ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Progesterone vaginal ring versus vaginal gel for luteal support with in vitro fertilization: a randomized comparative study

Laurel Stadtmauer, M.D., Ph.D.,[a] Kaylen M. Silverberg, M.D.,[b] Elizabeth S. Ginsburg, M.D.,[c] Herman Weiss, M.D.,[d] and Brandon Howard, Ph.D.[e]

[a] Jones Institute for Reproductive Medicine, Norfolk, Virginia; [b] Texas Fertility Center, Austin, Texas; [c] Brigham and Women's Hospital, Center for Reproductive Medicine, Boston, Massachusetts; and [d] Teva Women's Health, Petah Tikva, Israel; [e] Teva Women's Health, Frazer, Pennsylvania

Objective: To compare the efficacy and safety of luteal phase support in IVF with a progesterone (P) vaginal ring or gel (VR or VG).

Design: Prospective, randomized, single-blind, multicenter, phase III clinical trial (ClinicalTrials.gov identifier: NCT00615251).

Setting: Nineteen private and three academic high-volume U.S. IVF centers.

Patient(s): One thousand two hundred ninety-seven infertile patients were randomized to a weekly P VR (n = 646) or a daily P 8% VG (n = 651).

Intervention(s): IVF was performed per site-specific protocols. The day after egg retrieval, patients were randomized and began VR or VG therapy, which continued for up to 10 weeks' gestation.

Main Outcome Measure(s): Clinical pregnancy rates at 8 and 12 weeks of pregnancy; rates of biochemical pregnancy, live birth, spontaneous abortion, ectopic pregnancy, and cycle cancellation; and safety and tolerability were secondary measures.

Result(s): Clinical pregnancy rates at 8 and 12 weeks were high and comparable between groups: 48.0% for VR and 47.2% for VG at week 8 and 46.4% (VR) and 45.2% (VG) at week 12. Live-birth rates were 45% (VR) and 43% (VG). Adverse event profiles were similar between groups.

Conclusion(s): The weekly P VR provided similar pregnancy rates to the daily VG, with no major differences in safety. (Fertil Steril® 2013;■:■–■. ©2013 by American Society for Reproductive Medicine.)

Key Words: Progesterone, luteal phase support, in vitro fertilization, progesterone supplementation, assisted reproductive technology, vaginal ring, pregnancy

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Normal luteal function is essential for maintaining early pregnancy, and data suggest that progesterone (P) is necessary for this maintenance [1]. Normal luteal function may be compromised as a result of pharmacological manipulation associated with assisted reproductive technology (ART) procedures [2, 3]. Various hormonal compounds have been used to correct this dysfunction and provide luteal support and supplementation during ART cycles and early pregnancy.

While both P, available in oral, IM, and vaginal preparations, and hCG are efficacious, P is considered to be the agent of choice as hCG is associated with a higher risk of ovarian hyperstimulation syndrome (OHSS) [3–6]. Oral P formulations require high dosing, undergo a hepatic first pass, and appear to be clinically inferior for

luteal support (1, 7–10). IM P (50–100 mg/day) requires daily injections, which may be painful, uncomfortable, and inconvenient for patients. High serum P levels are attained via IM administration; however, vaginal administration allows for targeted drug delivery to the uterus, resulting in higher endometrial P levels and the most consistent endometrial morphology (1, 9–13). Vaginal administration also provides low, continuous, and stable hormone levels and may allow for nondaily dosing. Because vaginal P administration is associated with lower serum levels, it is also possible that this route of administration may reduce the risk of systemic side effects and ultimately improve patient adherence (14). Current US Food and Drug Administration (FDA)-approved vaginal P dosage forms include a gel (Crinone, Watson Pharmaceuticals, Inc.) and a vaginal tablet insert (Endometrin, Ferring Pharmaceuticals, Inc.), both of which require dosing 1 or more times daily (15–17). While the vaginal gel (VG) is approved for both luteal phase supplementation and replacement, the vaginal tablet is approved only for luteal phase supplementation. In addition, vaginal administration of P suppositories twice daily and micronized P capsules (Prometrium, Abbott Laboratories) several times daily has been performed clinically (18, 19). However, neither luteal phase supplementation nor replacement with these products has been approved by the FDA.

