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ASSISTED REPRODUCTION TECHNOLOGIES

Study of two strategies to induce follicular wave emergence for assisted reproductive treatments (ART)—a preliminary trial

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Abstract
Purpose This study aimed to induce follicular wave emergence (FWE) using pharmacological (recombinant hCG administration) or mechanical (aspiration of dominant follicle) interventions in infertile women.
Methods Sixteen infertile women (≤35 years) with indications for in vitro fertilization due to tubal and/or male factor infertility were randomized into three groups: control (n=6), pharmacological (n=5) and mechanical (n=5) groups. Women in both experimental groups underwent serial transvaginal sonograms (TVS) from menstrual cycle day 10 until identification of a dominant follicle ≥15 mm. Women in the pharmacological group received 250 μg of recombinant-hCG to induce ovulation, and resumed serial TVS 2 days later. In the mechanical group, dominant and subordinate follicles ≥10 mm were aspirated, and daily TVS was resumed on the following day. An increased pool of follicles ≥5 and ≤9 mm after interventions characterized FWE. Women in the control group underwent ovulation induction (OI) with 150 IU/day of recombinant follicle-stimulating hormone started on menstrual cycle day 3 (D3). OI was started on the day of FWE in the experimental groups. Endometrial asynchrony with development of the embryo was expected in the experimental groups. Therefore, all viable embryos were cryopreserved and transferred in an endometrial-stimulated cycle.
Results The number of follicles ≥5 and ≤9 mm increased after the interventions in both experimental groups (p<.001), indicating induction of FWE. OI outcomes were similar among the groups.
Conclusions The pharmacological and mechanical interventions are efficient in inducing FWE; outcomes of OI synchronized with FWE should be further investigated.

Keywords Assisted reproductive treatment · Ovulation induction · Luteal phase · Follicular wave emergence

Capsule A follicular wave emergence can be elicited through pharmacological and mechanical interventions, but the outcomes of OI synchronized with FWE should be further evaluated

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Introduction

Proper use of exogenous gonadotropins for ovulation induction (OI) relies on a comprehensive knowledge of ovarian physiology [1]. According to the most accepted model of human folliculogenesis, follicles continuously and randomly grow from the primordial pool to reach the antral stage, acquiring follicle-stimulating hormone (FSH) and luteinizing hormone receptors [2–5]. The early follicular phase of the menstrual cycle is propitious for follicular development, while the luteal phase exhibits low follicular growth activity. Based on this model, OI is recommended to start on menstrual cycle day 3 (D3) in most protocols, to allow growth of a cohort of follicles.

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Serial ultrasonography scanning was first used to evaluate the behavior of antral follicles in farm animals, showing that they do not develop randomly but rather in synchronized groups called follicular waves (FWs) [6]. Synchronizing the beginning of OI with follicular wave emergence (FWE) results in an improved ovarian response to treatment [7, 8], so strategies for inducing FWE are currently an integral part of OI protocols in some domestic animal species [9–11]. The FW phenomenon has also recently been observed in women [12, 13]. Interestingly, however, evaluation of current OI protocols for assisted reproductive treatment (ART) according to the FW model shows that the start of gonadotropin stimulation is not synchronized with wave emergence [14].

Considering the similarities of folliculogenesis in large animals and humans [15, 16], we hypothesize that synchronizing OI with FWE would also benefit humans. Therefore, the objective of this pilot, randomized, controlled trial was to evaluate the effect of two strategies to induce FWE in infertile women. The first was pharmacological, involving the administration of recombinant human chorionic gonadotropin (rec-hCG). The other strategy was mechanical, involving aspiration of the dominant follicle. Additionally, we aimed to evaluate the feasibility of synchronized OI with an induced FWE comparing it with a conventional OI protocol starting on D3.

Materials and methods

Patients

The inclusion criteria of this pilot, parallel, randomized, prospective trial were as follows: (1) infertile couples with tubal or male factor infertility requiring IVF treatment; (2) women's age ≤35 years, (3) body mass index (BMI) between 19 and 30 kg/m^2; (4) day 3 serum FSH levels ≤12 mIU/mL and serum estradiol levels ≤80 pg/mL; (5) antral follicle count ≥10 and ≤25; (6) absence of uterine anomalies according to recent (<6 months) transvaginal sonography (TVS) and/or hysteroscopy; and (7) male partner <50 years old with ≥5 million motile spermatozoa on semen analysis. The exclusion criteria were as follows: (1) infertility caused by an ovarian factor; (2) failure to identify one or both ovaries on TVS; (3) untreated endocrine disorders; and (4) a smoking habit.

