17-alpha-hydroxyprogesterone caproate and natural progesterone in assisted reproduction: a comparative study.

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Summary

The use of luteal phase support has been demonstrated in patients undergoing an IVF/ET procedure. This study was designed to compare the absorption and the efficacy of two different luteal supports: 17-alpha-hydroxyprogesterone caproate (Lentogest, AMSA, Italy) and natural Progesterone (Prontogest, AMSA, Italy). A total of 80 patients received luteal supplementation with 50 mg of natural P/day intramuscularly, until ß-hCG evaluation. Then, in case of positive ß-hCG, patients were randomly dividied into two groups (A and B) in order to compare two different protocols: Group A, 17-OHPc (341 mg once a week) and Group B, natural P (50 mg/day) both intramuscularly and extended for 10-12 weeks. Our study showed that the treatment with 17-OHPc results in a higher percentage of pregnancy rate compared to natural P, but the differences are not statistically significant. Thus, we emphasize that 17-OHPc preparation for better acceptance appears to be the most suitable and comfortable method for luteal phase support.

Introduction

The role of progesterone (P) support in pregnancy is incompletely understood, but it appears to be effective for implantation and manitenance of early gestation [1]. Several steps are involved in this process. In particular, fertilization, implantation and post-implantation embryo development are very important stages for the establishment of a successful pregnancy. Nevertheless, implantation appears to be the major limiting step in the reproductive process. Probably it is because of frequent luteal phase deficiency (LPD) due to insufficient progesterone production by the corpus luteum. This results in inadequate endometrial conditions for embryo implantantion [2, 3].

It is still an open question if *in vitro* fertilization-embryo transfer (IVF-ET) techniques, such as superovulation induction and oocyte aspiration, are responsible for luteal phase deficiency [3, 4]. The necessity of luteal phase support after GnRHa/Gn stimulation for IVF cycles has been provided by prospective randomized studies [5, 6]. Recent evidence suggests that natural progesterone (P) could be succesfully used in this aim [1].

Natural P plays a role in the induction of endometrial maturation in oocyte donation programmes [7, 8], in frozen embryos [9, 10] and blastocystis transfers [11], in persistently retarded endometrium maturation [12] and in 17-alpha-hydroxylase deficiency syndrome [13]. Without any doubt, the most important role of P is as luteal phase support.

Moreover, many authors believe that 17-alpha-hydroxyprogesterone caproate (17 OHPc), which is a synthetic progestinic preparation, plays an important role in the treatment of threatening and recurrent abortions [14, 15]; in the prevention of endometrial hyperplasia [16] and in the treatment of peri- and postmenopausal osteopenic pathology [17].

The aim of our study was to compare the effectiveness and the absorption of two different preparations for early luteal phase support of GnRHa/Gn stimulated IVF cycles: 17 OHPc (Lentogest, AMSA, Italy) and natural P (Prontogest, AMSA, Italy).

The former derives from progesterone. It has no estrogenic and androgenic effects, whereas, its progestinic effectiveness is four times higher than natural progesterone. It is administered intramuscularly once a week at a dose of 341 mg, which corresponds to a dosage of 250 mg of Prontogest. It provides endometrial secretory transformation within 48 hours after administration, and its effect lasts for 8-10 days.

The latter is administered intramuscularly at a dose of 50 mg per day. It provides endometrial secretory transformation within 2 hours after administration and its effect lasts for 24 hours.

Material and Methods

Patients

A total of 80 patients, aged ≤ 37 years entered the IVF programme if the diagnoses were tubal patency, oligospermia or unexplained infertility.

Two groups of 40 patients comparable for age and clinical indications for assisted reproduction, were randomly allocated after informed consent, to either treatment from September 1996 to August 1997.

Treatment protocol

Prior to ovarian stimulation, GnRHa (Buserelin-Suprefact, Hoechst/UK, Ltd) 400 µg by subcutaneous injection was admi-

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nistered twice a day from day +20 of the previous menstrual cycle until HCG administration (Table 1).

In general, after 14 days of densitization (17-ß-Estradiol plasma levels < 40 ng/l; LH < 6 mIU/ml), all patients were administered follicle stimulating hormone (pFSH, Metrodin, Serono, Italy; 75 IU FSH/ampoule).

Follicular growth was assessed on days +5, +7 and +12 of stimulation by monitoring of serum concentrations of 17-ß-Estradiol (17-ß-E_2) and by ultrasonographic determinations of follicular size and number. Thus, the dosage of gonadotrophins could be adjusted according to individual response. When serum 17-ß-E_2 concentration exceeded 200 pg/follicle and when, at ultrasound, at least three follicles had a minimum diameter of 17 mm, 10,000 IU of human chorionic gonadotropin (hCG, Profasi, Serono, Italy) was administered by intramuscular injection, in all patients, in order to induce ovulation (Table 1).

