Patient experience in a randomized trial of a weekly progesterone vaginal ring versus a daily progesterone gel for luteal support after in vitro fertilization

Elizabeth S. Ginsburg, M.D.,[a] Teru Jellerette-Nolan, Ph.D.,[b] Gaurang Daftary, M.D., M.B.A.,[b] Yunling Du, Ph.D.,[c] and Kaylen M. Silverberg, M.D.[d]

[a] Department of Obstetrics, Gynecology and Reproductive Biology, Harvard Medical School, Boston, Massachusetts; [b] Ferring Pharmaceuticals, Inc., Parsippany, New Jersey; [c] Ferring International Pharmascience Center US, Parsippany, New Jersey; [d] Texas Fertility Center, Austin, Texas

Objective: To assess patient experience and convenience of using progesterone vaginal ring (VR) versus vaginal gel for women requiring luteal phase support during in vitro fertilization (IVF).
Design: Post hoc analysis of a prospective, randomized, single-blind, multicenter, phase 3 clinical trial.
Setting: Twenty-two U.S. IVF centers.
Patient(s): Women undergoing IVF (N = 1,297).
Intervention(s): Randomization to weekly VR or daily gel the day after egg retrieval for up to 10 weeks, with fresh embryo transfer IVF per site-specific procedures.
Main Outcome Measure(s): Patient satisfaction questionnaire completed at final study visit.
Result(s): In the women who were taking ≥1 dose of either VR (n = 647) or gel (n = 650), >97% reported that learning to use the formulation, remembering to take it at the correct time, and using it as prescribed was "easy" or "somewhat easy." More VR than gel users reported noninterference with daily activity (93.3% vs. 74.7%, $P<.001$), sexual comfort (80.3% vs. 67.8%, $P<.001$), and sexual desire (73.8% vs. 61.8%, $P<.001$), as well as not being bothered during sexual intercourse (66.9% vs. 39.2%, $P<.001$). More gel than VR users reported no difficulty with application (97.4% vs. 80.9%, $P<.001$). Among women who had previously used progesterone during IVF, more VR users than gel users preferred their currently assigned treatment to their previous treatment (91.4% vs. 83.0%, $P=.03$).
Conclusion(s): Weekly progesterone VR and daily progesterone gel were easy to use, with limited impact on quality of life. Overall, the VR appeared to interfere less with daily life, social activities, and sexual activity although the gel was less difficult or stressful to apply.
Clinical Trial Registration Number: NCT00615251. (Fertil Steril® 2018;110:1101–8. Copyright ©2018 The Authors. Published by Elsevier Inc. on behalf of the American Society for Reproductive Medicine. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).)
El resumen está disponible en Español al final del artículo.

Key Words: In vitro fertilization, luteal phase support, progesterone, vaginal gel, vaginal ring

Received March 29, 2018; revised June 30, 2018; accepted July 12, 2018.
E.S.G. has received support for past research from EMD Serono, and royalties from BioMed Central, Sanders & Parks, Springer, and UpToDate. T.J.-N. is an employee of Ferring Pharmaceuticals, Inc. G.D. is an employee of Ferring Pharmaceuticals, Inc. Y.D. is an employee of Ferring Pharmaceuticals, Inc. K.M.S. is an advisor/consultant for EMD Serono, Good Start Genetics, Illumina, and Myriad, has received speaker fees for AbbVie, and has received research support from Finox, Ovation Fertility, and Teva.
Supported by Teva Global Branded Products R&D, Inc., with analysis funded by Ferring Pharmaceuticals, Inc. Products and manufacturers in article: Milprosa (progesterone vaginal ring), Ferring Pharmaceuticals, Inc., Parsippany, New Jersey; Crinone (progesterone gel), Actavis Pharma, Parsippany, New Jersey.
Reprint requests: Elizabeth S. Ginsburg, M.D., Professor, Department of Obstetrics, Gynecology and Reproductive Biology, Harvard Medical School, Medical Director, Assisted Reproductive Technologies, Brigham and Women's Hospital, 75 Francis St, Boston, Massachusetts 02115 (E-mail: eginsburg@partners.org).

Fertility and Sterility® Vol. 110, No. 6, November 2018 0015-0282

https://doi.org/10.1016/j.fertnstert.2018.07.014

Multifollicular development induced by the administration of gonadotropins during ovarian stimulation has been shown to disrupt normal luteal phase physiology and progesterone production, resulting in an altered endocrine environment and disrupted functioning of the corpus luteum (1–5). Exogenous supplementation with either progesterone or human chorionic gonadotropin (hCG) during the luteal phase results in higher pregnancy rates and improved outcomes compared with no supplementation (6, 7). Of the two, progesterone is currently the preferred method for luteal phase support due to the increased risk of ovarian hyperstimulation syndrome associated with hCG (6, 8). Accordingly, luteal phase progesterone supplementation is an integral component of current in vitro fertilization (IVF) treatment protocols (3, 6).

In contrast with most parts of the world, in the United States the most common form of progesterone used for luteal phase support has been intramuscular (IM) injections of progesterone in oil (3). Although IM progesterone increases pregnancy rates in IVF cycles compared with no therapy, IM injections are painful, inconvenient, and can result in significant and sometimes severe side effects, including infections, abscesses, and even pulmonary complications requiring hospital admission (3, 9). To improve the convenience and tolerability of luteal phase support, vaginal routes of progesterone administration have been developed and shown to result in consistent transformation of endometrial morphologic characteristics and substantially higher endometrial tissue levels of progesterone compared with IM administration (10–14).

