

Random-start controlled ovarian hyperstimulation with letrozole for fertility preservation in cancer patients: Case series and review of literature

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Abstract

The aim of this case series was to describe our experience with random-start controlled ovarian hyperstimulation (RS-COH) with the use of letrozole for fertility preservation. GnRH antagonist and letrozole cycles were started in three patients with a diagnosis of cancer and had a limited time window for fertility preservation for COH before initiating cancer therapy. Cycles were started in the late follicular or luteal phase, and the duration of COH ranged between 7-8 days. A total of 4-14 oocytes were retrieved, the peak E2 levels were 252-354 pg/ml and the saved time for start of the cancer treatment were 16-26 days for each patient. In conclusion, RS-COH with letrozole cycle is a reasonable option for fertility preservation in cancer patients for whom the treatment window may be narrow. Also, the use of a letrozole for COH may decrease the potential risk of ovarian hyperstimulation syndrome.

Keywords: Fertility preservation, Letrozole, RS-COH.

Introduction

The number of cancer survivors are increasing due to advances in cancer treatment. It is estimated that 14% of these patients are diagnosed in their reproductive ages and unfortunately, 1% are under the age of 20 years.¹ As a result of the use of pelvic radiotherapy and/or cytotoxic chemotherapeutic agents in cancer treatment, many women are facing an increased risk of ovarian failure. Recent cancer therapy has improved the survival of younger females diagnosed with malignancy. This calls for preservation of future fertility.

The controlled ovarian hyperstimulation (COH) and subsequent embryo or mature oocyte cryopreservation is the well-known and preferred technique due to its high cumulative pregnancy rates.² Although there are other methods described, some are not still well established

therefore not in routine use such as, ovarian tissue cryopreservation and in-vitro maturation. Unfortunately, the biggest disadvantage of conventional COH for embryo cryopreservation or mature oocyte cryopreservation is the requirement of sufficient time. If there is no contraindication for ovarian stimulation, COH is the most preferable approach.³

Due to the dates of the menstrual cycle, the average time required from the start of ovulation induction day through the oocyte pick-up date may take up to 6 weeks. Therefore, the biggest concerns is the delay in a patient's cancer treatment. If there is not enough time for COH, the other method which is not well established may be offered to a cancer patient including ovarian tissue cryopreservation and in vitro maturation of oocytes.⁴ However recent findings of Oktay K et al, demonstrated that there are multiple major follicle recruitment waves during a menstrual cycle, thus the consideration of a narrow window of opportunity for follicle recruitment may not be true⁵ From this point of view, we performed random-start COH with the use of recombinant FSH (rFSH) plus an aromatase inhibitor; Letrozole in three women who were diagnosed with cancer and required immediate treatment.

Case Reports

Three patients with the diagnosis of an invasive ductal carcinoma of the breast, a Non-Hodgkin lymphoma and a recurrent borderline ovarian tumour, respectively were referred to our tertiary center's IVF unit for fertility preservation between January 2012 and May 2012. Adriamycin plus cyclophosphamide therapy was planned for 4 cycles to the first patient, R-CHOP (Rituximab-Cyclophosphamide, Doxorubicine, Vincristine, Prednisolone) was planned for 6 cycles to the second patient and an oophorectomy was scheduled for the third patient. The last patient had unilateral oophorectomy 4 years ago with the diagnosis of borderline tumour of the ovary. The patients were discussed at our oncology council and the necessity of immediate start of treatment was decided due to the patients' advanced stage diseases.

Random-start COH was initiated immediately after oncology council to the patients with an administration of

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Table-1: Baseline characteristics and cycle outcomes of patients undergoing random-start controlled ovarian hyperstimulation.

Characteristic	Case 1	Case 2	Case 3
Age (year)	27	24	28
Type of Cancer	Breast Cancer	Non-Hodgkin Lymphoma	Borderline over tumor
Type of planned treatment	Adriamycin and Cyclophosphamide (4 cycle)	Ritucimab, Cyclophosphamide, Doxorubicin, Vincristine and prednisolone (6 cycle)	Oophorectomy
AFC (Total)	16	12	5 (Single Ovary) ^a
FSH (mIU/ml)	4.2	4.1	6.4
AMH	1.8	1.7	1.1
LH	7.4	8.2	6.9
E2 (pg/mL)	104	68	76
Starting day of COH	8	15	5
Starting day of the GnRH Antagonist	6	6	6
Duration of COH (day)	7	8	7
Total Gonadotropin dose (IU)	1050	1200	1050
Peak E2 (pg/ml)	354	341	252
Number of retrieved oocyte	7	16	4
Number of MII Oocyte	5	9	4
Fertilization rate, n (%)	-	-	3/4 (75 %)
Number of Frozen Embryos and oocyte (n)	5	9	3
The saved time for start of the cancer treatment (day)	23	16	26

^aFour years ago, unilateral oophorectomy was performed to the patient with the diagnosis of borderline tumor of the ovary.

