



ARTICLE

Risk of progesterone elevation in patients with low ovarian reserve using long-acting FSH IVF protocol: a randomized controlled trial



BIOGRAPHY

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KEY MESSAGE

In women with low ovarian reserve, long-acting corifollitropin alfa followed by low-dose recombinant FSH significantly reduces premature progesterone elevation and increases the fresh embryo transfer rate, offering a promising strategy to improve IVF outcomes in this high-risk group. Further studies are needed to confirm these findings and better define their clinical applicability.

ABSTRACT

Research question: Does the long-acting stimulation protocol with corifollitropin alfa (CFA) followed by daily low-dose recombinant FSH (r-FSH) reduce the risk of premature progesterone elevation (PPE) in women with low ovarian reserve compared with daily high-dose r-FSH?

Design: This randomized controlled trial, conducted from February 2022 to May 2024, enrolled 110 patients who met the Bologna criteria for poor ovarian responders. Participants were randomized into two groups: the intervention group received long-acting CFA followed by daily 150 IU r-FSH from day 8; and the control group received daily 300 IU r-FSH. The primary outcome was the proportion of patients with progesterone ≥ 1.1 ng/ml on the day of human chorionic gonadotrophin trigger. Secondary outcomes included number of retrieved oocytes, fertilization rate, fresh embryo transfer rate, and pregnancy rate.

Results: A significantly lower rate of PPE was observed in the CFA group compared with the control group [2/56 (3.6%) versus 12/54 (22.2%), respectively]. CFA stimulation was associated with an 89% reduction in the odds of PPE (OR 0.11, 95% CI 0.02–0.55; $P = 0.007$). Fresh embryo transfer was achieved in 34/52 (65%) patients in the CFA group versus 21/48 (44%) patients in the control group ($P = 0.04$).

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KEY WORDS

Poor ovarian responders
Progesterone elevation
Fresh embryo transfer
Long-acting stimulation
Progesterone at trigger
Freeze-all

Conclusions: Ovarian stimulation with long-acting CFA plus daily 150 IU r-FSH significantly reduced the risk of PPE and increased the feasibility of fresh embryo transfer in patients with low ovarian reserve. This strategy may offer a better approach for managing PPE, and may improve overall IVF success for this specific patient population.

INTRODUCTION

The treatment of patients with a poor ovarian response (POR) is still under debate in assisted reproduction technology (ART). POR is characterized by a reduced number of ovarian follicles, fewer retrieved oocytes, and often poorer oocyte quality, which can significantly affect the likelihood of a successful ART cycle.

Recent evidence from the US Society for Assisted Reproductive Technology (SART) registry (Acharya et al., 2018) suggests that, for patients with low oocyte recovery (fewer than five oocytes) in IVF treatment, the best approach is to perform fresh embryo transfer, which appears to be associated with more favourable clinical pregnancy and live birth rates (LBR) compared with freeze-all and subsequent frozen embryo transfer (FET) cycles.

One of the main indications for freeze-all as a rescue strategy in IVF cycles is premature progesterone elevation (PPE) (Kaponis et al., 2018), reported to affect up to 25% of patients with POR (Mitra et al., 2021).

Previous evidence has suggested that high serum progesterone on the day of human chorionic gonadotrophin (HCG) trigger can have a negative impact on pregnancy outcomes in IVF cycles (Bosch et al., 2010). Indeed, an elevated progesterone concentration can jeopardize endometrial receptivity (Hussein et al., 2019), and this has been associated with a reduced implantation rate in fresh IVF cycles.

The cut-off value of progesterone on the day of HCG trigger that can significantly impact the success rate of a fresh IVF cycle has been studied extensively, and the latest evidence suggests that the value of 1.14 ng/ml is the most appropriate for use in clinical practice because the LBR after freeze-all and subsequent warmed embryo transfer cycles significantly surpasses that of fresh embryo transfer cycles (Vuong et al., 2019).

PPE in assisted reproduction is associated with various factors, including age, ethnicity (Hill et al., 2017), body mass index (BMI) (Shen et al., 2023), type of ovarian stimulation protocol, baseline

progesterone concentration at the beginning of ovarian stimulation (Papaleo et al., 2014), daily FSH dosage, total gonadotrophin dosage, duration of ovarian stimulation cycle, number of oocytes retrieved, and peak oestradiol concentration. These factors can impact the risk of PPE and should be considered in ART treatment planning to optimize fertility outcomes.

In current clinical practice, ovarian stimulation in patients with POR is carried out by daily administration of high-dose gonadotrophins up to 300 IU, with the aim of increasing the number of oocytes retrieved and minimizing the risk of cycle cancellation due to non-response (Ngwenya et al., 2024).

However, this treatment regimen has not shown significant effects on clinical outcomes in ART and was most associated with risk of PPE (Lawrenz et al., 2018), which would significantly impact the percentage of IVF cycles in which a rescue freeze-all strategy should be applied, ultimately decreasing the possibility of fresh embryo transfer and thus the total number of IVF pregnancies in patients with POR.

In patients with POR, the choice of treatment protocol for ovarian stimulation must take into account the fact that one of the aims of treatment is the feasibility of achieving a fresh embryo transfer.

