

# DOUBLE STIMULATION in the Same Ovarian Cycle (DuoStim) to Maximize the Number of Oocytes Retrieved From Poor Prognosis Patient .



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## CASE STUDY 1

### Patient Information:

Mrs. X, a 35-year-old woman, has been married for 12 years with regular menstrual cycle of 24 days, and three days of moderate flow. She is diagnosed with hypothyroidism for the past 5 years, managed with thyronorm 125 micrograms. Additionally, she has been dealing with hypertension for 3 years, under medication.

### Previous Treatment History:

In January 2021, Mrs. X underwent her first cycle, three oocytes were retrieved, resulting in the formation of one embryo, which was transferred on day 2 without success.

During the second IVF cycle in May 2021, she was injected with recombinant FSH and LH injections, resulting in the retrieval of seven oocytes, five of which fertilized, leading to the formation of four blastocysts. However, the fresh embryo transfer (ET) was unsuccessful. A subsequent ET after laparoscopic right salpingectomy was also negative.

In April 2022, one blastocyst was transferred without success.

In September 2022, a third frozen embryo transfer (FET) resulted in a biochemical pregnancy but unfortunately did not progress further.

The third IVF cycle in December 2022 was cancelled due to poor response. In April 2023, the fourth IVF cycle yielded five retrieved oocytes, three of which fertilized, but the resulting blastocyst transfer was unsuccessful.

The fifth IVF attempt in August 2023 was also cancelled due to poor response.

A hysteroscopy conducted in 2021 revealed normal findings. Throughout these cycles, despite numerous attempts and interventions, Mrs. X faced challenges in achieving a successful pregnancy.

### Husband Information:

Mr. Y, aged 39, is a software engineer with known hypothyroidism managed with thyronorm 75 micrograms. His semen analysis showed normal parameters.

### Presenting to MOM IVF:

Following a comprehensive history assessment, Mrs. X underwent several investigations. Transvaginal ultrasound (TVS) was performed on day 8 of her menstrual cycle, revealing a normal uterine anatomy with an endometrial thickness of 7.8mm, displaying a triple-line pattern. Additionally, the right ovary (RO) exhibited 1-2 antral follicle counts (AFC), as did the left ovary (LO). Semen analysis conducted at MOM IVF showed promising results with a sperm count of 100 million, 70% motility, and 4% morphology. However, Mrs. X's anti-Mullerian hormone (AMH) levels were notably low at 0.3ng/ml, indicating compromised ovarian reserve.

Following counselling for IVF treatment, Mrs. X returned on day 2 of her menstrual cycle for further evaluation. A subsequent scan revealed thin endometrium with 1-2 AFC in both ovaries.

Stimulation was initiated with 150IU of recombinant FSH (recFSH) and recombinant LH (recLH) using an antagonist protocol for 10 days. This resulted in the development of two follicles measuring approximately 18mm each in both ovaries. Triggering with an agonist was performed, and oocyte retrieval was conducted after 35 hours, yielding 4 oocytes. Subsequently, 2 grade 2 blastocysts were formed and cryopreserved.

On day 2 post oocyte retrieval, Mrs. X opted for luteal phase stimulation, revealing 1-2 follicles around 10mm in each ovary. Stimulation was adjusted to 225 IU of recFSH and recLH for 7

days, following the antagonist protocol. Triggering was achieved with an agonist, resulting in the retrieval of 3 oocytes. One grade 1 blastocyst was formed and cryopreserved.