Multiple clinical trials and meta-analyses have demonstrated that the vaginal progesterone products approved by the U.S. Food and Drug Administration (FDA) have efficacy comparable to the off-label administration of IM progesterone, as determined by rates of clinical pregnancy, delivery, and miscarriage (13–17). The current vaginal progesterone products include vaginal gels, creams, suppositories, and inserts (3, 6). The formulations approved by the FDA for luteal phase supplementation as part of an assisted reproductive technology (ART) treatment include a vaginal gel (Crinone; Actavis Pharma, Parsippany, NJ) and a vaginal tablet insert (Endometrin; Ferring Pharmaceuticals, Parsippany, NJ) (18, 19). These formulations are more convenient and are associated with fewer adverse events than IM progesterone, but they typically require one or more daily doses, can be messy, and may be associated with vaginal discharge (18–21). Such inconveniences and side effects can potentially add additional stress to the IVF cycle.

The vaginal ring (VR), which is currently under investigation, was designed to provide continuous release of progesterone, enabling less frequent (once weekly) dosing, and potentially improved comfort and convenience (22). In a small pilot study performed in donor-egg recipients, the VR adequately transformed the endometrium in a mock cycle and was associated with similar pregnancy rates compared with those achieved with vaginal gel after embryo transfer (23). A large, randomized, single-blind, controlled, phase 3 study demonstrated comparable clinical pregnancy rates, live-birth rates, and adverse event profiles in women using the VR compared with gel (22). Specifically, the clinical pregnancy rates were 48.0% (310 of 646) with the VR and 47.2% (307 of 651) with gel at week 8 (intergroup difference: 0.8%; 95% CI, −4.6%, 6.3%). At week 12, the clinical pregnancy rates were 46.4% (300 of 646) with the VR and 45.2% (294 of 651) with gel (intergroup difference, 1.3%; 95% CI, −4.1%, 6.7%) (22). The live-birth rates were 45.2% (292 of 646) with the VR and 43.3% (282 of 651) with gel. None of these differences were statistically significant.

In this post-hoc analysis of the phase 3 trial of the VR, we evaluated the experience of VR or gel patients with a patient satisfaction survey that study participants completed at the final study visit.

MATERIALS AND METHODS

The results of this study are based on responses to a questionnaire obtained during a randomized, single-blind, multicenter study of progesterone supplementation in women undergoing IVF with fresh egg transfer, conducted at 22 clinical sites in the United States between February 2008 and January 2009 (ClinicalTrials.gov identifier: NCT00615251) (22). The study complied with the ethical principles of good clinical practice as required by the FDA, and it was conducted in accordance with the Declaration of Helsinki. Institutional review board approval was obtained for all study sites, and the patients provided informed consent to participate using a consent form approved by the institutional review board before undergoing any study-specific procedures (22).

Survey Participants

Healthy premenopausal women aged 18–42 years with tubal factor, idiopathic, male factor, ovulatory dysfunction, or endometriosis-associated infertility and a normal uterine cavity were considered eligible. The ART cycles included in this study could be associated with the use of fresh or frozen sperm (22). The exclusion criteria included, but were not limited to, known sensitivity to progesterone, undiagnosed vaginal bleeding, a history of more than one failed IVF cycle, more than two consecutive miscarriages, or male partners with nonobstructive azoospermia (22). Women with clinically significant gynecologic pathology (e.g., submucosal fibroids, intramural fibroids >5 cm, communicating hydrosalpinx, etc.) or with an elevated cycle day-2 or day-3 follicle-stimulating hormone (FSH) level of >15 mIU/mL were also excluded, as were women with a body mass index (BMI) >38 kg/m^2 or with an endometrial thickness <6 mm on the day of hCG trigger (22).

Study Design

The design of the phase 3, randomized, single-blind, multicenter study was previously described elsewhere (22). In brief, the eligible patients underwent ovarian suppression starting in the cycle just before ovarian stimulation, using standard down-regulation protocols selected at the investigator's discretion. Administration of 10,000 IU hCG by IM injection was initiated when a transvaginal ultrasound scan indicated the presence of at least two follicles ≥17 mm in conjunction

with a serum E_2 level of <5,000 pg/mL (22). Egg retrieval occurred 35–37 hours after hCG administration.

The patients were then stratified by age and sequentially randomized on the day after egg retrieval to either once weekly treatment with a flexible silicone VR containing micronized progesterone (11 mg/day) or daily treatment with progesterone 8% gel (90 mg/day) in a 1:1 fashion. The first dose of progesterone was administered the day after egg retrieval. Patients were instructed to replace the VR every 7 days. The VR could be removed for up to 1 hour per day if desired, including for sexual intercourse. Patients returned 3 or 5 days after egg retrieval for embryo transfer, depending on the study site's protocol and guidelines for number of embryos to transfer (22). All patients who underwent embryo transfer continued progesterone treatment for a minimum of 2 weeks. Women with an intrauterine gestational sac after 21 days continued taking the study medication for 10 weeks after egg retrieval.

At the week-10 study visit, all participants completed a patient satisfaction questionnaire, regardless of their pregnancy status. The survey contained questions that covered topics such as ease of administration and portability, intercourse, daily activities, travel, and social and professional life (Appendix 1). Women were also asked to compare their experiences with their assigned study progesterone formulation to any progesterone methods they had used in prior cycles. The results were analyzed based on the total number of responses to each question and not on the total number of women who had reported previous progesterone use. All study participants who were pregnant through week 12 were subsequently contacted by telephone approximately 2 weeks after their expected delivery date to obtain safety and pregnancy outcome information (22).

