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ARTICLE

# A randomized, non-inferiority trial on the DuoStim strategy in PGT-A cycles

## BIOGRAPHY

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## KEY MESSAGE

DuoStim could be considered an alternative in cases where it is necessary to obtain a higher number of oocytes in the shortest possible time, to decrease the time required to obtain euploid blastocysts and minimize treatment discontinuation.

## ABSTRACT

**Research question:** Is the DuoStim strategy an effective alternative to two conventional ovarian stimulation cycles in poor-prognosis patients undergoing preimplantation genetic testing for aneuploidies (PGT-A) to improve euploidy rates and obtain the first euploid embryo in less time?

**Design:** This randomized controlled trial was performed at IVI Madrid between June 2017 and December 2020 and included 80 patients with a suboptimal profile aged 38 or older undergoing PGT-A cycles. Patients were blindly randomized into two groups: 39 women underwent two ovarian stimulations in consecutive cycles (control group), whereas the double stimulation strategy was applied to 41 women (DuoStim group). The main outcome was the euploidy rate in each group. The secondary outcomes were the time it took to obtain a euploid embryo and the main cycle outcomes.

**Results:** The baseline characteristics of the patients were similar. No differences were found between the control group and the DuoStim group in the mean days of stimulation (21.3 ± 1.6 versus 23.0 ± 1.4, $P = 0.10$), total gonadotrophins (4005 ± 450 versus 4245 ± 430, $P = 0.43$), metaphase II oocytes (8.7 ± 1.8 versus 6.8 ± 1.7, $P = 0.15$) or euploid embryos obtained (0.8 ± 0.4 versus 0.6 ± 0.4, $P = 0.45$). The euploid rate per randomized patient (ITT) was 16.1% in the control group versus 22.7% in the DuoStim group, with *P*-values of 0.371, and the euploidy rate per patient treated was 39.0% versus 45.7% in the control versus DuoStim groups. However, there was a significant difference in the average number of days it took to obtain a euploid blastocyst, favouring the DuoStim group (44.1 ± 2.0 versus 23.3 ± 2.8, $P < 0.001$).

**Conclusions:** The use of the DuoStim strategy in poor-prognosis patients undergoing PGT-A cycles maintains a similar euploidy rate while reducing the time required to obtain a euploid blastocyst.

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## KEYWORDS

DuoStim
Euploid blastocyst
IVF
PGT-A
Poor responders

## INTRODUCTION

Treatment with assisted reproductive techniques (ART) has seen two major advances over recent years: preimplantation genetic testing for aneuploidies (PGT-A) reduces the time to pregnancy and miscarriage rates in some cases, while vitrification allows for fertility preservation and increases the likelihood of pregnancy by enhancing the number of oocytes and embryos available (*Cobo et al., 2016*; *Niederberger et al., 2018*). Meanwhile, the age of patients undergoing IVF cycles has increased significantly, leading to the wide use of PGT-A in order to improve embryo selection and the pregnancy rates per embryo transfer (*Franasiak et al., 2014*). The patient's age and the number of oocytes retrieved during the IVF treatment have a critical impact on clinical outcomes and have been considered independent pregnancy predictors (*Polyzos et al., 2018*; *Sunkara et al., 2011*). Indeed, for patients with poor reproductive prognosis according to the POSEIDON criteria (*Esteves et al., 2019*), each additional oocyte represents a significant improvement in live birth rates, especially in cases of advanced reproductive age (*Sunkara et al., 2011*).

Often, low responders and patients with a suboptimal reproductive profile require several ovarian stimulation cycles and oocyte or embryo vitrification to achieve a cost-effective approach and a successful outcome (*Vaiarelli et al., 2020a*). In recent years, folliculogenesis has been shown to occur in a wave-like pattern, replacing the theory of a single follicular recruitment episode during the menstrual cycle (*Baerwald et al., 2003*). Consequently, new stimulation protocols, such as luteal phase stimulation, random start stimulation and double stimulation (DuoStim) have emerged (*Vaiarelli et al., 2017*). Such strategies allow us to start ovarian stimulation at different times in the menstrual cycle, shortening the time required to complete reproductive treatments.

