

COMPARISON OF THE EFFICACY OF TWO VAGINAL PROGESTERONE FORMULATIONS, CRINONE 8% GEL AND UTROGESTAN CAPSULES, USED FOR LUTEAL SUPPORT IN BLASTOCYST STAGE EMBRYO TRANSFERS

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SUMMARY

Objective: To compare the efficacy of two vaginal progesterone formulations, Crinone gel and Utrogestan capsules, for luteal phase support in blastocyst stage embryo transfers.

Materials and Methods: We analyzed 460 consecutive cycles in patients undergoing *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI)–blastocyst transfer (BT) treatment at our institution between January 2004 and December 2007. Patients applied either Crinone 8% vaginal gel (90 mg, once daily) or Utrogestan vaginal capsules (200 mg, four times daily) for luteal supplementation. Progesterone was administered from the day of oocyte retrieval to pregnancy confirmation. Clinical pregnancy and implantation rates were the main outcome measures.

Results: The clinical pregnancy rate (58.7% vs. 44.3%) and implantation rate (32.04% vs. 23.89%) were significantly higher in the Crinone group compared with the Utrogestan group after IVF/ICSI–BT treatment.

Conclusion: Luteal phase support with Crinone 8% vaginal gel (90 mg daily) resulted in better clinical pregnancy and implantation rates than Utrogestan vaginal capsules (200 mg, 4 times daily) in IVF/ICSI–BT cycles. [*Taiwan J Obstet Gynecol* 2009;48(4):375–379]

Key Words: blastocyst transfer, Crinone 8% gel, luteal support, Utrogestan

Introduction

Stimulated *in vitro* fertilization (IVF) cycles are associated with defective luteal phases in almost all patients [1], particularly with the induction of high estradiol levels [2,3]. The use of a long protocol with a gonadotropin-releasing hormone agonist during assisted reproductive technology (ART) treatment is commonly used to prevent the premature luteinizing hormone surge and to

control the number and growth of follicles. The long protocol suppresses the pituitary gland and blocks the secretion of luteinizing hormone for at least 10 days following the last dose of gonadotropin-releasing hormone [4]. It is, therefore, not surprising that the luteal phase becomes dysfunctional and an inadequate amount of progesterone is produced in ART cycles stimulated after downregulation with gonadotropin-releasing hormone agonists. In addition to a low luteinizing hormone serum concentration during the luteal phase, supraphysiologic steroid levels during the early and mid-luteal phases of stimulated cycles may advance endometrial development and inhibit embryo implantation [5,6].

The benefit of luteal phase support (LPS) in downregulated cycles has been verified in prospective randomized trials [7–9]. However, a standard protocol for LPS has not been established (i.e. optimal formula,



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dose, route, timing, and duration). Both human chorionic gonadotropin (hCG) and progesterone have been used for LPS. Progesterone is used more frequently than hCG because of a lower risk of ovarian hyperstimulation syndrome [10].

Progesterone can be administered orally, vaginally or intramuscularly. Orally administered progesterone is rapidly metabolized in the gastrointestinal tract and has been shown to be inferior to intramuscular and vaginal routes, leading to a poorer outcome of IVF. Comparisons of vaginal and intramuscular progesterone have yielded conflicting results. Nevertheless, the vaginal route may provide a valuable route for drug delivery because of the postulated first uterine pass effect and the avoidance of the discomfort and side effects of an intramuscular injection [11].

Blastocyst transfer (BT) is a valuable tool in the hands of practitioners of IVF, and has been accepted by many IVF programs throughout the world. BT has facilitated the natural selection of good-quality embryos that are reported to generate high implantation rates, while lowering multiple gestation rates following IVF [12]. The issue of LPS in BT cycles (higher stimulated estradiol levels than in cleavage stage cycles) has been less thoroughly assessed.

The purpose of this study was to compare the efficacy of two vaginal progesterone preparations (Utrogestan capsules and Crinone 8% gel), which are used for LPS during IVF in BT.

