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.
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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.

In the event of a positive pregnancy test and subsequent confirmation of an on-going nonectopic pregnancy, patients continued their treatment for a further 8 weeks until the final study visit.

Assessments

During each visit (i.e., on ET day, on hCG pregnancy test day, on pregnancy confirmation visit at 6–7 weeks of gestation, and after 10 weeks of treatment), patients were asked by the study investigator to assess their overall health. The investigator also checked the administration site, reporting in the patient file any tolerability issue. In addition, the investigator interviewed the patients about the onset of any adverse event (AE), paying special attention to vaginal reactions and drug tolerability: the study specifically requested to check vaginal reactions and to report the information in the patient file. In case of symptoms related to a possible genital tract infection, patients were examined and tested according to the standard practice of each clinic. Throughout the study, patients recorded daily AEs and concomitant medication usage in a patient diary. Any change in the clinical assessment of the patient compared with previous visits was considered to be an AE and was reported as such. The investigator examined the injection site for patients allocated to Prolutex at each visit. Patients with an on-going pregnancy at the final visit were provided with a pregnancy outcome form for completion by their obstetrician after delivery.

Outcomes

The primary efficacy variable was the proportion of patients who were pregnant 10 weeks after the start of treatment. The secondary efficacy variables were implantation rate, positive β-hCG test rate, clinical pregnancy rate, early spontaneous abortion rate, delivery rate, live birth rate, and newborn status.

Implantation rate was defined as the number of gestational sacs divided by the number of embryos transferred per patient. A mean was then calculated. Clinical pregnancy was defined as the presence of one or more gestational sacs detected on ultrasound scan performed $\geq$4 weeks after embryo transfer. Biochemical pregnancy loss was defined as a rise of β-hCG with no further evidence of the gestational sac on an ultrasound scan. Miscarriage was defined as a pregnancy loss after ultrasound confirmation of embryo implantation and before 12 weeks. Live birth was defined as the delivery of one or more live babies.

The expected side effects of Prolutex (local reaction at the injection site) or Crinone treatment (vaginal irritation, inflammation, itching, leakage, and bleeding), as well as the systemic side effects (e.g., nausea, dizziness, breast pain) were of particular interest.

Statistical Analysis and Sample Size

The intention-to-treat (ITT) population (including all of the randomized patients) constituted the denominator for the efficacy analyses. Analyses were performed also on the per-protocol (PP) population (including all patients who underwent ET with no major protocol deviation). Safety analysis was performed on all patients who had at least one dose of P. The sample size required for this trial was determined by an a priori defined noninferiority margin. Noninferiority was assessed by calculating the 95% confidence interval (CI) of the difference in ongoing pregnancy rate per ITT between the two groups. If the lower bound of the 95% CI of the difference was greater than -10% then Prolutex was considered to be noninferior to the Crinone treatment. A sample size of 660 subjects was calculated to be the minimum required to demonstrate noninferiority with a power of 80%, using a -10% noninferiority margin for the lower limit of the two-sided 95% CI and assuming an ongoing pregnancy rate of 30%. The primary efficacy variable was the proportion of patients who were pregnant 10 weeks after the start of treatment. Pregnancy rates in the Prolutex group were compared with pregnancy rates in the Crinone group with the use of the Cochran-Mantel-Haenszel (CMH) test, adjusting for investigational site. Homogeneity of effect between investigational sites was assessed with the use of the Breslow-Day test.

Multiple logistic regression models were used to assess the effect of baseline variables on pregnancy and on the estimated effects of treatment on pregnancy. In general, a quasi-stepwise procedure was used in which a forward regression phase based on maximizing model fit was followed by a backward regression phase where nonsignificant parameters were removed.

The secondary outcome variables were compared with the use of an unpaired Student *t* test for continuous variables and chi-square tests for rates and categoric variables. For these parameters, the CMH test stratified by investigational center and a multivariate analysis of variance were used to estimate the difference between the two treatment groups.

The incidence of AEs was compared with the use of the chi-square test or two-tailed Fisher exact test as appropriate. No correction for multiplicity of testing was applied.