The DuoStim strategy comprises two consecutive stimulations in the same menstrual cycle, one in the follicular phase (FPS) and the other in the luteal phase (LPS). This seems to be an adequate strategy to obtain a greater number of oocytes and blastocysts per cycle, especially in low responders. Several studies have also reported a higher number of oocytes retrieved during LPS (*Alsbjerg et al., 2019*; *Kuang et al., 2014*; *Liu et al., 2020*; *Vaiarelli et al., 2018*). Most authors compared outcomes between FPS and LPS and showed similar results, but very few well-designed studies compared the reproductive outcomes when performing two conventional stimulations versus the DuoStim protocol. Thus, the purpose of this study was to validate the DuoStim strategy as a good alternative to two consecutive conventional ovarian stimulation cycles in poor-prognosis patients undergoing PGT-A, to improve euploidy rates and obtain the first euploid embryo in less time.

## MATERIALS AND METHODS

### Study design and population

A prospective randomized trial including patients aged ≥38 years old with poor reproductive prognosis as defined by the POSEIDON criteria (6): anti-Müllerian hormone (AMH) <1.2 ng/ml, Antral Follicular Count (AFC) <5, and previous ovarian response of <4 or 4–9 eggs retrieved. A total of 80 women with a suboptimal profile undergoing PGT-A cycles were blindly randomized into two groups: 39 patients underwent two ovarian stimulations in consecutive cycles (control group) whereas the DuoStim strategy was used for 41 patients (DuoStim group). A total of 28 patients per group fulfilled the complete treatments to which they were randomized (FIGURE 1).

### Procedures: ovarian stimulation protocol and oocyte retrieval

#### *Control group*

This group underwent two conventional ovarian stimulations in consecutive cycles using an antagonist protocol with individualized doses of gonadotrophins. Both ovarian stimulations started 5 days after the last contraceptive pill or 3 days after the onset of menstruation. When the leading follicle reached a mean diameter of 14 mm, patients were started on a daily dose of 0.25 mg gonadotrophin-releasing hormone (GnRH) antagonist. Final oocyte maturation was achieved with 0.2 mg of triptorelin when at least two follicles reached a mean size of 18 mm. Egg retrieval was performed 36 h later, and all