A vaginal ring (VR) designed to provide continuous release of P offers the advantages of less frequent dosing and possibly improved patient comfort. A randomized clinical trial with 153 patients conducted in South America found that administration of P via a 90-day VR (continuous release of P 10–20 nmol/L for 90 days) significantly improved implantation rates compared with IM P 50 mg/day in women undergoing IVF with donor oocytes (39.8% vs. 28.6%, respectively) (20). Another randomized controlled trial in 505 women undergoing IVF with autologous oocytes reported similar implantation rates between VR and IM P (36.6% for each group) (20).

A small pilot study of a weekly P VR for luteal phase replacement in donor oocyte recipients was conducted at a single site (21). In a "mock cycle," VR was able to adequately transform the endometrium, and when used during an actual ET cycle, pregnancy rates were similar to those achieved with VG.

The objective of this randomized phase III study was to compare clinical pregnancy rates using P supplementation with VR versus VG.

MATERIALS AND METHODS

This randomized, single-blind, multicenter study of P supplementation (luteal phase support [LPS]) in women undergoing IVF with fresh oocytes was conducted at 22 clinical sites in the United States between February 2008 and January 2009 (ClinicalTrials.gov identifier: NCT00615251). Clinical pregnancy rates at 8 and 12 weeks of pregnancy (6 and 10 weeks after egg retrieval) were compared among women who received P supplementation using either a weekly P VR or a daily P VG.

Sponsor procedures that comply with the ethical principles of Good Clinical Practice, as required by the FDA, and are in accordance with the Declaration of Helsinki were followed. Institutional Review Board (IRB) approval was obtained from all study sites before the start of the trial. Patients gave written informed consent to participate using an IRB-approved consent form before undergoing any study-specific procedures.

Patient Selection

Healthy premenopausal women aged 18–42 years with a normal uterine cavity as documented by hysteroscopy, hydrosonogram, or hysterosalpingogram and tubal, idiopathic, male factor, ovulatory dysfunction, or endometriosis-associated infertility were screened for participation. Patients were required to have at least one cycle without reproductive hormone medication before a cycle day 2 or 3 screening for FSH and E_2 blood draw. Either fresh or frozen sperm was allowed.

Patients with known sensitivity to P, undiagnosed vaginal bleeding, significant liver dysfunction, uncontrolled hypertension, psychiatric disease, active cancer or a history of cancer, or hormone-related thromboembolic disorders were excluded. A history of more than one failed IVF cycle, more than two consecutive miscarriages, or male partners with nonobstructive azoospermia (fresh sperm) also precluded enrollment. Other exclusion criteria included clinically significant gynecologic pathology (including submucosal fibroids, intramural fibroids >5 cm, cervical stenosis, communicating hydrosalpinx, uncorrected uterine septum, endometrial cancer or endometrial atypia, scar tissue inside the cavity, or poorly developed uterine lining from prior uterine surgery), an elevated cycle day 2 or 3 FSH level (>15 mIU/mL), and squamous intraepithelial lesion considered low-grade or worse based on a Pap smear at screening. Because pregnancy rates and medication requirements may differ in obese women compared with in women of normal weight (22–24), patients with a body mass index (BMI) >38 kg/m^2 also were excluded.

Experimental Design

After a screening process that included a medical/gynecologic history, physical examination (including pelvic examination), and laboratory assessment, ovarian suppression began in the cycle just before ovarian stimulation by standard down-regulation protocols determined for each patient at the investigator's discretion. These protocols included ovarian down-regulation with combined oral contraceptives (COCs) for between 14 and 21 days and the use of GnRH agonist, leuprolide acetate (Lupron, Abbott Laboratories), at a dose of 0.1 mL (500 μg/day) 4 days before the last COC tablet. Transvaginal ultrasound (TVU) and a serum E_2 level <60 pg/mL confirming adequate ovarian suppression preceded ovarian stimulation. Individual ovarian stimulation protocols included FSH (75–450 IU/day) in combination with a LH-containing product (75–150 IU/day). The length of stimulation was variable and dependent on each patient's response, the site's standard protocols, and/or the investigator's

discretion. Administration of $\leq 10,000$ IU hCG by IM injection was initiated when a TVU indicated the presence of at least two follicles ≥ 17 mm (mean of two dimensions) in conjunction with a serum E_2 level $<5,000$ pg/mL. Egg retrieval occurred 35–37 hours after hCG administration. If a patient's endometrial thickness was <6 mm on the day of the hCG trigger, she was excluded from the study. In addition, uterine factors as described in the Methods section were exclusionary.