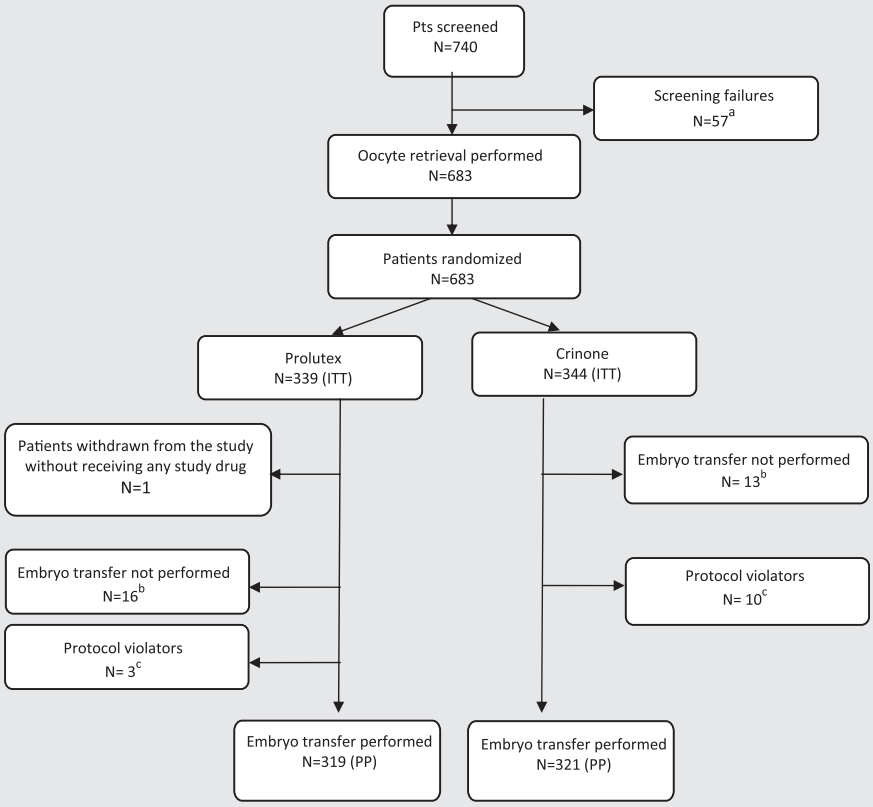
RESULTS

Patient Disposition and Basal Characteristics

The ITT population included 683 patients, of whom 640 followed the protocol without violations and had ET performed. ET was not performed in 29 patients (16 randomized to Prolutex and 13 to Crinone). The principle reasons were similar between groupse failed fertilization, risk of OHSS, and embryonic arrest. Intake of additional drugs for luteal support (E_2) or drugs that may modify endogenous production of P (dexamethasone) was considered to be a major protocol violation and caused exclusion from the PP analysis. Participant flow through the trial is depicted in Figure 1.

The patients were generally healthy and were considered to be representative of the patient population undergoing IVF treatment. The two groups were well matched in terms of baseline demographic characteristics (Table 1). The mean age of patients was ~34 years in each treatment group, and >90% of patients in each group were White. No notable differences between the treatment groups in infertility history, infertility diagnostic variables, infertility classification,

FIGURE 1



Participant flow through the trial. ITT = intention to treat; PP = per protocol. [a]Screening failures because inclusion/exclusion criteria not met (n = 36): <3 oocytes retrieved (n = 24); basal 17β-E_2 level and/or normal uterine cavity (n = 11); >3 previous ART treatments (n = 1); cycle interrupted due to poor response (n = 8); cycle interrupted due to ovarian hyperstimulation syndrome (OHSS) risk (n = 5); voluntary withdrawal (n = 3); only atretic oocytes collected (n = 2); adverse event (n = 1); violation of the protocol (need of a concurrent medication prohibited by the protocol [n = 1]); embryo transfer (ET) not performed (endometrial thickness <4 mm [n = 1]). [b]ET not performed for following reasons: Prolutex: failed fertilization (n = 6); risk of OHSS (n = 3); OHSS (n = 1); no progressing embryos (n = 6). Crinone: failed fertilization (n = 8); risk of OHSS (n = 2); no progressing embryos (n = 3). [c]Protocol violators: Prolutex, intake of not allowed medication progynova-E_2 for luteal support (n = 2), intake of not allowed medication dexamethasone (n = 1); crinone, intake of not allowed medication progynova-E_2 (n = 5), intake of not allowed medication dexamethasone (n = 5).

