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ASSISTED REPRODUCTION TECHNOLOGIES

Severe ovarian hyperstimulation syndrome after letrozole-gonadotropin stimulation: a case report

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Introduction

Ovarian hyperstimulation syndrome (OHSS) results from an exaggerated response to ovulation induction, characterized by a fluid shift from the intravascular space to third space compartments. The incidence of moderate OHSS is approximately 3–6% and severe OHSS occurs in 0.1–3% of treatment cycles [1, 2]. A number of causal mechanisms have been investigated, involving estradiol (E_2), human chorionic gonadotropin (hCG), and vascular endothelial growth factor (VEGF). A strong association between E_2 concentrations and risk for developing OHSS has been observed consistently [3].

A growing awareness and interest in treatments aimed at fertility preservation (FP) has led many women to pursue urgent oocyte or embryo cryopreservation. Those with estrogen-sensitive cancers often receive adjunctive treatment with letrozole, in efforts to limit exposure to elevated estrogen concentrations that typically result from exogenous gonadotropin stimulation; letrozole inhibits estrogen production by binding competitively to the cytochrome P450 component of the aromatase enzyme. Combination stimulation regimens yield results comparable to those achieved with standard gonadotropin stimulation protocols, but are associated with significantly lower E_2 levels [4].

The risk of OHSS for women receiving adjunctive treatment with letrozole generally is considered low, because E_2 levels are markedly lower than in cycles stimulated with gonadotropins alone. In fact, no cases of severe OHSS have been reported in a patient receiving combined treatment with letrozole and gonadotropins. Here, we report a case of severe OHSS arising in a woman with breast cancer after stimulation with exogenous gonadotropins, despite treatment with letrozole and having only moderately elevated E_2 concentrations.

Case report

A 35-year-old G3P1021 with a recent diagnosis of breast cancer underwent FP consultation. She had an established pattern of irregular menses, but had conceived previously without medical assistance and delivered a healthy child. Two subsequent pregnancies ended in miscarriages. Recent treatment with clomiphene citrate succeeded in inducing ovulation, but failed to achieve pregnancy. After discovering a lump in her right breast, a biopsy of the 1.8 cm mass revealed a breast cancer that was positive for both estrogen and progesterone receptors. Her prescribed treatment included mastectomy and adjuvant chemotherapy with adriamycin and cisplatin. Her BMI was 19.3 kg/m^2 and she had mild hirsutism. Transvaginal ultrasonography demonstrated multicystic ovaries. Her anti-mullerian hormone (AMH) concentration was 12.0 ng/mL. The patient chose to pursue urgent IVF and embryo cryopreservation after breast surgery, before receiving chemotherapy.

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Capsule A woman with breast cancer seeking fertility preservation developed severe ovarian hyperstimulation syndrome after combined treatment with letrozole and gonadotropins.

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A unilateral mastectomy was performed, and subsequently, the patient received treatment with letrozole (Femara, Novartis, 5 mg daily) beginning on cycle day 2, followed by recombinant follicle-stimulating hormone (Gonal F, Serono Inc., Rockland, MA; 225 IU daily) 2 days later (day 4) [4]. Cetrorelix (Cetrotide, Serono Inc., Rockland, MA) was started when the lead follicle reached 14 mm (day 10). Recombinant hCG (Ovidrel 250 μg, Serono Inc., Rockland, MA) was administered on day 14 when the lead follicles reached 20 mm, 22 follicles were 14–20 mm, 2 were 10–14 mm, and the E_2 was 636 pg/mL (Table 1). Two days later, 40 oocytes were retrieved; 28 mature oocytes received intra-cytoplasmic sperm injection (ICSI) and 19/28 (68%) fertilized, ultimately yielding 9 embryos for cryopreservation. Treatment with letrozole was continued.

On day 19, the patient complained of abdominal bloating; the E_2 was 99 pg/mL. On day 22 she presented with abdominal distension and respiratory discomfort; her E_2 was 177 pg/mL, her hematocrit was 43.1%, and no electrolyte abnormalities were evident. Her weight was 101 lb (99 lb at baseline) and an abdominal fluid wave was demonstrable. Transvaginal ultrasound revealed markedly enlarged ovaries (8×8 cm, bilaterally) and significant free fluid; paracentesis removed 1.5 l. The patient was admitted to the hospital and treatment with cabergoline 0.5 mg/day was initiated. She was discharged on day 23 but returned with recurrent symptoms 1 day later, when a second transvaginal paracentesis removed 900 ml of fluid, resolving her symptoms. On day 29, the E_2 concentration was 45 pg/mL and treatment with both letrozole and cabergoline was discontinued. Her planned regimen of chemotherapy began on day 27.

Discussion

This is the first report describing a case of severe OHSS arising in a patient receiving adjunctive treatment with letrozole during gonadotropin stimulation for IVF. Whereas the peak E_2 was only 636 pg/mL, she exhibited features of polycystic ovary syndrome (irregular menses, multicystic ovaries, and a relatively high serum AMH) and had a relatively low BMI, both recognized as independent risk factors for OHSS [5]. Our case illustrates that severe OHSS can develop in patients with risk factors, even when E_2 levels are not grossly elevated.

