Random-start ovarian stimulation in patients with cancer

Hakan Cakmak and Mitchell P. Rosen

Purpose of review
Awaiting menses to start ovarian stimulation for oocyte/embryo cryopreservation in patients with cancer may result in a significant delay of cancer treatment that may lead to patients forgoing fertility preservation. The purpose of this review is to describe the new protocols to facilitate the start of ovarian stimulation, including random-start ovarian stimulation.

Recent findings
In random-start protocols, the number of total and mature oocytes retrieved, oocyte maturity rate, mature oocyte yield and fertilization rates are similar to those in conventional (early follicular phase start) protocols. Starting ovarian stimulation in the late follicular or luteal phase did not show any superiority against the other. The presence of corpus luteum or luteal phase progesterone levels did not adversely affect synchronized follicular development, number of mature oocytes retrieved, and/or fertilization rates.

Summary
Random-start ovarian stimulation provides a significant advantage by decreasing total time for the IVF cycle, and in emergent settings, ovarian stimulation can be started at a random cycle date for the purpose of fertility preservation without compromising oocyte yield and maturity.

Keywords
fertility preservation, oocyte/embryo cryopreservation, random-start ovarian stimulation

INTRODUCTION

Improvements in cancer treatment have had a significant impact on long-term survival. Therefore, quality-of-life issues such as fertility preservation have become paramount in the lives of reproductive-age women battling malignancy and an integral component in cancer management. Controlled ovarian stimulation (COS) for embryo or mature oocyte cryopreservation, which is the only technique endorsed by the American Society of Reproductive Medicine, is the most preferred method for fertility preservation in patients with cancer because of its higher success rates compared with other more experimental technologies [1,2]. Therefore, it should be recommended as long as the patient's medical condition does not preclude safely performing COS or oocyte retrieval, and the patient has adequate time to undergo COS and oocyte retrieval [1,2]. Conventionally, ovarian stimulation for oocyte/embryo cryopreservation is initiated at the beginning of the follicular phase with the idea that this optimizes clinical outcomes. However, this methodology may require 2–6 weeks depending on the women's menstrual cycle phase at the time of presentation. As a result, there remains the possibility of a significant delay of cancer treatment and the potential for increased psychological stress for the patient and oncologist that may lead to patients forgoing fertility preservation. As there is often an urgent need to start cancer treatment, new protocols to facilitate the start of the ovarian stimulation and oocyte/embryo cryopreservation process have been proposed. In this review article, the evolution of these new COS protocols, including random-start ovarian stimulation, will be discussed.

Division of Reproductive Endocrinology and Infertility, Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California, San Francisco, California, USA

Correspondence to Mitchell P. Rosen, MD, HCLD, Department of Obstetrics, Gynecology and Reproductive Sciences, 499 Illinois Street, 6th Floor, San Francisco, CA 94158, USA. Tel: +1 415 353 3040; fax: +1 415 353 7744; e-mail: rosenm@obgyn.ucsf.edu

KEY POINTS

- Random-start ovarian stimulation provides a significant advantage by decreasing total time for the IVF cycle without compromising oocyte yield and maturity.

- Starting ovarian stimulation in the late follicular or luteal phase did not show any superiority against the other.

- The presence of corpus luteum or luteal phase progesterone levels do not adversely affect synchronized follicular development, number of mature oocytes retrieved, and/or fertilization rates.

- Random-start ovarian stimulation with letrozole along with gonadotropins in patients with estrogen-sensitive cancers is well tolerated, and yields similar number of oocytes and embryos compared with standard protocols while minimizing the risk of high estrogen exposure.

CONVENTIONAL (EARLY FOLLICULAR PHASE START) CONTROLLED OVARIAN STIMULATION PROTOCOLS

Conventional COS involves the administration of gonadotropins starting at menses with either a gonadotropin-releasing hormone (GnRH) agonist or antagonists to suppress ovulation. The treatment time for ovarian stimulation ranges typically from 9 to 14 days. The choice of the specific COS protocol (and whether to use a GnRH agonist or antagonist) is generally determined based upon the preference of the individual provider and influenced by the time available until the initiation of gonadotoxic cancer treatment.

