Vaginal (Crinone 8%) gel vs. intramuscular progesterone in oil for luteal phase support in in vitro fertilization: a large prospective trial

Kaylen M. Silverberg, M.D., Thomas C. Vaughn, M.D., Lisa J. Hansard, M.D., Natalie Z. Burger, M.D., and Tamara Minter, B.S.

Texas Fertility Center and Austin IVF, Austin, Texas

Objective: To compare the efficacy of intravaginal and IMP for luteal phase support in IVF cycles.
Design: Prospective trial.
Setting: Tertiary care private practice.
Patient(s): Women 25–44 years old with infertility necessitating treatment with IVF. From April 1, 2008–April 1, 2009, 511 consecutive patients were enrolled; 474 completed participation, and 37 were excluded for no autologous ET (freeze all, donor recipients, failed fertilization/cleavage). There were no demographic differences between the two treatment groups.
Intervention(s): Luteal phase support using either Crinone or P in oil starting 2 days following oocyte retrieval.
Main Outcome Measure(s): Pregnancy and delivery rates stratified by patient age.
Result(s): Overall, patients who received vaginal P had higher pregnancy (70.9% vs. 64.2%) and delivery (51.7% vs. 45.4%) rates than did patients who received IMP. Patients <35 who received vaginal P had significantly higher delivery rates (65.7% vs. 51.1%) than did patients who received IMP. There were no differences, regardless of age, in the rates of biochemical pregnancy, miscarriage, or ectopics.
Conclusion(s): In younger patients undergoing IVF, support of the luteal phase with Crinone produces significantly higher pregnancy rates than does IMP. Crinone and IMP appear to be equally efficacious in the older patient. (Fertil Steril® 2012;97:344–8. ©2012 by American Society for Reproductive Medicine.)
Key Words: In vitro fertilization, progesterone, luteal phase support, vaginal progesterone

Luteal hormonal support is a mainstay of successful IVF treatment. Previous reports suggested that successful supplementation could be provided with injections of either hCG or P (1, 2). A comparative trial suggested that, although both treatment options were effective, hCG injections were associated with a higher incidence of ovarian hyperstimulation syndrome (3). As a result, most programs gravitated toward the use of P.

Although P was effective, initially it could be administered only via IM injection. These injections were often painful and occasionally produced untoward effects including abscess formation, infection, and neuropathy (4). Despite these limitations, IM progesterone (IMP) rapidly became the criterion standard for luteal phase support in patients undergoing IVF. As a result of the significant incidence of adverse effects, however, there was a need for alternative forms of delivery. Many alternatives have since been proposed, including compounded suppositories, SC injections, and oral capsules (5). More recently, there has been a focus on the development of vaginally administered products.

Over the past several years, many studies have evaluated the safety and efficacy of different vaginal P preparations—including capsules, tablets, gel, and a ring (5). The primary goal of these trials has been to supplant the use of IMP, without decreasing the success of IVF. At least eight retrospective and/or small trials and three prospective trials have suggested that pregnancy rates (PRs) with vaginal preparations are equivalent to those achieved with IMP (6–9). One trial suggested that a particular vaginal preparation may not be efficacious in women >35 years of age (10).

This trial was designed to prospectively evaluate the use of a vaginal gel, Crinone 8% (90 mg, Watson Pharmaceuticals, Morristown, NJ), for luteal phase support in patients undergoing IVF with their own oocytes. Our primary objective was to compare the efficacy (live birth rate) of vaginal gel to that of IMP.

Received February 23, 2011; revised October 4, 2011; accepted November 15, 2011; published online December 19, 2011.
K.M.S. has received consulting fees from Watson Pharmaceuticals and EMD Serono and payment for lectures from Watson Pharmaceuticals. T.C.V. has nothing to disclose. L.J.H. has nothing to disclose. N.Z.B. has nothing to disclose. T.M. has nothing to disclose.
Reprint requests: Dr. Kaylen M. Silverberg, M.D., Texas Fertility Center, 6500 N. Mopac Suite 1200, Austin, TX 78731 (E-mail: kaylen@txfertilty.com).