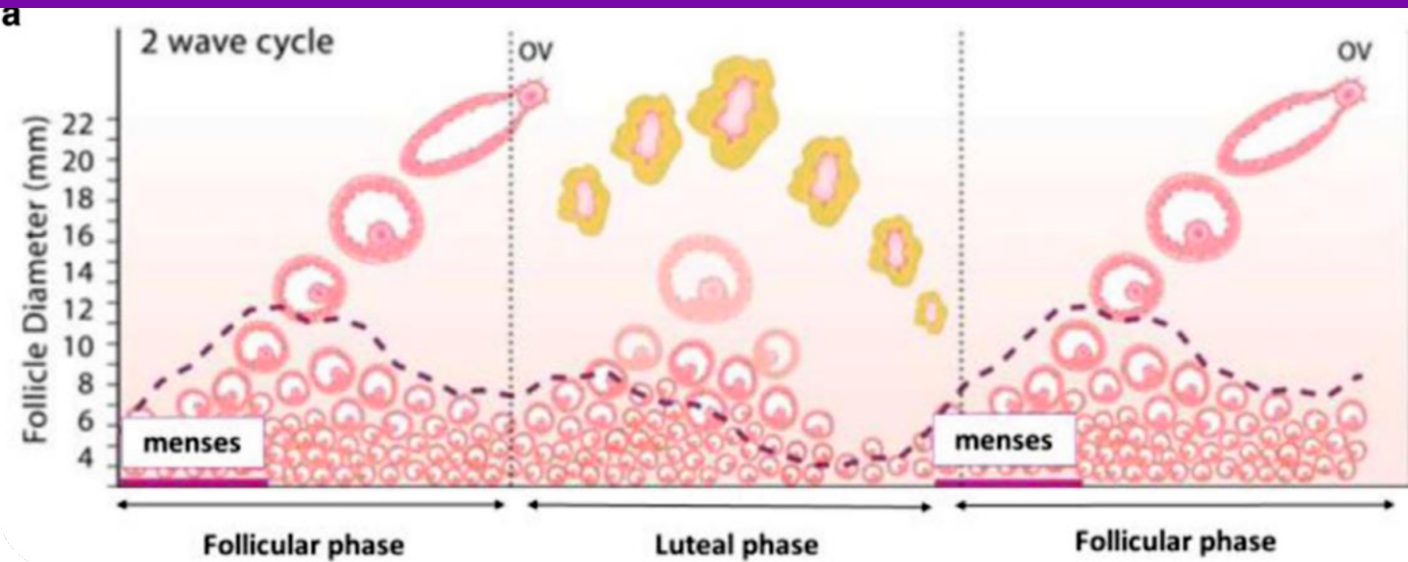
**Frozen Embryo Transfer (FET):**

Following counselling for double stimulation IVF, frozen embryo transfer (FET) was conducted when the endometrium reached approximately 9mm. Two blastocysts, graded as grade 1 and grade 2, were transferred. After 12 days, the beta HCG level was measured at 278.70, indicating a positive pregnancy outcome.

**DISCUSSION:**

A panel of experts known as the POSEIDON group has redefined the spectrum of poor responder patients and introduced the concept of suboptimal response. Since an ideal management for these patients is still missing, they highlighted the importance of tailoring the ovarian stimulation based on the

chance of each woman to obtain an euploid blastocyst Interestingly, a novel pattern of follicle recruitment has been defined: multiple waves may arise during a single ovarian cycle. This evidence opened important clinical implications for the treatment of poor responders.