In the field of ovarian stimulation, corifollitropin alfa (CFA) has proven to be a promising drug (Drakopoulos et al., 2017; Kolibianakis et al., 2015). With a pharmacokinetic profile that mimics a step-up/step-down protocol (Zandvliet et al., 2016), CFA seems to play a key role in managing intrafollicular progesterone production. A post-hoc analysis of data from two multicentre, randomized, blinded, non-inferiority trials, ENGAGE (Devroey et al., 2009) and PURSUE (Boostanfar et al., 2015), showed that the incidence of PPE among patients treated with CFA alone was 5.4%, which represents very low incidence (Lawrenz et al., 2016).

The aim of this prospective study was to investigate whether ovarian stimulation

with CFA followed by daily low-dose recombinant FSH (r-FSH) can reduce the incidence of PPE in patients with POR, compared with conventional stimulation with daily high-dose r-FSH.

MATERIALS AND METHODS

This monocentric, unblinded, superiority, explanatory randomized controlled trial aimed to investigate whether a long-acting stimulation protocol with CFA followed by daily 150 IU r-FSH could reduce the proportion of patients with progesterone ≥ 1.1 ng/ml on the day of human chorionic gonadotrophin (HCG) trigger among a POR population, compared with a stimulation protocol with daily 300 IU r-FSH.

Participants in the study were individuals seeking fertility care at San Raffaele Hospital in Milan, Italy. Enrolment of patients started in February 2022 and concluded in January 2024. Follow-up concluded in May 2024. There were no significant changes to the methods or outcome assessment throughout the study period. The trial was concluded upon completion of planned enrolment and follow-up.

Inclusion criteria

Women undergoing IVF cycles, regardless of whether or not they were undergoing intracytoplasmic sperm injection (ICSI), who met the criteria for POR were considered for study enrolment. In accordance with the Bologna criteria, individuals who met one or more of the following conditions were included in this study: antral follicle count (AFC) < 7 ; anti-Müllerian hormone (AMH) < 1.1 ng/ml; and history of retrieving three or fewer oocytes in a previous ART cycle.

To be eligible for recruitment, patients had to meet all the following criteria at the time of randomization: age between 25 and 42 years; normal BMI (between 18.5 and 24.9 kg/m²); and regular menstrual cycles.

Exclusion criteria

Patients were considered ineligible for the trial if they met any of the following exclusion criteria: other indications for elective freeze-all; diagnosis of polycystic

ovary syndrome; personal history of untreated autoimmune diseases and/or endocrine or metabolic disorders; chronic kidney disease; previous ovarian surgery (cystectomy or oophorectomy); current ovarian endometriosis; diagnosis of malignant gynaecological cancer; basal FSH ≥ 20 IU/l; and hypersensitivity to the investigated drugs. Patients were also excluded from the trial if they were concurrently using hormonal therapies that are not conventional for treating infertility, such as transdermal testosterone or specific hormonal priming regimens prior to ovarian stimulation, which are currently considered experimental or used in specific research protocols. Each patient could be enrolled in the trial only once.

Patient and public involvement

Development of the research questions, selection of outcome measures, study design, and study conduct did not involve the participation or input of the patients or the general public.

Intervention

This study investigated whether a long-acting stimulation protocol with CFA might reduce the risk of progesterone ≥ 1.1 ng/ml on the day of HCG trigger in patients with POR compared with a daily stimulation protocol with r-FSH alone. Randomization for the study protocol was performed at the time of scheduling the patient for IVF treatment.

Treatment plans

The treatment plan for both ovarian stimulation protocols began on day 2–3 of the menstrual cycle. Starting from day 6, patients initiated a daily subcutaneous injection of 0.25 mg of the GnRH antagonist ganirelix (Orgalutran; Organon, USA), which continued until the day of HCG trigger. In the investigation group, a single subcutaneous injection of 150 μ g CFA (Elonva; Organon) was administered on day 2 or 3 of the menstrual cycle, and ovarian stimulation continued with a daily dose of 150 IU r-FSH (Puregon; Organon) from stimulation day 8 if the criteria for HCG trigger were not met. In the control group, patients received a daily subcutaneous injection of 300 IU r-FSH until the criteria for HCG trigger were met. The absence of adequate follicular growth was defined as ‘no response’, and the ovarian stimulation cycle was cancelled.

Ovulation triggering was performed if at least one leading follicle reached a diameter ≥ 17 mm, with the administration of 10,000 IU urinary HCG (Gonas; IBSA, Switzerland).

Oocyte retrieval took place 36 h after the administration of HCG. Retrieved metaphase II (MII) oocytes were fertilized with the partner’s spermatozoa on the same day.

After oocyte collection, cumulus–oocyte complexes were incubated for 3 h in pre-equilibrated IVF medium (Quinn’s Advantage Fertilization Medium; Cooper Surgical, USA) supplemented with human serum albumin (HSA) at 37°C in a controlled atmosphere (6% CO₂ and 5% O₂). For ICSI, denudation was performed using HEPES-buffered medium (Quinn’s Advantage Medium with HEPES; Cooper Surgical) supplemented with HSA and 20 IU/ml of hyaluronidase solution. ICSI was conducted in microdroplets of pre-warmed HEPES-buffered medium supplemented with HSA and PVP (polyvinylpyrrolidone solution with HSA-7%).

