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Authors

Wald, Kaitlyn
Cakmak, Hakan
Mok-Lin, Evelyn
et al.

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FERTILITY PRESERVATION

Back-to-back random-start ovarian stimulation prior to chemotherapy to maximize oocyte yield

Kaitlyn Wald[1] · Hakan Cakmak[1] · Evelyn Mok-Lin[1] · Marcelle Cedars[1] · Mitchell Rosen[1] · Joseph Letourneau[1,2]

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Abstract

Purpose To evaluate the feasibility of utilizing back-to-back random-start ovarian stimulation to increase oocyte yield for fertility preservation prior to cancer treatment.

Methods A case series of 15 patients who underwent back-to-back random-start stimulation cycles prior to chemotherapy.

Results Of the 15 back-to-back random-start stimulation cases, 13 had breast cancer and 2 had other cancers. The average age was 38 years (range 30–43) and average AFC was 8 (range 3–14). Fourteen of the 15 women (93%) who underwent two ovarian stimulation cycles completed both of them. The average time to complete back-to-back random-start ovarian stimulation was 33 days (range 13–43 days). The average time between the first cycle completion and the second cycle start in our back-to-back random-start stimulations was 9 days (range 0–14 days). Two of the women underwent back-to-back random-start ovarian stimulation prior to starting neoadjuvant chemotherapy for breast cancer. Eleven of our 15 women at least doubled their oocyte or embryo yield relative to their first cycle. Only 1 of the 15 second cycles was canceled. The mature oocyte rate, fertilization rate, and embryo yield were similar among the first and second cycles.

Conclusions Back-to-back random-start ovarian stimulation may be an effective way to maximize fertility preservation, even in time-limited settings.

Keywords Fertility preservation · Diminished ovarian reserve · Cancer · Ovarian stimulation

Introduction

Cryopreservation of oocytes or embryos prior to cancer treatment has become an increasingly well-established means of helping patients to build families and improve long-term quality of life [1, 2]. While we have not yet been able to predict the ideal number of oocytes or embryos to cryopreserve, the number needed to reach one's family-building goals likely varies based on individual circumstances [3–6]. Some of these circumstances include the following: patient age, ovarian reserve, cancer treatment type, gene mutation status, the need for adjuvant hormonal treatment, response to initial ovarian stimulation cycle, and number of future children desired. In women less than 35 years old, estimates suggest that 8 to 10 oocytes are needed to achieve a good chance of a single live birth. In women over 35 years old, the number of oocytes needed may reach 15 or 20. In women over 40, more than 20 oocytes may be needed to achieve a single live birth [3–6]. If a patient is a carrier of an autosomal dominant mutation, such as BRCA, and desires pre-implantation genetic testing for the monogenetic disorder (PGT-M), half of the embryos created will test positive for the mutation. This means that twice the number of eggs should be collected, in order to meet family-building goals. A desire for multiple children also increases the ideal number of oocytes.

The traditional paradigm for performing oocyte or embryo cryopreservation has been to perform one conventional-start ovarian stimulation cycle prior to chemotherapy [7]. While conventional-start ovarian stimulation remains common, random-start ovarian stimulation has quickly become a standard practice in fertility preservation centers prior to cancer treatment [8]. Random-start stimulation, meaning the

✉ Kaitlyn Wald
Kaitlyn.Wald@ucsf.edu

[1] Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco, 499 Illinois Street, 6th Floor, San Francisco, CA 94158, USA

[2] University of Utah Center for Reproductive Medicine, Salt Lake City, UT, USA

initiation of ovarian stimulation at any point during the menstrual cycle, is associated with no difference in outcomes compared to conventional start [8]. Additionally, a single cycle of random-start stimulation can save 2 to 6 weeks of time versus a single cycle of conventional-start stimulation. Prior studies have examined the feasibility of performing follicular start stimulation followed immediately by a second cycle luteal start stimulation for patients with diminished ovarian reserve [9, 10]. Prior studies have also shown the feasibility of back-to-back conventional-start ovarian stimulation cycles in breast cancer patients, after breast cancer surgery and before adjuvant chemotherapy [11].