Materials and Methods

Patients

Data were collected from consecutive infertile couples who underwent ART and transcervical fresh BT between January 2004 and December 2007. All patients were unselected and were included without regard to age, sperm parameters or infertility criteria. During the study period, 547 patients underwent BT using IVF or intracytoplasmic sperm injection (ICSI) with vaginal luteal support in our hospital. A total of 299 patients received luteal progesterone support with Crinone 8% gel during BT cycles and 248 patients received Utrogestan vaginal capsules. Eighteen patients receiving Utrogestan vaginal capsules, who experienced difficulties in BT or donor cycles, or who had rare treatment indications, were excluded from this study. For outcome comparison and to avoid selection bias, a case-control design was used to recruit 230 patients with Crinone 8%-supported cycles, based on the demographic characteristics of the 230 patients with Utrogestan-supported cycles. Demographic characteristics were selected in the following decreasing

order of priority: (1) age, (2) embryos transferred and number of top-quality embryos transferred, (3) estradiol and progesterone level on hCG day, (4) number of oocytes retrieved, (5) follicle-stimulating hormone (FSH) treatment period and protocol, and (6) etiology of infertility. We ideally aimed to control for all six variables; but if this was not possible, we tried to control for at least the first four variables in each case-control pair.

This study was approved by the ethics committee of Chang Gung Memorial Hospital. Approval from the institutional review board was obtained for analysis of this series.

Controlled ovarian hyperstimulation and oocyte retrieval

The protocol for controlled ovarian hyperstimulation followed the standard downregulation regimen, as previously reported [13,14]. Briefly, all women received either the long or short protocol for pituitary downregulation with leuprolide acetate (Lupron; Takeda, Tokyo, Japan), depending on ovarian reserve, as assessed by the patient's age, baseline serum FSH concentration or previous response to ovarian stimulation. Exogenous FSH was administered at an initial dose of 150–300 IU, with further doses given according to the individual's ovarian response, as assessed by serum estradiol level determination and sonographic follicular growth monitoring. When the lead follicle reached 16–18 mm in diameter, leuprolide acetate and FSH were discontinued and hCG was administered. Oocyte retrieval was performed by transvaginal ultrasound-guided follicle aspiration 36–38 hours after hCG administration.

Embryo culture, embryo grading, and embryo transfer

A single team of embryologists coordinated all procedures, thus ensuring that both the culture protocols and the embryo assessment were standardized, as described previously [15]. Any zygotes with two pronuclei were cultured until the day of embryo transfer. G1 medium (Scandinavian IVF Science, Kungsbacka, Sweden) was used for culturing embryos on days 1–3. G2 medium (Scandinavian IVF Science, Kungsbacka, Sweden) was used for culturing embryos from days 3–5 or 6. In our program, we have routinely offered BT of embryos to patients with more than three eight-cell embryos on day 3. We strictly defined “top-quality” embryos as follows: (1) embryos that formed full blastocysts (full blastocysts onward, the development of an inner cell mass with many tightly packed cells, and with trophectoderm and many cells forming a cohesive epithelium); (2) embryos derived from Z1 zygotes (zygotes with equal numbers of nucleoli aligned at the pronuclear junction; the absolute number was not counted, but

was between 3 and 7); and (3) embryos that were grade 1 (eight cells, blastomeres of equal size, and no cytoplasmic fragments) and had day 3 embryo morphology [14]. All embryo transfers were performed gently using a Labotect catheter (Labotect, Göttingen, Germany).

Luteal support

The study population was divided into two groups. One group received Crinone 8% gel (90 mg daily; Fleet Laboratories Ltd., Watford, UK), and one group received Utrogestan vaginal capsules (200 mg four times daily; Piette International Laboratories, Drogenbos, Belgium). Luteal phase supplementation of micronized progesterone was begun on the day of oocyte retrieval and continued until the day pregnancy was confirmed by detection of hCG in the urine. These two formulas were available from the hospital during the study period. However, the choice of a particular formula depended on the affordability to the patient and the convenience of application. The day after BT, we offered a single booster dose of 250 µg recombinant hCG (Ovidrel; Industria Farmaceutica Serono S.p.A, Rome, Italy).