Injected oocytes were cultured in pre-equilibrated CSCNX (Irvine Scientific, USA) or Quinn’s Advantage Cleavage-Blastocyst Medium (Cooper Surgical) supplemented with serum substitute supplement in a controlled atmosphere incubator. After 16–18 h, fertilization was evaluated, and oocytes were considered to be normally fertilized when they exhibited two pronuclei and two polar bodies.

In cases where embryo cryopreservation and subsequent FET were required, following artificial shrinkage, expanded blastocysts were cryopreserved using a simplified vitrification procedure developed by Irvine Scientific (<https://www.irvinesci.com/>, accessed 8 April 2024). The equilibration step was carried out at room temperature for 10 min. Blastocysts were transferred to vitrification solution drops for 1 min before being individually loaded and frozen. After warming with the Vit Kit-Thaw system (Irvine Scientific), the blastocysts were placed in culture dishes containing six 30- μ l drops of blastocyst medium (Quinn’s Advantage Blastocyst Medium; CooperSurgical) overlaid with 3 ml of sage mineral oil (CooperSurgical). All blastocysts were cultured for at least 3 h before embryo transfer.

Embryo transfers were carried out according to the standard IVF procedure, either 3 or 5 days after fertilization. In case of supernumerary embryos, freezing at blastocyst stage was performed. In cases where progesterone > 1.1 ng/ml on the day of HCG trigger, embryo culture was extended to the blastocyst stage, and a freeze-all strategy was applied mandatorily to minimize the potential detrimental impact of PPE on endometrial receptivity. Embryos were vitrified and transferred in a subsequent FET cycle using either hormone replacement therapy with oral oestradiol and vaginal progesterone, or a controlled natural modified cycle with HCG trigger and luteal phase progesterone supplementation. Pregnancies achieved from these cycles were therefore included in the FET cohort for analysis.

Fourteen days following embryo transfer, a pregnancy test was performed. A result was considered positive if serum beta-HCG > 10 mIU/ml. All participants with a positive pregnancy test result underwent an ultrasound scan at both 6 and 12 weeks of gestation to confirm clinical pregnancy. Follow-up continued until 20 weeks of gestation, at which time point it was considered an ongoing pregnancy.

Primary outcome

The primary outcome under investigation in this study was the proportion of subjects with progesterone ≥ 1.1 ng/ml on the day of HCG trigger, with an expected rate of 5% in the investigation group compared with an expected rate of 25% in the control group. Progesterone concentration was determined through blood sample testing using an AIA fluorometric system with ST-AIA-PACK immunoassay (Tosoh, Japan). The assay demonstrated sensitivity of 0.1 ng/ml, and intra-assay and interassay coefficients of variation were 11% and 13%, respectively.

Secondary outcomes

The secondary outcomes were: number of oocytes retrieved; fertilization rate (calculated as the number of normally fertilized oocytes divided by the total number of injected MII oocytes, expressed as a percentage); number of embryos obtained on day 3; percentage of freeze-all cycles due to PPE; biochemical pregnancy rate, defined as a positive pregnancy test; ongoing pregnancy rate, defined as the presence of a viable fetus at 20 weeks of gestation; and cumulative pregnancy rate, defined as the number of pregnancies

(biochemical/clinical/ongoing, as applicable) resulting from a single oocyte retrieval and all associated fresh embryo transfers and subsequent FET until a pregnancy occurred or all embryos derived from that retrieval were used.

Sample size

The sample size for this study was determined based on the following assumptions: (i) estimated 10% cancellation rate due to no response; (ii) desired statistical power of 80% for the study; and (iii) type I error rate (α) of 0.05 for a two-sided test. It was assumed that the incidence of progesterone elevation in the CFA + 150 IU/day r-FSH group would be similar to that reported in the CFA-only arm of the study by [Lawrence et al. \(2016\)](#), while the incidence of progesterone elevation in the control group was derived from existing literature on conventional stimulation protocols. Using a continuity-corrected formula ([Bell et al., 2014](#)) and the pre-specified parameters, it was determined that a sample size of 55 women in each study arm, totalling 110 patients, was appropriate. This sample size was designed to detect a reduction in the risk of PPE from 25% in the control group to 5% in the intervention group.

Recruitment and randomization

All women scheduled for IVF treatment at the study centre were assessed for eligibility. Those who agreed to participate and provided written informed consent were enrolled in the study. Study participants were allocated to the two intervention arms based on the allocation sequence in a 1:1 ratio, generated using permuted block randomization with a fixed block size of 4. The randomization was unpaired. The allocation sequence was generated before the start of the study using the R package `randomizeR` ([Uschner et al., 2018](#)). The allocation sequence was generated and maintained solely by the study statistician, who assigned treatment groups without disclosing the sequence to investigators or the principal investigator, ensuring strict allocation concealment.