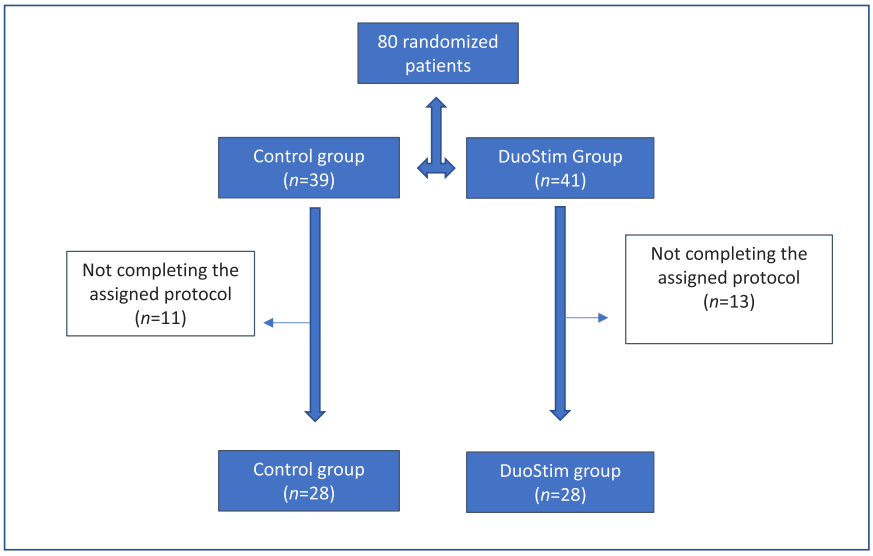


**FIGURE 1** Flow chart of the study population.

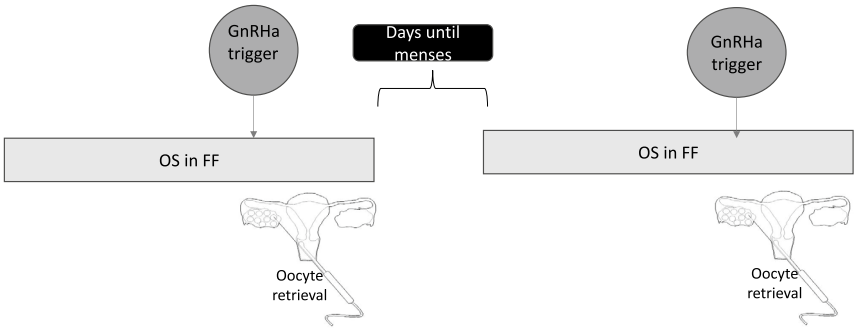


**FIGURE 2** Conventional protocol. FF =; GnRHa = gonadotrophin-releasing hormone antagonist; OS = ovarian stimulation.

the eggs were vitrified. The second ovarian stimulation started after menstruation in the following cycle, with a similar protocol. On the day of the egg retrieval, the first cohort of oocytes was thawed, and intracytoplasmic sperm injection (ICSI) was performed on all eggs (FIGURE 2).

### *DuoStim group*

FPS and LPS were performed using an antagonist protocol with individualized gonadotrophin doses. Like in the control group, the first ovarian stimulation started 5 days after the last contraceptive pill or 3 days after the onset of menstruation. When the leading follicle reached a mean diameter of 14 mm, patients were started on a daily dose of 0.25 mg GnRH antagonist. Final oocyte maturation was achieved with 0.2 mg of triptorelin when at least two follicles reached a mean size of 18 mm. Egg retrieval was performed 36 h later, and any follicles under 10 mm measured by ultrasound during the ovarian puncture were left, while all mature eggs were retrieved and vitrified. LPS started 5 days after the first egg retrieval using the same protocol, without the use of GnRH antagonist, because the high progesterone concentrations of the luteal phase are known to inhibit premature LH surges, except in women whose menses come in the middle of the second ovarian stimulation. On the day of the second egg retrieval, the first cohort of oocytes was thawed, and ICSI was performed on all eggs (FIGURE 3).

In both groups, embryos were cultured in a single droplet of culture media (Global Plus, Life Global) until day 5 or 6 and laser-assisted biopsy was used to facilitate the removal of 5–10 trophectoderm cells for PGT-A analysis. All blastocysts were frozen after this procedure (*Polyzos and Sunkara, 2015*).

## Outcomes

The main outcome measured was the euploidy rate based on an intention to treat (ITT) approach, and whether it was similar or different in the two groups, with less time required to obtain a euploid blastocyst in the DuoStim group, defined as the mean number of days between the first day of stimulation and the day of the PGT-A biopsy.

Secondary outcomes included: days of stimulation (expressed as mean ± SD), dose of gonadotrophin (mean ± SD), number of eggs, number of metaphase II (MII) oocytes, fertilization and blastulation rates, the number of euploid embryos obtained, ITT pregnancy rate (defined as the number of patients with a appositive serum concentration of Human Chorionic gonadotropin (HCG) per randomized patient), miscarriage rate (the number of spontaneous pregnancy losses in which gestational sacs were previously observed, per number of pregnancies) and ITT live birth rate (number of deliveries that resulted in at least one live birth per randomized patient). The study also compared between FPS and LPS results in the DuoStim group, and the pregnancy, miscarriage and live birth rates were calculated per transfer.

## Ethical approval

All the included participants signed an informed consent. The final version of the study protocol was approved by the IVI Madrid Institutional Review Board (1704-MAD-025-MC, approved 18 October 2017), in compliance with Spanish legislation on ART (14/2006). This trial was registered in Clinical Trials under NCT03291821 in 2017.

