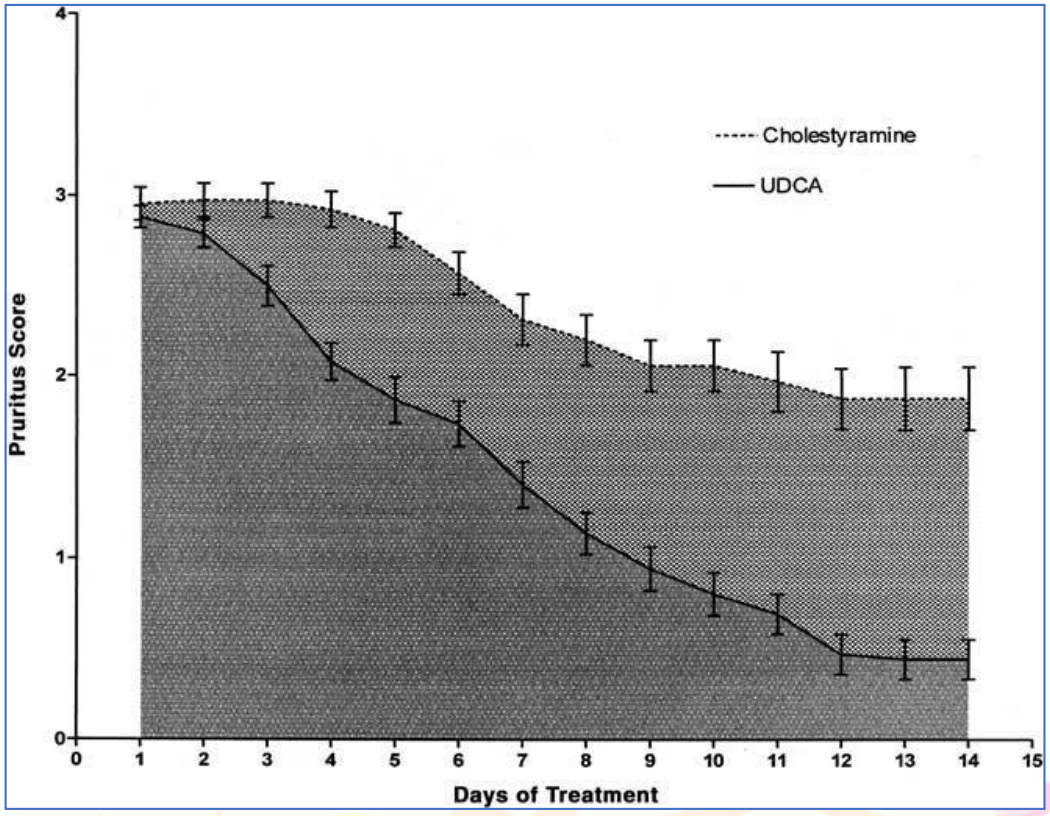

Figure 6.1: Change of pruritus intensity in patients with ICP treated with UDCA or cholestyramine as evaluated by a pruritus score. Data arepresented as means ± SD.

At baseline, pruritus severity was comparable in both treatment groups (2.88 0.40 vs. 2.95 0.60), and it decreased after each treatment. Analysis of the variation in pruritus score between the start of the research and its conclusion, however, showed a significant difference between treatments.

When using UDCA to treat pruritus, relief was shown after 3 to 4 days, but cholestyramine medication often only caused a reduction in itch severity after 7 to 10 days.

Pruritus score: 2.08 0.63 vs. 2.92 0.62, respectively; P .05; and the difference was even more pronounced after 14 days (pruritus score: 0.44 0.65 vs. 1.88 0.98, respectively; P .001). Patients receiving UDCA had significantly lower pruritus scores than patients receiving cholestyramine after 4 days. As demonstrated in Figure 6.1, UDCA is more effective at relieving pruritus than cholestyramine, with a reduction of the pruritus score by more than 50% being seen in 67% (28 of 42) of patients treated with UDCA compared to 19% (8 of 42) of patients treated with cholestyramine (P =.0021).

