Intramuscular vs intravaginal natural progesterone in patients undergoing *in vitro* fertilization-embryo transfer cycles.
A retrospective observational, case-control study

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Abstract. – *Objective:* To compare the effectiveness of intramuscular (IM) and intravaginal (IV) progesterone for luteal phase support, in patients undergoing in vitro fertilization-embryo transfer cycles (IVF-ET).
Design: retrospective, observational, case-control study
Setting: Centro Natalità, San Raffaele Hospital, Milan, Italy, from July 2007 to June 2009.
Patient(s): 172 A-GnRH down-regulated IVF-ET cycles in patients with age <40 years.
Intervention(s): Luteal phase support with IM progesterone (50 mg daily) or IV progesterone (90 mg daily).
Main Outcome Measure(s): Biochemical pregnancy, clinical pregnancy, miscarriage, ongoing pregnancy rates and patient's acceptability.
Results: IM progesterone conferred more benefit compared with IV progesterone in terms of ongoing pregnancy rate (24,4% vs 12,7%; P<0.05)
Conclusions: In standard IVF cycles, our data showed that IM progesterone appears to be more effective at providing luteal support, thus rendering with IV progesterone.

Key Words:

Intramuscular progesterone, Intravaginal progesterone, IVF-ET cycles.

Introduction

During assisted reproductive technology (ART) treatment, the use of gonadotropin-releasing hormone (GnRH) agonists and the aspiration of follicular fluid can lead to a relative progesterone deficit and inappropriate preparation of the endometrium for embryo implantation. Defective production of progesterone (P4) may impair implantation and pregnancy rates, given the important role of this hormone in early pregnancy[1,2]. Supplementation of progesterone in the luteal phases after *in vitro* fertilization (IVF) cycles significantly improves fertility outcomes compared with no treatment[3].

Nowadays the need for luteal support in IVF treatment has been universally recognized. Progesterone can be administered by oral, intramuscular or vaginal routes. However, the optimal route has not yet been established. Particularly in these cycles, progesterone supplementation is given as IM injection of natural progesterone-in-oil. The IM administration of an oily preparation has not aroused great enthusiasm in most patients and it is often associated with painful injection and rash. Unfortunately, there are few practical alternatives to this route of the administration. Indeed, although progesterone can be also administered orally or vaginally, the former route is inappropriate for inducing the endometrial trasformations normally seen in the luteal phase and it is associated with a significantly lower implantation rate per embryo transferred[4,5].

Although there is increasing evidence that vaginal and intramuscular progesterone are at least equally effective in IVF treatment outcomes[6], lower clinical pregnancy and delivery rates when using vaginal progesterone rather than intramuscular progesterone-in-oil has been reported in a meta-analysis of randomized trials[5]. However, through the use of vaginal progesterone, painful application of intramuscular injections and their complications, such as local soreness, abscesses, and inflammatory reactions, were avoided[7].

The purpose of this retrospective study was to compare the efficacy of these 2 forms of proges-

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terone for luteal phase support during IVF-ET cycles, in terms of pregnancy outcomes and patient acceptability.

Materials and Methods

This was a retrospective, observational case-control (1:1), study including a total of 172 patients, aged <40 years and at the first long protocol IVF-ET cycle. The data were collected from the medical records at the Centro Natalità, Vita-Salute San Raffaele University, Milan, Italy, between July 2007 and June 2009. All the patients signed terms of informed consent before the fertilization treatment.

Stimulation Procotocol

Study participants received ovarian stimulation according to a standardized protocol involving luteal phase gonadotrophin-releasing hormone (GnRH) agonist down-regulation. In accordance with this protocol, 0.5 mg of leuprolide acetate, administered daily by s.c. injection, was initiated during the mid luteal phase. This dose was continued until ovarian suppression was achieved, as confirmed by oestradiol concentrations and sonography. The pituitary suppression was continued until human chorionic gonadotrophin (hCG) administration. Ovarian stimulation was initiated using r-FSH (Gonal-F®, Merck-Serono, Rome, Italy). The starting dose ranged between 150 and 225 IU/day for 5 days, based on body mass index (BMI) and/or basal FSH values and/or antral follicles count. Further dosing adjustments were based on ultrasound findings and plasma hormone concentrations.