Our Hospital's Ethics Committee approved this study; women were enrolled only after signing a written informed consent.

Randomization

The participants were randomized into one of three groups (control, experimental group 1 [pharmacological group], and experimental group 2 [mechanical group]) (1:1:1) by a computer-generated numerical sequence. The sequence was kept concealed from the main investigator. The chief nurse of the infertility unit allocated patients into the groups according to the computerized sequence. The investigator and the participants were not blinded to the allocation.

OI

Control group

Women in the control group received oral contraceptive pills (OC; 0.03 mg of ethinyl estradiol and 0.15 mg of levonorgestrel) as needed to schedule procedures avoiding weekends. On the second day of the menstrual cycle following OC discontinuation, the women undertook TVS. In the absence of ovarian cysts >10 mm in diameter, they received 150 IU of recombinant FSH (rec-FSH; follitropin alfa; Gonal F®; Merck Serono, Sao Paulo, Brazil) subcutaneously on a daily basis from cycle D3 onwards. Follicular development was assessed by TVS on the fifth day of OI and every other day until ≥2 dominant follicles reached ≥18 mm. The rec-FSH dose was increased by 75 IU on the fifth day of OI if the number of growing follicles was ≤4 or if the mean diameter of the largest follicle was ≤10 mm. The daily rec-FSH dose was decreased by 75 IU on the fifth day of OI if ≥15 growing follicles were identified. When the larger follicles reached a mean diameter of 13–14 mm, a daily subcutaneous dose of 0.25 mg of cetrorelix acetate (Cetrotide®, Merck Serono) was administered. When at least two follicles reached a mean diameter of 18 mm, 250 μg of rec-hCG (choriogonadotropin alfa, Ovidrel®, Merck Serono) was administered, and follicular aspiration was scheduled for 35–36 h later.

Experimental groups

The women in the experimental groups also received OC as needed to schedule procedures. Daily TVS was performed from menstrual cycle 10 following OC discontinuation until a dominant follicle reached 15 mm in diameter. From this time onwards, the experimental groups were subdivided into two groups: (1) in the pharmacological group, women received 250 μg of rec-hCG subcutaneously to trigger ovulation. This was followed by daily TVS starting 2 days after the intervention to monitor ovulation and FWE; (2) in the mechanical group, women were submitted to aspiration of the dominant follicle through a TVS-guided puncture under mild sedation. Daily TVS was performed starting on the day after the aspiration.

For both groups, FWE was defined as an increase in the number of follicles ≥5 and ≤9 mm in mean diameter at TVS [12]. Women from both experimental groups started the OI protocol as described for the control group on the day of FWE.

In vitro fertilization and cryopreservation of embryos

Mature oocytes were fertilized by intracytoplasmic sperm injection with a fresh, ejaculated and processed semen sample obtained from the male partner on the same day of oocyte retrieval [17]. Evaluation and classification of embryos were performed on the 3rd day of in vitro development according to international standards [18]. The proportion of embryos with good morphology on day D3 relative to the total number of embryos (good quality rate) was compared between the groups.

Because OI in the experimental groups began in the luteal phase of the menstrual cycle, asynchrony between embryo development and endometrial growth was anticipated. Therefore, all embryos from all groups were cryopreserved on the 3rd day of embryonic development. Cryopreservation was performed by vitrification using a kit (Irvine Scientific, Santa Ana, CA) according to the manufacturer's instructions.

Frozen/thawed embryo transfer (FET)

All subjects underwent hormonal stimulation of the endometrium for FET. FET started on D2 of a spontaneous menstrual cycle following oocyte retrieval. We used a protocol containing 2 mg of oral estradiol valerate dispensed twice daily over 14 days. Endometrial growth was monitored by TVS on a weekly basis until its thickness reached ≥8 mm (after at least 14 days of estradiol intake). When this thickness was achieved, a vaginal daily dose of 600 mg of natural micronized progesterone was added.

