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Luteal phase support using either Crinone® 8% or Utrogest®: results of a prospective, randomized study

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Abstract

The Crinone® 8% preparation makes it possible to administer natural progesterone (90 mg) vaginally once daily for luteal phase support (LPS). Until now, no prospective, randomized studies have directly compared this new preparation with widely used Utrogest® capsules, which were originally designed for oral administration but are used routinely as a vaginal preparation. A prospective, randomized study investigated 126 patients undergoing cycles of in vitro fertilization (IVF) and IVF/intracytoplasmic sperm injection (ICSI). Patients received either Crinone® 8% ($n = 73$) vaginally once daily or two Utrogest® capsules ($n = 53$) vaginally three times daily (600 mg). Clinical pregnancy rates were comparable (28.8 versus 18.9%), as were clinical abortion rates until 12 weeks of gestation (14.3 versus 10.0%) and clinical ongoing pregnancy rates (24.7 versus 17.0%) in the Crinone® 8% and Utrogest® groups, respectively. Forty-seven non-pregnant patients were randomly selected to answer questions regarding comfort during LPS. Crinone® 8% had a clear advantage over Utrogest® as it resulted in less vaginal discharge ($P < 0.01$) and fewer application difficulties ($P < 0.05$). Twenty patients familiar with the alternative preparation from a previous cycle also noted that Crinone® 8% was easier to apply ($P < 0.01$) and less time consuming ($P < 0.05$) to use than Utrogest®.

Keywords: Crinone®; First uterine pass effect; Luteal phase support; Progesterone; Utrogest®

1. Introduction

Progesterone is commonly used in luteal phase support (LPS), and may be given orally [1,2], intramuscularly [3] or vaginally [3–5]. Oral administration is less effective than the other routes, as has been shown in a recent prospective, randomized study [4]. This is due to low bioavailability as a result of the hepatic first pass effect, leading to production of substances with more psychotropic side-effects [6]. Furthermore, it has been demonstrated that oral administration of progesterone leads to few secretory changes in the endometrium [7]. Progesterone should therefore be given either intramuscularly or intravaginally.

These two routes of application lead to similar good results [3,5]. Recently, Damario et al. (1999) [26] showed that intramuscular administration of progesterone was preferable to vaginal application. However, this study was retrospective and not prospectively randomized. The odds ratio of 0.53 had a 95% confidence interval of 0.27–1.04 for the clinical ongoing pregnancy rate in favor of the intramuscular preparation. There was, in fact, no clear advantage of the intramuscular protocol over vaginal application. Furthermore, there were methodological problems, since the group of patients using intravaginal progesterone showed some parameters which are related to a low response. This may have influence the results of the comparison.

Utrogest® capsules (Dr. Kade, Berlin, Germany) contain 100 mg of natural progesterone and can be given intravaginally to circumvent hepatic metabolism. This preparation has often been used in luteal phase support, but was originally designed for oral administration. Recently, a new preparation, Crinone® 8% vaginal gel (Serono International SA, Geneva, Switzerland), has become available. This is the first preparation specifically designed for vaginal administration. It contains 90 mg of natural progesterone dissolved in a bioadhesive substance—polycarbophil—and is delivered as a constant slow and sustained release through its oil-in-water emulsion system. Crinone® 8% has been shown to diffuse to the endometrium and myometrium [8,9] with an excellent inhibitory effect on the contractility of the

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myometrium [10]. Until now, no prospective, randomized study has been published comparing vaginal Utrogest® and Crinone® 8% for luteal phase support in vitro fertilization–embryo transfer (IVF–ET) cycles, to show the same effectiveness of both preparations.

2. Materials and methods

2.1. Inclusion and exclusion criteria, and ethical considerations

A total of 126 patients were included in the study. Only patients aged up to 40 years undergoing controlled ovarian stimulation for IVF or IVF/intracytoplasmic sperm injection (ICSI) were included. After successful oocyte retrieval, patients attending the clinic for ET were asked for written informed consent and prospectively randomized into one of the two arms of the study. To prevent the inclusion of poor responders, patients with oestradiol levels below 2000 pg/ml, on the day of human chorionic gonadotrophin (HCG) administration, were not selected. The protocol was approved by the ethical board of the Medical University of Lübeck.