Statistical analysis

Descriptive analysis of the study population was performed to evaluate differences between the two study groups. Continuous variables were analysed using the Mann–Whitney *U*-test and are presented as median and IQR.

The primary study outcome (proportion of patients with progesterone ≥ 1.1 ng/ml at

induction) was initially evaluated in the intention-to-treat (ITT) population, followed by analysis in the per-protocol (PP) population. The ITT population comprised all randomized participants, whereas the PP set only included patients who completed the study without major protocol deviations and met the criteria for HCG trigger in the ovarian stimulation protocol.

The primary outcome in both ITT and PP datasets was assessed using logistic regression models adjusted for potential confounding factors, including BMI (kg/m²), maternal age (years), ovarian reserve (AMH, ng/ml) and basal progesterone (ng/ml).

Progesterone values of patients with cycle cancellation prior to HCG trigger were addressed in the ITT population through multiple imputation using predictive mean matching. Maternal BMI, maternal age and treatment group (intervention or control), all with no missing data, were included as predictor variables in the imputation model ([Austin et al., 2021](#)). Multiple imputation was performed using the `mice` package in R, generating five imputed datasets ([van Buuren and Groothuis-Oudshoorn, 2011](#)).

Secondary outcomes were evaluated to identify potential differences between the intervention group and the control group in the PP population. Continuous secondary outcomes are reported as median and IQR, and were analysed using the two-sided Mann–Whitney *U*-test, with 95% CI obtained by bootstrap with 10,000 resamples and percentile-based intervals (2.5th–97.5th percentiles). Categorical secondary outcomes are presented as frequency and percentage, and were analysed using chi-squared test. The Wilson score interval method was used to calculate 95% CI.

All analyses adhered to a pre-specified significance level (α) of 0.05. R studio version 2022.12.0.353 was used to perform statistical analyses.

Ethical approval and trial registration

The study proposal was approved by the Ethics Committee of IRCCS San Raffaele Institute (2020-004329-21, approval date 8 February 2021). The trial was registered on EudraCT.ema.europa.eu under number 2020-004329-21 and on ClinicalTrials.gov under number NCT04695483 on 1 December 2020.

RESULTS

Patient selection and baseline characteristics

FIGURE 1 depicts the study inclusion process. In total, 147 patients were considered eligible for inclusion. Of these, 110 were randomized: 56 in the intervention group (long-acting stimulation protocol with CFA) and 54 in the control group. One hundred participants completed the study: 52 in the intervention group (withdrew consent $n = 1$, treatment discontinued for concurrent medical condition $n = 1$, treatment discontinued for no response $n = 2$) and 48 in the control group (natural pregnancy before ovarian stimulation $n = 1$, withdrew consent $n = 2$, treatment discontinued for concurrent medical condition $n = 1$, treatment discontinued for no response $n = 2$).

TABLE 1 presents the baseline characteristics of the study population, including age, ovarian reserve parameters (AMH, AFC), BMI, basal FSH concentration, and total motile sperm count of the partner.

Primary outcome

TABLE 2 presents the number of patients with progesterone > 1.1 ng/ml on the day of HCG trigger for both the PP and ITT populations. In the ITT population, two (3.6%) patients in the intervention group and 12 (22.2%) patients in the control group (OR 0.11, 95% CI 0.02–0.55; $P = 0.007$) exceeded this threshold. The PP analysis had similar results, with two (3.8%) patients in the intervention group and 10 (20.8%) patients in the control group exceeding the threshold (OR 0.13, 95% CI 0.02–0.68; $P = 0.02$).

IVF laboratory outcomes

TABLE 3 shows the IVF cycle outcomes per group and the comparison across study arms. The median duration of stimulation was 10 (IQR 9–12) days in both the intervention and control groups. In the intervention group, six patients received CFA injections alone, and the HCG trigger was administered without any additional gonadotrophin dose.

Median peak oestradiol concentration on the day of HCG trigger was 901 (IQR 673–1382) pg/ml in the intervention group and 973 (IQR 600–1301) pg/ml in the control group. Median progesterone concentration on the day of HCG trigger was 0.47 (IQR 0.28–0.72) ng/ml in the intervention group and 0.64 (IQR

