Continuous ovarian stimulation: a proof-of-concept study exploring the uninterrupted use of corifollitropin α in DuoStim cycles for enhanced efficiency and patient convenience (Alicante protocol)

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Objective: To explore the use of weekly continuous dosing of corifollitropin α in DuoStim cycles.
Design: Pilot-matched case-control study.
Setting: Private fertility center.
Patient(s): Cases were defined as DuoStim cycles performed from November 2022 to May 2023 receiving weekly continuous dosing of corifollitropin α (n = 15). Controls were chosen from a database comprising DuoStim cycles conducted at our institution during the years 2021/2022. Matching was done on a 1-to-1 basis, based on antimüllerian hormone values (±0.4 pmol/L) and age (n = 15).
Intervention(s): Injections of corifollitropin α once every 8 days, along with uninterrupted oral administration of micronized progesterone 200 mg/d (for luteinizing hormone surge prevention) throughout the follicular and luteal phases for ovarian stimulation. Oocyte retrieval.
Main outcome measure(s): Total number of cumulus-oocyte complexes and metaphase II oocytes obtained in follicular + luteal phase stimulation. Secondary outcomes evaluated fertilization rates, number of blastocysts, days of stimulation, number of injectables required, and gonadotropin cost.
Result(s): The study group achieved similar total oocyte and MII yield vs. daily follicle-stimulating hormone protocol (13.3 ± 6.9 vs. 11.8 ± 6.1 and 10.4 ± 6.3 vs. 9.2 ± 4.6, respectively). All secondary outcomes showed no significant differences. The study group experienced a significant reduction of injections to complete a DuoStim cycle (4.5 ± 1.4 vs. 35.2 ± 12.2; mean deviation -30.7; 95% confidence interval, −37.5– to −23.9)].
Conclusion(s): Corifollitropin α on a weekly basis throughout a DuoStim cycle yields an equivalent number of oocytes as standard daily follicle-stimulating hormone administration while drastically reducing the number of required injections.
Trial registration number: NCT05815719. EudraCT: 2022-003177-32. (F S Rep® 2024;5:176–82. ©2024 by American Society for Reproductive Medicine.)
Key Words: Ovarian stimulation, assisted reproduction, corifollitropin α, cost effectiveness, cumulus-oocyte complex

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Based on the description of "follicular waves" (1), the group led by Kuang et al. (2) challenged conventional wisdom by demonstrating the viability of conducting stimulation protocols during the luteal phase. This breakthrough led to the development of the DuoStim protocol, which combines traditional ovarian stimulation in the follicular phase with additional stimulation in the luteal phase. To further optimize the treatment and avoid early luteinizing hormone (LH) surges, incorporating progesterone/progestins (3) seems to be an optimal way to complement this freeze-all segmented approach.

The DuoStim protocol is used frequently in patients with poor response or low-ovarian reserve. However, its use recently has been proposed in patients who require elective oocyte/embryo freezing with the aim of maximizing the number of gametes/embryos obtained in a menstrual cycle (4). Although its popularity is growing, the prolonged stimulation period involves the administration of a high number of injectable medications adding to the treatment burden. Therefore, there is a need to explore simplified protocols that can provide optimal results without compromising the efficacy in patients undergoing DuoStim.

On the other hand, one of the aspects with the most significant physical and emotional impact in in vitro fertilization (IVF) treatments is the requirement for multiple injections during the controlled ovarian stimulation process to obtain oocytes. Simplifying assisted reproduction treatments represents a substantial challenge for reproductive medicine. In response to this need, corifollitropin α was developed as an alternative to traditional follicle-stimulating hormone (FSH) receptor-stimulating medications. Corifollitropin α's extended half-life enables a single injection to replace daily FSH medication administration for up to 7 days. Marketed as Elonva, this molecule has become a standard part of controlled ovarian stimulation for IVF procedures.

The objective of this study was to investigate the use of long-acting FSH (corifollitropin α) combined with micronized natural progesterone in DuoStim cycles, guided by the concept of the follicular waves. Could continuous weekly dosing constitute a viable alternative to daily FSH administration, to obtain a comparable oocyte yield?

MATERIALS AND METHODS

Study design

This prospective pilot-matched case-control study was registered (NCT05815719. EudraCT: 2022-003177-32) and validated by the Instituto Bernabeu review committee (IBMR31/01-06-2022) and the official local ethical committee (Minute nº11/22).

