

Random Start Ovarian Stimulation

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ABSTRACT

Fertility preservation is emerging in recent years as an important option for various indications many of which being for cancer patients and for certain benign conditions as well. In the present case report, we set out to utilise the same protocol, however, for different indications.

KEYWORDS: Breast cancer, fertility preservation, hysterectomy, oocytes, ovarian stimulation, random start

INTRODUCTION

Follicular development involves a single cohort of antral follicles that is selected and grown in response to gonadotropins in the early follicular phase of the menstrual cycle. Hence, the process of controlled ovarian stimulation (COS) cycle usually starts on cycle day 2 or 3. However, various studies have challenged the traditional paradigm by suggesting that women experience waves of follicular growth during the interovulatory interval.^[1]

The process of folliculogenesis involves multiple waves which allow for 'random start' and double ovarian stimulation protocols. 'Random start' involves stimulation of ovary at any time during the ovarian cycle. The concept of 'random start' proves to be beneficial for patients with limited time for assisted reproductive technologies.^[2] A conventional ovarian stimulation starts in the early follicular phase and may require 2–6 weeks which is challenging in the context of fertility preservation.^[3] With the advent of GnRH antagonist, the time interval from patient presentation, ovarian stimulation to embryo cryopreservation has drastically reduced but it still requires awaiting menses before initiating ovarian stimulation. As a result of this, there seems to be a delay in cancer treatment initiation in addition to the psychological stress bared upon by the patient.

Due to the urgency to start the cancer treatment, various protocols in the literature with alternative timing are tried: (1) initiating luteolysis followed by COS with

menses, (2) inducing luteolysis with simultaneous COS and (3) performing a random-start COS in either the follicular or the luteal phase.^[4-7] However, in this study, we report two cases of random start, however, for different indications, i.e., fertility preservation for cancer treatment and in post-hysterectomy patients. Although there have been till date no studies or case reports on random-start ovarian stimulation for a post-hysterectomy patient, we believe that it offers a satisfactory option to obtain good oocytes and embryos.

CASE REPORT

A 28-year-old, nulligravida with primary infertility was diagnosed with infiltrating ductal carcinoma breast (Grade 3) with oestrogen/progesterone receptor status negative. She was offered fertility preservation as the chemotherapy treatment would be associated with 33%–76% risk of permanent amenorrhoea.^[8,9] She was found to have an anti-Mullerian hormone level – 1.81 ng/ml. After a clear discussion involving the medical oncologist and infertility specialist, she opted for embryo cryopreservation in view of impending chemotherapy. During the first visit to the infertility specialist, it was noted that she had regular menstrual cycles with the last menstrual period 16 days ago and transvaginal ultrasound revealed normal-sized uterus and ovaries.

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There was a total of eight antral follicles in both ovaries. She received an injection Orgalutran 0.25 mg (MSD Pharma) for 3 days to induce luteolysis following which the blood tests showed oestradiol = 121 pg/mL, progesterone – 1.6ng/mL, LH – 8.9Miu/mL and follicle-stimulating hormone (FSH) – 3.5 Miu/ML. She was then commenced on injection FSH 300 IU (Follisurge; Instas Pharmaceuticals Ltd 300 IU) and (Human menopausal gonadotropin [HMG] [Koye pharma]) 150 IU. Due to the urgent need to start chemotherapy, it was best considered to start the stimulation even though the oestradiol level was at a higher range. We considered this as day 1 of stimulation. On day 5 of stimulation, and according to antagonist protocol, we repeated her hormone levels and found it as follows, oestradiol – 833 pg/mL, LH – 4.7 Miu/mL and a gonadotropin-releasing hormone antagonist was restarted. She was stimulated for a total of 9 days, and the total dose of FSH given was 2700 IU and HMG, 1350 IU.