Back-to-back random-start ovarian stimulation prior to cancer treatment has not yet been reported. In this study, we report on the feasibility of performing back-to-back random-start stimulations in the cancer setting. For women whose first cycle yielded too few oocytes or embryos for their family-building desires, we initiated a second random-start stimulation within 14 days. We aim to show that this process results in a significant increase in oocyte and embryo yield.

Materials and methods

We performed a retrospective chart review. For this type of study, formal consent is not required. All study procedures were approved by University of California, San Francisco (UCSF) Committee on Human Research and the Institutional Review Board.

Study population

An electronic chart review was performed to select all patients from our clinic who underwent back-to-back random-start ovarian stimulation cycles for fertility preservation prior to cancer treatment. Inclusion criteria for the chart review included the following: ages 18 to 44 years old, no prior ovarian stimulation cycles, oocyte/embryo cryopreservation prior to cancer treatment (chemotherapy, abdominal-pelvic radiation, pelvic surgery, or prolonged adjuvant hormone therapy that will delay childbearing).

Back-to-back random-start ovarian stimulation

Antagonist-based, random-start ovarian stimulation was performed as described by Cakmak et al. [8]. Briefly, baseline ultrasound was performed prior to starting ovarian stimulation in each ovarian stimulation cycle to assess antral follicle count (AFC). AFC visualization was not a requirement for initiation of cycle 1 and did not impact the timing of stimulation initiation; however, AFC was used to tailor gonadotropin dosing in the first random-start cycle. Antagonist-based random-start ovarian stimulation was performed with recombinant FSH 300-450 IU (Gonal-f; EMD Serono/Follistim; Merck) and Menopur 150-225 IU (Ferring). Women with estrogen-receptor positive breast cancer were treated with concomitant letrozole or tamoxifen during their ovarian stimulation. Oocyte maturation was triggered by 2500–10,000 IU of human chorionic gonadotropin (hCG; Organon) or GnRH agonist (leuprolide acetate, 4 mg; Ferring) when at least two follicles had reached the mean diameter of 18–20 mm. All follicles $\geq$ 10 mm in diameter were aspirated during egg retrievals. All embryos were preserved on day 3, as standard for cancer patients at our clinic.

Back-to-back random-start stimulation was performed for women whose circumstances dictated a likely benefit of cryopreservation of more oocytes or embryos. These circumstances included the following: less than expected response to initial ovarian stimulation cycle (expectation based on baseline AFC), patient age, ovarian reserve, cancer treatment type, presence of genetic cancer-predisposition mutations leading to a desire for PGT-M, and number of future children desired. Back-to-back random-start ovarian stimulation was defined as starting a second random-start ovarian stimulation cycle within 14 days of completion of the first random-start cycle. If a second cycle was desired, we communicated this preference to the patient's oncologist and informed them of our estimated date of the second retrieval, to assure that oncology care could be planned accordingly. All candidates for back-to-back random-start stimulations were monitored every 2 to 3 days subsequent to the first retrieval to identify emerging antral follicles. We began ovarian stimulation of the second cycle once follicles were visible on ultrasound. We did not routinely obtain any labs prior to initiation of the second cycle. We generally used the same starting dose of gonadotropins in both cycles.

The demographics for the 15 identified back-to-back random-start stimulation cases were obtained. Outcomes of the first and second cycle in back-to-back random-start ovarian stimulation cycles were reviewed.

Results

Patient characteristics

There were a total of 90 patients who underwent more than one ovarian stimulation cycle for oocyte or embryo cryopreservation. Fifteen of these women underwent back-to-back random-start ovarian stimulation cycles and were included in our case series. The remaining 75 patients had a greater than 14-day interval between their stimulation cycles. The desire and estimated timeline of completing a second cycle was communicated to their primary oncologist prior to initiation. In each of these 15 cases, our oncology colleagues were comfortable with the patient undergoing a second cycle and did not advise against a second stimulation cycle in order to

pursue cancer treatment earlier. Of the 15 back-to-back random-start stimulation cases, 13 had breast cancer and 2 had other cancers (one patient with concurrent endometrial and ovarian cancers, one with Hodgkin's disease). The average age was 38 years (range 30–43) and average AFC was 8 (range 3–14) (Table 1).

