Two-year experience of obstetric cholestasis: outcome and management

R. Deveer, Y. Engin-Ustun, Ş. Çelen, Ö.G. Eryılmaz, E. Tonguç, L. Mollamahmutoğlu, A. Oksuzoglu, N. Danisman

Dr. Zekai Tahir Burak Women Health Research and Education Hospital, Ankara (Turkey)

Summary

Purpose: Our aim was to evaluate the management and outcome of obstetric cholestasis in our perinatology unit. *Methods:* We analyzed 44 pregnant women complicated by cholestasis. Data were collected retrospectively. Details of patient demographics and outcomes of pregnancy were recorded. Patients were randomized due to their decision to take ursodeoxycholic acid (UDCA) therapy or not. *Results:* Forty-four women of age 28.09 ± 4.6 years delivered 45 newborns. The mean gestational age at diagnosis of obstetric cholestasis was 32.36 ± 3.75 weeks. The mean delivery time was 38.25 ± 1.5 weeks. Spontaneous premature delivery occurred in five (11.4%) of the patients. No stillbirths were observed. Serum transaminases decreased significantly in 26 of the patients who were treated with oral UDCA therapy. Twelve (27.2%) babies were admitted to the neonatal intensive care unit (NICU). Out of 12 mothers whose babies were admitted to NICU, nine patients had not received UDCA ($p = 0.07$). *Conclusion:* UDCA is effective in lowering transaminases.

Key words: Obstetric cholestasis; Pregnancy outcome; Ursodeoxycholic acid.

Introduction

Obstetric cholestasis (OC) is a reversible form of cholestasis occurring in the third trimester of pregnancy, with symptoms resolving postpartum. The incidence in Europe is approximately 10-150 per 10,000 pregnancies [1]. The major consequences of OC are premature births [2], intrapartum fetal distress [3, 4] and stillbirths [5, 6].

The etiology of OC is multifactorial involving genetic, hormonal and environmental factors. Total bile acid (TBA) assays are important for the diagnosis. Ursodeoxycholic acid (UDCA) therapy is being used in the treatment [7-10]. The optimal time for delivery is not clear.

The purpose of this study was to report our experience with 44 cases of OC seen at our perinatology unit and to evaluate the management and discuss the delivery time.

Materials and Methods

This was a retrospective study over a 24-month period. The study was approved by the local ethics committee. Details of patient diagnosis and pregnancy outcomes were collected. The diagnosis of OC was based on the following criteria: 1) generalized pruritis without skin changes in the second half of pregnancy; 2) elevated liver function tests and/or serum bile acids; 3) Other dermatologic and/or internal conditions known to cause pruritus or other causes of abnormal liver function tests were excluded; 4) Postnatal resolution of symptoms and of biochemical abnormalities. Laboratory results reviewed in all patients included levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total serum bilirubin. Details of patient demographics and outcomes of pregnancy were collected. Data recorded at delivery included gestational age, mode of delivery, spontaneous or induced labor, and admission to neonatal intensive care unit (NICU). All women who presented with idiopathic pruritus in pregnancy had liver function tests (serum transaminases and bilirubin). Thirteen of them underwent fasting TBA. After verbal and written informed consent was obtained, patients decided whether to take UDCA therapy or not. Follow-up assessment of serum liver function tests was obtained one week after diagnosis. These results and obstetric outcomes of the patients were compared between the groups who received therapy and who did not. The management protocol consisted of serial evaluation of serum liver function tests and monitoring of fetal well-being with weekly non-stress tests, amniotic fluid volume and Doppler assessment starting at the time of diagnosis. Hospitalization was decided in the presence of severe symptomatology, highly elevated liver function tests or at 38 weeks of pregnancy. Labor induction was performed after completing 40 weeks for undelivered patients. Serum liver function tests were obtained one week after delivery.

Statistical analysis was performed with the software package SPSS for windows 11.0 (Statistical package for Social Sciences; SPSS Inc. Chicago, IL). The normality of distribution of variables was tested by using the Kolmogorov-Smirnov test. Data are expressed as means (± SD) for normally distributed variables or as medians for asymmetrically distributed variables, unless otherwise specified. When the Kolmogorov-Smirnov normality test revealed normal distribution, we used an independent sample *t* to compare the differences between the two groups. When the test failed, the Mann-Whitney *U* test was used to compare the differences between the groups. Pre- and post-treatment values in both groups were compared by the paired *t*-test. Statistical significance was defined as $< .05$.

