Effect of 17α-hydroxyprogesterone caproate before embryo transfer on the outcome of in vitro fertilization and embryo transfer: a randomized trial

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Objective: To assess the effect of 17α-hydroxyprogesterone caproate (17-HPC) given before embryo transfer on the pregnancy outcome of IVF–embryo transfer (ET) cycles.
Design: Randomized controlled study.
Setting: A university-based hospital IVF unit.
Patient(s): One hundred twenty-five consecutive patients undergoing IVF-ET were randomly assigned into treatment and control groups.
Intervention(s): In the treatment group, 63 patients received 17-HPC (250 mg, IM), 1 day before ET. The control group consisted of 62 patients who did not receive any injections.
Main Outcome Measure(s): Pregnancy and multiple-pregnancy rates.
Result(s): The two groups were similar with respect to the age of patients, total dose of FSH, number of oocytes and embryos obtained, and number and quality of embryos transferred. There was no significant difference in the pregnancy rate (34.9% vs. 38.7%) or in the rate of multiple gestation (15.9% vs. 9.7%) between cases and controls, respectively.
Conclusion(s): The use of 17-HPC before ET does not appear to affect the outcome of IVF-ET. (Fertil Steril® 2008;89:1098–102. ©2008 by American Society for Reproductive Medicine.)

Key Words: 17α-hydroxyprogesterone caproate, IVF-ET, pregnancy outcome

The attempt to improve the implantation process in IVF–embryo transfer (ET) programs has been the subject of numerous studies. Most of these studies have focused on the induction and selection of the best quality embryos and on the improvement in uterine receptivity. Several developments in controlled ovarian hyperstimulation (COH), fertilization, and embryo culture techniques have contributed to the improvement of the quality of embryos that are available for ET. In contrast, little has been achieved in improving uterine receptivity. The evaluation and improvement of uterine receptivity are limited by the fact that the process of implantation is regulated by multiple and complex morphological and biochemical factors (1). Thus, all of these factors should be investigated simultaneously to clearly assess the receptivity status of the endometrium. In addition, tissue sampling for the direct assessment of markers of uterine receptivity is inherently impossible in the actual ET cycles.

Recently, the direct visualization of the uterine contractile activity by using high-resolution ultrasound has been evaluated as a noninvasive prognostic factor of uterine receptivity (2, 3). The uterus has typically three patterns of contractility throughout the menstrual cycle that influence embryo implantation (4–7). Increased uterine contractility at the time of ET has been shown to adversely affect embryo implantation and pregnancy rates in IVF, probably because of the mechanical expulsion of embryos from the uterine cavity (8). This suggests that uterine contractility can be an important factor in determining endometrial receptivity. Embryo transfer itself can provoke a uterine response as a result of stimulation of the cervix and intracavitary canalization. In this respect, it has been suggested that the use of adjuvants, such as uterine relaxants, to decrease uterine contractility during ET should be considered to prime a uterus and make it suitable for embryo implantation (9).

Progesterone acts to relax smooth muscles in many organs, including the uterus. 17α-Hydroxyprogesterone caproate is a P derivative. Esterification of 17α- hydroxyprogesterone with caproic acid provides much greater and more prolonged progestational activity after IM injection. The aim of this study was to examine the effect of 17-HPC treatment for priming of the uterus on the pregnancy outcome in IVF-ET cycles. The hypothesis was that 17-HPC would improve the pregnancy rate in IVF-ET cycles.

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MATERIALS AND METHODS

This study was performed on 125 consecutive patients undergoing IVF-ET at the IVF Unit of the American University of Beirut Medical Center. All patients who presented for their first IVF cycle at our center were eligible to participate in the study. The study included women who underwent IVF between June and December 2006 because of tubal, male-factor infertility, unexplained, polycystic ovary syndrome, or endometriosis factors. Tubal-factor infertility was based on laparoscopic diagnosis of severe pelvic adhesions or blocked tubes. Male-factor infertility was considered when at least two semen analyses were abnormal according to the World Health Organization laboratory manual (10). Patients were considered to have unexplained infertility if their workup was negative, including normal semen analysis, patent tubes confirmed by either a hysterosalpingogram or laparoscopy, and ovulatory cycles. The diagnosis of polycystic ovary syndrome was made according to the Rotterdam consensus (11). None of the patients who were eligible for the study declined to participate.