The most common reasons for undergoing a second stimulation cycle were diminished ovarian reserve (52%) and reduced/unsatisfactory response to the first ovarian stimulation cycle (20%). Fourteen of the 15 women (93%) who underwent two ovarian stimulation cycles completed both of them (one patient had both her first and second cycles canceled prior to egg retrieval due to a poor response). In back-to-back random-start cycles, the most common timing for fertility preservation among patients with breast cancer was to have both cycles after surgery, while awaiting chemotherapy for breast cancer. Two women underwent back-to-back random-start ovarian stimulation prior to neoadjuvant chemotherapy for breast cancer.

The average time to complete back-to-back random-start ovarian stimulation was 33 days (range 13–43 days), from the start of the first cycle until the second oocyte retrieval (Tables 2 and 3). The average time between first cycle completion and second cycle start in our back-to-back random-start stimulations was 9 days (range 0–14 days). The first and second cycle length and total gonadotropins used varied from one another; however, the gonadotropin dose per day was unchanged in 12 of the 15 cycles (Table 4).

Back-to-back random-start cycle results

Eleven of our 15 women in this case series at least doubled their oocyte or embryo yield relative to their first cycle (Tables 2 and 3). The mature oocyte rate (range 27–100%), fertilization rate (range 50–100%), and embryo yield (20–100%) were similar among the first and second cycles (Table 5). Only one of the 15 second cycles was canceled for poor response and this was in a patient who also had their first cycle canceled for a poor response. Case 3 was notable for a less than expected egg yield per AFC from the first cycle. The second cycle was complicated by premature ovulation, with a day of retrieval P4 of 13.8 ng/mL and no eggs were collected.

Discussion

There is, of course, no set number of eggs or embryos that should be cryopreserved to help assure that building one's biological family is a possibility. Fertility preservation counseling is often highly personalized, and a wide variety of factors are taken into account in order to cater to the patient's needs: patient age, ovarian reserve, genetic mutation status, cancer type, adjuvant treatment considerations, and the number of desired children. For many young women with excellent ovarian reserve and no desire for PGT-M due to a genetic mutation, a single random-start cycle may yield sufficient oocytes. However, in cases where more oocytes or embryos are desired, this retrospective case series suggests a second random-start ovarian stimulation cycle that be performed in rapid succession after their first cycle.

Modern breast cancer care now includes neoadjuvant chemotherapy in at least 10% of cases (and a much higher percentage in some settings) and consequently limited

Table 1 Demographic characteristics

Case	Age at cancer diagnosis	Gravidity	Parity	BMI (kg/m^2)	Initial AFC	Cancer type	Stage	Neoadjuvant chemotherapy
1	33	1	1	25.9	8	Breast	2	No
2	42	2	0	17.5	14	Breast	2	No
3	35	1	1	26.3	11	Breast	2	Yes
4	42	0	0	23.7	3	Breast	2	Yes
5	43	1	0	36	7	Breast	2	No
6	40	1	0	28.5	10	Breast	2	No
7	43	5	1	19.2	8	Breast	2	No
8	38	1	1	20.9	6	Breast	2	No
9	35	0	0	23.4	6	Breast	2	No
10	38	1	1	18.7	4	Breast	1	No
11	37	2	0	30.9	12	Breast	2	No
12	37	1	0	21.7	8	Breast	1	No
13	34	0	0	28.6	9	Breast	1	No
14	43	2	0	26.8	8	Concurrent endometrial and ovarian	4, 2	No
15	30	0	0	21.3	3	Hodgkin's lymphoma	2	N/A

