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Luteal Phase Support with 17α-Hydroxyprogesterone versus Unsupported Cycles in in vitro Fertilization: A Comparative Randomized Study

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Key Words

Luteal phase · 17α-Hydroxyprogesterone · In vitro fertilization · Placebo

Abstract

This study was designed to determine the efficacy of 17α-hydroxyprogesterone caproate (17-OHPc) for luteal phase support in in vitro fertilization (IVF). For this purpose, a total of 86 IVF patients undergoing embryo transfer were randomly allocated to two groups as follows: (1) group A, including 43 patients who received the support of luteal phase through the intramuscular administration of 17-OHPc at a dosage of 341 mg every 3 days, and (2) group B, including 43 patients who received the intramuscular administration of a saline solution as placebo every 3 days. In both groups, the treatment was started within 24 h after embryo transfer until β-HCG evaluation. In case of positive β-HCG, it was extended until 12 weeks. Efficacy was assessed using the pregnancy rates, which was, per transfer, statistically significantly higher in group A than in group B (32.5 vs. 18.3% respectively). On the basis of our results, we emphasize the use of 17-OHPc for luteal phase support after IVF and embryo transfer.

Introduction

Establishment of a successful pregnancy requires a complex preparation of the endometrium beginning in the proliferative phase and extending throughout the luteal phase. Late luteal phase hormonal deficiencies may impair endometrial growth and might lead to failure or abnormal implantation [1–3].

Luteal phase support is routinely used in in vitro fertilization (IVF). This approach is based on the earlier observation that pregnancy rate is higher in IVF cycles with a significantly higher progesterone serum level [4, 5]. Nevertheless, subsequent trials produced conflicting results either regarding the choice of the drug supporting the luteal phase or the effectiveness of the luteal phase support itself [6].

It has been demonstrated that natural progesterone improves pregnancy rate in IVF cycles using a down-regulation protocol; it is also preferred in cases with an increased risk of ovarian hyperstimulation syndrome (OHSS) [3]. On the other hand, human chorionic gonadotrophin (HCG) is a better luteal support in ultrashort protocols [7].

The aim of this study is to determine whether the use of luteal phase support through the 17α-hydroxyprogesterone caproate (17-OHPc), which is a synthetic progestin, improves the establishment of a successful pregnancy in IVF cycles. Therefore, two groups of patients were com-

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pared regarding the pregnancy rates: group A including patients who received the 17-OHPc to support the luteal phase and group B including patients who received a placebo after embryo transfer (ET).

Materials and Methods

Patients

A total of 86 IVF patients (duration of infertility ≥ 3 years), undergoing ET for the first time and aged ≤ 37 years, were randomly allocated to either treatment of this study between March 1996 and February 1997. The indication for the assisted reproductive technique was the tubal factor.

Controlled Ovarian Hyperstimulation

All patients underwent pituitary desensitization by the administration of GnRH-a 400 μg subcutaneously twice a day from day +20 of the previous menstrual cycle until the injection of HCG 10,000 IU intramuscularly. Then, COH was performed in all patients by administration of follicle-stimulating hormone. Patients were monitored measuring plasma concentration of 17β-estradiol and by ultrasonographic determinations of follicular size and number on days +5, +7 and +12 of stimulation. The dosage of gonadotrophins was adjusted according to the individual response. HCG 10,000 IU was injected intramuscularly in all patients when serum 17β-estradiol exceeded 200 pg/follicle and when there were at least 3 follicles with a minimum diameter of 18 mm.

In vitro Procedures

Oocytes were retrieved 34–36 h after HCG administration under vaginal ultrasound control (day 0). IVF medium (Medi-Cult A/S, Innogenetics, Denmark) was used for culturing. Spermatozoa for insemination were prepared using the swim-up technique. The embryo transfer was performed at the 2- to 4-cell stage, 40–44 h after insemination (day +2). A maximum of 4 embryos was placed.

Luteal Phase

Starting the day before ET (day +1), all patients were randomly allocated in two groups:

Group A (n = 43 ET cycles): intramuscular administration of 341 mg every 3 days of 17-OHPc, which is a synthetic progestinic preparation available in Italy).

Group B (n = 43 ET cycles): intramuscular administration of saline solution every 3 days as placebo.