Although multiple different COS protocols are being used, the majority of patients diagnosed with cancer are treated with a GnRH antagonist-based protocol, which likely allow the shortest deferral of the initiation of cancer treatment. Evidence suggests that the development of GnRH antagonists has significantly decreased the interval from patient presentation to embryo/oocyte cryopreservation [3]. The reason for the shorter time interval may be due to less ovarian suppression with use of GnRH antagonists compared with agonists [4]. Another reason is that, in contrast to GnRH agonists, GnRH antagonists rapidly act to suppress pituitary release of gonadotropins, primarily luteinizing hormone (LH). Typically, GnRH antagonists are initiated to prevent premature LH surge when the lead follicle reaches 12–14 mm at approximately day 6 of gonadotropin stimulation that begins on day 2–3 of a menstrual cycle (Fig. 1a). In contrast, GnRH agonist may require a pretreatment phase to downregulate

GnRH receptors (i.e., downregulated or long luteal protocols) prior to the administration of gonadotropins, which adds to the total treatment time.

Patients with cancer may present mid-cycle or in the luteal phase. Adhering to the convention of initiating COS at the beginning of the follicular phase may result in either significant delay of cancer treatments or forgoing fertility preservation because of time constraints. Alternatives to starting ovarian stimulation at the time of menses have been explored. However, the dogma suggesting a single wave of follicular development and that only early follicular phase start ovarian stimulation would result in a synchronized follicular development [5,6], the strong belief of the local inhibitory effects of the corpus luteum and progesterone in the luteal phase [7], questioned the success of these alternate timing protocols.

LUTEAL HALT PROTOCOLS

In order to decrease the potential delays for cancer treatment, breaking down of the corpus luteum (to stop progesterone production) and initiating menses were proposed once a patient was in the luteal phase. The use of GnRH antagonists has been explored as a method to induce corpus luteum regression [8,9]. The studies showed that after the administration of GnRH antagonist in the luteal phase (e.g., a single 3 mg dose or 2–3 consecutive daily 250 μg doses of GnRH antagonist), serum progesterone levels decreased and menses ensued 2–4 days later [8,9]. As a result, ovarian stimulation would be initiated earlier than awaiting spontaneous menses (Fig. 1b). GnRH antagonist would be restarted in a standard fashion to prevent premature LH surge during ovarian stimulation [9]. Although only few studies have been reported, the evidence suggests that a synchronized cohort of follicles can develop with normal fertilization rates and embryo quality.

Others have suggested a way to initiate menses, irrespective of the phase of menstrual cycle. This protocol involves the use of oral contraceptive pills (OCPs) for 4–6 days and use of daily 250 μg dose of GnRH antagonist on the last 2–3 days of OCP treatment [10]. At present, there are no studies comparing the outcomes of this protocol with conventional COS.