A statistician not assigned to this study generated the randomization schedule for treatment assignments. Each site was given a list of sequential randomization numbers, and treatment groups were randomized within sites in blocks of four. Patients were stratified by age (18–34 years or 35–42 years) at the time of consent and sequentially randomized on the day after egg retrieval in a 1:1 fashion to either weekly treatment with a flexible silicone VR containing micronized P (11 mg/day) or daily treatment with P 8% VG (90 mg/day). P was the only luteal support administered. An unblinded staff member instructed patients on proper administration of treatment to maintain the single-blind study design. The first dose of P (VR or VG) was administered on the day after egg retrieval. Patients were instructed to self-replace the VR every 7 days and to continue use throughout the treatment period. Patients were permitted to remove the VR for up to 1 hour per day if desired; this included removing the VR for sexual intercourse, although removal was not necessary.

Patients returned 3 or 5 days after egg retrieval for ET, as conducted per the study site's protocol and following the 2006 American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology guidelines for number of embryos transferred (25). One or two embryos were transferred for patients aged ≤ 37 years, and two or three embryos were transferred for patients aged 38–42 years. All patients who underwent ET continued P treatment for a minimum of 2 weeks. Serum β-hCG levels were measured at approximately 14, 16, and 21 days after egg retrieval to confirm pregnancy. If the pregnancy test was negative or if a miscarriage occurred, the patient was withdrawn from the study. Women who were still pregnant 21 days after retrieval were examined by TVU to confirm the presence of an intrauterine gestational sac. Those patients with an intrauterine gestational sac continued taking the study medication for 10 weeks after egg retrieval, an approach that is recommended in the literature (22) and consistent with the maximal duration of luteal support used by participating investigators in IVF patients. Women who remained pregnant through week 12 were contacted by telephone approximately 2 weeks after their expected delivery date to obtain safety and pregnancy outcome information.

Efficacy was evaluated by comparing the clinical pregnancy rate (i.e., visualization of intrauterine gestation with fetal heart motion present on ultrasound) among women using the weekly P VR with the rate among women using VG at two time points after egg retrieval: 8 weeks of pregnancy (6 weeks after egg retrieval) and 12 weeks of pregnancy (10 weeks after egg retrieval). The study also evaluated the rates of live births, cycle cancellation, spontaneous abortion, biochemical pregnancy, and ectopic pregnancy for each treatment group. Safety measures assessed included an evaluation of the frequency of adverse events (AEs) and the occurrence of vaginal bleeding, spotting, or hemorrhaging (loss of >500 mL). AEs related to OHSS and procedures (egg retrieval and ET) were listed separately. Birth outcomes were also evaluated for each treatment group.

Statistical Analysis

The modified intent-to-treat cohort, consisting of all randomized patients who had a successful egg retrieval performed and who received at least one dose of investigational P product, served as the primary efficacy analysis set.

Sample size determination was based on the assumption that approximately 50% of patients aged 18–34 years in both treatment groups would achieve pregnancy. To achieve at least 90% power to demonstrate noninferiority with a one-sided noninferiority test at the significance level of 2.5% and a maximum allowable difference in pregnancy rates between the two treatment groups of 10% (allowing for approximately a 5% dropout rate), the optimal sample size was determined to be 1,100 women aged 18–34 years. Because many candidates for luteal supplementation are 35 years or older, approximately 200 women aged 35–42 years were also enrolled to estimate pregnancy rates in this population.
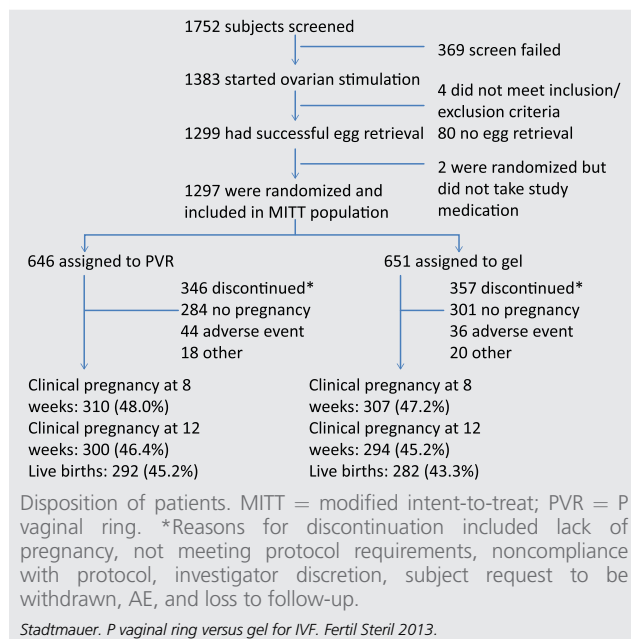
The normal approximation for the difference in clinical pregnancy rates between the two treatment groups (VR, VG) was calculated for all patients and each age group. Using a two-sided 95% confidence interval (CI) for the difference in pregnancy rates, VR would be considered noninferior to VG if the lower bound of the CI was greater than -10% for the study population at both time points (weeks 8 and 12).

