Report of a Case with Bilateral Multiple Ovarian Cysts and Hyperandrogenism in a Twin Pregnancy: Hyperreactio Luteinalis

İkiz Gebelikte Bilateral Multiple Ovaryan Kistler ve Hiperandrojenizm: Hiperreaksio Luteinalis

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ABSTRACT Hyperreactio luteinalis is a quite infrequent lesion that is characterized with benign cystic enlargement of the ovaries during pregnancy. Its sonographic appearance usually mimics features of a malignant ovarian neoplasm, therefore differential diagnosis should rule out it. Maternal hyperandrogenism may be the leading and most considerable symptom at the referral. The management strategy during pregnancy should be conservative, unless maternal decompensation emerges due to decreased intravascular blood volume and inadequate oxygenation. Appropriate assessment of an ovarian cystic tumor, and recognizing such a phenomenon would help to prevent unnecessary interventions.

Key Words: Pregnancy; hyperandrogenism; ovarian cysts

ÖZET Hiperreaksio Luteinalis gebelerde, overlerde multiple benign kistik yapıların varlığı ile karakterize nadir görülen bir lezyondur. Ultrasonografik görünümü malign karakterli overyan kitlelere benzerlik gösterdiği için ayırıcı tanısının dikkatle yapılması gerekir. Maternal hiperandrojenizm en dikkat çekici ve başlıca semptomu olabilir. Gebelik esnasında annede dekompresyon bulguları ve yetersiz intravasküler kan hacmi oksijenizasyon bulguları olduğu takdirde konservatif bir yaklaşım ile takip edilebilir. Overyan kistik kitlelerin dikkatli değerlendirilmesi ve tanının konulabilmesi gereksiz müdahalelerin önüne geçer.

Anahtar Kelimeler: Gebelik; hiperandrojenizm; over kistleri

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Hyperreactio luteinalis (HL) is the cystic enlargement of the ovaries due to multiple theca lutein cysts.[1] It is a benign, but quite uncommon, phenomenon which is mostly associated with trophoblastic diseases or multiple pregnancies. HL is mostly asymptomatic, and enlarged multicystic ovaries are usually discovered incidentally on routine prenatal sonographic survey. Sonographically it can mimic either malignant ovarian tumors or ovarian hyperstimulation syndrome (OHSS). Although the main reason for HL is unknown, increased levels of maternal serum androgens and human chorionic gonadotrophin (HCG) or an abnormal ovarian response to the pituitary gonadotrophins are thought to be related with the disease.[2,3] Maternal virilization was reported to be present in 15 to 25% of cases with HL.[4,5] Symptomatic women may present mostly with hirsutism, dyspnea, abdominal discomfort or pain due to capsule distention or ovarian

torsion.[3] HL is usually a self-limited condition and regresses spontaneously at postpartum period.[5]

We report here a case with HL in whom an obvious maternal hirsutism and enlarged ovaries (20 cm in longitudinal diameter) were observed in a twin pregnancy after an assisted reproduction cycle with *in-vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI).

CASE REPORT

A 31-year-old primipara was referred to our clinic at postoperative 2nd day for the follow-up and definitive treatment of bilateral multiple ovarian cysts after her delivery has been achieved with cesarean section at the 28th gestational week of pregnancy. She has conceived artificially with IVF-ICSI procedure that yielded a twin pregnancy. First trimester and subsequent antenatal visits have yielded an intrauterine twin pregnancy with mild to moderately stimulated ovaries. Her past medical history has been uneventful and she has not been using any medications other than oral folic acid and elementary iron supplementation in the current pregnancy. Her main complaints by the antenatal 22nd gestational week were abdominal discomfort, abdominal pain, prominent growth of the body hair that were localized over the abdomen, chin and legs, and fatigue. At 26th week of pregnancy, she attended to the hospital because she was exhausted with increased abdominal discomfort, fatique and dyspnea. Considerable growth of the ovaries with multiple anechoic cysts were detected by transabdominal ultrasonographic examination (left ovary was measured 200x180 mm, right was measured 220x190 mm). Transabdominal ultrasonography (US) confirmed the viable intrauterine twin pregnancy with normal fetal growths. The amniotic fluid index of one of the fetuses was below the normal limits (<5 cm in total). Hair growth was observed to increase extremely on her face, abdomen, legs and forearms. She had dyspnea and abdominal distension without acute abdomen symptoms at her physical examination. There were no ascites and pleural effusion either. She has been decided to follow-up for the next couple of weeks until fetal lung maturation was achieved. However, cesarean section has been performed due to development of acute fetal distress in the fetus with oligohydramnios after two weeks of the hospitalization (at 28th week). Postoperative laboratory data evaluating renal function, coagulation, and blood count within the first 48 hrs after delivery were in normal ranges. Liver enzymes including AST and ALT were slightly elevated (37 mg/dL and 45 mg/dL, respectively), whereas levels of direct and indirect bilirubin were markedly increased (2.9 mg/dL (normal ranges are 0-0.5 mg/dL) and 3.8 mg/dL (normal ranges are 0.2-1.2 mg/dL), respectively). Laboratory values were notable for hormon profile comprising total testosterone level of >15 ng/mL (normal ranges are 0.09-1.09 ng/mL), free testosterone level of 33 ng/mL (normal ranges are 0.06-4.1 ng/mL), androstenedione level of >10 ng/mL (normal values are between 0.3 and 3.3 ng/mL) and cortisol level of 29.3 μg/dL (normal values are between 6.0 and 19.0 μg/dL). Accordingly, our diagnosis was consistent with ovarian luteal hyperreaction (hyperreactio luteinalis). Since there was no evidence for malignancy, and delivery has already been performed, we recommended a conservative management. Our treatment based on providing the fluid and electrolyte balance, and directed to the pain control.

