### Title

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FERTILITY PRESERVATION

# Outcomes of random-start letrozole protocol with PGT-A in women with breast cancer undergoing fertility preservation

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## Abstract

**Purpose** To compare the cycle characteristics and outcomes of random-start-controlled ovarian stimulation (RSCOS) protocols to the outcomes of standard-start-controlled ovarian stimulation (SSCOS) cycles and to report the utility of PGT-A in these cycles.

**Methods** One hundred and seventeen who underwent SSCOS and 39 who underwent RSCOS for oocyte and/or embryo cryopreservation before breast cancer chemotherapy were retrospectively evaluated. Mean number of embryos and blastocyst euploidy rates were the main outcome measures.

**Results** A majority of RSCOS cycles were initiated in the luteal phase (66.6% luteal vs. 33.3% follicular). While the total dose of gonadotropins was significantly higher in the RSCOS (3720.8 ± 1230.0 vs. 2345.1 ± 803.6 IU; $P < 0.001$), the mean number of mature oocytes and embryos was similar to SSCOS. However, there was a trend for a higher number of mean embryos with luteal start RSCOS (6.9 ± 2.7 in late follicular start vs. 9.4 ± 4.2 in luteal start, $P = 0.08$). PGT-A was performed in 48% of the cases that underwent embryo cryopreservation in RSCOS (12 women, mean age = 35.3 ± 4.1; 87 blastocysts), revealing a euploidy rate of 36.2 ± 22.3% per patient. This rate was comparable to a 45% aneuploidy rate from similarly aged published data. Of the 7 RSCOS patients who returned for frozen embryo transfer, 5 delivered and one has an ongoing pregnancy, while in SSCOS, 18 out of 40 cycles resulted in live birth.

**Conclusion** Our data suggests that RSCOS fertility preservation cycle outcomes are similar to those with SSCOS and result in age-appropriate euploidy rates.

**Keywords** Random-start-controlled ovarian stimulation · Breast cancer · Letrozole · Embryo · Preimplantation genetic testing

## Introduction

Breast cancer is the most common type of malignancy during reproductive age, accounting for approximately a quarter of all female cancers in that age group [1]. Although advances in screening technologies and treatment modalities increased survival rates, breast cancer chemotherapy is still highly nonselective and, as a result, carries systemic toxicity including that on the ovary [2]. Though the severity will vary depending on the woman's age and the type of chemotherapy regimen, ovarian insufficiency, and infertility are the common consequences of breast cancer treatments [3]. Reproductive adverse effects of breast cancer chemotherapy are now well recognized, and as a result, fertility preservation is considered an integral part of cancer care. While ovarian tissue cryopreservation has been moved to a nonexperimental category [4], embryo and oocyte cryopreservation are more frequently utilized due to their long track record and the fact that they allow the preservation of mature gametes, or embryos with high implantation potential, especially if tested euploid [5].

However, in women with breast cancer, in addition to the delay that an early follicular start ovarian stimulation

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may cause, estrogen exposure is of concern. We have previously developed a protocol where an aromatase inhibitor, letrozole supplements gonadotropins to minimize estradiol (E2) rise during controlled ovarian stimulation (COS) [6, 7]. It is in that setting that we reported a non-cycle-day dependent stimulation approach and coined the term random-start-controlled ovarian stimulation (RSCOS) [8]. RSCOS takes advantage of the continual antral follicle waves present in the ovary. Several studies have now shown the feasibility of RSCOS in the cancer setting in general [9–12] and even in the setting of infertility [13].

In addition, while the routine utility of preimplantation genetic testing for aneuploidy (PGT-A) is debated in the general infertility population [14], there is limited data on its use in the fertility preservation setting. The storage of euploid embryos may provide further reassurance for future success and fertility preservation, and the absence of euploid embryos may prompt patients to undergo repeat RSCOS cycles before initiating gonadotoxic chemotherapy.

Therefore, we hypothesized that RSCOS is equally effective as SSCOS, and we conducted this study to compare the cycle outcomes between these two approaches in women with breast cancer undergoing letrozole-supplemented (COSTLES) cycles, as well as to report the utility of PGT-A in that setting. To our knowledge, no previous study has compared RSCOS to SSCOS and reported the utility of PGT-A in a pure population of women with breast cancer undergoing COSTLES.

