Luteal phase GnRHa trigger in random start fertility preservation cycles

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Introduction

Depending on the type of cancer and how early the patient is referred before chemotherapy, there may nor may not be sufficient time to wait for the menstrual period to initiate ovarian stimulation for embryo or oocyte freezing. We have previously reported a “Random Start Controlled Ovarian Stimulation”(RSCOH) protocol where females with breast cancer were initiated on letrozole and gonadotropins followed by human chorionic gonadotropin (hCG) trigger, regardless of where they were in their menstrual cycle, even postovulation [5]. This approach resulted in a considerable number of oocytes and embryos. We have also reported previously that use of GnRHa trigger instead of hCG reduces ovarian hyperstimulation syndrome (OHSS) risks and estrogen exposure in letrozole-gonadotropin cycles [4]. OHSS may carry additional risks, as cancer patients are already prone to thromboembolic events. In addition, development of severe OHSS as well as hCG trigger-induced false positive pregnancy tests prior to initiation of chemotherapy may result in further delay of chemotherapy. Here we report an index case where the use of GnRHa trigger was tested in a luteal start COH (RSCOH)ovarian stimulation cycle which was initiated immediately after an LH surge.

Capsule Oocyte maturation can be successfully achieved by a GnRHa trigger in random start controlled ovarian stimulation cycles initiated in luteal phase for the purpose of emergency fertility preservation.

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Case

The patient was a single nulliparous 27 years-old female with Hodgkin lymphoma who was referred by her medical oncologist for fertility preservation. At the time of fertility preservation consultation, she was on the 11th day of her menstrual cycle and the ultrasound examination showed a right ovary with 6 antral follicles and a 19-mm dominant follicle, and a left ovary with 11 antral follicles and a 16.5-mm follicle. There was free fluid around the right ovary. Hormonal evaluation revealed serum levels of LH=71.3 mIU/ml, FSH=16.3 mIU/ml, progesterone=1.08 ng/ml, and estradiol=244.5 pg/ml. Because chemotherapy had to be initiated within two weeks, we began ovarian stimulation immediately with rFSH 450 IU and Ganirelix 250 mcg/day. We summarized the stimulation cycle of the patient in Table 1. After 4 days of ovarian stimulation, the dominant follicles disappeared, LH dropped to 0.9 mIU/mL, FSH was 28.5 mIU/mL, progesterone rose to 2.75 ng/mL, and there was free fluid in the cul de sac. These findings indicated that despite the administration of a GnRH antagonist, the patient had ovulated. However, her estradiol levels continued to rise, it was 837 pg/mL on the 4th day of stimulation. On the 10th day of ovarian stimulation, which corresponded to her menstrual cycle day 21, the lead follicles reached 19.5, 19, and 18.5-mm in diameter with a total of seven large follicles. Her E2 peaked at 2620 pg/ml. Given the large number of follicles developing we decided to administer 1 mg of leuprolide acetate for trigger. Ten hours after the trigger her LH was 89 mIU/mL, FSH 35 mIU/mL and progesterone 9.4 ng/ml, confirming that the GnRHa administration triggered a second LH surge 10-11 days after the patient's spontaneous LH surge (Fig. 1). Thirty-six hours after the GnRHa trigger, we performed a transvaginal oocyte retrieval, which resulted in the recovery of 31 oocytes of that 17 (52 %) were mature. After in vitro maturation of five

Table 1 Summary of stimulation cycle

	rFSH(450 ius) plus Ganirelix(250 mcg/day) for 10 days			GnRHa trigger at 11 pm	Testing at 9 am
Stimulation Day	1	5	8	11	Post-trigger
Cycle day	11	15	18	21	22
FSH(mlU/ml)	16.3	28.5	30.1	32	35
LH(mlU/ml)	71	0.9	0.3	0.1	89
Estradiol (pg/ml)	245	831	1280	2627	2201
Progesterone(ng/ml)	1.08	2.75	1.56	2.2	9.4
Follicles(mm)					
Right ovary	19, 6×<10	4×11, 12×<10	15, 4×13, 4×11, 7×<10	17.5, 7×14, 2×12, 7×<10	
Left ovary	16.5, 11×<10	4×11, 7×<10	4×15, 3×12, 9×<10	19.5, 2×19, 3×18, 3×14, 3×12	

additional oocytes to maturity, a total of 22 oocytes were vitrified. The patient developed no signs of OHSS and began receiving chemotherapy within 48 h of the retrieval.

Discussion

While GnRHa trigger has been successfully used in fertility preservation [4] as well as fresh IVF-ET cycles to reduce the risk of OHSS, its effectiveness has never been shown in luteal phase start cycles. The current case presentation shows that it is possible to trigger an LH surge with a GnRHa within 10 days of the spontaneous LH surge. Not only does this case report demonstrate a new practical approach to preserving fertility in cancer patients who are short of time before chemotherapy, but it also has implications for normal ovarian physiology. It illustrates that, despite the initiation of the luteinization process, hypothalamic-pituitary axis is capable of re-triggering ovulation within a short time period.

This case report supports the emerging notion that there is more flexibility built into an ovarian cycle than previously

thought. In a study where healthy women of reproductive age were followed daily by ultrasound examinations, it was determined that there are three waves of follicle recruitment in each cycle [1]. Our previous cases of RSCOH and the current report are in support of the aforementioned study. The current report, in addition, suggests that the hypothalamic-pituitary axis is capable of triggering ovulation in these additional waves of follicles even in the luteal phase [5]. Nayak and Wakim have recently reported a series of 4 patients who underwent RSCOH which was initiated at various times during the menstrual cycle and triggered by GnRHa [2]. Though none of the patients presented with an elevated P4 level at the commencement of ovarian stimulation, one patient had a subsequent rise in P4 following the initiation of antagonist treatment. In our case we clearly demonstrated that the patient was in luteal phase by hormonal measurements and ultrasound monitoring, who subsequently underwent luteolysis and responded to GnRHa trigger. In RSCOH cycles, when there is a dominant follicle is present or ovulation has already occurred, we initiate a GnRH antagonist simultaneously with FSH administration. In addition, with the assumption that

Fig. 1 Occurrence of a second LH surge within 10 days of the first in response to GnRHa trigger. Estradiol levels continued to rise in response to ovarian stimulation while progesterone levels were suppressed with a GnRH antagonist. Please note that progesterone levels were given in ng/cl to match the curve in the same scale as LH measurements

follicles may have a higher threshold of FSH to be rescued at this late stage, we use larger doses (typically 450 IU) of gonadotropins. The purpose of antagonist use post-ovulation is luteolysis [3]. We successfully achieved this in the current case, allowing a second LH surge to be triggered within two weeks of the first one. To confirm that the GnRHa triggered the LH surge, we measure LH, FSH, and P4 levels the next morning. In our experience with over 75 cycles, we have seen one case of failure to initiate an LH surge by a GnRHa. That patient had a brain tumor, which probably impaired the functionality of the hypothalamic-pituitary axis.

Further follow up and larger prospective studies will determine the pregnancy success rates of RSCOH with luteal phase GnRHa trigger in comparison to standard early follicular phase start cycles. Currently, we have no reason to suspect that luteal start-GnRHa trigger RSCOH cycles will have inferior results. This approach is likely to shorten the time to chemotherapy from the initiation of ovarian stimulation, and reduce OHSS. We recommend that a GnRHa trigger be used in all fertility preservation cycles when there

is no CNS tumor that can interfere with the hypothalamo-pituitary communication.

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