

Comparative study of the efficacy and tolerability of two vaginal progesterone formulations, Crinone^{*} 8% gel and Utrogestan[†] capsules, used for luteal support

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Objective: To compare the efficacy and tolerability of two different types of vaginal progesterone (P), Crinone 8% gel (Fleet Laboratories Ltd., Watford, United Kingdom) and Utrogestan capsules (Laboratories Besins International, Paris, France), used for luteal support after in vitro fertilization (IVF) cycles.

Design: Cohort study.

Setting: In Vitro Fertilization Polyclinic, Zagreb, Croatia.

Patients: A total of 285 women aged ≤ 37 years undergoing IVF-embryo transfer treatment.

Interventions: Patients were treated with either Crinone 8% vaginal P gel (90 mg) administered daily, or Utrogestan vaginal capsules (2 \times 100 mg) administered three times daily. Progesterone was administered from the day of oocyte retrieval (day 0) to menses or, in a case of pregnancy, until week 12.

Main Outcome Measure: Clinical pregnancy rate. The tolerability and acceptability of both preparations were determined by a questionnaire given to patients.

Results: The similar rates of clinical pregnancies (33 [1%] vs. 30 [9%]) were obtained by using either Crinone 8% vaginal P gel or Utrogestan vaginal capsules. Overall tolerability and acceptability were significantly better in the Crinone group than in the Utrogestan group.

Conclusions: The efficacy of the two vaginal P formulations was nearly the same, but the tolerability and acceptability of Crinone 8% gel were superior, in the opinion of patients. (Fertil Steril[®] 2007;87:83–7. ©2007 by American Society for Reproductive Medicine.)

Key Words: Luteal phase support, vaginal progesterone, efficiency, tolerability, pregnancy rate

In induced IVF cycles, the use of GnRH agonists (1) and the removal of granulosa cells during aspiration of the oocyte can lead to a relative P deficit (2,3) and inappropriate preparation of the endometrium for implantation of an embryo and survival of pregnancy (4). The use of GnRH agonists in ovarian stimulation, which prevents a premature surge of LH, ultimately leads to suppression of the pituitary gland, thereby blocking the secretion of LH at least 10 days following the last applied GnRH dose (5), as well as the pulsatile secretion of P (6). In addition, high levels of estrogen observed during induced cycles result in an inhibiting effect on the implantation of human embryos (7). The use of pharmaceutical luteal support to reach the physiological ratio of estrogen to P could only be beneficial (8).

Luteal support in IVF cycles can be prolonged using hCG and/or P. Since it was noted that the use of hCG was related to higher risks of the onset of ovarian hyperstimulation syndrome (OHSS), P is nowadays a product of choice in luteal support (9).

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Progesterone could be administered orally, vaginally, or by intramuscular injection. Progesterone administered orally demonstrated lower bioavailability due to the first-liver-pass effect (10), which calls for the use of higher doses that give rise to a fairly large number of side effects (11) such as somnolence and sedation, which are also associated with a lower pregnancy rate (12). There is increasing evidence that vaginal and intramuscular P are at least equally effective, considering the rate of biochemical and clinical pregnancies as well as their outcomes (13–15). However, through the use of vaginal P, reiterated painful application of IM injections and their complications, such as local soreness, abscesses, and inflammatory reactions (16), were avoided.

The purpose of this study was to compare the efficacy and tolerability of two vaginal Ps, Crinone 8% gel (Fleet Laboratories Ltd., Watford, United Kingdom) and Utrogestan capsules (Laboratories Besins International, Paris, France), used as luteal-phase support during IVF.

MATERIALS AND METHODS

Patient Characteristics

The study groups consisted of patients undergoing an IVF or intracytoplasmic sperm injection (ICSI) cycle of assisted fertilization during an 18-month period (January 2004–July 2005). After successful oocyte retrieval, patients were in-

formed of the purpose of the study and asked to participate. A total of 285 women confirmed their participation, and afterwards were randomly assigned into two groups, receiving P support with either Crinone 8% gel ($n = 140$) or Utrogestan vaginal capsules ($n = 145$). Participants were alike in terms of these criteria: applied routine ovulatory induction protocol, <37 years of age (age 32 years, on average), maximum of two prior IVF attempts, minimum of three oocytes obtained by aspiration, and body mass index (BMI) <25 . The study protocol and patients' written consent were approved by our Institutional Review Board.

