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CLINICAL EVALUATION INTRAHEPATIC CHOLESTASIS OF PREGNANCY: IMPROVED OBSTETRIC OUTCOMES WITH URSODEOXYCHOLIC ACID THERAPY

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SUMMARY

Aim: *Intrahepatic cholestasis of pregnancy (ICP) is a condition that manifests during the second or third trimester as pruritus, with or without jaundice. Although it is a disease that alters maternal well-being, no severe maternal morbidity or mortality is attributed to it. The purpose of this study was to focus on the clinical features of ICP and to determine the influence of ursodeoxycholic acid (UDCA) on the prognosis of pregnancy in terms of symptomatic relief and obstetric outcome.*

Material-Methods: *Forty-seven patients diagnosed with ICP were enrolled in this study. Of these, 35 received cholestyramine (4gr/day) and 12 received UDCA (750 mg/day). The severity of pruritus was graded before treatment and once a week following treatment.*

Results: *UDCA administration significantly improved fetal prognosis and maternal symptoms ($p<0,05$).*

Conclusion: *Early and accurate detection of ICP is important in order to provide sufficient obstetric surveillance and fetal monitoring. The results of this study suggest that UDCA alters the pathogenesis of the disease and prevents adverse effects on pregnancy.*

Key Words: *Intrahepatic Cholestasis, Pregnancy, Cholestyramine, Ursodeoxycholic Acid*

ÖZET

GEBELİĞİN İNTRAHEPATİK KOLESTAZINDA KLİNİK DEĞERLENDİRME: URSODEOKSİKOLİK ASİD (UDCA) TEDAVİSİNİN GEBELİĞİN PROGNOZUNA ETKKİSİ

Amaç: *Gebeliğin intrahepatik kolestazı, gebeliğin ikinci veya üçüncü trimestirinde kaşıntı ve /veya sarılık ile ortaya çıkan bir hastalıktır. Annenin iyilik halini etkilese de bu hastalığa bağlı ciddi maternal morbidite veya mortalite bildirilmemiştir. Bu çalışma ile hastalığın klinik özelliklerini ortaya koymayı ve UDCA tedavisinin gebelik prognozu ile maternal semptomatik rahatlama üzerine olan etkisini araştırmayı amaçladık.*

Materyal-Metod: *Çalışmaya gebeliğin intrahepatik kolestazı tanısını almış 47 hasta dahil edildi. 35 hastaya kolesteramin (4 gr/gün) ve 12 hastaya da UDCA (750 mg/gün) doğum gerçekleşinceye kadar verildi. Tüm hastalarda tedaviye başlanmadan ve tedavi sonrası da her hafta tekrarlanmak üzere kaşıntının şiddeti derecelendirildi.*

Bulgular: *UDCA tedavisinin maternal semptomları ve fötal prognozu belirgin düzelttiği saptandı ($p< 0,05$).*

Sonuç: *Yeterli obstetrik takip ve fötal monitörizasyon hastalığın erken ve kesin tanısı önemlidir. Bu sonuçlar, UDCA'nın, hastalığın patogenezi üzerine etki ederek gebelik seyirindeki olumsuzlukları önlediğini düşündürmektedir.*

Anahtar Kelimeler: *İntrahepatik Kolestaz, Gebelik, Kolesteramin ,Ursodeoksikolik Asid*

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Intrahepatic cholestasis of pregnancy (ICP) is characterised by pruritus in almost every patient with the disease, a minority of which have signs of jaundice. The symptoms usually appear late during pregnancy and disappear after delivery. The disease was first described by Alvar Svanborg and other Scandinavian clinicians as 'Jaundice in late pregnancy'. Later, when it was understood that pruritus rather than jaundice was the most common clinical symptom of this disease, those names that emphasised jaundice were abandoned, and 'intrahepatic cholestasis of pregnancy' or 'cholestasis of pregnancy' became the accepted terms with which to define the disease. High rates of ICP have been reported in Sweden and Chile (3% and 15%, respectively). Although the cause of ICP is unknown, the pathogenesis of the disease seems to be multifactoral, including hereditary predisposition, abnormal hepatic metabolism due to elevated hormones, environmental, and, possibly, dietary factors.

The main consequence of this disease is a high rate of perinatal morbidity and mortality. Serious fetal monitoring should be considered in order to prevent adverse obstetric outcomes. The disease affects the mother mildly, and no maternal mortality has been attributed to it.

Several drugs have been used to relieve maternal symptoms and to correct cholestasis. The most promising results have been reported in connection with the use of UDCA, due to its influence on both prognosis of pregnancy and severity of pruritus. However, delivery provides the only cure for ICP.

Materials and Methods

This study comprised 47 patients with ICP admitted to the Department of Gynecology and Obstetrics at Ankara University School of Medicine (mean patient age: 26.9 years; age range: 19-39). Improvement of symptoms and obstetric outcomes were analysed according to patients' preferred drug therapy.