## Materials and methods

The data were generated by retrospective analysis of a database of all women with newly diagnosed stage 1–3 breast cancer who underwent ovarian stimulation for fertility preservation. We excluded patients > 45 years of age and those who were infertile, had a history of ovarian surgery, or had prior exposure to chemotherapy or radiotherapy (Fig. 1). The study protocol was approved by the institutional review board at Yale University School of Medicine (IRB Protocol ID 2000030279).

### Standard start controlled ovarian stimulation with letrozole

The details of our letrozole protocol with RSCOS and SSCOS have been previously reported [6]. Ovarian stimulation was started with 5 mg/day letrozole (Femara; Novartis, East Hanover, NJ, USA) on days 2 and 3 of the menstrual cycle followed ≤ 2 days later by recombinant follicle-stimulating hormone (rFSH, Follistim, Organon, West Orange, NJ, USA). The initial gonadotropin dose was determined based on the patient's age, body mass index (BMI), antral follicle count, and baseline hormone levels, as previously described [6]. Ovarian follicle growth was monitored via transvaginal ultrasound examination, and hormonal monitoring was achieved with follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E2) measurements, and the rFSH dose was adjusted accordingly. When the lead

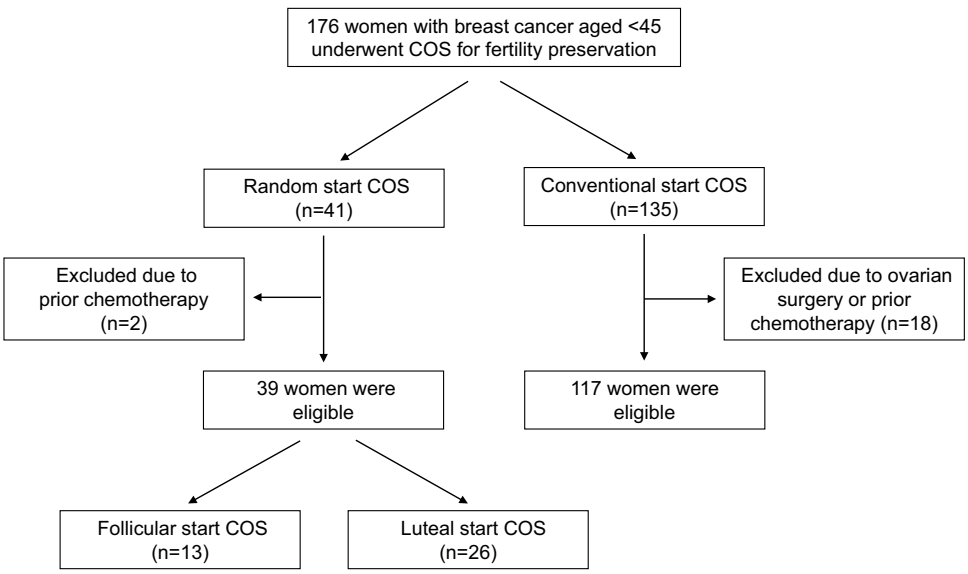


**Fig. 1** Inclusion–exclusion flowchart

follicle diameter reached 13 mm, a GnRH antagonist was added (0.25 mg/day, Ganirelix; Organon), and the daily dose was continued until the trigger day. When a minimum of two follicles reached ≥ 20 mm mean diameter, oocyte maturation was triggered with either 125–250 µg human chorionic gonadotropin (hCG; Ovidrel; EMD Serono, Rockland, MA, USA), 2–4 mg leuprolide acetate (Lupron; Ferring Pharmaceuticals, Parsippany, NJ, USA) or both. Transvaginal oocyte retrieval was performed under intravenous sedation 35 h following the trigger. If an hCG trigger was utilized, letrozole was continued until E2 levels estradiol levels dropped < 50 pg/ml in the luteal phase. This was done because hCG tends to stimulate luteinized granulosa cells and causes a further increase in E2 levels. All oocytes and embryos were cryopreserved using a vitrification technique. The blastocyst biopsy was performed by opening a 10–20 mm hole on the zona pellucida with a diode laser and removing 5–10 trophectodermal cells.

### Random-start-controlled ovarian stimulation

The RSCOS protocols are summarized in Fig. 2. We considered any stimulation that started after cycle day 5 as follicular random start. When the stimulation was started postovulation, as determined by ultrasound and hormonal evaluation, this was considered a luteal start (Fig. 2C). If the patient presented with a preovulatory follicle in the late follicular stage, in some cases, the ovulation was triggered with a GnRHa and the stimulation was begun 2–3 days later in the luteal phase [15] (Fig. 2B). These cases were also considered luteal start.