The leading symptoms including growth of the body hair and the ovarian multicystic pattern were similar at the postoperative first month visit (Figure 1). Pelvic magnetic resonance imaging (MRI) also depicted same findings as US (Figure 2a, 2b). About one month later, the patient's second presentation

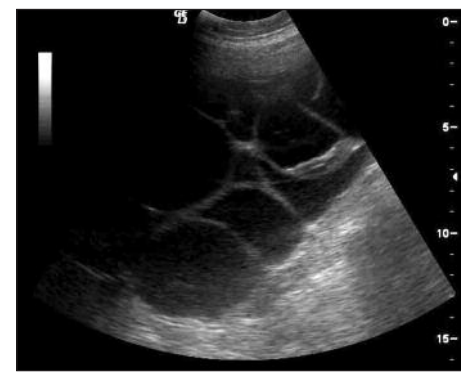

FIGURE 1: Multicystic appearance of ovary in transvaginal USG.

to our department was because of persisted pelvic pain, dyspnea and unchanged size of both ovaries despite delivery. Tables 1 and 2 list the follow-up laboratory values. It took 7 months for her symptoms to resolve and the ovarian masses to return to normal size after the cesarean section (Figure 3).

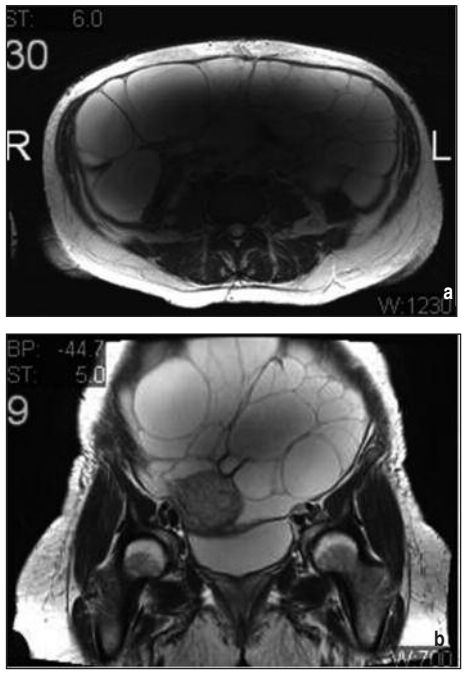

FIGURE 2: a. Multicystic appearance of bilateral ovaries in axial cross-section in MRI. **b.** Multicystic appearance of bilateral ovaries in coronal cross-section in MRI.

TABLE 1: Maternal hormone profile at follow-up.

Hormone Profile	27th gestational week	Postpartum 30th day	Postpartum 210th day
Total T (ng/mL)*	> 15	> 15	
Free T (ng/mL)*	40	33	---
Progesterone (ng/mL)	43.8	39.9	11.5
Cortisole (µg/dL)*		29.3	---
Prolactin (ng/mL)	25.17	10.7	19.92
FSH (mIU/mL)	0.13	< 0.05	8
LH (mIU/mL)	0.01	0.01	0.47
Estradiol (pg/mL)		3,226	134
TSH (µIU/mL)		0.88	1.54
Androstenedione (ng/mL)*		>10	2.2
Free Beta-HCG (ng/mL)		3.47	<1.20

FSH: Follicule stimulating hormone; HCG: Human chorionic gonadotropin; LH: Luteinizing hormone; T: Testosterone; TSH: Thyroid-stimulating hormone.
*Identifies hormone levels elevated than the normal values.

TABLE 2: Maternal postpartum biochemistry profile.