Statistical Analysis

The efficacy analysis population included the modified intent-to-treat cohort, consisting of all randomized patients who had undergone successful egg retrieval and received at least one dose of progesterone (22). The percentages of patients who responded to each question in each group were calculated and analyzed using two-sided Fisher's exact tests or chi-square tests. Statistical analyses performed were exploratory in nature and excluded missing data.

RESULTS

A total of 1,752 patients were screened, of whom 369 were considered screen failures because they did not meet criteria for initiation of ovarian stimulation (22). Of the 1,299 women who underwent egg retrievals, 1,297 were randomized and took at least one dose of progesterone. As reported previously, demographic and baseline characteristics for each treatment group were similar between the VR and gel treatment groups (22). Overall, 79.1% of patients were Caucasian, 7.9% were African American, 6.6% were Hispanic, 5.5% were Asian, and 1% did not specify. The mean age across all patients was 31.7 years.

Convenience and Sexual Intercourse

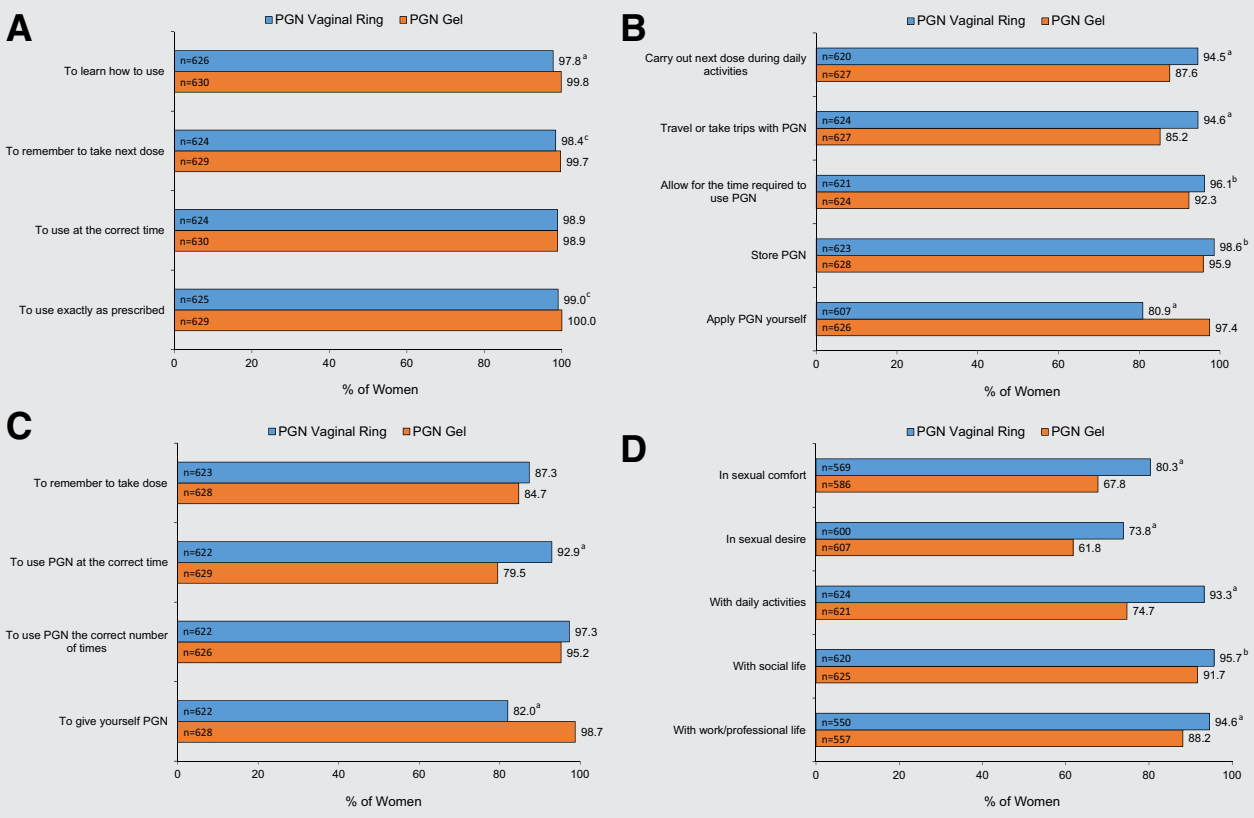
Nearly all women reported that their assigned progesterone supplementation method was either "easy" or "somewhat easy" (Fig. 1A) to learn to use, to remember to take the next dose, to use at the correct time, and to use exactly as prescribed. More patients assigned to the VR than to gel responded that it was "not at all a problem" to use progesterone during daily activities, to travel while continuing to use progesterone, to allow for the time required to administer progesterone, or to store their progesterone (see Fig. 1B). In addition, more VR users than gel users were completely confident they had received the full dose (61.6% vs. 50.2%; $P<.001$). However, statistically significantly more patients assigned to gel said that it was "not at all a problem" to apply the progesterone themselves (97.4% vs. 80.9%; $P<.001$; see Fig. 1B) and were completely confident they had used the progesterone medication properly (85.0% vs. 79.6%; $P=.015$).