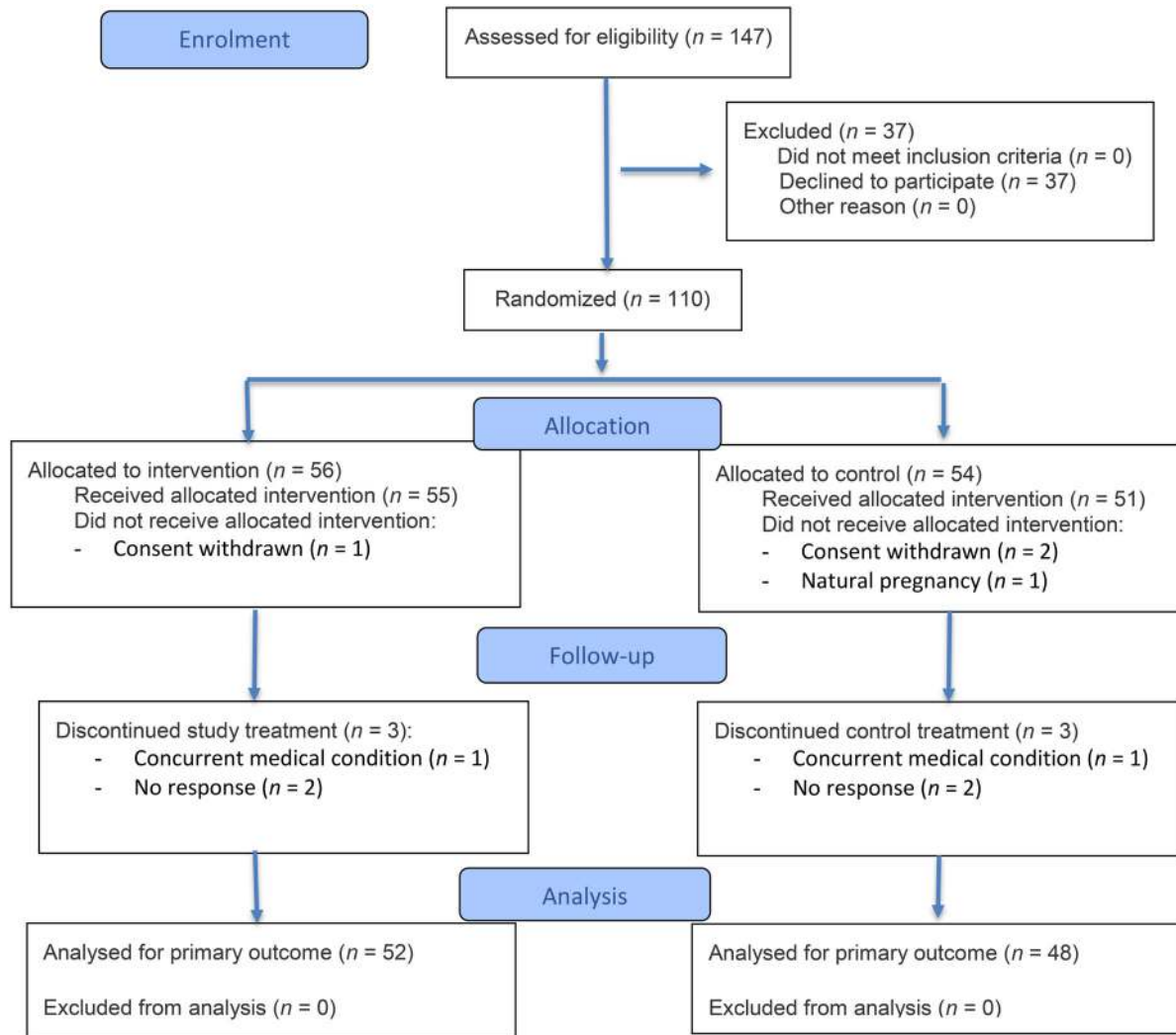


FIGURE 1 CONSORT flow diagram of patient enrolment, randomization and follow-up in the study. This figure presents the progression of participants through the randomized controlled trial, including reasons for exclusion prior to randomization, number of patients who did not receive the allocated intervention, discontinuation of the intervention, and the number of participants included in the primary outcome analysis. The diagram is structured according to the CONSORT 2025 guidelines.

TABLE 1 BASELINE CHARACTERISTICS OF THE INTENTION-TO-TREAT STUDY POPULATION: INTERVENTION GROUP AND CONTROL GROUP

Characteristic	Intervention group (n = 56)	Control group (n = 54)	P-value
Age (years)	39.0 (37.0–40.0)	39.0 (38.0–41.0)	0.09
BMI (kg/m ²)	21.4 (19.9–23.4)	21.0 (19.5–22.9)	0.39
AMH (ng/ml)	0.67 (0.34–0.86)	0.58 (0.35–0.8)	0.37
FSH (mIU/ml)	9.3 (7.1–13)	9 (7–11.7)	0.63
AFC (n)	6 (4–7)	5.5 (4–7)	0.99
Basal progesterone (ng/ml)	0.37 (0.22–0.57)	0.41 (0.22–0.48)	0.09
TMSC (million)	22.5 (7.3–58.4)	21.6 (5.9–54.0)	0.97

Data presented as median (IQR), and groups compared using Mann–Whitney *U*-test.

BMI, body mass index; AMH, anti-Müllerian hormone; AFC, antral follicle count; TMSC, total motile sperm count (initial sample).

0.45–0.98) ng/ml in the control group ($P = 0.0.007$).

The median number of oocytes retrieved was 3 (IQR 2–6) in the intervention group and 3 (IQR 1–4) in the control group. The median number of MII oocytes was 3 (IQR 1–5) and 2 (IQR 1–3) in the intervention and control groups, respectively. The median fertilization rate was 79% (IQR 30–100%) in the intervention group and 78% (IQR 0–100%) in the control group. The median total number of embryos obtained on day 3 was 2 (IQR 0.8–4) in the intervention group and 1.5 (IQR 0–3) in the control group.