Study Protocols

Participants underwent routine ovarian down-stimulation protocol with GnRH agonists. After day 21 of the preliminary cycle, buserelin nasal spray (Suprefact; Aventis Pharma, Frankfurt, Germany) 2mg was used, 4 times daily. Following day 2 of the ongoing cycle, recombinant FSH (rFSH, Gonal-F; Serono, Geneva, Switzerland) was subjoined in a dosage of 225 or 300 IU for a further 3 or 4 days. The dose was subsequently reduced to a total of 150 IU to the day of hCG (Ovitrelle; Serono) application.

The ovarian response was monitored by measuring the serum level of E_2 and ultrasound monitoring of the follicular maturation. When at least two follicles were 16–17 mm in diameter, hCG (Ovitrelle) 6,500IU was administered. Approximately 36–40 hours after the application of hCG, the aspiration of oocytes was performed under the control of transvaginal ultrasound. Afterwards, oocytes were cultivated in the culture medium, and 3–4 hours later they were associated with sperm. If fertilization occurred, the best embryos would be selected, and 3–5 days after aspiration, applied in the uterine cavity. A maximum of three embryos was transferred, and all other supernumerary embryos were frozen by agreement of the patients for any future attempts.

Luteal Support

The study population was divided into two groups. The first group ($n = 140$) received P support in the form of Crinone 8% gel, 90 mg daily. The second group ($n = 145$) received Utrogestan vaginal capsules, 3×2 at 100 mg. Progesterone support was administered on the day of oocyte aspiration and continued until the day of testing for pregnancy, and in the case of pregnancy until week 12.

Determination of Pregnancy Status

Pregnancy was detected by serum level of β -hCG approximately 2 weeks after ET, and by ultrasound for the detection of clinical pregnancy 2–4 weeks later.

Patient Safety and Acceptability

Acceptability and safety of the preparations from the patients' point of view were determined by a questionnaire that

was distributed to patients on the day of ET. The questions asked for yes or no answers regarding certain symptoms that the preparations could cause. The questions included the occurrence of nausea and/or vomiting, constipation, abdominal pain, dizziness, headache, breast fullness, perineal irritation, and vaginal itching, burning, and leakage. Patients ($n = 48$) familiar with Utrogestan or Crinone vaginal P from prior IVF cycle(s) were urged to compare them by answering four questions concerning administration simplicity, convenience in everyday use, messiness, and personal preference for one preparation or the other.

Statistical Analysis

The outcomes of IVF treatment in patients who received luteal support with either vaginal P gel (the Crinone group) or vaginal capsules (the Utrogestan group) were compared with the use of Fisher's exact test. The acceptability and tolerance of both preparations were estimated using the chi-square test. $P < .05$ was considered statistically significant.

RESULTS

The study included a population of 285 patients, divided into two groups: those receiving Crinone ($n = 140$), and those receiving Utrogestan ($n = 145$). During the study, 19 patients withdrew due to fertilization failure (Crinone = 7, Utrogestan = 6), local drug intolerance (Crinone = 2, Utrogestan = 3), and one OHSS incident in a patient who received Crinone 8%. The total study population consisted of 266 patients: 130 in the Crinone group, and 136 in the Utrogestan group. The questionnaires were in nine cases only partially completed (Crinone group = 5, Utrogestan group = 4), and were excluded from the final analysis.

The study groups were almost equal in the number of administered gonadotropin ampules, serum level of E_2 on day of hCG application, number of aspirated oocytes, number of fertilized oocytes, embryos transferred, age, BMI, and IVF attempts made previously, i.e., no statistically significant difference was established between groups (Table 1).