6.3 : Biochemical Parameters treatment with UDCA and Cholestyramine

ALT, AST Endogenous bile acid, , γ-glu-tamyltransferase (γ-GT), Bilirubin and AP was measured before and after treatment with drug

Table 6.2: Biochemical Parameters of Patients with ICP before and after treatment with UDCA and Cholestyramine

Biochemical parameters	***Mean* ± SD**	***P* value**	***Mean* ± SD**	***P* value**
ALT (*U/L*)				
Before	194.0 ± 155.4	<.0001	189.1 ± 115.5	NS
After	78.2 ± 57.4		222.4 ± 128.0	
AST (*U/L*)				
Before	125.0 ± 101.3	<.0001	139.4 ± 87.4	NS
After	48.8 ± 31.6		151.9 ± 85.2	
AP (*U/L*)				
Before	364.9 ± 124.3	NS	384.0 ± 145.7	<.05
After	369.4 ± 120.7		425.9 ± 155.9	
γ-GT (*U/L*)				
Before	27.4 ± 15.1	NS	24.1 ± 14.2	NS
After	25.1 ± 11.0		24.4 ± 15.1	
Endogenous bile acids (µ*mol/L*)				
Before	46.5 ± 41.3	<.01	38.8 ± 38.5	NS
After	24.4 ± 29.2		26.2 ± 23.3	
Bilirubin (µ*mol/L*)				
Before	17.2 ± 15.2	NS	13.3 ± 7.4	<.05
After	13.2 ± 8.5		15.9 ± 10.0	

In both groups, the baseline serum levels of ALT, AST, bilirubin, -glutamyltransferase (-GT), -AP, and endogenous bile acids were comparable. UDCA had no effect on the levels of bilirubin, -GT, or AP in the serum, but it dramatically decreased the activities of serum aminotransferases and endogenous bile acids (Table 6.2). In contrast, cholestyramine did not significantly affectserum aminotransferases and endogenous bile acids levels, whereas serum levels of bilirubin and AP significantly increased.