On the day of human chorionic gonadotropin (HCG) trigger (ovitrelle (Merck) 13,000 IU), serum oestradiol (E2) level was 1580 pg/mL, progesterone (P4) – 0.8 ng/ML and luteinising hormone level – 1.2 Miu/mL. Thirty-five hours later, an oocyte pick-up procedure was carried out, 14 follicles were aspirated and 6 mature (M2) oocytes were retrieved, out of which 4 fertilised and resulted in 4 day 3, Grade 1 embryos. They were vitrified for future use [Table 1].

A 33-year-old, nulligravida who underwent total abdominal hysterectomy in view of recurrent multiple fibroids, presented to our fertility centre desirous of a genetically related child. Her surgical history revealed that she was a known case of multiple fibroids who had undergone myomectomy twice with the histopathology of the fibroid showing cellular leiomyoma with 2 mitoses/hpf. Post-myomectomy, she had a rapid recurrence of fibroids in a span of 1 year where the ultrasound and per abdomen findings before hysterectomy showed 24 cm × 20 cm size uterus with multiple fibroids. In view of rapid recurrence and growth of fibroids and the patient's fear of the possibility of malignancy, she opted for hysterectomy and surrogacy later. She had also undergone one

cycle of *in vitro* fertilisation (IVF), but the cycle was cancelled in view of poor response in follicular development.

On further assessment in our clinic, her anti-Mullerian hormone was 1.89 ng/ml with a baseline scan showing normal size ovaries with antral follicle count of 11. She received antagonist for 3 days (injection Orgalutran 0.25 mg) following which, the reports showed a serum E2 level – 39.9 pg/ml, LH – 7.7 Miu/ml, FSH – 7.0Miu/ml and P4 – <0.05 ng/ml. The patient received an injection FSH (Recagon 350 IU (MSD Pharma) for 5 days. On repeating her E2 on day 5 of stimulation, it was found to be 841.6 pg/ml, and hence, in accordance with antagonist protocol, an antagonist (injection Orgalutran 0.25 mg) was added to prevent LH surge. The dose of gonadotropin was titrated depending on the response seen on the transvaginal ultrasound. She underwent a total of 10 days of stimulation with a total dose of 2800 IU of injection Recagon. On the day of the trigger with HCG (ovitrelle (Merck) 13,000 IU), there were eight follicles ranging from 16 to 21 mm. Transvaginal oocyte pickup was performed 35 h after the trigger, and a total of five mature (M2) oocytes were retrieved. Out of the five oocytes, four were successfully fertilised by intracytoplasmic sperm injection (ICSI) and were vitrified for future use [Table 1].

DISCUSSION

In the present case report, the patient profiles selected are completely different, i.e., for the first patient, we initiated random-start ovarian stimulation considering the urgency to start the cancer treatment which may prove to be detrimental to the ovaries, and for the second patient, we chose to start random-start ovarian stimulation principally because of the previous failure experienced by COS. Till date, this has been the first documented case report where random-start stimulation was initiated in a hysterectomised woman.

In the first patient, we managed to retrieve six mature oocytes, similar to a study done by Courbiere *et al.*^[10,11] This optimal response further supports the effectiveness of the random-start protocol, wherein oocytes can be obtained efficiently irrespective

Table 1: The hormone levels, total dose of gonadotropins used and the outcome in both cases

	Day 1 of stimulation - oestradiol level and LH level	Day 5 of stimulation - oestradiol level and LH level	Day of trigger oestradiol level	Total dose of gonadotropins used	Total days of stimulation	Number of oocyte retrieved
Case 1	121 pg/ml 8.9 Miu/ml	833 pg/ml 4.7 Miu/ml	1580 pg/ml	FSH – 1800 IU HMG – 1350 IU	9	6 mature (M2)
Case 2	39.9 pg/ml 7.7 Miu/ml	841.6 pg/ml 50.2 Miu/ml	1991 pg/ml	FSH – 2800 IU	10	5 mature (M2)

of the phase of the menstrual cycle, in an urgent situation. In a cohort study done in 2013, the leading indication for emergency IVF was haematological cancer (42%).^[10] However, another study reported the most common indication for random-start stimulation was breast cancer.^[12] It is well known that chemotherapy for breast cancer has been associated with infertility and early menopause.^[13,14] Having the opportunity to discuss one's future reproductive potential before chemotherapy, as well as the ability to freeze oocytes or embryos for future use has made a positive difference in terms of improvement in the quality of life.^[14,15]