Figure 1C illustrates the patients' responses regarding the stress of using progesterone. Most users of either formulation indicated that progesterone use was not stressful, but statistically significantly more patients using the VR than the gel reported that remembering to use progesterone and taking progesterone at the correct time was "not stressful." However, statistically significantly more patients using the gel reported that it was "not stressful" to give themselves progesterone. Most women using the VR or gel reported that progesterone "caused no interference" with regard to sexual comfort, sexual desire, daily activities, social life, or work/professional life; however, statistically significantly more patients using the gel than the VR reported that progesterone caused interference in each of these measures (see Fig. 1D). Among the participants who reported on sexual intercourse during treatment, a statistically significantly greater percentage of VR than gel users indicated that they and their partners were "not at all bothered" by progesterone supplementation during sexual intercourse (Fig. 2).

Comparison with Previous Progesterone Use

Approximately 20% of participants (n = 262) had used progesterone supplementation for luteal support in a prior ART cycle (Table 1). More than half of these participants (n = 150) had previously used IM progesterone. Approximately11% of the participants currently assigned to the gel reported using the gel in a prior cycle, and 18% of the women had previously used more than one progesterone formulation. When the women were asked how their currently assigned progesterone medication compared with the progesterone medications they had previously used for luteal phase support, more women assigned to the VR than the gel said that their current formulation was "easier" or "much easier" to use, "less" or "much less" messy to use, "more" or "much more" convenient to use, "less" or "much less" stressful to use, and led to "less" or "much less" vaginal leakage than their previously used formulation (Fig. 3). These study participants also indicated that it took "less" or "much less" time to administer the VR. Additionally, more VR than gel users preferred their assigned treatment method over their previous one

FIGURE 1



Percentage of women who responded that various aspects of using their assigned progesterone (PGN) medication were (**A**) "easy or somewhat easy," (**B**) "not at all a problem," (**C**) "not stressful," or (**D**) "caused no interference." [a]$P<.001$ versus gel; [b]$P<.01$ versus gel; [c]$P<.05$ versus gel.

Ginsburg. Ease of use of P ring vs. gel in IVF. Fertil Steril 2018.

(91.4% vs. 83.0%; $P=.03$) and claimed that they would recommend the currently assigned treatment method in a future cycle (91.4% vs. 83.7%; $P=.052$).

DISCUSSION

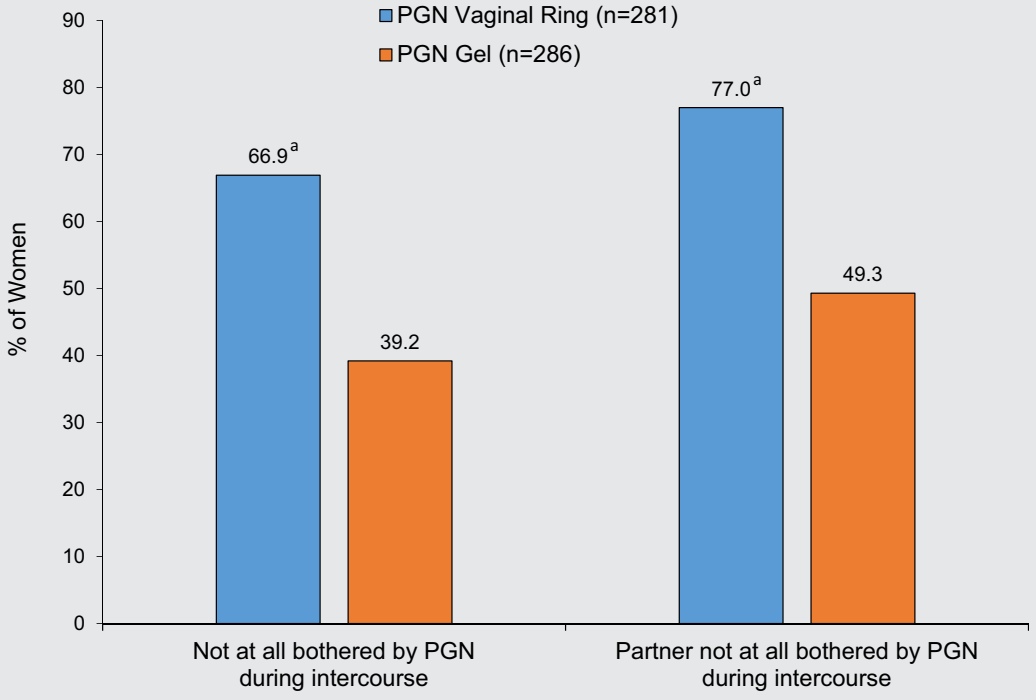
Evidence from a number of clinical trials has demonstrated equivalent efficacy and safety of vaginal progesterone compared with IM progesterone for luteal support in IVF (15–17). Although vaginal preparations are more convenient and better tolerated than IM progesterone (24, 25), some limitations still remain with the current vaginal formulations, including the need for frequent dosing, messiness, and vaginal leakage. It should be noted that vaginal discharge was potentially attributed to gel leakage and thus may have been underreported by vaginal gel users, in contrast with the VR users.

The VR was developed to provide predictable, targeted progesterone delivery with once weekly administration (22). In our progesterone supplementation clinical trial, both the weekly VR and the daily gel were associated with similar clinical pregnancy rates at 8 and 12 weeks' gestation as well as comparable live-birth rates (22). The clinical pregnancy rates with the VR were consistent with the expected results from ART programs at the time of the trial (22, 26).

