Conventional follicular-phase ovarian stimulation vs. luteal-phase stimulation in suboptimal responders: a randomized controlled trial

Jorge Suñol, M.D.,[a] Juan Carlos Castillo, M.D., Ph.D.,[b] José Antonio Ortiz, M.Sc., Ph.D.,[b] Jorge Ten, M.Sc. Ph.D.,[b] Ana Fuentes, M.D.,[c] Belén Moliner, M.D., Ph.D.,[b] María Martínez, M.D.,[d] Joaquín Llácer, M.D., Ph.D.,[b] Jaime Guerrero, M.Sc. Ph.D.,[b] Ana Pitas, M.Sc. Ph.D.,[b] Andrea Bernabeu, M.D., Ph.D.,[b] and Rafael Bernabeu, M.D., Ph.D.[b]

[a] Bernabeu Institute, Reproductive Medicine, Palma de Mallorca, Spain; [b] Bernabeu Institute, Reproductive Medicine, Alicante, Spain; [c] Bernabeu Institute, Reproductive Medicine, Elche, Spain; and [d] Bernabeu Institute, Reproductive Medicine, Cartagena, Spain

Objective: To compare the oocyte yield between follicular-phase stimulation (FPS) and luteal-phase stimulation (LPS) in suboptimal responders.
Design: Prospective, randomized, crossover clinical trial.
Patient(s): Forty-one patients with infertility according to the POSEIDON (Patient-Oriented Strategies Encompassing IndividualizeD Oocyte Number) criteria (1b/2b).
Intervention(s): Crossover study on 2 assigned ovarian stimulations that started randomly in the follicular or luteal phase. The in vitro fertilization cycles were not consecutive but separated in time (45 days to 6 months). The random crossover design ensured that all subjects received the first treatment by chance.
Main Outcome Measure(s): The primary objective was the number of cumulus-oocyte complexes retrieved in each cycle. Secondary objectives were number of metaphase II and fertilized oocytes, additional doses of recombinant follicle-stimulating hormone, and the duration of ovarian stimulation (days).
Result(s): The mean number of cumulus-oocyte complexes retrieved was similar between the FPS and LPS groups (7.5 ± 4.6 vs. 7.0 ± 4.1; 95% confidence interval [CI] for the mean, 5.8–8.7 vs. 5.6–8.3, respectively; the difference between means, −0.5; 95% CI, −1.8 to +1.5). Similarly, the mean number of metaphase II oocytes retrieved was not different between the FPS and LPS groups (5.4 ± 3.6 vs. 5.2 ± 2.8; 95% CI for the mean, 4.2–6.5 vs. 4.3–6.1, respectively; the difference between means, −0.2; 95% CI, −1.2 to +1.1). Moreover, the secondary objectives were similar between FPS and LPS groups.
Conclusion(s): In this study, the oocyte yield in LPS did not increase in suboptimal responders compared with that in FPS when the onset of LPS was separated in time from FPS.
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Key Words: IVF, ovarian stimulation, follicular-phase stimulation, luteal phase stimulation, suboptimal ovarian responders

Poor response to controlled ovarian stimulation is a major challenge in assisted reproduction and affects 9%–24% of women undergoing in vitro fertilization (IVF). Improving follicle and oocyte count increases pregnancy rates in IVF/intracytoplasmic sperm injection treatments (1).

Little progress has been achieved in managing patients with reduced ovarian reserve or poor ovarian response (POR) to stimulation, being frustrating for patients and clinicians. Despite the efforts to optimize the definition of this patient's subgroup, the existing POR criteria comprise a heterogeneous population and lack of clinical guidance. Recently, the Patient-Oriented Strategies Encompassing IndividualizeD Oocyte Number (POSEIDON) group proposed a new stratification of assisted reproductive technology (ART) in patients with a reduced ovarian reserve or unexpected,

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Correspondence: Jorge Suñol, M.D., Bernabeu Institute, 8, Aragó, 07006, Palma de Mallorca, Spain (E-mail: jsunol@institutobernabeu.com).

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inappropriate ovarian response to exogenous gonadotropins (2). Four subgroups have been suggested based on quantitative and qualitative parameters (age and expected aneuploidy rate, ovarian biomarkers [antral follicle count and antimüllerian hormone], and ovarian response)—provided that a previous stimulation cycle was performed.

