



Ovarian stimulation for emergency fertility preservation in cancer patients: A case series study



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Introduction

Increasing survival rates in patients who suffer from oncological disease and improvement in reproductive medicine techniques have led to increasing use of different fertility preservation methods. Controlled ovarian stimulation (COS) for mature oocyte cryopreservation or embryo cryopreservation has highest success rates compared with other technologies, therefore it is considered the preferred method for fertility preservation in cancer patients (American Cancer Society, Cancer facts and figs., 2012). Most cancer patients are treated with a GnRH antagonist-based protocol since this protocol provides the shortest delay of the cancer treatment and the lowest risk of impending ovarian hyperstimulation syndrome (OHSS) by induction of ovulation with GnRH agonist (McLaren and Bates, 2012).

Conventionally, ovarian stimulation for oocyte/embryo cryopreservation with GnRH antagonist is initiated at the beginning of the follicular phase. This stimulation protocol may require 2–6 weeks, depending on the patient's menstrual cycle day. Due to the urgent need of medical or surgical intervention in patients with known malignancies, antagonist protocols with random start COS have been proposed (Quinn et al., 2008; Signorello et al., 2010). This approach was designed to provide the shortest time for oocyte collection and claimed to be as

effective as conventional-start COS in cancer patients (Cakmak et al., 2013; Cakmak and Rosen, 2013).

In addition the success of using GnRH antagonist during the preceding luteal phase of stimulation cycle was shown resulting in a rapid fall of progesterone (Anderson et al., 1999).

In this case series study we aimed to evaluate stimulation outcome following conventional start or random-start controlled ovarian stimulation in gynecologic cancer women.

Materials and methods

This prospective study was performed at a tertiary referral university hospital from January 2013 to February 2014, and was approved by The Institutional Review Board and Ethical Committee of the hospital. A written informed consent was obtained from all participants at the first visit. All patients were recently diagnosed with cancer and were planned to receive treatments (surgical or non surgical) which could lead to a significant chance of disruption to their ovarian function and therefore referred for counseling for fertility preservation methods.

Patients were evaluated for fertility preservation within 48 h. Time frame until the initiation of cancer treatment was at least 2 weeks. The decision to perform with a conventional versus a random-start COS was elected based on the patients' menstrual cycle on the admission day. All participants received COS cycles using GnRH antagonist for pituitary suppression. No patient in either group had received chemotherapy or radiotherapy before undergoing COS cycles.

Controlled ovarian stimulation protocols

Conventional COS or random start COS protocol were offered to the patients based on their menstrual cycle day, the start dose and adjustment of gonadotropins were based on their body mass index (BMI), age and ovarian reserve. Ovarian reserve was estimated by antral follicle count (AFC), anti-Mullerian hormone (AMH) and FSH when available. Patients received daily doses of Gonal F (Serono Laboratories Ltd, Geneva, Switzerland), while being monitored by vaginal ultrasound. The gonadotropin dose was adjusted according to the size and the number of developing follicles. Patients in the conventional-start group received ovarian stimulation on day two or three of their menstrual cycles; when the lead follicle measured ≥ 14 mm, GnRH antagonist 0.25 mg (Cetrotide, EMD-Serono) was administered to prevent

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premature ovulation, and daily injection was continued until at least two follicles ≥ 18 mm were detected. Ovulation induction was performed by using human chorionic gonadotropin (Pregnyl®; Darou Pakhsh Pharmaceutical, Tehran-Iran) 10,000 IU, intramuscularly.

The random start group patients received COS irrespective of their menstrual cycle (from days 4 to 23). Ovarian stimulation without pre-administration of GnRH antagonist was proceeded; when the follicle cohort after stimulation reached 12 mm, to eliminate premature LH surge, GnRH antagonist was then initiated and continued until triggering final oocyte maturation with hCG. Only in one patient in random-start group, final oocyte maturation was triggered with GnRH agonist (subcutaneous injection of 500 μ g buserelina (Superfact; Aventis Pharma Deutshlan, Frankfurt, Germany) to reduce the risk of OHSS. In both groups oocyte retrieval followed 34–36 h after final oocyte maturation. Intra-cytoplasmic sperm injection (ICSI) was undertaken in all patients to mitigate fertilization failures. For embryo banking only metaphase II (MII) oocytes were fertilized by ICSI. Embryos were cryopreserved on either day 3 or day 5.

Outcome measures

Our main outcome measure was the number of mature (MII) oocytes retrieved in both groups. Secondary outcome measures were total dosage of gonadotropins, number of days needed for ovarian stimulation, total number of oocytes retrieved, oocyte maturity rate (MII oocytes/total oocytes), and fertilization rate (percentage of 2PN stage/total injected oocytes).