Statistical software (SAS Version 9.1.3) was used for all output processing associated with this study, such as case-report form tabulations, patient profiles, summary tables, and statistical analysis.

RESULTS

A total of 1,752 patients were screened; 369 were considered screen failures, having not met the criteria for initiation of ovarian stimulation (Fig. 1). Successful egg retrievals were performed in 1,299 patients, 1,297 of whom were randomized and took at least one dose of P: 646 were randomized to the weekly VR and 651 to the daily VG. Of the randomized patients, a total of 26 did not undergo ET, largely because of AEs, mostly OHSS, or a lack of fertilized eggs. Demographic and baseline characteristics for each treatment group were similar (Table 1). Almost 80% of patients were Caucasian, and the mean age across all patients was 31.7 years. The BMI range was 15.1–38.2 kg/m^2, with a mean of 25.5 kg/m^2. Sixteen percent of patients randomized to VR and 21% of patients randomized to VG were obese (BMI ≥ 30 kg/m^2). There were no notable differences between the two treatment groups with respect to obstetric history; approximately half of the patients in each treatment group had no prior pregnancy. The infertility diagnosis was self-reported by patients and confirmed by the treating physician, and patients were allowed to select more than one etiology of their infertility.

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FIGURE 1

Disposition of patients. MITT = modified intent-to-treat; PVR = P vaginal ring. *Reasons for discontinuation included lack of pregnancy, not meeting protocol requirements, noncompliance with protocol, investigator discretion, subject request to be withdrawn, AE, and loss to follow-up.

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Approximately 43% reported more than one diagnosis. Male factor was the most commonly selected diagnosis. The vast majority of subjects (97%) in both groups had FSH levels of <10 mIU/mL.

Efficacy

Clinical pregnancy rates were similar across treatment groups (Table 2). Because patients were randomized only after egg retrieval, pregnancy rates were reported per retrieval and not per cycle. Clinical pregnancy rates with VR and VG at week

TABLE 1

Demographic and infertility characteristics.

	VR (n = 646)	VG (n = 651)	Total (n = 1,297)
Race, n (%)			
African American	54 (8.4)	48 (7.4)	102 (7.9)
Asian	34 (5.3)	37 (5.7)	71 (5.5)
Caucasian	519 (80.3)	507 (77.9)	1,026 (79.1)
Hispanic	34 (5.3)	51 (7.8)	85 (6.6)
Other	5 (0.8)	8 (1.2)	13 (1.0)
Age			
Mean age (SD)	31.7 (3.7)	31.6 (3.9)	31.7 (3.8)
Body mass index, kg/m²			
Mean (SD)	25.3 (4.6)	25.7 (5.0)	25.5 (4.8)
Obese, n (%)[a]	104 (16.1)[b]	134 (21)	238 (18.3)
FSH levels (mIU/mL)			
<10	618 (96.5)	632 (97.3)	1,250 (96.9)
10–15+	22 (3.4)	17 (2.6)	39 (3.0)
Subjects with embryos transferred, n (%)	631 (49.7)	640 (50.4)	1,271

[a] Defined as BMI ≥30 kg/m².
[b] Two subjects from the VR group are not included owing to missing weight data.