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gynecologic examination, prior and concomitant pathology, medication use for cycle synchronization, pituitary desensitization and ovarian stimulation, oocyte retrieval data, ET data, mean basal FSH and E_2 levels, or prior and concomitant medication use were reported. The mean duration of infertility was reported as 47 months in both groups, and "male factor" was the most frequently reported cause of infertility (>65% of patients in each group).

Table 2 presents down-regulation regimen and ovarian stimulation protocol for the patients.

Efficacy Results

Table 3 shows the primary endpoint, ongoing pregnancy rate, and the secondary endpoints by ITT and PP populations. In the ITT population, ongoing pregnancy rates at 10 weeks were similar between the two treatment groups (27.4% and 30.5% in the Prolutex and Crinone groups, respectively). The nonsignificant difference between the groups was −3.09% (95% CI −9.91 to 3.73) indicating noninferiority of Prolutex to Crinone.

The ongoing pregnancy rate per protocol was 29.2% and 31.2% in the Prolutex and Crinone groups respectively (difference −2.00%, 95% CI −9.12–5.13).

The Breslow-Day chi-square statistic was used to examine whether the odds ratio of ongoing pregnancy rate is homogeneous across the 13 strata (centers). The Breslow-Day *P* value was equal to 0.031, suggesting that the stratum-to-stratum variability in terms of the odds ratio was slightly different. However, the CMH statistic for association between treatment and ongoing pregnancy rate adjusted for the center was not significant (P=.352). This means that there was no difference in ongoing pregnancy rate across the 13 centers in patients treated with Prolutex and Crinone.

Logistic regression modeling confirmed that the likelihood of an ongoing pregnancy of an individual patient within the trial was not related to treatment type, i.e., Prolutex vs.

TABLE 1

Demographic characteristics and infertility classification (intention-to-treat population).

	Prolutex (n = 339)	Crinone (n = 344)
Demographic characteristics		
Age (y), mean (SD)	33.8 (4.3)	33.9 (4.3)
BMI (kg/m^2), mean (SD)	22.8 (3.2)	22.9 (3.1)
Race, n (%)		
White	312 (92.0)	315 (91.6)
Black	8 (2.4)	6 (1.8)
Asian	15 (4.2)	16 (4.7)
Other	4 (1.2)	7 (2.0)
Basal FSH (IU/L), mean (SD)	6.9 (2.1)	6.9 (2.1)
Basal E_2 (ng/mL), mean (SD)	43.1 (17.8)	42.0 (17.9)
Infertility classification, n (%)		
Male factor	223 (65.78)	232 (67.44)
Tubal	88 (25.96)	79 (22.97)
Polycystic ovary syndrome	15 (4.42)	12 (3.49)
Anovulatory	17 (5.01)	12 (3.49)
Endometriosis	20 (5.90)	22 (6.40)
Luteal phase defect	32 (9.44)	30 (8.72)
Unexplained	45 (13.27)	49 (14.24)
Other	11 (3.24)	14 (4.07)

Note: BMI = body mass index.

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Crinone. The following confounders were found to be independently associated with the likelihood of pregnancy: age, indication for treatment, and endometrial thickness.

No statistically significant differences between the Prolutex and Crinone groups were reported for any of the secondary efficacy endpoints (ITT; Table 3). For both the primary and the secondary efficacy analyses, data similar to those for the ITT population were reported for the PP population.

Pregnancy follow-up and baby status information revealed 91 deliveries (with 118 babies born) in the Prolutex group and 103 deliveries (with 125 babies born) in the Crinone group (ITT population) and showed no differences regarding delivery rate and live birth rate (26.8% vs. 29.9%; P=.37), number of singleton (78% vs. 78.6%; P=.92) or multiple (22% vs. 21.4%; P=.92) deliveries, gestational age in weeks at delivery (38.3 ± 2.7 vs. 38.5 ± 2.6; P=.67), preterm delivery rate (23.1% vs. 21.4%; P=.77), or birth weight (2.84 ± 0.75 kg vs. 2.93 ± 0.75 kg; P=.33).

TABLE 2

Medication used for cycle synchronization, pituitary desensitization, ovarian stimulation, and hCG trigger (intention-to-treat population), n (%).