Setting

The study was conducted at Instituto Bernabeu Alicante from November 2022–May 2023. All procedures were performed at a single laboratory. Before participating, all individuals provided informed consent.

Participants

The cohort consisted of patients undergoing the DuoStim protocol, with baseline assessments involving the measurement of age, antimüllerian hormone (AMH), and body mass index (BMI). In the study group (n = 15), after basal assessment of the ovaries, patients received consecutive subcutaneous injections of 100/150 μg corifollitropin α (Elonva N.V., Organon, the Netherlands) based on body weight once every 8 days starting on days 1–3 of the menstrual cycle, along with uninterrupted oral administration of natural micronized progesterone 200 mg/d for LH surge prevention (SEID, S.A., Barcelona, Spain) throughout the follicular and luteal phases (Fig. 1). It is essential to note that during luteal phase monitoring, if the time interval between the last corifollitropin α injection and the trigger medication was <5 days, patients were administered additional daily doses of gonadotropins to complete the luteal phase stimulation (cost/benefit balance).

The control group (n = 15) was formed from historical records of patients undergoing DuoStim from 2021–2022. They followed our standard daily FSH protocol, as described previously (5). In summary, all stimulations commenced in the follicular phase and were conducted with recombinant FSH or highly purified FSH and human menopausal gonadotropin. Follicular phase stimulation began between the 2nd and 4th day of the menstrual cycle. Daily gonadotropin-releasing hormone (GnRH) antagonists were initiated when the leading follicle had a diameter of $\geq$13 mm. Ovulation was triggered when at least 2 follicles reached 17–18 mm in diameter. Luteal phase stimulation started 0–6 days after the first oocyte retrieval. The LH surge prevention during the luteal phase was achieved with 200 mg oral micronized progesterone daily. Ovulation was triggered when at least 2 follicles had reached 17–18 mm in diameter. This approach mirrors the current methodology in use (4).

For triggering in both groups, a GnRH-agonist trigger (0.2 mg triptorelin; Decapeptyl; Ipsen Pharma, Spain), was used in the follicular phase, whereas either recombinant human chorionic gonadotropin (Merck Europe) and/or GnRH-agonist triggering was allowed in the luteal phase. Oocyte retrieval was performed 36 hours after triggering in all cases.

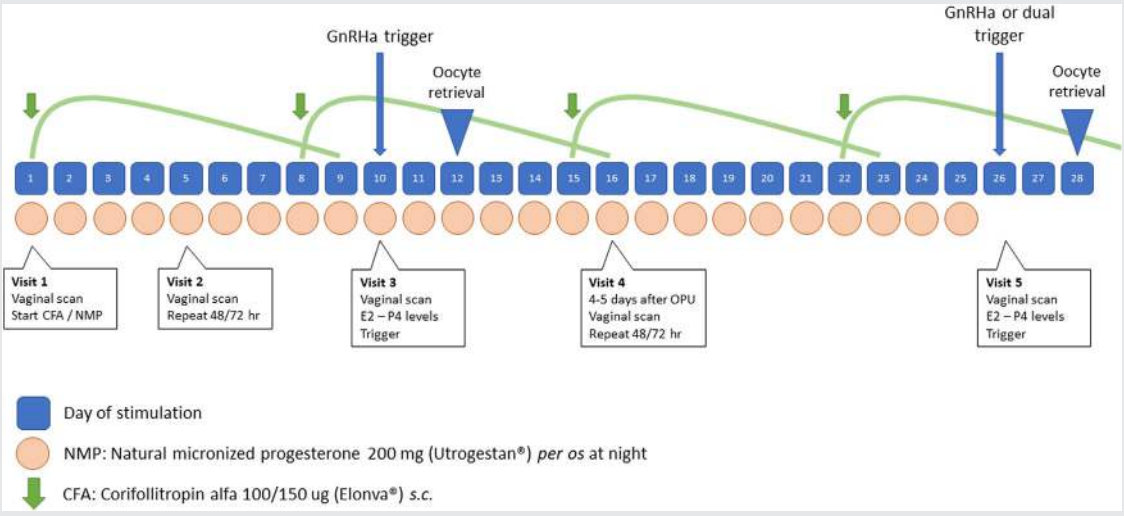
Matching of controls

Controls were chosen from a database comprising DuoStim cycles conducted at our institution during the years 2021/2022 (n = 541 cycles). Matching was done on a 1-to-1 basis, based on AMH values ($\pm$0.4 pmol/L) as the primary criterion, and age as the secondary criterion. In instances where multiple suitable control matches were available, preference was given to the most recent cycle preceding the index cycle. Because BMI was not available consistently in the control group, this criterion was not included in the matching process. Only 1 DuoStim cycle per patient was included.