In total, 34 (65%, 95% CI 51.8–76.8) fresh embryo transfers were performed in the

TABLE 2 NUMBER OF PATIENTS WITH PROGESTERONE CONCENTRATION ON DAY OF HUMAN CHORIONIC GONADOTROPHIN TRIGGER ≥ 1.1 NG/ML IN THE INTENTION-TO-TREAT AND PER-PROTOCOL STUDY POPULATIONS

Analysis	Intervention group	Control group	OR (95% CI)	P-value
ITT population ^a	n = 56	n = 54		
Progesterone ≥ 1.1 ng/ml, n (%)	2 (3.6%)	12 (22.2%)	0.11 (0.02–0.55)	0.007
PP population	n = 52	n = 48		
Progesterone ≥ 1.1 ng/ml, n (%)	2 (3.8%)	10 (20.8%)	0.13 (0.02–0.68)	0.02

Progesterone concentration on day of HCG trigger was analysed as a dichotomous variable using a cut-off of 1.1 ng/ml. Analyses were performed using logistic regression adjusted for confounders (body mass index, maternal age, anti-Müllerian hormone, basal progesterone). Control group was used as reference level.

^a Progesterone values of the patients with cycle cancellation prior to HCG trigger were addressed in the ITT population through multiple imputation using predictive mean matching for four patients in the intervention group and six patients in the control group.

ITT, intention to treat; PP, per protocol; HCG, human chorionic gonadotrophin.

intervention group, compared with 21 (44%, 95% CI 30.7–57.7) in the control group ($P = 0.04$).

In the intervention group, 24 (46.2%) and 10 (19.2%) fresh embryo transfers were performed at cleavage stage (day 3) and blastocyst stage (day 5), respectively; 19 (36.5%) patients did not undergo a fresh embryo transfer. In the control group, 19 (39.6%) and two (4.2%) fresh embryo transfers were performed at cleavage stage and blastocyst stage, respectively; 27 (56.3%) patients did not undergo a fresh embryo transfer.

In total, 36 (69%) patients in the intervention group and 29 (60%) patients in

the control group had at least one cleavage stage embryo available in the cycle. Among them, two (5.5%) patients in the intervention group and six (20.7%) patients in the control group underwent a freeze-all strategy due to progesterone elevation on the day of HCG trigger ($P = 0.13$). The mean \pm SD number of cryopreserved blastocysts was 0.79 ± 1.07 in the intervention group and 0.5 ± 0.85 in the control group. In the intervention group, 25 (48%) patients had at least one blastocyst cryopreserved, of which nine (17%) patients had two or more blastocysts cryopreserved. In the control group, 15 (31%) patients had at least one blastocyst cryopreserved, and seven (15%) patients had two or more blastocysts cryopreserved.

Pregnancy outcomes

TABLE 4 depicts the pregnancy outcomes in patients who completed the study. In the entire population, 21 patients had a biochemical pregnancy after a fresh embryo transfer: 10 (20.8%) patients in the control group and 11 (21.2%) patients in the intervention group ($P = 1.00$). Six (12.5%) patients in the control group and five (9.6%) patients in the intervention group had an ongoing pregnancy beyond 20 weeks of gestation ($P = 0.65$). Analysing by IVF cycle, also considering all FET, 17 (32.7%) patients in the intervention group and 15 (31.2%) patients in the control group had at least one positive pregnancy test ($P = 0.99$), of whom 15 (28.8%) patients in the intervention group and 10 (20.8%) patients in the control group had at least an ongoing pregnancy ($P = 0.49$). At the time of data collection, five (9.6%) patients in the intervention group and one (2.1%) patient in the control group had not yet achieved a clinical pregnancy but still had at least one cryopreserved embryo available for transfer ($P = 0.2$); all of these patients had already undergone at least one embryo transfer during the study period.

DISCUSSION

This study demonstrated that, in patients with low ovarian reserve, the combination of CFA followed by daily low-dose r-FSH reduced the risk of PPE effectively

TABLE 3 PER-PROTOCOL ANALYSIS RESULTS: IVF CYCLE OUTCOMES IN PATIENTS WHO COMPLETED THE STUDY

Outcome	Intervention group (n = 52)	Control group (n = 48)	Median difference (95% CI)	P-value
Duration of ovarian stimulation (days)	10.0 (9.0–12.0)	10.0 (9.0–12.0)	0.00 (-0.01 to 2.00)	0.29
Peak oestradiol concentration (pg/ml)	901.0 (673.2–1382.2)	973.0 (599.5–1301.0)	-72.0 (-266.0 to 219.5)	0.80
Progesterone concentration (ng/ml)	0.47 (0.28–0.72)	0.64 (0.45–0.98)	-0.17 (-0.30 to -0.01)	0.007
Oocytes retrieved (n)	3.0 (2.0–6.0)	3.0 (1.0–4.0)	0.00 (-1.00 to 2.50)	0.06
MII oocytes (n)	3.0 (1.0–5.0)	2.0 (1.0–3.0)	1.00 (-0.50 to 2.00)	0.10
Fertilization rate	0.79 (0.3–1.0)	0.78 (0.0–1.0)	0.01 (-0.31 to 0.30)	0.80
Day 3 embryos (n)	2.0 (0.75–4.0)	1.5 (0.0–3.0)	0.50 (-0.50 to 2.00)	0.06
			OR (95% CI)	P-value
Fresh embryo transfer performed	34 (65%)	21 (44%)	2.41 (1.01 to 5.90)	0.04
Cycles with at least one day 3 embryo	36	29	1.47 (0.60 to 3.66)	0.48
Freeze-all cycles due to PPE/patients with day 3 embryos ^a	2 (5.6%)	6 (20.7%)	0.23 (0.02 to 1.44)	0.13

Data presented as median (IQR) or n (%).