Results from the end-of-study survey indicate that the patients viewed both the VR and gel to be easy to use, convenient, and causing little interference with daily activities. Compared with the patients assigned to gel, those assigned to the VR reported less interference with daily activities, less stress associated with administration at the correct time, less worry about not receiving the full dose, and less difficulty when traveling while using the VR. The gel users reported statistically significantly less difficulty applying progesterone, but more than 80% of VR users reported no problems with its administration. Importantly, among the approximately 50% of study participants who had sexual intercourse during the trial, the VR users were less bothered by their progesterone medication during intercourse and were less likely to report that their partners were bothered by the medication during intercourse. The VR users were also less likely to report that the progesterone interfered with sexual comfort and sexual desire.

Relatively few studies on luteal phase support with progesterone have evaluated treatment convenience, satisfaction, and acceptance. Of the studies that have evaluated these end points, most have compared outcomes in patients receiving IM to those receiving vaginal progesterone (24, 25, 27). The preponderance of evidence from these trials demonstrates that vaginal progesterone is associated

FIGURE 2



Percentage of women who had intercourse during treatment and reported that they or their partner were not at all bothered by progesterone (PGN) medication during intercourse. [a]$P<.001$ versus gel.

Ginsburg. Ease of use of P ring vs. gel in IVF. Fertil Steril 2018.

with higher patient satisfaction, greater convenience, and less time required to administer the medication (24). Smaller studies have also reported that progesterone vaginal gel is superior to vaginal micronized progesterone tablets, capsules, or suppositories in their impact on tolerability and ease of use (20, 28–30).

Most patients in this study who had previously used a progesterone formulation for luteal support had used IM progesterone. Among the patients who had previously used any progesterone formulation, the majority of women in both groups felt that their assigned formulation was easier to use, required less time, was more convenient, and was less stressful than their previous agent. However, more patients assigned to the VR group compared with the gel group indicated that the medication was easier to use, took less time to use, and was less messy, more convenient, less stressful, and was associated with less leakage compared with their previous formulation. More patients in the VR group preferred the VR over their previous medication than did patients in the gel group.

This analysis has several limitations. The results were derived from a post hoc analysis of data collected using a survey whose reliability has not been evaluated in other trials. In addition, certain data, such as patients' comparisons of their current progesterone to previous progesterone, are retrospective in nature and are subject to recall bias. The statistical analyses were post hoc and exploratory in nature. Additional investigations are needed to confirm the preliminary findings of this analysis.

Due to the complexity of IVF protocols, strategies for minimizing inconvenience and maximizing ease of progesterone use for luteal phase support should be adopted to promote patient well-being and possibly to maximize the chances of a successful outcome. Improving the ease of use of progesterone therapies may be particularly important during the luteal phase (the time between embryo transfer and the detection of pregnancy), one of the most stressful and longest periods during an IVF treatment cycle (31, 32). One such strategy might be using a weekly VR for luteal phase support after IVF. Additional research on patient

TABLE 1

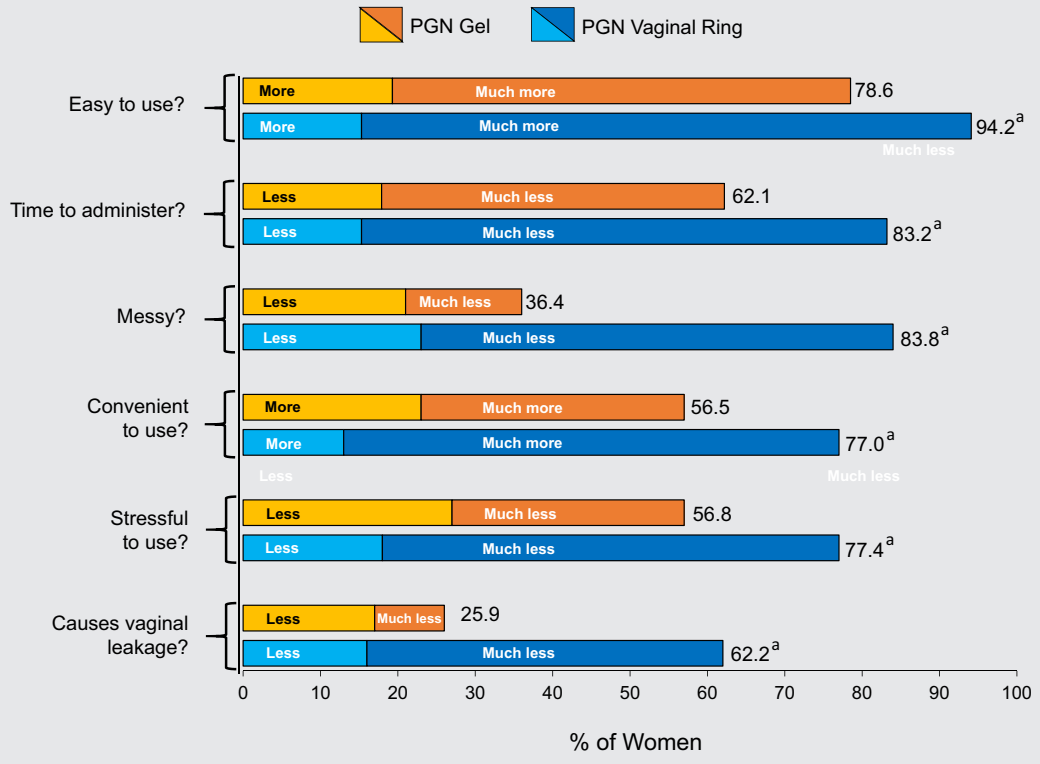
Previous progesterone experience.