Results

During the study period, 10 patients with ovarian cancer, three patients with uterine cancer and one patient with breast cancer were referred to our centers for fertility preservation. Seven patients underwent conventional-start and seven with random-start COS. Oocyte cryopreservation was performed in one patient (14%) in each group (one patient was not married, and the husband of the other one could not obtain semen for injection) and embryo cryopreservation was done in six patients (86%) in conventional-start group and also five patients (71%) in random start group. One patient with random start group did not have any embryo to freeze. Baseline and cycle characteristics of study cases were presented in Table 1.

Table 2 shows demographic characteristics of patients in the two groups according to conventional-start or random-start COS. The differences between the two groups regarding age, body mass index (BMI), AMH, cancer type, pregnancy history, and infertility history were not

Table 2

Comparison of the cycle characteristics of patients undergoing conventional- or random-start controlled ovarian stimulation cycles for fertility preservation.

Variables	Protocol		P value
	Conventional N = 7	Random start N = 7	
Age of patients (years)	29.1 \pm 4.8	28.1 \pm 2.5	0.6
BMI	25.7 \pm 4.3	23.2 \pm 2.5	0.2
AMH ^a	1.7 \pm 1.1	1.7 \pm 1.7	
Cancer type n (%)			0.5
Ovarian cancer	5 (71.4)	5 (71.4)	
Uterine cancer	1 (14.3)	2 (28.6)	
Breast cancer	1	0	
Previous live birth	2 (28.6)	3 (42.9)	0.5
Infertility +	4 (66.7)	2 (40)	0.4
Infertility duration	3.2 \pm 1.8	3.0 \pm 0.0	0.8
Type of infertility			
Cause of infertility n (%)			0.2
Male	1 (25)	–	
PCOS	2 (50)	–	
Unexplained	1 (25)	2 (100)	
Days of ovarian stimulation (SD)	7.8 \pm 1.0	8.7 \pm 2.0	0.3
Start dose of gonadotropins (IU)	257.1 \pm 95.4	235.7 \pm 51.7	0.6
Total dose of gonadotropins (IU)	2153 \pm 850	2100 \pm 806	0.9
No. of follicles ≥ 12 mm	9.8 \pm 5.1	10.7 \pm 7.6	0.8
No. of oocytes retrieved	5.8 \pm 3.9	7.8 \pm 0.0	0.5
No. of MII ^b oocytes	5.2 \pm 3.6	7.2 \pm 6.6	0.5
No. of MII oocytes/oocytes retrieved	0.96 \pm 0.06	0.92 \pm 0.13	0.5
Fertilization rate	0.60 \pm 0.34	0.74 \pm 0.25	0.4
No. of embryos	3.6 \pm 2.3	6.0 \pm 6.3	0.4
No of freezed embryos	3.5 \pm 2.3	7.2 \pm 6.3	0.2

Data are presented as means \pm SD and number %.

^a Anti-Mullerian hormone.

^b Metaphase II.

significant. Fortunately we did not have any cancellation cycle due to no ovarian response. In the random start group one patient had no fertilized oocyte after ICSI. Ovarian stimulation was started in late follicular phase (days 8–13 of menstrual cycle) in one patient and in luteal phase (≥ 14 day of menstrual cycle) in three patients. No differences were observed in total dose of gonadotropins ($P = 0.9$). In both groups, the duration of gonadotropin administration was slightly but not significantly higher in the random-start group (7.8 ± 1.0 vs. 8.7 ± 2.0 days, $P = 0.3$). The mean number of oocytes retrieved, metaphase II (MII) oocytes, was slightly but not significantly higher in the random-start group (7.8 ± 0.0 and 7.2 ± 6.6) vs. (5.8 ± 3.9 and 5.2 ± 3.6), $P = 0.5$. However oocyte maturity rates (MII oocytes/total oocytes) were similar between the groups (0.92 ± 0.13 vs. 0.96 ± 0.06). Fertilization rates per MII oocyte were similar between the two groups.

Table 1

Baseline characteristics of study cases.

