CASE REPORT

Luteal Start of Stimulation in a Case of Expected Poor Response with the Successful Outcome: A Case Report

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Abstract

Purpose: Poor responder is a quasi-cluster of patients whose management has confounded clinicians. Luteal phase stimulation as a solution is proposed on a new principle of follicular development.

Case description: Mrs. X, a 34-year-old woman with an anti-Mullerian hormone (AMH) of 0.86 ng/mL and a history of failed *in vitro* fertilization (IVF) with the recovery of one egg was stimulated in the luteal phase. The patient's ovarian stimulation was done with menopur 375 IU, cetrotide 0.25 mg was added after 8 days. The stimulation lasted for 15 days.

Results: There were seven oocytes recovered, two blastocysts were formed and transferred in a freeze–thaw cycle. This resulted in a live-born preterm fetus at 27 weeks in view of bleeding placenta previa.

Conclusion: Luteal phase stimulation can be another reasonable solution in the long list of stimulation regimens for patients who are poor responders.

Keywords: Luteal start, Poor responder, Random start.

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Introduction

Poor responders have often confounded *in vitro* fertilization (IVF) specialists around the world. Much of the research is directed to the finding of reasonable solutions in this group of patients. The lack of a universal definition has induced a considerable degree of heterogeneity to research on stimulation protocols in poor responders.

Random start of stimulation was started for women with malignancy and disorders, where limited time is available to the patient before beginning cytotoxic and gonadotoxic treatment. This has given us information that luteal stimulation even when longer may be associated with a higher number of eggs retrieved.

Here, we are reporting a case where this approach was used in an established poor responder patient with endometriosis.

Case Description

Patient X, a 34-year-old woman with 4 years of infertility was operated on laparoscopically 1 year ago where grade IV endometriosis was diagnosed, and cystectomy was performed bilaterally. Postoperatively, she underwent one cycle of superovulation and intrauterine insemination (IUI), which was unsuccessful. Thereafter, a cycle of IVF was performed elsewhere. The stimulation was an antagonist cycle, which started with 225 IU of recombinant follicle-stimulating hormone (FSH) (Gonal F, Merck Serono, Italy), and 150 IU luteinizing hormone (LH) (Luveris, Merck Serono, Italy). The cycle resulted in the retrieval of one egg, which did not fertilize.

The patient presented with the above history and on the investigation, her anti-Mullerian hormone (AMH) was 0.86 ng/mL and antral follicle count (AFC) was 6 (2 + 4). The patient was planned for a luteal start of stimulation. The experimental nature of the procedure was explained to her.

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Stimulation

The patient was called on day 10/26 day of her cycle. A follicle of 14 mm was seen in her right ovary. On further follow-up on day 14 at the follicle size of 19 mm, ovulation was triggered with inj. Triptorelin (Decapeptyl, Ferring, Switzerland) 0.2 mg. Ovulation was confirmed on day 16 on ultrasound (USG) and progesterone levels in the blood. The AFC on day 16/D1 of stimulation was 6 (2 + 4). Stimulation was started with urinary highly purified human menopausal gonadotropin, u-hMG 375 IU (Menopur, Ferring, Switzerland). When the lead follicle was 12 mm in diameter and cetrorelix acetate was added (cetrotide, Merck Serono, Italy). Egg retrieval was planned at 36 hours of inj. triptorelin 0.2 mg. She had seven oocytes retrieved, three metaphase II (MII), two metaphase I (MI), and the rest were germinal vesicle (GV). The MII and MI oocytes (after *in vitro* maturation) were injected with sperms. Intracytoplasmic sperm injection (ICSI) was performed in view of previous fertilization failure. There were three 2PN embryos at 24 hours and on day 3, (1) 8 cell grade I + (2) 8 cell grade II (20% fragmentation). The embryos were frozen for transfer at a later date because of asynchrony between the embryo and the endometrium in luteal phase stimulation.

The embryo transfer was done in a down-regulated, programd hormone replacement cycle in view of her adenomyosis and

endometriosis. The patient was administered a depot injection of triptorelin (Decapeptyl, Ferring, Switzerland) 3.75 mg and after 3 weeks estrogen was started (Estrabet, Abbott India Ltd.). She was started on injectable progesterone intramuscularly (Gestone, Ferring, Switzerland) 100 mg at an endometrial thickness of 10 mm. The embryos on thawing were cultured to blastocysts. At 118 hours, two embryos were transferred (3.1.1 and 2.1.2, Istanbul consensus).[1] Her b-hcg was 846 IU/mL and clinical pregnancy was confirmed at 6 weeks.