In another protocol, GnRH antagonists and gonadotropins were administered simultaneously during the luteal phase of the menstrual cycle and have observed shorter treatment times due to not awaiting for menses [11]. In this protocol, only recombinant follicle-stimulating hormone (FSH) was used for follicular stimulation to avoid
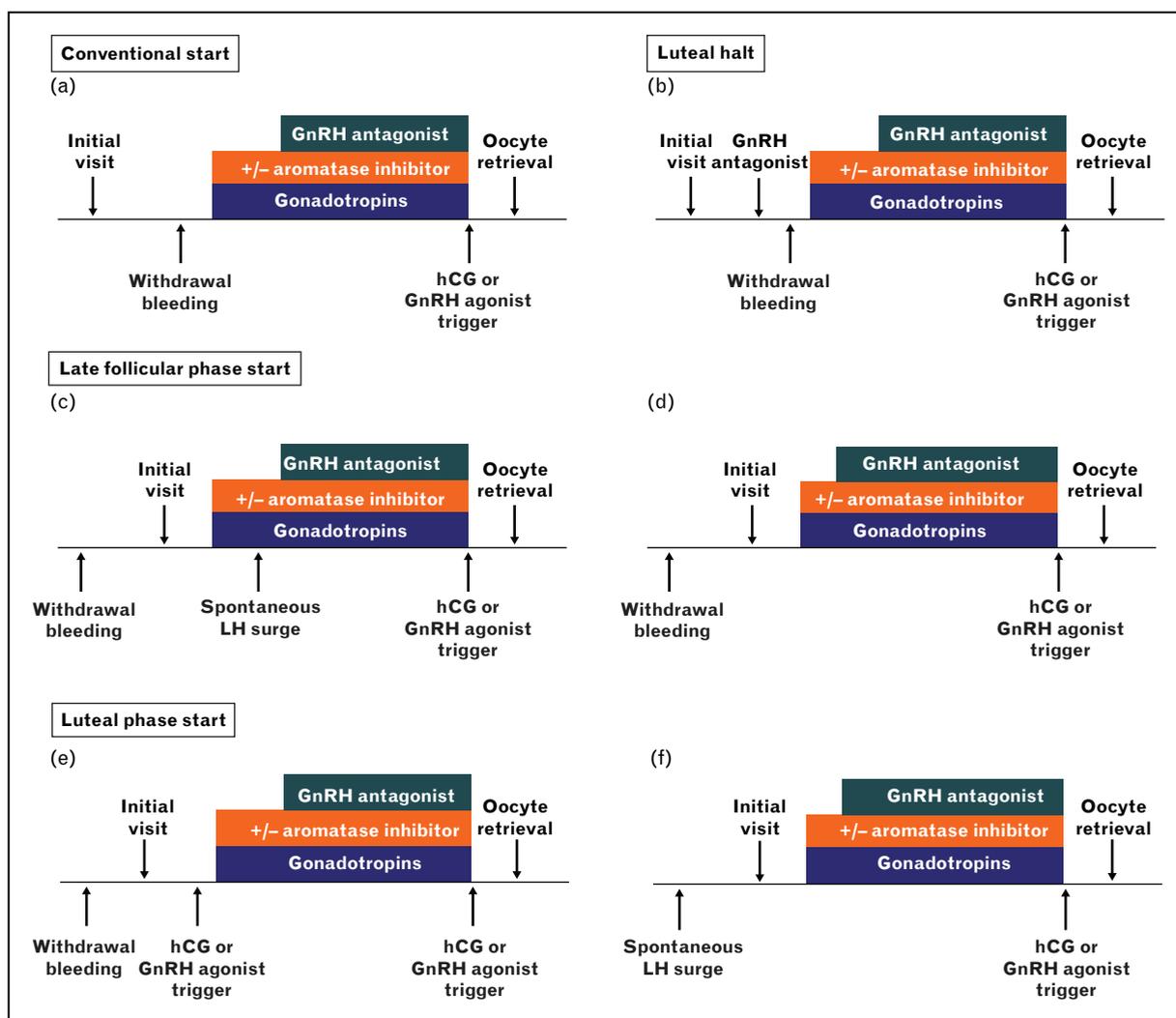
FIGURE 1. Controlled ovarian stimulation protocols in patients with cancer. (A) In conventional (early follicular phase start) antagonist protocol, ovarian stimulation starts with menses and GnRH antagonist is initiated to prevent premature LH surge when the lead follicle reaches 12 mm. (B) In luteal halt protocol, administration of GnRH antagonist in the luteal phase induces corpus luteum regression, menses ensues 2–4 days later and ovarian stimulation is initiated earlier than awaiting spontaneous menses. If the patient with cancer presents in the late follicular phase, (C) ovarian stimulation without GnRH antagonist can be started if the follicle cohort following the lead follicle is smaller than 12 mm and stays smaller than 12 mm before a spontaneous LH surge. After the LH surge, GnRH antagonist is started when the secondary follicle cohort reaches 12 mm to prevent premature secondary LH surge. (D) If the follicle cohort following the lead follicle reaches 12 mm before the spontaneous LH surge, pituitary suppression with GnRH antagonist is initiated and continued until triggering final oocyte maturation. If the patient with cancer presents in the late follicular phase, (E) ovulation can be induced with hCG or GnRH agonist when the dominant follicle reaches 18 mm in diameter and ovarian stimulation is started in 2–3 days in luteal phase. If the patient with cancer presents in the luteal phase, (F) ovarian stimulation can be started in the absence of GnRH antagonist and GnRH antagonist administration is initiated later in the cycle, when the follicle cohort reached 12 mm to prevent premature secondary LH surge. GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin.

exogenous LH activity that might prevent luteolysis. Compared with cancer patients stimulated throughout the follicular phase ($n = 28$), the luteal phase group ($n = 12$) had a similar number of aspirated oocytes and metaphase II oocytes as well as comparable fertilization rates [11]. In the same study, it was also shown that in several patients whose ovarian stimulation started in late follicular phase, the oocyte recovery and normal fertilization was possible.