2.2. Controlled ovarian stimulation and assisted reproduction procedure

Controlled ovarian stimulation was carried out according to the long luteal protocol using a gonadotrophin-releasing hormone (GnRH) agonist depot preparation (Decapeptyl Gyn Depot, triptorelin; Ferring Arzneimittel GmbH, Kiel, Germany) or according to the multiple dose GnRH antagonist protocol using cetrotide (Cetrorelix, ASTA Medica AG, Frankfurt, Germany and Serono International SA, Geneva, Switzerland). For ovarian stimulation either recombinant follicle stimulating hormone (FSH) (Gonal F 75; Serono International SA, Geneva, Switzerland) or human menopausal gonadotrophin (HMG) (Menogon; Ferring Arzneimittel GmbH, Kiel, Germany) was used. IVF with or without ICSI was carried out as described previously [11]. HCG was administered when the leading follicle reached a diameter of 18–22 mm.

2.3. Cumulative embryo score

The cumulative embryo score, as published by Steer et al. [12], was slightly modified as three rather than four criteria of embryo quality were used. The quality score of a single embryo was calculated as the product of the number of blastomeres and the embryo's quality (1, fair; 2, moderate; 3, ideal). The cumulative embryo score was calculated as the sum of all single embryo scores.

2.4. Luteal phase support protocols

Patients began vaginal administration of progesterone on the evening before ET using either Utrogest®, 200 mg (i.e. two capsules) three times a day or Crinone® 8% vaginal gel once daily until either menstrual bleeding occurred or there was a positive pregnancy test. When patients became pregnant they received 2 ml of Gravibinon (250 mg 17-hydroxyprogesterone caproate and 5 mg oestradiol valerate) (Schering AG, Berlin, Germany) intramuscularly, twice a week for 10 more weeks or until an abortion occurred. Patients were randomized on an individual basis by a use of an open computerized randomization list.

2.5. Pregnancies

Pregnancies were defined as clinical pregnancies by ultrasonography and only those with positive fetal heartbeats were included. All pregnancies were followed up until 12 weeks of gestation. The final outcome parameter was the clinical ongoing pregnancy rate for more than 12 weeks of gestation.

2.6. Discomfort scale during luteal phase support

Forty-seven non-pregnant, randomly selected patients were interviewed using a standardized questionnaire after finishing the luteal phase. A total of 21 of these patients had received Crinone® 8% and 26 were given Utrogest® in their study cycle. Questions were answered on a scale from 1 (absolutely true) to 7 (not true at all). All patients were asked the same two questions.

(1) Did you experience any vaginal discharge?
(2) Did you experience any difficulties with application?

Twenty patients who were familiar with the alternative progesterone preparation from a previous cycle were also asked.

(3) Was administration of the current medication less time consuming?
(4) Was administration of the current medication less painful?
(5) Was administration of the current medication easier?

2.7. Statistical analysis

Statistical analyses were carried out using the Chi-square test and the Mann–Whitney test.

3. Results

The numbers of patients randomized to receive Crinone® 8% and Utrogest® were 73 and 53, respectively. All demographic data, such as patient age, number of previous treatment cycles, percentage of primary infertility, presence of male factor and percentage of ICSI cycles, were comparable in the two groups (Table 1). A comparable number of oocytes was retrieved (12.67 ± 5.01 versus 13.94 ± 5.93),

Table 1
Demographic and treatment data for patients receiving Crinone® 8% and Utrogest®

Parameter	Crinone® 8%	Utrogest®
Number of patients	73	53
Age (years)	31.41 ± 5.52	31.45 ± 4.29
Number of previous treatment cycles	1.07 ± 1.15	1.04 ± 1.14
Number of previous pregnancies	0.51 ± 0.80	0.58 ± 0.82
Number of previous deliveries	0.26 ± 0.67	0.25 ± 0.48
Primary infertility	47/73 (64.4%)	36/53 (67.9%)
Male factor present	47/73 (64.4%)	37/53 (69.8%)
ICSI cycles	56/73 (76.7%)	42/53 (79.2%)
Basal FSH (U/l)	5.59 ± 1.83	6.59 ± 2.23
Duration of stimulation (days)	13.52 ± 2.77	13.98 ± 3.27
Dose of FSH (IU)[a]	3161 ± 1129	3430 ± 1616
Cycles with recombinant FSH[b]	50/73 (68.5%)	40/53 (75.5%)
Long GnRH[c] agonist protocol	47/73 (64.4%)	41/53 (77.4%)
Multiple dose GnRH antagonist protocol	26/73 (35.6%)	12/53 (22.6%)
Oestradiol on the day of HCG (pg/ml)	2646 ± 1369	2712 ± 1540
Number of oocytes	12.67 ± 5.01	13.94 ± 5.93
Number of oocytes with two pronuclei	6.01 ± 3.49	5.74 ± 3.48
Number of cryopreserved oocytes with two pronuclei[d]	5.36 ± 2.75	5.70 ± 2.87
Number of embryos transferred	2.78 ± 0.45	2.77 ± 0.47
Cumulative modified embryo score	25.55 ± 10.44	23.60 ± 10.90
Number of clinical pregnancies	21/73 (28.8%)	10/53 (18.9%)
Number of clinical abortions until 12 weeks of gestation	3/21 (14.3%)	1/10 (10.0%)
Number of clinical ongoing pregnancies above 12 weeks of gestation	18/73 (24.7%)	9/53 (17.0%)

