Ovarian Hyperstimulation Following GnRH Analogue Administration

GnRH AGONİST UYGULANIMINI TAKİBEN OHSS GELİŞİMİ

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Abstract

We reported a case who developed ovarian hyperstimulation (OHSS) on two occasions following daily injections of leuprolide acetate starting from the mid luteal phase. In both cycles, within 2 weeks of GnRH agonist therapy, massive ovarian multifollicular enlargement occurred, concomitant with high serum estradiol levels that resolved spontaneously following expectant management. The patient developed clinical pregnancy following pituitary suppression with GnRH antagonists and ovulation stimulation with gonadotropins. GnRH antagonists may be used as an alternative for pituitary suppression in patients who developed OHSS following GnRH-analogue administration in their previous cycles.

Key Words: GnRH agonists, ovarian hyperstimulation syndrome, GnRH antagonists

Özet

Luteal dönem ortasından itibaren, günlük leuprolid asetat uygulanımı sonrası, ardı ardına iki siklusunda over hiperstimülasyon sendromu (OHSS) gelişen bir olguyu sunduk. Her iki siklusta da GnRH agonist tedavisine başlanılan 2 hafta içinde over çaplarının multifoliküler genişlemesi ile beraber yüksek serum östradiol düzeyleri tespit edildi. İzlem sonrası over çaplarının ve serum östradiol düzeylerinin kendiliğinden basal seviyelerine gerilediği görüldü. GnRH antagonistleri ile pituiter supresyon ve gonadotropinlerle ovulasyon stimülasyonu sonrası hastada klinik gebelik elde edildi. Daha önceki sikluslarında GnRH analogları ile over hiperstimülasyon sendromu geliştirmiş olan hastalarda, pituiter supresyon için GnRH antagonistleri alternatif olabilir.

Anahtar Kelimeler: GnRH agonistleri, over hiperstimülasyon sendromu, GnRH antagonistleri

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Pituitary desensitization with Gonadotropin Releasing Hormone (GnRH) agonists is a routine part of in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) procedures.[1] Failure to achieve prompt pituitary sensitization and ovarian cyst formation > 15-20 mm in diameter, as a complication of gonadotropin releasing hormone agonist therapy has been detected in 2-40% of treatment cycles, concomitant with raised serum estradiol levels has been reported before.[2-8] The etiology of such ovarian cyst formation still remains unclear.

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This case report describes successful pregnancy with GnRH antagonist administration for pituitary desensitization in a case with previous ovarian hyperstimulation syndrome (OHSS) caused by GnRH-analogue administration.

Case Report

A 30 years old woman admitted to our infertility unit due to primary infertility for 6 years, related to male factor. Sperm analysis was consistent with azospermia. IVF was considered. The patient had normal serum basal Estradiol (E2), Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) and prolactin levels (31 pg/mL, 4.8 mIU/mL, 5.2 mIU/mL and 18 ng/mL respectively).

Sonohysterography revealed a normal uterine cavity. On day 21 of her menstrual cycle, 0.5 mg leuprolide acetate subcutaneously (sc) daily administration (Lucrin®; Abbot) was started as per

the usual protocol. After 12 days of leuprolide acetate administration, the patient presented to our unit with the signs of ovarian hyperstimulation.

Ultrasonographic examination revealed free fluid in douglas and multicystic ovaries with multiple follicles ranging from 25 mm to 35 mm, diameters of 7.0 cm X 6.4 cm X 7.5 cm (left ovary) and, 7.5 cm X 6.0 cm X 8.2 cm (right ovary) respectively. The hematocrit was 36.11% and the hemoglobin level was 11.6 mg/dL. E2, LH and FSH evaluation revealed 1505 pg/mL, 5.5 and 0.4 mIU/mL serum levels, respectively. Blood urea nitrogen and creatinine levels were in the normal range. Serum βhCG levels was 0.8 mIU/mL. The patient was diagnosed as OHSS and monitored daily with estradiol levels, ultrasonography and 24 hour urine excretion.

E2 levels returned to hypoestrogenemic stage within one week after the diagnosis. The diameters of ovaries declined to 6.2 X 5.1 X 5.9 cms. The diameters returned to normal range one month later. In the following cycle pituitary suppression with GnRH agonist starting from the day 21 for 11 days revealed the same clinical findings and the IVF cycle was cancelled. Two months later after the basal E2, FSH, LH levels and ultrasonographic appearance of the ovaries returned to normal, GnRH antagonist (Cetrotide®; Serono) administration for pituitary suppression was considered. At the day 3 of cycle, ovulation stimulation was carried out using recombinant FSH (Gonal-F®; Serono). It was administered 225 IU daily for 4 days and then 150 IU daily for 4 days. GnRH antagonist was coadministered with gonadotropins at the day 6 when the E2 levels reached to 598 pg/ml and the leading follicle was 12.5 mm. HCG (Profasi®; Serono) 3300 IU was administered on the day 11. when a total of 12 leading follicles measuring ≥ 16 mm was present at 3125 pg/mL E2 levels. Thirty four hours after HCG administration, all of the available follicles were transvaginally aspirated. Oocyte pick up (OPU) revealed 11 metaphase 2 oocytes. Seven of the oocytes fertilized. Two grade 1 embrios were transferred at the day 3, finally leading to clinical pregnancy. At the 38 weeks of gestation she delivered a healthy girl by cesarean section.

Discussion

OHSS is a severe iatrogenic complication in patients undergoing ovarian stimulation. This case demonstrate that the sole administration of GnRH agonists may cause OHSS. Three hypotheses have been proposed to explain how do GnRH agonists contribute to cyst formation. First theory is GnRH agonist administration either as a single depot form or as daily s.c. doses results in a transient 'flare up effect' on the pituitary leading to gonadotropin surge which trigger the growth of primordial follicles. The absence of a subsequent LH surge prevents luteinization of the follicles and cause cyst formation.[1,3-5,7] However this theory fails to explain how these follicles continue growing and the presence of high serum estradiol levels after prolonged use of GnRH agonists.

Second theory is pituitary desensitization may take > 15 days in some women. However functional cysts are reported despite achieving pituitary desensitization as evidenced by low FSH and LH levels.[1,6,7]

Third hypothesis is GnRH agonists may have a direct effect on the ovaries and steroidogenesis by exerting a direct dose-dependent stimulative effect on the aromatase activity and progesterone production which is independent of its action on the pituitary.[6,8-10]

HCG administration and oocyte retrieval are considered to be alternatives to cycle cancellation.

Due to the development of OHSS on two occasions following GnRH agonist administration, we switched to pituitary suppression with GnRH antagonists and ovulation stimulation with gonadotropins which finally led to clinical pregnancy.

GnRH antagonists may be used as an alternative for pituitary suppression in patients who had previous OHSS following GnRH-analogue administration.[11] However, for definite conclusions about the safety of GnRH antagonists, continued assessment with carefully designed, prospective, randomized clinical studies is mandatory.

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