Results

Clinical characteristics and therapy

During the study period 44 women were diagnosed as OC based on inclusion criteria. The mean age at presentation was 28.09 ± 4.6 years (range, 19-38 years). Diag-

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nosis was established at a mean ± SD of 32.36 ± 3.75 weeks' gestation (range, 23-38 weeks). Twenty-one of the patients were primigravid while 23 were multigravid. The mean body mass index was 27.20 ± 3.63 kg/m². There was only one twin gestation. A previous history of OC was documented in only five (27.7%) cases. Seven (16%) of the patients had received progesterone treatment and 12 (27%) of them had received antibiotics during pregnancy, and all had negative serologic findings for hepatitis A, B, C virus, cytomegalovirus, herpes simplex virus, and Ebstein-Barr virus. Six (13.6%) patients had a positive family history. An upper abdominal ultrasonography was performed in all our patients, three (16.6%) of whom had concomitant cholelithiasis. The disease started with sudden severe, generalized pruritis, often pronounced on the palms and soles. None of the patients presented with jaundice. Oral therapy with UDCA was started in 26 (59%) cases at a dose of 750 mg per day. Symptoms and laboratory findings improved within five to seven days in all patients who took therapy and treatment was continued until delivery. Eighteen patients (41%) were not treated with UDCA.

Laboratory findings

Serum concentrations of AST and ALT were elevated in 39 (89%) patients. (Median, 126 U/l for ALT; (range, 20-714) and 81 U/l for AST (range, 15-187), respectively). Levels of total serum fasting bile acids (TBA) were studied in only 13 patients (median, 44 μmol/l; range, 11-111 μmol/l). Total serum bilirubin levels were within normal limits in all patients. AST and ALT levels decreased significantly after one week in 26 of the patients who had received oral UDCA therapy (Table 1).

Obstetric characteristics

Five (11.4%) patients had IVF pregnancies. Mild preeclampsia developed in two (5.9%) patients. One (2.3%) had postpartum hemorrhage; she was treated expectantly. Twenty-seven (61%) patients had spontaneous labor, while seven (15.9%) patients had induced labor. Spontaneous premature delivery occurred in five (11.4%) of the patients. Fourteen (32%) patients delivered vaginally, while 30 (68%) had cesarean section; eight (18%) of these underwent emergency cesarean section for fetal distress. At 39 weeks, elective cesarean section was performed for those with a history of previous cesarean section, breech presentation and IVF pregnancy. The rest of the patients were allowed to await spontaneous labor with close surveillance, hospitalized at 38 weeks and induced after $40+^{6}$ weeks. The mean birth weight was 3154 ± 551 g (range 1760-4450). Twelve (27.2%) babies were admitted to the neonatal intensive care unit (NICU). Out of 12 mothers whose babies were admitted to NICU, nine patients had not received UDCA ($p = 0.007$). The main indication for NICU admission was respiratory distress, which was significantly higher in the non treated group ($p = 0.005$). Meconium staining of amniotic fluid (MSAF) and apgar score < 7 at 5 min were seen in two babies in the non treated group but these differences were not significantly different. There were no statistically significant differences among birth weight, delivery time, mode of delivery and spontaneous premature delivery rate between treated and non treated groups (Table 2).

Table 1. — *Changes of ALT and AST between groups*.

	AST			ALT		
	On admission	1 week later	*p*	On admission	1 week later	*p*
Group 1 (n = 26)	154.5 (15-432)	80.9 (15-334)	0.001	263.3 (24-714)	133.2 (11-339)	0.001
Group 2 (n = 18)	77.7 (20-214)	66.5 (14-181)	0.078	102 (20-308)	85.3 (20-193)	0.133

Group 1: Patients who received oral UDCA therapy. Group 2: Patients who did not receive UDCA therapy.
AST: Aspartate aminotransferase. ALT: Alanine aminotransferase.

Table 2. — *Characteristics of treated and non treated groups*.

	Group 1	Group 2	*p*
Age (years)	28.6 ± 4.2	26.2 ± 4.4	0.079
BMI (kg/m²)	27.6 ± 3	27 ± 3.9	0.571
Gravida	2 (1-5)	1 (1-6)	0.292
Parity	0 (0-2)	0 (0-2)	0.678
Time of diagnosis (wks)	31 ± 3.9	33.1 ± 3.4	0.08
Time of delivery (wks)	38.2 ± 1.5	38.2 ± 1.4	0.921
Cesarean section (%)	61.5	66.7	0.761
Birth weight (g)	3161.9 ± 464.4	3221.6 ± 593.1	0.710
Apgar < 7 at 5 min (n, %)	0	2 (11.1)	0.162
MSAF (n, %)	0	2 (11.1)	0.162
Preterm delivery (n, %)	3 (11.5)	2 (11.1)	0.965
Admission to NICU (n, %)	3 (11.5)	9 (50)	0.007
NICU admission indication			
Respiratory distress (n, %)	1 (3.8)	2 (7.7)	0.005
Low birth weight (n, %)	2 (7.7)	2 (11.1)	0.545

Group 1: Patients who received oral UDCA therapy. Group 2: Patients who did not receive UDCA therapy.
BMI: Body mass index, MSAF: Meconium staining of amniotic fluid, NICU: Neonatal intensive care unit.