There were no statistically significant differences between the groups for any parameter listed.

[a] If HMG was used for stimulation, only the dose of FSH was calculated.

[b] All other cycles were stimulated using HMG.

[c] GnRH: gonadotrophin releasing hormone.

[d] If available.

with a similar number of regularly fertilized oocytes with two pronuclei (6.01 ± 3.49 versus 5.74 ± 3.48) and a comparable mean number of embryos per transfer (2.78 ± 0.45 versus 2.77 ± 0.47) in the Crinone® 8% and Utrogest® group, respectively. The mean cumulative modified embryo scores were comparably high (25.55 ± 10.44 versus 23.60 ± 10.90), with a similar percentage of clinical pregnancies (28.8 versus 18.9%) and percentage of clinical abortions until 12 weeks of gestation (14.3 versus 10.0%), and there was a comparably high clinical ongoing pregnancy rate above 12 weeks of gestation (24.7 versus 17.0%) in the Crinone® 8% and Utrogest® group, respectively (Table 1).

Evaluation of patient comfort using the questionnaire found most respondents to be in favor of Crinone® 8%, with fewer patients having difficulties with application ($P < 0.05$) or vaginal discharge ($P < 0.01$) compared with those receiving Utrogest® (Fig. 1). When patients were familiar with the alternative medication from a previous cycle ($n = 20$), answers to the additional questions were also in favor of Crinone® 8%. More patients felt that Crinone® 8% was less time consuming ($P < 0.01$) and easier to apply ($P < 0.05$) than Utrogest® (Fig. 2). Of these 20 patients, 11 received Utrogest® and nine received Crinone® 8% in their actual study cycle.

Some patients informed us about non-absorbed material, which was kept in the vagina when using Crinone® 8%. However, this did not result in a worse estimation of Crinone® 8% versus Utrogest® capsules overall.

4. Discussion

This is the first prospective, randomized study comparing Crinone® 8% and Utrogest®, and including an evaluation of patient comfort with these two preparations. There was no statistically significant difference in demographic characteristics or outcome parameters, and no significant difference in

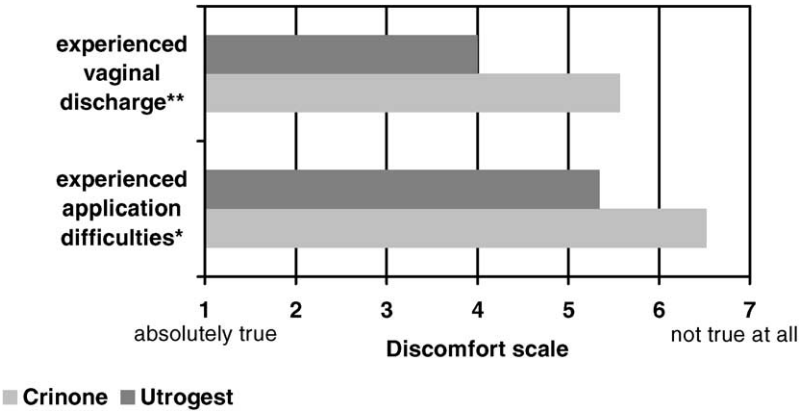

Fig. 1. Response to questionnaire (mean scores) asking 47 randomly selected non-pregnant patients about aspects of comfort during luteal phase support with Crinone® 8% and Utrogest® after IVF/ICSI. $^{*}P < 0.05$ and $^{**}P < 0.01$ in favor of Crinone® 8%.