6.4 : Serum bile acid before and after treatment drugs

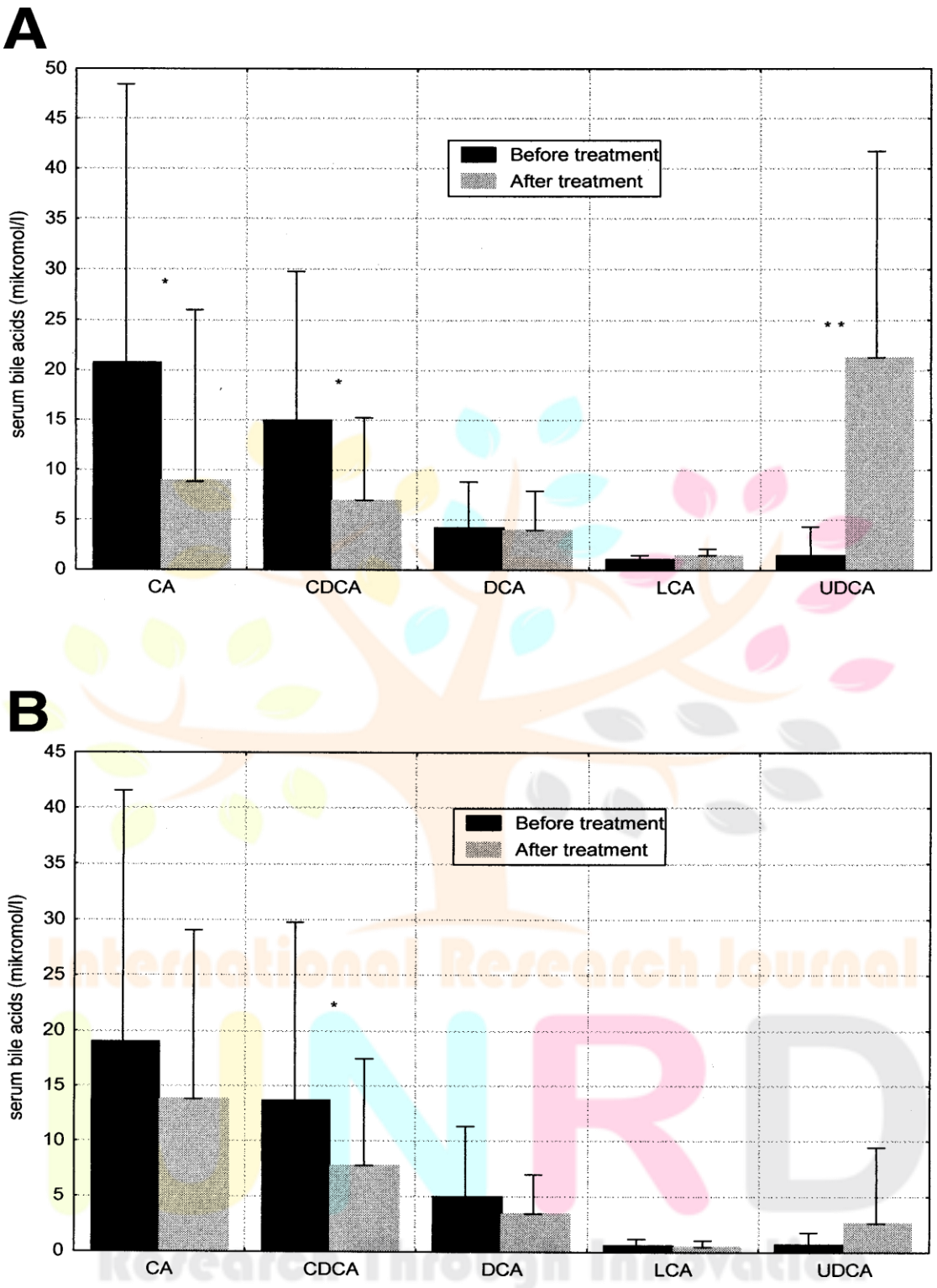

Figure 6.2. Serum bile acids before and after (*A*) UDCA therapy and (*B*) cholestyramine therapy. Data are means ± SD; **P* < .05, ***P* <.0001.

Serum levels of primary bile acids decreased significantly during treatment with UDCA:CA from 20.7 ±26.4 µmol/L to 8.9 ± 16.7 µmol/L (*P* < .01) and CDCA from 14.9 ± 13.9 µmol/L to 7.0 ± 8.3 µmol/L(*P* < .01). In parallel, UDCA increased from 1.4 ± 2.8µmol/L to 21.2 ± 20.2 µmol/L (*P* < .0001). Serum levels of the secondary bile acids DCA and LCA were notsignificantly altered by UDCA administration (Figure 6.2*A*).

Serum levels of CDCA also decreased during treatment with cholestyramine from 13.0 ± 14.6 µmol/L to 7.8 ± 6.8 µmol/L ($P < .05$), whereas serum levels of all other bile acids were unaltered during treatment with cholestyramine (Figure 6.2*B*).

6.5 : Maternal and neonatal outcomes in ICP Patients

Maternal and neonatal outcome was assessed with the Apgar Score

Table 6.3: Maternal and Neonatal outcomes in ICP patients receiving treatmentdrug

Characteristic	**UDCA group**	**Cholestyramine group**	**P value**
Still birth of neonates	0	0	P<0.0001
Apgar score – 5min	9.4 ± 0.5	8.7 ± 0.6	P<0.05
Mean Patients delivery	38.7 ± 1.7 weeks	37.4 ± 1.5 weeks	-
Post anatal development	Normal	Normal	-
Birth weight of neonatal(g)	2925	2722	-
Premature pregnancy (%)	3 (7%)	5 (12%)	-
Cesarean section ofmaternal	7 (16.7%)	3 (7%)	-
Admission to NICU	2 (5.2%)	4 (10.5%)	-

No stillbirths were observed, and no significant differences of newborns' weight were found in both groups.The Apgar score at 1 minute was similar in both groups but was significantly higher at 5 minutes in the UDCA group than in the cholestyramine group:Apgar score: 9.4 ± 0.5 vs 8.7 ± 0.6, respectively; $P < .05$.

