

Recurrent Spontaneous Ovarian Hyperstimulation Syndrome with Hypothyroidism: A Case Report

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ÖZET

Hipotiroidinin eşlik ettiği tekrarlayan spontan ovaryan hiperstimülasyon sendromu: Olgu sunumu

Ovarian hiperstimülasyon yardımcı üreme teknikleri ile birlikte gelişen iatrojenik bir durumdur. İatrojenik ovarian hiperstimülasyonun insidansı %0,2-1 arasynda değişmektedir. Literatürde nadir olarak spontan hiperstimülasyon sendromu bildirilmiştir. Makalede hipotiroidinin eşlik ettiği spontan rekürren ovarian hiperstimülasyon sendromu tanımlanmıştır. Spontan ovarian hiperstimülasyon sendromunun etyopatogenezi bilinmemektedir. Polikistik over sendromu, endojen hCG seviyelerinin yüksek seyrettiği çoğul gebelikler ve molar gebelikler, FSH reseptör mutasyonu varlığı ve hipotiroidi risk faktörleri olarak saptanmıştır.

Anahtar kelimeler: Ovarian hiperstimülasyon sendromu, hipotiroidizm

ABSTRACT

Recurrent spontaneous ovarian hyperstimulation syndrome with hypothyroidism: a case report

Ovarian hyperstimulation most commonly occurs iatrogenically in association with assisted reproductive technologies. Incidence of iatrogenic ovarian hyperstimulation is 0,2-1%. There are only a few cases of pregnancies associated with recurrent spontaneous ovarian hyperstimulation. This report describes a case in which a naturally conceived pregnancy was associated with recurrent spontaneous ovarian hyperstimulation with hypothyroidism. The etiopathogenesis of spontaneous ovarian hyperstimulation is unclear. It was suggested that polycystic ovary syndrome, twin and molar pregnancies in which the endogenous hCG levels were higher than normal, mutation in the FSH receptor could be risk factors for spontaneous ovarian hyperstimulation. Hypothyroidism is another risk factor for the development of spontaneous ovarian hyperstimulation.

Key words: Ovarian hyperstimulation syndrome, hypothyroidism

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INTRODUCTION

Spontaneous ovarian hyperstimulation (SOHSS) most commonly occurs iatrogenically in association with assisted reproductive technologies. Incidence of iatrogenic OHSS is 0,2- 1%. It can rarely occurs spontaneously without ovulation induction therapies. Clinic signs and symptoms include abdominal distention, abdominal pain, nausea and vomiting with ovarian enlargement. It may cause severe morbidity with ascites, dyspnea, adnexal mass electrolyte imbalance, hemoconcentration

and oliguria (1,2). While extremely rare in naturally conceived pregnancies, SOHSS tends to present late in the first trimester at 8 to 14 weeks of gestation, while iatrogenic OHSS usually present earlier at 3 to 8 weeks of gestation (2,3). Recurrent SOHSS is much rare than SOHSS. Here we report a case of recurrent SOHSS in sequential pregnancy with hypothyroidism.

CASE REPORT

A 24 years old female patient, was followed for her sequential pregnancies in our clinic with OHSS diagnosis. In her first pregnancy, -3 years ago- she applied to our clinic with the complaints about abdominal distension, pelvic pain and breathing problem that had been persisting for 2 weeks. Any specifications haven't been seen in her medical and gynecological history, and she hadn't had any medication for her ovulation induction.

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In the physical examination, there were distension and sensitivity in the abdomen.

In ultrasonographic observation (5 MHz vaginal probe 3.5 MHz convex abdominal probe, GE 200 pro, Korea), according to the CRL (crown-rump length); along with 10 weeks single, viable fetus, it was monitored that bilateral multilobulated cystic 13x8 cm. sized ovaries and free fluid in the abdomen.

The laboratory test results were as follows: Hb: 10 g/dl, Hct: 30%, WBC: 7000/mm³, Na: 135 mEq/l, K: 3.5 mEq/l, total protein: 5.8 g/dl, albumin: 3.3 g/dl, SGOT: 22 U/l, SGPT: 13 U/l, Creatinine: 0.5 mg/dl, Thyroid stimulating hormone (TSH): 8,75 IU/mL, CA-125: 146.8 IU/ml, Inhibin A: 861, Ristocetin co-factor (von Willebrand factor (VWF) activity): %100 (N: %50-150), VWF antigen: %150 (N: %60-150). Serologic tests (Anti-HAV IgM, HbsAg, Anti-HCV) were negative, thyroid function tests and PT, PTT, fibrinogen were normal. Beta HCG levels were coherent with the week of gestation. In doppler ultrasonography observation, low-resistant arterial flow was determined in bilateral ovaries.