A diagnosis of ICP was made if the prominent symptom of skin pruritus, with no skin lesions except those caused by scratching, appeared during pregnancy. In addition to routine biochemical and urine examinations, liver function tests (SGOT, SGPT, GGT, Alkaline phosphates, serum proteins, prothrombin time, 5 nucleotidase), hepatitis markers and thyroid functions were checked, and all patients underwent ultrasonographic examination to exclude any hepatobiliary abnormality.

Patients were divided into two groups, according to their choice of cholestyramine or ursodeoxycholic acid (UDCA) for drug therapy. Patient histories are summarised in Tables 1 and 2.

Patients in Group 1 were administered cholestyramine (4gr/day) and those in Group 2 UDCA (750 mg/day) orally up until delivery. The severity of pruritus was graded before treatment and once a week following treatment, according to Ribalta et al (Table 3; Figure 1) (1).

Obstetric prognosis and newborn status of the two groups were also compared, and the differences between the groups were evaluated using student's t test or ANOVA analysis.

Results

Values of biochemical parameters did not differ significantly between the two groups, except in those cases whose dominant symptom was jaundice. However, there was a statistical difference between the two groups in terms of symptomatic relief and obstetric prognosis ($p<0,05$).

Maximum levels of laboratory results for the ichteric form of ICP cases are shown in Table 5. Four patients received cholestyramine and two patients received UDCA treatment. Significant symptomatic relief was observed in those patients treated with UDCA. Due to the limited number of patients in the study, no statistical parameters are provided.

Symptoms in patients in both groups showed improvement, but the improvement in pruritus was higher, according to Ribalta's scale, in the UDCA group (1). All the newborns had apgar scores greater than six at five minutes, and their weights were appropriate for their gestational age. No fetal distress was detected during ante-

Table 1: Patient Histories

	Mean	(n)	Range
Age	26,9		19-39
Parity			1-5
Family History of ICP		5	
History of ICP in previous pregnancy (Table 3)		5	
Twin Pregnancy		2	

Table 2: Distribution of Patients According to Trimester

Trimester	Gestational week	n (total 47)
I	(4-14)	1
II	(15-27)	22
III	(28-40)	24

natal monitoring using a non-stress test, and Caesarean sections in the UDCA group were performed only as a result of cephalopelvic disproportion or patient preference.

Obstetric complications in the cholestyramine group were: premature delivery (n=5), intrauterine growth retardation (n=2), fetal distress (n=8), twin pregnancy (n=1), antenatal urinary infection (n=4), presence of meconium (n=13) and intrauterine exitus (n=1).

Mean newborn weights for Groups 1 and 2 were 2600 gr and 3300 gr, respectively ($p<0.05$).

Table 3: Obstetric History of the Patients with Recurrent ICP

No	Parity	Onset of Pruritus (Week)	Delivery	Newborn Weight (gram)	Presence of Meconium
1 UDCA	2G1P Current P. Previous P.	 36 30	 Vaginal Vaginal	 3600 3000	 + -
2	2G1P Current P. Previous P.	 28 20	 Sectio/Cesarian Intrauterin exitus (IUEx)	 3040 2200	 +
3	2G1P Current P. Previous P.	 30 34	 Vaginal Vaginal	 3350 2750	 - -
4 UDCA	2G1P Current P. Previous P.	 31 28	 Vaginal Vaginal	 3660 2300	 - -
5	5G4P Current P. Previous P.	 28 36	 Vaginal IU Ex	 3570 3600	 + -