This new classification introduces a more nuanced picture of the "low prognosis patient" in ART, using clinically relevant criteria to guide the physician to optimally manage this group of patients. The POSEIDON group also introduced a new success measure for ART: the ability to retrieve enough oocytes from the patient to get at least 1 healthy embryo for transfer. This feature represents a pragmatic endpoint to clinicians and enables the development of prediction models aiming to reduce time to pregnancy. Consequently, the POSEIDON stratification should not be applied for retrospective analyses, having live birth rate as an endpoint. Such an approach would fail because the attribution of patients to each POSEIDON group is related to specific requirements and could only be made prospectively. On the other hand, any prospective approach (i.e., randomized controlled trial) should be performed separately in each specific group (3). The optimal number of oocytes for effective and safe ART is controversial but, in recent years, an effort has been made to define a group of patients with a poor prognosis due to low ovarian response. In 2011, the European Society of Human Reproduction and Embryology established the "Bologna criteria" to define poor response to IVF (4), criticized for including patients with different characteristics and poor prognosis regardless of any intervention (5). On the other hand, the POSEIDON group coined the concept of suboptimal responder (SOR) to identify patients (subgroups 1b and 2b) who may benefit from specific interventions to improve outcomes.

After this reasoning, patients with oocyte yields 4–9 (in the presence of adequate ovarian reserve parameters) might be considered SORs and of interest for clinical trials (6).

On the other hand, the sonographic documentation of 2–3 follicle waves in healthy women suggested that follicles seen in the luteal phase (LP) may have the potential to ovulate (7). Pioneering studies showed the feasibility of luteal-phase stimulation (LPS) to obtain viable eggs. For poor responders, the use of LPS after conventional stimulation has been proposed to increase egg retrieval (8, 9). Is the number of oocytes obtained in an IVF cycle different based on the timing of stimulation (follicular-phase stimulation [FPS] vs. LPS)? Although it is important to note that most studies do not demonstrate increased yield or improved outcomes, there have been a few studies that have reported higher oocyte yields in Duo-Stim protocols (9). This question deserves further investigation.

The aim of this study was to test whether controlled ovarian stimulation in the LP offers any advantage over the conventional follicular phase regarding oocyte yield SORs (POSEIDON subgroups 1b/2b). Secondary endpoints were the number of metaphase II (MII) oocytes, number of fertilized oocytes, additional doses of recombinant follicle-stimulating hormone (rFSH), duration of ovarian stimulation (days), endocrine profile, and number of follicles $\geq$ 17 mm on the triggering day. Other outcomes included the overall treatment cost and cancelation rate.

MATERIALS AND METHODS

The trial was approved by the Ethics Committee for Research involving medicinal products (reference, CEIm:2019/001) and by the Spanish Agency for Medicine and Health Products. All patients gave written informed consent to participate in this study. The EUDRACT number of the trial was 2019-001342-18, and the study was registered in ClinicalTrials.gov (NTC03939390).

Trial Design

This prospective, randomized, crossover clinical trial enrolled 41 patients with infertility with a clinical indication of IVF treatment and history of SOR in previous IVF cycles, including all women who have 4–9 cumulus-oocyte complexes (COCs) retrieved after conventional stimulation in the presence of adequate ovarian reserve markers. After fully informing the couples about voluntary participation in the study, they signed the informed consent form to agree to participate in the study and for each IVF cycle initiated.

Patients were randomly assigned to start stimulation in either the luteal or follicular phase. After completing the first stimulation and observing the waiting period, they were switched to the alternate treatment type (Fig. 1).