Medication type and drug	Prolutex (n = 339)	Crinone (n = 344)	*P* value[a]
Cycle synchronization			
Oral contraceptive pill	13 (3.83)	13 (3.78)	.969
LH suppression			
GnRH agonist	233 (68.73)	242 (70.35)	.646
GnRH antagonist	106 (31.27)	102 (29.65)	
Ovarian stimulation			
Human FSH	109 (32.15)	122 (35.47)	.777
Recombinant FSH	162 (47.79)	156 (45.35)	
hMG	50 (14.75)	51 (14.83)	
Other	18 (5.31)	15 (4.36)	
hCG triggering			
Human hCG	248 (73.16)	254 (73.84)	.828
Recombinant hCG	91 (26.84)	89 (25.87)	
GnRH agonist	0 (0.00)	1 (0.29)	

[a] χ^2 test for categoric variables.

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Safety Results

The frequency and incidence of treatment-related nonserious AEs were similar between the Prolutex and Crinone groups and are reported in Supplemental Table 1 (419 events in 42.3% of Prolutex patients vs. 459 events in 45.4% of Crinone patients). The most frequently reported AEs were reproductive system and breast disorders (more frequent in the Crinone group than in the Prolutex group [40.4% and 29.3%, respectively; P=.002]), gastrointestinal disorders (with diarrhea being significantly more frequent in the Crinone group than in the Prolutex group [2.3% and 0.0%, respectively; P=.011]), and nervous system disorders. AEs in the skin and subcutaneous disorders were significantly more frequent in the Prolutex group than in the Crinone group (3.9% and 1.2%, respectively; P=.03).

Even if not statistically significant, a higher number of patients reported genital tract infections in the Crinone group (1.5% vs. 3.8% in the Prolutex and Crinone groups, respectively; P=.09).

The proportion of patients experiencing serious adverse events (SAEs) (Supplemental Table 2) was similar between the two treatment groups (4.1% and 5.8% in the Prolutex and Crinone groups, respectively; P=.32). The most frequently reported individual SAEs were ectopic pregnancy (0.6% and 0.0% in the Prolutex and Crinone groups, respectively; P=.25), ovarian hyperstimulation syndrome (OHSS; 1.2% and 2.0%; P=.55), and spontaneous abortion (1.5% in both groups; P=1.0). Only two SAEs (swelling face and deep vein thrombosis) in the Crinone group were considered to be related to treatment.

Safety issues related to pregnancy outcomes and newborn status emerging from the analysis of the pregnancy follow-up forms data found seven babies in the Prolutex group and two babies in the Crinone group reported as having abnormalities (P=.09), a difference considered not to be clinically significant.

Tolerability Result

Regarding local tolerability at administration site (Supplemental Table 3), 57% of patients in the Prolutex group experienced discomfort (irritation, pruritus, or hematoma) at the injection site, mainly of mild intensity. Regarding vaginal discomfort, 50.8% of the patients in the Crinone group experienced irritation, inflammation, dryness, pruritus, discharge, or pain (with only 10.4% of the patients reporting the same symptoms in the Prolutex group; P=.0001).

Patient well-being remained high throughout the study in both treatment groups, with >78% of patients considered to be very healthy at all clinical assessments. No statistically

TABLE 3

Pregnancy rate and live birth rate by treatment.