Table 2 Egg cryopreservation back-to-back random-start cycle results

Case	AFC	FP consult to start cycle 1 (days)	FP consult to start chemo (days)	Length cycle 1+ (days)	Between cycles ++ (days)	Length cycle 2+ (days)	Total length+++ (days)	Eggs cycle 1	Eggs cycle 2	Total eggs
1	8	14	60	11	11	15	37	5	10	15
2	14	0	238	11	13	14	38	17	25	42
3	11	1	17	9	0	4	13	3	0	3
4	3	2	43	12	9	14	35	6	2	8
7	8	36	N/A	13	10	15	38	8	2	10
11	12	0	30	9	1	9	19	6	12	18
12	8	9	51	‘6	12	‘7	25	0	0	0
13	9	2	36	15	0	9	24	2	2	4

+Days from stimulation start to egg retrieval

‘Day of stimulation, given no egg retrieval

++ Days from cycle 1 retrieval to cycle 2 start

+++Days from start cycle 1 to retrieval cycle 2

time for ovarian stimulation [12]. We have demonstrated that random-start stimulation can be performed without delaying chemotherapy, even in the time-limited and increasingly popular setting of neoadjuvant chemotherapy [13]. It has previously been shown that the average time from cancer diagnosis to chemotherapy start, with the majority of women undergoing a single preservation, was similar between women who undergo ovarian stimulation and those who do not (38.1 ± 11.3 versus 39.4 ± 18.5 days) [13]. This study, in which women underwent two back-to-back random-start cycles, took 34 days. Oktay et al. have reported on the feasibility of performing consecutive ovarian stimulations prior to chemotherapy for breast cancer [11]. However, in their study, conventional-start ovarian stimulation was used, and both cycles were performed after breast cancer surgery and before adjuvant chemotherapy. Oktay et al. reported 63.7 days from surgery to initiation of chemotherapy and 81.3 days from diagnosis to initiation of chemotherapy. It is difficult to compare our patients to Oktay’s given that we also included those undergoing neoadjuvant chemotherapy. Further, our patients were not exclusively breast cancer patients. We have a total of 5 patients who, like those in Oktay's cohort, underwent surgery prior to completing two cycles. We found an average of 95.6 days from surgery to initiation of chemotherapy and 158 days from diagnosis to the initiation of chemotherapy. We suspect that the longer duration noted in our patients is due to small sample size, as a random-start approach, as shown in Fig. 1, clearly minimizes the total duration required to complete two simulation cycles. In this case series, we have shown further plasticity by completing back-to-back random-start stimulation cycles. These cycles may both be completed prior to chemotherapy, even if undergoing neoadjuvant therapy.

Table 3 Embryo cryopreservation back-to-back random-start cycle results

Case	AFC	FP consult to start cycle 1 (days)	FP consult to start chemo (days)	Length cycle 1+ (days)	Between cycles ++ (days)	Length cycle 2+ (days)	Total length+++ (days)	Eggs cycle 1	Eggs cycle 2	Total eggs	Day 3 embryos cycle 1	Day 3 embryos cycle 2	Total day 3 embryos
5	7	13	N/A	12	14	12	38	19	23	42	5	9	14
6	10	6	N/A	16	14	13	43	11	18	29	7	12	19
8	6	5	112	15	9	11	35	5	11	16	1	3	4
9	6	14	62	12	12	14	38	8	9	17	6	7	13
10	4	0	143	11	13	14	38	7	12	19	4	4	8
14	8	0	156	12	12	15	39	6	9	15	4	9	13
15	3	7	84	15	7	15	37	1	3	4	1	2	3