According to the Golan classification the patient was interned with grade 2 spontaneous OHSS and conservative treatment has been applied to the patient. Levothyroxin was started with 1x1mg /day. Due to the persistence of clinic complaints, the observation was extended for 20 days more. At the end of the observation, she was discharged from the hospital and followed by antenatal polyclinic. On the 38th weeks of gestation, she delivered a male baby that weighed 2690 gr via a normal spontaneous delivery. On the 3rd month of her postpartum period, both ovaries were monitored as normal sized and shaped by transvaginal ultrasonography and doppler observations. TSH was 3,19 IU/mL. Levothyroxin 1 mg./dl. was continued by daily dosage.

During her second pregnancy, 23-year-old case applied for abdomen pain, abdominal tension and nausea. In USG observation, along with 12 weeks single, viable intrauterine pregnancy, bilateral multilobulated cysts of 13x70 mm on the right side and 110x70 mm on the left side with minimal free fluid in the abdomen and Douglas was detected.

According to the Golan classification; the laboratory tests of the patient who was interned with grade 1 spontaneous OHSS diagnosis were determined as; Hb: 10 g/ dl, Hct: 30 WBC: 8700, Na: 136 mEq/l, K:3,5 mEq/l, total protein: 5,9 g/dl, albumin: 3,1/dl, SGOT: 13 U/l, SGPT: 10 U/l,

creatinine: 0,6 mg/dl, TSH: 2,16 IU/mL, CA-125: 289 IU/ml.

A conservative treatment has been applied to the patient on Levothyroxin treatment 1 mg/day. After 5 days observation, she was discharged from the hospital to be followed by antenatal polyclinic as an outpatient. On her 27th week of her pregnancy, the patient was rehospitalized by the threat of premature delivery, and in USG, it was seen that bilateral ovaries were multicystic and 110x70 cm. sized. No free fluid has been determined in the abdomen. After 3 days hospitalization, she was discharged from the hospital. Then, on the 38th week, she delivered a viable, male baby of 3050 gr, APGAR score 1. On the 8th week of the patient's postpartum, her bilateral ovaries were monitored as normal sized and shaped by USG.

DISCUSSION

Ovarian hyperstimulation syndrome usually occurs in association with ovulation induction, but the physiopathologic mechanisms are understood poorly. There are only a few cases of pregnancies associated with recurrent spontaneous ovarian hyperstimulation at a search of Ovid MEDLINE(R)(1950-2008) and PubMed (1950-2008) with the terms "recurrent spontaneous ovarian hyperstimulation syndrome," "hypothyroidism".

This report describes a case in which a naturally conceived pregnancy is associated with recurrent spontaneous ovarian hyperstimulation with primary hypothyroidism. In our case, a woman, currently 24 years of age, had developed ovarian hyperstimulation syndrome in each of 2 pregnancies.

Although there are no clear predictive risk factors for the development of OHSS, young age, polycystic ovarian syndrome, asthenic habitus, luteal supplementation of hCG, protocols with GnRH α , high level of serum estradiol, multiple follicles and ovarian necklace sign were reported as the possible risk factors (4). This syndrome is characterized by massive transudation of protein-rich fluid (mainly albumin) from the vascular space especially into the peritoneal and pleural cavities. It has been reported that the intensity of the syndrome is related to the degree of the follicular response in the ovaries to the ovulation inducing agents (5).

However, why should the ovarian hyperstimulation syndrome develop? After all, it usually is due to excessive hCG that is associated with the syndrome. It is known

that, hCG is a member of the family of glycoprotein hormones that also includes FSH, luteinizing hormone (LH), and thyroid-stimulating hormone (TSH). These 4 hormones have 2 subunits: a common alpha subunit and a beta subunit that is specific to each molecule. Their subunits, albeit distinct, share greater than 40% amino acid homology. In addition, the receptors for the glycoprotein hormones have related structures. LH and hCG both bind to the LH receptor, whereas TSH and FSH under normal circumstances bind to separate TSH and FSH receptors, respectively. The hypothesis is that once the hormone binds to its receptor, it stabilizes the conformation of the receptor's extracellular portion, initiating downstream signaling events (4,6,7).

The exact pathogenesis of OHSS is not yet clearly determined. It has been suggested that vasoactive substances such as histamine, serotonin, prostoglandins, interleukins, TNF- α , ovarian renin-angiotensin system and vascular endothelial growth factor (VEGF) which are activated by exogenous gonadotropins can lead to increased vascular permeability and extravascular fluid accumulation in OHSS (4,6,7). In recent years particularly VEGF became more popular on the pathogenesis of OHSS. It has been reported that it is responsible for the significant increase in the capillary permeability, extravascular fluid accumulation, hemoconcentration and elevated plasma concentration of von Willebrand factor, all known complications of OHSS (3,8). Elevated levels of this cytokine were found both in the serum and in the ascitic fluid of patients with severe OHSS (3,8,9). However it has been also reported that the serum concentrations of VEGF does not predict the course of the disease (10).