Variable	Prolutex	Crinone	*P* value[a]
Primary endpoint			
Ongoing pregnancy—ITT, n (%)	93 (27.4)	105 (30.5)	.40
Difference vs. Crinone (95% CI)	−3.09 (−9.91 to 3.73)		
Ongoing pregnancy—PP, n (%)	93 (29.2)	100 (31.2)	.61
Difference vs. Crinone (95% CI)	−2.00 (−9.12 to 5.13)		
Secondary endpoints			
Implantation rate—ITT mean (SD)	22.6 (35.0)	23.1 (33.1)	.85
Difference vs. Crinone (95% CI)	−0.52 (−5.75 to 4.72)		
Implantation rate—PP mean (SD)	22.8 (35.1)	22.7 (32.9)	.97
Difference vs. Crinone (95% CI)	0.12 (−5.16 to 5.39)		
Positive β-hCG test—ITT, n (%)	134 (39.5)	148 (43.0)	.35
Difference vs. Crinone (95% CI)	−3.5 (−10.89 to −3.90)		
Positive β-hCG test—PP, n (%)	134 (42.0)	141 (43.9)	.62
Difference vs. Crinone (95% CI)	−1.9 (−9.60 to 5.77)		
Clinical pregnancy—ITT, n (%)	103 (30.4)	113 (32.9)	.49
Difference vs. Crinone (95% CI)	−2.47 (−9.45 to −4.52)		
Clinical pregnancy—PP, n (%)	103 (32.3)	108 (33.6)	.72
Difference vs. Crinone (95% CI)	−1.36 (−8.65 to 5.94)		
Early spontaneous abortion[b]—ITT, n (%)	14 (4.1)	14 (4.1)	.97
Difference vs. Crinone (95% CI)	0.06 (−2.92 to 3.04)		
Early spontaneous abortion[b]—PP, n (%)	14 (4.4)	14 (4.4)	.99
Difference vs. Crinone (95% CI)	0.03 (−3.15 to 3.20)		
Delivery and live births—ITT, n (%)	91 (26.8)	103 (29.9)	.37
Difference vs. Crinone (95% CI)	−3.10 (−9.87 to 3.68)		
Delivery and live births—PP, n (%)	91 (28.5)	98 (30.5)	.58
Difference vs. Crinone (95% CI)	−2.00 (−9.08 to 5.08)		

Note: ITT population: n = 339 in the Prolutex; n = 344 in the Crinone group. PP population: n = 319 in the Prolutex group; n = 321 in the Crinone group. CI = confidence interval; ITT = intention to treat; PP = per protocol.

[a] Student *t* test for continuous variables, χ^2 test for categoric variables.

[b] Spontaneous abortion occurring during the first trimester of pregnancy.

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significant differences between the two treatment groups were reported during the study ($P>.05$) at each assessment except for visit 4, where more patients in the Crinone group reported feeling "mildly unhealthy" (7.3% vs. 19.6% in the Prolutex and Crinone groups respectively; $P=.012$).

Overall, the majority of patients in both treatment groups rated the treatment as comfortable or very comfortable (71.4% and 70.3%; $P=.77$, in the Prolutex and Crinone groups, respectively). Furthermore, most patients were satisfied or very satisfied with treatment (77.6% and 78.7%; $P=.75$).

DISCUSSION

In this study, for the first time, a low-dose SC P preparation was tested in IVF patients and compared with a vaginal preparation. The ongoing pregnancy rates were 27.4% with Prolutex and 30.05% with Crinone. Noninferiority could be claimed, because the lower limit of the 95% CI for the treatment difference in ongoing pregnancy was above the prespecified noninferiority limit for both the ITT and the PP populations. No difference in any of the secondary endpoints, including implantation rate and early pregnancy loss rate, was reported.

The use of luteal hormone support is an accepted aspect of IVF treatment. Although hCG and P both have demonstrable efficacy, P became the drug of choice because of the lower incidence of OHSS. Parenteral P in the form of IM injections in oil gained and retained popularity because of its consistent and measurable serum levels. Patients and clinicians continue to favor a medication that they could be certain was "being absorbed", notwithstanding the significant clinical drawbacks of these IM injections, which include pain, low patient acceptance, and the logistics associated with IM injections, which can not be self-administered, and complications such as pain, irritation, and occasionally sterile abscess formation (3, 6, 7).

Numerous meta-analyses of RCTs of LPS have been published (23–26). The most recent Cochrane database systemic review (1) included a comparison of 32 studies involving 9,839 women in which different P administration regimes (IM, vaginal/rectal, and oral) were investigated. The main results of this comparison showed a significant effect in favor of P for LPS, favoring synthetic P over micronized P. Overall, the addition of other substances, such as estrogen or hCG, did not seem to improve outcomes. In addition, no evidence favoring a specific route or duration of administration of P was found. On the other hand, hCG and hCG plus P were associated with a higher risk of OHSS. There were significant results showing a benefit from addition of GnRH agonist to P for the outcomes of live birth, clinical pregnancy, and ongoing pregnancy. According to the authors, P remains the best option as LPS.

There is a general consensus that P is the major hormonal supplementation for LPS in assisted reproductive treatment, but there is continued debate about the optimum protocol.

