COVER PAGE

Official Title:

Random-start Ovarian Stimulation in Egg-donors (ROSE) Trial: a Self-controlled Pilot Study

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STUDY PROTOCOL

1. Scientific background

Random-start ovarian stimulation (OS) cycles have been well described in oncologic patients for female fertility preservation. In this scenario, (usually) young women have initiated ovarian stimulation independently of the menstrual cycle following an specific ovarian stimulation protocol (1)

Recently, Kuang *et al*. (2) showed that it was feasible to perform a "lutheal phase" stimulation or even two consecutive ovarian stimulations in the same cycles (the so-called "DUOSTIM" protocol). This "luteal" phase stimulation protocol has been also described in egg-donors in a pilot trial (3). Importantly, in egg-donors, luteal phase stimulation seems to provide competent eggs.

The physiologic fundamentals for the optimal results in these "non-conventional" stimulation protocol is derived from the "follicular waves" theory described by Baerwald *et. al*. (4).

Of notice, random-start stimulation protocols initiating in the mid/to late follicular phase have been essentially in the oncologic population and, so far, optimal results are described (5-6). The same optimal results have been also described in luteal phase stimulation protocols, nonetheless, at least one study has related luteal phase stimulation protocol with suboptimal results in terms of pregnancy achievement (7).

The current trial aims to explore the concept of random-start stimulation protocols, namely, initiating ovarian stimulation on the mid/late follicular and luteal phase and to compare the results versus conventional stimulation protocols initiating OS in the early follicular phase in the egg-donor population. This approach might facilitate schedules in egg-donor IVF programs.

2. Methods

2.1 Design

This is a prospective, open, randomized, self-comparative, pilot study. The type of protocol (antagonist/GnRH-a trigger) and gonadotrophin type/dose will be identical between the study and control groups; except for the day of starting the OS process in relation to the last menses. The control cycle includes a conventional previous cycle underwent by the same population in the six previous months of the randomization, thereby, decreasing inter-subject variability. The eggs from the study group will be

inseminated using IVF conventional / ICSI using partner´s sperm. Fertilization will be evaluated 18-24 hours later.

2.2 Study population

a) Inclusion criteria:

- Egg-donors having at least one previous ovarian stimulation for egg-donation in our institution within the six months before being enrolled in the current trial.
- Regular cycles 27 +- 7 days
- Written / signed informed consent.

b) Exclusion criteria:

- Ovarian pathology at the moment of initiating COS (e.g ovarian cysts)
- Simultaneous participation in another study.

2.3 Objectives

a) Main outcome

- Total number of collected eggs
- Total number of metaphase II eggs
- Proportion of metaphase II eggs: total number/number of metaphase II

B) Secondary outcomes

- To evaluate the total number of days for COS
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- To evaluate the amount of gonadotrophin consumption (IU)

2.4 Statistical analysis plan and sample size

The sample size was calculated assuming a non-inferiority margin of 5 eggs SD 6.7 (based on: Devroey et al. Hum Reprod. 2009;24(12):3063-72). A unilateral alpha level of 0.05 was stablished. With the aim to show that the difference in the mean number of collected eggs will not exceed 5, a statistical power of 80% required 30 patients per group (1:1 allocation, total sample: 60). Statistical analysis was performed using t-student test for continuous variables and chi-square test for categorical parameters. A P value of <.05 was considered significant.

STUDY PROTOCOL OVERVIEW

Visit:	Schedule	Investigation:
Visit 0 (pre-study)	30 days prior to starting Controlled Ovarian Stimullation	· Verification of inclusion criteria · Informed consent form
Visit 1	From day 1º - 3º of the cycle for ovarian stimulation	· Signature of informed consent · Blood simple for Estradiol levels · Vaginal scan and follicular count · Height and weight · Randomization

STUDY GROUP:

Visit:	Schedule	Investigation:
Start of treatment (S1)	Beginning of gonadotrophins administration (according to randomization): - 5º day of the cycle - 7º day of the cycle - 9º day of the cycle - 11º day of the cycle - 13º day of the cycle	· Starting dose: identical to the dose used in the control cycle. · S1 refers to the first day of ovarian stimulation
Visit 2 (1st control)	On the 5º-6º of ovarian stimulation (S5-S6)	· Transvaginal scan and folliculometry · Starting of GnRH antagonist (Cetrotide®) · Blood samples: Estradiol, Progesterone, FSH, LH
Follow-up	Every 24-72 hours	· Transvaginal scan and folliculometry
Visit 3 (Agonist)	On the day of triggering (final follicular maturation)	· Transvaginal scan and folliculometry · Administration of 2 ampules of Decapeptyl® (0,2 mg triptorelin acetate) with follicles 18-20 mm.
Visit 4 (Egg collection)	Egg collection	· Transvaginal egg retrieval 36 hours after triggering. · Blood samples: Estradiol, Progesterone, FSH, LH.

CONTROL GROUP:

A previous cycle underwent by the egg-donor within 6 months previously to the inclusion in the study group for the ROSE trial; in brief:

- Day 1-2 of the cycle. Transvaginal scan and follicular count. Starting of gonadotrophins 150-225 IU (Fostipur®) according to BMI and AFC (D1 of ovarian stimulation).
- Day 5-6 of ovarian stimulation. Transvaginal scan and folliculometry. Starting of GnRH antagonists (Cetrotide®) beginning with a dominant follicle ≥ 14 mm.
- Follow-up every 24-72 hours.
- Administration of 2 ampules of Decapeptyl® (0,2 mg triptorelin acetate) with follicles 18-20 mm to induce the final follicular maturation.
- Transvaginal egg retrieval 36 hours after triggering

Main outcome

To evaluate and compare the total number and MII rate of eggs collected after beginning the ovarian stimulation in different moments of the follicular phase vs standard protocol.

Secondary outcomes

To evaluate differences with regards to the duration of the ovarian stimulation, FSH consumption and fertilization rates between groups.