Variables

The study's primary objective was to assess the total number of cumulus-oocyte complexes and metaphase II oocytes

FIGURE 1



A visual representation illustrating the stimulation process and medication used in the study group taking into account the average duration of ovarian stimulation in a DuoStim cycle.

Castillo. DuoStim continuous ovarian stimulation. F S Rep 2024.

(MII) obtained in follicular + luteal phase stimulation. Secondary outcomes evaluated fertilization rates and number of blastocysts in patients undergoing intracavernous sperm injection (ICSI) in the study group and their counterparts in the control group. Exploratory outcomes evaluated days of stimulation, number of injectables required and gonadotropin cost (limited to ovarian stimulating drugs, excluding medications for preventing LH peak surges). To ensure an equivalent comparison of the variable "total days of stimulation" in this exploratory study, the calculation included the sum of days from the initial gonadotropin injection until and including the day of triggering in the follicular phase, as well as from the day after oocyte retrieval until and including the day of triggering in the luteal phase, for both the study and control groups.

Statistical analysis

A noninferiority trial was planned with a minimum sample size of 13 patients per group, based on a tolerated difference of ±1 oocyte, a standard deviation (SD) of 1, a statistical power of 80%, and a type 1 error of 5%. Data were presented as mean ± SD or frequency (percentage). Because our data have not been selected randomly but rather prematched cases and controls based on age and AMH levels, our samples are related or paired. Therefore, the statistical tests used were the paired *t*-test if the variables exhibit a normal distribution, or the Wilcoxon signed-rank test if we assume nonnormality. Effect size with 95% confidence intervals (95% CI) were calculated and displayed when appropriate.

Regression analysis was performed for key variables (number of oocytes, MII, and fertilization rate) as a dependent variable and protocol for stimulation, age, AMH, and length of stimulation as independent variables to determine if differences in these parameters could be of influence on the estimated effect of the main outcomes and relevant secondary outcome (fertilization rates concerns only the very small subset of patients who underwent ICSI, n = 9). Because BMI was not consistently available, this criterion was not included in this analysis.

The analysis was performed using the R version 4.2.2 for Windows package (R Foundation for Statistical Computing, Vienna, Austria). If the *P* value was $<.05$, results were considered to indicate statistical significance. This study is reported according to STROBE guidelines (6).