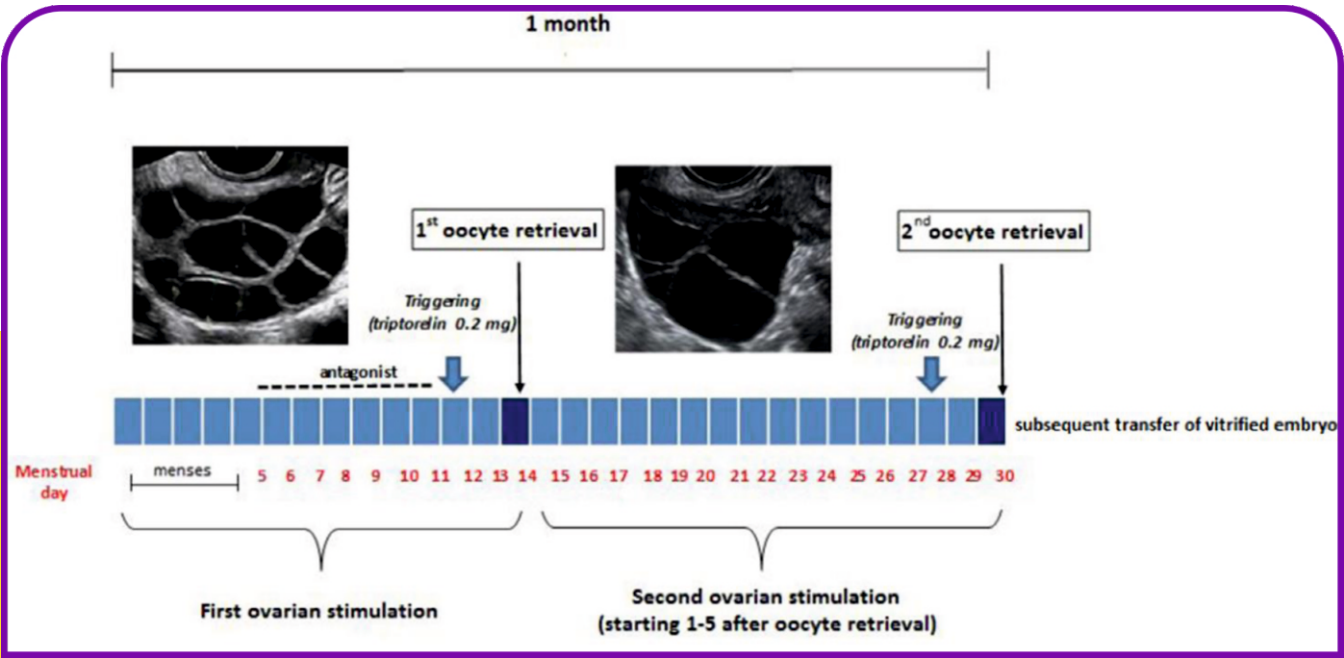


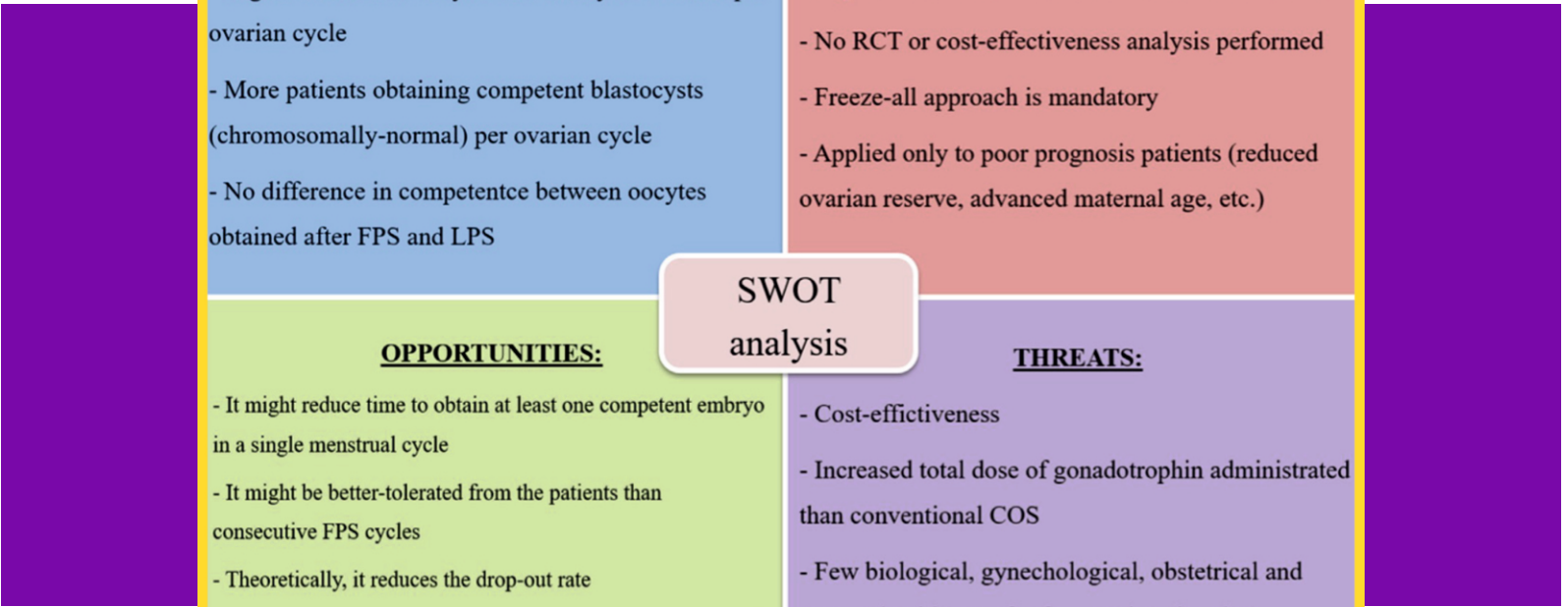
For instance, double stimulation in the follicular (FPS) and luteal phase (LPS) of the same ovarian cycle (DuoStim) is an intriguing option to perform two oocyte retrievals in the shortest possible time In IVF, poor response to controlled ovarian stimulation (COS) represents an important issue, which may