## Statistical analysis

Sample size calculation was conducted considering an approximate euploid embryo rate of 27% in the case of PGT-A cycles for conventional stimulation and an effect size of 10%; a sample size of 120 patients (60 patients per group) is

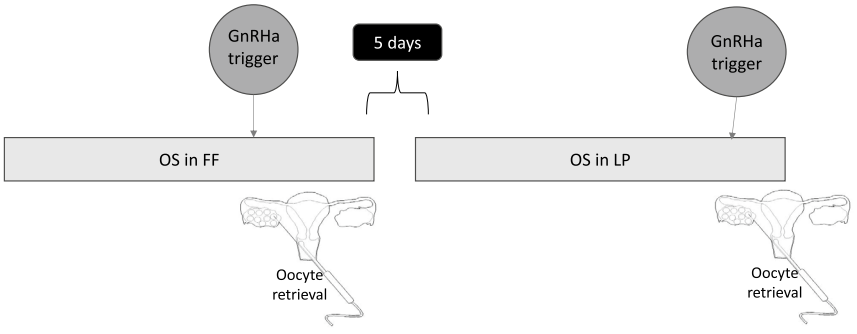


**FIGURE 3** DuoStim protocol. FF =; GnRHa = gonadotrophin-releasing hormone antagonist; LP = luteal phase.

estimated to obtain a power of 80% with 0.05 error. A loss rate of 10% was considered in the calculations.

Interim analysis was planned to decide on the continuation of the trial with 60% of patients recruited for the main outcome measure. This analysis was two-sided, establishing an alpha risk of 0.05, a beta risk of 10%, 90% conditional power to accept H1 and 80% for H0, by means of the Stochastic curtailment method (*Davis and Hardy, 1994*) using Macro!SCCT v 2007.09.27, for SPSS. The study was planned for 120 patients, and the analysis was performed after having recruited 80 patients.

Women were randomly assigned in a 1:1 ratio via a computer-generated randomization system included in the Electronic Medical Record. Randomization was not stratified. Researchers, embryologists and patients were not blinded to treatment allocation. The variables were expressed as mean ± SD. Analysis of variance was used for quantitative variables, while the chi-squared test was applied for qualitative variables. In the comparison between FPS and LPS in the DuoStim group, variables with normal distribution were compared as paired samples based on Student's *t*-test, whereas the Wilcoxon signed-rank test was used for those with non-normal distribution. Statistical significance was set at a two-tailed *P*-value of <0.05.

## RESULTS

### Clinical characteristics of patients

The baseline characteristics of the 80 patients recruited, including age, AMH concentrations, antral follicular count (AFC) and body mass index are shown in TABLE 1. The mean age was higher in the DuoStim group (39.9 ± 2.4 versus 39.0 ± 2.3 years old), but the AMH concentrations (0.84 ± 0.6 versus 0.87 ± 0.6), AFC (5.5 ± 2.9 versus 5.2 ± 1.2) and BMI (21.9 ± 2.6 versus 21.6 ± 2.7 kg/m$^2$) were similar between groups. Both groups consisted of patients with a suboptimal IVF profile.

### Main outcomes

When euploidy rates were defined as the mean euploidy rate per randomized patient, based on the ITT approach, also accounting for patients who dropped out of the trial, they were 16.1% (95% confidence interval [CI] 6.2–26.0) in the control group and 22.7% (95% CI 11.6–33.9) in the DuoStim group, with non-significant *P*-values of 0.371.

The euploidy rate, defined as the percentage of euploid embryos out of the total number of embryos analysed per group (39 in the DuoStim group and 59 in the control group), was 39.0% with a 95% CI of 26.5–51.4 in the DuoStim group and 45.7% with a 95% CI of 29.2–62.2 in the control group, resulting in a non-significant *P*-value of 0.679138.

When euploidy rates were considered as the mean euploidy rate per patient receiving the full treatment to which they were randomized, undergoing PGT-A analysis, 38.55% with a 95% CI of 22.4–54.7 of the embryos were euploid in the control group, and 38.9% with a 95% CI of 19.0–58.8 in the DuoStim group, with non-significant *P*-values of 0.976.