The median difference (calculated as the difference between the medians of the two groups, intervention group–control group) was assessed, and 95% CI were estimated using the bootstrap method. P-values were calculated using the two-sided Mann–Whitney test for continuous and count variables, and chi-squared test for categorical variables.

^a The percentage of freeze-all cycles due to PPE were calculated for cycles with at least one embryo obtained on day 3, with group sizes of 36 for the intervention group and 29 for the control group.

MII, metaphase II; PPE, premature progesterone elevation.

TABLE 4 PER-PROTOCOL ANALYSIS RESULTS: PREGNANCY OUTCOMES IN PATIENTS WHO COMPLETED THE STUDY

Outcome	Intervention group (n = 52)	Control group (n = 48)	OR (95% CI)	P-value
Positive pregnancy test ^a	11 (21.2%)	10 (20.8%)	1.02 (0.35–3.02)	1.00
Clinical pregnancy	10 (19.2%)	8 (16.7%)	1.19 (0.38–3.85)	0.80
Ongoing pregnancy ^b	5 (9.6%)	6 (12.5%)	0.74 (0.21–2.62)	0.65
Cumulative positive pregnancy test ^a	17 (32.7%)	15 (31.2%)	1.07 (0.42–2.71)	0.99
Cumulative ongoing pregnancy ^b per patient	15 (28.8%)	10 (20.8%)	1.53 (0.56–4.35)	0.49
Patients with cryopreserved embryos and no clinical pregnancy	5 (9.6%)	1 (2.1%)	5 (0.56–44.5)	0.2

Data presented as n (%). P-values were calculated using chi-squared test.

Positive pregnancy tests, clinical pregnancies and ongoing pregnancies refer to fresh embryo transfers. Cumulative pregnancies were defined as the number of pregnancies (biochemical/clinical/ongoing, as applicable) resulting from a single oocyte retrieval and all associated fresh and subsequent frozen embryo transfers, until a pregnancy occurred or all embryos derived from that retrieval were used.

^a Measured as beta-human chorionic gonadotrophin concentration >10 mIU/ml 14 days after embryo transfer.

^b Ongoing at 20 weeks.

compared with standard daily high-dose r-FSH. As a result, significantly more fresh embryo transfers were performed in the intervention group, reducing the need for a rescue freeze-all strategy. Given that fresh embryo transfer is particularly beneficial in patients with POR, this approach may improve treatment outcomes in this challenging population.

Elevated serum progesterone on the day of HCG trigger is well documented to have a negative impact on pregnancy rate after fresh embryo transfer, as it disrupts endometrial receptivity and shifts the implantation window. While a rescue freeze-all strategy can mitigate this issue by enabling embryo transfer in a more optimal endometrial environment (Celada and Bosch, 2020; Racca et al., 2021; Wong et al., 2021), this approach is less favourable for patients with low ovarian reserve. In this population, delaying embryo transfer may result in a lower overall pregnancy rate, as suggested by data from the US SART registry (Acharaya et al., 2018). More recently, evidence has emerged indicating that freeze-all strategies should even be considered contraindicated in patients with a poor prognosis, as they may further compromise the likelihood of success while increasing the financial burden of treatment (Gleicher et al., 2023).

The threshold for defining PPE remains debated, with initial studies suggesting 1.5 ng/ml as a critical cut-off. However, more recent findings indicate that progesterone >0.8–1.0 ng/ml (Venetis et al., 2013; Wu et al., 2019) may impair implantation, particularly in patients with

POR. Importantly, a threshold of 1.1 ng/ml has been identified as the point at which freeze-all becomes preferable to fresh embryo transfer (Vuong et al., 2019), forming the rationale for its adoption in the present study.

Various strategies have been explored to minimize PPE while maintaining effective follicular stimulation (Lawrenz et al., 2018), including step-down protocols (Lawrenz et al., 2021) and the use of human menopausal gonadotrophin instead of r-FSH (Bosch et al., 2024). The pooled analysis of the ENGAGE and PURSUE trials (Lawrenz et al., 2016) provided valuable insights into the role of CFA in modulating progesterone concentration, particularly when lower r-FSH doses are introduced from day 8 of stimulation. The present findings align with this evidence, reinforcing the efficacy of this approach in preventing PPE and thus preserving the opportunity for fresh embryo transfer.