Participants

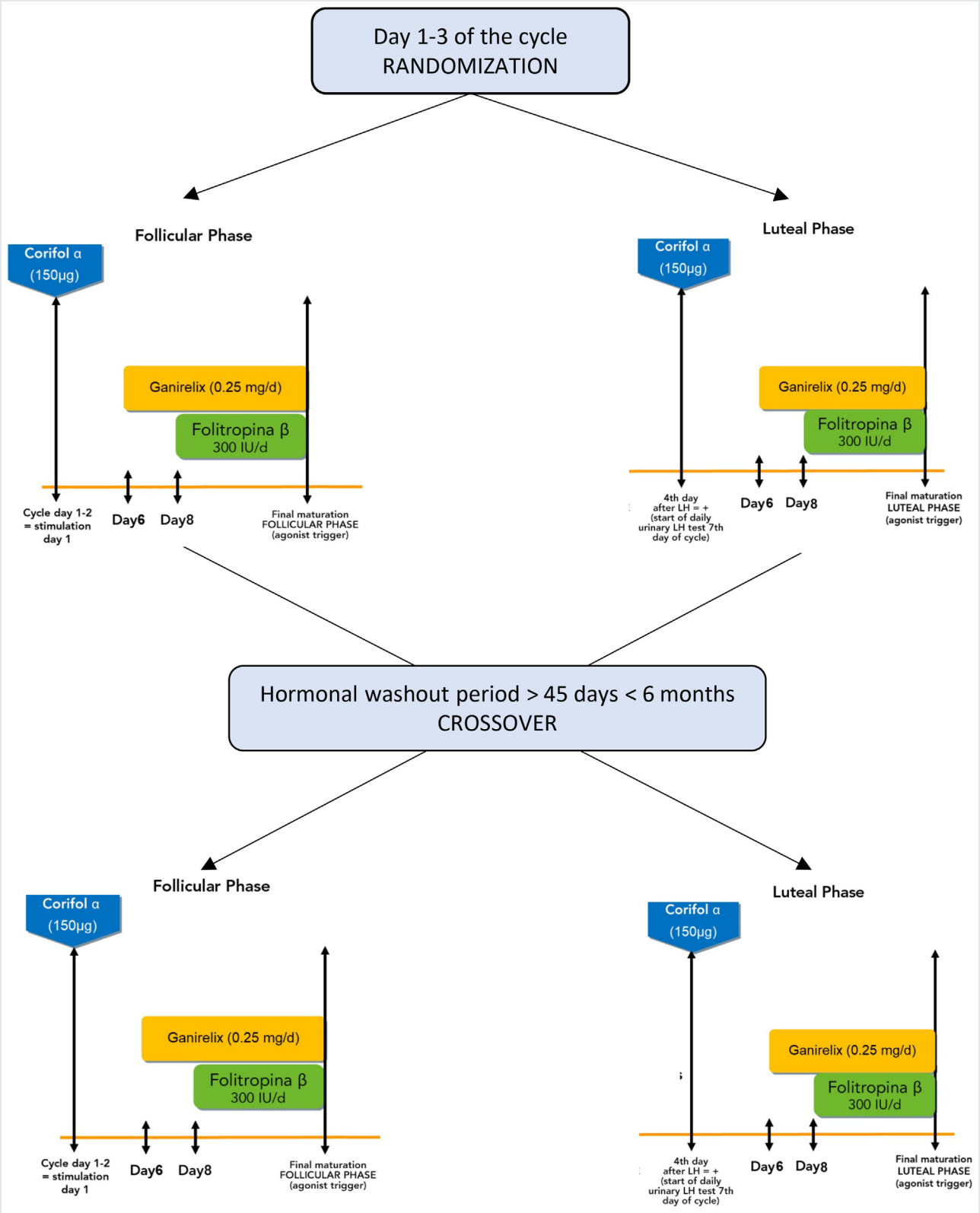
We conducted the study at the Fertility Units of Instituto Bernabeu in Alicante and Madrid. The trial began in January 2020; however, the coronavirus disease pandemic significantly slowed down the completion of the study, and the egg retrieval of the last patient was performed by April 2022. Eligible patients with infertility were SORs according to the POSEIDON criteria (POSEIDON group) (2) aged 18–41 years with regular menstrual cycles (21–35 days), the presence of both ovaries, and the ability to participate and comply with the study.

The exclusion criteria included women with ovarian follicles $>$ 10 mm in the randomization visit, endometriosis stage III/IV, concurrent uterine pathology (e.g., adenomyosis, submucosal myomas, and Asherman syndrome), and simultaneous participation in another study.

Interventions

Ovarian stimulation in the follicular phase Patients allocated to FPS received 150 μg of corifollitropin alfa (N.V. Organon, The Netherlands) on days 1–3 of the cycle after a baseline transvaginal scan, and the gonadotropin hormone-releasing hormone (GnRH) antagonist (ganirelix; N.V. Organon) on days 1–3 the cycle was added on day 6 of the stimulation cycle in a fixed protocol. On day 8, administration of a fixed daily dose of 300 IU of rFSH (follitropin beta, Puregon; N.V. Organon) was started until triggering. When at least 2 follicles reach $\geq$18 mm in diameter, 0.2 mg of

FIGURE 1



Schematic presentation of treatment groups.

