

**THE USE OF DOUBLE OVARIAN STIMULATION (DUAL-STIM) AND ITS PECULIARITIES: A
REVIEW**

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Propose of review

Double Ovarian Stimulation (Dual-Stim) is a strategy increasingly used in daily clinical practice by several fertility centers. Without contraindications, it presents promising results and varied indications. The purpose of this review is to provide updated information on this technique, the results obtained even now and its peculiarities.

Recent findings

Originating in emergency controlled ovarian stimulation (COS) protocol in cancer patients, Dual-Stim has spread widely in daily clinical practice for presenting good tolerability by patients. With similar or even better results than those obtained in conventional stimulation cycles, the technique is mainly used in patients with a poor prognosis, resulting in a greater amount of oocytes obtained per menstrual cycle.

With motherhood postponed by contemporary women, the use of genetic aneuploidy screenig (PGT-a) is increasingly recommended. As a limited number of oocytes are obtained in women of advanced age, and with improvements in oocyte freezing techniques, Dual-Stim has been proposed with the aim of optimizing the chances of obtaining euploid embryos and decreasing dropout rates from reproductive treatments.

Summary

This article provides an overview of the use of Dual-Stim, its results and indications, as also a comparison with the results obtained in conventional stimulation cycles.

Keywords

Ovarian stimulation, dual-stim, follicular waves recruitment, oocytes, embryos and life Birth rates.

INTRODUCTION

Since the emergence of controlled ovarian stimulation (COS) techniques, one of the greatest challenges for specialists in human reproduction is the customization and optimization of treatments aimed at patients with an unfavorable prognosis, which affects up to 24% of women undergoing in vitro fertilization (IVF) ^{1, 2}. The exponential increase in the number of poor responders is also due to the strong and increasing insertion of women in the labor market, which has considerably increased late maternity rates ³.

Knowing that women have limited reproductive potential, with progressive depletion of the follicular population throughout their lives, truly effective strategies for the management of these patients are constantly being sought, as well as more specific ways of classifying them ⁴.

In order to standardize the classification of infertile patients in poor responders, in 2011 the Bologna criteria were developed by ESHRE. Soon after, the POSEIDON group also proposed some changes in these concepts creating subgroups of more homogeneous classifications, and the concept of sub-optimal response. This new classification system should help doctors and patients to promote shorter times until pregnancy ^{2,5}.

Therefore, to optimize the treatments of this population, different strategies have emerged aiming at obtaining more oocytes and embryos in the shortest possible time². Stimulations with high dosages of different classes of gonadotropins, antioxidants, use of pre-stimulation androgens, inositol, melatonin and other alternative treatments have shown varied results and their use has remained in constant contradiction in the current Scientific Society ^{6,7,8,9}.

In parallel, emergency COS protocols were also created for cancer patients, in which the need to obtain oocytes quickly to preserve fertility prior to gonadotoxic treatments is essential. In addition, the survival of these women has progressively increased in recent years, with advances in early diagnosis methods and their more effective treatments, making possible future pregnancies feasible ¹⁰.

Immediately after starting treatment their COS is performed, often in the luteal phase of the menstrual cycle. In principle doubts arose about the real possibility of obtaining oocytes with this strategy, given the concept widely accepted and widespread in the literature about a single wave of follicular recruitment per menstrual cycle ^{11,16}.

However, recently conducted studies have shown similar amounts of oocytes obtained in these situations when compared to “classic” stimulation. In assessing the quality of these gametes, embryonic development capacity comparable to standard protocols also confirmed their viability ¹².

Taking this into consideration, two ovarian stimulations were then proposed in the same menstrual cycle, in order to optimize the results of reproductive treatments. Without presenting the classic ovarian rest between the follicle aspiration and the beginning of treatments with gonadotropins, the subsequent stimulation begins only 5 days after the extraction of oocytes (in luteal phase), receiving the name of Dual-Stim.