Vaisbuch et al. (27) recently presented the results of a worldwide web-based survey of P support in IVF. Responses were obtained from 84 treatment centers in 35 countries representing a total of 51,555 IVF cycles a year. Vaginal P alone was used for LPS in 64% of cycles and in combination with IM or oral P in another 16% of cycles. IM P was used as a single agent in 13% of cycles worldwide, and in North America IM P was used in 60% of cycles either as a single agent or in combination with vaginal P. This preference for an agent that is recognized to be both laborious and painful for the patient (7, 8) is also associated with prolongation of LPS until 10–12 weeks of pregnancy in 59.6% of cases and until the fetal heart beat is identified in another 38.4%. Worldwide, LPS is continued until 10–12 weeks of gestation in 66.5% of cycles notwithstanding the evidence base that P may be withdrawn on the day of positive pregnancy test (28, 29) or demonstration of fetal heart beat (1, 30) without impact on the miscarriage rate. In the present study, P was administered for 10 weeks to comply with the approved posology of the reference drug, Crinone.

It has been shown that the bioavailability of Prolutex administered SC is equivalent to the IM oil preparation, even though the absorption is definitely more rapid (18). Although IM P in oil and SC Prolutex result in higher serum levels than vaginal administration, levels in the endometrium are actually lower, as shown by Cicinelli et al. in 2000 (31). However, the endometrial levels obtained with 25 mg/d and 50 mg/d were sufficient to induce a correct endometrial decidualization (17).

Patient preference for vaginal over IM administration, as found by Levine (4) and later Yanushpolsky et al. (32), is clearly related to the pain and inconvenience associated with IM injections, which are difficult to self-administer and are painful, even when the injection is performed by a health care professional. Contemporary IVF, however, relies otherwise almost entirely on SC injections for agonist, antagonist, and gonadotropin therapy, and women feel confident and comfortable in self-administering these injections. Some women, for reasons of cultural and religious sensitivity, particularly once a pregnancy has been confirmed, are uneasy and reluctant to use medications that require vaginal insertion and are concerned about the leakage associated with gels and pessaries, fearing that they have not absorbed an adequate dose, and insertion of a vaginal preparation in case of spotting or vaginal bleeding can be unpleasant. In addition, the vaginal manipulation when performed in suboptimal conditions (a not properly clean environment) may increase the risk of genital tract infections, which have been shown to be one of the causes of spontaneous abortion (33), preterm births, and poor pregnancy outcome (34) if not treated in a timely manner. This new product may therefore be a good alternative for these patients.

This present study is the first large prospective randomized trial to demonstrate the noninferiority of Prolutex, a new water-soluble SC P, for LPS in IVF and ICSI treatment cycles compared with P gel. Prolutex (25 mg SC daily) was found to be noninferior to Crinone (90 mg intravaginally daily) as luteal support for patients undergoing IVF and ICSI based on the primary efficacy end point of ongoing pregnancy rate at 10 weeks of luteal support. Patient satisfaction was similar between the two groups, and overall the majority of patients in each treatment group rated the treatment as convenient or very convenient as well as comfortable or very comfortable.

A strength of this study lies with the heterogeneity of protocols used by the 13 separate European centers, suggesting that the two quite different formulations of P give clinically equivalent pregnancy outcomes across a range of treatment protocols. This was confirmed by a multivariate regression analysis assessing protocol choice as a potential confounder. Although there was, as expected, significant differences between centers in ongoing pregnancy rates owing to the different legal and regulatory requirements of the differing European jurisdictions, the intracenter randomization design assured that both P formulations were adequately tested in all centers. The ongoing pregnancy rates achieved in both arms of the study were strictly similar with those achieved by the 13 centers in the year preceding the start of the clinical trial and where, in many cases, LPS was supplied by P pessaries.

In conclusion, the present study provides evidence that Prolutex is safe and effective in supporting the luteal phase in IVF patients. The option of administering P SC for LPS in ART will broaden the spectrum of available treatments, an advantage for women needing sustained LPS (35) or disliking vaginal treatments for cultural, personal, or medical reasons.

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SUPPLEMENTAL TABLE 1

Nonserious adverse events.

