Ongoing Twin Pregnancy in an Obese, Polycystic Patient with Early Critical Ovarian Hyperstimulation Syndrome and Severe Liver Dysfunction: Case Report

Erken, Kritik Over Hiperstimülasyon Sendromu ve Ağır Karaciğer İşlev Bozukluğu Olan Obez, Polikistik Hastada Devam Eden İkiz Gebelik

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ABSTRACT Early ovarian hyperstimulation syndrome is an acute consequence of the excessive ovarian response to gonadotropin stimulation and has a higher risk of preclinical miscarriage. We reported a case of ongoing twin pregnancy in an obese patient with polycystic ovary disease, critical early ovarian hyperstimulation syndrome and liver dysfunction. This case demonstrates the severity of gastrointestinal symptoms and liver dysfunction that can occur with ovarian hyperstimulation syndrome. We tried to focus on the pathogenesis of liver dysfunction, which is a rare and life-threatening complication and suggested strategies to prevent similar cases in the future.

Key Words: Ovarian hyperstimulation syndrome; cholestasis

ÖZET Erken over hiperstimülasyon sendromu, gonadotropin uyarısına overler tarafından aşırı yanıt verilmesinin akut bir sonucudur ve bu tür hastalarda preklinik düşük riski yüksektir. Bu makalede, kritik, erken over hiperstimülasyon sendromu ve karaciğer işlev bozukluğu olan obez, polikistik over sendromlu bir hastada devam eden ikiz gebelik olgusu sunulmuştur. Bu olgu, over hiperstimülasyon sendromu ile birlikte olabilen gastrointestinal semptomların ve karaciğer işlev bozukluğunun ağırlığını göstermektedir. Makalede, nadir ve yaşamı tehdit edici bir komplikasyon olan karaciğer işlev bozukluğunun patogenezine odaklanılmış ve gelecekte benzer olguları önlemek için stratejiler önerilmiştir.

Anahtar Kelimeler: Ovaryan hiperstimülasyon sendromu; kolestaz

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Several classifications (early, late, mild, moderate, severe, and critical) of ovarian hyperstimulation syndrome (OHSS) have been proposed. The early type is usually related to excessive ovarian response to gonadotropin stimulation that occurs 3-7 days after human chorionic gonadotropin (hCG) injection. Critical OHSS is a recently described sub-classification of severe OHSS in which symptoms manifested are imminently life threatening such as profound hemoconcentration, adult respiratory distress syndrome, thromboembolic disease, renal failure and liver dysfunction (LD).[1] LD in OHSS were first reported in 1988 and may develop in 30-40% of patients.[2]

This case demonstrates the severity of gastrointestinal symptoms and LD that can accompany OHSS.

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CASE REPORT

A 28-year old polycystic, obese women with 6 years of primary infertility due to oligo-anovulation underwent in-vitro fertilization (IVF). Her body mass index was 38.3 and her waist circumference was 94 cm. She had oligo/amenorrhoea, clinical signs of hyperandrogenaemia and polycystic ovaries confirmed by vaginal ultrasonography (The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group, 2004a). The Insulin Resistans Index (HOMA-IR) value obtained was 3.

She was recommended to lose weight before infertility treatment but the couple wanted to be treated immediately and accepted the risks of obesity.

After using an oral contraceptive (OC) regimen for one month, down-regulation with leuprolid acetate (Abbott, Turkey) was followed by subcutaneous injection of 150 IU recombinant follicle stimulating hormone (FSH) daily for 11 days. Four follicles reached a maximum diameter of 18 mm, and 8-10 follicles reached 11-14 mm diameter. The patient wished to continue the treatment despite being warned of the danger of an OHSS and gave written consent. 250 mg of hCG (Serono, Turkey) was administered. The estradiol (E2) level on the day of hCG was 2.801 pg/ml. Intravenous albumin was administered at the time of oocyte retrieval to prevent OHSS. Two embryos were transferred on the 3rd day and luteal phase support was initiated by using progesterone gel **(Schering Pharmaceutical, Turkey).**

Four days after embryo transfer, the patient reported distension, reduced urine output, severe nausea and vomiting. The patient had been taking aspirin as a rutine procedure since the initiation of ovarian stimulation and had no history of exposure to hepatotoxins. Laboratory studies at admission were, hemoglobin 19 g/dL, hematocrit 55%, white blood cell count 21000/mm^3, total protein 49 g/L (normal range, 63-80 g/L), albumin, 25g/L (normal range, 32-50g/L), and alanine aminotransferase (ALT) 48 IU/L (reference ≤43 UI/L) (Figure 1). The remaining laboratory values were within normal ranges. Abdominal ultrasound examination showed severe bilateral ovarian enlargement (14 x 13 cm) with gross ascites and grade 2 hepatosteatosis but a normal liver size.