Biochemistry Parameters	Postpartum 30th day	Postpartum 210th day
Urea (mg/dL)	17	37
Creatine (mg/dL)	0.6	0.7
AST (IU/L)	33	17
ALT (IU/L)	57	15
Total bilirubin (mg/dL)	1.9	0.88
Direct bilirubin (mg/dL)	1.1	0.25
Wbc (K/µL)	13,690	12,100
Hg (g/dL)	12.2	13.0
Hct (%)	37	39.5
Plt (K/µL)	411 000	199 000

DISCUSSION

Obstetricians all over the world are pretty much unfamiliar with HL, but it may present during any trimester of pregnancy, and are one of the most important causes of maternal hirsutism, and pelvic or abdominal masses. The ovarian changes are usually bilateral and tend to resolve spontaneously after delivery.[6] HL is usually associated with gestational trophoblastic diseases or multiple pregnancies, nevertheless there are cases reported in singleton pregnancies.[6,7] The theory is either the elevation in the levels of human chorionic gonadotrophin (HCG) or the presence of a mutation at the follicule stimulating hormone receptor which leads to a hypersensitivity to HCG and TSH resulting in hyperreaction with normal HCG levels.[8] Patients with thyroid problems were also demonstrated to have increased incidence of HL.[6]

Pure hyperandrogenic state of pregnancy is also reported to be amply rare. Benign luteoma of pregnancy and HL are two major causes of hyperandrogenism in pregnancy.[9] Benign luteomas of pregnancy are usually solid masses of luteinized cells, and are unilateral in 65% of the cases. The ovaries are of normal size despite HL in which they become absolutely large and multicysyic.[10] Pregnancy luteomas are caused by hyperplasia of luteinized stromal cells.[9] Both luteomas and HL are asymptomatic most of the time.

Elevated androgen levels are also seen in pregnant women with OHSS. It is important to make the

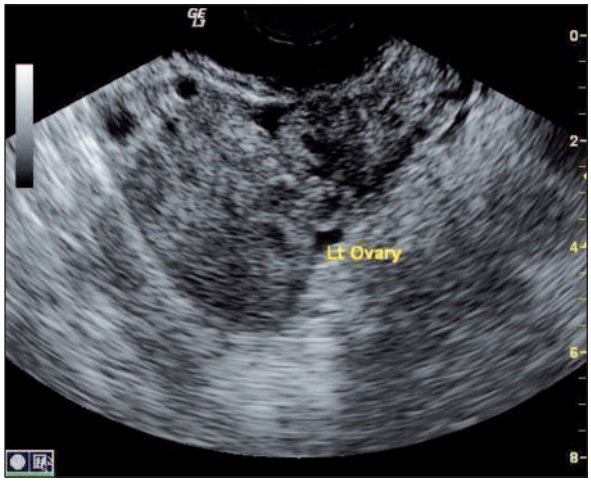

FIGURE 3: Normal appearance of the left ovary in control transvaginal USG.

differential diagnosis of HL and OHSS especially in the first trimester. Although HL is usually asymptomatic and 37% of HL cases are diagnosed at the time of cesarean section, OHSS has more pronounced symptoms threatening the woman's life.[7] OHSS is more frequent in patients with polycystic ovaries (PCOs) but there are cases of HL also reported in PCO patients.[11-13] The presentations of these two conditions may be similar whereby in OHSS ovarian expansion and concomitant fluid shift is more rapid. In our case HL could possibly be a complication of ovarian hyperstimulation in IVF protocol. The increased levels of HCG due to twin pregnancy and a possible pre-existing PCO pattern may be the triggering factors for excessive synthesis of testosterone. Virilization of the mother has also been reported in 14-25% of HL cases.[3] In our case neither mother nor the female twin were virilized.

The differential diagnosis of hirsutism during pregnancy must include germ cell tumors and gestational trophoblastic neoplasia also. In both cases the HCG levels are also elevated.[3] HL is almost always bilateral where as malignancies are not.

The management of HL is preferably conservative, and supportive treatment should be applied. It is important to avoid unnecessary laparotomy and oopherectomy. The normal levels of tumor markers, hyperandrogenism and ultrasonographic evaluation may help to differentiate HL from a malignancy. In our case, the diagnosis of HL is based on bilaterality and multicystic appearance of the ovaries without solid components detected in US. MRI also confirmed the benign nature of the multicystic ovaries.

In conclusion, once the ovarian and trophoblastic malignancies are ruled out conservative management and reassuring of the woman with HL is usually adequate. Maternal symptoms recede within months. Ultrasonography should be the method of choice in the follow-up. Recognizing such phenomenon may help to prevent unnecessary interventions.

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