Fertility and Sterility® Vol. 97, No. 2, February 2012 0015-0282/$36.00

doi:10.1016/j.fertnstert.2011.11.018

Our secondary objective was to assess live birth rates by patient age.

MATERIALS AND METHODS

Institutional review board approval was obtained before the start of this study. Between April 2008 and April 2009, 511 consecutive patients undergoing IVF with their own oocytes at Texas Fertility Center were offered inclusion in this trial; 474 patients were enrolled. Patients who did not undergo an ET because of failed fertilization, failed cleavage, or an increased risk of ovarian hyperstimulation syndrome were excluded from participation, as were patients who underwent either preimplantation genetic screening or diagnosis.

Enrolled patients were treated with at least 21 days of a low-dose monophasic oral contraceptive (OC), beginning on cycle day 3. Patients were then treated with one of two different stimulation protocols—an OC/leuprolide acetate (LA) overlap protocol for normal responders, or a microdose LA flare protocol for poor responders.

Normal responders underwent a transvaginal sonogram near the end of their OC treatment to rule out the presence of an ovarian cyst. They also underwent a trial ET. If no ovarian cyst was present, patients were started on LA 0.5 mg SC, and OCs were discontinued 5 days later. Patients returned for another transvaginal sonogram 7 days after stopping their OC, when the dose of LA was reduced to 0.25 mg and recombinant FSH (Gonal F, EMD Serono Pharmaceuticals, Rockland, MA, or Follistim, Merck, Whitehouse Station, NJ) was initiated. The starting dose of FSH was based on patient age and varied from 150–375 IU/d.

Poor responders underwent a transvaginal sonogram near the end of their OC treatment to rule out the presence of an ovarian cyst. They also underwent a trial ET. If no ovarian cyst was present, patients discontinued their OCs. Three days later, they started LA 40 μg SC two times per day. Two days after starting LA, patients began taking recombinant FSH 300 IU two times per day plus recombinant LH (Luveris, EMD Serono) 150 IU/d.

All patients were seen every 2 to 3 days for a vaginal sonogram and a serum E_2. Recombinant hCG (Ovidrel, EMD Serono) was administered when two follicles exceeded 19 mm in average diameter and a transvaginal oocyte retrieval was performed 36 hours later. Intracytoplasmic sperm injection (ICSI) was performed only for severe male factor infertility or in cases in which fewer than six oocytes were retrieved. Either Crinone or IMP was initiated two days following retrieval. Patients $\leq$39 years of age in the IMP group received 25 mg of P, whereas patients aged $\geq$40 years received 50 mg/d.

Patients who had six or more excellent-quality embryos—defined as at least six cells with minimal fragmentation—underwent ET on day 5. All other patients had day 3 transfers. Day 3 embryos underwent assisted hatching with a laser; blastocysts were not hatched. Patients with a peak serum E_2 exceeding 2,500 pg/mL started oral E_2 2 mg two times per day 7 days after the oocyte retrieval. A serum hCG test was performed 14 days after the oocyte retrieval. If the hCG test was negative, P supplementation was discontinued. If the hCG test was positive, the test was repeated weekly until sonographic confirmation of fetal cardiac activity was obtained. Serum P levels were obtained weekly and P supplementation was discontinued once the serum level exceeded 30 ng/mL.

Statistical Analysis

Collected data were analyzed using Student's t test and Fisher's exact test where appropriate. All tests were two tailed with a confidence level of 95% ($P<.05$).

RESULTS

All 474 patients successfully completed this trial ; 172 patients received Crinone, whereas 302 received IMP. There were no demographic differences between the two groups (Table 1). Patients in the Crinone group required more gonadotropin (3,757 IU vs. 3,397 IU, $P=.06$), and there were more patients $\geq$40 years in the Crinone group (16.9 vs. 12.3%, $P=.17$), although neither of these differences was statistically significant.

The number of oocytes retrieved, the number of embryos transferred per ET, and the number of embryos cryopreserved per patient were similar. There was no difference in the relative percentage of patients receiving ET on day 3 vs. day 5.

Although there was no difference in the total PR between the two groups (Table 2), there was a difference in the live birth rate (51.7% vs. 45.4%, $P<.05$) in favor of Crinone. No differences were noted in spontaneous miscarriage, biochemical pregnancy, or ectopic pregnancy.

