# Pilot study evaluating a progesterone vaginal ring for luteal-phase replacement in donor oocyte recipients

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**Objective:** To evaluate the proportions of women demonstrating adequate endometrial transformation during a mock cycle and the 8-week clinical pregnancy rate in a donor oocyte cycle using a P vaginal ring or P vaginal gel.
**Design:** Prospective, controlled, randomized trial.
**Setting:** Donor egg program at an academic center.
**Patient(s):** Women who are candidates for donor oocytes.
**Intervention(s):** Subjects were analyzed for adequate endometrial transformation after suppression and pretreatment with $E_2$. Subjects were treated with 18 days of $E_2$ coupled with a weekly P vaginal ring or 90 mg 8% vaginal gel twice daily. Endometrial biopsies were performed on cycle day 25 or 26. Nine subjects successfully completing the mock cycle participated in an ET cycle using the same randomly assigned study medication.
**Main Outcome Measure(s):** Adequate endometrial transformation, pregnancy, safety, and tolerability of the vaginal ring.
**Result(s):** Twenty women randomized 1:1 to either the P vaginal ring or vaginal gel completed the mock cycle. Endometrial histology was "in phase" for 8 of 10 (80%) in the vaginal ring group and 10 of 10 (100%) in the gel group. For the women who participated in the ET cycle, clinical pregnancies and live births were observed in 4 of 5 (80%) in the vaginal ring group and 1 of 4 (25%) in the vaginal gel group.
**Conclusion(s):** In women requiring luteal-phase replacement, the P vaginal ring was able to adequately transform the endometrium and was comparable to the P vaginal gel in efficacy and safety, while offering the advantage of weekly rather than multiple daily doses. (Fertil Steril® 2009;92:1600–5. ©2009 by American Society for Reproductive Medicine.)

**Key Words:** Donor eggs, vaginal, ring, progesterone, pregnancy, endometrial biopsy

The luteal phase of a natural menstrual cycle is characterized by the formation of a corpus luteum, which secretes steroid hormones, including P. After fertilization and implantation, the developing blastocyst secretes hCG, which maintains the corpus luteum and its secretions.

Unfortunately, not all women of reproductive age are able to become pregnant or maintain a pregnancy. Indeed, 12% of women of reproductive age in the United States have received infertility services at some time in their lives (1). In women with low ovarian reserve or ovarian failure due to natural menopause, gonadal dysgenesis, or acquired conditions, IVF with donor oocytes has been shown to be a more effective way, and in many cases the only way, to achieve a pregnancy (2). In many of these women, there is little or no endogenous source of P. In addition, recipients are administered oral contraceptives and/or GnRH agonists to suppress their ovarian function, to coordinate their cycles with those of the oocyte donor. Normal luteal function is essential for maintaining pregnancy, and data suggest that P is necessary for the maintenance of early pregnancy (3).

In 2005, more than 16,000 cycles of egg or embryo donation were performed in the United States, accounting for more than 12% of all assisted reproductive technology cycles. Success rates after egg donation are among the highest of all assisted reproductive techniques: 52% and 31% per transfer for fresh and frozen donor embryos, respectively (1).

Oral, IM, and vaginal P preparations are available. Oral formulations seem to be inferior for luteal support, whereas IM and vaginal preparations lead to comparable rates of implantation and clinical pregnancy (4–6). Serum P levels are highest with IM administration, but vaginal administration results in higher endometrial P levels, likely owing to the uterine first-pass effect (3, 7, 8). Intramuscular P (50–100 mg daily) is widely used but is not approved by the U.S. Food and Drug Administration (FDA) for this indication, requires daily injections, and is uncomfortable and inconvenient for subjects; some subjects may even develop a sterile abscess or an allergic response to the oil vehicle (3,9). Vaginal P gel (Crinone/Prochieve, 90 mg, one to two times daily;

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Columbia Laboratories, Livingston, NJ) is FDA approved for luteal supplementation and replacement and is less painful and easier to use than IM P, but it requires daily dosing and may be messy (10). A P vaginal insert (Endometrin, 100 mg, two to three times daily; Ferring Pharmaceuticals, Parsippany, NJ) was also recently approved by the FDA for luteal supplementation in assisted reproductive technology, but this also requires daily dosing (11). In addition, vaginal use of micronized P capsules (200 mg, three times daily) has been reported and is used clinically, but luteal-phase supplementation or replacement are not FDA-approved indications for these capsules (12).

Progesterone for either partial (IVF) or complete (oocyte donation) luteal support delivered by a vaginal ring is advantageous for a number of reasons: less frequent dosing is required, patient comfort and convenience are likely to be improved, and more convenient and reliable drug delivery is expected. Vaginal rings that release hormones have been successfully used in contraception and postmenopausal estrogen therapy for years.

