Journal of Obstetrics and Gynaecology of India Vol. 51, No. 6 November December 2001 Pg 66-68

Role of Ursodeoxycholic Acid in Intrahepatic Cholestasis of Pregnancy

Sudhanshu K Rath, Punita Arora, Anath B Chattopadhyay, Bhupinder S Duggal

Department of Obstetrics & Gynaecology, Armed Forces Medical College, Pune 411040

Summary

Intrahepatic cholestasis of pregnancy, characterised by pruritus and certain biochemical alteration in liver functions was considered earlier as a benign condition. It came to be realised in the last decade that the condition does have number of adverse effects on the fetus. Around the same time it was also found that the drug Ursodeoxycholic acid was effective in altering the bile acid composition which has a bearing on pruritus. This study was aimed at finding out if the drug in question can fulfill the twin objectives of relief of symptom and improvement of perinatal outcome. Total of fifteen patients were studied. Though biochemical parameters of live function did not return to complete normalcy during therapy, symptomatic relief was considerable. The effect on perinatal outcome has been found to be promising.

Introduction

Liver diseases in pregnancy are conveniently considered under three heads. These are, pre-existing liver diseases, coincident liver diseases and liver diseases peculiar to pregnancy (Burroughs, 1998). Intrahepatic cholestasis of pregnancy (ICP) falls in the last category. Until recently the problem was considered essentially benign with no serious effect on maternal health. Since the only irritating symptom was pruritus, treatment with any antipruritic drug was considered adequate. The response, however was not uniform. Obstetricians started realising in the last decade that this seemingly benign condition for the mother has got a number of adverse effects on the fetus. Preterm delivery, unexplained antepartum fetal death, and meconium aspiration syndrome were some of the problems reported in these patients (Alsulyman, 1996 Reyd, 1976). In ICP there is an alteration in bile acid composition and progesterone metabolite in maternal serum. Whether these alterations are directly responsible for the adverse outcome is not clear. However, it came to be realised that Ursodeoxycholic acid (UDCA) administered to the patients with ICP can alter the bile acid composition (Meng et al 1997). Hence it was thought that UDCA might influence the outcome of a pregnancy complicated by ICP. We decided to study the effect of UDCA in our patients of ICP and find out if there is any impact on the symptoms, maternal biochemistry and perinatal outcome.

Material and Method

Patients of intra hepatic cholestasis of pregnancy were included in the study on the basis of following criteria.

1. Antenatal cases reporting with pruritus
2. No apparent skin disease to account for the symptoms
3. Raised serum bilirubin
4. Presence of gall stones excluded on ultrasound
5. Hb S Ag negative status confirmed
6. No history of any preexisting liver disease

Base line liver function tests were recorded which consisted of Serum bilirubin, SGPT and alkaline

transaminase. The degree of pruritus was scored on the basis of the sites severity and nocturnal involvement. The scoring was done in an arbitrary scale of 0-4 Diatera 1996). All patients identified during the period of August 1998 July 1999 were included in the study. UDCA was administered in the doses of 300 mg in twice daily. No local or systemic antiipuritic agent was used. Pruritus score was assessed on a weekly basis. Liver function tests were also repeated every week. Antepartum tests of fetal well being were carried out routinely. Time and mode of delivery was decided on the merit of obstetric indication. Weight of the baby and Apgar score were noted. The primary outcome measures were taken as the effect on symptom, liver function tests, length of pregnancy and neonatal condition. In case of multigravidae with recurrent history of ICP some of the obstetric outcome could also be compared with their past obstetric performance when UDCA was not in use.

Results

During the period of study, 15 cases were identified for inclusion in the study from the antenatal cases attending the out patient department of a Service Hospital in Pune. The incidence of the condition was 1:350. The age of the patients ranged from 19 to 35 years. There were 6 primigravidae and 9 multigravidae in the study group. All the multigravidae had history of pruritus in previous pregnancy. The time of onset of the disease was in the third trimester in 13, second trimester in 1 and first trimester in 1 case.

Table I
Effect on Pruritus

Time After UDCA in weeks	Number of Cases with Score			
	0	1	2	3
Outset	0	2	8	5
One week	4	2	4	0
Two weeks	9	4	2	0
Three weeks	12	3	0	0

The effects of UDCA on pruritus, which was the only important symptom has been indicated in Table I. The improvement of this cardinal symptom was appreciable within a week and continued up to three weeks. Table II and III depict the effect on serum bilirubin and live enzymes respectively. It is interesting to note that though reduction in the level of serum bilirubin and liver enzymes is apparent, complete normalcy is achieved in very few cases. Our main concern however was about the obstetric results with particular reference to neonatal outcome. The data is shown in Table IV. The comparison between past and present neonatal outcome in respect of multigravidae with recurrent ICP as shown in Table V brings out the effect of UDCA since none of them has used this drug earlier.