Four days later, pre-embryos were thawed according to the manufacturer's instructions (Irvine Scientific). Blastomere survival rate was assessed post-thawing; only embryos with >80 % of blastomeres surviving the cryopreservation/warming process were suitable for transfer to the uterus. Two embryos were transferred to each woman. The remaining viable embryos were kept cryopreserved. Twelve days after FET, serum β-hCG levels were quantitatively determined to test for pregnancy.

Outcomes

The primary outcome was the presence of FWE after the interventions and the variation in follicle number (the number of follicles post-intervention minus the number of follicles pre-intervention). Secondary outcomes were the length of OI, the total dose of gonadotropins required for OI, the number of retrieved oocytes, and the rate of good quality embryos on D3.

Statistical analyses

This pilot study was designed to examine the feasibility of pharmacological and mechanical interventions to achieve FWE. Quantitative baseline characteristics are shown as the mean±standard error of the mean. Because of the small sample size, data were compared using the non-parametrical Kruskal–Wallis test (for comparisons between three groups) or Mann–Whitney test (for comparisons between two groups). Qualitative baseline characteristics are described as proportions, and associations between the groups were evaluated using Fisher's exact test [19]. Analysis of variance with two measures and two factors was used to compare more than one variable between groups. When a difference was found, Tukey's and Bonferroni's multiple comparisons were carried out [20]. The level of significance was set at 5 %.

Results

A flow diagram of the study is shown in Fig. 1. All patients were randomized and completed the assigned protocol. Data were collected between August 2012 and June 2013. The baseline characteristics of the groups were statistically similar (Table 1), with two exceptions. The mean women's age was significantly higher in the pharmacological group (p=.039) than in the other groups. Second, the interval between the end of OC use and the beginning of OI was significantly shorter in the control group (p=.016) than in the experimental groups. However, this difference was expected because of the study design for mechanical and pharmacological groups, which initiated the OI in the luteal phase of the cycle preceded by OC use. Differences were also observed between groups in the proportion of women with primary versus secondary infertility and in the rate of patients that used OC before OI; however, these differences were not statistically significant, probably because of the small sample size.

The time of the menstrual cycle when the interventions were performed was similar in the pharmacological (day 11 ±3.5 days) and mechanical (12±1.6 days) groups (p=.196). A significant increase in the number of follicles ≥5 and ≤9 mm was observed in every patient in the experimental groups 2 days after pharmacological intervention and 1 day after mechanical intervention (p<.05) (Fig. 2), which demonstrated induction of FWE. The number of follicles ≥5 and ≤9 mm was similar between the two experimental groups before and after the interventions (p=.591). Multiple linear regression analysis showed that the magnitude of increase in the number of small follicles (the number of follicles after interventions minus before interventions) was not influenced by the type of intervention (mechanical or pharmacological) performed to induce a FWE, adjusting for women's age and antral follicle count (Table 2).

Because the primary objective of this study was to evaluate the FWE independent of the type of intervention used, we calculated the study power using a paired test comparing

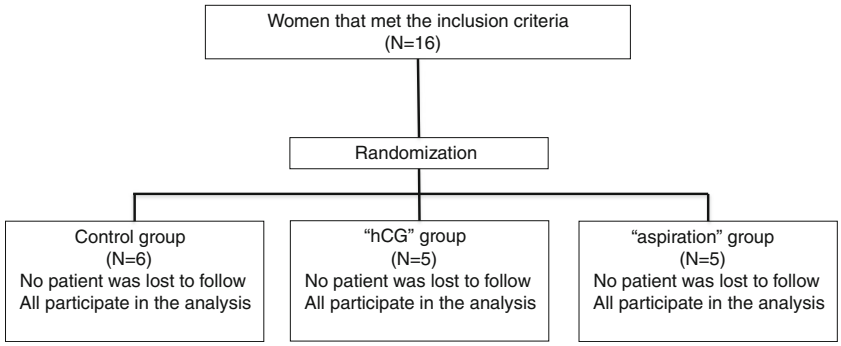

Fig. 1 Study flow diagram

two related means, based on the difference between the number of follicles before and after interventions in each of the experimental groups. For the pharmacological intervention, the sample power was 0.85 (follicle mean number pre-intervention=8.8; follicle mean number post-intervention=15.8, standard deviation of difference=3.9; sample size=5). For the mechanical intervention, the sample power was 0.98 (follicle mean number pre-intervention=11.6; follicle mean number post-intervention=16.4; standard deviation of difference=1.92; sample size=5).

