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REVIEW

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Double Ovarian Stimulation in the Same Ovarian Cycle

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ABSTRACT

The theory of multicyclic development of follicles during the menstrual cycle prompted new approaches to ovarian stimulation such as double stimulation within the same menstrual cycle, in both follicular and luteal phases. New stimulation approaches, together with cryopreservation techniques, provide higher chances for patients with poor ovarian response who undergo in vitro *fertilization (IVF) to get pregnant. The double ovarian stimulation protocol has been proposed to optimize the number of oocytes retrieved within the shortest possible timeframe. Moreover, the short overall duration of this strategy is also useful in cases of a fertility preservation that requires rapid intervention before administering a gonadotoxic therapy, such as in oncologic therapy. In general, the aim of DUOSTIM is to obtain the highest number of oocytes in the shortest time, thus avoiding waste of time, which is crucial for these patients. Several protocols have been proposed with similar results, regardless of the protocol used.*

Keywords: DuoStim, poor ovarian response, IVF, number of oocytes, fertility preservation.

INTRODUCTION

Nowadays, with the primary focus of women being on their career, there is an increased number of women who delay pregnancy and therefore must rely on assisted reproductive technology. This poses a great challenge for experts because finding an efficient ovarian stimulation protocol is difficult, and on the other hand, not every time oocyte donation is accepted. Furthermore, women aged over 40 years have a risk of 76% of aneuploidy for their blastocysts. Also, the ovarian response is not ideal and worsens with the time between treatments (1). The number of oocytes used in IVF is directly related to the reproductive outcome. Patients with few oocytes are less likely to get preg-

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nant and represent a challenge for experts. Therefore, with double stimulation within the same menstrual cycle in a shorter amount of time, a bigger number of oocytes can be obtained, resulting in a higher chance of getting an euploid embryo with potential for implantation and an ongoing pregnancy. Using an aggressive stimulation can not only lead to hyperstimulation but also lower the oocytes quality due to the risk of premature luteinization (1).

In order to undergo DuoStim, a patient has to be included in the poor responder category. A minimum of two of the subsequent characteristics must be present to define "a poor responder patient": advanced maternal age (>40 years) and/or scarce response to a previous conventional stimulation (three oocytes) and/or reduced ovarian reserve [antral follicle count (AFC) <5–7 follicles, and/or anti-Müllerian hormone (AMH) <1.1 ng/mL] (2). The prevalence of this condition is difficult to determine, but it has been estimated to range between 9% and 24% (3).

MATERIALS AND METHODS

Here we report a systematic literature search in PubMed database in order to select full-length articles that were published in English in peer-reviewed journals up to the 18th of September 2020, using the following keywords: DuoStim; double stimulation strategy, double ovarian stimulation, IVF, poor ovarian response (POR), luteal phase ovarian stimulation (LPS), follicular phase stimulation (FPS), fertility preservation, poor responders, reduced ovarian reserve, follicular waves.

The present review considered only studies using the same keywords that we used in our search strategy. Furthermore, we included only articles published during the last five years, that were specifically guided on the topic at hand, each of them with more than 50 stimulation cycles. We excluded articles older than five years, that had less than 50 stimulation cycles in total and either did not focus on the topic of our interest or had no significant or clear results.

Our primary outcome consisted of mean number of mature oocytes and clinical pregnancies, while the secondary outcome comprised ongoing pregnancies rate and live birth rate.

RESULTS

Using the search algorithm based on specific keywords on PubMed, we found 606 relevant articles published between 1966 and 2020. Out of those, we selected only full-text articles

TABLE 1. Summary of the clinical studies reporting DuoStim

Study	No. of patients	Mean age (y. o)	AMH level (ng/mL)	AFC	Mean number of oocytes collected		Mean number of mature oocytes		Clinical pregnancies	OPR	LBR
					FPS	LPS	FPS	LPS			
Bourdon et. al.	77	35.05±4.82	1.63±1.06	9.07±4.50	5.2±3.38	3.83±3.14	4.49±3.05	3.25±2.86	NR	NR	NR
Vaiarelli et. al.	100	42.1±1.4	0.56±0.3	3.8±1.2	237	309	70	107	15	15%	15%
Alsbjerg et. al.	54	36.7±3.6	NR	4.4±1.9	2.4	3.7	NR	NR	13	24%	NR
Madani et. al.	121	37.46±4.84	0.52±0.51	2.33±2.59	1.5±1.16	1.50±1.98	1.44±1.04	1.20±1.59	16	19.7%	16%
Liu et. al.	116	42.12±2.68	0.77±0.98	6.72±5.23	270	406	NR	NR	11	22%	NR
Zhang et. al.	153	37.62±5,98	0.46±0.32	3,1±1,3	2.2±1.6	3.3±2.6	2.03±1.53	3.16±2.55	10	31.25 %	NR
Cardoso et. al.	54	40.9	NR	NR	11.7		9.23		NR	NR	NR
Zhang et. al.	61	39.9±4.7	NR	5.3±2.9	22/4±1.5	2.7±2.1	57	72	31	33%	25.5 %
Wald et. al.	90	38	NR	8	NR	NR	NR	NR	NR	NR	NR

AFC=antral follicle count; AMH=anti-Müllerian hormone (ng/mL); FPS=follicular phase stimulation; LBR=live birth rate; LPS=luteal phase ovarian stimulation; NR=not reported; OPR=ongoing pregnancy rate describing studies performed on a population of adult females aged between 19 and 44 years old (y. o.) that were published over the last five years in trusted journals and which were written by experts in the field.

