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Homologous intrauterine insemination in controlled ovarian hyperstimulation cycles: A comparison among three different regimens

Luisa Casadei [a,*], Valentina Zamaro [a], Monica Calcagni [a], Carlo Ticconi [b], Maria Dorrucci [c], Emilio Piccione [b]

[a] *University of Rome "Tor Vergata", Department of Surgery, Division of Obstetrics and Gynecology, S. Eugenio Hospital, Piazzale dell'Umanesimo, 10, 00144 Rome, Italy*
[b] *University of Rome "Tor Vergata", Department of Surgery, Section of Gynecology and Obstetrics, Policlinico Tor Vergata, Rome, Italy*
[c] *Department of Epidemiology, MIPI Istituto Superiore di Sanità, Rome, Italy*

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Abstract

Objective: The objective was to assess the efficacy of double intrauterine insemination (IUI) over a single periovulatory IUI in patients undergoing controlled ovarian hyperstimulation with low-dose recombinant follicle stimulating hormone (rFSH) combined with human chorionic gonadotropin (HCG).
Study design: Ninety-four infertile women were randomly assigned to three groups; in group A (38 patients, 47 cycles) a single IUI was performed 36 h after HCG administration combined with timed intercourse the day of HCG administration; within group B (43 patients, 48 cycles) IUI alone was performed 36 h after HCG administration; in group C (39 patients, 43 cycles) a double IUI 12 and 36 h after HCG administration was performed.
Results: The mean age and the causes of infertility were similar between the three groups. The number of follicles greater than 15 mm on the day of HCG administration and the overall dose of rFSH required per cycle was not significantly different among the groups. The pregnancy rate (PR) per cycle and per patient was 14.9% and 18.4% in group A, 10.4% and 11.6% in group B, 20.9% and 23.1% in group C, respectively. There was no statistically significant difference in PR among the three groups.
Conclusion: In rFSH/HCG cycles, two IUIs performed 12 and 36 h after HCG administration do not significantly improve pregnancy rates over a single insemination performed 36 h after HCG administration combined with or without timed intercourse the day of HCG administration.

Keywords: Controlled ovarian hyperstimulation with rFSH; Intrauterine insemination (IUI); Timing of IUI; Pregnancy rate

1. Introduction

Controlled ovarian hyperstimulation (COH) combined with intrauterine insemination (IUI) is a procedure less expensive, stressful, complex and invasive than other assisted reproductive technologies with similar monthly fecundity rates [1–3].

There is consensus that COH combined with IUI should be attempted before IVF and GIFT in couples with unexplained infertility, ovulatory dysfunction, endometriosis in absence of anatomic distortion, cervical infertility, male factor infertility when there is evidence of patency of at least one fallopian tube [4–7].

There is consensus that COH combined with IUI is much more effective than either IUI or COH alone [8–12], that FSH/IUI significantly improves fecundity compared with untreated cycles, that the effects of FSH and IUI are independent [9].

* Corresponding author. Tel.: +39 0651002240; fax: +39 065919864.
E-mail address: Casadei@Med.uniroma2.it (L. Casadei).

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There is no consensus about the optimal time for IUI [13–19]. A window of several hours seems to exist in which IUI can be performed and randomized trials comparing single IUI with double IUI are lacking.

The purpose of this prospective, randomized study was to compare the efficacy of a single IUI performed in periovulatory period, combined or not with a timed intercourse before ovulation, with a double IUI performed before ovulation and in periovulatory period.

2. Materials and methods

2.1. Patients

Ninety-four infertile couples were prospectively included in the study from November 2001 to May 2003 at the Infertility Center of the S. Eugenio Hospital, University of Rome "Tor Vergata". The couples were selected from a larger group of infertile couples ($n = 525$), 401 couples were considered ineligible and of the 124 eligible couples, 30 declined to participate.

Mean age (±S.D.) of the patients was 35.0 ± 4.2 years ranging between 27 and 43 years. The average duration of infertility in years was 3.5 ± 2.0, ranging from 1 to 14.