Table II
Effect on Serum Bilirubin

Time after UDCA in weeks	Number of cases with levels (in mgm %)		
	<0.8	0.8-2.0	>2.0
Outset	Nil	12	3
One Week	Nil	14	1
Two Weeks	3	11	1
Three Weeks	3	12	Nil

Table IV
Obstetric Outcome

Event	Figure
Preterm Delivery	3
Term Delivery	12
Low Apgar	
Neonatal Death	Nil
Still Birth	Nil
Average Birth Weight	2560 GM
Mean Length of Pregnancy	261 days
Vaginal Delivery	10
Caesarean Delivery	5

Table V
Comparison of Past and Present Obstetric Outcome of Multi Gravidae with Recurrent ICP

Event	Past No. of Pregnancy = 8	Present No. of Pregnancy = 6
Term Delivery	4	5
Preterm Delivery	4	1
Low Apgar	2	1
Early Neonatal Death	2	Nil
Still Birth	2	Nil

Table III: Effect on Liver Enzymes

Time after UDCA	Number of Cases with SGPT Levels			Number of cases with ALP Levels.		
	Less than 40 IU/l	40 to 100 IU/L	More than 100 IU/L	Less than 60 IU/L	60 to 200 IU/l	More than 200 IU/l
Outset	1	2	12	Nil	5	10
One Week	2	2	11	Nil	7	8
Two Weeks	2	6	7	1	10	4
Three Weeks	2	10	3	2	12	1

Discussion

The incidence of ICP in various European studies have been reported between 0.2 to 1.7% (Diaferia 1996). The incidence in our study is on the lower side (0.22%). A low incidence in Asiatic women as compared to Northern Europe and South America has been reported (Sheila and Dooley Sherlock 1995). In our study all the 15 patients had raised serum bilirubin and abnormal liver enzymes. Though UDCA was effective in reducing the levels, it is observed that complete normalcy was achieved in 20% cases as regards to serum bilirubin and 26.6% cases as regards to liver enzymes. However complete amelioration of pruritus was observed in 80% cases. It is possibly because the agents responsible for pruritus were not billirubin or liver enzymes but the lipophilic primary bile acids like cholic acid chenodeoxycholic acid which is raised in ICP. (Heikinon 1991). UDCA, which in turn is a hydrophilic tertiary bile acid may be acting by replacing the primary bile acids (Brites et al 1998). Apart from the replacement role refered to above, other modes of action of the drug could be dilution and Kurtz hypercholeretic action (Palma 1992, Crossignanni 1991) and immune interference (Leuschman 1990).

The effect of alteration in maternal biochemistry after administration of UDCA is marked so far as fetal outcome is concerned. In our series only 1 case (6.6%) of low apgar score and 2 cases (13.3%) of preterm delivery have been observed. There has been no still birth or neonatal mortality. This is a very favorable observation when compared to high incidence of premature delivery (19-37%) and high perinatal mortality reported in untreated cases of ICP (Latikassen and Tulehhemia 1984). Encouraging results have also been reported with use of UDCA by Palma et al (1992).

ICP is said to be a recurrent condition (Diaferia 1996). All the 6 multigravidae in our study had history of pruritus in previous pregnancies corroborating above observation. When we tried to compare the past obstetric performance of these multigravidae involving 8 pregnancies with the present, it was found that they had experienced perinatal mortality in 50% cases in the past whereas all the 6 present pregnancies were salvaged. Davis (1993) has also reported 3 cases of recurrent ICP who had total of 8 stillbirths in the past but the next pregnancy could result in healthy new born after use of UDCA.

A potential problem with use of UDCA has been thought to be of production of some amount of lithocholic acid by intestine bacterial action on UDCA. This can be absorbed and can find it's way to fetal circulation with the possibility of harmful effects (Heikinon 1980). However, it has been observed that human fetal liver, despite its inability to detoxify lithocholic acid by sulfation, is able to rapidly change lithocholic acid into hyodeoxy cholic acid by hydroxylation (Gustfeson et al 1987). In conclusion it can be said that UDCA has a promising role to play not only in the amelioration of the distressing symptom of pruritus but also in improving the perinatal outcome. Since the incidence of the condition is low, large scale therapeutic study is possible only on a multicentric basis to augment our observations.

References

1. Alsulyman O M, Ouzonian J G, Ames Castro M, Goodwin T M. Am J. Obst Gyn; 175: 957, 1996.
2. Brites D, Rodriques CM, Van Zeller H, Bertolini F. Euro J Obst Gyn Reprod Biol; 80: 31, 1998.
3. Burroughs A K. Forum : 8(1): 42, 1998
4. Crossignanni A, Podola M, Bertolini F, Battezzati MP, Zuin M. Hepathology : 13, 1976, 1991
5. Davis M H, Da Silva RCMA, Jones S R. Gut, 37, 580, 1995.
6. Diaferia A, Nicastri P L, Tartagni M. Int. J. Obst Gyn, 52: 133, 1996.
7. Gustfesson J, Anderson S, Sjovell J. Pediatr Res; 21: 99, 1987.
8. Heikinon J, Maentausta O, Tulmala R, Janne O. Obst Gyn.; 56: 60, 1980.
9. Heikinon J. Obst. Gyn.: 98: 340, 1991.
10. Latikassen I, Tulehhemia A. Int. J. Gyn. Obst., 22, 91, 1984.
11. Leuschna U, Kurtz W. Diag. Dis. Sci.: 8: 12, 1990.
12. Meng L J, Reyes H, Axelson M, Palma J, Ribalta J. Hepatology; 26(6): 1573, 1997.
13. Palma J, Reyes H, Ribalta J, Iglesias J, Gonzales M J. Hepatology : 15: 1043, 1992.
14. Reyde R, Ivey K J, Recenet R H. Br. Med. J. 1: 570, 1976.
15. Sheila Sherlock & James Dooley : Diseases of the liver and biliary system 1995; 10th Edition P 480.