In patients receiving UDCA, delivery occurred significantly closer to term than in patients who received cholestyramine (38.7 ± 1.7 weeks vs 37.4 ± 1.5 weeks, respectively; $P < .05$).Postnatal development has been normal in all babies. Pregnancy ended prematurely in 3(7%) patients receiving UDCA and in 5 (12%) patients treated with cholestyramine.

Seven (16.7%) patients of the UDCA group underwent cesarean section because of multiple pregnancies (3 cases), placenta praevia (1 case),cephalo-pelvic disproportion (1 case), fetal distress (1 case), and advanced maternal age (1 case), and 3 (7%) patients of thecholestyramine group underwent cesarian section because of fetal distress (1 case), twin pregnancy (1 case), and cephalo-pelvic disproportion (1 case).

6.6 : Adverse drug reaction in the ICP Treatment patients

Table 6.4: Measurement of Adverse effects in the Patients treated with the drug.

Adverse effect	UDCA group (n=42)	Cholestyramine group (n=42)
Nausea	1	11
Vomiting	2	5
Diarrhoea	0	1
Abdominal pain	1	2
Headache	0	1

UDCA was well tolerated and did not cause any adverse effects. In the cholestyramine group, 12 patients (29%) reported treatment-related adverse effects (11 nausea, 5 vomiting, 1 diarrhoea).

7.0 DISCUSSION

According to the current study, treating ICP with UDCA for 14 days is preferable to treating it with cholestyramine in terms of alleviating pruritus, promoting near-term delivery, and enhancing maternal blood liver tests. Pruritus is usually handled as an expected side effect of pregnancy and is sometimes overlooked as a critical ICP sign. Although its severity can seriously weaken the mother, pruritus is not the main concern to mother and foetus. More gravely, ICP may affect the foetus and may abruptly come to an end with severe, fatal foetal anoxia. As of yet, there is no known therapy for ICP. Pruritus has been alleviated by cholestyramine. According to observational studies, cholestyramine may improve maternal morbidity without directly affecting foetal outcome. ICP has recently been treated with UDCA more often. To our knowledge, this investigation is the first prospective, randomised trial to compare these 2 medications side-by-side for the treatment of ICP.

The normalization of defective hepatobiliary secretion, the defence of cholangiocytes against the cytotoxicity of hydrophobic bile acids, and the defence of hepatocytes against bile acid-induced apoptosis are three key modes of action of UDCA in cholestatic liver disorders, according to experimental findings. Hepatocellular cholestasis, retention of endogenous bile acids, and sex hormone metabolites are common characteristics of ICP, indicating that a major mechanism of action of UDCA in ICP may include enhancing hepatocellular secretion. The effects of UDCA in ICP are similar to those seen in other cholestatic disorders, although they manifest in ICP more immediately and subside more quickly when the medication is stopped.[59]

Recent studies have confirmed that patients with ICP have evident changes in the metabolism of bile acids and sex hormones. The cholestatic potential of some D-ring estrogens, in particular glucuronides such as estradiol-17 -D-glucuronide, and mono- or disulfated progesterone metabolites, Experimental and clinical evidence support the hypothesis that the primary 3, 5 isomers.60 While the exact mechanism by which sex hormone metabolites may cause cholestasis in ICP is still being debated, abnormal metabolites that inhibit hepatobiliary transport proteins as well as physiologically occurring metabolites in pregnancy have also been linked to ICP. In ICP, the relief of cholestasis by UDCA has been suggested to be due to stimulation of vesicular exocytosis resulting in mobilization of

an increased number of transport proteins to the canalicular membrane and, th0ereby, stimulation of transport systems involved in the biliary secretion of steroid mono- and disulfates.[61]