The overall secondary outcome performance data were similar among groups (Table 3). Of note, three women in the pharmacological and mechanical groups required an increase in the daily rec-FSH dose during OI, but this was not necessary in the control group. There were also no differences among the three groups regarding the absolute number of retrieved oocytes, the proportion of oocytes relative to the number of follicles mapped by TVS at the end of OI, as well as the proportion of oocytes retrieved according to the number of follicles present at the beginning of OI. The proportion of good quality embryos at day 3 of in vitro development (good quality rate) was also similar between the experimental and the control groups. However, these results should be interpreted with caution because this study is underpowered to compare differences in outcomes of OI protocols.

All thawed embryos had more than 80 % of blastomeres surviving the cryopreservation/warming process. FET resulted in one pregnancy in the control group (biochemical pregnancy), one pregnancy and a live birth in the pharmacological group, and three pregnancies in the mechanical group (one clinical pregnancy terminated with a spontaneous miscarriage at 8 weeks of gestation and two biochemical pregnancies). The pregnancy rates were not compared among groups because of the small sample sizes.

Discussion

The present study is the first to evaluate the effect of two strategies (pharmacological and mechanical) to promote a FWE to synchronize OI for ART in humans. This study has sufficient power to conclude that both interventions were efficient in inducing a FWE, which was our primary outcome. Additionally, both interventions resulted in similar magnitudes of increase in the number of follicles ≥5 and ≤9 mm.

The observation of follicular wave patterns in women's ovaries has changed the paradigm of human follicular dynamics, resulting in a new field for investigation. OI might also be possible at other times during the menstrual cycle, rather than solely at the follicular phase. Furthermore, this understanding has provided the opportunity to reevaluate current OI protocols according to experience with appropriate animal models.

Synchronizing the start of OI with the first day of FWE is associated with a higher response to superovulation in some animal species [7, 8]. However, detection of natural emergence imposes some limitations on the need for frequent transvaginal ultrasound examinations, and also conditions OI to specific moments during the estrous cycle. Therefore, controlling a FWE offers some technical advantages in animal species.

Baerwald et al. [21] previously reported a higher number of growing follicles and higher serum estradiol levels when OI was started on the first day of the menstrual cycle in women (i.e., the expected time of a natural FWE for most women) [12]. Still, the numbers of metaphase II oocytes retrieved, cleavage stage embryos and blastocysts were not increased, and implantation and pregnancy rates were lower when OI started on day 1 of the menstrual cycle. However, a FWE was not confirmed before the start of OI in that study. Since evidence from animal models has demonstrated that starting OI even one day after the FWE is associated with worse outcomes [7], it could be argued that the results of Baerwald et al. [21] were influenced, at least in part, by the lack of OI synchronization with a FWE in some women. Additionally, the lower implantation and pregnancy rates reported [21] could have been associated with inadequate endometrial development during OI, rather than with embryo quality. Cryopreservation of all embryos might therefore overcome any possible endometrial effect of the synchronization of OI with FWE.

The administration of rec-hCG is intended to trigger ovulation and the first FWE, and ovulation is estimated to occur 36–72 h after the administration of rec-hCG when