The patient developed some bleeding at 20 weeks when the lower segment placenta was made note of. The patient developed leaking at 26 weeks with heavy bleeding at 27 weeks when a lower segment cesarean was performed in view of antepartum hemorrhage and major placenta previa. The baby is a healthy 1,000 g preterm and is doing well.

Discussion

In the present patient, the luteal phase was induced by decapeptyl trigger and confirmed by progesterone levels before starting the stimulation. We were successful in the luteal phase to obtain good quality mature oocytes in this patient with documented poor response. Researches have demonstrated the luteal phase to be equally productive in patients with neoplasia and normal responders.[2] The usage of the luteal phase has never been demonstrated in the poor responder. Dual stimulation (shanghai protocol) has been studied in poor responders and a yield of a higher number of oocytes in the second stimulation has been achieved.[3] Kuang et al. obtained 3.5 $\pm$ 3.2 oocytes in the luteal phase as compared to 1.7 $\pm$ 1.0 in the follicular phase. This formed the background for the work done in the present patient where stimulation began in the second half of the cycle.

According to a new theory on follicular development, there are multiple cohorts developing follicles in a menstrual cycle.[4,5] This purports that superovulation akin to IVF cycles can effectively begin at any day of the cycle. In relation to this theory random start, late follicular start and luteal start regimes have been proposed. Most of the evidence in poor responders comes from "duostim" (Shanghai protocol).[6] Accordingly, most of the researchers have obtained the same number of oocytes and blastocysts for transfer in follicular and luteal phase stimulation.[2,7]

Other studies have found no difference in the outcome of stimulation in different parts of the menstrual cycle in terms of eggs retrieved and embryos formed.[2,8,9] In our experience, we found that the stimulation was prolonged (15 days) and required a higher dose of gonadotropin but ended with the recovery of a significantly higher number of oocytes (Table 1). This was also the observation of Cakmak et al. that the total dose is higher in the late follicular phase and luteal phase.[10]

More recently, researchers in Greece accumulated oocytes from unstimulated cycles in a total of three follicular, luteal, and follicular phases. One hundred and fifty-three women were included and there was no statistically observed difference in the metrics of the outcome either in terms of eggs retrieved or embryos formed.[11]

More evidence is required to improve the performance of luteal phase stimulation, e.g., it has been suggested that antagonists may not be required for controlling LH surge because of the presence of progesterone in the hormonal milieu.[12] Kuang et al. studied 242 women in the luteal phase and none of them had a spontaneous LH surge without the antagonist. Follicle-stimulating hormone, LH, E2 (estradiol), and P4 (progesterone) were studied, though it is unclear how often the same were monitored.[13]

Table 1: Luteal phase follicular stimulation in Mrs. X

Date/day of stimulation	*Injection*	*Right ovary*	*Left ovary*
12/10/2017/day 1	Menopur 375	3 (3)	4 (3)
13/10/2017/day 2	Menopur 375		
14/10/2017/day 3	Menopur 375		
15/10/2017/day 4	Menopur 375	7, 6, 5, 5	6 (3)
16/10/2017/day 5	Menopur 375		
17/10/2017/day 6	Menopur 375		
18/10/2017/day 7	Menopur 375	7 (4)	7, 6 (3)
19/10/2017/day 8	Menopur 450		
20/10/2017/day 9	Menopur 450/ cetrotide 0.25	12, 11, 9, 8	9, 8
21/10/2017/day 10	Menopur 450/ cetrotide 0.25		
22/10/2017/day 11	Menopur 450/ cetrotide 0.25		
23/10/2017/day 12	Menopur 450/ cetrotide 0.25		
24/10/2017/day 13	Menopur 450/ cetrotide 0.25	17, 15 (2), 13	14 (2), 10 (3)
25/10/2017/day 14	Menopur 450/ cetrotide 0.25		
26/10/2017/day 15	Menopur 450/ cetrotide 0.25	19, 18, 17, 15	15, 14

(Cimadomo D 2018)

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