RANDOM-START (LATE FOLLICULAR OR LUTEAL PHASE START) CONTROLLED OVARIAN STIMULATION PROTOCOLS

Another alternative approach is to initiate ovarian stimulation regardless of the menstrual phase (i.e., random-start COS) [11,12■■,13–16].

A report of three patients with breast cancer evaluated the effectiveness of initiating ovarian stimulation at the time of patient presentation (menstrual cycle day 11, 14 and 17) rather than waiting for spontaneous menses [13]. GnRH antagonist was started to prevent premature LH surge when the lead follicle measured over 13 mm. The random-start ovarian stimulation resulted in a reasonable ovarian response with seven to 10 embryos cryopreserved per patient [13]. In another case report, two patients with cancer had successful COS initiated during the luteal phase that resulted in retrieval of 12 MII oocytes in both the cases [14]. One of the patients had oocyte cryopreservation and the other had intracytoplasmic sperm injection with 83.3% fertilization rate [14].

The recent report presenting our clinical experience on random-start ovarian stimulation demonstrated that late follicular or luteal phase start COS were as effective as early follicular start COS in patients with cancer [12■■]. If the patient with cancer presented in the late follicular phase, we proceeded with one of the following treatment plans:

(1) Ovarian stimulation without GnRH antagonist was started if the follicle cohort following the lead follicle was smaller than 12 mm and stayed smaller than 12 mm before a spontaneous LH surge (Fig. 1c). After the LH surge, GnRH antagonist was started when the secondary follicle cohort reached 12 mm to prevent premature secondary LH surge (Fig. 1c). If the follicle cohort following the lead follicle reached 12 mm before the spontaneous LH surge, pituitary suppression with GnRH antagonist was initiated and continued until triggering final oocyte maturation (Fig. 1d); or

(2) Ovulation was induced with human chorionic gonadotropin or GnRH agonist when the dominant follicle reached 18 mm in diameter and ovarian stimulation was started in 2–3 days in luteal phase (Fig. 1e) [12■■].

If the patient with cancer presented in the luteal phase or the ovulation was induced, ovarian stimulation was started in the absence of GnRH antagonist (Fig. 1e and f). Similar to conventional COS, GnRH antagonist administration was initiated later in the cycle, when the follicle cohort reached 12 mm to prevent premature secondary LH surge.

The number of total and mature oocytes retrieved, oocyte maturity rate (number of MII oocytes/number of total oocytes), mature oocyte yield (number of MII oocytes/antral follicle count) and fertilization rates were similar in early follicular and random-start protocols (Table 1) [17]. Moreover, starting COS in the late follicular or luteal phase did not show any superiority against the other (Table 1) [17].

In contrast to previous belief, the presence of corpus luteum or luteal phase progesterone levels did not adversely affect synchronized follicular development, number of mature oocytes retrieved, and/or fertilization rates [12■■,17]. Because spontaneous corpus luteum regression occurs possibly due to suppressive effect of rising estradiol levels on endogenous LH secretion during COS, corpus luteum regression with GnRH antagonist was not necessary to start COS [12■■]. The length of the cycle and daily gonadotropin dose were not affected by the serum progesterone level or whether COS was started in the early or mid-luteal phase [12■■,17]. In addition, the ovary with corpus luteum had similar number of dominant follicles (≥13 mm) compared with the patient's other ovary on the day of trigger shot [17].