RESULTS

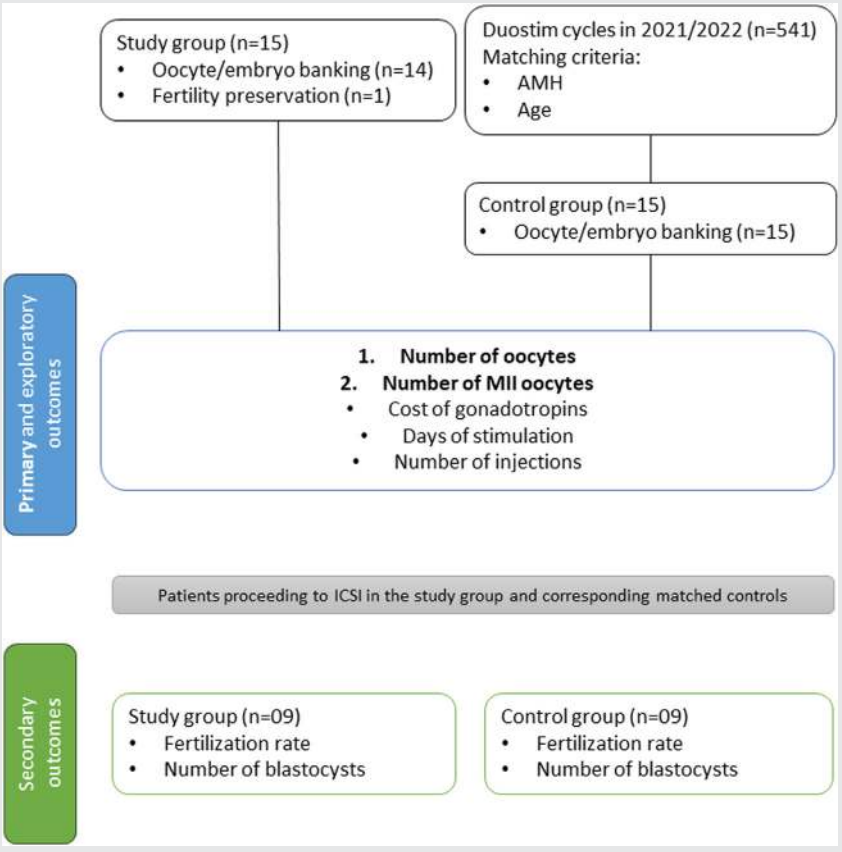
Participants

A total of 30 participants were included in the analysis, with 15 in the study group (corifollitropin α) and 15 in the control group (daily FSH). Participants in the control group were selected from a pool of 514 evaluated women undergoing DuoStim (years 2021 and 2022). In the study group, 14 patients underwent oocyte/embryo banking and 1 oocyte cryopreservation for social reason, whereas 15 in the control group underwent oocyte/embryo banking (n = 15). All participants in the study group successfully completed the double ovarian stimulation regimen. A summary of the study profile is shown in Figure 2.

Descriptive data

Baseline characteristics (age, AMH, and BMI) are presented in Table 1. The results were similar among the groups. Nonetheless, BMI was not consistently reported and date were only available for 13 patients.

FIGURE 2



Flowchart of the study.

Castillo. DuoStim continuous ovarian stimulation. F S Rep 2024.

Primary objective results

The number of cumulus-oocyte complexes and MII retrieved was not statistically different between the study group vs. the control group (13.3 ± 6.9 vs. 11.8 ± 6.1, $P=.2$ and 10.4 ± 6.3 vs. 9.2 ± 4.6, $P=.2$, respectively). It should be noted that all participants in both groups managed to proceed with retrieval (Table 2).

Secondary objective results

A total of 9 patients in the study group opted for ICSI to fertilize their oocytes and generate embryos. The fertilization rate between groups did not exhibit a statistically significant difference. Additionally, the rate of blastocyst stage embryo development was comparable (Supplemental Table 1, available online).

On the day of final follicular maturation triggering in the follicular phase, the study group exhibited elevated estradiol levels compared with the control group (2,009 ± 1,145 vs. 1,282 ± 1,029, respectively). In the luteal phase, estradiol levels were comparable between the groups. As expected, progesterone values were higher in the follicular phase for the study group but remained comparable during the luteal phase (Supplemental Table 2, available online).

Concerning the duration of ovarian stimulation, an average of ±25 days was noted as necessary to complete any of the compared protocols in this study, with no overall statistically significant distinction between the groups (Table 2 and Supplemental Table 3, available online). Of note, the study group experienced an eightfold decrease in the total number of injections required to complete a DuoStim cycle (4.5 ± 1.4 vs. 35.2 ± 12.2, $P=.0007$; M.D. −30.7; 95% CI, −37.5 to −23.9).

Exploratory objective results

Comparative analysis of the financial impact can be found in Table 2. Similar results were observed for the total cost of gonadotropin use required to complete a DuoStim cycle. The study and control groups incurred comparable expenses on gonadotropins to complete a full DuoStim cycle, indicating that the costs of both treatments are equivalent. It is noteworthy that the overall expenses per cumulus oocyte complex and MII oocyte were similar between the groups.

TABLE 1

Baseline characteristics

	Study group (n = 15)	Control group (n = 15)	*P* value*
Age (y, mean ± SD [range])	41.1 ± 3.8 (32–46)	40.6 ± 3.1 (31–44)	.2
AMH (pmol/l, mean ± SD [range])	7.7 ± 5.9 (1.2–21)	7.7 ± 5.8 (1.3–20)	.7
BMI (kg/m^2, mean ± SD [range])[a]	24.7 ± 4.9 (19–35)	23.8 ± 2.8 (20–32)	.7

AMH = antimüllerian hormone; BMI = body mass index.
[a] Data consistently available only for 13 patients.
* Wilcoxon test

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Other analyses

After adjustments to account for confounding variables, the regression analysis suggest superiority of corifollitropin α protocol in the rates of total and MII oocytes (odds ratio, 0.18 [0.006–5.96] and 0.28 [0.01–6.27], respectively). Conversely, the control group exhibited a slightly elevated fertilization rate with an odds ratio of 1.04 (0.79–1.36). However, because of the restricted sample size and broad confidence intervals, these outcomes should be interpreted cautiously (Supplemental Table 4, available online).