### Outcome measures

The primary outcome was the number of embryos obtained. The secondary outcome was blastocyst euploidy rates. In addition, we explored and compared the differences in the number of total oocytes retrieved and mature oocytes and fertilization rates between the groups, as well as late follicular vs. luteal start RSCOS.

### Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (release 15.0; SPSS Inc., Chicago, IL, USA). Data were presented as mean (standard deviation). The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk test) to determine whether they were normally distributed. If the data were normally distributed, Student's *t* test was used. Mann–Whitney *U* test was used for nonnormally distributed data. Chi-square, and where appropriate, Fisher's exact tests, was used to compare the proportions of different groups. A $P$ value < 0.05 was considered statistically significant.

## Results

### Comparison of RSCOS with SSCOS cycle outcomes

One hundred seventy-six women with breast cancer underwent COS for fertility preservation. After the exclusions, 117 women who underwent SSCOS and 39 women who underwent RSCOS for oocyte and/or embryo cryopreservation before breast cancer chemotherapy were included. RSCOS was initiated in the follicular phase in 33.3% of cycles/patients (13/39) and the luteal phase in 66.6% (26/39). A comparison of the demographic and cycle characteristics of the two groups is summarized in Table 1.

The mean age and body mass index were similar (RSCOS vs. SSCOS: 33.8 ± 4.6 vs. 33.1 ± 3.1 years; $P = 0.51$ and 22.3 ± 3.3 vs. 22.1 ± 3.0 kg/m$^2$; $P = 0.83$). While starting doses were similar, the total dose of gonadotropins was significantly higher in RSCOS compared to SSCOS (3,720.8 ± 1,230.0 vs. 2,345.1 ± 803.6 IU, respectively; $P < 0.001$). A trend towards longer stimulation length was found in RSCOS (11.2 ± 2.0 vs. 10.6 ± 1.6 days; $P = 0.089$) (Table 1). The majority of patients (74.3%; 29/39) was triggered by a GnRH agonist only. The embryo yield was not influenced by the trigger type (7.7 ± 4.1 vs. 7.5 ± 3.7 embryos with GnRHa vs. hCG; $P = 0.8$).

The 64.1% (25/39) in RSCOS and 81.1% (95/117) in SSCOS cryopreserved embryos, while the remaining 35.8% (14/39) and 19.9 (24/117) chose oocyte cryopreservation, respectively. The mean total number of oocytes ($P = 0.51$), mature oocytes ($P = 0.40$), and frozen embryos ($P = 0.99$) were similar between the groups (Table 2).

### Preimplantation genetic testing for aneuploidy outcomes

Of the 125 blastocysts cryopreserved from 21 women (6.9 ± 2.7 embryos per patient) in RSCOS, 87 were biopsied for PGT-A in 12 at the mean age of 35.6 ± 1.4 years.

PGT-A revealed 2.83 ± 2.1 euploid embryos per patient, with a mean euploidy rate of 36.2 ± 22.3% per patient. This euploidy rate was comparable to a 45% euploidy rate of the 4,833 individual IVF cycles from 23,561 embryos in the 35–37 years age bracket ($P = 0.15$), as extracted from a single-center retrospective cohort study spanning 2014–2019 [16].