Table 1 Baseline characteristics of the subjects

Variable	Control	Pharmacological	Mechanical	P^a
Women's age (years)	29±.8	33±1	31±1.4	0.039
Men's age (years)	30.8±1.4	40±3.8	30±2.1	0.089
Duration of infertility (months)	74±11.7	91.2±23.2	62.4±12.2	0.628
D3 FSH (mIU/mL)	5.7±.4	5.5±1	6.2±.2	0.847
D3 estradiol (pg/mL)	34.2±6.2	34.4±7.2	34.2±2.7	0.985
Antral follicle count	14.2±2.6	12.6±1.4	12.6±1.2	0.986
Sperm concentration (million/mL)	64.4±13.5	99.8±68.8	61.2±27.6	0.833
Proportion of progressive motile sperm (%)	44.3±11.8	12.6±5	33.2±14	0.143
Proportion of sperm with normal morphology (%)	2.2±1.4	1.0±.8	2.2±.6	0.203
Duration of OC (days)	17.8±0.9	20±1.6	26±5.5	0.327
OC - menstruation interval (days)	4.2±0.2	3.33±0.5	3.6±0.3	0.264
OC - beginning of OI interval (days)	7.2±0.2	17.6±1.2	17±0.8	0.016
Proportion of primary infertility (%)	50.0 %	60.0 %	100.0 %	0.09
Proportion of women who used OC (%)	83.3 %	60.0 %	60.0 %	0.604
Infertility factors				
Tubal factor infertility (%)	50.0 %	20.0 %	40.0 %	
Male factor infertility (%)	16.7 %	40.0 %	20.0 %	0.845
Tubal / male factor infertility (%)	33.3 %	40.0 %	40.0 %	

Data not specified as percentage (%) are presented as mean±SE (standard error)

OC oral contraceptive

[a] Statistical analysis was performed with the Kruskal–Wallis test (three groups)

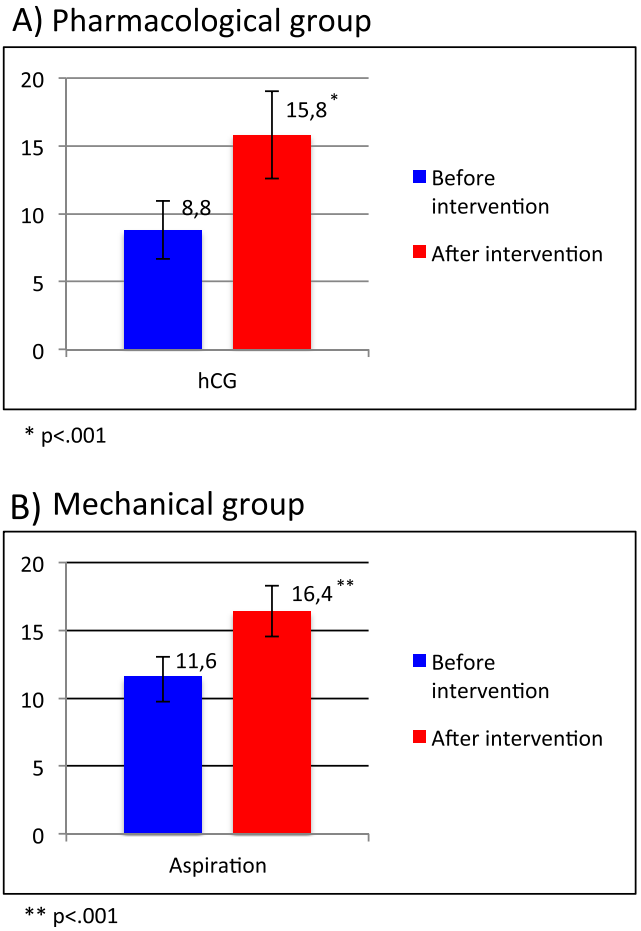

Fig. 2 Mean (±SE) number of follicles ≥5 and ≤9 mm before and after the interventions in the experimental groups. **a** The number of small follicles increased significantly 2 days after hCG administration when the dominant follicle was ≥15 mm ($p<.001$). **b** The number of small follicles increased significantly 1 day after the aspiration of a dominant follicle ≥15 mm ($p<.001$)

the dominant follicle is ≥12 mm [22–24]. Ovulation trigger with rec-hCG followed by OI was used in a previous study on the preservation of fertility in women presenting with cancer who were about to begin gonadotoxic therapy [25]; the results of this were similar to those observed following a conventional OI start. However, this earlier study did not document a FWE before the start of OI. Aspiration of the dominant follicle is a strategy commonly used in farm animals to trigger FWE [26, 27]. In a spontaneous cycle, the number of subordinated follicles progressively decreases once the dominant follicle grows above 10 mm in diameter [12]. Therefore, an observed increase in the number of small follicles after both interventions should be interpreted as FWE.

