A prospective, randomized and blinded comparison between 10,000 IU urinary and 250 µg recombinant human chorionic gonadotropin for oocyte maturation in in vitro fertilization cycles

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Purpose: To compare the efficacy and safety of u-hCG with r-hCG in IVF cycles.

Methods: A prospective, investigator-blind, randomized, comparative study. Patients (n = 100) ≤35 years with IVF indication were randomly assigned on the day of hCG administration for oocyte maturation to receive either u-hCG (10,000 IU) or r-hCG (250 µg).

Results: No statistical differences were found between groups in relation to total number of oocytes retrieved, percentage of mature oocytes, number of injected oocytes, fertilization rates and number of embryos transferred. The data indicate a possible trend toward a higher incidence of pregnancy in the r-hCG group. Adverse events, predominantly injection-site reactions, were significantly more common in the u-hCG group.

Conclusions: r-hCG is at least as effective for inducing final stages of oocyte maturation as 10,000 IU u-hCG and is also associated with significantly better patient tolerance and thus higher patient acceptability.

KEY WORDS: In vitro fertilization; luteinizing hormone; oocyte maturation; recombinant human chorionic gonadotropin; urinary human chorionic gonadotropin.

INTRODUCTION

It is well known that human chorionic gonadotropin (hCG) and luteinizing hormone (LH) have similar molecular structure and share 80% homology. Their capacity for binding to the same receptor was demonstrated more than 20 years ago (1). hCG extracted from the urine of pregnant women has been widely used in both men and women undergoing infertility treatment with gonadotropins.

The recent availability of recombinant hCG (r-hCG; Ovidrel®, Serono Inc., São Paulo, Brazil), produced by transfecting non-human cell lines (Chinese hamster ovary cells) with human genetic material, has obviously raised interest in the possible benefits of this medication over conventional u-hCG for final oocyte maturation in IVF/ICSI (intracytoplasmic sperm injection) cycles. The removal of urinary contaminants increases both the purity and the local tolerability of hCG. hCG can induce oocyte maturation and ovulation through its ability to trigger germinal vesicle breakdown and extrusion of the first polar body and induce an increase in progesterone production (2).
In limited, unpublished clinical studies, the half-life of r-hCG was estimated as \(\sim 30\) h (3). The efficacy of 250 \(\mu\)g r-hCG has been reported, and r-hCG has been shown to be well tolerated in the induction of final follicular maturation in women undergoing ART (4). Additionally, a dose of 250 \(\mu\)g r-hCG appears to be clinically equivalent to 10,000 IU u-hCG in this group (4).

A number of studies have compared r-hCG (250 \(\mu\)g) with a 5,000 IU dose of u-hCG. Driscoll et al., in a double-blind trial, found no statistically significant differences between intramuscular (i.m.) administration of u-hCG and subcutaneous (s.c.) administration of r-hCG in terms of the number of oocytes retrieved after stimulation with r-hFSH, meeting the predefined criteria for equivalence of the two drugs in ART (5). By contrast, a multicenter study comparing 250 \(\mu\)g r-hCG with 5,000 IU u-hCG reported that a statistically higher mean number of mature oocytes was retrieved for the r-hCG group than for the u-hCG group (9.4 vs. 7.1, respectively; \(p = 0.027\)) (6). This same study also reported significantly lower injection-site reactions for r-hCG, higher luteal progesterone levels and a trend to higher pregnancy and live birth rates in favor of r-hCG (33 vs. 25% and 27 vs. 23%, respectively). Finally, 250 \(\mu\)g r-hCG and 5,000 IU u-hCG have been shown to meet criteria for equivalence in women with group II anovulatory infertility who received hCG after follicular stimulation with r-hFSH in a chronic low-dose protocol (7). Again, local reactions to injection were significantly more common in patients treated with u-hCG.

The aim of the present study was to compare the efficacy of conventional u-hCG i.m. with r-hCG s.c. for inducing final oocyte maturation in IVF cycles, using a primary endpoint of mean number of retrieved oocytes.

**MATERIALS AND METHODS**

This prospective, blind, randomized comparative pilot study was conducted at Clínica e Centro de Pesquisa em Reprodução Humana Roger Abdelmassih, a private infertility center in São Paulo, Brazil.

**Patients**

One hundred patients \(\leq 35\) years of age and with indication for IVF were treated with a standard long GnRH agonist protocol of ovarian stimulation performed with r-hFSH (Gonal F\textsuperscript{®}, Serono Inc., São Paulo, Brazil). Informed consent was obtained from all patients enrolled in the study the approval for which was given by the local Ethical Committee.

**Treatment**

Pituitary down-regulation was achieved after 14 days of s.c. leuprolide acetate (Reliser\textsuperscript{®}, Serono Inc., São Paulo, Brazil), started on day 21 of the menstrual cycle (1 mg s.c. for 3 days followed by 0.5 mg daily up to day 5 of ovarian stimulation). r-hFSH (Gonal-f\textsuperscript{®}, Serono Inc., São Paulo, Brazil) was administered with 300 IU/day after transvaginal ultrasonography revealed a thin endometrium and, on the same day, serum estradiol (E\textsubscript{2}) concentrations were \(< 40\) pg/mL. After 5 days of stimulation, the GnRH agonist dosage was lowered to 0.25 mg/day. Ultrasond and E\textsubscript{2} monitoring were performed daily after 7 days of ovarian stimulation.

When at least two follicles of \(\geq 18\) mm mean diameter were detected, the GnRH agonist was discontinued and patients were randomly assigned to enter one of two groups: In the group receiving u-hCG, final oocyte maturation was induced with i.m. u-hCG (Profasi\textsuperscript{®} 10,000 IU, Serono Inc., São Paulo, Brazil), while in the group receiving r-hCG, final oocyte maturation was induced with s.c. r-hCG (Ovidrel\textsuperscript{®} 250 \(\mu\)g, Serono Inc., São Paulo, Brazil). Each patient was randomized blindly (using a computer-generated list) by a nurse on the day of hCG administration. The injection volume was 1.0 mL, the same for both hCG products. Patients self-administered the hCG injection. Prior to oocyte retrieval, a nurse interviewed the patient regarding injection site reactions attributed to the hCG injection.

For both groups, oocyte retrieval was carried out after a 34–36 h interval. Oocytes were denuded 1 h after retrieval with a Stripper Pipette\textsuperscript{®} 35 \(\mu\)m (Mid Atlantic Diagnostics Inc., Marlton, NJ, USA). Embryo transfer was performed 48–72 h later. Luteal phase support was started on the day of oocyte aspiration with vaginal progesterone, 90 mg twice a day (Crinone\textsuperscript{®}, Serono Inc., São Paulo, Brazil). Physicians responsible for ovarian stimulation follow-up, oocyte retrieval, and embryo transfer, as well as biologists involved in laboratory procedures, were not aware of the group to which each patient belonged.

**Assessment**

The primary endpoint of the study was the mean number of oocytes retrieved. Secondary study