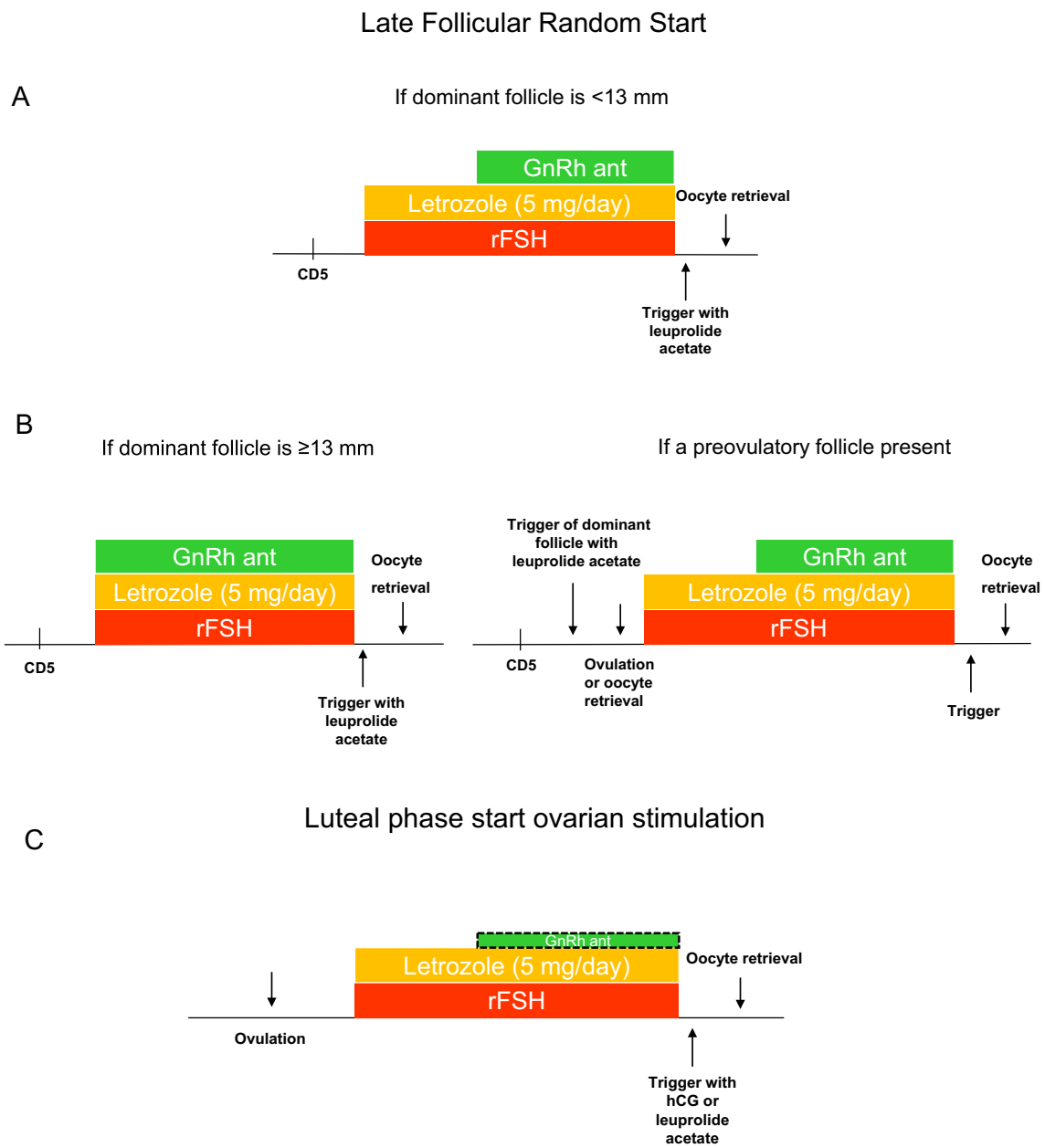


**Fig. 2** Random-start-controlled ovarian stimulation protocols. Key case scenarios and protocols in random-start stimulation cycles. A) If a patient presents after cycle day 5 (CD 5), ovarian stimulation is begun and an antagonist added when the lead follicle reaches 13 mm. If there is a dominant follicle present on the day of start, either an antagonist can be initiated simultaneously with rFSH (B1) or if the follicle is preovulatory (B2), it can be ovulated with a GnRHa trigger. If financially feasible for the patient, a single follicle retrieval can be done under local anesthesia, and the stimulation is started 2–3 days postovulation/retrieval, converting a follicular start to a luteal start. C) If a patient presents postovulation, rFSH is started without an antagonist. Because high progesterone (P4) levels suppress a spontaneous LH surge, antagonist administration can be delayed or lower doses of antagonist doses (1/2 or 1/3rd, etc. — denoted by dotted frame) depending on serum LH and P4 levels. A full-dose antagonist is started when P4 levels are below < 3 or LH shows a trend for a rise. In all case scenarios, we prefer a GnRHa trigger unless serum LH is overly suppressed [19]. In this case, either a dual trigger or an hCG-only trigger can be utilized. We recommend PGT-A in all FP cycles based on the reasoning explained in the text

Concurrently with PGT-A, PGT-M was performed concurrently in two women with *BARD1* and *BRCA1* mutations. The combined PGT-A and PGT-M revealed one euploid embryo without the *BARD1* mutation out of 9 blastocysts in 1 woman, and 4 euploid embryos without the *BRCA1* mutation out of 15 blastocysts in another woman. Thus both women had at least one healthy embryo that would not transmit a cancer-predisposing gene to her offspring.