Determination of pregnancy status

Pregnancy was confirmed by detecting hCG in the urine 2 weeks after transfer. Clinical pregnancy was determined by identifying a gestational sac at 7 weeks' gestation by means of transvaginal ultrasonography.

Statistical analysis

The SigmaStat statistical package (Jandel Corporation, San Rafael, CA, USA) was used for data analysis. Continuous data were summarized as the means \pm standard deviations. Unpaired Student's *t* tests or Mann-Whitney rank sum tests were used for comparisons between means, and Fisher's exact tests were used to compare proportions. All *p* values were two-sided, and a *p* value of <0.05 was considered statistically significant.

Results

Demographic data for 230 patients receiving luteal progesterone support with Crinone 8% gel during BT cycles and 230 patients receiving Utrogestan vaginal capsules are shown in Table 1. No significant differences were noted between the groups with regard to patient age, body mass index, days and dosage of stimulation, indication for treatment, endometrial thickness on day of hCG, and estradiol and progesterone levels on the hCG day.

There were no significant differences between the groups in terms of number of oocytes retrieved,

fertilization rate, number of embryos transferred or mean number of top-quality embryos transferred. The clinical pregnancy rates per transfer (58.7% vs. 44.3%) and implantation rates (32.04% vs. 23.89%) were significantly higher in the Crinone group, compared with the Utrogestan group. The pregnancy loss rates were similar in the two groups (Table 2).

Discussion

In general, LPS is more important in high-responding cycles with advanced endometrial histology [16–18]. It increases uterine contractions at the time of embryo transfer [19]. In an earlier study, we showed that in day-3 cleavage stage embryo transfers, usually with an inferior ovarian response, LPS with Crinone 8% gel or micronized progesterone had comparable effects (data not shown). The primary objective of the current study was to compare the efficacy of two vaginal formulations of progesterone (Crinone 8% and Utrogestan capsules) used for LPS in ART cycles, especially in a BT program.

The demographics and ART-specific characteristics of the patients were similar in the two groups. The results showed that Crinone 8% gel resulted in higher implantation (32.04% vs. 23.89%) and clinical pregnancy rates (58.7% vs. 44.3%) than Utrogestan capsules. The pregnancy loss rates were not significantly different between the two groups. These findings suggest that for similar numbers of BT, LPS with Crinone 8% gel is more effective than with Utrogestan capsules in high responder cycles.

LPS with progesterone has become a standard treatment in IVF/ICSI cycles to overcome the luteal phase defect and to improve the result of ART. No significant differences were found between progesterone and hCG in terms of pregnancy or miscarriage rates, but the risk of ovarian hyperstimulation syndrome was more than twofold higher with treatments involving hCG than with progesterone alone [20]. Various routes of progesterone administration have been developed and tested. There is increasing evidence in the literature to suggest that vaginal administration of progesterone could be superior to other routes, mainly because of the postulated first uterine pass effect, which results in better local progesterone bioavailability in the uterus [11]. Patients may also feel more comfortable with the vaginal route, which avoids the painful injection of intramuscular progesterone and its side effects [10].

No significant differences in pregnancy rates have been observed between vaginal progesterone gel and other types of vaginal progesterone [20]. To date, few studies have compared vaginal gel (Crinone 8%) and