To our knowledge, this was the first use of a P vaginal ring in the United States for luteal support, although researchers in other countries have evaluated similar P-releasing rings in IVF and donor oocyte candidates (13, 14). The primary objective of this phase II pilot study was to evaluate, in women with clinical or medically induced agonadism, the rates of adequate endometrial transformation with a P vaginal ring or a P vaginal gel in donor oocyte recipients. Specifically, adequate endometrial transformation (as determined by endometrial biopsy) in a mock cycle, safety and tolerability of the vaginal ring, and 8-week clinical pregnancy, biochemical pregnancy, and live birth rates in a fresh ET cycle were examined.

## MATERIALS AND METHODS

This was a phase II, single-center, open-label, randomized, active-control study to evaluate a single dose of P, delivered by vaginal ring, for resultant endometrial transformation and luteal-phase replacement with assisted reproductive technology. The study had two treatment arms: P vaginal ring and P vaginal gel. This study was approved by the Eastern Virginia Medical School institutional review board/ethics committee. The study was performed in accordance with the Declaration of Helsinki (revised Edinburgh, Scotland, 2000) applicable guidelines for good clinical practice.

### Subject Selection and Inclusion and Exclusion Criteria

All subjects were required to be 18–50 years old, not pregnant, clinically or medically agonadal, and eligible for oocyte donation. Subjects were excluded from participation if they had any contraindication to P or pregnancy, diabetes, hyperprolactinemia or hypothyroidism, clinically significant uterine pathology (e.g., uterine fibroids, cervical stenosis, severe intrauterine adhesive disease), significant prior uterine surgery, history of chemotherapy or pelvic radiation, or history of more than two failed donor egg cycles.

Subjects with adequate endometrial transformation in the mock cycle who had accepted an oocyte donor and were synchronized with this donor were invited to participate in a follow-on ET cycle. Subjects continued the same P treatment to which they had been randomized in the mock cycle.

### Treatment Regimen

Subjects enrolled in the mock cycle received oral contraceptives for 2 weeks and a GnRH agonist (Lupron; TAP Pharmaceuticals, Chicago, IL) to suppress ovarian function. The GnRH agonist was initiated on day 8 of oral contraceptives in the cycle preceding the mock and/or transfer cycle and continued until $E_2$ patches were initiated. Estradiol pretreatment was administered in a step-up fashion (Vivelle patches: 0.2 mg days 1–7, 0.3 mg days 8–11, and 0.4 mg days 12–14 every other day; Novartis Pharmaceuticals, East Hanover, NJ) to generate a proliferative phase of the endometrium. Subjects with an endometrial thickness >6 mm were randomized in a 1:1 fashion to either a P vaginal ring (14 mg/d; Duramed Research, Bala Cynwyd, PA) or P vaginal gel (Crinone, 180 mg/day) and taught to administer the product. Progesterone vaginal ring or vaginal gel, together with $E_2$ 0.2 mg, was administered over the next 18 days to transform the endometrium to the secretory phase. The vaginal gel was administered twice daily. The P vaginal ring was scheduled to be replaced one time on cycle day 21. An endometrial biopsy was performed on cycle day 25 or 26, and endometrial dating was performed according to Noyes et al. (15). Vaginal ring compliance was determined at each study visit. Vaginal colposcopy was performed at screening and on cycle day 31 to evaluate any potential vaginal and cervical irritation.

Subjects with secretory endometrial transformation were invited to participate in a follow-on ET cycle study to evaluate clinical pregnancy rates in women undergoing donated oocyte IVF with a fresh ET. Because the initial subject pool for this pilot study was small, the voluntary nature of this phase of enrollment and the criteria for the use of fresh ET resulted in a smaller number of subjects for the ET cycle study. Subjects were assigned to receive the same P treatment to which they had been randomized in the mock cycle. For subjects in the vaginal ring group, a new vaginal ring was placed at the time of transfer, and the vaginal ring was scheduled to be replaced weekly until the pregnancy test was performed 2 weeks after ET. Subjects in the vaginal gel group continued to self-administer the vaginal gel twice daily until 2 weeks after ET. If a pregnancy was detected, the $E_2$ replacement was continued for a total of 8 weeks and the P for a total of 10 weeks after ET. Pelvic ultrasound examination was performed at 8 weeks and 12 weeks to confirm a clinical pregnancy. Follow-up of any pregnancies continued until delivery.

### Determination of Pregnancy Status

Biochemical pregnancy, clinical pregnancy (8 and 12 weeks of pregnancy), and live birth rates were assessed. A