Type of PGN	Vaginal ring (n = 132)	Vaginal gel (n = 130)
Vaginal gel	19 (14.4)	15 (11.5)
Vaginal capsule	24 (18.2)	24 (18.5)
Vaginal insert	28 (21.2)	24 (18.5)
IM progesterone	74 (56.1)	76 (58.5)
Other	12 (9.1)	7 (5.4)
Unknown	2 (1.5)	5 (3.8)

Note: All values are number and percentage. Participants may have previously used more than one progesterone (PGN) formulation. A total of seven participants with previous PGN experience (vaginal ring, n = 5; gel, n = 2) did not indicate what medications they had used previously. IM = intramuscular.

Ginsburg. Ease of use of P ring vs. gel in IVF. Fertil Steril 2018.

FIGURE 3



Responses from the subset of women who had previously used a different progesterone (PGN) medication indicating how their current method compared with their previous method. [a]$P<.001$ versus gel.

Ginsburg. Ease of use of P ring vs. gel in IVF. Fertil Steril 2018.

acceptance, convenience, and satisfaction with luteal progesterone support and other IVF therapies is needed.

Acknowledgments: The authors thank Jason Heale, Ph.D., and Daniel Lightfoot, Ph.D., for contributions to earlier versions of this manuscript and Nicole Cooper of MedVal Scientific Information Services, LLC, for medical writing and editorial assistance, which was funded by Ferring Pharmaceuticals, Inc. This manuscript was prepared according to the International Society for Medical Publication Professionals' "Good Publication Practice for Communicating Company-Sponsored Medical Research: The GPP3 Guidelines."

REFERENCES

1. Fatemi HM, 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.
2. Erdem A, Erdem M, Atmaca S, Guler I. Impact of luteal phase support on pregnancy rates in intrauterine insemination cycles: a prospective randomized study. Fertil Steril 2009;91:2508–13.
3. Yanushpolsky EH. Luteal phase support in in vitro fertilization. Semin Reprod Med 2015;33:118–27.
4. Tavaniotou A, Devroey P. Luteal hormonal profile of oocyte donors stimulated with a GnRH antagonist compared with natural cycles. Reprod Biomed Online 2006;13:326–30.
5. Beckers NG, Macklon NS, Eijkemans MJ, Ludwig M, Felberbaum RE, Diedrich K, et al. Nonsupplemented luteal phase characteristics after the administration of recombinant human chorionic gonadotropin, recombinant luteinizing hormone, or gonadotropin-releasing hormone (GnRH) agonist to induce final oocyte maturation in in vitro fertilization patients after ovarian stimulation with recombinant follicle-stimulating hormone and GnRH antagonist cotreatment. J Clin Endocrinol Metab 2003;88:4186–92.
6. Van der Linden M, Buckingham K, Farquhar C, Kremer JA, Metwally M. Luteal phase support for assisted reproduction cycles. Cochrane Database Syst Rev 2015;7:CD009154.
7. Soliman 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.
8. Ludwig M, Diedrich K. Evaluation of an optimal luteal phase support protocol in IVF. Acta Obstet Gynecol Scand 2001;80:452–66.
9. Bouckaert Y, Robert F, Englert Y, De Backer D, De Vuyst P, Delbaere A. Acute eosinophilic pneumonia associated with intramuscular administration of progesterone as luteal phase support after IVF: case report. Hum Reprod 2004;19:1806–10.
10. Penzias AS. Luteal phase support. Fertil Steril 2002;77:318–23.
11. Bourgain C, Devroey P, Van WL, Smitz J, Van Steirteghem AC. Effects of natural progesterone on the morphology of the endometrium in patients with primary ovarian failure. Hum Reprod 1990;5:537–43.
12. Bulletti C, de Ziegler D, Flamigni C, Giacomucci E, Polli V, Bolelli G, et al. Targeted drug delivery in gynaecology: the first uterine pass effect. Hum Reprod 1997;12:1073–9.
13. Miles RA, Paulson RJ, Lobo RA, Press MF, Dahmoush L, Sauer MV. Pharmacokinetics and endometrial tissue levels of progesterone after administration by intramuscular and vaginal routes: a comparative study. Fertil Steril 1994;62:485–90.