**Table 1** Patient and cycle characteristics

| Variables (mean ± SD) | Random start ($n=39$) | Standard start ($n=117$) | $P$ value |
|---|---|---|---|
| Age, years | 33.8 ± 4.6 | 33.1 ± 3.1 | 0.38 |
| Body mass index, kg/m$^2$ | 22.3 ± 3.3 | 22.1 ± 3.0 | 0.83 |
| Baseline FSH levels, IU/ml | 7.0 ± 3.9 | 8.4 ± 3.8 | 0.08 |
| Baseline E2 levels, pg/ml | 82.9 ± 96.7 | 43.6 ± 27.0 | 0.02 |
| AMH levels, ng/ml[a] | 2.7 ± 2.2 | 2.2 ± 2.0 | 0.51 |
| Starting gonadotropin dose, IU | 263.3 ± 85.7 | 242.4 ± 75.4 | 0.21 |
| Total gonadotropin dose, IU | 3720.8 ± 1230.0 | 2345.1 ± 803.6 | < 0.001 |
| Ovarian stimulation length, days | 11.2 ± 2.0 | 10.5 ± 1.6 | 0.08 |
| E2 levels on the trigger day, pg/ml | 685.4 ± 753.2 | 670.5 ± 575.2 | 0.91 |
| GnRHa trigger % | 74.3 (29/39) | 32.4 (38/117) | < 0.001 |

[a]Nine datapoints in RSCOS and 60 in SSCOS group were missing

**Table 2** Comparison of cycle outcomes

| Variables (mean ± SD) | Random start ($n=39$) | Standard start ($n=117$) | $P$ value |
|---|---|---|---|
| No. of total oocytes | 16.5 ± 7.1 | 15.6 ± 7.9 | 0.51 |
| No. of mature oocytes | 10.9 ± 4.2 | 10.1 ± 5.8 | 0.40 |
| Maturity rate (%) | 73.0 ± 19.7 | 67.8 ± 22.9 | 0.19 |
| Fertilization rate (%) | 85.5 ± 13.6 | 80.6 ± 17.2 | 0.25 |
| No. of embryos frozen[a] | 7.7 ± 4.0 | 7.7 ± 4.8 | 0.99 |

[a]Embryo cryopreservation was performed in 25 women in RSCOS and 95 in SSCOS. The remaining cases had oocyte cryopreservation

**Table 3** Comparison of cycle outcomes between follicular-phase start and luteal-phase start ovarian stimulation

| Variables | Follicular-phase start ($n=13$) | Luteal-phase start ($n=26$) | $P$ value |
|---|---|---|---|
| Age | 34.6 ± 4.2 | 33.2 ± 4.9 | 0.72 |
| No. of total oocytes | 18.0 ± 7.7 | 15.7 ± 6.8 | 0.70 |
| No. of mature oocytes | 10.9 ± 3.8 | 10.9 ± 4.5 | 0.75 |
| Maturity rate (%) | 68.6 ± 20.3 | 75.1 ± 19.6 | 0.38 |
| Fertilization rate (%) | 89.2 ± 12.2 | 81.3 ± 15.0 | 0.33 |
| No. of embryos frozen[a] | 6.9 ± 2.7 | 9.4 ± 4.2 | 0.08 |
| Euploidy rate/ patient (%) | 46.4 ± 0.4 | 34.1 ± 24.1 | 0.35 |

[a]Nine women in the follicular-phase start group and 16 women in the luteal-phase start group underwent embryo cryopreservation. Results were given as mean ± SD. A $P$ value < 0.05 was considered statistically significant

## Comparison of follicular vs. luteal RSCOS cycle outcomes

Of the 39 women with RSCOS, 13 were follicular, and 26 were luteal start with similar mean ages (34.6 ± 4.2 vs. 33.2 ± 4.9 years). The mean total gonadotropin dose (3,495.8 ± 1,188.2 vs. 3,833.3 ± 1,259.9 IU; $P=0.44$) and stimulation length (11.0 ± 1.9 vs. 11.2 ± 2.0 days; $P=0.78$) were similar between the follicular and luteal RSCOS (Table 3).