affect 9–24% of the infertile women The Bologna criteria represented the first successful attempt to outline some guidelines in the definition of poor ovarian response. At least two of the following characteristics must be present to define “a poor responder patient”: advanced maternal

age (>40 years) and/or scarce response to a previous conventional stimulation ( $\leq 3$  oocytes) and/or reduced ovarian reserve (antral follicle count, AFC < 5–7 follicles, and/or AMH < 1.1 ng/ml). A new classification by a panel of experts, known as the POSEIDON (Patient-Oriented Strategies Encompassing Individualized Oocyte Number) group, has been introduced to better categorize the spectrum of poor responder patients. The POSEIDON group then introduced the concept of “sub-optimal response.” In this group of patients collecting 4–9 oocytes, 4 sub-clusters were outlined according to both the ovarian reserve and the maternal age. Specifically, groups 3 and 4 are represented from women younger than 35 or older than 35, respectively, with a compromised ovarian reserve (AFC < 5 and AMH < 1.2 ng/ml), an issue, which cannot be resolved pharmacologically, as already reported in several studies double stimulation in the same ovarian cycle (DuoStim). Such protocol particularly suits poor prognosis and oncological patients, who require maximizing the exploitation of their

ovarian reserve in a limited time. DuoStim, by combining conventional follicular phase stimulation (FPS) with luteal phase stimulation (LPS), can be considered a valuable option in patients with reduced ovarian reserve and/or advanced maternal age to maximize the number of oocytes retrieved in a single ovarian cycle, and for patients who did not collect oocytes or did not produce competent embryos after conventional FPS. The very first experience with double stimulation has been reported by Kuang and colleagues who showed that COS conducted in both the FPS and LPS of the same ovarian cycle results in the collection of oocytes with similar developmental competence. The drugs used for COS in the Shanghai protocol, as it was called in the paper, were clomiphene citrate 25 mg/day, letrozole 2.5 mg/day, and mild dose of human menopausal gonadotrophin 150–225 IU/day. Moreover, the final oocytes maturation was induced with triptorelin followed by ibuprofen 0.6 g the day of trigger and the day after, in both FPS and LPS.





**Conclusion:**

The evidence that multiple waves of follicle recruitment may arise during a single ovarian cycle in women opened important clinical implications for the treatment of poor prognosis patients. LPS in general has become a promising protocol for patients who need to collect the highest number of oocytes in the shortest possible time (e.g., oncological patients). DuoStim approach conjugates FPS to LPS with very successful results reported to date. Still, any stimulation protocol, which exploits anovulatory waves of follicle recruitment should undergo a thorough biological and clinical investigation before it can be generally implemented. To this regard, DuoStim still needs a more extensive and wider validation to testify its safety. Interesting future perspectives to investigate its clinical efficacy/efficiency would entail (i) a RCT comparing double-FPS versus DuoStim; (ii) the application of DuoStim in cancer patients for fertility preservation;