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subcutaneous triptorelin (0.1 mg; IPSEN PHARMA, S.A. Barcelona, Spain) was administered, and oocyte retrieval was scheduled 36 hours later.

Ovarian stimulation in the LP Patients allocated to LPS started with daily urinary luteinizing hormone stick controls on day 7 until positive. Four days after the detection of luteinizing hormone peak, patients received 150 μg of corifollitropin alfa (N.V. Organon) after a baseline transvaginal scan. The additional controls, medication, and triggering criteria were identical to the FPS cycle.

Patients were requested to use a barrier contraceptive method during the cycle to prevent any unintended pregnancies that could occur during the process of ovarian stimulation in the LP and, thereby, mitigate the potential risks, specifically those related to ovarian hyperstimulation syndrome and poor laboratory outcomes (10, 11).

Both groups After retrieval, the mature oocytes collected were either cryopreserved or inseminated on the basis of the clinical criteria of each case. A new ovarian stimulation was commenced changing to the other group as per the crossover design. The administration of the 150 μg of corifollitropin alfa in the second ovarian stimulation did not occur before 45 days or after 6 months from the first oocyte retrieval. After the second pickup, oocytes were either vitrified or fertilized according to the clinical plan. It is important to note that in this trial, no fresh embryo transfer was performed in any case.

Outcomes

The primary outcome was the number of COCs collected. The secondary objectives included the number of MII oocytes, number of fertilized oocytes, additional doses of rFSH, duration of ovarian stimulation (days), endocrine profile, and number of follicles $\geq$ 17 mm on the day of triggering. Other outcomes included the overall treatment cost and cancelation rate. The study included costs for pharmacological compounds employed for ovarian stimulation purposes only, namely, gonadotropins and GnRH antagonists. We defined a canceled cycle as any cycle failing to progress to oocyte pickup after having received corifollitropin alfa and cancelation rate as the ratio of canceled cycles to the number of initiated ovarian stimulation cycles in both groups.

Blood Samples

Antimüllerian hormone, estradiol, and progesterone were assessed on the day of randomization. Progesterone and estradiol were additionally assessed on the day of the corifollitropin alfa administration, on the day of the GnRH antagonist initiation, and on the triggering day.

Sample Size

Sample size estimation showed that accepting an alpha risk of 0.05 and a beta risk of 0.20 (statistical power of 80%) in a matched pair design, a sample size of 34 patients was required to detect a minimum difference of 1 oocyte (standard deviation, $\pm$2 points) and a correlation between groups of 0.5. Assuming a dropout rate of 20%, a sample size of 41 patients was deemed appropriate. Furthermore, the difference of 1 COC—assuming the attainment of a mature oocyte (MII) and fertilization rate of 74% (9, 12)—would result in an augmented pool of available embryos. This increase holds clinical relevance, particularly for women with a history of suboptimal response to ovarian stimulation. Moreover, the difference of 1 COC, given the delivery rate of 5% per oocyte with IVF, would be likely to result in approximately 1 embryo difference between groups, assuming a fertilization rate of 74%; this difference would be clinically relevant in women with a previous suboptimal response (13, 14).

Randomization and Allocation of Patients

Patients were randomized to either FPS or LPS on days 1–3 of the menstrual cycle only after patient eligibility was established and patient's consent was obtained. Randomization sequence and allocation were created using a computer-generated randomization list, stratified by center, using 1:1 allocation. The randomization list was generated by the statistical program SAS (PLAN procedure, Copyright(c) 2002–2012 by SAS Institute Inc., Cary, NC), in such a way that both treatments have an equal probability of being assigned. Investigators had no access to this list. A nurse coordinator placed treatment allocation in a sealed, opaque envelope and picked it up consecutively at the moment of randomization. Patients were included in the study consecutively from the inclusion of the first eligible patient according to the screening criteria. The study was not blinded.

The prospective, randomized crossover design was chosen to assure that all subjects receive the 2 treatments randomly; thus, improving precision by basing the evaluation of the treatment on within-person comparisons. In addition, the subsequent ovarian stimulation cycle (either FPS or LPS) was performed with a temporal separation (hormonal washout period, $>$45 days and $<$6 months) allowing for an evaluation of the results concerning the different timing of the start of gonadotropin administration.