	Prolutex (n = 338)			Crinone (n = 344)			
Body system/preferred term	**n[a]**	**n[b]**	**%**	**n[a]**	**n[b]**	**%**	***P* value[c] (χ^2)**
Not serious adverse event (all excluding tolerability)	420	144	42.60	460	157	45.64	.425
Gastrointestinal disorders—all	135	56	16.57	156	63	18.31	.548
Abdominal discomfort	3	1	0.30	2	1	0.29	1.000
Abdominal distension	34	22	6.51	35	26	7.56	.592
Abdominal pain	33	19	5.62	33	22	6.40	.671
Abdominal pain, lower	5	3	0.89	11	8	2.33	.223
Abdominal pain, upper	8	7	2.07	6	3	0.87	.220
Abdominal tenderness	1	1	0.30	1	1	0.29	1.000
Constipation	10	5	1.48	16	9	2.62	.419
Diarrhoea	0	0	0.00	8	8	2.33	.008
Dry mouth	0	0	0.00	1	1	0.29	1.000
Flatulence	2	2	0.59	5	3	0.87	1.000
Gastrointestinal disorders	3	1	0.30	0	0	0.00	.496
Gastrointestinal pain	1	1	0.30	0	0	0.00	.496
Nausea	26	17	5.03	34	16	4.65	.818
Retching	1	1	0.30	0	0	0.00	.496
Vomiting	8	5	1.48	4	3	0.87	.502
Infections and infestations—all	5	5	1.48	0	13	3.78	.092
Herpes virus infection	0	0	0	1	1	0.29	1.000
Urinary tract bacterial infection	2	2	0.59	4	4	1.16	.686
Vaginal bacterial infection	0	0	0	4	4	1.16	.124
Vulvovaginal mycotic infection	3	3	0.89	4	4	1.16	1.000
Nervous system disorders—all	39	21	6.21	24	20	5.81	.827
Dizziness	4	3	0.89	3	3	0.87	1.000
Headache	29	18	5.33	20	17	4.94	.820
Somnolence	6	2	0.59	1	1	0.29	.621
Renal and urinary disorders—all	1	1	0.30	6	4	1.16	.373
Bladder discomfort	0	0	0.00	1	1	0.29	1.000
Pollakiuria	0	0	0.00	5	3	0.87	.249
Urinary tract pain	1	1	0.30	0	0	0.00	.496
Reproductive system and breast disorders[d]	189	99	29.29	233	139	40.41	.002
Breast discomfort	0	0	0.00	1	1	0.29	1.000
Breast enlargement	1	1	0.30	0	0	0.00	.496
Breast pain	16	11	3.25	17	12	3.49	.866
Breast swelling	3	2	0.59	0	0	0.00	.245
Breast tenderness	34	23	6.80	22	21	6.10	.710
Nipple pain	3	2	0.59	3	1	0.29	.621
Nipple swelling	1	1	0.30	0	0	0.00	.496
Pelvic pain	0	0	0.00	5	4	1.16	.124
Premenstrual syndrome	0	0	0.00	2	1	0.29	1.000
Uterine spasm	42	42	12.43	60	60	17.44	.066
Vaginal discharge	13	13	3.85	60	60	17.44	<.0001
Vaginal bleeding/spotting	48	48	14.20	63	63	18.31	.146
Vaginal inflammation	4	4	1.18	0	0	0.00	.060
Vulvovaginal burning sensation	1	1	0.30	0	0	0.00	.496
Vulvovaginal discomfort	11	10	2.96	0	0	0.00	<.0009
Vulvovaginal pain	1	1	0.30	0	0	0.00	.496
Vulvovaginal pruritus	11	11	3.25	0	0	0.00	<.0005
Skin and subcutaneous tissue disorders—all	20	13	3.85	4	4	1.16	.028
Acne	1	1	0.30	0	0	0.00	.496
Dermatitis	3	2	0.59	0	0	0.00	.245
Dermatitis allergic	1	1	0.30	0	0	0.00	.496
Dry skin	1	1	0.30	1	1	0.29	1.000
Erythema	1	1	0.30	1	1	0.29	1.000
Night sweats	0	0	0.00	1	1	0.29	1.000
Pigmentation disorder	1	1	0.30	0	0	0.00	.496
Pruritus	5	2	0.59	0	0	0.00	.245
Rash	4	3	0.89	1	1	0.29	.370
Rash, papular	2	2	0.59	0	0	0.00	.245
Skin discoloration	1	1	0.30	0	0	0.00	.496

[a] Total number of reported events.
[b] Number of patients with a reported event.
[c] Fisher exact test for categoric variables.
[d] Reproductive system and breast disorders: adverse events related to the vaginal administration of Crinone (e.g., vaginal discomfort, vaginal bleeding and spotting, vaginal discharge, vulvovaginal pruritus, vulvovaginal discomfort, uterine spasm) were collected separately as "administration site discomfort" and included in the Tolerability Assessment Table (Supplemental Table 3).

