Subcutaneous progesterone versus vaginal progesterone gel for luteal phase support in in vitro fertilization: a noninferiority randomized controlled study

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Objective: To compare the safety, efficacy, and tolerability of subcutaneous progesterone (Prolutex, 25 mg; IBSA Institut Biochimique SA) with vaginal progesterone gel (Crinone, 8%; Merck Serono) for luteal phase support (LPS) in assisted reproduction technologies (ART) patients.
Design: Prospective, open-label, randomized, controlled, parallel-group, multicenter, two-arm, noninferiority study.
Setting: Thirteen European fertility clinics.
Patient(s): A total of 683 ART patients randomized to two groups: Prolutex, 25 mg subcutaneously daily (n = 339); and Crinone, 90 mg 8% gel daily (n = 344).
Intervention(s): In vitro fertilization and embryo transfer were performed according to site-specific protocols. On the day of oocyte retrieval, Prolutex or Crinone gel was begun for LPS and continued for up to 10 weeks.
Main Outcome Measure(s): Ongoing pregnancy rate.
Result(s): The primary end point, ongoing pregnancy rates at 10 weeks of treatment were 27.4% and 30.5% in the Prolutex and Crinone groups, respectively (intention to treat [ITT]). The nonsignificant difference between the groups was −3.09% (95% confidence interval [CI] −9.91–3.73), indicating noninferiority of Prolutex to Crinone. Delivery and live birth rates resulted to be equivalent between the two treatments (26.8% vs. 29.9% in the Prolutex and Crinone groups, respectively [ITT]; difference −3.10 [95% CI −9.87–3.68]). No statistically significant differences were reported for any of the other secondary efficacy endpoints, including comfort of usage and overall satisfaction.
Conclusion(s): Implantation rate, pregnancy rate, live birth rate, and early miscarriage rate for Prolutex were similar to those for Crinone. The adverse event profiles were similar and Prolutex was safe and well tolerated.
Clinical Trial Registration Number: NCT00827983. (Fertil Steril® 2014;101:112–9. ©2014 by American Society for Reproductive Medicine.)
Key Words: Luteal phase support, in vitro fertilization, intracytoplasmic sperm injection, progesterone, pregnancy

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The requirement for luteal phase support (LPS) in stimulated IVF cycles is well established, although there continues to be active disagreement about the optimum drug, route of administration, timing of initiation of treatment, and duration of use. Notwithstanding several well powered randomized controlled trials (RCTs) and meta-analyses, one of few points of consensus is that hCG injections are associated with a significantly increased risk of ovarian hyperstimulation syndrome (OHSS) (1). LPS is required principally because of the supraphysiologic levels of circulating E_2 resulting from stimulation with gonadotropins, the aspiration of granulosa cells from the follicles during oocyte retrieval, and the suppression of pituitary LH in GnRH agonist and antagonist cycles resulting in premature luteolysis. In stimulated IVF cycles, it is well recognized that most cycles are characterized by an abnormal luteal phase, leading to poor endometrial development and asynchrony between endometrial receptiveness and the timing of embryo transfer (2). Progesterone for LPS is available as an intramuscular (IM) injection in oil, as progesterone-in-oil capsules for vaginal or rectal administration, as a bioadhesive vaginal gel, as oral capsules, or as oral dydrogesterone. The IM injection in oil at a dose of 50–100 mg per day has been associated with local pain, the development of local inflammatory reactions, and occasionally sterile abscesses (3–10). Vaginal P, either capsules (pessaries) or gel, provides a well accepted and effective form of LPS with adequate endometrial secretory transformation notwithstanding low circulating P levels (3, 10–13). This is a result of direct transport across the vaginal epithelium described as the uterine "first pass" effect. This is in contrast with orally administered P, where there is poor bioavailability and rapid liver inactivation with systemic side effects, noticeably excessive drowsiness, and gastrointestinal upset (3, 10, 14, 15).