In the final analysis we included nine articles that were published between 2016 and 2020 and which matched our inclusion and exclusion criteria.

DISCUSSION AND CONCLUSION

Bourdon M *et al.* conducted a study on 77 women who completed the first controlled ovarian stimulation (COS 1) and began the second conventional ovarian stimulation (COS 2). The subjects' mean age, mean AMH level and mean AFC were 35.05±4.82 y. o., 1.63±1.06 ng/mL, and 9.07±4.50, respectively. Of these 77 women, 53 were poor responders who underwent a double stimulation for infertility, while 24 received a double stimulation for fertility preservation. For the intention to treat population, the number of oocytes retrieved and the number of metaphase II (MII) oocytes were higher after the COS 1 than after the COS 2. The duration of the stimulation and the total dose of injected gonadotropins were lower, and the estradiol (E2) level on the trigger day was significantly higher for COS 1 than COS 2 (4).

Maria Cecilia de Almeida Cardoso *et al.* performed 54 cycles of DuoStim for IVF and 11 for fertility preservation (1). Of these 54 IVF DuoStim cases, 13 patients had been previously submitted to IVF with conventional antagonist protocol stimulation (1). The authors analyzed the two treatment cycles from each of the 13 patients, comparing the quantity of oocytes collected, mature oocytes collected, fertilization rates, blastocyst rates, biopsied blastocyst rates and euploidy rates. The subjects' mean age was 40.9 years (37–44 y. o.). Five patients were classified as poor responders. The mean number of oocytes collected was 6.7 in the antagonist cycle and 11.7 in the DuoStim group. Of the oocytes collected, the mean number of mature oocytes was 5.3 in the conventional group and 9.23 in the DuoStim group. There was no statistical difference in fertilization and blastocyst rates (1).

In the study of Vaiarelli *et al.*, 91 of 100 patients who underwent DuoStim completed both stimulations. There were no complications after a repeated oocyte retrieval in a single menstrual cycle. The number of oocytes after FPS and LPS was 237 and 309, respectively. The number of blastocysts after FPS and LPS was 70 and 107, respectively. The number of euploid blastocysts after FPS and LPS was 14 and 21, respectively (5). Only two patients obtained euploid blastocysts from both FPS and LPS (5). In the DuoStim group, all patients underwent two ovarian stimulations, whereas in the single COS group only 9% of them returned for a second COS, as they did not achieve a pregnancy after the first try. After DuoStim, more women obtained and transferred a minimum of one euploid blastocyst compared to two conventional COS. The time between the first and second oocyte retrieval was shorter between FPS and the following LPS (2.6-15.8 days) than between a primary and a secondary conventional COS (83.6-141.4 days). The number of patients who were not pregnant and returned for a second attempt in the conventional COS group, during the study period, was significantly lower (5).

Alsbjerg *et al.* conducted a study on 54 patients aged less than 42 (mean age 36.7 years). The mean AFC was 4.4 and it was measured on the first day of stimulation in the FPS. Besides the diagnosis of POR, 45 patients had also a secondary infertility diagnosis (6). The mean number of oocytes retrieved in FPS and LPS was 2.4 and 3.7, respectively (1.3 more oocytes were retrieved in LPS). In contrast, more FSH was consumed in LPS (1.37 times higher). Neither the number of embryos cryopreserved, nor the number of patients with no cryopreserved embryos differed significantly when comparing FPS to LPS. Only 6% (3/54) of patients did not have any oocytes retrieved at all. A total of 32 patients underwent at least one embryo transfer. The ongoing pregnancy rate (OPR) *per* transfer (week 12) was 24%. Thirty-six single embryo transfers (21 from FPS and 15 from LPS) resulted in five ongoing pregnancies; two of these pregnancies arose from 'FPS oocytes' and three pregnancies arose from 'LPS oocytes'. Four pregnant patients still have cryopreserved embryos (6).

Madani *et al.* reported that 17 of the 121 eligible patients who were enrolled in their study had their second stimulation canceled due the low AFC (<2); the remaining subjects (104) completed the two stages of stimulation protocol, with a total of 164 viable embryos obtained from double stimulations in 81 patients. The cancellation rate in the LPS was 19% due to no oocyte retrieval and no embryo formation (7). The clinical pregnancy and live birth rates after frozen embryo transfers were clinical pregnancy rate (CPR) of 19.7% and life birth rate (LBR) of 16%. The mean age was 37.46±4.84, BMI 26.40±3.61 and serum AMH level 0.52±0.51. The number of oocytes retrieved after both stimulations did not make a statistic difference, but the number of frozen embryos and fertilization rate were higher after FPS, suggesting a better quality of retrieved oocytes after FPS (7).