Lockwood. Subcutaneous progesterone. Fertil Steril 2014.

SUPPLEMENTAL TABLE 2

Serious adverse events.

	Prolutex (n = 338)			Crinone (n = 344)			
Body system/preferred term	**n[a]**	**n[b]**	**%**	**n[a]**	**n[b]**	**%**	***P* value[c] (χ^2)**
Any serious adverse event—all	16	14	4.14	23	20	5.81	.316
Gastrointestinal disorders—all	2	2	0.59	1	1	0.29	.621
Abdominal pain	–	0	0.00	1	1	0.29	1.000
Gastroenteritis	1	1	0.30	–	0	0.00	.496
Vomiting	1	1	0.30	–	0	0.00	.496
Pregnancy, puerperium and perinatal conditions—all	10	10	2.96	9	8	2.33	.606
Abortion spontaneous—all	5	5	1.48	5	5	1.45	1.000
Abortion incomplete	–	0	0.00	1	1	0.29	1.000
Abortion missed	4	4	1.18	3	3	0.87	.723
Abortion spontaneous	1	1	0.30	1	1	0.29	1.000
Abortion threatened	3	3	0.89	4	3	0.87	1.000
Ectopic pregnancy	2	2	0.59	–	0	0.00	.245
Reproductive system and breast disorders—all	4	4	1.18	9	9	2.62	.262
Ovarian hyperstimulation syndrome	4	4	1.18	7	7	2.03	.546
Ovarian torsion	–	0	0.00	1	1	0.29	1.000
Ovarian cyst	–	0	0.00	1	1	0.29	1.000
Respiratory, thoracic and mediastinal disorders—all	–	0	0.00	1	1	0.29	1.000
Pleural effusion	–	0	0.00	1	1	0.29	1.000
Skin and subcutaneous tissue disorders—all	–	0	0.00	1	1	0.29	1.000
Swelling face (TR)	–	0	0.00	1	1	0.29	1.000
Surgical and medical procedures—all	–	0	0.00	1	1	0.29	1.000
Abortion induced	–	0	0.00	1	1	0.29	1.000
Vascular disorders—all	–	0	0.00	1	1	0.29	1.000
Deep vein thrombosis (TR)	–	0	0.00	1	1	0.29	1.000

Note: TR = treatment-related.
[a] Total number of reported events.
[b] Number of patients with a reported event.
[c] χ^2 test for categoric variables.

Lockwood. Subcutaneous progesterone. Fertil Steril 2014.

SUPPLEMENTAL TABLE 3

Tolerance assessment.

	Prolutex (n = 338)		Crinone (n = 344)		
Body system/preferred term	**n[a]**	**%**	**n[a]**	**%**	***P* value[b] (χ^2)**
Patients with a side effect related to treatment administration—all	193	57.10	108	31.40	<.0001
General disorders and administration site—all[c]	184	54.44	71	20.64	<.0001
Administration site irritation	45	13.31	2	0.58	<.0001
Administration site pain	168	49.70	25	7.27	<.0001
Administration site pruritus	41	12.13	33	9.59	.287
Administration site swelling	37	10.95	1	0.29	<.0001
Administration site discomfort	–	0.00	28	8.14	<.0001
Injection site hematoma	7	2.07	–	0.00	.007
Injection site induration	7	2.07	–	0.00	.007
Vaginal inflammation	–	0.00	26	7.56	<.0001
Vaginal dryness	–	0.00	5	1.45	.062

[a] Number of patients with a reported side effect related to treatment administration.
[b] Fisher exact test for categoric variables.
[c] Patients could report more than one side effect.

Lockwood. Subcutaneous progesterone. Fertil Steril 2014.