High circulating E_2 levels are strongly associated with OHSS. The American Society of Reproductive Medicine (ASRM) recommends caution when E_2 levels are rising rapidly or exceed 2,500 pg/mL [5]. However, in cycles involving adjunctive treatment with letrozole, serum E_2 concentrations have limited utility. Studies in infertile

Table 1 Clinical events and laboratory test results

Cycle day	−12	1	2	4 to13	14	16	19	22	23	24	26	27
Clinical Events	Surgery	Initiation of Menses	Letrozole started	rFSH administration	hCG trigger	Oocyte retrieval	Presented complaining abdominal discomfort	Transvaginal paracentesis and hospitalization	Discharge	Transvaginal paracentesis		Chemotherapy
Estradiol (pg/mL)				Day 6: 31 Day 8: 298 Day 12: 561	636		99	177			45	
Hemoglobin (g/dL)								15.3	11.2			
Hematocrit (%)								43.1	32.5			

anovulatory women have demonstrated that letrozole can induce ovulation and is associated with lower peak E_2 levels than with other methods of ovulation induction [6, 7]. Because E_2 levels rise only modestly during treatment with gonadotropins and letrozole, it might be assumed that risk for developing OHSS is low. Although this patient developed severe OHSS despite treatment with letrozole, the clinical course of this patient may have been worse if she had not been on letrozole. In a study involving 74 patients receiving stimulation with letrozole and gonadotropins for FP, 11/74 (15%) developed mild-moderate OHSS [8], but none developed severe illness.

High concentrations of E_2 alone are unlikely to cause OHSS unless hCG also is elevated [9]. The use of hCG to promote the final stages of oocyte maturation in gonadotropin-stimulated cycles is another factor contributing to risk for developing OHSS. A retrospective study of cycles stimulated by combined treatment with letrozole and gonadotropins wherein final oocyte maturation was achieved by treatment with hCG or a GnRH agonist (GnRHa, leuprolide acetate) found that GnRHa treatment was followed by a significant decrease in serum E_2 levels and a lower incidence of OHSS [8]. This retrospective study demonstrated that OHSS can occur after stimulation with letrozole and gonadotropins and that use of GnRHa can mitigate the risk of its development.

We report a case of severe OHSS arising in a cycle involving combined treatment with letrozole and gonadotropins despite a relatively low peak E_2. Our observations may help to raise awareness of the risk for OHSS in such cycles, particularly in patients having other known risks factors, including young age, a low BMI, and polycystic ovary syndrome. Available evidence suggests that in antagonist cycles, treatment with GnRHa, instead of hCG should be considered when the risk of OHSS is increased. It is important to minimize risk of OHSS in patients receiving urgent FP treatment because prolonged exposure to elevated E_2 is best avoided, the disorder can be more serious in patients already in poor health, and severe illness can delay cancer treatment.

References

1. Delvigne A, Rozenberg S. Epidemiology and prevention of ovarian hyperstimulation syndrome (OHSS): a review. Hum Reprod Update. 2002;8(6):559–77.
2. Vlahos NF, Gregoriou O. Prevention and management of ovarian hyperstimulation syndrome. Ann N Y Acad Sci. 2006;1092:247–64.
3. Asch RH, Li HP, Balmaceda JP, Weckstein LN, Stone SC. Severe ovarian hyperstimulation syndrome in assisted reproductive technology: definition of high risk groups. Hum Reprod. 1991;6 (10):1395–9.
4. Oktay K, Hourvitz A, Sahin G, Oktem O, Safro B, Cil A, et al. Letrozole reduces estrogen and gonadotropin exposure in women with breast cancer undergoing ovarian stimulation before chemotherapy. J Clin Endocrinol Metab. 2006;91(10):3885–90.
5. Practice Committee of American Society for Reproductive Medicine. Ovarian hyperstimulation syndrome. Fertil Steril. 2008;90(5 Suppl): S188–93.
6. Shetty G, Krishnamurthy H, Krishnamurthy HN, Bhatnagar S, Moudgal RN. Effect of estrogen deprivation on the reproductive physiology of male and female primates. J Steroid Biochem Mol Biol. 1997;61(3–6):157–66.
7. Badawy A, Elnashar A, Totongy M. Clomiphene citrate or aromatase inhibitors combined with gonadotropins for superovulation in women undergoing intrauterine insemination: a prospective randomised trial. J Obstet Gynaecol;30(6):617–21.
8. Oktay K, Turkcuoglu I, Rodriguez-Wallberg KA. GnRH agonist trigger for women with breast cancer undergoing fertility preservation by aromatase inhibitor/FSH stimulation. Reprod Biomed Online;20(6):783–8.
9. Aboulghar MA, Mansour RT. Ovarian hyperstimulation syndrome: classifications and critical analysis of preventive measures. Hum Reprod Update. 2003;9(3):275–89.