Statistical Analysis

We compared the COC of the follicular phase and LP (paired study) in patients to analyze our objective and, thus, to determine whether there is a benefit in using stimulation in any of the phases of the menstrual cycle (follicular vs. luteal).

The primary outcome (COCs) was analyzed using 2 different procedures: intention to treat (ITT) and per protocol (PP, complete cases). Thus, in the ITT analysis, all patients were included in the final analysis provided that after meeting the inclusion criteria, they were randomly assigned to one of the treatment groups, whereas the PP analysis included only patients who completed both FPS and LPS and were not lost to follow-up. To conduct the ITT analysis, it was necessary to perform a multivariate imputation of missing values, using the Multiple Imputation by Chained Equations method algorithm (15, 16), as described in other randomized controlled trials (17). In our case, we chose the imputation using the classification trees (cart) among the different options of the algorithm.

For categorical variables, a descriptive analysis was performed using frequency and percentage. Numerical variables were shown as counts, means, and standard deviations. The Shapiro-Wilk test was used to assess the normality of the distributions.

A comparison of the follicular-phase vs. LP cycles was performed using a paired study in which each patient is her own control. The means were compared using paired Student's *t*-test or the Wilcoxon test according to normal distribution. Qualitative variables were analyzed using McNemar's test.

To determine whether randomization had been performed correctly, the 2 groups were compared using the χ^2 test or Fisher's exact test for categorical variables and (in case of normal distribution) Student's *t*-test or the Wilcoxon rank sum test for numerical variables. Significance was defined as $P<.05$, and analysis was performed using R v4.1.2 and SPSS v20.0 software (Chicago, IL).

RESULTS

Overall, 41 suboptimal ovarian responders defined by the POSEIDON criteria were included in the study (CONSORT flowchart shown in Fig. 2). The mean number of oocytes obtained in previous IVF cycles was 5.9 ± 1.9.

The baseline characteristics of the randomized patients are presented in Table 1. The analysis showed no evidence of significant differences between groups.

Primary Outcome Measure

Using an ITT analysis, the number of COCs retrieved did not significantly differ between the FPS and LPS groups (7.5 ± 4.6 vs. 7.0 ± 4.1; $P=.5$; 95% CI for the mean, 5.8–8.7 vs. 5.6–8.3, respectively; the difference between means, −0.5; 95% CI, −2.1 to +1.1), as shown in Table 2.

In the PP analysis, excluding 2 patients (4 cycles), the number of COCs retrieved was still not significantly different between the 2 study groups (7.2 ± 4.4 vs. 7.1 ± 4.0; $P=.8$; 95% CI for the mean, 5.8–8.7 vs. 5.8–8.4, FPS vs. LPS, respectively; the difference between means, −0.1; 95% CI, −1.8 to +1.5) (Table 2).

Secondary Outcomes and Other Efficacy Endpoint Results

In the ITT analysis, the mean number of MII oocytes retrieved was not different between the FPS and LPS groups (5.4 ± 3.6 vs. 5.2 ± 2.8; $P=.6$; 95% CI for the mean, 4.2–6.5 vs. 4.3–6.1, respectively; the difference between means, −0.2; 95% CI, −1.2 to +1.1). Using the PP analysis, excluding the 2 patients who did not complete both FPS and LFP, the number of COCs retrieved did not change the direction of the results obtained (Table 2).

The number of fertilized oocytes was also similar between the FPS (4.3 ± 3.7) and LPS (4.0 ± 2.4) groups ($P=.286$). The total additional doses of rFSH (Puregon) and duration of stimulation did not significantly differ between the FPS and LPS groups. Similarly, the number of follicles ≥ 17 mm was not significantly different between the 2 groups compared with the triggering day. As expected, the estradiol levels were higher on the day of corifollitropin alfa in the LPS group but progressed to similar levels between groups in subsequent controls. The overall cost of ovarian stimulation was similar between the FPS and LPS groups (€924.77 vs. €924.77, respectively) (Table 2). In 1 patient, the cycle had to be canceled due to a lack of response in the first stimulation (FPS). This patient also decided not to proceed with the second stimulation; thus, the cancelation rate was 1 (0.01%) of 80 cycles.