The mean number of total oocytes ($P=0.70$), mature oocytes ($P=0.75$), and frozen embryos ($P=0.08$) were not statistically different between the follicular and luteal start RSCOS, though there was a trend for a higher number of embryos with the luteal start (6.9 ± 2.7 in the late follicular vs. 9.4 ± 4.2 in luteal start).

## RSCOS preliminary pregnancy outcome data

To date, seven women returned to utilize their cryopreserved embryos after RSCOS. Of those, six were conceived after the first single embryo transfer. Three of these transfers were with euploid embryos, and the other three patients had not had PGT-A. These conceptions resulted in five live births at term (71% live birth rate per transfer), and one is currently ongoing. This compares to a per embryo transfer live birth rate of 45.0% in women who had cryopreserved embryos without PGT-A (18 out of 40 cycles in 33 women) after SSCOS [17]. No fetal anomalies were reported with either approach.

# Discussion

In this study, we compared the outcomes of RSCOS in the follicular or luteal phase of the menstrual cycle to those of SSCOS in patients with breast cancer undergoing fertility preservation with COSTLES. We found that the number of oocytes and embryos was similar between RSCOS and SSCOS, with a trend towards a higher number of embryos in the luteal RSCOS vs. follicular (9.4 ± 4.2 vs. 6.9 ± 2.7 $P=0.08$). In addition, we also reported the utility of PGT-A along with the RSCOS approach in women with breast cancer and found that the aneuploidy rates were age-appropriate

in comparison to published data in the literature [16]. The preliminary pregnancy data suggested high implantation rates with RSCOS, though this was based on a small number of attempts.

With the recent trend towards neo-adjuvant chemotherapy, where chemotherapy is initiated shortly after the diagnosis and the breast surgery is performed after tumor shrinkage [18], there is even less time to execute an SSCOS in women with breast cancer. Following this trend, most ovarian stimulation protocols have shifted towards RSCOS in recent years, which prompted us to conduct this study.

We first coined the term "random-start-controlled ovarian stimulation" in a case series where we reported successful oocyte retrievals and embryo cryopreservation with the COSTLES protocol in three women with breast cancer [8]. Since then, there have been several other reports on the utility of RSCOS in mixed cancer populations. One study reported the results of 138 newly diagnosed cancer patients, of whom 35 were treated with RSCOS [10]. The study found no difference in the numbers of total and mature oocytes and fertilization rates between RSCOS and SSCOS protocols. However, that study did not provide information on embryo development. Another study reported 46 women with various malignancies, including 28 with breast cancer, who underwent RSCOS compared to 65 women (34 with breast cancer) who underwent SSCOS [12]. The authors concluded that the RSCOS protocol was as effective as the SSCOS approach for fertility preservation in a mixed cancer population. In a large retrospective multicenter analysis, reporting on 684 women undergoing ovarian stimulation for fertility preservation before gonadotoxic therapies for benign or malign conditions (311 women with breast cancer), 472 (69.0%) were started on ovarian stimulation between menstrual cycle days 1–5, 109 (15.9%) between days 6–14, and 103 (15.1%) after day 14 [9]. The cycle outcomes including the number of oocytes and cryopreserved two pronuclei–stage zygotes were comparable regardless of the phase of the menstrual cycle that the RSCOS was initiated. In that study, embryos could not be cryopreserved beyond 2-PN stage due to restrictive laws in Germany and Switzerland. In addition to the similarities in ovarian response to gonadotropin stimulation in different studies, expression of the enzymes involved in cholesterol utilization and steroid hormone biosynthesis pathways, gonadotropin receptor expression, and estradiol and progesterone production were found to be identical between conventional and random-start cycles [19].

In previous studies, COSTLES was not used uniformly. In a prospective multicenter study including women with breast cancer ($n=401$), letrozole was concurrently used in 59% of the ($n=224$) of the 380 antagonist cycles reported. RSCOS was utilized in 201 cycles compared with 179 cases of conventional start. The study reported that women undergoing RSCOS required a higher total dose of gonadotropins, while the number of cryopreserved oocytes and embryos was similar between RSCOS and conventional start [11]. However, the number of women who received letrozole was not specified in the RSCOS group, and PGT-A was not employed.