Briefly, when at least two follicles were 18 mm in diameter, 10.000 IU of hCG (Gonasi 5000 IU, AMSA, Rome, Italy, 2 vials) were injected. Oocyte retrieval was performed 36 to 38 hours after hCG administration. All cases underwent conventional in vitro fertilization technique. The embryo transfer was performed at the 2-to 4-cell stage, 40-44 h after insemination. According to the Italian IVF law (40/2004) no more than three embryos were transferred.

Luteal Phase Support

Luteal support was initiated in the evening of oocyte retrieval irrespective of whether this was provided from the intramuscular injections (Prontogest 50 mg, AMSA, Rome, Italy) or intravaginal administrations Crinone 8% (90 mg), Serono, Rome, Italy.

Patients receiving IM progesterone in oil for luteal support were retrospectively matched to other patients undergoing IVF-ET during the same time period, and receiving protocol of vaginal progesterone supplementation.

Patients were matched for age, baseline FSH, endometrial thickness on the day of hCG trigger administration, stage of embryo transfer, and number of embryos transferred age. 86 women received luteal support from daily i.m. injections of progesterone, and compared to 86 women who received single daily dose of intravaginal progesterone.

In either case, luteal support was continued until a serum pregnancy test result was negative or embryonic heart beat was sonographically confirmed.

Determination of Pregnancy Status

Pregnancy status was determined by serum β-hCG concentration approximately 2 weeks after embryo transfer and by ultrasounds 2-4 weeks later. A biochemical pregnancy was defined as a small and transitory increase in β-hCG levels. A clinical pregnancy was defined by visualization of an embryo with cardiac activity at 6-7 weeks of gestation. Miscarriage was classified as clinical loss of an intrauterine pregnancy between the seventh and twelfth week of gestation. Ongoing pregnancies were considered those reaching 20 weeks of gestation.

Patient Acceptability

The acceptability of both progesterone different administrations was assessed using a patient questionnaire that was completed by each subject after their last administration of Prontogest or Crinone. Subjects were asked to rank their overall experience on degree of difficulty of administration, messiness, presence of pain and interference with intercourse. A scale of 1 (very much) to 7 (not at all) was used to assess the subject's overall experience in both groups in regard to these factors.

Statistical Analysis

All data were analyzed using the commercially available software package SPSS version 11.0 (SPSS Inc., Chicago, IL, USA) and presented as mean ± SD or number (%).

Statistical analysis was carried out using Student's t-test, Mann Whitney and χ^2 analyses. Results were considered to be significant when $P<0.05$.

Table I. Individual characteristics and ovum pick-up outcome for the two concurrent IVF patient groups.

Parameters	Intramuscular progesterone Group A (n = 86)	Intravaginal progesterone Group B (n = 86)	P value
Age (years)	35.8 ± 3.9	35.9 ± 4.4	NS
Years of infertility	6.2 ± 1.9	5.4 ± 1.7	NS
Cause of infertility			
Tubal factor	20 (23%)	17 (20%)	
Endometriosis	15 (17%)	17 (20%)	
Male factor	28 (33%)	34 (39%)	
Unexplained infertility	23 (27%)	18 (21%)	
Number of oocytes retrieved	12.5 ± 6.0	11.9 ± 5.8	NS
Fertilized oocytes	8.0 ± 5.6	7.3 ± 6.3	NS
Number of embryos transferred	2.85 ± 0.35	2.82 ± 0.27	NS

Data are presented as means ± SD or n (%). NS = not significant.

Results

During the study period, IVF-ET outcome of 172 patients conforming with inclusion criteria were retrospectively analyzed.