Oocytes were retrieved 34-36 hours after hCG administration (day 0), under ultrasound vaginal control. An intra-uterine transfer of pre-embryos from the 2nd to 4th cell stage was performed 40-44 hours after insemination (day +2). A maximum of four embryos were placed.

Starting the day before embryo-transfer (day +1), all patients received luteal phase supplementation with 50 mg of natural P (Prontogest, AMSA, Italy) administered intramuscularly until ß-hCG evaluation (day +14).

Then, in case of positive ß-hCG, patients were randomly divided into two groups (A and B) in order to compare two different treatment protocols:

1. Group A (n = 40 ET-cycles): 341 mg of 17-OHPc (Lentogest, AMSA, Italy) was administered intramuscularly once a week for 10-12 weeks.

2. Group B (n = 40 ET-cycles): 50 mg per day of natural P (Prontogest, AMSA, Italy) was intramuscularly administered for 10-12 weeks.

Morning blood samples were requested on days +7, +12 after transfer and in case of positive ß-hCG, once a week until the end of the luteal phase support.

Assays

17-ß-E_2 and P serum concentration were evaluated by radioimmunoassay (RIA), utilizing tritiated tracers and a Dextran T-70 coated charcoal separation (materials purchased from Radim, Rome, Italy).

Intra- and interassay coefficients of variations were 6.5% and 11.5%, respectively, for 17-ß-E_2. Intra- and interassay coefficients of variations were 6.2% and 10.8%, respectively, for P.

Statistical analysis

Statistical differences were evaluated by applying the chi-square test. P<0.05 was considered as appropriate.

Table 1. — *Patient characteristics in the two study groups*

Patient characteristics	Group A 17-OHPc (Lentogest protocol)	Group B Natural P (Prontogest protocol)
No. of patients	40	40
Age*	30.2±1.5	29.1±3
Days of Gn treatment*	12.5±1.5	11.7±2
FSH ampoules*	16.1±5.8	15.9±6.1
Follicles ≥ 16 mm*	8.2±3.2	8.3±3.5
Metaphase II oocytes	85%	87%

* Values are mean ± SD

Table 2. — *Results of fertilization and cleavage in the two study groups*

Parameters	Group A 17-OHPc (Lentogest protocol)	Group B Natural P (Prontogest protocol)
Fertilization rate	71.3%	70%
Cleavage rate	86%	85.4%
Embryos/transfer*	4±1.2	3.8±1.1

* Values are means ± SD

Table 3. — *Pregnancy rate*

Parameters	Group A 17-OHPc (Lentogest protocol)	Group B Natural P (Prontogest protocol)
No. of clinical pregnancies	15 (37.5%)	14 (35%)
No. of early abortions	5 (12.5%)	5 (12.5%)
No. of term pregnancies	10 (25%)	9 (22.5%)

Results

As Table 1 shows, patient characteristics were not statistically different between the two groups. The mean ages were 30.2±1.5 and 29.1±3.0 years, respectively, for groups A and B. The mean duration of Gn treatment (12.5±1.5 and 11.7 ± 2 in groups A and B, respectively), the mean number of FSH ampoules administered (16.1 ± 5.8 and 11.7 ± 2 in groups A and B, respectively), the mean number of follicles with a diameter ≥ 16 mm (8.2 ± 3.1 and 8.3 ± in groups A and B, respectively), and the percentage of metaphase II oocytes per patient (85% and 87% in groups A and B, respectively), were similarly distributed in the two groups. Table II shows the results of fertilization and cleavage rates (71.3% and 70%; 86% and 85.4% in groups A and B, respectively) and the mean number of embryos transferred per patient (4±1.2 and 3.8±1.1 in groups A and B, respectively). There were no statistically significant differences between the two groups.

Moreover, there were no significantly statistical differences in the increase of the P serum levels during the whole period of treatment in the two protocols.

A higher number of clinical (37.5% vs 35%) and term pregnancies (25% vs 22.5%) appeared in group A, but this was not statistically significant (Table III).

Conclusion

The hypotesis that luteal phase support with exogenous natural P improves pregnancy rates has been supported by many trials [18, 19, 20, 21].

The effectiveness of synthetic progestinic preparations in many gynecological disorders is also well known [16]. On the other hand, there is no evidence as to its efficacy for luteal phase support in assisted reproduction techniques.

Our study shows that treatment with 17-OHPc results in a higher percentage of pregnancy rate when compared

to the protocol with natural P, but the differences are not statistically significant.

Considering the benefits associated with patient compliance, the 17OHP-c preparation appears very suitable. However, more studies are necessary to support the hypothesis that it might replace natural P in the supplementation of the luteal phase.

Therefore, we emphasize the use of the injectable synthetic progestinic preparation for patients showing high discomfort with the daily intramuscular administration of natural progesterone.

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