### Interim analysis results: early suspension of the trial

*Z*-values calculated to decide whether to stop the trial based on net beneficial/harmful effects were >3.66411, corresponding to *P*-values = 0.00025. On the other hand, the *Z*-value threshold to stop the trial due to lack of power was 0.06972, corresponding to *P*-values = 0.48567.

Based on the above-mentioned comparison, a *P*-value of 0.976 exceeded the stopping threshold due to lack of power, meaning that with the results obtained so far, there was a significantly high probability that no statistical differences would be confirmed at the end of the study.

The trial was stopped after the interim analysis, due to lack of power, and the secondary outcomes were analysed. The ethics committee was informed of the end of the trial.

### Characteristics of ovarian stimulation and IVF laboratory outcomes

When comparing the control group and the DuoStim group, there were no significant differences in the total mean days of stimulation (21.3 ± 1.6 versus 23.0 ± 1.4 days; *P* = 0.10), amount of gonadotrophins required (4005 ± 450 versus 4245 ± 430 IU; *P* = 0.43), number of MII oocytes (8.7 ± 1.8 versus 6.8 ± 1.7; *P* = 0.15), fertilization rates (55.1% versus 54.7%, *P* = 0.95), total biopsied blastocysts (2.1 ± 0.5 versus 1.5 ± 0.6, *P* = 0.10) or number of euploid embryos (0.8 ± 0.4 versus 0.6 ± 0.4; *P* = 0.45). However, there was a significant difference in the average number of days required to obtain a euploid blastocyst, favouring the DuoStim group (44.1 ± 2.0 versus 23.3 ± 2.8 days; *P* < 0.001). Similarly, there were no statistical differences between the groups in the implantation rate (64.3% versus 66.7%; *P* = 0.35), pregnancy rate per ITT (23.1% versus 24.4%; *P* = 0.33), miscarriage per ITT (0% versus 0.05%; *P* = 0.80) or live birth per ITT (23.1% versus 19.5%; *P* = 0.49) rates. These data are shown in TABLE 2.

### Comparison between FPS and LPS in the DuoStim group

LPS took significantly longer (10.3 ± 0.8 versus 12.7 ± 0.9 days; *P* < 0.001) and required higher gonadotrophin doses, although with borderline statistical significance (1937 ± 300 versus 2396 ± 350; *P* = 0.04). However, the number of eggs retrieved was similar in both phases (4.1 ± 1.0 versus 5.1 ± 1.5; *P* = 0.23), as was oocyte maturity (3.3 ± 1.0 versus 3.6 ± 1.2; *P* = 0.65).

Regarding IVF laboratory outcomes, a significantly higher fertilization rate was observed in the LPS (49.1% versus 64.4%; *P* = 0.03), as well as a higher number of biopsied blastocysts (0.5 ± 0.1 versus 1.5 ± 0.3; *P* = 0.04), but the number of euploid embryos obtained in both phases was similar (0.2 ± 0.1 versus 0.5 ± 0.1; *P* = 0.20). The implantation (75% versus 77.8%; *P* = 0.70) and pregnancy (75%

**TABLE 1 BASAL CHARACTERISTICS**

| Characteristic | Control group (*n* = 39) | DuoStim group (*n* = 41) |
|---|---|---|
| Age (years) | 39.0 ± 2.3 | 39.9 ± 2.4 |
| AMH (ng/ml) | 0.87 ± 0.6 | 0.84 ± 0.6 |
| AFC | 5.5 ± 2.9 | 5.2 ± 2.8 |
| BMI (kg/m$^2$) | 21.9 ± 2.7 | 21.6 ± 2.7 |

Data are presented as mean ± SD.

AFC = antral follicle count; AMH = anti-Müllerian hormone; BMI = body mass index.