+Days from stimulation start to egg retrieval

++ Days from cycle 1 retrieval to cycle 2 start

+++Days from start cycle 1 to retrieval cycle 2

Table 4 Back-to-back random-start cycle medications

Case	Total gonadotropin dose cycle 1 (IU)	Total gonadotropin dose cycle 2 (IU)	Days gonadotropin use cycle 1	Days gonadotropin use cycle 2	Average gonadotropin dose per day cycle 1 (IU)	Average gonadotropin dose per day cycle 2 (IU)	Trigger shot cycle 1 (IU)	Trigger shot cycle 2 (IU)
1	4050	5850	9	13	450	450	10 k hCG	10 k hCG
2	4050	5400	9	12	450	450	10 k hCG	10 k hCG
3	3150	900	7	2	450	450	1500 hCG + Lupron 4 mg	8500 hCG
4	4500	5400	10	12	450	450	10 k hCG	10 k hCG
5	4500	4500	10	10	450	450	10 k hCG	10 k hCG
6	6300	4950	14	11	450	450	5 k hCG	10 k hCG 450 FSH
7	4950	5850	11	13	450	450	10 k hCG	10 k hCG
8	5850	4050	13	9	450	450	10 k hCG	10 k hCG
9	4500	5400	10	12	450	450	10 k hCG	10 k hCG
10	4050	5400	9	12	450	450	10 k hCG	10 k hCG
11	3150	3150	7	7	450	450	10 k hCG	10 k hCG
12	2700	3150	6	7	450	450	Canceled*	Canceled**
13	5925	3300	13	7	456	471	5 k hCG	10 k hCG
14	4500	5850	10	13	450	450	10 k hCG	10 k hCG
15	4950	5850	13	13	381	450	10 k hCG	5 k hCG

*Canceled for single dominant follicle

**Canceled for a poor response—no mature follicles after 17 days of stimulation

Alternatively, they may be completed following surgery, but prior to adjuvant chemotherapy. The initiation of stimulation at any time during the menstrual cycle, as opposed to awaiting for a conventional start, both

Table 5 Mature oocyte rate, fertilization rate, and embryo yield

Case	MII retrieved cycle 1	MII retrieved cycle 2	MII/total oocytes cycle 1	MII/total oocytes cycle 2	MII/AFC cycle 1	MII/AFC cycle 2	Fert 2PN/ MII cycle 1	Fert 2PN/ MII cycle 2	D3 embryos/ oocytes cycle 1	D3 embryos/ oocytes cycle 2
1	2	8	0.40	0.80	0.25	1	*n/a	*n/a	*n/a	*n/a
2	15	20	0.88	0.80	1.07	1.43	*n/a	*n/a	*n/a	*n/a
3	3	0	1.00	n/a	0.27	n/a	*n/a	*n/a	*n/a	*n/a
4	5	1	0.83	0.50	1.67	0.34	*n/a	*n/a	*n/a	*n/a
5	8	16	0.42	0.70	1.14	2.29	0.63	0.75	0.26	0.39
6	8	16	0.73	0.89	0.80	1.60	0.88	0.81	0.64	0.67
7	4	2	0.50	1.00	0.50	0.25	*n/a	*n/a	*n/a	*n/a
8	2	3	0.40	0.27	0.33	0.50	0.50	1.00	0.20	0.27
9	7	7	0.88	0.78	1.17	1.17	0.86	1.00	0.75	0.78
10	5	9	0.71	0.75	1.25	2.25	0.80	0.56	0.57	0.33
11	2	6	0.33	0.50	1.67	0.50	*n/a	*n/a	*n/a	*n/a
12	0	0	n/a	n/a	n/a	n/a	*n/a	*n/a	*n/a	*n/a
13	2	2	1.00	1.00	0.22	0.22	*n/a	*n/a	*n/a	*n/a
14	6	9	1.00	1.00	0.75	1.13	0.83	1.00	0.67	1.00
15	1	2	1.00	0.67	0.33	0.67	1.00	1.00	1.00	0.67

