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

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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;99:1543–9. ©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

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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