Treatment was continued until β-HCG evaluation (day +14). Blood samples for 17β-estradiol and progesterone serum level evaluations were taken every 2 h for 12 h on days +1 and +2 after oocyte retrieval. In case of positive β-HCG, morning blood samples were requested once a week until the end of luteal phase.

Assays

17β-Estradiol and progesterone serum levels were determined by radioimmunoassay.

Statistical Comparison

Statistical analysis was performed using χ^2 test. $p < 0.05$ was assumed as significant.

Results

Patients' characteristics were identical for the two groups. The mean ages were 32.6 ± 3.2 and 33.1 ± 3.0 years respectively for groups A and B. The indications for the treatment were similar. There was no significant difference in the mean dosage of FSH (15.2 ± 5.2 vs. 16.1 ± 6.7 ampoules/cycle), in the duration of treatment (11.5 ± 1.7 vs. 10.8 ± 1.5 days) and in the number of preovulatory follicles (8.7 ± 4.6 vs. 8.5 ± 4.6) on the day of HCG administration (table 1).

The number of oocytes per transfer cycle (8.6 ± 4.9 vs. 8.2 ± 4.1), percentage of oocytes at metaphase II (78 vs. 80%), regular fertilization at the two pronuclei stage (75.6 vs. 72.9%) and cleavage rates (84.5 vs. 85.8%) were not statistically different between the two groups. The number of transferred embryos was also similar (3.2 ± 1.3 vs. 3 ± 1.5). Moreover, there was a higher pregnancy rate (PR) (32.5 vs. 18.3%) in group A (supported with 17-OHPc) than in group B (unsupported), marking the importance of progestinic support in the luteal phase (table 2).

Table 1. Patients' characteristics in the two study groups

Patients' characteristics	Group A 17-OHPc	Group B Unsupported
Patients	43	43
Age	32.6 ± 3.2	33.1 ± 3.0
Days of Gn treatment	11.5 ± 1.7	10.8 ± 1.5
FSH ampuoles	15.2 ± 5.2	16.1 ± 6.7
Follicles ≥ 16 mm	8.7 ± 4.6	8.2 ± 4.1

Table 2. Results of fertilization, cleavage and pregnancy rates in the two study groups

Parameters	Group A 17-OHPc	Group B Unsupported
Oocytes/transfer	8.6 ± 4.9	8.2 ± 4.1
Metaphase II oocytes	78%	80%
Fertilization rate	75.6%	72.9%
Cleavage rate	84.5%	85.8%
Embryos/transfer	3.2 ± 1.3	3 ± 1.5
Pregnancy rate	32.5%	18.3%

The administration of 17-OHPc resulted in a significant increase from the baseline after 5 h (41.9 ± 13 vs. 8.9 ± 5.3 ng/ml). There was not any statistical difference in 17β-estradiol serum levels between the two groups.

Discussion

This study confirmed the effectiveness of luteal phase support in IVF cycles using a long-term protocol and demonstrated the advantages of the use of a synthetic progestin, i.e. 17β-OHPc.

Previous studies demonstrated the importance of administering progesterone to support the luteal phase [6]. In this regard, progesterone was administered through oral or transvaginal route and it was demonstrated that the pregnancy rate (PR) per transfer is not significantly different but the vaginal preparation is more advantageous because it avoids metabolic inactivation of progesterone during its first liver pass [8–10]. However, other studies demonstrated that there are disturbances of the endometrium in the luteal phase of cycles stimulated for IVF and of normal cycles treated with vaginal progesterone [1].

Moreover, a study which compared three different protocols for luteal phase support (group I intramuscular progesterone, group II vaginal progesterone and group III unsupported) demonstrated that PR differences were statistically significant only between group I and groups II and III, but between groups II and III there were no statistically significant differences [11].

Without any doubt, natural progesterone plays an important role in supporting the luteal phase [6], but there is also evidence that synthetic progestinic preparations are very important in different pathologic situations, such as in threat of recurrent abortions [12, 13], to prevent development of endometrial hyperplasia [14], and in the peri- and postmenopausal osteopenic pathology [15]. In particular, 17-OHPc appears to be the drug of choice in the support of the luteal phase because of its better acceptance if compared to the standardized natural progesterone preparation that is administered daily through the intramuscular route.

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