n/a, not applicable

*n/a, not applicable due to egg cryopreservation cycle

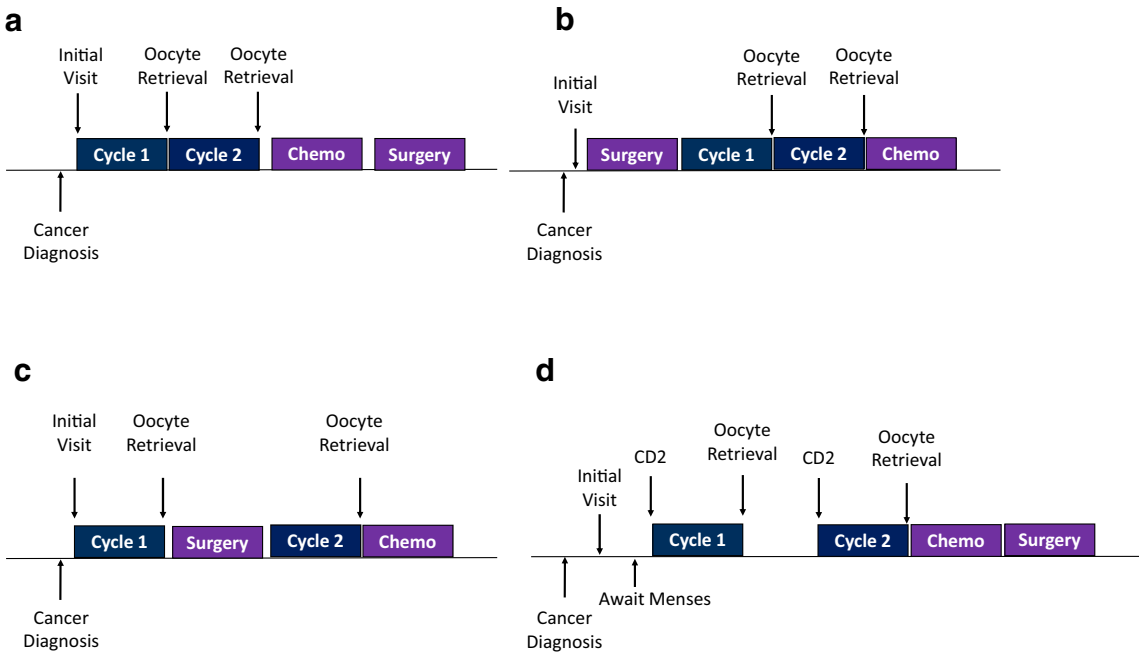

Fig. 1 Back-to-back stimulation timing. In cancer patients, the goal is to complete ovarian stimulation prior to the initiation of chemotherapy. The time from diagnosis to initiation of chemotherapy varies, with some patients receiving neoadjuvant chemotherapy and other receiving adjuvant chemotherapy only. In all scenarios, this figure illustrates how depending on where a woman is in her menstrual cycle at the time of presentation and the time to initiation of cancer treatment is minimized when a back-to-back random-start approach is used. **a** Demonstrates timeline of patient undergoing back-to-back random-start stimulation prior to chemotherapy. **b** Demonstrates timeline of patient undergoing back-to-back random-start stimulation after surgery but prior to chemotherapy. **c** Alternative strategy for more than one cycle, in which cycles are not back-to-back, but random start remains important to avoid delays in cancer treatment. **d** Timeline when multiple cycles completed prior to chemotherapy, but using conventional-start stimulation. *CD, cycle day

minimizes delays in initiation of treatment and provides significant flexibility (Fig. 1).

Several prior studies have examined the feasibility of performing follicular phase start stimulation followed immediately by a second cycle luteal start stimulation. These studies have not been performed in the oncology setting and have been limited in scope to women with diminished ovarian reserve who were being treated for infertility [9, 10]. The oocyte yield and laboratory parameters from the second of our back-to-back random-start ovarian stimulation cycles were similar to those of the first cycle. These data are consistent with the "DuoStim" or back-to-back stimulations performed by Kuang et al. and Ubaldi et al. Similar to our results, performing back-to-back stimulations in their studies allowed for a doubling of oocyte yield, with similar laboratory outcomes for the first and second cycle [9, 10]. In our study, we demonstrate that back-to-back random-start stimulations can be achieved with patients that have a higher ovarian reserve than those from prior studies (average AFC 8 (range 3–14) in our study, versus average AFC of 3.8 (range 1–8) and 5.2 (range not available) in prior studies) [9, 10].