**TABLE 2 OUTCOMES OF CYCLES FOR BOTH GROUPS**

| Outcome | Control group (*n* = 39) | DuoStim group (*n* = 41) | *P*-value |
|---|---|---|---|
| Days of stimulation | 21.3 ± 1.6 | 23.0 ± 1.4 | 0.10 |
| Dose of gonadotrophin (IU) | 4005 ± 450 | 4245 ± 430 | 0.43 |
| No. of oocytes | 13.4 ± 2.5 | 9.2 ± 2.1 | 0.01 |
| No. of MII oocytes | 8.7 ± 1.8 | 6.8 ± 1.7 | 0.15 |
| Fertilization rate (%) | 55.1 | 54.7 | 0.95 |
| Total no. of blastocysts | 2.1 ± 0.5 | 1.5 ± 0.6 | 0.10 |
| Blastocyst rate (%) | 51.4 | 34.8 | 0.11 |
| No. of euploid embryos | 0.8 ± 0.4 | 0.6 ± 0.4 | 0.45 |
| Implantation rate (%) (no. of sacs/no. of embryo transfers) | 64.3 (9/14) | 66.7 (10/15) | 0.35 |
| Pregnancy rate (%) | | | |
| ITT | 23.1 (9/39) | 24.4 (10/41) | 0.33 |
| Per transfer | 64.3 (9/14) | 66.7 (10/15) | 0.28 |
| Miscarriage rate (%) | | | |
| ITT | 0.0 | 0.05 (2/41) | 0.80 |
| Per transfer | 0.0 | 13.3 (2/15) | 0.36 |
| Live birth rate (%) | | | |
| ITT | 23.1 (9/39) | 19.5 (8/41) | 0.49 |
| Per transfer | 64.3 (9/14) | 53.3 (8/15) | 0.41 |
| Time to euploid embryo (days) | 44.1 ± 2.0 | 23.3 ± 2.8 | <0.001 |

Data are presented as mean ± SD unless otherwise stated.

ITT = intention to treat; MII = metaphase II.

versus 77.8%; $P = 0.69$) rates were similar in both groups, whereas the miscarriage rate was 25% versus 12.5% ($P = 0.23$) and the live birth rate was 50% versus 66.7% ($P = 0.59$). These data are summarized in TABLE 3.

## DISCUSSION

From these results, it can be concluded that the DuoStim protocol is not improving the mean euploidy rates compared with conventional stimulation, as the ITT analysis reveals. An early suspension of the trial was decided, based on the interim analysis and lack of power when 60% of patients were recruited.

The current study also suggests that the DuoStim strategy offers patients with poor reproductive prognosis an alternative that allows them to obtain a euploid embryo in less time compared to two conventional stimulation cycles, without affecting other outcomes. No differences were found in total days of stimulation, gonadotrophin doses, number of retrieved and mature eggs, or even in fertilization and blastulation rates, or in the number of euploid embryos obtained. The single parameter showing a significant difference was the time required to obtain a euploid embryo. This could represent an important advantage for poor-prognosis patients, because it shortens the time to pregnancy and may decrease the dropout rate (*Vaiarelli et al., 2020b*).

**TABLE 3 DUOSTIM GROUP, COMPARATIVE CYCLE PARAMETERS BETWEEN FPS AND LPS**

| Parameter | FPS | LPS | *P*-value |
|---|---|---|---|
| Days of stimulation | 10.3 ± 0.8 | 12.7 ± 0.9 | <0.001 |
| Dose of gonadotrophin | 1937 ± 300 | 2396 ± 350 | 0.04 |
| No. of eggs | 4.1 ± 1.0 | 5.1 ± 1.5 | 0.23 |
| No. of MII (mature eggs) | 3.3 ± 1.0 | 3.6 ± 1.2 | 0.65 |
| Fertilization rate (%) | 49.1 (54/110) | 64.4 (76/118) | 0.03 |
| Total no. of blastocysts | 0.5 ± 0.1 | 1.5 ± 0.3 | 0.04 |
| Blastocyst rate (%) | 24.1 (13/54) | 46.1 (35/76) | 0.01 |
| No. of euploid embryos | 0.2 ± 0.1 | 0.5 ± 0.1 | 0.20 |
| Implantation rate (%) | 75 (3/4) | 77.8 (7/9) | 0.70 |
| Pregnancy rate (%) | 75 (3/4) | 77.8 (7/9) | 0.69 |
| Miscarriage rate (%) | 25 (1/4) | 12.5 (1/8) | 0.23 |
| Live birth rate (%) | 50 (2/4) | 66.7(6/9) | 0.59 |

Data are presented as mean ± SD unless otherwise stated.