Various mechanisms have been proposed for spontaneous ovarian hyperstimulation syndrome. The etiopathogenesis of spontaneous OHSS is less clear. Some authors suggested that polycystic ovary syndrome (PCOS) could also be a risk factor for spontaneous OHSS (3,11). However some cases developed this condition without underlying PCOS (11,12,13). Spontaneously developed OHSS has been reported in twin and molar pregnancies in which the endogenous hCG levels were higher than normal (10-18). However, OHSS also been observed in women with normal or lower than normal hCG concentration. Thus, it is postulated that high concentrations of hCG are not responsible for every case of OHSS (19). Hypothyroidism is another postulated risk factor for the development of spontaneous OHSS (10,17).

De Leener et al, proposed to classify spontaneous ovarian hyperstimulation syndrome into three types, based on clinical presentation and FSH receptor mutation. Identification of the four FSH receptor mutations has allowed for creation of a pathophysiological classification of spontaneous ovarian hyperstimulation syndrome (15). Type I corresponds to the mutated FSHr cases. Type II corresponds to the sOHSS secondary to high levels of hCG. This type is probably the most frequent one. The third one is related to hypothyroidism (16). This classification could be useful for clinicians and scientists positions are adopted, clinicians will rapidly extent our knowledge on the precise origins of sOHSS, which could result in delineation of new types of sOHSS and certainly help with future counseling and treatment of their patients. Our case was admitted as type 3. Her TSH was 8,5 IU/ mL, free T3 and free T4 were normal (14).

The exact mechanism by which ovarian hyperstimulation syndrome might occur in hypothyroid patients is not understood clearly. A possible explanation was suggested by Rotmensch and Scommegna, on the basis of preferential formation of estriol via the 16- hydroxylation pathway instead of the normal 2-hydroxylation that has been demonstrated in hypothyroid patients (16). Excessive gonadotropin release, due to decreased feedback regulation caused by substitution of estradiol by the less potent estriol, would result in excessive ovarian stimulation (17-23).

In a recent report, a pregnant woman with spontaneous ovarian hyperstimulation syndrome, uncontrolled hypothyroidism, elevated human chorionic gonadotropin (hCG), deep vein thrombosis, and Rh isoimmunization was reported by Edwards-Silva et al (24). Cardoso et al, described a case of consistent regression of large bilateral ovarian cysts in a hypothyroid patient after the institution of thyroid hormone replacement therapy, suggesting the causal relationship between primary hypothyroidism and spontaneous ovarian hyperstimulation syndrome (17). Nappi et al. presented a case of untreated hypothyroidism associated with spontaneous ovarian hyperstimulation syndrome. In their patient, thyroid replacement therapy and fluid administration also led to prompt resolution of the spontaneous ovarian hyperstimulation syndrome (18).

The sOHSS was developed with uncontrolled hypothyroidism in our case at her first pregnancy. After hormonal replacement and supplementary therapy led to

prompt resolution of the symptoms of sOHSS. But the size of ovaries hadn't decreased until 2 months after delivery. In second pregnancy of our case, sOHSS was occurred under levothyroxine therapy with normal TSH levels. This was suspected as a mutation of the FSH receptor, but we couldn't investigate receptor mutation in our case.

Women with severe hypothyroidism experience greater perinatal complications including prematurity, preeclampsia, impaired intrauterine growth, stillbirth, nonreassuring fetal heart tracings, and cesarean delivery. These known morbidities of hypothyroidism, in addition to the development of spontaneous ovarian hyperstimulation syndrome with deep venous thrombosis, gestational diabetes, and incidental Rh isoimmunization, presented an extremely challenging clinical case (18).

In the report by Smits et al, spontaneous ovarian stimulation also occurred in a woman during 4 of her pregnancies, and she also had a heterozygous mutation in the FSH receptor (2). Each glycoprotein hormone receptor counterpart also shares a 40% concordance

in their hormone binding domains. Mutations in the receptors may lead to promiscuous ligand recognition and cross-stimulation of end-organs (2).

The elevated concentrations of CA-125 that we found in our patient have already been observed in sOHSS. Elevated concentrations of this marker is a commonly finding in pregnancy and OHSS following ovulation induction (21). Moreover, all the processes that irritate the peritoneum increase the concentrations of CA-125 (22). In our patient, increased CA-125 concentrations that we observed in both two pregnancies.

This case suggests spontaneous ovarian hyperstimulation syndrome can occur in pregnant women with severe hypothyroidism or extremely elevated hCG levels and present with enlarged adnexal masses and acute abdominal pain. Accurate diagnosis and continuation of pregnancy with conservative management is a viable option, once ovarian malignancy is ruled out. Also, thyroid function should be measured in women with spontaneous hyperstimulated ovaries.

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