Tolerance of the preparations, as examined by the questionnaire, showed a statistically significant difference in total number of side effects between Crinone 8% and Utrogestan that were more often present with the use of Utrogestan vaginal capsules (Table 2). A few side effects occurred more frequently in the Crinone group, including breast fullness (4 times) and nausea with or without vomiting (2 times). Burning (7 times) and vaginal leakage (18 times) were noted more often in the Utrogestan group, along with perineal irritation and vaginal itching, which reached statistical significance ($P < .05$). All data are presented in Table 2.

Patients who had previously undergone the alternative treatment (Utrogestan or Crinone) compared the acceptability of both preparations by choosing which one was, in their opinion, easier to administer, more convenient in everyday

TABLE 1**Demographic and specific treatment characteristics of patients.**

| Parameter | Patient group | |
|---|----------------------|-------------------------|
| | Crinone (n = 130) | Utrogestan (n = 136) |
| Patient age (y) | 32.4 ± 2.1 | 31.9 ± 2.3 |
| Body mass index | 22.5 ± 2.1 | 22.3 ± 2.2 |
| Gonadotropin ampules | 25.0 ± 11.1 | 27.0 ± 11.2 |
| Serum level of E ₂ on day of hCG application (pg/mL) | 2,120 ± 1,006 | 2,240 ± 1,100 |
| Aspirated oocytes | 8.0 ± 3.2 | 8.4 ± 3.8 |
| Fertilized oocytes | 6.3 ± 2.8 | 6.0 ± 2.8 |
| Embryos transferred | 2.1 ± 0.6 | 2.0 ± 0.7 |
| Clinical pregnancies | 33.1% (43/130) | 30.9% (42/136) |
| Prior IVF attempts | 1.1 ± 0.5 | 1.2 ± 0 |

Note: Values are percentages or means ± SD. No statistically significant differences between groups were found by Fisher's exact test.

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use, less messy, and more preferable. All statistically established differences were in favor of Crinone 8% gel (Fig. 1).

DISCUSSION

Progesterone luteal support has become a standard procedure in IVF- and ICSI-induced cycles, to prevent deficient P

secretion from the corpus luteum (9). In stimulated cycles, the use of GnRH agonists causes a suppression of LH secretion from the pituitary gland at least 10 days after the last applied dose (17,18). The retrieval of granulosa cells during oocyte aspiration can lead to insufficient luteal function and underproduction of P (19). Hence there is a need for luteal support in cycle stimulation with the use of GnRH agonists, in oocyte aspiration among women with P levels ≤30 ng/mL measured after ovulation (20), and in cases of increased E₂ levels during ovulatory induction to avoid a negative effect on the endometrium, thereby endangering the successful implantation of embryos (21).

Progesterone can be found in several formulations: oral, IM, and vaginal. Oral P was linked with a significant range of side effects: dryness, flushing, and nausea (22). Sedative and hypnotic effects were related to its metabolites binding to specific sites within GABA receptors (11). Orally administered P is rapidly metabolized during first liver pass, and then disappears from the general circulation (23). However, even the heightened dose of oral P (200 or 300 mg daily) failed to induce homogenous secretory endometrial transformation among menopausal women (24). On the other hand, vaginally applied P reached higher concentrations in the endometrial tissue than did oral or IM P (25). Vagina to uterus transport as a characteristic of the vaginal P is responsible for its direct action upon the endometrium (26–28). Homologous secretory transformation of the endometrium is thereby achieved (29).

There is increasing evidence in the literature that vaginal P is at least effective as IM P at providing luteal support in induced cycles (30). Because daily injections of IM P are painful and also have the potential to induce soreness, abscesses, and inflammatory reactions (31), vaginal adminis-

TABLE 2**Tolerability of Crinone and Utrogestan in study groups.**

| Parameter | Patient group | |
|------------------------|----------------------|-------------------------|
| | Crinone (n = 125) | Utrogestan (n = 132) |
| Nausea and/or vomiting | 2 | 1 |
| Constipation | 0 | 0 |
| Abdominal pain | 2 | 2 |
| Dizziness | 0 | 1 |
| Headaches | 1 | 2 |
| Breast fullness | 4 | 3 |
| Perineal irritation | 6 | 13 ^a |
| Vaginal itching | 10 | 29 ^a |
| Burning | 4 | 7 |
| Vaginal leakage | 9 | 18 |
| Total | 38 | 68 ^a |