The general characteristics of the study population are summarized in Table I. There were 86 subjects assigned to each of the two treatment groups. The age of patients in IM Group (35.8 ± 3.9) was equal (P=0.92) to that of patients in IV Group (35.9 ± 4.4 y). An equal distribution (P>0.05) of the other main characteristics was also observed for the two groups.

Cause of infertility did not differ in the two groups.

Regarding ovum pick-up (Table I), there were no differences in the mean number of oocytes retrieved, the mean number of oocytes fertilized or the mean number of embryos transferred for these two groups of IVF patients.

IVF-ET outcome is reported in Table II.

Biochemical pregnancy rates per cycle achieved in women receiving IM progesterone were similar to those seen in the IV group (6.9% vs 5.8 %, P not significant). The IM progesterone groups showed a not statistically tendency to higher clinical pregnancy rate (31.3% vs 19,7% P=0.08); and a significantly increased ongoing pregnancy rate (24,4% vs 12,7%; P<0.05). At least, miscarriage rate, calculated per clinical pregnancy was not statistically different in the two groups

The overall acceptability, from patient questionnaire analysis, resulting in a better compliance of intravaginal progesterone, due to some local side effects registered during the intramuscular administration.

Discussion

Normal luteal function is essential for maintaining first-trimester pregnancy, but corpora lutea may be compromised during controlled ovarian hyperstimulation, when GnRH agonists are used and during oocyte retrieval.

Luteal support in IVF cycles with progesterone or hCG is a standard procedure to improve

Table II. Pregnancy outcome of patients who received 17-HPC and IV progesterone.

	Intramuscular progesterone (n = 86)	Intravaginal progesterone (n = 86)	P value
Pregnancy rate/cycle (%)	33 (38.4)	25 (29.1)	NS
Biochemical pregnancy/cycle (%)	6 (6.9)	5 (5.8)	NS
Clinical pregnancies/cycle (%)	27 (31.3)	17 (19.7)	= 0.08
Miscarriage/clinical pregnancy (%)	6 (22.2)	6 (35.3)	NS
Ongoing pregnancy/cycle (%)	21 (24.4)	11 (12.7)	<.05

Data are presented as number (%). NS = not significant.

pregnancy outcomes, but hCG increases the Odds of OHSS, a relatively common and potentially life-threatening complication of ovarian stimulation[8].

A meta-analysis of randomized trials showed, without doubts, that luteal supplementation is beneficial for these women[6].

Now the question is which kind of administration of progesterone is to prefer?

Oral progesterone as luteal support is, of course, appealing due to its simplicity of administration. However, of many modes of progesterone administration, the oral route is associated with the lowest efficacy and largest number of side-effects. Moreover, the breakdown products from metabolism of oral progesterone have been associated with sedation, drowsiness and other hypnotic effects, as well as flushing, nausea, and fluid retention[2].

The most common form of progesterone supplementation in Italy is daily IM progesterone-in-oil administration. This may lead to severe inflammation reactions, sterile abscesses, and significant patient discomfort. Another route of progesterone supplementation is the vaginal one. Nevertheless, some Authors report no statistically differences in terms of pregnancy outcomes comparing with the intramuscular progesterone[10].

On the contrary, Cochrane database noted an evidence of benefit of the intramuscular over the vaginal route for the outcomes of ongoing pregnancy and live birth, while no significant difference in pregnancy rate was observed between vaginal progesterone gel and other types of vaginal progesterone. Authors concluded that the optimal route of progesterone administration has not yet been established[2].

In our retrospective case-control trial we found better pregnancy outcomes for intramuscular progesterone.

We should moreover consider the benefits associated with patient compliance. Indeed, an effective drug supplementation is important not only during the actual cycle of IVF-ET. Acceptance or repeated cycles in case of failure depends also on previous complaints experiences like the discomfort of progesterone intramuscular injections that lasted sometimes for a long time after administration suspension.

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