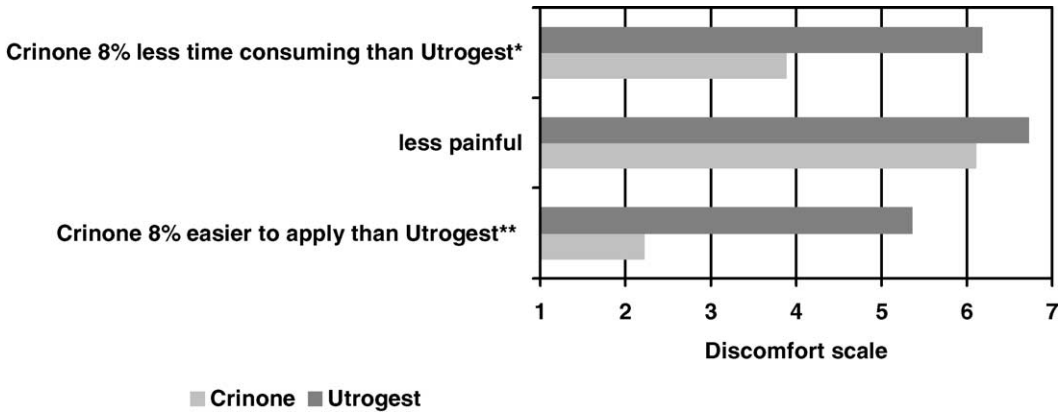

Fig. 2. Response to questionnaire (mean scores) asking 20 of the patients in Fig. 1 who had experience with the alternative medication for a direct comparison of the two agents during luteal phase support after IVF/ICSI. $^{*}P < 0.05$ and $^{**}P < 0.01$ in favor of Crinone® 8%.

clinical ongoing pregnancy rate between the Crinone® 8% (24.7%) and Utrogest® (17.0%) groups. However, this study clearly highlights advantages of Crinone® 8% compared with Utrogest®. Crinone® 8% is easier to apply and administration is less time consuming as it must be given only once daily. Furthermore, Crinone® 8% produces less vaginal discharge and more patient comfort overall. As only patients who did not become pregnant in the study cycle were included in this subanalysis of comfort, this bias was excluded. In addition, recall bias can be excluded as similar numbers of patients from each arm of the study were recruited for this subanalysis.

One has to be aware, however, that the study population is still small—even when it is one of the more larger study regarding the topic of luteal phase support. To make a significance of 5% pregnancy rate statistically significant, more than 1000 patients would have to be included in each study arm (alpha 0.05, power 80%).

We have recently shown that vaginal progesterone is as effective as HCG or a combination of HCG plus progesterone for luteal phase support in IVF–ET cycles [13,14]. This was also shown by several other authors [14–19], as well as in a recent metaanalysis [20]. Therefore, there no longer seems to be a place for HCG supplementation during the luteal phase. An advantage of HCG supplementation for low responders has never been shown. A prospective, randomized trial [21], showed no benefit in terms of clinical ongoing pregnancy rate when HCG was given in addition to luteal phase support using intramuscular progesterone. However, all the patients included in this study had oestradiol levels above 2000 pg/ml on the day of HCG administration and there were no low responders.

Progesterone supplementation during the luteal phase is advantageous as it is a physiological substance that is normally released from the corpus luteum. Furthermore, HCG is a known risk factor for triggering ovarian hyperstimulation syndrome, potentially life-threatening condition, whereas progesterone is not.

The vaginal route of application allows optimal progesterone concentrations to be achieved in the uterine milieu using the so-called first uterine pass effect without unphysiologically high serum levels [8,22,23]. Furthermore, progesterone inhibits uterine contractility; this has been shown to be a positive factor for embryo implantation and clinical ongoing pregnancy rates, as increased uterine contractions are known to have a negative effect on implantation [10]. Therefore, administration of progesterone should be started at least before the day of ET—as was done in the present study.

Until now, no difference has been shown in prospective, randomized trials when vaginal progesterone was compared with HCG [27] or intramuscular progesterone [3] in IVF–ET cycles. In oocyte donation, intramuscular progesterone was equally effective as was Crinone® 8% in two prospective, randomized trials [24,25]. As vaginal progesterone is easier to apply compared to HCG and i.m. progesterone, is less painful than i.m. progesterone and can be administered by the patient herself, it is the preparation of choice for luteal phase support. The data presented here show that Crinone® 8% has equal efficacy but is associated with more comfort for patients compared with Utrogest® capsules administered vaginally.

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