In our study, the difference in the mean patient age in the pharmacological group is of negligible clinical relevance,

Table 2 Multiple linear regression analysis evaluating the association of intervention type, maternal age, and antral follicle count with the difference of small follicle number before and after the interventions

	Coeff.	Std. Err.	t	P
Intervention	3.315911	2.224049	1.49	0.187
Women's age (years)	−0.37197	0.405454	−0.92	0.394
Antral follicle count	0.609173	0.37336	1.63	0.154
Constant	8.283534	11.7173	0.71	0.506

Table 3 Outcomes of ovarian stimulation in experimental and control groups

Variable	Group			p[a]
	Control	Pharmacological	Mechanical	
Total rFSH dose* (IU)	1346±89.4	1755±276	1754±148	0.195
OI duration* (days)	9.3±.4	10.0±.7	10.4±.5	0.352
Number of harvested oocytes*	9.3±1.5	10.6±.8	10.0±.8	0.799
Retrieved oocytes/ follicles at the beginning of OI (%)	73.0 %	60.0 %	78.0 %	0.749
High quality embryos rate (%)	35.7 %	25.0 %	26.7 %	0.781

There were no statistically significant differences in the outcomes of OS in the pharmacological or the mechanical groups compared to the control group. The outcomes of OS were also statistically similar between the two experimental groups

* Data are shown as the mean±SE

[a] Statistical analysis was performed with the Kruskal–Wallis test

because ART performance is relatively stable in women younger than 35 years of age [28]. Indeed, multivariate analysis found that women's age had no effect on the difference in follicle number before and after both interventions. Similarly, the shorter OC-free interval before starting OI in the control group is also probably of minimal clinical significance, because when the OC-free interval exceeds 4 days OI outcomes are similar to when OI is not preceded by OC use [28–30]. For the same reason, any difference in the proportion of women who used OC before OI was likely to have no effect on this study's outcomes.

It could be argued that the age of the male partner and the inclusion of men with teratozoospermia are a source of bias in this study. However, despite the fact that advanced age has been associated with worse treatment results, there is no consensus on the cut-off value of male age with respect to ART outcomes [31]. Moreover, IVF/ICSI outcomes are apparently not influenced by male age (<50 years) when the female is ≤35 years [31]. Additionally, evidence suggests that ICSI outcomes are not impaired in the presence of teratozoospermia [32].

Overall, our observed outcomes of OI synchronized with a controlled FWE were similar in both experimental groups and the control group. However, this study was not designed to compare the outcomes of OI, but rather to demonstrate the feasibility of OI synchronization with a FWE in humans. Therefore, these results should be interpreted with caution, because this study lacks the statistical power to draw definitive conclusions on the outcomes of OI synchronization with FWE.

The total gonadotropin dose used for OI might be higher and the length of interval for OI longer among the synchronized groups than those of the control group. Two studies on fertility preservation for cancer patients reported similar results when rec-FSH was started in the luteal phase [25, 33], suggesting a possible luteal interference on follicular development. Conversely, this might also be a characteristic of OI synchronization with FWE. Baerwald et al. [21] reported similar results when OI was started on day 1 of the menstrual cycle, when no luteal activity is expected.

In contrast to the practice with animals, we did not observe a significant increase in the number of retrieved oocytes when OI was synchronized to FWE. Additionally, there might have been a reduction in the number of embryos with good morphology. Despite the low number of participants in this study, which could have biased these observations, it could also be speculated that progesterone interfered with follicular development and oocyte competence. However, previous studies showed an improvement in the bovine embryo quality following exogenous progesterone addition when OI was synchronized with the first FW [34]. The bovine ovulatory follicle naturally develops in a high progesterone environment, whereas it develops under low progesterone levels (follicular phase) in humans. Nonetheless, Kuang et al. [35] reported the production of viable human embryos, with highly acceptable pregnancy rates, when OI occurred during the luteal phase.

In conclusion, our findings suggest that a FWE can be elicited through pharmacological (administration of recombinant hCG) and mechanical (aspiration of the dominant follicle) interventions. The outcomes of OI synchronized with FWE should be further evaluated in studies with larger sample sizes before any conclusion on the possible benefits and harms of these protocols can be drawn.

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This study has been registered at ClinicalTrials.gov as NCT 01668056.

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Merck Serono (São Paulo, Brazil) donated the medication used in the study.

Compliance with ethical standards Our hospital's Ethics Committee approved this study, and women were only enrolled after signing a written informed consent form.

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