Initial management included prophylactic subcutaneous heparinization with low moleculer weighed heparin (Sanofi aventis, Turkey) and paracentesis to decrease her distension.

Monitoring of the patient included daily measurement of body weight, abdominal girth, fluid intake, urine output and periodic routine blood parameter measurements at intervals of 2-3 days.

Twelve days after embryo transfer, the combination of intractable vomiting, intravenous rehydration, paracentesis, hypercatabolism and proteinuria led to severe hypoalbuminaemia with gross edema and progressive LD. The patient's serum albumin value dropped to 16 g/L with LD peaking with ALT 583 U/L, aspartate aminotransferase (AST) 311 U/L, alkaline phosphatase 583 IU/L, and bilirubin 0.5 mg/dL (Figure 1). The presumptive diagnosis was atypical cholestasis and she was consulted with hepatologists. Ursodeoxycholic acid (UDCA) (Ali Raif Pharmaceutical, Turkey) was initiated 8 mg/kg/day in two divided doses. Serologic screening for HIV and hepatitis were negative. The treatment regimen also included IV 4.5% human albumin solution; she received a total of 11 x 250 ml bottles over 25 days. Serum beta-hCG level of the patient was elevated to 220 IU/L. After thirteen days, two viable intrauterine gestations with cardiac activities were documented. The judicious use of paracentesis (totally 7900 cc in 34 days) and UDCA (for 15 days) coincided with clinical improvement. Her vomiting stopped and the OHSS appeared to be clinically resolving with improvement in her appetite, abdominal symptoms and general condition. Laboratory data then showed the following: hematocrit 38%, AST 55 IU/L and ALT markedly decreased to 89 IU/L.

The patient was finally discharged from the hospital 34 days after her first admission. One month after discharge, the patient was asymptomatic with normal liver function.

The remainder of the patient's prenatal course was unremarkable until third trimester. At 33

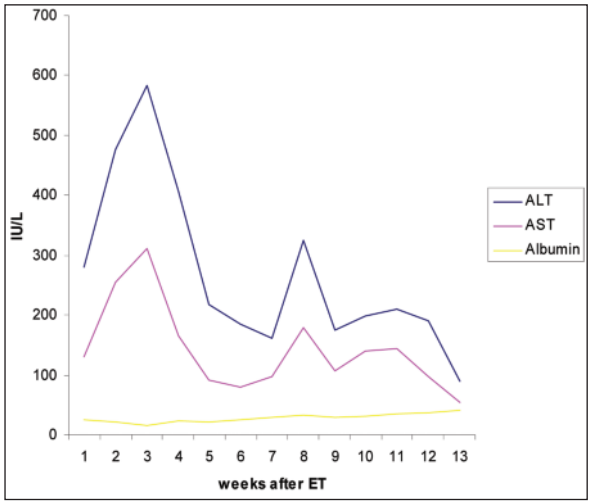

FIGURE 1: Changes in liver function and albumin fallowing embryo transfer. ALT, alanine aminotransferase; AST, aspartate aminotransferase; ET, embryo transfer; Albumin (g/l).
(See for colored form http://tipbilimleri.turkiyeklinikleri.com/)

weeks of gestation, she had hypertension. With planned caesarean at 34 weeks of gestation, two healthy girls weighing 1680 and 1745 grams were born.