By combining CFA with a lower dose of r-FSH in a GnRH antagonist ovarian stimulation protocol, this study aimed to achieve two key objectives: ensuring effective follicular recruitment and preventing excessive progesterone production. This strategy is particularly relevant as it mimics the physiological FSH decline observed in natural ovulatory cycles, where the FSH concentration decreases naturally as dominant follicles mature (Ecochard et al., 2014), promoting optimal follicular development while maintaining endocrine balance. By applying this principle to ovarian stimulation, the protocol may support a more physiological hormonal

environment, reducing the risk of excessive progesterone elevation while maintaining follicular growth.

The study results confirm that this strategy significantly reduces the risk of PPE and increases the likelihood of fresh embryo transfer compared with high-dose r-FSH protocols. This is a clinically meaningful outcome for patients with POR, who may gain greatest benefit from tailored stimulation strategies that also optimize hormonal dynamics.

Currently, no single ovarian stimulation protocol has been definitively proven to be superior in terms of clinical pregnancy rate and LBR across different responder populations, as highlighted in the latest ESHRE guidelines (ESHRE Guideline Group on Ovarian Stimulation et al., 2020). However, refining protocols to better accommodate the unique challenges of patients with low ovarian reserve remains a critical area of research.

These findings suggest that the combination of CFA with daily low-dose r-FSH alongside a GnRH antagonist offers an advantage over standard daily high-dose r-FSH by reducing PPE and, consequently, lowering the need for a rescue freeze-all strategy. This may enhance the likelihood of fresh embryo transfer and, on a broader scale, improve the ART success rate in patients with POR. However, given that this study was not powered to detect significant differences in LBR, further research is needed to validate these findings and assess their impact on clinically important outcomes.

873 Limitations

874 One limitation of this study is the choice of
875 progesterone cut-off value, as there is no
876 established consensus on the optimal
877 threshold. Using different cut-offs could
878 impact the final results. Beyond the
879 primary comparison of CFA 150 µg versus
880 rFSH 300 IU during the first 7 days of
881 stimulation, the two groups followed
882 different fixed protocols from day 8
883 onwards. In the CFA group, patients
884 received a lower fixed daily dose of rFSH,
885 while in the control group, the initial
886 300 IU/day dose was maintained until the
887 end of stimulation. This resulted in higher
888 total gonadotrophin exposure in the
889 control group. Therefore, the observed
890 difference in progesterone elevation
891 cannot be attributed solely to the use of
892 CFA, as it may also have been influenced
893 by the higher FSH dosage administered in
894 the control group. This protocol reflects
895 common clinical practice in low
896 responders, where dose reductions are
897 rarely applied due to the minimal risk of
898 ovarian hyperstimulation syndrome;
899 however, it represents a limitation of the
900 study and should be taken into account
901 when interpreting the results.

902
903 The trial was designed as a superiority study
904 for the primary outcome of progesterone
905 elevation on the day of HCG trigger, with the
906 aim of assessing whether the intervention
907 reduced the proportion of patients
908 experiencing PPE compared with the control
909 group. This study design led to a sample size
910 which was not powered to formally assess the
911 non-inferiority of the two treatments in terms
912 of clinical outcomes. Therefore, while clinical
913 outcomes were analysed, the sample size
914 does not allow for definitive conclusions
915 regarding non-inferiority between the two
916 protocols.

917
918 Finally, the monocentric study design,
919 while ensuring consistency in protocols
920 and patient management, may limit the
921 generalizability of the findings to other
922 settings with different patient populations,
923 clinical practices, or laboratory conditions.

924 CONCLUSIONS

925
926 The results suggest that the long-acting
927 ovarian stimulation protocol with
928 corifollitropin alfa followed by daily low-
929 dose r-FSH, in a GnRH antagonist ovarian
930 stimulation protocol, could have
931 advantages over the conventional
932 stimulation protocol with daily high-dose r-
933 FSH, particularly in terms of reducing the

934 risk of PPE among women expected to
935 demonstrate POR. This could potentially
936 lower the cancellation rate for fresh cycles,
937 and increase the likelihood of IVF success
938 in this particular population. The data show
939 that patients in the intervention group had
940 a lower progesterone concentration on
941 the day of HCG trigger, and a lower
942 proportion of patients had PPE compared
943 with the control group. Further analyses
944 are advisable to confirm these preliminary
945 findings and to better understand their
946 potential clinical implications. This study
947 was conducted in a population of patients
948 with POR identified based on established
949 classification criteria. To broaden the
950 applicability and relevance of these results,
951 it will be important for future studies to
952 validate the findings in comparable
953 populations classified using different
954 criteria.

AUTHOR CONTRIBUTIONS

955 E.P., A.Q. and M.Z. conceived the original
956 idea and the overall design of the study. D.
957 M. performed the statistical analysis. V.S.
958 V., E.D. and G.B. contributed substantially
959 to data acquisition, interpretation and
960 critical review. A.Q. wrote the first draft of
961 the article. E.P. and M.C. critically revised
962 the initial and all subsequent drafts and the
963 final manuscript. All authors have read and
964 approved the final manuscript.

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DECLARATION OF GENERATIVE AI IN SCIENTIFIC WRITING

977 During the preparation of this work, the
978 authors used ChatGPT-4o to assist with
979 language editing and improve readability.
980 After using this tool, the authors reviewed
981 and edited the content as needed, and
982 take full responsibility for the content of
983 the publication.

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