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The DuoStim strategy shortens the time to obtain an euploid embryo in poor prognosis patients: a non-inferiority, randomized controlled trial

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Study question:
Is there any difference in the time to obtain euploid embryos from poor prognosis patients who performed two conventional cycles versus double stimulation (DuoStim) in the same cycle?

Summary answer:
DuoStim showed similar ovarian response and *in vitro* fertilization (IVF) laboratory outcomes while shortening the time to obtain an euploid embryo in poor prognosis patients.

What is known already:
Several waves of cyclic development of antral follicles within the same menstrual cycle have been demonstrated. Likewise, it has been shown that oocytes obtained from luteal phase ovarian stimulation (OS) have similar competence than those obtained in the follicular phase OS. Often, some patients require sequential OS in order to obtain more oocytes and increase their chances to reach embryo transfer. Thus, the DuoStim strategy could be an attractive alternative to reduce the time-to-pregnancy. However, prospective data and randomized trials that validate this strategy are lacking.

Study design, size, duration:
We conducted a prospective, randomized controlled trial at our institution from[MCM1] [JAGV2] January 2017 to December 2020. A total of 80 poor prognosis patients aged over 38 years undergoing PGT-A were enrolled in two groups: 39 patients did two OS in consecutive cycles (control) whereas 41 women underwent two OS in the same menstrual cycle (DuoStim).

Participants/materials, setting, methods:
Poor prognosis was defined as suboptimal responders. The primary outcome was the time needed to obtain an euploid embryo. The secondary outcomes were duration of stimulation, dose of gonadotropins, oocyte maturity rate, fertilization and blastocyst formation rates. Variables were expressed as mean ± standard deviation. Statistical analyses was performed by ANOVA and Chi-square tests, as appropriate. Differences were considered significant when *p-value* < 0.05.

Main results and the role of chance:
The patients' baseline characteristics were similar between groups. We did not find any difference in the mean days of stimulation between the control and the DuoStim group (21.3 ± 1.6 *vs.* 23 ± 1.4, *p=0.105*), nor in the amount of gonadotropin required (4005 ± 450 *vs.* 4245 ± 430, *p=0.43*), number of MII oocyte (8.7 ± 1.8 *vs.* 6.8 ± 1.7, *p=0.159*), blastocyst rate (51.4% *vs.* 34.8%, *p=0.113*) and the number of euploid embryos (0.8 ± 0.4 *vs.* 0.6 ± 0.4, *p=0.45*). However, there was a significant difference in the average number of days until reaching an euploid blastocyst, favoring the DuoStim group (44.1 ± 2 *vs.* 23.3 ± 2.8, *p<0.001*). Comparing the follicular versus the luteal phase within the DuoStim group, the only difference detected concerns to the mean days of stimulation (10.3 ± 0.8 *vs.* 12.7 ± 0.9, *p<0.001*). We also observed a trend towards a higher fertilization (38.1% *vs.* 61.8%, *p=0.02*) and blastulation rate (23% *vs.* 53%, *p=0.03*) in the luteal phase of the DuoStim cycle.

Limitations, reasons for caution:
The major limitation is related to the limited sample size, as it limits our power analysis (70%). On the other hand, it is one of the first randomized prospective pilot trial that compared the efficiency of performing two consecutive ovarian stimulation in different menstrual cycles with the DuoStim strategy.

Wider implications of the findings:
This study clearly showed that the DuoStim protocol is not inferior to the conventional stimulation in terms of ovarian response and laboratory outcomes. Moreover, the DuoStim reduces the time to obtain an euploid embryo in poor prognosis patients, which is of great clinical utility.

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