Table 1. Comparison between conventional, late follicular and luteal start IVF cycles; median (interquartile range)

	Conventional start (n = 136)	Late follicular start (n = 32)	Luteal start (n = 44)	P Value
Follicles ≥ 13 mm	12.5 (6.5–17)	14.0 (9.0–19.75)	13.0 (8.25–16.75)	NS
Mature oocytes (MII) retrieved	11 (6.5–16)	12.0 (7.0–16.75)	10.0 (5.25–15)	NS
MII oocyte/total oocyte ratio	0.71 (0.60–0.82)	0.75 (0.63–0.83)	0.72 (0.60–0.84)	NS
Mature oocyte/AFC ratio	0.83 (0.46–1.12)	0.91 (0.64–1.27)	0.86 (0.58–1.17)	NS
Fertilization rate (2PN/MII)	0.79 (0.67–0.85)	0.86 (0.78–1.00)	0.87 (0.76–1.00)	NS
High-quality day 3 embryos/2PN ratio	0.92 (0.76–1.00)	0.91 (0.81–1.00)	0.88 (0.83–1.00)	NS

AFC, antral follicle count; NS, not significant.

RANDOM-START CONTROLLED OVARIAN STIMULATION IN PATIENTS WITH ESTROGEN-SENSITIVE CANCERS

During ovarian stimulation, there is a potential risk that the supraphysiological estrogen levels resultant of multiple follicle growth may promote the growth of estrogen-sensitive tumors such as endometrial and estrogen-receptor-positive breast cancers [18]. Therefore, alternative and potentially safer protocols have been introduced for fertility preservation for patients with estrogen-sensitive cancer including stimulation protocols with tamoxifen or aromatase inhibitors to reduce the activity or production of estrogen [19].

Tamoxifen has a well known antiestrogenic action on breast tissue with the inhibition of growth of breast tumors by competitive antagonism of estrogen at its receptor site [20]. Tamoxifen, apart from its effect in the breast, has also an antagonist action in the central nervous system and interferes with the negative feedback of the estrogen on the hypothalamic/pituitary axis leading to an increase in GnRH secretion from the hypothalamus and a subsequent release of FSH from the pituitary stimulating follicular development. Tamoxifen can be used in combination with gonadotropins in doses of 20–60 mg/day [19]. Although peak estradiol levels in ovarian stimulation with tamoxifen are not altered, due to its antiestrogenic effect on breast tissue, it is desirable to be used in patients with estrogen-receptor-positive breast cancer. Although information is present regarding its safety and effectiveness when used with gonadotropins in early follicular start COS [21,22], there is currently no information regarding its use in random-start protocols.

Aromatase inhibitors, such as letrozole, significantly suppress plasma estrogen levels by competitively inhibiting the activity of the aromatase enzyme [23]. Centrally, aromatase inhibitors release the hypothalamic/pituitary axis from estrogenic negative feedback, increase the secretion of FSH by the pituitary gland, stimulate follicle growth, and, thereby, can be used for ovulation induction [24]. In patients with estrogen-sensitive cancers, the main advantage of adding daily letrozole to gonadotropins in ovarian stimulation protocols is to decrease serum estradiol levels closer to that observed in natural cycles (i.e., estradiol < 500 pg/ml) without affecting oocyte or embryo yield [25,26]. The short-term follow-up of patients with breast cancer, who have undergone ovarian stimulation with letrozole along with gonadotropins for fertility preservation, has not shown to raise the risk of breast cancer recurrence [27]. In addition, COS with aromatase inhibitors in combination with gonadotropins was also safely used for embryo cryopreservation in patients with endometrial cancer [28].

In our clinical practice, we start letrozole 2.5 or 5 mg/day, depending on the ovarian reserve of the patient, with the ovarian stimulation (Fig. 1) and titrate letrozole dose up to 10 mg/day to keep estradiol levels lower than 500 pg/ml [29]. The mature oocyte/embryo yield after COS is not affected by letrozole at any dose used in our clinical practice if final oocyte maturation is triggered when the lead follicle reaches 20 mm in diameter (compared with 18 mm in nonletrozole cycles). We also continue letrozole after the oocyte retrieval if serum estradiol levels are still elevated (i.e., estradiol > 500 pg/ml). Discontinuation of letrazole can either be at menses or with initiation of chemotherapy.

In random-start protocols, addition of daily letrozole during ovarian stimulation resulted in a similar number of total oocytes retrieved, oocyte yield and length of ovarian stimulation as compared with protocols without letrozole [12■■]. Similar to early follicular-start protocols, we and others demonstrated comparable number of mature oocytes retrieved as well as comparable oocyte maturity and fertilization rates in random-start COS cycles, with and without letrozole [12■■,16].