To evaluate previous data suggesting diminished efficacy of vaginal P supplementation in the older patient, subgroup analyses were performed by patient age. Patients were segregated using breakpoints of 35 and 40 years of age. There were 238 patients aged <36 years in this trial and there were no demographic differences in terms of patient age, total gonadotropin dose, or number of oocytes retrieved. Similarly, there were no differences in the number of embryos transferred per ET, the number of cryopreserved embryos per patient, or the total PR (79.8% vs. 70.5%, $P>.05$). Again, however, patients in the Crinone group had a significantly higher live birth rate (65.7% vs. 51.1%, $P<.05$) (Fig. 1).

There were 236 patients aged >35 who completed this trial. Although the 73 patients in the Crinone group were not older than patients in the IMP group (38.9 vs. 38.3, $P=.06$), they did require more total gonadotropin (4,622 IU vs. 3,811 IU, $P<.005$). Otherwise, there were no differences in terms of number of retrieved oocytes, number of embryos transferred per ET, or number of cryopreserved embryos per patient. There were also no differences in live birth rates between the two groups (30.1% vs. 36.8%, $P=.38$) (Fig. 1).

Among those patients who completed the trial, 408 were aged <40. As with patients $\leq$35 years of age, there were no demographic or stimulation parameter differences in patients aged <40 years. There were also no differences in live birth rates (57.3% vs. 49.4%, $P=.15$). Finally, there were 66 patients aged $\geq$40 who completed this trial. Again, there were no demographic or stimulation differences between the two groups, nor were there any differences in live birth rates (24.1% vs. 13.5%, $P=.34$) (Fig. 1).

TABLE 1

Clinical results: all patients.

Variable	Crinone (n = 172)	IMP (n = 302)	*P* value
Patient age	34.5	35.4	NS
Patients aged ≥40 y	29 (16.9)	37 (12.3)	.17
FSH dose (IU)	3,757	3,397	.06
No. of oocytes	14.6	14.9	NS
No. of embryos/ET	2.45	2.49	NS
Day 3 ET (%)	113 (65.7%)	181 (59.9%)	NS
Day 5 ET (%)	59 (34.3%)	121 (40.1%)	NS
No. of embryos frozen	0.62	0.67	NS

Note: NS = not significant.

Silverberg. Intravaginal vs. intramuscular progesterone. Fertil Steril 2012.

TABLE 2

Cycle outcome: all patients.

Variable	Crinone (n = 172)	PIO (n = 302)	*P* value
Total pregnancy rate (%)	122 (70.9%)	194 (64.2%)	.16
Live birth rate (%)	89 (51.7%)	137 (45.4%)	<.05
Spontaneous abortion (%)	8 (4.7%)	19 (6.3%)	NS
Biochemical (%)	22 (12.8%)	36 (11.9%)	NS
Ectopic (%)	3 (1.7%)	3 (1.0%)	NS

Note: NS = not significant.

Silverberg. Intravaginal vs. intramuscular progesterone. Fertil Steril 2012.

DISCUSSION

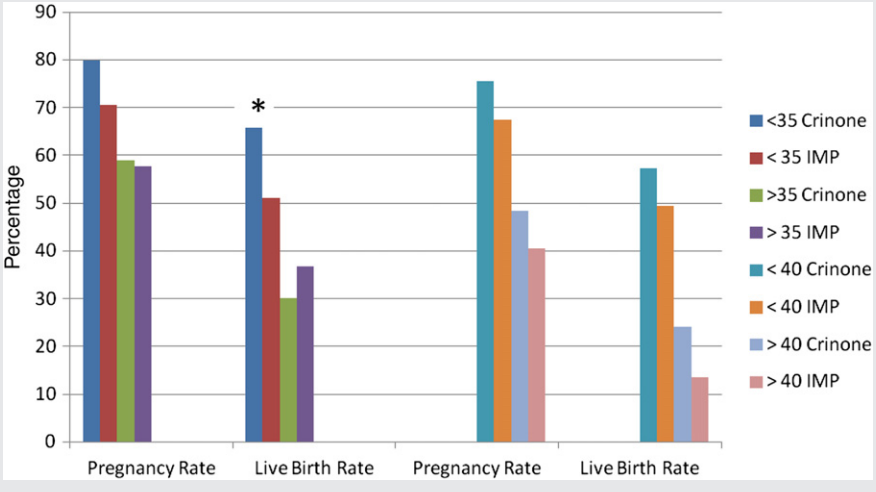
The use of luteal hormonal support is an essentially universally accepted aspect of IVF treatment (3, 5). There are many conceptual bases for luteal support, including the theories that aspiration of the luteinized granulosa cells during retrieval could deplete the resulting corpora lutea of the primary source of P production (11), that a delay in the recovery of pituitary function following GnRH agonist suppression results in inadequate support of the corpus luteum (12) and that IVF stimulation produces an iatrogenic luteal phase defect (13). Regardless, in the absence of P secretion, the endometrium fails to undergo adequate secretory change leading to either failed or faulty implantation (14). Therefore, IVF practitioners include hormonal support in their stimulation protocols.

