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Case Report

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Ovarian Hyperstimulation Syndrome in a Patient with Hypogonadotropic Hypogonadism

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ABSTRACT

Traditionally, women with hypogonadotropic hypogonadism (HH) were considered to be at lower risk for the development of ovarian hyperstimulation syndrome (OHSS), although they usually required higher doses of gonadotrophins and longer periods of treatment. However this case emphasize that OHSS can be seen in patients with HH especially in a group of patients with the ultrasound findings of PCO.

Key words: *Ovarian hyperstimulation syndrome, Hypogonadotropic hypogonadism, Ovulation induction*

ÖZET

Hipogonadotropik Hipogonadizm Olan Bir Hastada Ovarian Hiperstimulasyon Sendromu

Daha uzun tedavi periyodu ve daha yüksek doz gonadotropin kullanımı gerekse de hipogonadotropik hipogonadizm (HH) olan hastalarda ovarian hiperstimulasyon sendromu (OHSS) gelişme riskinin daha düşük olduğu bilinen bir gerçektir. Ancak bu vaka HH olan ve özellikle polikistik over ultrason bulgusu taşıyan hastalarda OHSS gelişebileceğini vurgulamaktadır.

Anahtar Sözcükler: *Ovarian hiperstimulasyon sendromu, Hipogonadotropik hipogonadizm, Ovulasyon indüksiyonu*

Hypogonadotropic hypogonadism (HH) is defined as a medical condition with low or undetectable gonadotropin secretion, associated with a complete arrest of follicular growth and very low estradiol level. It is most frequently acquired and caused by a number of pathologic processes but it can also occur as part of various congenital syndromes.

Fertility can be restored with exogenous administration of gonadotropins or pulsatile gonadotropin releasing hormone (GnRH) in these patients. Traditionally, women with HH were considered to be at lower risk for the development of ovarian hyperstimulation syndrome (OHSS), although they usually required higher doses of gonadotrophins and longer periods of treatment.

However recently, a group of patients with HH and ultrasound findings of polycystic ovaries (PCO), in whom the ovarian response to gonadotrophin therapy was similar to those with polycystic ovary syndrome (PCOS), was characterized. The incidences of mild and severe OHSS in treatment cycles of HH patients were given as 5.5 and 0.6% respectively (1, 2).

We present a patient with hypogonadotropic hypogonadism and a typical ultrasound appearance of PCO, who developed OHSS during ovulation induction with human menopausal gonadotrophin (HMG) and human chorionic gonadotrophin (HCG).

CASE REPORT

A 24 year old, gravida 0, para 0 woman, with a 2-year history of primary infertility had admitted to our clinic. She had idiopathic hypothalamic primary amenorrhea and had been using cyclic estrogen-progestin preparation for 6 years.

A baseline transvaginal ultrasound scan was performed at the start of the treatment cycle to exclude any residual cyst and showed a typical PCO appearance with multiple 2-8 mm diameter cysts arranged around a dense stroma. Blood tests showed the hypogonadotropic hypogonadism (serum concentrations of LH 0,4 mU/ml and FSH 0,9 mU/ml, estradiol 39,25 pg/ml). She had otherwise normal anterior pituitary hormone secretion and sellar anatomy.

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The initial work up done for both of the partners at our infertility clinic revealed a normal spermiogram and a normal histerosalpingography. Her body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) was 21.

Controlled ovarian hyperstimulation (COH), had commenced with HMG (Menogon, Ferring) at a dose of 2 ampoule/day from days 1 to 7, 3 ampoules/day from days 8 to 18. Serum estradiol levels were measured and ultrasound scans were done every 1-3 days during COH to confirm follicular development. 10000 IU hCG (Pregnyl 5000 IU amp. Organon) was given by i.m. injection on treatment day 18, when oestradiol concentrations reached 1760 pmol/1 and vaginal ultrasound revealed two leading follicles (18 mm in diameter), six intermediate-sized follicles (13-15 mm in diameter) and >10 small-sized follicles (<9 mm).

Swim-up and Percoll gradients were indiscriminately employed for insemination using her husband's sperm. Intrauterine insemination was performed 36 h after IM hCG administration. The luteal phase was supported with 100 mg/day micronized progesterone (Progestan 200 mg, Kocak Farma). She was informed of the signs of OHSS and was instructed to maintain regular follow-ups at our outpatient units. Nine days after insemination, the patient returned to our center with a greatly distended abdomen, and associated symptoms of nausea, vomiting, dyspnea, constipation, oliguria, and weight gain.