A conventional ovarian stimulation takes up to 4–6 weeks to complete a single cycle of egg or embryo freezing and this may delay the initiation of adjuvant chemotherapy for breast cancer.^[16,17] However, over the last few years, due to significant advances in ovarian stimulation techniques, there have been various studies which demonstrate that stimulation can be started at any random point in the menstrual cycle with similar outcomes and shorter duration.^[12,18] Such an effect was observed in our study where we achieved an adequate number of oocytes in a shorter duration of time, and at the same time, avoid the delay in the initiation of neoadjuvant chemotherapy. There are few studies examining the importance of the time interval from diagnosis to neoadjuvant chemotherapy start, and no prospective trial can ethically subject patient to intentional delays to determine a threshold for harm.^[19] The American Society of Clinical Oncology meeting in 2016 showed that a delay >9 weeks post-diagnosis is associated with a decrease in 5-year overall survival (86% vs. 81%).^[20] In our patient, the time from diagnosis to the initiation of chemotherapy was 4 weeks which encompasses their fertility preservation consultation with oocyte pickup procedure after the patient understanding the diagnosis and accepted the oncology treatment plan. However, as patients, oncologists and infertility specialists are eager for chemotherapy to begin, the process of fertility preservation should always be expedited and made as efficient as possible.

Similarly, we retrieved five mature oocytes in the second patient and there were successfully fertilised by ICSI with three Grade 1 embryo and one Grade 2 embryo. This response justifies our plan of random-start stimulation especially since this patient had a cancellation of previous IVF in view of poor response. Several studies have reported fertility preservation and subsequent IVF surrogate pregnancy after ovarian stimulation of hysterectomised patients.^[21] An interesting suggestion made by Meniru, and Craft suggested that ovarian stimulation should be conducted before

hysterectomy so that embryos can be frozen for a future pregnancy by surrogacy. These researchers emphasised that oocyte retrieval was much easier in these conditions as opposed to retrieval from a pelvis that had already undergone surgery/irradiation.^[22] In our study, however, the decision for hysterectomy was carried out in view of recurrence of fibroids and its symptoms and her failure to respond to any conservative medical treatment. We also experienced that there was poor visualisation of the ovaries during the ovarian stimulation and at the same time, a poor response to the gonadotropins received for which we had to cancel an IVF cycle. However, on random-start stimulation, we obtained adequate response and hence the decision to go ahead and retrieve oocytes, despite the difficulties, we may encounter during the oocyte pickup. In this case report, the total time from the referral to fertility preservation clinic to oocyte pick up was around 15–17 days which is very similar to a study done by Letourneau *et al.* where their meantime was 12 days.^[23] Another study by Baynosa *et al.* in 2009 reported a median time for fertility preservation referral to oocyte retrieval was 32 days.^[16]

Our case report merits discussion from both oncological, fertility preservation and an ethical perspective. It underlines the fact that progress in medically assisted procreation, as well as the possibility of recourse to surrogacy, make it feasible to achieve pregnancy after hysterectomy or before chemotherapy. Because of the wide dissemination of information on the technical progress in this area, patients are now able to make therapeutic choices that are no longer guided by strictly medical considerations.

CONCLUSION

Fertility preservation is becoming increasingly common. The result observed in our case reports clearly suggests that oocyte/embryo cryopreservation by random-start ovarian stimulation is effective and safe and can be offered to young women under different indications. However, early referral may lessen the burden of perceived time pressure on the patients and providers.

Consent

Consent taken from the concerned participant to publish.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal the identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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