Although both hCG and P have been used effectively, P gradually became the drug of choice because of a lower incidence of ovarian hyperstimulation syndrome (15). The most popular form of P has been IMP because of its consistent delivery and measurable serum levels (16). IMP has significant clinical drawbacks, however, including pain, patient acceptance, the logistics associated with IM injections, and complications such as abscess formation and infection (17).

As a result, other P delivery systems have been evaluated (15). Despite desire on the part of patients to replace IMP, physicians have been reluctant to change protocols, presumably because of concern that alternative formulations will not be able to deliver the same success rates. Many recent studies have suggested at least equivalent efficacy between vaginal P and IMP (8, 18, 19).

Dal Prato compared IMP (50 mg/d) to Crinone (90 mg) given either once or twice daily in a prospective, randomized trial. Although there was a trend toward higher pregnancy, delivery, and implantation rates with the vaginal gel administered twice daily, these differences were not statistically significant (19). In a large prospective, randomized trial, Yanushpolsky showed similar results between Crinone and IMP in 407 patients (7). Ongoing PRs were 45% for the patients in the Crinone group compared with 42% in the IMP group (P=.53). Kahraman recently demonstrated similar PRs in a prospective, randomized trial of 426 patients treated with either IMP (100 mg/d) or Crinone administered two times per day (8). These patients were treated with a GnRH

FIGURE 1



Pregnancy and live birth rates stratified by patient age. *P<.05.

Silverberg. Intravaginal vs. intramuscular progesterone. Fertil Steril 2012.

antagonist, and P treatment was initiated the day after oocyte retrieval. Implantation rates were 33.4% with IMP compared with 35.1% for patients who received Crinone gel (nonsignificant). Schoolcraft demonstrated similar findings in an earlier prospective nonrandomized trial in 89 patients (9). Patients started P supplementation 2 days following oocyte retrieval, and the live birth rate was 53.5% in the Crinone group compared with 50.0% in the IMP group (nonsignificant). Similarly, Berger at all demonstrated no significant difference in ongoing PRs in a large (n = 1,525), retrospective evaluation comparing two different vaginal preparations (Crinone and P capsules) with IMP (20). Pregnancy rates were 44.2% in the Crinone group, 44.9% in the P capsule group, and 39.6% in the IMP group.

A meta analysis evaluating nine studies comparing IMP to vaginal P gel or capsules and published between 1992 and 2008 also found no significant differences in outcome (18). Clinical PRs per ET were similar (OR = 0.91, 95% CI = 0.74–1.13), as were delivery rates per ET (OR = 0.94, 95% CI = 0.71–1.26). There was also no significant difference in miscarriage rates (OR = 0.54, 95% CI = 0.29–1.02).

Although IM administration results in higher serum levels than does vaginal administration, levels in uterine tissue are actually lower (21). In a randomized trial in 14 women undergoing hysterectomy, Cicinelli et al administered either Crinone 90 mg vaginally or IMP 50 mg the morning and evening prior to hysterectomy as well as the morning of surgery. Although serum levels were higher after IMP administration (29.4 vs. 4.8 ng/mL), endometrial P levels were significantly higher in patients who received Crinone (1.05 vs. 0.43 ng/mg of protein). This suggests the presence of a first uterine pass effect that could potentially minimize systemic P effects while maximizing tissue delivery. It is also important to note that, despite physician comfort from being able to monitor serum P levels, these levels neither correlate with nor predict pregnancy (22, 23).