DISCUSSION

In the present open-label randomized, crossover clinical trial, similar numbers of COCs were collected in the follicular-phase ovarian stimulation compared with those obtained in the LPS (7.2 vs. 7.1, respectively). Testing DuoStim IVF in suboptimal responders is of special interest because they may be one of the few ovarian response groups in which optimizing protocols could improve response to stimulation (6). Double stimulation has been proposed as one of the treatment strategies for the management of POSEIDON groups 1 and 2 demonstrating suboptimal response (6, 18). Limited research on SOR exists; however, early findings indicate that LPS (compared with FPS) in women with POR leads to better outcomes, such as higher numbers of retrieved mature eggs, fertilized oocytes, and day-3 embryos (19, 20).

A recent case-control study of 188 poor-prognosis patients with POR showed that FPS in DuoStim cycles resulted in fewer collected oocytes (3.6 ± 2.1) and euploid blastocysts (0.5 ± 0.8) compared with LPS (4.3 ± 2.8 and 0.7 ± 1.0, $P<.01$ and $P=.02$, respectively) (21).

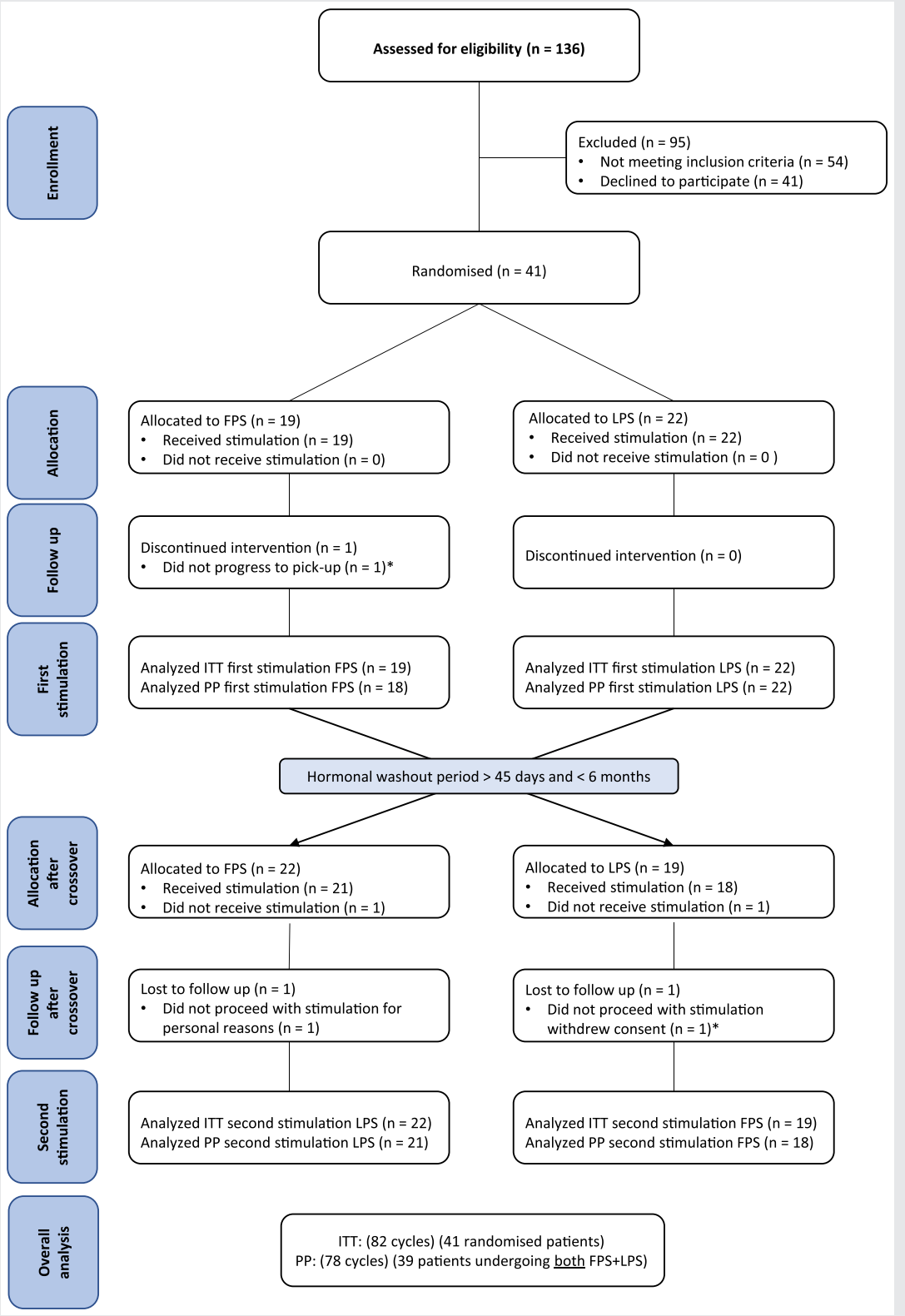
Thus, nonrandomized trials show a higher number of collected oocytes after LPS in POR.