AFC: Antral Follicle Count; FSH: Follicle Stimulating Hormone; AMH: Anti Mullerian Hormone; LH: Luteinizing Hormone; E2: Estradiol; COH: Controlled Ovarian Hyperstimulation; GnRH: Gonadotrophine Releasing Hormone; IU: International Unit.

aromatase inhibitor, Letrozole 2.5 mg/day (Femara; Novartis, Istanbul, Turkey) then rFSH 150-300 IU/day (Gonal-F; Merck Serono, Istanbul, Turkey) was added to the protocol two to three days later.⁶ GnRH antagonist (0.25 mg/day Cetrotide; Merck) was used from the 6th day of the stimulation protocol to prevent premature LH surge. The total time duration of COH ranged between 7 to 8 days, and the peak E2 levels were recorded between 252 and 354pg/mL. When at least two follicles had a mean follicular diameter of ≥ 17 mm, ovulation was triggered with the administration of 250 mg recombinant hCG (Ovitrelle; Serono). The assessment of the oocytes is made according to the results of the evaluation Alpha Consensus 2011 meeting. For assessment of the oocyte maturation, control and evaluation of the meiosis was made with PolScope (Spindle View; CRI, Woburn, MA, USA).⁷ The patients were informed in detail and an informed consent form was signed to each.

The baseline characteristics and cycle outcomes of the patients are demonstrated in Table-1. The first patient with breast cancer and the second patient with Non-Hodgkin Lymphoma were not married, therefore oocyte cryopreservation procedure was planned for both. The third patient who had borderline ovarian tumour was married, and embryo freezing was performed to three embryos fertilized out of four oocytes following intracytoplasmic sperm injection (ICSI). Cryopreservation of

the three embryos was done on the second day after oocyte pick-up; two embryos were grade-1 (five and four blastomers), and one embryo was grade-2 (two blastomers). The total saved time to start cancer treatment was calculated as 16 to 26 days. In these three patients 4 to 17 oocytes were retrieved and the numbers of metaphase II oocytes were between 4 and 9. Fertilization rate of the third patient was 75 %. The numbers of the frozen oocyte in first and second patients were 5 and 9, respectively. The number of frozen embryo in third patient was 3. In these patients, Currently, frozen embryos and oocytes were not thawed.

Discussion

The expectancy of fertility is a significant concern for patients undergoing cancer treatment due to increased survival rate. Approximately 8% of female cancers are occurring under the age of 40. Although the survival rates are increasing, these patients are facing fertility issues due to treatment induced ovarian failure.

Among the described methods in the prevention of fertility in women, embryo/oocyte cryopreservation with COH appears to be the best option. In these patients, the period between cancer diagnosis and the need for the initiation of treatment may be very short, approximately 3 weeks. However the conventional stimulation protocol may take up to 6 weeks, which will lead to a significant

delay in cancer treatment.

Baerwald A. R et al. described multiple cohorts or 'waves' of antral follicle recruitment which exist in women during the menstrual cycle.⁸ Previous studies reveal limited data related to random-start COH in cancer patients in which majority used rFSHA plus a GnRH antagonist. To our knowledge, there is only one study that an aromatase inhibitor, Letrozole plus rFSH was used for ovarian stimulation.⁴ In the presented case series, we have shown that COH can be started at any time in a menstrual cycle in the case of emergency fertility preservation. In two cases, 4 out of 12 MII oocytes were obtained and 5 to 12 oocytes were frozen. In one case, 4 MII oocytes were collected and three embryos were obtained with a favourable (75%) fertilization rate.

Bedochi et al. reported two cases; one had infiltrative ductal carcinoma of the breast and the other had Hodgkin's lymphoma.⁹ COH protocols of both were performed with rFSH and a GnRH antagonist, during the luteal phase of their menstrual cycles. Twelve mature oocytes were retrieved from each. ICSI was performed to all mature oocytes of the patient with breast cancer. The fertilization and cleavage rates were 83.3% and 70%, respectively and seven good quality embryos were obtained finally. All mature oocytes of the Hodgkin's lymphoma case was cryopreserved.

Sonmezer M et al. described emergency COH in three patients with breast cancer for fertility preservation in the late follicular or luteal phases of their cycles.⁴ COH was started on cycle days 11, 14, or 17 with the use of Letrozole 2.5mg/d and rFSH 150 to 300 IU/day. GnRH antagonist was administered to all subjects to prevent ovulation. Nine to 17 oocytes were retrieved and 7 to 10 embryos were cryopreserved. The mean maturity and fertilization rates were 58.8% to 77.7% and 69.2% to 87.5%, respectively.

Also, increased estrogen levels during an IVF cycle may be a major concern especially in estrogen dependent cancers such as breast cancer. Thus, to limit the increasing estrogen level is foremost important in these conditions. The use of aromatase inhibitor in random-COH cycle bring

us the advantages of the reduced peak E2 levels, slightly increased number of mature oocytes retrieved with a good clinical pregnancy rate.⁶ As for comparison, the peak E2 level of our patients was lower (between 252 and 354pg/ml) than other protocols (between 1181 and 9672 pg/mL).¹⁰

Conclusion

The results of our case series could be interpreted as the preliminary results of random start-COH with the use of aromatase inhibitor plus rFSH, and we could suggest this regimen as a time saving protocol in cancer patients for fertility preservation.

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