After the two IVF specialists (A.A.-M. and A.H.) checked them for eligibility, the 125 patients were randomly divided into treatment and control groups by using computer-generated random tables (generated by A.N., a non-IVF specialist). Randomization was performed after oocyte pickup by using sealed envelopes. The infertility specialist attending to the patients was not blinded to the arm to which patients were assigned; however, the research assistant who entered the data and performed the statistical analysis was. The primary outcome of the study was to assess the difference in pregnancy rate between patients and controls.

The study was institutional review board approved, and patients were not entitled to any financial reimbursement.

Controlled Ovarian Stimulation and Intracytoplasmic Sperm Injection Procedures

Controlled ovarian hyperstimulation was performed by a long standard protocol with GnRH agonist (GnRH-a; Decapeptyl, Beaufour Ipsen Pharma, France) and recombinant FSH (Puregon, Organon, the Netherlands). In brief, GnRH-a was started in the mid-luteal phase at a daily dose of 0.05 mg until the day of hCG injection. Recombinant FSH (200 U/d) was started on the 3rd day of the cycle. Follicular development was assessed by transvaginal ultrasonography. When at least two dominant follicles were $\geq$18 mm, hCG (10,000 IU; Pregnyl, Organon) was administered. Oocyte retrieval by transvaginal ultrasonographic guidance was performed approximately 36 hours after the hCG administration. Intracytoplasmic sperm injection was used almost routinely in all our patients regardless of the cause of infertility; however, regular IVF was used in a few patients according to the preference of the attending physician. The ET was performed with a Wallace transfer catheter (Smiths Medical, Hythe, Kent, UK) 2 days after oocyte recovery under ultrasound guidance. The embryos were scored according to a grading system published elsewhere (12). All patients received vaginal micronized P (200 mg) every 8 hours, starting the afternoon of the oocyte pickup and continuing up to the day of β-hCG measurement; this was maintained throughout the first trimester if the β-hCG was positive.

There were two outcome variables in this study. The clinical pregnancy rate was defined as the presence of a positive fetal heart rate, detected by vaginal ultrasound that was performed 20 days after a positive pregnancy test. Multiple pregnancy was defined as the presence of two or more gestational sacs with positive fetal heart rates.

Treatment With 17-HPC

Patients in the treatment group received a dose of 17-HPC (Proluton depot, 250 mg, IM; Schering, Germany) 24 hours before ET, whereas patients in the control group did not receive any injections.

Statistical Analysis

Data entry was performed by using SPSS software (SPSS for Windows XP, version 12; SPSS, Chicago, IL), and statistical analysis was performed by using the Mann-Whitney test for nonparametric variables. For discrete variables, the χ^2-test was used, and the Fisher's exact test was used if the expected number in a cell was less than five or when >20% of the expected counts were <5 or if any were <1. Multiple logistic regression was used to identify significant factors affecting clinical pregnancy rates.

A P value of $<.05$ was considered statistically significant. Odds ratios (ORs) for outcome variables, with 95% confidence intervals (CIs), were cited where appropriate.

RESULTS

Cases and controls were similar with respect to the age of patients, total dose of FSH, number of oocytes and embryos obtained, and number and quality of embryos transferred (Table 1). However, the percentage of patients undergoing intracytoplasmic sperm injection was significantly lower in controls, and the percentage of patients $\geq$40 years of age tended to be higher in controls. This is believed to be entirely due to chance, because the study was a randomized trial. The two groups had similar pregnancy rates (OR, 0.85; 95% CI, 0.41–1.75; Table 2). Although there was a tendency for an increase in the rate of multiple gestation in the 17-HPC group (45.5% vs. 25.0%), this difference did not reach statistical significance (OR, 1.76; 95% CI, 0.62–5.00).

When the pregnancy rates were compared according to the causes of infertility, there was no significant difference between the treatment and control groups. There was also no significant difference in total pregnancy rates between the two groups when they were subgrouped according to age (Table 3). Multiple logistic regression including factors of age of $\geq$40 years, Proluton, and intracytoplasmic sperm injection showed no significant association between Proluton