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8 were 48.0% and 47.2%, respectively (between-group difference, 0.8%; 95% CI, −4.6%, 6.3%), and at week 12 were 46.4% and 45.2%, respectively (between-group difference, 1.3%; 95% CI, −4.1%, 6.7%). These rates were consistent with the prespecified rate of 50% used in the calculation of sample size. Among patients aged 18–34 years, the clinical pregnancy rate at 8 weeks was 49.3% for VR and 48.0% for VG (between-group difference, 1.2%; 95% CI, −4.6%, 7.1%). Similarly, 48.2% of patients treated with VR and 46.1% who received VG were pregnant at 12 weeks' gestational age (between-group difference, 2.1%; 95% CI, −3.7%, 8.0%). The lower bound of the 95% CI for each comparison in the overall population and in women aged 18–34 was above the lower bound of −10% specified in the protocol and statistical analysis plan, thus demonstrating noninferiority of VR compared with VG.

As would be expected, success rates in the older patient stratum were somewhat lower at both weeks 8 and 12 compared with younger patients, but the rates themselves were comparable across the treatment groups. The study was not powered to demonstrate noninferiority for the older reproductive-aged subgroup (35–42 years). However, 179 women in this age range were randomized and did receive treatment (n = 88 VR; n = 91 VG). Because the sample size of this subgroup was less than what would be required for a strict statistical inference regarding noninferiority, the CIs are presented in Table 2 primarily for reference.

The majority of patients who were pregnant at 12 weeks had a live birth: 97.4% for VR and 96.5% for VG. Live-birth rates per retrieval were 45.2% for VR and 43.3% for VG in the overall population and 47.0% for VR and 44.5% for VG among patients aged 18–34 years (95% CI for difference, −3.3%, 8.3%). Live-birth rates among patients aged 35–42 years were 34.1% for VR and 36.3% for VG.

The overall cycle cancellation rate was calculated using all patients who were deemed eligible for study participation and who initiated ovarian stimulation. Because randomization did not occur until after egg retrieval, the cancellation rate by treatment group could not be determined. The overall percentage of cycles canceled after oocyte retrieval for all patients was 5.9%.

Total pregnancy rates were similar between groups: 62.5% for the VR group and 63.6% for the VG group. When evaluating only those women who underwent ET, 64.0% of those randomized to VR and 64.7% of those randomized to VG had a positive serum pregnancy test result approximately 2 weeks after ET. Ectopic pregnancy rates were low and similar in both treatment groups: 1.1% for the VR group and 1.2% for the VG group (95% CI for difference, −1.3%, 1.0%). Spontaneous abortion rates, defined as the loss of pregnancy before 12 weeks' gestation, were similar for both treatment groups for all patients (5.4% for VR and 5.5% for VG; 95% CI for difference, −2.6%, 2.4%) and for those aged 18–34 years (4.8% for VR and 5.4% for VG; 95% CI for difference, −3.1%, 2.1%). Rates of spontaneous abortion were 9.1% with VR and 6.6% for VG in the older patient group, which were not significantly different (95% CI, −5.4%, 10.4%).

TABLE 2

Clinical pregnancy rate per retrieval.

Weeks of pregnancy		VR (n = 646) n (%)		VG (n = 651) n (%)		DIFF (VR-VG)	95% CI for DIFF
All ages, 18–42	8	646	310 (48.0)	651	307 (47.2)	0.8%	(−4.6%, 6.3%)
	12		300 (46.4)		294 (45.2)	1.3%	(−4.1%, 6.7%)
Ages, 18–34	8	558	275 (49.3)	560	269 (48.0)	1.2%	(−4.6%, 7.1%)
	12		269 (48.2)		258 (46.1)	2.1%	(−3.7%, 8.0%)
Ages, 35–42[a]	8	88	35 (39.8)	91	38 (41.8)	−2.0%	(−16.4%, 12.4%)
	12		31 (35.2)		36 (39.6)	−4.3%	(−18.5%, 9.8%)

Note: DIFF = between-group difference.
[a] The sample size of this subgroup does not allow statistical inferences regarding noninferiority.