Discussion

The frequency of OC is influenced by geographic and ethnic differences. The highest incidence is considered to be in Chile (16%) and Bolivia (9%); rates of 0.1% to 1.5% have been described for Europe and North America [1]. In the present study we found the incidence of OC to be 0.09% in which 47,081 deliveries had occurred over a 24-month period. The major prognostic factor for the diagnosis of OC is elevation (> 11 μmol/l) of total serum bile acid levels [1]. It was our limitation that we could study the serum bile acids only in 13 of our patients. The incidence of OC might be higher; if we could study the bile acids in every patient with pruritus.

The pathogenesis of OC is multifactorial, involving genetic, hormonal and environmental factors. Genetic factors can be explained by positive familial cases and the higher incidence in same ethnic groups [7, 11]. In our series, recurrence was noted in five (27.7%) of 18 multiparous women and six patients (13.6%) had a positive family history. Other postulated causes such as progesterone or antibiotic treatment [1, 12] were present in 19 (43%) of our patients.

OC typically occurs in the third trimester of pregnancy, as it did in our patients. Pruritus is typically worse at night, is often widespread and usually starts in the palms and soles. There can be significant maternal morbidity in association with the intense pruritus. None of our patients presented with jaundice. One patient suffered from postpartum hemorrhage.

Potential fetal risks are the major complications of OC. The most concerning consequence is the 3-to-5-fold increased risk for fetal death in utero [13]. The cause of fetal distress and stillbirth in OC is not fully understood, however elevated bile acid levels seem to induce vasoconstriction of human placental chorionic veins, and myometrial sensitivity to oxytocin [14, 15]. Elective delivery at 37 weeks has been discussed to prevent intrauterine deaths [16]. We did not perform any elective delivery before 39 weeks. Our hospital is a tertiary care maternity center that provides all obstetric services for women with complicated pregnancies. Most high-risk deliveries in the central part of Turkey took place in this clinic, so our clinic's cesarean section ratio is around 60%. Moreover, previous section, breech presentation and IVF pregnancies are absolute indications for cesarean section. For all these reasons our cesarean section rate was 63.6%. Pregnancies complicated by OC may lead to premature births in up to 60%, fetal distress in up to 33%, and intrauterine death in up to 2% of patients [1]. In this study we observed no stillbirths. The rate of spontaneous preterm delivery was 11.4% and there was no statistically significant difference between treated and nontreated groups. Cesarean section was performed for fetal distress in eight patients (18%). Our mean gestation at delivery was 38.25 ± 1.5 weeks.

Treatment of OC should ideally reduce both fetal risk and maternal symptoms. UDCA, a naturally hydrophilic nontoxic bile acid, is the treatment of choice for patients with OC [17-20] and has been successfully used to improve clinical and biochemical indices in a variety of cholestatic liver diseases [1]. It stimulates the extraction of hydrophobic bile acids, other potentially hepatotoxic compounds, and sulfated progesterone metabolites. Although the exact mechanism of action is still not fully understood, experimental evidence suggests that it improves impaired hepatocellular secretion and corrects the maternal serum bile acid profile [21], decreases the delivery of bile acids to the fetus, and restores the function of the bile acid transport system across the trophoblast [22], thus representing a valuable contribution to fetal well-being and outcome [19]. UDCA has virtually no side-effects except for mild diarrhea in rare cases. It can reduce the risk of premature delivery [17, 18]. In the present study, UDCA was used to treat 26 of 44 cases. Out of 12 cases whose babies were admitted to NICU, nine patients did not receive UDCA. The difference was statistically significant. Also in the treated group liver transaminases decreased significantly in one week. UDCA was tolerated without adverse effects in all our patients.

In conclusion, the occurrence of pruritus in pregnancy, particularly in the last trimester, must never be neglected. Because OC may be associated with increased fetal risks, close obstetric surveillance is essential. Treatment with UDCA is considered as first-line therapy. We observed a significant effect of the treatment with UDCA on maternal pruritus and serum liver tests. Instead of induction of labor at around 37 weeks of gestation, which is commonly practiced, we allowed for term delivery (> 37 weeks). However, the treatment group did not differ significantly in the number of premature deliveries (< 37 weeks gestation). Therefore larger prospective studies are required to predict increased risk of spontaneous preterm births in patients with OC.

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Address reprint requests to:
R. DEVEER, M.D.
30. cad. 340. Sok.
5/5 Çiğdem Mah./Ankara (Turkey)
e-mail: deveer3@hotmail.com