Knowing that the live births rates is proportional to the amount of oocytes obtained during fertility treatments, strategies such as this would provide higher success rates by intention to treat, with good treatment tolerability ¹².

Therefore, this strategy started to be used mainly in patients with poor prognosis, where the obtaining of oocytes per stimulation is small, and the need to perform multiple stimulation until obtaining a significant amount of oocytes to fertilize and generate a viable embryo can take time ^{10,12,13}.

CHARACTERISTICS OF DUAL-STIM

The main objective of dualstim is to increase the amount of oocytes obtained, fertilized, and consequently embryos generated, in the shortest possible time. Responding poor prognosis patients seem to be the population that most benefits from this strategy, since obtaining transferable embryos in this population may take long periods.

An observational study conducted between 2015 and 2017 compared poor responders who underwent Dual-Stim with patients who underwent two conventional COS. The study concluded that the use of luteal stimulation significantly decreased treatment abandonment. Agreeing with studies that pointed out the failure to obtain transferable embryos in the first attempt (even if in free IVF / ICSI cycles) as the main cause of abandonment of reproductive treatments.

The psychological impact exerted by reproductive treatments can also be mitigated with this strategy, since it can decrease the time that the patient remains in medical treatment. This study highlighted that the time until the transfer of the euploid embryo was considerably reduced when Dual-Stim was used ^{10,22}.

In addition, due to the increase in the average age of patients who seek maternity, a considerable increase in pre-implantation genetic diagnosis (PGT-a) has been reported ^{14,15}. These patients, when submitted to PGT-a, have a high risk of not obtaining a viable embryo. Thus, increasing the number of available oocytes would also increase the chances of finding a healthy embryo and achieving embryo transfer.

Recently, Dual-Stim was proposed as an alternative to accumulate oocytes before the final cycle in which they will be fertilized, cultured and biopsied. Strategies like this would provide higher success rates per intention to treat, with good tolerability to treatment ^{12,15,16,17}.

The viability of these treatments is also due to the important improvement of oocyte freezing techniques, mainly due to the discovery of vitrification. Similar live births rates between fresh versus frozen embryos have been reported in recent years, breaking existing paradigms about the impact of freezing on gametes, and possible interference with embryonic metabolism. With this technique, the generated embryos are usually frozen before transfer, as the trigger is usually performed with a GnRH agonist to prevent Ovarian Hyperstimulation Syndrome (OHSS) ^{12,13,21}.

QUALITY AND POTENTIAL DEVELOPMENT WITH OOCYTE FROM DUAL STIM

In order to prove the quality and viability of the gametes obtained in the two COS of Dual-Stim, a prospective study included 42 patients with low ovarian reserve submitted to PGT-a, and compared the blastocyst formation rates in the same ovarian cycle between stimulations. The results did not show any significant differences, since the rates of MII oocytes, biopsied and euploids embryos were similar between groups. Therefore, this study points to similar viability of the gametes obtained in both phases of the menstrual cycle, without discrepancies also in the risk of aneuploidies^{12,23}. Chen had previously published that the incidence of birth defects was not higher in embryos obtained in luteal phase²⁴. The birth weight and the length of the newborns from both stimulations appear to be the same, however a greater number of embryos transferable by menstrual cycle was observed with Dual-Stim¹².

Also with the aim of assessing embryonic viability, a prospective study published in 2014 analyzed 242 patients. Excellent results were found in clinical pregnancy rates in cycles of transfer of frozen embryos from the luteal phase (55.4%), as well as ongoing pregnancy rates (48.9%). This study confirmed that luteal ovarian stimulation is viable for the production of competent oocytes and embryos in women undergoing IVF / ICSI treatments²⁹.

If we focus on embryonic development, Vairelli et al. also conducted a study with 310 poor responders patients who underwent Dual-Stim and PGT-a. The general rates of fertilization, blastocyst and euploid blastocyst were also similar in FPS and LPS. After stimulation in the follicular phase 131 (42.3%) obtained at least one euploid blastocyst and 129 (41.6%) at LPS, respectively²³.