Although it is generally well accepted that patients do not like IMP, until recently, there was a paucity of confirmatory data. Levine was the first to objectively demonstrate a profound patient preference for vaginal P supplementation in their survey of 407 women who took either Crinone or IMP (24). Eighty-four percent of the patients who responded to their survey preferred vaginal P, compared with 16% who preferred IMP. Yanushpolsky observed similar findings, reporting that a significantly greater percentage of patients in their prospective, randomized trial preferred Crinone over IMP ($P<.0001$) (7).

The present study is the first large prospective trial to demonstrate statistical superiority of vaginal P compared with IMP for luteal support in patients undergoing IVF. Strengths of our trial include the large patient population, concurrent treatment groups, and the facts that all patients came from the same medical practice and were treated by the same physicians using the same clinical protocols. Most importantly, all patients used the same IVF laboratory and followed the same lab protocols. An obvious weakness is the lack of randomization. Although this study began as a randomized trial, we eventually allowed patients to choose their own P. Although it is true that some patients who had previously delivered following an IVF cycle in which they used IMP chose to use IMP in this study, that potential bias in favor of IMP did not alter our results. We observed a random distribution of choice between the two groups. In addition, analyzing patients by age nullified a selection bias if, for example, younger patients would have chosen to use the vaginal gel. In addition, P assignment or selection was made prior to beginning ovarian hyperstimulation, as all medications were ordered in advance of stimulation start. Therefore, patients were obviously not assigned to one group or the other based either on their response to stimulation or ultimate embryo quality.

In our tertiary care center, using the same patient population, the same physicians, and the same clinical and laboratory protocols—with P type being the sole difference between the two groups —we found that Crinone produces significantly higher live birth rates than does IMP. Furthermore, when we stratified patients by age, vaginal P resulted in significantly higher live birth rates than did IMP for patients $\leq$35 years of age. Although there were trends toward higher live birth rates in patients both $<$40 and $>$40 years with vaginal P, these differences failed to achieve statistical significance. The fact that Crinone was at least as effective as IMP in the older patient is significant, as Schoolcraft previously reported that another vaginal P, Endometrin, produced PRs in women $\geq$35 years that were significantly lower than those observed in women $<$35 years (25).

Vaginal P supplementation appears to be a viable alternative to IMP for support of the luteal phase in patients undergoing IVF. Further analysis using a prospective, randomized design to evaluate different P regimens in specific patient subgroups such as poor responders is certainly warranted.

REFERENCES

1. Mahadevan M, leader A, Taylor P. Effects of low dose human chorionic gonadotropin on corpus luteum function after embryo transfer. J In Vitro Fertil Embryo Transfer 1985;2:190–4.
2. Trounson A, Howlett D, Rogers P, Hoppen HO. The effect of progesterone supplementation around the time of oocyte recovery in patients superovulated for in vitro fertilization. Fertil Steril 1986;45:532–5.
3. Solimon S, Daya S, Collins J, Hughes EG. The role of luteal phase support in infertility treatment: a meta analysis of randomized trials. Fertil Steril 1994;61:1068–76.
4. Lightman A, Kol S, Itskovitz-Eldor J. A prospective randomized study comparing intramuscular with intravaginal natural progesterone in programmed thaw cycles. Hum Reprod 1999;14:2596–9.
5. Fatemi H, Popovic-Todorovic B, Papanikolaou E, Donoso P, Devroey P. An update of luteal phase support in stimulated IVF cycles. Hum Reprod Update 2007;13:581–90.
6. Zarutskie P, Phillips JA. A meta-analysis of the role of administration of luteal phase support in assisted reproductive technology: vaginal vs. intramuscular progesterone. Fertil Steril 2009;92:163–9.
7. Yanushpolsky E, Hurwitz S, Greenberg L, Racowsky C, Hornstein M. Crinone vaginal gel is equally effective and better tolerated than intramuscular progesterone for luteal phase support in in vitro fertilization-embryo transfer cycles: a prospective, randomized study. Fertil Steril 2010;94:2596–9.
8. Kahraman S, Karagozoglu SH, Karlikaya G. The efficiency of progesterone vaginal gel versus intramuscular progesterone for luteal phase supplementation in gonadotropin-releasing hormone antagonist cycles: a prospective clinical trial. Fertil Steril 2010;94:761–3.