DISCUSSION

This exploratory pilot-matched case-control study presents preliminary evidence that the sequential administration of corifollitropin α at 8-day intervals, maintained throughout a DuoStim cycle, yields comparable outcomes concerning the total count of retrieved oocytes and mature (MII) oocytes when contrasted with the conventional protocol involving daily injections. Importantly, the study protocol significantly reduces the quantity of injectables needed to complete a DuoStim cycle. To our knowledge, the sequential and continuous use of corifollitropin α within DuoStim cycles has not been documented previously.

The analysis of primary objectives underscores that the protocol using corifollitropin α does not exhibit inferiority compared with daily gonadotropin dosing with respect to ovarian stimulation. Furthermore, it achieves a similar retrieval of total oocytes and MII oocytes. Encouragingly, the examination of secondary variables, such as fertilization rate and embryo development, also reveals comparable results between the 2 study groups. However, because of the limited patient pool available for the analysis of these secondary variables, the results must be approached with caution, acknowledging the potential for a type II error risk. Similarly, the findings originating from the laboratory beyond the oocyte collection stage will necessitate validation through studies of a larger sample size currently underway at our center.

Analyzing hormonal fluctuations on the day of triggering revealed higher estradiol levels during the follicular phase in the study group compared with the control group. This discrepancy could be attributed to the intense stimulation induced by corifollitropin α, especially during early follicular recruitment, as supported by the shorter ovarian stimulation duration (Supplemental Table 3). In contrast, estradiol levels remained similar between the groups in the luteal phase, likely because of the suppressive effect of elevated progesterone levels at this stage of stimulation. However, it is crucial to note that the observational nature of this study prevents the establishment of causality. Therefore, more extensive prospective evaluations are necessary to draw stronger and more definitive conclusions on this topic.

A challenging variable to evaluate was the total number of stimulation days (including the follicular and luteal phases) across the different groups. In the conventional DuoStim protocol, a brief drug-free interval of 1–5 days is observed after the initial puncture before resuming injectables for luteal stimulation. This selection of the time interval often leans toward being arbitrary and is based primarily on logistical considerations (5). In contrast, stimulation in the study group is

TABLE 2

Primary and exploratory outcomes

	Study group (*n*=15)	Control group (*n*=15)	Effect size (95% CI)[a]	*P* value*
Number of oocytes (mean ± SD [range])	13.3 ± 6.9 (3–26)	11.8 ± 6.1 (1–23)	1.46 (−2.00 to +5.00)	.2
Number of MII oocytes (mean ± SD [range])	10.4 ± 6.3 (2–23)	9.2 ± 4.6 (1–16)	1.26 (−1.50 to +4.50)	.2
Days of stimulation (mean ± SD [range])	24.4 ± 3.5 (20–33)	25.2 ± 4.9 (16–36)	−0.86 (−5.00 to +4.00)	.4
Number of injections (mean ± SD [range])	4.5 ± 1.4 (3–8)	35.2 ± 12.2 (16–57)	−30.73 (−37.50 to −23.99)	.0007
Cost of gonadotropins (Euros €, mean ± SD [range])				
Per DuoStim cycle	1,932 ± 368 (1,355–2,548)	1,677 ± 411 (996–2,384)	254.94 (−35.21 to +549.84)	.06
Per oocyte retrieved	212 ± 193 (52–849)	225 ± 236 (78–996)	−13.53 (−86.67 to +37.29)	.6
Per oocyte MII retrieved	298 ± 298 (58–1,274)	267 ± 228 (78–996)	30.84 (−98.59 to +141.20)	.7

[a] Median difference.
* Wilcoxon test.

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characterized by its "continuous" nature. To facilitate a comparative analysis, follicular phase stimulation was defined for both groups, commencing from the day of the initial injectable administration and extending up to and including the oocyte trigger day. Additionally, luteal phase stimulation was defined from the day after the initial puncture and extended up to (and including) the day of trigger administration in the luteal phase. With these parameters in mind, it can be deduced that both protocols require a comparable number of days for completion.