This work demonstrates that the oocyte freezing process performed in the oocytes generated in the follicular phase does not interfere with its embryo metabolism and in your capacity of development. The high concentrations of estradiol present during luteal stimulation did not cause any apparent damage to the gametes subsequently obtained.

Two years earlier, Ubaldi et al. published that the rates of aneuploidies were also similar among blastocysts obtained after stimulation of FPS and LPS, with similar rates of simple / double and complex aneuploidies. In this study, stimulation in the luteal phase increased the rate of patients with at least one possible transfer of euploid embryo from 41.9% to 69.8%. Dual-Stim was successful for this group of patients, resulting in a similar number of MII oocytes after stimulation in FPS and LPS. The competence of in vitro development for the blastocyst stage was also similar, and with PGT-A no statistically significant difference was found in the proportion of euploid blastocysts derived from both stimulations¹².

Therefore, studies show that the quality of the gametes obtained in the FPS and LPS of the dualstim are matched, without differences in the rates of blasturation and

aneuploidy. A significant percentage of patients would not have transferable embryos if they had not undergone Dual-Stim, which confirms its clinical usefulness.

FOLLICLE ASPIRATION FROM DUAL-STIM CYCLES

Previously, we mentioned that the use of this technique in well-indicated cases can result in shorter times until embryo transfer, pregnancy and lower abandonment of treatment rates, since a greater amount of oocytes per menstrual cycle is obtained. However, some recent studies have reported a greater amount of oocytes obtained in the luteal phase of Dual-Stim when compared to follicular stimulation. This curious fact can be justified by the better synchrony in the follicular development in the luteal phase, probably by the high concentrations of estradiol (E2) from the first stimulation ^{18,19,20}.

In 2018, a case control study published these findings. Luteal phase stimulation resulted in a greater amount of captured oocytes and developed blastocysts, however embryonic competence was similar between groups. The authors hypothesize that the flare-up effect of the trigger with GnRH agonist performed in the follicular phase may justify these findings ²⁵.

Another study led by Yanqun Luo published in 2020 also found interesting results. In the analysis performed on 304 patients classified by the Bologna criteria as poor responders who underwent Dual-Stim, luteal phase stimulation resulted in a greater amount of oocytes, embryos and clinical pregnancy when compared to follicular stimulation. Another analysis carried out within this same population showed that better results were obtained by performing the trigger with GnRh-A and recombinant HCG compared to urinary HCG in both phases of the cycle stimulation ²⁸.

Unlike that, the supremacy of luteal stimulation in dual-stim was not evidenced in Shanghai in a study of 30 women in 2013. The rates of oocytes and mature oocytes obtained in both phases of stimulation were similar. Similar results were published years later by Tsampras et. al, where no stimulation has shown better results ^{16,26}.

Regardless of whether Dual-Stim luteal stimulation has the same or greater amount of oocytes, mature oocytes and embryos generated, the strategy is a viable alternative that must be considered in reproductive treatments.

CONCLUSION

Dual-Stim is a current and promising technique, which should be proposed for patients undergoing in-vitro fertilization treatments, especially women poor responders or cancer patients. Studies show less abandonment of treatment and greater amount of oocytes and embryos obtained by menstrual cycle when compared to classic stimulations. The oocytes obtained and the embryos generated from the FPS and LFS of the dualstim seem to match the rate of maturity, embryonic development and aneuploidy. The technique also maximizes the chances of pregnancy by menstrual cycle.

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KEY POINTS

- Dual-Stim is indicated especially for low responders or previously to gonadotoxic treatments.
- Its use seems to decrease the rates of abandonment to reproductive treatment and maximizes the chances of getting embryos transferable by menstrual cycle.
- The luteal phase stimulation produces similar or even greater amounts of oocytes when compared to follicular phase stimulation.
- Embryos produced in both phases of stimulation do not appear to differ in relation to aneuploidies.