Liu *et al.* studied 116 patients with a mean age of 42.12±2.68 (range 38–48) years. Ovarian reserve markers were: mean basal FSH, 10.83±5.88 IU/l; mean AMH 0.77±0.98 ng/mL; mean estradiol 40.55±51.41 pg/ml; and mean AFC 6.72±5.23 follicles, and 49.14% of patients had at least one failed IVF attempt, suggesting that most enrolled cases were low ovarian reserve (8). The cancellation rate (37.07%) due to no available oocytes, immature oocytes, non-fertilization or poor-quality embryos in FPS was higher than in LPS. The number of oocytes retrieved, MII oocytes, fertilized oocytes, cleaved embryos, top-quality embryos and cryopreserved embryos in LPS increased, and the cancellation rate of no available embryos reduced significantly compared with FPS (8). Out of all 116 subjects receiving double stimulation, a total of 270 and 406 oocytes were collected in the FPS and LPS, respectively. Also, 81.90% (95/116) of all patients had viable embryos cryopreserved. No ovarian hyperstimulation syndrome (OHSS) occurred (8). Forty-eight cases underwent 50 cryopreserved embryo transfer cycles by January 2017. Four pregnancy cases originated from FPS and seven from LPS. The implantation rate (10.53% *vs* 10.67%) and early abortion rate (0 *versus* 14.29%) were comparable between embryos originating from FPS and LPS (8).

Zhang *et al.* evaluated 153 subjects with a mean age of 37.62±5,98 and a mean AFC of 3,1±1,3. The mean number of oocytes retrieved, MII oocytes and 2PN zygotes obtained were significantly higher for LPS than FPS. The rates of clinical pregnancy and embryo implantation increased progressively from pure follicular phase embryos to mixed embryos to pure luteal phase embryos. The clinical pregnancy rates were positively affected by endometrial thickness and embryo source, and negatively affected by age (9).

Zhang *et al.* reported no differences in AFC, BMI or baseline hormone levels (FSH, LH and E2) comparing the Luteal (Lu) and Follicular (Fo) groups. The subjects in Group Lu were older than the patients in Group Fo. Length of stimulation, dosage of human menopausal hormone (HMG) and MII oocyte rate in Group Lu were significantly higher than in Group Fo. There were no significant differences between the two groups on number of retrieved oocytes, fertilization rate, cleavage rate, and top-quality embryo rate [10]. There were no significant differences in clinical pregnancy rate (CPR), life birth rate (LBR), miscarriage rate, or ectopic pregnancy rate (one in group Lu and one in group Fo – both underwent laparoscopic surgery) between the two groups offered frozen-thawed embryo transfer (FET) (10). Comparison of the two protocols in the same patients with POR showed that there were no significant differences in length of stimulation and dosage of HMG between the Lu and Fo protocols performed in the same patients. The number of retrieved oocytes in luteal phase ovarian stimulation was significantly higher than in follicular phase ovarian stimulation. The MII oocyte rate was lower in the luteal phase ovarian stimulation protocol. Cleavage and top-quality embryo rates were not statistically different (10).

Wald *et al.* reported that 15 of 90 oncologic female patients who received more than one ovarian stimulation cycle for oocyte or embryo cryopreservation underwent back-to-back random-start FPS and were included in the case series. The main reason for using LPS was the low ovarian reserve and reduced response to the first stimulation cycle. LPS was not canceled in order to pursue cancer treatment earlier. The average age was 38 years and average AFC 8 (11). Fourteen out of the 15 women included in the study completed both FPS and LPS (one patient had both cycles canceled prior to egg retrieval due to a poor response). The average time to complete back-to-back random-start FPS was 33 days from the start of the FPS until the second oocyte retrieval in the luteal phase. The average time between FPS and LPS was nine days (11). Eleven out of 15 women at least doubled their oocyte or embryo yield relative to FPS. The mature oocyte rate, fertilization rate, and embryo yield were similar among FPS and LPS, but LPS was complicated by premature ovulation (11).

DuoStim decreases the time between the first and second oocyte retrieval. Hence, this is very important, especially in cases of infertility or patients needing cancer treatment and fertility preservation, where a longer waiting time can decrease the chances of pregnancy and increase the chance of abandonment. Most patients included in these studies had low ovarian reserve. The intention to treat population often has advanced age and reduced ovarian reserve or reduced response to the first stimulation cycle. By using DuoStim, the number of collected oocytes may increase, and a higher rate of women may obtain and transfer at least one euploid blastocyst even if the FSH consumption is higher in LPS. Furthermore, no ovarian hyperstimulation syndrome occurred. ❑

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