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Safety

The mean duration of use was 40.9 days for VR and 41.0 days for VG. AEs reported during the treatment period (those that occurred from the day of first dose of study medication through 14 days after the last dose) were similar between the two groups and consistent with known AEs associated with P (Table 3). The most commonly reported AEs were nausea, headache, abdominal pain, postprocedural discomfort, abdominal distension, back pain, fatigue, and constipation. Vaginal discharge was reported slightly more frequently among patients who received VR (9.4%) as compared with those treated with VG (3.2%). Rates of vaginal discharge deemed by investigators to be possibly, likely, or definitely related to treatment were 4% for VR and 2% for VG. There were no differences observed in the rates of vaginal infection, vaginal irritation, or urinary tract infections. Rates of discontinuation were low and similar between the treatment groups; approximately 6% of study patients discontinued the study owing to an AE. Most AEs leading to discontinuation were related to pregnancy loss (which would necessitate study

TABLE 3

Incidence of treatment-emergent AEs occurring in 5% or more of patients—safety cohort.

MedDRA preferred term	VR (n = 647) n	%	VG (n = 650) n	%
Nausea	166	25.7	145	22.3
Headache	132	20.4	167	25.7
Abdominal pain	131	20.3	150	23.1
Postprocedural discomfort	102	15.8	98	15.1
Abdominal distension	88	13.6	78	12.0
Back pain	82	12.7	84	12.9
Fatigue	81	12.5	80	12.3
Constipation	74	11.4	69	10.6
Pelvic pain	55	8.5	73	11.2
Vomiting	66	10.2	55	8.5
Dyspepsia	52	8.0	68	10.5
Breast tenderness	55	8.5	39	6.0
Diarrhea	37	5.7	56	8.6
Dizziness	48	7.4	35	5.4
Vaginal discharge	61	9.4	21	3.2
Procedural pain	36	5.6	35	5.4
Urinary tract infection	26	4.0	35	5.4

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withdrawal) or OHSS. The most commonly reported AEs leading to discontinuation with VR and VG were missed abortion (2.5% and 1.9%, respectively), spontaneous abortion (0.93% and 0.92%, respectively), ectopic pregnancy (0.93% and 0.77%, respectively), blighted ovum (0.77% and 0.77%, respectively), and OHSS (0.93% and 0.62%, respectively).

Rates of vaginal bleeding and/or spotting AEs, which included vaginal hemorrhage, metrorrhagia, vaginal bleeding, vaginal spotting, and uterine bleeding, were similar with VR (4.9%) and VG (5.8%). No patient discontinued the study owing to vaginal bleeding, and no VR patient was placed on an alternative form of P owing to vaginal bleeding issues.

In the VR treatment group, two patients were switched to alternate forms of P, one of whom withdrew from the study on the day of ET and one of whom developed a rash approximately 2–3 weeks after her first dose and discontinued. There were no reports of the VR falling out. One patient in the VG group was switched to a P vaginal insert owing to abnormally increasing β-hCG levels and subsequently experienced a missed abortion.

Serious adverse events (SAEs) occurred in about 12% of all patients and were similar in frequency between the two treatment groups. The majority of SAEs occurring during the treatment period were mild to moderate in severity, not related to treatment, and consisted primarily of pregnancy-related events (intrauterine death, missed abortion, blighted ovum, spontaneous abortion), as well as OHSS. Rates of first trimester loss and preterm birth were similar between the treatment groups. The rate of birth defects observed in this study was not higher in infants born to those women randomized to VR compared with those randomized to VG and was consistent with the background rate of 4% in the U.S. general population (26, 27). No specific pattern of birth defect or organ class event was noted as being prevalent between the treatment groups.

DISCUSSION

Typical IVF protocols involve pituitary down-regulation with GnRH agonists (e.g., leuprolide), resulting in suppression of LH and FSH and subsequently low P and E_2 levels. LPS in the form of P supplementation during and immediately after ET results in higher pregnancy rates as compared with no LPS treatment (2).