DISCUSSION

The patient presented, manifested critical, early form of OHSS, which has a higher risk of preclinical miscarriage. With proper medication, pregnancy could proceed uneventfully until the third trimester. To our knowledge, there are only 4 previous reports of severe LD (alanine aminotransferase >10 times the normal upper limit and/or total bilirubin >5 mg/dL) during critical OHSS (Table 1). Highest peak transaminase levels were reported by Davis et al. (AST 756 U/L, ALT 4622 U/L).[2-4] The pathophysiology of the condition was suggested to be intrahepatic cholestasis (IHCP) due to elevated maternal estrogens and progestins during pregnancies conceived through assisted reproduction techniques (ART). In support of the etiologic role of estrogen, the risk of IHCP and hyperemesis gravidarum (HG) is increased in multiple gestations and in mothers of female offspring as in the presented case. In our case, the severity of gastrointestinal symptoms leading to hypovolemia and malnutrition, are believed to play a role.

Drugs used during controlled ovarian stimulation (COH), especially OCs and aspirin may form reactive, potentially toxic metabolites, produce liver cell damage and cause reactive cholestatic hepatosis in genetically susceptible patients [aminophospholipid translocases (ATP8B1), multi-drug–resistant protein 3 (MDR3/ABCB4), and a bile acid export pump (ABCB11/BSEP)]. Morbid obesity and polycystic ovarian syndrome are the two most common conditions associated with insulin resistance (IR) which causes increased ALT activity.

Obrzut et al. recommend the use of UDCA, which is a natural occurring hydrophilic nontoxic bile acid, in the cases of LD accompanying an early stage of OHSS. It is the treatment of choice for patients with IHCP, and safe for the mother and the fetus.[2]

In conclusion, we suggest that, during COH of obese, polycystic, insulin resistant patients, much more caution must be taken to prevent OHSS due to the vulnerability of obese patients to LD associated with nonalcoholic fatty liver disease, IR and metabolic syndrome. Family history of HG, OC induced cholestatic hepatitis, IHCP should also be known before COH. Such patients can be informed about the risk of HG in early pregnancy and IHCP in the later stages of pregnancy.

TABLE 1: Previous reports of severe liver dysfunction during critical OHSS.

Author (year)	Age	BMI	Infertility etiology	Assisted reproduction techniquetomes	Stimulation protocol	Estradiol on day of HCG	Onset day of abnormal LFT	Maximum ALT level U/l	Maximum AST level U/l	Total bilirubinmg/dl	Serum bile acid Mmol/l	Pregnancy outcome	Fetal sex	Treatment	Additional symp
Obrzut et al. (2005)	32	NA	Anovulation	Natural intercourse	Urinary FSH+ HCG 5000	2850 pg/ml	2 days after HCG	3372	1156	5	NA	38 Weeks singleton	NA	Hydration + Hydrocortisone+ diuretic + heparin hepatoprotective medications (Heparegen, Sylimarol, Essentialepleural)	Jaundice, pleural effusion
Davis et al (2002)	.28	23	Oligospermia	IVF	GnRHa+recF SH+HCG? + progesteron pessaries	12883 pmol/l	1 day after ET	4622	706	26	166	Miscarriage 9 weeks	NA	Total parenteral nutrition+ 20l parasentesis+29 *250 ml bottles 4.5%HAS	Intractable vomiting, hypertension (secondary to hyperaldosteronism)
Tortoriello et al (1998)	.40	23	Tubal obstruction teratozoospermia	IVF?	OC+GnRHa+Urinary FSH+ HCG 10000+50mg progesterone in oil IM	2775 pg/m l	3 days after ET	87	46	?	?	Nonpregnant		Hydration	Pleural effusion, emesis
Nawroth et al. (1996)	33	NA	Polycystic ovary	Natural intercourse or IUI	HMG+HCG 10000	2063 ng/l	7 days after HCG	3.06 Mmol/l/s	1.96 Mmol/l/s	89 Mmol/l/s	-	Nonpregnant	-	3200 ml parasentesis	Icterus, pruritus

ALT: Alanine aminotransferase; AST: Aspartam aminotransferase; BMI: Body mass index; ET: Embryo transfer; FSH: Follicle stimulating hormone; GnRHa: Gonadotrophin releasing hormone agonist; HAS: Human albumin solution; HCG: Human chorionic gonadotrophin; HMG: Human menopausal gonadotrophin; IUI: Intrauterine insemination; IVF: In-vitro fertilization; LFT: Liver function test; NA: Not available; OC: Oral contraceptive; recFSH: Recombinant follicle stimulating hormone.

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