However, our results found no significant difference in the cumulus-oocyte collection between FPS vs. LPS in SOR (difference, −0.5; 95% CI, −1.8 to +1.5), indicating that any difference between the protocols could not be attributed to merely initiating the stimulation in the LP.

As potential hypotheses, the differences may be due to a varying hormonal environment in LPS, starting right after FPS, which could enhance ovary receptivity to exogenous hormones, improving the recruitment of preantral and antral follicles. Alternatively, it is possible that clinicians intentionally choose not to aspirate all available follicles after the first FPS procedure. This decision may stem from the belief that the smaller follicles have the potential to continue growing and can be more easily aspirated during the LPS. The clinicians may anticipate that these smaller follicles could yield higher-quality oocytes and embryos. Thus, the presence of "physician bias" could play a role in this process.

The difference may also stem from the time gap between the 2 stimulation cycles and the order of initiation (e.g, the result of starting a second stimulation in the follicular phase after finishing the first cycle that started in the LP could not be determined) and the mechanical impact of follicular

FIGURE 2



Consort flowchart.

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TABLE 1

Baseline characteristics of the 2 treatment groups.

Variables	N	Overall, N = 41[a]	First LPS and second FPS, N = 22[a]	First FPS and second LPS, N = 19[a]	*P* value[b]
Age (y)	41	36.67 (2.78)	36.74 (2.84)	36.58 (2.78)	>.9
Body mass index (kg/m^2)	36	23.67 (3.85)	24.68 (4.24)	22.67 (3.22)	.13
Smoking	33				.4
Nonsmokers		24/33 (73%)	13/16 (81%)	11/17 (65%)	
Former smokers		5/33 (15%)	1/16 (6.2%)	4/17 (24%)	
Smokers		4/33 (12%)	2/16 (12%)	2/17 (12%)	
Basal estradiol (pg/mL)	39	45.77 (21.70)	43.51 (23.25)	48.15 (20.30)	.5
Basal progesterone (ng/mL)	39	0.20 (0.14)	0.18 (0.11)	0.23 (0.17)	.6
Basal FSH (mUI/mL)	40	8.43 (2.43)	8.57 (2.60)	8.28 (2.28)	.7
Basal LH (mUI/mL)	40	6.37 (2.89)	5.97 (2.65)	6.82 (3.16)	.4
AMH (ng/mL)	41	10.70 (7.51)	9.83 (6.22)	11.70 (8.84)	.5
AFC	39	9.72 (4.87)	9.52 (5.28)	9.94 (4.49)	.6
No. of previous ovarian stimulations	41	1.90 (1.14)	2.14 (1.36)	1.63 (0.76)	.3
No. of previous stimulations canceled	41				.5
0		38/41 (93%)	19/22 (86%)	19/19 (100%)	
1		2/41 (4.9%)	2/22 (9.1%)	0/19 (0%)	
2		1/41 (2.4%)	1/22 (4.5%)	0/19 (0%)	
Mean number of oocytes obtained in previous stimulations	41	5.99 (1.92)	5.61 (1.70)	6.43 (2.12)	.3
Cancelation	41				.5
No		40/41 (97.6%)	21/21 (100%)	18/19 (94.7%)	
Yes		1/41 (2.4%)	0/21 (0%)	1/19 (5.3%)	

AFC = antral follicle count; AMH = antimüllerian hormone; FSH = follicle-stimulating hormone; FPS = follicular-phase stimulation; LPS = luteal-phase stimulation.
[a] Mean (standard deviation), n/N (%),
[b] Wilcoxon rank sum test, Wilcoxon rank sum exact test, and Fisher's exact test.

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puncture on the ovary's cortical and medullar tissue during egg retrieval, which may activate the Hippo signaling pathway (22).

