

# LUTEAL PHASE STIMULATION AFTER FOLLICULAR PHASE STIMULATION DURING THE SAME MENSTRUAL CYCLE (DUOSTIM) IN A REDUCED OVARIAN RESERVE POPULATION: WHEN IS IT COST-EFFECTIVE?

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## OBJECTIVE

1- To compare the number of eggs, mature eggs and blastocysts obtained during stimulation in follicular phase (FP) versus stimulation in luteal phase (LP) of the same menstrual cycle (DUOSTIM) in patients with decreased ovarian reserve.

2- To evaluate the same outcomes according to the count of visible antral follicles (AF) at the time of the first oocyte retrieval.

## DESIGN

Prospective paired observational study.

## MATERIALS & METHODS

From January 2020 to March 2021, We selected women who would be submitted to in vitro fertilization cycle with embryo freezing. Inclusion criterion was AF count (AFC) less than 7.

All patients underwent two cycles of ovarian stimulation: one in FP and the other in LP. FP stimulation (FPS) has started on day 3 of the cycle and LP stimulation (LFS), 5 days after the first oocyte retrieval. Both stimulations were performed with gonadotropin-releasing hormone antagonist protocol using the following medication subcutaneously:

-150 IU/day of recombinant FSH (Puregon™; Schering-Plough Indústria Farmacêutica Ltda, São Paulo, Brazil);

-150 IU/day of recombinant FSH + 75 IU of recombinant LH (Pergoveris™, Merck SA, Rio de Janeiro, Brazil);

- 0,25 mg/day of ganirelix acetate (Orgalutran™, Schering-Plough Indústria Farmacêutica Ltda, São Paulo, Brazil), starting when the largest follicle reached 14 mm);

- oocyte maturation was triggered by administration of 0,2 mg triptorelin (Gonapeptyl daily™; Laboratórios Ferring, São Paulo, Brazil) when most of follicles were higher than 18 mm.

Egg retrieval was performed 35 h after trigger. During the first oocyte retrieval, It was counted the number of AF (2 to 9 mm). These follicles were not aspirated.

In a second analysis, the patients were separated into two groups:

**Group 1:** AFC, at the time of the first collection, greater than the number of eggs obtained.

**Group 2:** AFC at the time of the first egg retrieval, equal to or less than the number of eggs obtained in this moment .

FPS and LFS according to the mean number of days of stimulation, number of eggs, mature eggs (MII) and blastocysts. We compared the total number of women and each group separately. Means were compared using t-Student test.

## RESULTS

Forty-nine women complete the study. The mean age was 40.3 and the mean AFC was 4.2. In FPS, it was required 11.04 days and it was obtained 3.96 eggs, 2.67 mature eggs and 0.90 blastocysts. In LPS, 13.51 days were necessary and 4.83 eggs, 3.59 mature eggs and 1.20 blastocysts were obtained. All results were statistically significant (Table 1).

**Table 1. Comparison of Follicular Phase Stimulation (FPS) to Luteal Phase Stimulation (LFS)**

	FPS	LPS	p
Days <sup>1</sup>	11.04	13.51	<0.0001 <sup>2</sup>
Oocytes <sup>1</sup>	3.96	4.83	0.0050 <sup>2</sup>
MII <sup>1</sup>	2.67	3.59	0.0017 <sup>2</sup>
Blastocysts <sup>1</sup>	0.90	1.20	0.0175 <sup>2</sup>

<sup>1</sup>Mean number / <sup>2</sup>significant

Analyzing group 1 (n=23), a greater mean number of eggs (5.70), mature eggs (4.48) and blastocysts (1.57) were obtained in LPS, comparing to FPS (3.39, 2.13 and 0.65, respectively), all statistically significant. The number of days was also significantly higher in LPS (12.87 vs 11.04) (Table 2).

**Table 2. Comparison of Follicular Phase Stimulation (FPS) to Luteal Phase stimulation (LPS) for Group 1**

Group 1	FPS	LPS	p
Days <sup>1</sup>	11.04	12.87	<0.0001 <sup>2</sup>
Oocytes <sup>1</sup>	3.39	5.70	<0.0001 <sup>2</sup>
MII <sup>1</sup>	2.13	4.48	<0.0001 <sup>2</sup>
Blastocysts <sup>1</sup>	0.65	1.57	<0.0001 <sup>2</sup>

<sup>1</sup>Mean number / <sup>2</sup>significant

In group 2 (n=26) 4.46 eggs, 3.15 mature eggs and 1.12 blastocysts were obtained during FPS and 4.08 eggs, 2.81 mature eggs and 0.88 blastocysts in LPS (not significant), Greater number of days were required in LPS (14.07 vs 11.02, p <0.05) (Table 3).

**Table 3. Comparison of Follicular Phase Stimulation (FPS) to Luteal Phase stimulation (LPS) for Group 2**

Group 2	FPS	LPS	p
Days <sup>1</sup>	11.04	14.07	<0.0001 <sup>2</sup>
Oocytes <sup>1</sup>	4.46	4.08	0.5892
MII <sup>1</sup>	3.15	2.81	0.1058
Blastocysts <sup>1</sup>	1.12	0.88	0.1101

<sup>1</sup>Mean number / <sup>2</sup>significant

## CONCLUSION

In patients with low reserve, LFS leads to a greater number of eggs, mature eggs and embryos than the previous FPS when the number of AF at the time of egg collection exceeds the number of eggs obtained in this moment.

When the number of AF count at this time is less than the number of eggs obtained, LPS does not increase the number of eggs, mature eggs and blastocysts, comparing to FPS, on the other hand, It requires more days of stimulation and, therefore, higher cost. In this case, LFS is not cost-effective.

## IMPACT STATEMENT

This study helps to define the group of patients who benefit from DUOSTIM protocol: when the number of AF at the time of the first egg collection exceeds the number of eggs obtained in this moment.