Couples were evaluated with at least two semen analysis, hysterosalpingogram, and/or laparoscopy, transvaginal sonographic screening performed in the early follicular phase of cycle, ultrasonographic evidence of ovulation by a serial transvaginal ultrasound monitoring. In all women a basal FSH, LH, 17βE2, PRL, T, FT3, FT4, TSH measurements on day 3 of cycle were made after a spontaneous or progesterone-induced bleeding.

In PCOS patients screening included also BMI, serum assays of androstenedione (AD), sex hormone-binding globulin (SHBG), cortisol, dehydroepiandrosterone sulphate, fasting glucose and insulin.

The study was approved by the local ethics committee in accordance with the Helsinki Declaration for Medical Research involving Human Subjects. All patients gave their written informed consent before enrollment in the study and after a detailed explanation of the procedure.

The couples underwent COH-IUI cycles on the following indications:

a. *mild male factor* (at least two criterion of the following: sperm ana1ysis with 10 to 20 $\times$ 10^6 sperm/ml, 15%–25% progressive motility and/or <20 million progressively motile spermatozoa in the ejaculate, 30%–50% norma1 morphology);
b. *unilateral tubal factor* (delayed passage or interrupted passage through one tube, and/or signs of intraperitoneal adhesions, but evidence of at least one patent fallopian tube. Delayed passage through one tube was defined as the visualization of the passage of medium – radio-opaque or methylene blue in the case of hysterosalpingography or laparoscopy respectively – 30 seconds after the injection through the cervix. All hysterosalpingographies have been conducted in our department by means of video amplifier and television);
c. *PCOS* (oligomenorrhea-amenorrhea, combined with three or more of the following criteria: polycystic appearance of ovaries by transvaginal ultrasonography [20], obesity with BMI > 26 kg/m^2, hirsutism – Ferriman and Gallwey score > 8; hyperandrogenaemia, elevated LH Ievels – >10 mIU/ml – or an LH/FSH ratio >2, fasting glucose to insulin ratio of 4, 5 or less [21] and/or fasting insulin level of 15 mU/ml);
d. *endometriosis* (minimaI or mild endometriosis diagnosed visually at laparoscopy);
e. *unexplained infertility* (no evident fertility disorder found by the above standard fertility evaluation).

Diagnoses by cycle included unexplained infertility ($n = 38$), unilateral tubal factor ($n = 23$), male factor ($n = 46$), PCOS ($n = 13$), two infertility factors ($n = 18$).

The sample size of the present trial was based on the results reported by Ragni et al. [16], and it was estimated considering the following quantities: alfa = 0.05, expected proportion of pregnancy per patient = 15%, expected mean difference between groups = 10% (considered as clinically relevant for us), power of the test = 80%. Similarly, we calculated the number of cycles considering the same previous quantities [same alfa, clinically relevant difference and statistical power (80%)] except for the proportion of pregnancy that it was considered per cycle (equal to 10%; based on that reported per cycle by Ragni et al.). Further, the test used to determine the sample size was a Chi-squared for equal proportions in three groups with unequal n's applying nQuery Advisor.

2.2. Ovulation induction

Follicular stimulation was initiated with recombinant human follicle stimulating hormone (Gonal F. Serono Laboratories, Rome, Italy) at a dose of 75 IU/day for 6 days from day 2 of the cycle. A baseline transvaginal ultrasound scan was performed on day 2 of the cycle to rule out preexisting ovarian cyst(s), and from day 8 of the cycle follicular development was monitored by only transvaginal ultrasound examination every 1–3 days until the mean diameter of the dominant follicle reached ≥17 mm.

The initial dose of 150 IU/day for 5 days have been used in women with unilateral tubal factor, in order to increase the likelihood of the growth of at least one follicle in the ovary omolateral to the tuba that had been previously documented to be patent, the. The dosage was then reduced by 75 IU if the leading follicles achieved a mean diameter of 14 mm.

In oligomenorrhoeic or amenorrohoeic PCOS patients, a withdrawal bleeding was induced using progesterone 100 mg i.m. (Prontogest, Amsa s.r.l., Rome, Italy). In