The key strength of our study is the separate evaluation of LPS from double ovarian stimulation, avoiding any priming effect from the previous stimulation. Using the same protocol

TABLE 2

Comparison of the follicular-phase vs. luteal-phase stimulation.

Primary outcome measure: intention-to-treat analysis

Variables	Overall, N = 82[a,b]	FPS, N = 41[b]	LPS, N = 41[b]	95% CI of the difference between means	*P* value[c]
No. of cumulus-oocyte complexes	7.27 (4.36)	7.51 (4.62)	7.02 (4.13)	−2.1 to 1.1	.546
No. of metaphase II oocytes	5.34 (3.22)	5.46 (3.63)	5.22 (2.80)	−1.4 to 0.9	.669
Primary outcome measure: per-protocol analysis					
Variables	**Overall, N = 78[b]**	**FPS, N = 39[b]**	**LPS, N = 39[b]**	**95% CI of the difference between means**	***P* value[c]**
No. of cumulus-oocyte complexes	7.18 (4.23)	7.26 (4.41)	7.10 (4.09)	−1.8 to 1.5	.85
No. of metaphase II oocytes	5.29 (3.18)	5.31 (3.57)	5.28 (2.77)	−1.2 to 1.1	.965
Secondary outcome measure: per-protocol analysis					
Variables	**Overall, N = 78[b]**	**FPS, N = 39[b]**	**LPS, N = 39[b]**		***P* value[c]**
No. of fertilized oocytes	4.18 (3.13)	4.33 (3.71)	4.00 (2.43)		.286
Total additional FSH dose	700.00 (510.92)	700.00 (547.72)	700.00 (478.48)		1.00
Duration of stimulation (d)	10.17 (1.70)	10.08 (1.74)	10.26 (1.68)		.570
No. of follicles ≥ 17 mm at trigger	6.40 (4.17)	6.38 (4.08)	6.41 (4.33)		.856
Estradiol (pg/mL) at trigger	1,500.18 (1,350.88)	1,528.86 (923.46)	1,471.49 (1,686.21)		.793
Cost of treatment (euros)	924.77 (229.91)	924.77 (246.48)	924.77 (215.32)		1.00

FSH = follicle-stimulating hormone.
[a] Multivariate imputation of missing values, using the Multiple Imputation by Chained Equations method algorithm.
[b] Mean (standard deviation).
[c] Paired t-test.

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for both cycles in the same participants but spaced apart by >45 days and <6 months, we can assess the results on the basis of different timing of gonadotropin administration and minimize distortion from the previous cycle. The 2-center design adds to the strength of this study by increasing the generalizability of the protocol and results.

Some study limitations need to be considered. First, the study was not blinded because of the intrinsic and obvious clinical and sonographic differences between a follicular phase and LP. Second, sponsorship by the pharmaceutical company manufacturing follicle-stimulating hormone medication can be considered as a possible bias. However, the company did not have any influence on the study and was not involved in the study design, data analysis, or interpretation of the study results. Finally, the study was not designed to explore outcomes beyond fertilization.

A note of caution should be introduced, although the investigators have provided complementary reassurance that no differences in euploid embryos are identified (23) and confirm the same rate of euploid embryos per mature oocyte microinjected, in the follicular phase or the LP of the DuoStim. Some doubts have arisen regarding the long-term safety of applying the DuoStim. The major concern involves the potential risk of forcing the maturation of the oocyte, not preselected by physiological mechanisms, during the development of the luteal cycle (24). The investigator draws attention to the lack of experience on the quality effect and unknown risk, gestation evolution, and newborns obtained with this type of oocytes. More studies need to be conducted in the future to confirm the safety of LPS, in terms of the ovarian (and follicular) environment, as well as clinical, perinatal, and postnatal outcomes.

All in all, the results obtained in this study are not consistent with previous reports finding differences according to the phase of ovarian stimulation initiation in favor of LPS. Although several studies have reported better outcomes with LPS when performed immediately after FPS (9), our study, which allowed for a time interval between stimulations, found no significant difference in oocyte yield between the 2 protocols. Additionally, key secondary measures, such as the number of MII oocytes, cancelation rate, stimulation length, and stimulation process cost, were comparable in both the FPS and LPS groups.

In conclusion, the current trial in a selected population of SORs (POSEIDON subgroups 1b/2b) provides evidence that LPS does not increase the number of oocytes obtained compared with FPS when the onset of LPS is separated in time. Additional studies are required to validate our results.

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