On admission, her vital signs were stable: a pulse rate of 98/min, temperature of 36.5 °C, and blood pressure of 120/80 mmHg. Laboratory evaluation was significant with a hematocrit of 47%, a white blood count of 17,500/mm, serum sodium of 131 mEq/L, serum albumin of 2 g/dL, serum E2 of > 3600 pg/mL, and serum progesterone of > 40 ng/mL. Renal and liver function studies were normal. Abdominal sonography revealed bilateral enlarged ovaries (mean diameter of the right ovary of 16.4 cm and of the left ovary of 12.5 cm) with a massive amount of intraperitoneal fluid. A chest Xray revealed bilateral pleural effusions.

The patient was treated with bed rest and intravenous fluid replacement with a normal saline solution and 25% human albumin solution and prophylactic subcutaneous heparinization which is routine policy in the management of OHSS in our program. Oral intake of water was restricted, monitoring of fluid intake and output, and daily monitoring of body weight was performed. Hematocrit, electrolytes, plasma proteins, a complete blood count, and the creatinine clearance rate were recorded daily during hospitalization.

By the 4th day of hospitalization, the dyspnea had further deteriorated, and we decided to perform abdominal paracentesis. One liter of an ambercolored fluid was drained. Temporary diuresis occurred, which resulted in marked improvement of the pulmonary distress. The serum ß-hCG level was 76 mIU/ml the following day. A transvaginal sonographic examination revealed an empty uterus, but the endometrium was thickened (single layer of 14 mm); a diagnosis of OHSS exacerbated by early pregnancy was established. Shortly thereafter, 3 more paracentesis were performed on the 6th, 8th, and 11th days of hospitalization, at which time 2, 1.5, and 1.5 L of ascitic fluid were removed, respectively. The patient was finally discharged from hospital 31 days after her first admission with a viable intrauterine pregnancy.

DISCUSSION

Our report describes the development of OHSS after ovulation induction with HMG in a HH woman with a PCO-like ovarian ultrasonographic appearance. OHSS is a serious and potentially life-threatening iatrogenic complication of ovulation induction. The syndrome almost always presents either after hCG administration in susceptible patients or during early pregnancy. Before commencing treatment with gonadotrophins, one should identify those patients who are at increased risk of developing OHSS. Multiple factors have been proposed to be related to an increased risk of OHSS; young age (<35 years), lean habitus, and hormonal or morphological signs of PCOS an excessively high estradiol (E2) response (>1700 in COH cycles, >4000-6000 pg/ml, in IVF cycles) on the day of hCG administration and with multiple (more than 35) small and intermediate follicles that will yield more than 30 oocytes on retrieval, higher doses of exogenous gonadotropins and previous episodes of OHSS (3). However, there are reports of occurrence of severe OHSS in patients who conceived spontaneously (4-10) or in those with low serum E2 levels on the day of hCG (11) as in the case described here or the well known practice that high estrogen levels do not always lead to hyperstimulation (12).

Although HH appears to be an optimal condition for achieving a good response to ovulation induction with minimal complication rates, one should bear in mind that this is not a homogeneous group. An individual approach for ovulation induction should be applied in HH patients. Before commencing treatment with gonadotrophins, one should identify those patients who are at increased risk of developing OHSS. It is suggested that in the absence of an obvious predictive factor in these patients, other markers, such as the ultrasound findings of PCO, younger age and lean habitus would be more significant when compared with serum oestradiol concentrations. Some of the patients with HH respond with a shorter follicular phase, multiple folliculogenesis and a higher multiple pregnancy rate. Thus the question arises whether the pre-existing pituitary and/or ovarian priming renders

these subjects sensitive to gonadotrophin stimulation, or whether this condition may be an expression of inherent primary ovarian disorder (11, 13).

The frequency and amplitude of GnRH pulses determine gonadotropin subunit gene expression and secretion of pituitary LH and FSH. Related to the age of onset, genetic, environmental or behavioral predisposition of the person and based on the degree of GnRH suppression a number of reproductive disorders in women including; inadequate luteal phase, hypogonadotropic hypogonadism, hypothlamic amenorrhea, hyperprolactinemia and PCOS develop. Disruption of the normal pulsatile GnRH secretion leads to PCOS (too fast LH frequencies) and hypothalamic amenorrhea (too slow LH frequencies) as the diseases at the two end of the spectrum (14).

Very little information is available on the high-risk groups and prophylaxis of OHSS in HH patients. This case emphasize that OHSS can be seen in patients with HH especially in a group of patients with the ultrasound findings of PCO. An individual approach for ovulation induction should be applied in HH patients. Furthermore, until the ultimate predictive factor for OHSS is established, ovulation induction or cycle cancellation in HH patients should not be decided solely by the number of leading follicles or oestradiol concentration.

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