In summary, COS with letrozole or tamoxifen along with gonadotropins in patients with estrogen-sensitive cancers undergoing fertility preservation is well tolerated, and yields similar number of oocytes and embryos compared with standard protocols while minimizing the risk of high estrogen exposure. Therefore, we highly recommend the routine use of letrozole or tamoxifen during COS in both early follicular and random-start protocols in patients with estrogen-sensitive cancers.

MULTIPLE CONTROLLED OVARIAN STIMULATION CYCLES FOR FERTILITY PRESERVATION

In certain situations, it may be beneficial to do multiple cycles prior to cancer treatment to obtain more oocytes/embryos to improve the chance of pregnancy. These include patients with low ovarian reserve, predispositions to genetic conditions and patients of older age. The timing of these multiple ovarian stimulations can either be based on cancer treatment windows (i.e., prior to or after surgery and prior to chemotherapy) or possibly can be done one after the other. The evidence indicates that there are more than one follicle recruitment waves during a menstrual cycle [30]. Therefore, to minimize delays, an ovarian stimulation can be started couple days after egg retrieval (i.e., in luteal phase). With this

approach, mature eggs and cleavage stage embryos were obtained in poor responders [31,32▪]. Although effective with patients with poor ovarian reserve, there are limited data on the effectiveness with patients that have good ovarian reserve and/or with persistent cysts left over from the prior stimulation.

TIMING OF OVARIAN STIMULATION

All reproductive-age women undergoing cancer treatment who desire fertility preservation should be informed of their options and referred promptly for fertility preservation counseling by an experienced provider. Early referral to fertility specialist and random-start ovarian stimulation affords an interested patient the greatest opportunity for successful fertility preservation treatment and minimizes the delays for cancer treatment.

In order to perform a successful oocyte/embryo cryopreservation cycle, the treating fertility specialist must not only address the concurrent medical processes that can afflict patients with cancer but also remain cognizant of time constraints surrounding the patient's cancer treatment. In patients with hematological malignancies (i.e., lymphoma and leukemia), the tumor burden is generally high at the outset of diagnosis, requiring that cancer therapy begins almost immediately. Therefore, in these patients, random-start ovarian stimulation can be initiated immediately after the initial visit start and delays to the cancer treatment can be minimized.

In other cancer types in which the surgery is the first step in tumor management (e.g., breast cancer), the patient may have a 4–6 week window before or between surgery and adjuvant therapy. In these cases, ovarian stimulation can be performed before and/or immediately after the surgery. Oocyte/embryo cryopreservation can be accomplished with random-start COS within 2–3 weeks and thereafter patients can proceed with surgery or additional cancer treatment (i.e., chemo, radiation, and/or hormonal therapy).

Young patients are often already on OCPs, allowing fertility providers to initiate cryopreservation treatment right away after discontinuation of OCPs, which significantly abbreviates delay in cancer treatment. In another scenario, in which the patient's cancer work up has not been completed and the patient is about to start or has just started her menstrual cycle, GnRH antagonist can be given to the patient to hold her cycle to finish her cancer evaluation. This approach was shown to have no negative impact on embryo quality and to improve synchronous follicular growth in poor responders [33▪].

CONCLUSION

Random-start ovarian stimulation provides a significant advantage by decreasing total time for the IVF cycle, and in emergent settings, ovarian stimulation can be started at a random cycle date for the purpose of fertility preservation without compromising oocyte yield and maturity. Although random-start COS protocols are efficient in obtaining appropriate number of mature oocytes/embryos, only a minority of the patients underwent thawing and embryo transfer, and therefore, there are not enough reported consistent data to evaluate the implantation rate and pregnancy rates in patients with cancer. However, comparable pregnancy rates after transferring embryos created from donor eggs obtained after luteal phase start protocols are encouraging [34▪]. Therefore, additional clinical studies are needed to assess the efficacy of this strategy, especially regarding the rates of clinical pregnancy and of liveborn infants originating from the use of cryopreserved embryos and oocytes obtained by random-start ovarian stimulation.

Conflicts of interest
There are no conflicts of interest.

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