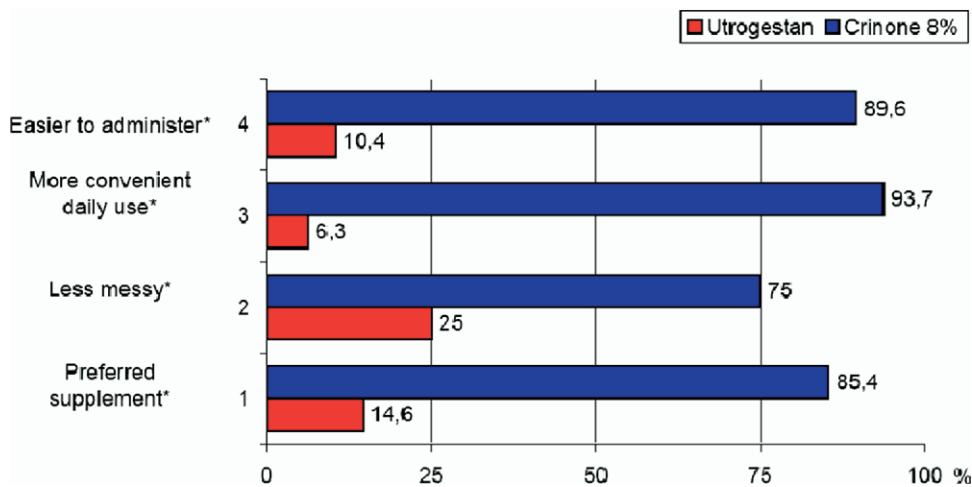
Note: Values are numbers of positive (yes) answers for symptoms.

^a Statistically significant difference from Crinone group by χ^2 test, $P<0.05$.

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FIGURE 1

Preparation acceptability in the opinion of 48 patients familiar with the use of Utrogestan or Crinone 8% supplements from previous IVF cycle(s). * $P < .05$ by chi-square test, in favor of Crinone 8%.



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tration of P seems to be the optimal choice for luteal-phase support in IVF cycles.

The primary objective of this study was to compare the efficacy of two formulations of micronized P, Crinone 8% gel and Utrogestan capsules, used as vaginal P luteal support in IVF treatment. The results show a similar efficiency of both preparations, producing almost identical pregnancy rates. Our results are in agreement with other studies (32,33) reporting comparable IVF success with the use of both supplements.

The secondary objective of our study was to compare the tolerability and acceptability of both preparations from our patients' point of view. Crinone 8% gel proved to be far more tolerable than Utrogestan vaginal capsules, in terms of a lower number of side effects. The clear advantage of Crinone over Utrogestan is based on polycarbophil, a polymer base known for vaginal adhesiveness to the epithelial surface (26), resulting in reduced vaginal leakage and perineal irritation. Vaginal itching and burning were noted more frequently with the use of Utrogestan capsules compared to Crinone 8% gel, and could be linked to Utrogestan's bovine origin and the fact that it contains peanut oil.

Our patients who had previously undergone the alternative treatment declared Crinone 8% to be a far more acceptable preparation at providing luteal-phase support due to easier administration, more convenience, and less messiness in everyday use.

In conclusion, this study showed nearly the same efficacy for both vaginal Ps (Crinone 8% gel and Utrogestan vaginal capsules) at providing luteal support. The onset of symptoms such as breast fullness and vaginal itching or burning varied

from one preparation to the other, but more frequently occurred in patients using Utrogestan vaginal capsules. Crinone 8% gel, 90 mg once daily, appeared to be safer and, from the patients' standpoint, a more acceptable way of providing adequate luteal support than Utrogestan vaginal capsules in induced cycles.

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