Table 1. Demographic and specific treatment characteristics of patients*

	Patient group		<i>p</i>
	Crinone (<i>n</i> = 230)	Utrogestan (<i>n</i> = 230)	
Patient age (yr)	32.78 ± 3.84	33.05 ± 4.78	0.505
Body mass index (kg/m ²)	21.54 ± 3.07	21.92 ± 3.62	0.098
Duration of infertility (yr)	4.09 ± 2.79	3.98 ± 2.91	0.682
Indication for treatment			
Tubal factor	64	52	0.198
Male factor	80	78	0.845
Endometriosis	20	19	0.867
Ovulatory factor	21	19	0.741
Unexplained	33	47	0.085
Other	12	15	0.553
Days of FSH treatment	9.07 ± 1.50	8.82 ± 1.89	0.119
Ampoules of 75 IU FSH	32.07 ± 11.85	30.29 ± 10.61	0.091
Endometrial thickness on hCG day (cm)	1.34 ± 0.30	1.32 ± 0.34	0.626
Estradiol (pg/mL) on hCG day	2,313.31 ± 1,241.30	2,201.74 ± 1,212.26	0.34
Progesterone (ng/mL) on hCG day	1.50 ± 0.89	1.59 ± 1.49	0.436

*Data are presented as mean ± standard deviation or *n*. FSH = follicle-stimulating hormone; hCG = human chorionic gonadotropin.

Table 2. Results in study groups

	Patient group		<i>p</i>
	Crinone (<i>n</i> = 230)	Utrogestan (<i>n</i> = 230)	
No. of oocytes retrieved, mean ± SD	8.43 ± 2.85	7.93 ± 2.85	0.086
Normal fertilization rate (%)	83.51	81.96	0.211
Mode of fertilization			
Conventional IVF, <i>n</i>	165	166	0.917
ICSI, <i>n</i>	65	64	0.917
No. of embryos transferred, mean ± SD	2.47 ± 0.57	2.44 ± 0.68	0.603
No. of top-quality embryos transferred, mean ± SD	1.59 ± 0.69	1.66 ± 0.67	0.272
Clinical pregnancy rate/transfer cycle, <i>n</i> (%)	135/230 (58.7)	102/230 (44.3)	0.001
Implantation rate, <i>n</i> (%)	182/568 (32.04)	134/561 (23.89)	0.002
Abortion rate (%)	5.19	8.82	0.269

SD = standard deviation; IVF = in vitro fertilization; ICSI = intracytoplasmic sperm injection.

vaginal progesterone capsules (Utrogestan) used for LPS. Kleinstein et al [21] reported that the use of vaginal progesterone capsules (Utrogest 200 mg, three times per day) compared with vaginal gel (Crinone 8%, twice per day) for LPS in ART cycles resulted in similar outcomes. Geber et al [22] concluded that there was no statistically significant difference in pregnancy rates between vaginal capsules of 200 mg of micronized progesterone (Utrogestan, three times daily) and micronized progesterone gel (Crinone 8%, once daily), although the pregnancy rate was higher in those patients receiving progesterone gel, compared with capsules (44.26% and 36.06%, respectively). Simunic

et al [23] also reported similar efficacies of the two vaginal progesterone formulations, but the tolerability and acceptability of Crinone 8% gel were superior.

The present study showed that the vaginal formulation of Crinone 8% gel (90 mg, once daily) resulted in higher implantation and clinical pregnancy rates when used for LPS during IVF with BT. Although the optimal length of treatment is unclear, our experience suggests that it is sufficient to support the luteal phase until the day of a positive hCG test, as recommended in the recent literature [1].

Admittedly, the results of this retrospective case-control study do not provide any definitive conclusions.

However, all participants underwent BT and had similar numbers of top-quality embryos to transfer, unlike in other associated studies. In our previous top-quality embryo transfer study [14], we identified a subpopulation of blastocysts (top-quality blastocysts) with high implantation potential. Nevertheless, the results of the present study demonstrated superiority of Crinone 8% gel over Utrogestan capsules for LPS in BT cycles using equal numbers of top-quality embryos.

In conclusion, LPS with Crinone 8% vaginal gel (90 mg daily) resulted in better clinical pregnancy and implantation rates than Utrogestan vaginal capsules (200 mg, four times daily) in IVF/ICSI-BT cycles. A well-designed, adequately powered, multicenter, prospective, randomized, controlled trial should be undertaken to verify these findings.

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