Patients	Age	Cancer type	Previous pregnancy	Previous live birth	Infertility type	Day of stimulation	Total dose of gonadotropin (IU)	Stimulation duration	Retrieved oocyte	MII oocyte	2PN	Freezed products
1	29	Cervical cancer	Yes	Yes	Secondary	21	3300	11	23	20	17	17 embryos
2	32	Submucous leiomyosarcoma	No	No	–	16	2700	9	7	6	4	4 embryos
3	26	Borderline ovarian papillary serous tumor	Yes	Yes	–	23	2250	10	1	1	0	–
4	24	Borderline ovarian papillary serous tumor	Yes	Yes	–	1	1800	8	4	3	3	3 embryos
5	37	Breast cancer	No	No	Primary	3	1800	6	10	7	4	3 embryos
6	32	Borderline ovarian papillary serous tumor	No	No	Primary	3	2025	9	1	1	1	1 embryo
7	24	Endometrioid and mucinous ovarian carcinoma	No	No	Primary	2	1575	7	12	12	8	8 embryos
8	29	Borderline ovarian papillary serous tumor and endometrioid carcinoma	No	No	Primary	3	1800	8	4	3	3	3 embryos
9	32	Borderline ovarian papillary serous tumor	Yes	Yes	Secondary	3	4050	9	3	3	3	3 embryos
10	29	Ovarian serous carcinoma	No	No	–	5	1125	5	2	2	2	2 embryos
11	26	Borderline ovarian papillary serous tumor	Yes	Yes	–	4	1050	7	6	6	3	3 embryos
12	26	Endometrial adenocarcinoma	No	No	–	2	2025	8	7	7	–	7 oocytes
13	30	Ovarian papillary serous adenocarcinoma	No	No	Primary	4	2250	10	4	4	4	4 oocytes
14	25	Ovarian papillary serous adenocarcinoma	No	No	–	8	2025	9	12	12	10	10 embryos

Discussion

In this prospective, case series study, we evaluated the outcomes of the emergency fertility preservation protocol (random start) in cancer patients including ovarian tumor.

All cancer patients of reproductive age (or younger) must be informed and discussed about fertility issues associated with their cancer and foreseen treatments. However the role of conservative treatment, that is aimed at preserving subsequent fertility with borderline ovarian tumor, has gained considerable attention during the last decade (Morice, 2006). The management of such cases has been a matter of controversy. Particularly based on initial publications that theoretically contraindicated infertility treatment in patients who were treated for ovarian malignancies. Fortunately, these data have not been confirmed and newer data are quite reassuring (Fortin et al., 2007; Fasouliotis et al., 2004).

The choice of the specific COS protocol is influenced by the available time until the initiation of cancer therapy. There is emerging evidence that oocytes can be obtained before cancer treatment efficiently, irrespective of the phase of the menstrual cycle (Von Wolff et al., 2009).

Evidence to support the hypothesis of efficacy of random start COS is ovarian physiology. The time that takes in progressing from a primary follicle to ovulation is about 85 days (Gougeon, 1986). The late stage of this development is dependent on hormonal regulation. Where, without rescue by follicle-stimulating hormone (FSH), atresia will occur (Oktay et al., 1998).

Administration of GnRH antagonists in luteal phase has been used to reduce time frame for cancer patients.

In a study by Anderson et al corpus luteum breakdown was induced by GnRH antagonists during the preceding luteal phase, resulting in a rapid fall of progesterone. COS stimulation was followed 4 days after administration of GnRH antagonists. Eight and 6 oocytes were retrieved, and then 6 and 4 mature oocytes were successfully fertilized by IVF (Anderson et al., 1999).

In a pilot study by Von wolf, no time was left for luteolysis before starting ovarian stimulation by recombinant FSH after administration of GnRH antagonists, and combination of both medications was continued to ovulation induction time. In comparison with stimulation in the follicular phase group, both groups had a similar number of retrieved oocytes and MII oocytes as well as similar fertilization rates. They conclude that high progesterone concentrations at the beginning of ovarian stimulation in the luteal phase group did not affect oocyte quality (Von Wolff et al., 2009).

In another study by Cakmak et al., women diagnosed with cancer were stimulated on presentation regardless of their menstrual-cycle day (Cakmak et al., 2013).

In our study, one patient was in the late follicular phase (days 8–13) and GnRH antagonist was started when the secondary follicle cohort following stimulation reached 12 mm, after induction of ovulation, 12 metaphase II (MII) oocytes were collected, and 8 oocytes were successfully fertilized by ICSI, resulting in a fertilization rate of 66.6%, which shows similar results to Cakmak and Rosen (2013) study.

GnRH antagonist administration could be initiated later in the cycle, when the follicle cohort (has) reached 12 mm to precede fertility

preservation without compromising oocyte yield and maturity. The concept of our protocol for the patients in luteal phase differs from the described protocol suggested by von wolf, but is in concordance with the study conducted by Cakmak et al. (2013) and Von Wolff et al. (2009). In our study COS without GnRH antagonist was started. Similar to conventional antagonist protocol, when the follicle reached 12 mm, GnRH antagonist was initiated and continued until final oocyte maturation.

In summary, GnRH antagonist administration could be initiated at any time, to prevent premature LH surge and would continue until the final oocyte maturation. This approach decreases total time for the IVF cycle in urgent settings without compromising oocyte yield and maturity.

Conclusion

According to our preliminary report, considering the limitation of the sample size, the promising results should encourage oncologists for early referral of women with different types of cancer to fertility specialists for emergency fertility preservation. In addition, this method may prevent delay in cancer treatment.

Conflict of interest statement

The authors declare no conflicts of interest.

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