Previous studies are strengthened by the consistency of having started the second cycle about 5 days after the first cycle's oocyte retrieval. In our study, if follicles smaller than 10 mm in size were visualized at the first retrieval, the second stimulation was started at the time of the first retrieval. However, if no small follicles were present at the time of the first retrieval, the second cycle was delayed until antral follicles were visualized on ultrasound. In our limited experience, among those with higher ovarian reserve (10 or more 13 mm or greater follicles), short intervals to second cycle start led to possible cancelation due to an inability to visualize both antral and growing follicles in the second cycle. The delay may also simply be due to the absence of follicles mature enough to respond to FSH stimulation. This delay in the development of new, FSH sensitive, antral follicles may be a result of high progesterone levels within the ovary or simply due to the difficulty of visualizing the antral follicles among multiple corpora lutea [14, 15]. Cancelations are concerning in a cancer population, due to limited time to perform fertility preservation. Our protocol therefore entailed a monitoring phase until new antral follicles developed among the corpora lutea, rather than a fixed interval start. It is possible that shorter intervals than the average of 9 days between cycles in our study can be performed, but more observation is needed.

Is back-to-back random-start stimulation feasible in the fertility preservation setting?

Multiple cycles are advantageous as more oocytes (or embryos) can be cryopreserved, potentially leading to greater

success rates. However, as stated above, performing back-to-back random-start stimulation in the setting of fertility preservation prior to cancer treatment may pose some challenges. First, delays in referral could create an apparent time pressure in which the patient, fertility preservation provider, or oncologist may feel uncomfortable with a second stimulation cycle; therefore, delays in referral should be minimized [16]. Using random start, we can perform both stimulations efficiently and can incorporate them into any part of the cycle.

Attaining visual discrimination between growing follicles and shrinking corpora lutea can be a challenge in the second cycle. To the extent it is possible, the same examiner should perform ultrasounds throughout both cycles. An ultrasound could be performed 5 to 7 days after the first retrieval to determine if the ovaries are ready for a second stimulation. Also, at the time of the first retrieval, consider that some follicles in the 2 to 10 mm range are antral follicles emerging for the next wave (i.e., to be used in the second stimulation): it may be pertinent to not go after every small follicle at the time of the first oocyte retrieval. If we suspect someone we will undergo a second stimulation, we often refrain from aspirating the very small follicles. These small follicles that emerge near the end of the first cycle will continue to respond to stimulation and create fertilizable oocytes in the second cycle, where they are of more use, as large follicle size is thought to correlate with higher rates of maturity [17].

Strengths and limitations

This case study is a preliminary look at outcomes following back-to-back random-start stimulation. It is limited by its retrospective nature and the potential for selection bias. Such bias could result in unmeasured differences among those who underwent back-to-back random-start ovarian stimulation and those who did not. For instance, there were likely patients who underwent a single fertility preservation cycle who desired a second ovarian stimulation cycle, but the issue was not raised due to concerns about costs or timing of the onset of cancer treatment. Additionally, although we saw a good response with the use of hCG for trigger, the use of a GnRH agonist for trigger should be considered. GnRH agonists are known to induce a gonadotropin surge sufficient for oocyte maturation, with a shorter half-life and duration of LH exposure than hCG. This has been associated with an improved safety profile and a smaller chance of functional corpora lutea [18]. Further, it may decrease the risk of premature luteinization in the subsequent cycle.

We did not measure AMH, a common ovarian reserve marker. In order to begin random-start stimulation as soon as possible after fertility preservation consultation, serum lab results that inform ovarian stimulation regimens should be available promptly. In the absence of these labs, we view AFC as a timely assessment of ovarian reserve, which, despite inter-operator variability, does correlate well with oocyte yield and helps to determine ovarian stimulation regiments and set expectations for patients in the random-start setting [19–21]. We waited until antral follicles were visible to perform ovarian stimulation in the second cycle. The timing of the second cycle start, and how it relates to cyclicity of follicle emergence, is not well understood and warrants further study. Shorter times to the second cycle start would further minimize cancer treatment delays.

Conclusion

Back-to-back random-start ovarian stimulation resulted in the recovery of eggs and embryos from both cycles. The recovery appeared to be similar in both cycles and therefore back-to-back random-start ovarian stimulation may be an effective way to maximize fertility preservation, even in extremely time-limited settings. Further study in a large number of patients in need.

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Compliance with ethical standards

All study procedures were approved by University of California, San Francisco (UCSF) Committee on Human Research and the Institutional Review Board.

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