9. Schoolcraft WB, Hesla J, Gee MJ. Experience with progesterone gel for luteal support in a highly successful IVF programme. Hum Reprod 2000;15:1284–8.
10. Endometrin [package insert]. Parsippany, NJ: Ferring Pharmaceuticals Inc; June 2007.
11. Kerin J, Broom TJ, Ralph MM, Edmonds DK, Warne GM, Jeffrey R, et al. Human luteal phase function following oocyte aspiration from the immediately preovular Graafian follicle of spontaneous ovular cycles. Br J Obstet Gynecol 1981;88:1021–8.
12. Smitz J, Erard P, Camus M, Devroey P, Tournaye H, Wisanto A, et al. Pituitary gonadotrophin secretory capacity during the luteal phase in superovulation using GnRH-agonists and HMG in a desensitization or flare-up protocol. Hum Reprod 1992;7:1225–9.
13. Macklon NS, Fauser BC. Impact of ovarian hyperstimulation on the luteal phase. J Reprod Fertil 2000;55(Suppl):101–8.
14. Pritts EA, Atwood AK. Luteal phase support in infertility treatment: a meta analysis of the randomized trials. Hum Reprod 2002;17:2287–99.
15. Daya S, Gunby J. Luteal phase support in assisted reproduction cycles. Cochrane Database Syst Rev 2008;3:CD004083.
16. Bourgain C, Smitz J, Camus M, Erard P, Devroey P, Van Steirteghem AC, et al. Human endometrial maturation is markedly improved after luteal supplementation of gonadotrophin-releasing hormone analog/human menopausal gonadotrophin stimulated cycles. Hum Reprod 1994;9:32–40.
17. Tavaniotou A, Smitz J, Bourgain C, Devroey P. Comparison between different routes of progesterone administration as luteal phase support in infertility treatments. Hum Reprod Update 2000;6:139–48.
18. Zarutskie PW, Phillips JA. A meta-analysis of the route of administration of luteal phase support in assisted reproductive technology: vaginal vs. intramuscular progesterone. Fertil Steril 2009;92:163–9.
19. Dal Prato L, Bianchi L, Cattoli M, Tarozzi N, Flamigni C, Borini A. Vaginal gel versus intramuscular progesterone for luteal phase supplementation: a prospective randomized trial. Repro Biomed Online 2008;16:361–7.
20. Berger B, Ezcurra D, Alper MM. Crinone 8% (progesterone gel) vs. progesterone capsules vs. intramuscular progesterone for luteal phase support in older women. Fertil Steril 2009;92:S23.
21. Cicinelli E, de Ziegler D, Bulletti C, Matteo MG, Schonauer LM, Galantino P. Direct transport of progesterone from vagina to uterus. Obstet Gynecol 2000;95:403–6.
22. Chantilis S, Zeitoun KM, Patel SI, Johns DA, Madziar VA, McIntire DD. Use of Crinone vaginal progesterone gel for luteal support in in vitro fertilization cycles. Fertil Steril 1999;72:823–9.
23. Williams SC, Donahue J, Muasher S. Vaginal progesterone therapy during programmed cycles for frozen embryo transfer: an analysis of serum progesterone levels and pregnancy rates. Fertil Steril 2000;74(Suppl):S209.
24. Levine H. Luteal support with Crinone 8% in 1827 women undergoing assisted reproductive technology (ART) procedures. Fertil Steril 2000;74(Suppl 1):S152–3.
25. Schoolcraft WB, Miller C, Check J, Foulk R. Efficacy of a novel form of vaginal progesterone on continuing pregnancy rates in women undergoing IVF with elevated BMI and advanced age. Fertil Steril 2007;87:S24.