Comparisons between IM and vaginal P administration in IVF have produced conflicting results. Several initial studies found lower pregnancy rates with P VG in comparison with IM delivery (28–30). More recently, randomized controlled trials have found comparable results in clinical and ongoing pregnancies with the use of vaginal or IM P (31), whereas a 2009 meta-analysis reported slightly reduced rates of miscarriage associated with vaginal P administration (26, 27). However, in a recent large prospective trial comparing IM P with VG for LPS, patients who received vaginal P had higher pregnancy and delivery rates, specifically among patients younger than 35 years (32). In addition, a recent randomized study comparing a vaginal P insert with IM P reported similar pregnancy rates between groups, although administration convenience, ease of use, and overall satisfaction scores were higher with vaginal P administration (33). Vaginal regimens, including 200 mg P in oil capsules inserted vaginally 3 times daily, 90 mg P 8% bioadhesive VG once daily, or 100 mg P vaginal inserts used 2 or 3 times daily (15–17, 26), have resulted in similar pregnancy and implantation rates in a comparative randomized study and a meta-analysis of vaginal P LPS in IVF procedures (2, 17).

In the present trial, no significant differences were found in the clinical pregnancy rates at 8 and 12 weeks' gestation between the P VR administered once weekly and the FDA-approved active comparator, P 8% VG, dosed daily. Clinical pregnancy rates achieved with VR of 49.3% at 8 weeks and 48.2% at 12 weeks were comparable with reported ART rates (34). For the two primary endpoints of clinical pregnancy rates at weeks 8 and 12 of gestation, efficacy of VR was demonstrated to be noninferior to VG, with the lower bound of the two-sided 95% CI falling well within the prespecified limit of -10% ($\geq -4.6\%$). Rates of live births, multiple gestations, biochemical pregnancy, ectopic pregnancy, and spontaneous abortion were similar between the two active treatment groups and consistent with reported background rates, supporting two premises: the dose of P delivered by VR is comparable with the dose provided by VG, and VR provides sufficient progestational support for implantation and establishment of early pregnancy.

The weekly P VR appeared to be well tolerated and safe. AEs and SAEs were similar for both treatment groups, and there were no significant safety trends noted for VR. Treatment-related AEs were generally similar between the two groups and consistent with the known safety profile of P. Rates of patient discontinuation owing to an AE (approximately 6%), OHSS (5%), and postprocedural AEs (18%) were similar between the treatment groups.

Rates of vaginal discharge reported as an AE were increased in the VR group, but it should be noted that patients were not blinded to treatment group. Vaginal discharge that occurred in VG users may have been underreported and possibly attributed to residue from the VG. No differences were observed between the two treatment groups regarding the rates of vaginal infections, urinary tract infections, or cervical/vaginal irregularities. There were no increased rates of cervical/vaginal abrasions or irritation associated with use of VR compared with VG and no reports of the VR falling out. In general, the VR appeared to be well tolerated when administered weekly for up to 10 weeks.

AEs related to vaginal bleeding were similar between the treatment groups. No patient discontinued because of bleeding, and no patient was switched to an alternative P product because of a bleeding issue.

A VR formulation offers unique advantages over other vaginal P delivery methods. Once weekly dosing is more convenient and likely to improve patient adherence to the regimen. An earlier study evaluated a similar VR for P delivery in two prospective controlled trials (20). In one, an ET trial involving 505 women, VR and IM P resulted in comparable clinical pregnancy rates of 36.6% in both groups. In the other, an oocyte donation trial of 153 women, clinical pregnancy rates were 39.8% and 28.6% for the VR and IM formulations, respectively. In establishing comparability between the VR and IM routes, these trials lend credence to a postulated uterine first-pass effect, that is, direct delivery of P to the uterus via VR provides sufficient endometrial P levels to support pregnancy despite lower serum levels than those observed with IM administration (11, 12). The comparable clinical pregnancy rates observed in the current study provide additional evidence that use of a comfortable, once-weekly VR provides adequate progestational LPS and eliminates the need for multiple daily IM injections.

Cost can also be of concern for some patients and may play an important role in their selection of treatments for infertility. However, pricing for the P VR is yet to be determined and was not available at the time of publication.

In summary, the current study demonstrates that weekly P VR is effective and safe for luteal supplementation and progestational support as part of ART treatments for women with infertility. For both primary efficacy endpoints, noninferiority of VR to VG was demonstrated. Pregnancy was achieved at comparable high rates in patients treated with the investigational VR and FDA-approved VG product, and no concerning safety trends were identified.

editorial assistance. This manuscript was prepared according to the International Society for Medical Publication Professionals' "Good Publication Practice for Communicating Company-Sponsored Medical Research: The GPP2 Guidelines."

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