14. 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.
15. Zarutskie PW, Phillips JA. A meta-analysis of the route of administration of luteal phase support in assisted reproductive technology: vaginal versus intramuscular progesterone. Fertil Steril 2009;92:163–9.
16. Silverberg KM, Vaughn TC, Hansard LJ, Burger NZ, Minter T. Vaginal (Crinone 8%) gel vs. intramuscular progesterone in oil for luteal phase support in in vitro fertilization: a large prospective trial. Fertil Steril 2012;97:344–8.
17. Yanushpolsky E, Hurwitz S, Greenberg L, Racowsky C, Hornstein MD. Comparison of Crinone 8% intravaginal gel and intramuscular progesterone supplementation for in vitro fertilization/embryo transfer in women under age 40: interim analysis of a prospective randomized trial. Fertil Steril 2008;89:485–7.
18. Crinone 4% and Crinone 8% (progesterone gel) [prescribing information]. Morristown, NJ: Watson Pharmaceuticals, August, 2014.
19. Endometrin (progesterone) vaginal insert, 100 mg [prescribing information]. Parsippany, NJ: Ferring Pharmaceuticals, September, 2016.
20. Ludwig M1, Schwartz P, Babahan B, Katalinic A, Weiss JM, Felberbaum R, et al. Luteal phase support using either Crinone 8% or Utrogest: results of a prospective, randomized study. Eur J Obstet Gynecol Reprod Biol 2002;103:48–52.
21. Tomic V, Tomic J, Klaic DZ, Kasum M, Kuna K. Oral dydrogesterone versus vaginal progesterone gel in the luteal phase support: randomized controlled trial. Eur J Obstet Gynecol Reprod Biol 2015;186:49–53.
22. Stadtmauer L, Silverberg KM, Ginsburg ES, Weiss H, Howard B. Progesterone vaginal ring versus vaginal gel for luteal support with in vitro fertilization: a randomized comparative study. Fertil Steril 2013;99:1543–9.
23. Stadtmauer L, Harrison DD, Boyd J, Bocca S, Oehninger S. Pilot study evaluating a progesterone vaginal ring for luteal-phase replacement in donor oocyte recipients. Fertil Steril 2009;92:1600–5.
24. Beltsos AN, Sanchez MD, Doody KJ, Bush MR, Domar AD, Collins MG. Patients' administration preferences: progesterone vaginal insert (Endometrin) compared to intramuscular progesterone for luteal phase support. Reprod Health 2014;11:78.
25. Schoolcraft WB, Hesla JS, Gee MJ. Experience with progesterone gel for luteal support in a highly successful IVF programme. Hum Reprod 2000;15:1284–8.
26. Society for Assisted Reproductive Technology. Clinic Summary Report. Available at: https://sartcorsonline.com. Accessed June 28, 2017.
27. 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.
28. Ng EH, Miao B, Cheung W, Ho PC. A randomised comparison of side effects and patient inconvenience of two vaginal progesterone formulations used for luteal support in in vitro fertilisation cycles. Eur J Obstet Gynecol Reprod Biol 2003;111:50–4.
29. Simunic V, Tomic V, Tomic J, Nizic D. Comparative study of the efficacy and tolerability of two vaginal progesterone formulations, Crinone 8% gel and Utrogestan capsules, used for luteal support. Fertil Steril 2007;87:83–7.
30. Bergh C, Lindenberg S. A prospective randomized multicentre study comparing vaginal progesterone gel and vaginal micronized progesterone tablets for luteal support after in vitro fertilization/intracytoplasmic sperm injection. Hum Reprod 2012;27:3467–73.
31. Skiadas CC, Terry K, De PM, Geoghegan A, Lubetsky L, Levy S, et al. Does emotional support during the luteal phase decrease the stress of in vitro fertilization? Fertil Steril 2011;96:1467–72.
32. Yong P, Martin C, Thong J. A comparison of psychological functioning in women at different stages of in vitro fertilization treatment using the mean affect adjective check list. J Assist Reprod Genet 2000;17:553–6.

Experiencia de las pacientes con anillo de progesterona vaginal semanal vs gel diario de progesterona en el soporte de fase lútea después de una Fecundación in Vitro

Objetivo: Evaluar la experiencia y comodidad de utilizar un anillo vaginal (VR) de progesterona vs progesterona en gel en mujeres que requerían soporte de fase lútea durante una fecundación in vitro (IVF).

Diseño: Análisis post hoc de un ensayo clínico prospectivo, aleatorizado, simple-ciego, multicéntrico, fase 3.

Sitio: Veintidós centros de IVF de U.S.

Paciente(s): Mujeres que realizaron IVF (N: 1297).

Intervención(es): Aleatorización a VR semanal o gel diario el día posterior a la captación de ovocitos y duración hasta 10 semanas, con transferencia de embriones en fresco en IVF según procedimientos específicos de cada centro.

Medida del Resultado(s) Principal(es): Cuestionario de satisfacción de la paciente completado en la visita final del estudio.

Resultado(s): De las mujeres que tomaron $\geq$ 1 dosis, bien de VR (N=647) o de gel (N=650), >97%, consideraron que aprender el uso de la formulación, recordando tomarla en el momento adecuado y utilizándola tal como estaba prescrita era "fácil" o "relativamente fácil". Más usuarias de VR que usuarias de gel informaron de no interferencia con la actividad (93.3% vs 74.7%, P<.001), comodidad sexual (80.3% vs 67.8%, P<.001), y deseo sexual (73,8% vs 61,8%, P<.001), así como no interferencia durante las relaciones sexuales (66.9% vs 39.2%, P<.001). Más usuarias de gel que de VR informaron de ausencia de dificultad con la aplicación (97.4% vs 80.9%, P<.001). Entre las mujeres que habían usado previamente progesterona durante un ciclo de IVF, más usuarias de VR que de gel prefirieron el tratamiento actualmente asignado al tratamiento utilizado previamente (91.4% vs 83.0%, P=0.03).

Conclusión(es): El VR semanal de progesterona y el gel vaginal diario de progesterona fueron fáciles de utilizar, con impacto limitado sobre la calidad de vida. Globalmente, el VR de progesterona pareció interferir menos en la vida diaria, en las actividades sociales y en la actividad sexual, aunque el gel era más fácil de usar o menos estresante en su aplicación.
Palabras clave: Fecundación In Vitro, Soporte de fase lútea, progesterona, gel vaginal, anillo vaginal.