We could find one study reporting the utility of PGT-A in the FP setting but none specifically with COSTLES and RSCOS in women with breast cancer. In that retrospective report, patients with various cancer types underwent in vitro fertilization with ($n=29$; 34 cycles) or without PGT-A ($n=22$; 24 cycles) for FP. Of the 29 patients (34 cycles) undergoing PGT-A with a mean age of $34.2\pm4$, only 12 cycles were random start, while others were day-2 or oral contraceptive-controlled cycle start. The FP/PGT-A cycles had an average of $3.5\pm3$ euploid embryos cryopreserved per patient (48.2% of the embryos biopsied). In that study, euploidy rates were not broken down based on the stimulation type, and the patient diagnoses included numerous cancer types [20].

Because breast cancer is the most common type of cancer encountered in the fertility preservation setting, it is critical that the most optimal approaches are utilized. Based on the data presented here and in previous publications, we currently utilize the protocols shown in Fig. 2. According to the modern protocol, we recommend rFSH and avoidance of LH-containing preparations to minimize the rise in E2, and we only add human menopausal gonadotropin if LH levels are suppressed [21]. We recommend a GnRHa trigger to minimize the risk of OHSS and to avoid false positive pregnancy tests prior to initiation of chemotherapy [22]. A GnRHa trigger may also be used to ovulate a dominant follicle in late-luteal start cycles, followed by ovarian stimulation in the early luteal phase [15], and may allow the ovaries to quiet down sooner if a back-to-back RSCOS is needed. For example, if PGT-A reveals very few or no euploid embryos from the first cycle, the patient may elect to undergo another RSCOS without a delay, if her chemotherapy can be safely postponed [23].

In addition, we have recently observed but not systemically tested that dividing the letrozole dose to 2.5 mg twice a day provides deeper E2 suppression. While we previously published short [24] and long-term follow-ups [25] on women with breast cancer who were treated with COSTLES and found no increase in relapse-free survival rates, modifications to minimize estrogen exposure can only make these protocols safer.

While oocyte and embryo yields were similar between the RSCOS and SSCOS cycles, there were some differences. RSCOS required larger doses of gonadotropins and tended to last longer, likely due to higher steroid hormone levels suppressing endogenous gonadotropin secretion [21]. In fact, we found that in RSCOS, baseline E2 levels were higher and that there

was a trend for lower FSH levels (Table 1). It is also possible that the ovarian milieu differs in the late follicular or luteal phase, potentially slowing down follicle development [26, 27]. Further basic studies will be needed to explain the relatively slower follicle growth and "FSH resistance" seen in random-start protocols.

In our study, as the RSCOS protocol evolved subsequent to SSCOS, a larger proportion of cycles was triggered with GnRHa and coupled with PGT-A. However, within the RSCOS, we did not find a difference in oocyte or embryo yield between the GnRHa- vs. hCG-triggered cycles, albeit the sample size was limited for subgroup comparisons. However, in a previous study with COSTLES, we showed that a GnRHa trigger resulted in a higher number and percentage of mature oocytes and a higher number of cryopreserved embryos compared with the hCG trigger [22].

Our study has limitations as it is a retrospective data analysis, and the protocol has evolved over a period of time. Nevertheless, our study is providing practical information on an innovative and evolving approach to ovarian stimulation in women with breast cancer. Because of the lag period between oocyte/embryo freezing and the attempt in pregnancy and because of the mobility of many patients, the pregnancy data are also limited. Although pregnancy outcome data from cancer patients undergoing RSCOS is limited, in a study including an infertile population, the clinical and ongoing pregnancy rates were 55.5% (127/229) and 48.9% (112/229), respectively [28]. A limitation of our PGT-A data is that a subset of women, mostly in the RSCOS group, underwent embryo biopsies. While the routine utility of PGT-A is questioned in an infertility population [14], in cancer patients with high prospects of POI, PGT-A may provide further reassurance and guide the decision for a duo-stim when no euploid embryo is present.

In conclusion, the RSCOS approach appears to be a comparable alternative to SSCOH to avoid further delays in initiating chemotherapy. Its combination with PGT-A may provide further reassurance to our patients, and potentially guide them in their decisions to undergo repeat cycles. Based on our extended experience, we recommend the approaches summarized in Fig. 2 when managing ovarian stimulation in women with breast cancer undergoing FP.

**Author contribution** KO designed the study, provided the funding, conducted all procedures, and wrote the manuscript. VT collected and tabulated the data, performed the statistical analysis, and participated in manuscript writing. HB performed statistical analysis. SGL collected data.

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**Data availability** The data that support the findings of this study are available upon reasonable request.

## Declarations

**Conflict of interest** The authors declared no competing interests.

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