FPS = follicular phase stimulation; LPS = luteal phase stimulation.

An ever-increasing number of couples rely on treatment with ART to conceive a child. Although advances in embryo culture have led to increases in the success rates of clinical ART, it often takes more than one treatment cycle to conceive a child (*Ferrick et al., 2019*). The time to complete an IVF programme can be reduced if practices are modified based on the most up-to-date research, using a patient-tailored approach. 'Time to pregnancy' is an essential concept in human reproduction, which explains the increasing interest and clinical relevance of shortening treatment times and the overall time to a successful outcome (*Bosch et al., 2019*). Any intervention that could shorten the time to pregnancy should be considered beneficial because

it offers less stress, fewer visits, and perhaps less anxiety compared with longer treatments.

It is well known that there are two variables that have an important impact on treatment results, namely a woman's age and the number of retrieved oocytes, because it has been shown that, as a woman gets older, more oocytes are required to obtain at least one euploid embryo and, ultimately, a newborn (*Ferrick et al., 2019*; *Polyzos et al., 2018*; *Vaiarelli et al., 2018*). Based on these results, we recommend the DuoStim protocol to our suboptimal patients to obtain a higher number of oocytes for later preimplantation genetic diagnosis. The results of this study show that applying personalized treatment to poor-prognosis patients may significantly reduce the time to pregnancy. Moreover, when we used a DuoStim protocol *versus* two consecutive conventional stimulations, and continued applying PGT-A in both groups, we observed that it also took less time to obtain a euploid embryo, which is considered a key performance indicator to help determine the effectiveness of the treatment. It has been reported that PGT-A enables more viable embryos to be transferred earlier and reduces the risk of miscarriage, so it can be expected to decrease the time to pregnancy (*Franasiak et al., 2017*; *Rubio et al., 2017*); DuoStim, on the other hand, offers advantages related to a potentially increased number of oocytes retrieved over a short period of time (*Bosch et al., 2019*). The combination of both strategies highlights our focus on timely and individualized care for infertile patients, as we try to maximize the ovarian response and the likelihood of success in poor-prognosis patients while decreasing the risk of discontinuation associated with no embryo transfer (*Vaiarelli et al., 2020b*).

All previously published studies on DuoStim compared follicular versus luteal phase outcomes. At this point, it should be emphasized that the current results agreed with those of other authors (*Alsbjerg et al., 2019*; *Cecchino et al., 2020*; *Ubaldi et al., 2016*; *Vaiarelli et al., 2020a*) in terms of longer stimulation periods and higher gonadotrophin doses in LPS, in contrast to other studies that reported no differences between the two stimulation phases analysed (*Liu et al., 2017*). Although the current results did not show a higher oocyte yield in the luteal phase, we did find higher fertilization and blastocyst development rates. Among the reasons that could explain this circumstance is the fact that the oocytes were vitrified after the FPS; however, the literature published to date does not support this claim. Finally, in agreement with other authors, the euploidy rate is similar for both stimulation phases, which means that LPS does not worsen clinical results and allows us to shorten the time required to obtain a euploid embryo (*Franasiak et al., 2017*).

The main limitation of the study is the final sample size, which contributes to reducing the statistical power. Although it reached a statistical power of 70% and, to the best of our knowledge, it is the first randomized trial to compare DuoStim to two conventional stimulations, larger randomized clinical trials and cost-effectiveness studies are needed.

In summary, DuoStim could be considered an alternative in cases where it is necessary to obtain a higher number of oocytes in the shortest possible time, to decrease the time required to obtain euploid blastocysts and minimize treatment discontinuation. These aspects play a crucial role in reducing the dropout rate in poor-prognosis patients without compromising the overall efficacy of the treatment.

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