APPENDIX 1: TRIAL SATISFACTION SURVEY

1A. How easy or difficult was it for you to learn how to use your progesterone medication?
- Easy
- Somewhat easy
- Neither
- Somewhat difficult
- Difficult

1B. How easy or difficult was it for you to remember to take your next dose of progesterone medication?
- Easy
- Somewhat easy
- Neither
- Somewhat difficult
- Difficult

1C. How easy or difficult was it for you to use your progesterone medication at the correct time?
- Easy
- Somewhat easy
- Neither
- Somewhat difficult
- Difficult

1D. How easy or difficult was it for you to use your progesterone medication exactly as prescribed?
- Easy
- Somewhat easy
- Neither
- Somewhat difficult
- Difficult

2A. How much of a problem was it for you to carry out your next dose of progesterone medication with you during your daily activities?
- Not at all
- A little
- Somewhat
- Quite a bit
- A lot
- I didn't apply progesterone

2B. How much of a problem was it for you to travel or take trips with your progesterone medication?
- Not at all
- A little
- Somewhat
- Quite a bit
- A lot
- I didn't apply progesterone

2C. How much of a problem was it for you to take/allow for the amount of time that is required to use your progesterone medication?
- Not at all
- A little
- Somewhat
- Quite a bit
- A lot
- I didn't apply progesterone

2D. How much of a problem was it for you to store your progesterone?
- Not at all
- A little
- Somewhat
- Quite a bit
- A lot
- I didn't apply progesterone

2E. How much of a problem was it for you to apply or administer the progesterone medication yourself?
- Not at all
- A little
- Somewhat
- Quite a bit
- A lot
- I didn't apply progesterone

3A. How stressful was it for you to remember to take your next dose of progesterone medication?
- Not at all
- A little
- Somewhat
- Quite a bit
- A lot
- I didn't apply progesterone

3B. How stressful was it for you to remember to use your progesterone medication at the correct time?
- Not at all
- A little
- Somewhat
- Quite a bit
- A lot
- I didn't apply progesterone

3C. How stressful was it for you to use your progesterone medication the correct number of times?
- Not at all
- A little
- Somewhat
- Quite a bit
- A lot
- I didn't apply progesterone

3D. How stressful was it for you to give yourself the progesterone medication?
- Not at all
- A little
- Somewhat
- Quite a bit
- A lot
- I didn't apply progesterone

4. How often did you forget to take your progesterone medication exactly as prescribed?
- Never
- Rarely
- Sometimes
- Always

5A. How much did you worry that you were not receiving the full dose of your progesterone medication?
- Not at all
- A little
- Somewhat
- Quite a bit
- A lot

5B. How much did you worry that you were not using your progesterone medication properly?
- Not at all
- A little
- Somewhat
- Quite a bit
- A lot

6. How bothered were you by your progesterone medication during intercourse?
- Not at all
- A little
- Somewhat
- Quite a bit
- A lot
- I didn't have intercourse

7. How bothered do you think your partner was by your progesterone medication during intercourse?
- Not at all
- A little
- Somewhat
- Quite a bit
- A lot
- I didn't have intercourse

8A. How much did your progesterone medication interfere with your sexual comfort?
- Not at all
- A little
- Somewhat
- Quite a bit
- A lot
- Not applicable

8B. How much did your progesterone medication interfere with your sexual desire?
- Not at all
- A little
- Somewhat
- Quite a bit
- A lot
- Not applicable

8C. How much did your progesterone medication interfere with your daily activities?
- Not at all
- A little
- Somewhat
- Quite a bit
- A lot
- Not applicable

8D. How much did your progesterone medication interfere with your social life?
- Not at all
- A little
- Somewhat
- Quite a bit
- A lot
- Not applicable

8E. How much did your progesterone medication interfere with your work/professional life?
- Not at all
- A little
- Somewhat
- Quite a bit
- A lot
- Not applicable

9. Have you had previous in vitro fertilization/intracytoplasmic sperm injection cycles when you used a different progesterone medication (brand or route of administration) to prepare and support your uterus for pregnancy?
- No
- Yes

10. If yes, what was the progesterone medication you previously used?
    - Crinone or Prochieve (vaginal gel)
    - Prometrium (oral capsule [sometimes used vaginally])
    - Endometrin (vaginal insert/tablet)
    - Progesterone injection
    - Other
    - Unknown brand

11A. Comparing your current progesterone medication to your previous progesterone medication, is your current easier or more difficult to use than your previous progesterone medication?
    - Much easier
    - Easier
    - About the same
    - More difficult
    - Much more difficult

11B. Is your current progesterone medication taking more or less time to use (apply or administer) than your previous medication?
    - Much more
    - More
    - About the same
    - Less
    - Much less

11C. Is your current progesterone medication more or less messy?
    - Much more
    - More
    - About the same
    - Less
    - Much less

11D. Is your current progesterone medication more or less convenient?
    - Much more
    - More
    - About the same
    - Less
    - Much less

11E. Is your current progesterone medication more or less stressful?
    - Much more
    - More
    - About the same
    - Less
    - Much less

11F. Is your current progesterone medication causing more or less vaginal leakage or product?
    - Much more
    - More
    - About the same
    - Less
    - Much less

12. Would you prefer to use your current or your previous progesterone medication in a future cycle?
    - Current
    - Previous

13. Would you recommend to use your current or your previous progesterone medication in a future cycle?
    - Current
    - Previous