In assisted reproduction, patient care is important, especially regarding stress management and making the most of each couple's reproductive potential (7). More than half of women who undergo assisted reproduction treatment eventually drop out, despite being able to reimburse the costs associated with the treatment. In fact, patients/couples with fertility disorders are very likely to fail to reach their reproductive potential, because of premature termination of treatment (8). Emotional distress during important decision making in stressful circumstances increases the likelihood of dropping out (9). Current treatment protocols prescribe daily injectable gonadotropins, increasing the physical burden, psychologic stress, and risk of injection errors for the patient, particularly in protocols requiring long periods of drug treatment, such as DuoStim. Therefore, it is essential to develop simpler therapies to reduce the burden on women. Furthermore, some studies have shown that simpler protocols are associated with reduced treatment burden and psychological distress, optimizing the patient's experience toward ovarian stimulation protocols (10).

Corifollitropin α, with its prolonged half-life and sustained gonadotropin activity, is the ideal choice for the extended stimulation period required in DuoStim cycles. In our trial, corifollitropin α was administered every 8 days throughout the cycle, regardless of the triggering or egg retrieval day. This administration schedule demonstrated comparable effectiveness, but improved efficiency compared with daily injection protocols. Additionally, this fixed administration protocol reduces the number of injections and the potential for administration errors while minimizing nurse surveillance. During treatment, patients receive corifollitropin α every 8 days in a fixed manner, and progesterone is administered daily throughout the entire stimulation period, adding convenience for patients and IVF staff. However, these aspects need validation in future studies.

Another aspect under analysis was the economic impact of the study strategy. Findings reveal that the cost per oocyte and MII oocyte is similar for both strategies. Additionally, the total cost per DuoStim cycle is comparable, reinforcing the efficacy of the study's protocol. To complement this patient-friendly approach, the incorporation of oral progesterone for LH surge prevention (11) emerges as an optimal strategy. This approach also falls within the realm of "nonconventional ovarian stimulation strategies" (3). An additional advantage is its oral administration, diverging from injections and further reducing the treatment burden on the patient. In particular, the continuous administration of natural progesterone in our protocol starts on the day of follicular phase stimulation and extends up to the luteal phase trigger day. This implementation ensures a reduction in administration errors, because the intake is sustained throughout the completion of the DuoStim cycle.

Our study strengths include the comparison with a highly similar control group, as evidenced by the remarkably similar AMH values, patient age, and comparable BMI. Limiting the analysis to a single cycle per patient also mitigated potential biases, especially considering the small group sizes under evaluation. This indicates that a fairly accurate matching was performed. In addition, it should be noted that case and control laboratory procedures were performed at a single center. Therefore, it ensures optimal comparison of laboratory results between groups, avoiding possible variations that could arise when analyses are performed at different centers.

Despite the strengths of our study, some limitations must be acknowledged. First, the calculated sample size, indicating the need for at least 13 patients in each group to demonstrate an oocyte difference (± 1), highlights the preliminary nature of this study. The limited sample size increases the risk of over- or under-matching, adding complexity to the interpretation of the results. Uncontrolled confounding variables cannot be ruled out because of the study design. Additionally, the small sample size hampers the ability to draw firm conclusions regarding laboratory objectives, except for oocyte recovery. To obtain more robust data, future studies with larger sample sizes are essential. Incorporating cases that examine embryo chromosomal status through preimplantation genetic screening testing will offer more detailed information on the embryonic safety of the studied strategy. Therefore, our center is considering the design of a prospective comparative study with a larger population.

CONCLUSIONS

In conclusion, our pilot study provides evidence that using corifollitropin α on a weekly basis throughout a DuoStim cycle offers a patient-friendly and efficient approach to ovarian stimulation. This strategy provides a viable option for patients with low-ovarian response or those seeking oocyte preservation, particularly in the context of DuoStim. Moreover, the current protocol yields comparable oocyte retrieval outcomes while employing fewer injectables, all without extending the treatment duration or increasing costs. As a result, this approach alleviates emotional and therapeutic burdens on patients, thereby improving patient experience and optimizing fertility treatments. To consolidate and expand research in this area further, a larger scale, multicenter, randomized controlled trial is warranted.

CRediT Authorship Contribution Statement

Juan Carlos Castillo: Conceptualization of the study, data interpretation, and writing of manuscript. Ana Fuentes: Data interpretation, review of paper. Jose Antonio Ortiz: Statistical analysis, review of paper. Esther Abellán: Embryo handling, embryo data interpretation, review of paper. Andrea Bernabeu and Rafael Bernabeu: Data interpretation, review of paper.

Declaration of Interests

J.C.C. has nothing to declare. A.F. has nothing to declare. J.A.O. has nothing to declare. E.A. has nothing to declare. A.B. has nothing to declare. R.B. has nothing to declare.

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