PROTOCOL

"Continuous ovarian stimulation in DUOSTIM cycles"

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Despite its growing popularity, ovarian stimulation over prolonged periods involves the application of a large number of injectable medications, resulting in an increased therapeutic burden for the patient. Therefore, there is a need for research into simplified protocols to guarantee optimal patient outcomes not affecting the DuoStim treatment efficiency. At present, we have the physiological basis and optimal drugs to achieve this objective.

1. Objectives

The present study aims to explore the progesterone and Corifolitropin alpha application in DuoStim cycles, following the follicular surges concept, in order to alleviate treatment burden in patients indicated for DuoStim cycles and without diminishing the technique's efficacy or safety. Could continuous weekly dosing constitute a viable alternative to daily FSH administration, to obtain a comparable oocyte yield?

2. Materials and methods

2.1. Study design and Patients

From November 2022 to May 2023, an observational cohort study was conducted at Instituto Bernabeu Alicante to assess non-inferiority. All procedures were performed in a single laboratory and the study was registered (NCT05815719) and validated by the Instituto Bernabeu review committee (IBMR31/01-06-2022). All subjects provided informed consent prior to participation.

The cohort included patients under the DuoStim protocol at the beginning of the stimulation process. Patients with ovarian pathology (e.g., cysts or tumours, with the exception of endometriomas <4 cm) at the time of stimulation initiation were not included.

Baseline determination included age, AMH levels and body mass index (BMI) measurements.

2.2. Procedures

On the one hand, the study group **(n=15)** received subcutaneous injections of 150 µg Corifolitropin alpha (Elonva®) consecutively for eight days, together with oral administration of micronized natural progesterone 200 mg/day (to prevent LH peak) during follicular and luteal phase.

On the other hand, the control group **(n=15)** was formed from historical records of patients undergoing DuoStim over the course of 2021 to 2022, following a standard daily FSH/flexible GnRH antagonist protocol. Controls were matched 1 to 1 for age and AMH values (± 0,4 pmol/l).

During follicular phase, the GnHR agonist was administered as trigger, whilst the use of hCG or GnHR agonist in luteal phase was permitted.

2.3. Result measurements

The study's main objective was to study the total number of obtained oocytes and the metaphase II stage oocytes rate (stimulation in follicular phase + luteal phase). Secondary objectives included: total number of required injectable and the duration of ovarian stimulation (total days of follicular and luteal phases):

- Stimulation in follicular phase: from the day of the first injectable administration in follicular phase and up to (inclusive) trigger day.
- Stimulation in luteal phase: starting from the day after the first punction up to and including trigger day in luteal phase.

2.4. Statistical analysis

A non-inferiority trial was planned with a minimum sample size of 13 patients per group, based on a tolerated difference of ± 1, a standard deviation of 1, a statistical power of 80%, and a type 1 error of 5%.

Data were presented as mean ± standard deviation (SD). As our data are not random but come from chosen cases and controls with similar age and AMH levels, the samples would be matched. Therefore, differences were analysed using Student's t-test for paired simples if variables had a normal distribution or, the Wilcoxon sign-rank test if a non-normal distribution was assumed.