Approximately 30% to 60% of UDCA is absorbed in the stomach after oral delivery. Following chronic consumption, the amount of UDCA enrichment in biliary bile corresponds with the dosage given. 13–15 mg/kg/day of UDCA has been utilised in the majority of clinical studies. Recently, high-dose UDCA (1.5-2 g/day) was shown to have positive results and no negative side effects by Mazzella et al. The effectiveness of UDCA at a modest dosage (8–10 mg/kg per day) in individuals with ICP is not well understood.[62] We wanted to know how effective this modest dosage was in preventing the growth of the possibly harmful bacterial byproduct of UDCA, monohydroxy bile acid LCA, in the human colon. When administered orally, UDCA at 8–10 mg/kg per day results in a 40% enrichment of biliary bile acids. The results of our study demonstrate a beneficial effect of a moderatedose of UDCA on relief of pruritus when compared with cholestyramine (50% relief in67% vs 19% of those treated with cholestyramine). The present study confirmed rapidrelief of pruritus in patients receiving UDCA, and most of them experienced a clear relief of pruritus after 3–4 days, whereas during treatment with cholestyramine, pruritususually attenuated only after 7–10 days.

In agreement with the literature, elevation of aminotransferase activities from 2- to 15-fold was noticed in 85% of patients, bilirubin from 2- to 4-fold in 14% of patients, andfasting serum bile acids from 1.5- to 20-fold in 78% of patients.3,36 Sensitive serum markers for cholestasis such as -GT and AP were usually normal or slightly elevated: -GT was elevated up to 3-fold in 11% of patients, and AP was elevated 2- to 3-fold in 60% of patients. When -GT levels are high, a mutation of the gene encoding the canalicular phosphatidylcholine translocase (multidrug resistance gene 3; MDR3) is suspected.[63]

Aminotransferase activities and fasting serum bile acids levels weresignificantly reduced after treatment with UDCA, whereas cholestyramine did not affect these parameters. Serum bilirubin and -GT levels were normal in 86% and 89% of patients, respectively, before treatment and were not significantly affected by UDCAor cholestyramine. Serum alkaline phosphatase activity, which is mainly of placental origin in the third trimester of pregnancy, was not altered by medical treatment.[64]

Our data also confirm earlier findings demonstrating that an increase of serum bile acids and especially of CA appears to be a sensitive indicator of ICP. The measurement of serum bile acids is particularly helpful in patients with pruritus but normal transaminase activities. CA predominated in the spectrum of serum bile acids during ICP when compared with healthy pregnant women. In a prospective cohort study fromSweden, Glantz et al demonstrated a correlation between fetal complications and serumbile acids levels. Stronger uterine muscle contractions and placental chorionic vein vasoconstriction have been reported to be correlated

with elevated CA levels in maternal blood, which may result in fetal discomfort.[65] After UDCA therapy, it was shown that the concentrations of CA and CDCA had dramatically decreased, but under cholestyramine administration, the serum concentrations of bile acids had not significantly altered, with the exception of CDCA. The binding of bile acids by cholestyramine and the stoppage of their enterohepating circulation may be one explanation for this decline in CDCA. Unabsorbed UDCA is partially transformed into LCA, which is known to be embryotoxic in rats, in the colon by intestinal bacteria.1,41 Our research has demonstrated that when UDCA is used in therapy at reasonable levels, LCA is not appreciably elevated. Given that a reduction in CA has been linked to foetal discomfort, it could have therapeutic significance. The Apgar score at 5 minutes was much higher in the UDCA group, and the delivery occurred significantly closer to term than in the individuals who got cholestyramine. However, neither stillbirths nor significant changes in neonatal weight were identified in either group.[66]

The current results support UDCA's outstanding safety profile: No negative effects were noticed. On the other hand, 12 patients (or 29% of the patients) could not tolerate cholestyramine due to nausea and vomiting. ICP and cholestyramine therapy both have the potential to cause vitamin K insufficiency on their own. In order to reduce pruritus in ICP, prolonged high-dose cholestyramine therapy may also raise the risk of coagulopathy. However, we found no evidence of coagulopathy in this investigation. This could be because the course of therapy was so brief.

8.0 CONCLUSION

As a consequence of therapy with a modest dose of UDCA, the findings of our study demonstrated a substantial reduction in the degree of pruritus, aminotransferase activity, and serum bile acid concentrations as well as a more favourable pregnancy outcome and lack of side effects. When compared, Cholestyramine had negative effects and very slightly increased pruritus. These encouraging outcomes from the current and earlier studies support the use of UDCA as the first-line treatment for ICP.

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