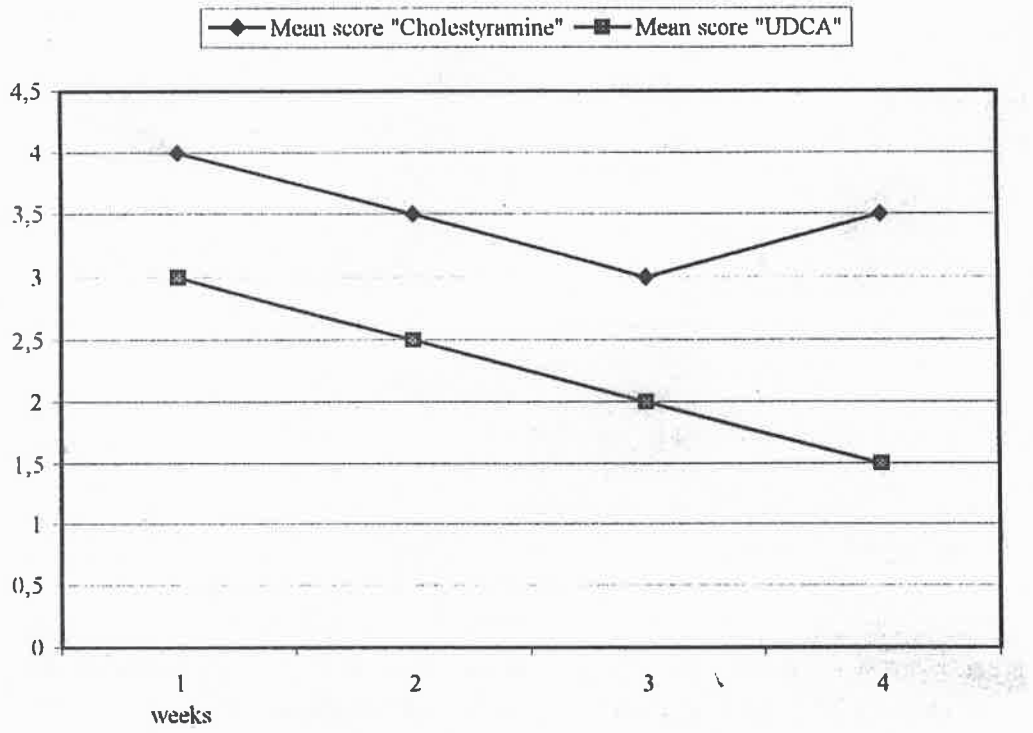

Figure 1: Comparison between cholestyramine and UDCA effects in patinets with ICP

There was no significant difference between the groups in onset of symptoms in terms of mean gestational age or patient age or parity. No correlation was observed between the trimester of pregnancy in which the disease was first diagnosed and the rate of adverse obstetric outcome.

Discussion

ICP is among the hepatic disorders that occur during pregnancy in normal healthy women and resolve after delivery. ICP is also known as recurrent intrahepatic cholestasis of pregnancy, obstetric hepatosis and pruritus gravidarum (2). It is characterised by pruritus, with or without jaundice, and increased levels of serum bile acids. ICP is often associated with premature delivery, fetal distress and perinatal mortality. There have been many studies whose main aim was to show the effect of UDCA treatment on the bile acid pool (3). Although the effect of UDCA on serum

Table 4: Severity of Pruritus

Score	Severity of Pruritus
0	Absence of pruritus
1	Occasional pruritus
2	Discontinuous pruritus every day, prevailing asymptomatic lapses.
3	Discontinuous pruritus every day, prevailing symptomatic lapses.
4	Permanent pruritus, day and night.

Table 5: Maximum Values of Biochemical Cholestatic Criteria of Ichteric ICP Cases (n=6)

Lab Parameters	Normal Ranges	Unit	Maximum Values
SGOT	0-40	U/L	140
SGPT	0-38	U/L	180
T. Bilurubin	0-1,4	mg/dl	2,9
Direct Bilurubin	0-0,25	mg/dl	1,34
Alkaline phosphatase	25-100	IU/L	341
5' Nucleotidase	2-10	U/L	24

steroid sulphate profiles in patients with ICP has been shown, the mechanism behind it is still unclear. UDCA has been found to stimulate biliary excretion of sulphated progesterone metabolites and restore the placenta's ability to carry out vectorial bile acid transfer (4). The impairment in bile acid transport across the placenta during ICP has been shown to reverse with UDCA, accompanied by the apparent clinical improvement in symptoms such as the relief of pruritus (5). Our study showed compatible results. We also found statistically significant improvement in symptoms of patients using UDCA ($P<0.05$) (Figure 1). Because the prognosis of obstetric outcome was significantly better in this treatment group, we believe that there must be an increase in placental bile acid transfer in patients using UDCA. Similar findings have been reported by other authors, who observed that 'deliveries occurred at or near term in all mothers who received UDCA, while in the placebo group, they occurred before 36 weeks of pregnancy, including one intrauterine excitus' (6,7).

Although cholestyramine is used to increase the excretion of bile acids into feces by reducing their enterohepatic circulation, it has not been fully satisfactory in ICP (8). The reported risk of hemorrhage due to hypoprothrombinemia, a result of malabsorbtion of fat and fat-soluble vitamins, was not observed in our patients. We evaluated the prothrombin time of Group 1 at weekly intervals. In spite of the administration of 4gr/day cholestyramine for at least two weeks, we did not observe any abnormal prothrombin time; however, we also administered vitamin K parenterally at weekly intervals to patients receiving cholestyramine for more than two weeks. No hemorrhagic obstetric complication was seen in this group. In Group 2, UDCA was administered at a dose of 750 mg/day (3x1) for at least one week, and significant clinical improvement was observed in almost every patient. No adverse effect was reported on the fetus due to long-term administration of UDCA, which some patients received for as long as four weeks. A previous study showed administration of UDCA for up to seven weeks had no side effects on the newborn, with an apgar score of 9 (9). We believe that by decreasing the passage of bile salts to the fetus, UDCA may improve the outcome of pregnancy (9). Although further investigation is required to establish the usefulness of UDCA in patients with ICP, the clinical improvement in symptoms and fetal prognosis should be taken seriously. In conclusion, although there is currently no specific treatment for ICP, therapeutic measures using UDCA may be of benefit to mother, fetal-placental unit and baby.

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