Given the reluctance of some patients to use vaginal preparations owing to the discomfort of administration, vaginal discharge, and, rarely, intolerability, as well as the inconvenience and discomfort associated with prolonged IM administration of P in oil (castor or sesame oil), a water-soluble injectable P has been developed that may be administered by subcutaneous (SC) injection. Prolutex is a complex of P and hydroxypropyl-β-cyclodextrin in water (16) which has been demonstrated to produce adequate endometrial decidualization at a daily dose of 25 mg or 50 mg in a dose-finding study (17).

Pharmacokinetics profiles of IM and SC administration of 25 mg, 50 mg, and 100 mg Prolutex have been published by Sator et al. (18). In these preliminary studies it was demonstrated that the serum levels of P achieved with 25 mg were above the threshold necessary for predecidualization to occur (19, 20). In addition, an earlier phase II study (21) performed in 24 healthy subjects provided evidence that Prolutex administered SC at a daily dose of 25 mg or 50 mg was effective at priming the endometrial changes seen in the menstrual cycle in the absence of endogenous P. Because of no difference in the endometrial biopsies having been shown between the two doses tested, the lowest dose (25 mg/d, which corresponds to the physiologic amount produced by the ovary in the midluteal phase [22]) was selected for the phase III trials of LPS in assisted reproduction technologies (ART).

The aim of the present clinical trial was therefore to compare the efficacy and tolerability of 25 mg/d of the new SC P (Prolutex) with 90 mg/d of vaginal gel P (Crinone) for LPS in IVF and intracytoplasmic sperm injection (ICSI) treatment cycles.

MATERIALS AND METHODS

Study Design

This prospective, open label, randomized, controlled, parallel-group, multicenter (n = 13), two-arm, noninferiority study was conducted to compare the safety, effectiveness and tolerability of SC P (Prolutex; IBSA Institut Biochimique SA) with vaginal P gel (Crinone; Merck Serono) for LPS in IVF/ICSI cycles. The study was designed, conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP) guidelines. The trial was registered with clinicaltrials.gov with the identifier NCT00827983. Reporting of this study follows the recommendations of the CONSORT 2010 statement. The study was conducted at 13 sites in Europe from January 2009 to September 2010. Institutional Review Board approvals were obtained from all sites before initiation of the trial. Before any study-specific procedures were performed, written informed consent was obtained from each patient.

Patients with infertility, planning to undergo IVF with or without ICSI, were selected for possible study inclusion from January 2009 to September 2010. The eligibility criteria were female age 18–42 years, body mass index <30 kg/m^2, fewer than three prior ART cycles, baseline (day 2–3) FSH <15 IU/L and E_2 <80 pg/mL, and a normal uterine cavity as demonstrated on recent hysteroscopy, sonohysterogram, or hysterosalpingogram. Eligibility for randomization required at least three oocytes being retrieved.

Significant exclusion criteria included cavity-distorting intramural fibroids, stage III or IV endometriosis, hydrosalpinx, history of previous poor response, recurrent miscarriage, adrenal or thyroid disease, and thromboembolic disease or disorder.

Treatment

Eligible patients were allowed any kind of LH suppression (agonist or antagonist with or without oral contraceptive pill before treatment) and any gonadotropin stimulation regimen (recombinant or urinary FSH, hMG, or combination at doses individually determined by the treating physicians).

Randomization to one of the two treatment arms (1:1 ratio) was done per center by sequentially numbered sealed envelopes with the use of computer generated randomly permutated blocks with an undisclosed fixed block size of 4. Randomization was performed after oocyte retrieval by a study nurse or a study doctor.

The first dose was administered on the day of oocyte retrieval. Daily treatment, which was self-administered by the patient after training, was continued through embryo transfer (ET), which was performed on day 2–3 or 5 (for blastocyst) according to local custom, for a total of 15 ± 2 days, at which point a serum pregnancy test was performed.