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Research Article

# Successful Outcomes of Fresh and Frozen Donor Ovum Cycles Among Recipients Using Oral Estradiol and Vaginal Progesterone Gel vs. Intramuscular and Vaginal Progesterone

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## Abstract

**Background**: There is a paucity of data evaluating the efficacy of vaginal progesterone replacement in both fresh and frozen transfers of recipients of oocyte donors.

**Method**: This was a multicenter, IRB approved, retrospective analysis from January 2009 through June 2013 of 255 cycles among women less than 55 years of age who were oocyte recipients in an anonymous donor program. Oocyte recipients from fresh and frozen cycles received vaginal progesterone gel (Crinone 8%) 90 mg twice daily and oral estradiol 2 mg 2–3 times daily in a step-up protocol. The comparative groups of fresh and frozen donor oocyte cycles took progesterone intramuscular 50 mg once a day, 5 days prior to transfer, Progesterone 200 mg vaginal capsule beginning the day of transfer and Estrogen 2 mg orally three times daily continuing until the tenth week of pregnancy. Subjects were monitored via transvaginal ultrasound, serum estradiol and progesterone levels, both on baseline and the week prior to transfer. A serum beta-hCG, estradiol, and progesterone were obtained 10 days after Blastocyst transfer. Hormone levels and pregnancy rates were summarized with descriptive statistics.

**Results**: It was showed that the fertility interventions did not significantly differ with regard to number of positive pregnancy tests, $\chi^2(3)=4.41$, $p=0.220$. Results also showed that the fertility interventions did not significantly differ with regard to number of clinical pregnancies, $\chi^2(3)=4.68$, $p=0.196$.

**Conclusion**: Preparing the endometrium with oral estradiol and vaginal progesterone gel among recipients treated in a contemporary donor oocyte program is highly effective.

**Keywords:** Vaginal progesterone; Estradiol; Assisted reproductive technology; Donor egg; Progesterone gel

## Introduction

Historically, women without ovarian function and those with poor oocyte quality can become pregnant through in vitro fertilization/embryo transfer (IVF/ET) using oocytes donated by fertile women [1]. The implantation process requires synchronization between the development of the embryo and optimal endometrial receptivity [1]. In a natural cycle, these processes are regulated by ovarian hormones [1,2]. However, in oocyte recipients, progesterone replacement or supplementation during the luteal phase is needed to help prepare the endometrium for implantation and to improve fertility outcomes [1,3].

Women undergoing IVF/ET with donor oocytes are typically treated with estrogen in addition to progesterone to synchronize the cycle and help prime and prepare the endometrium before embryo transfer [2]. In a natural cycle, estrogen stimulates the growth of the functional endometrium, priming the endometrium, and progesterone contributes to histological transition to a secretory endometrium, which is necessary preparation for implantation [2]. In some studies, estrogen plus progesterone has been shown to improve fertility outcomes compared with progesterone alone [3]. Findings from a study of 271 patients undergoing 285 cycles of IVF demonstrated that pregnancy rates were higher in patients who were treated with estrogen and progesterone compared with those treated with only progesterone during the luteal phase (33.8% vs. 23.4%) [4].

Patients can take estrogen and progesterone via various routes of administration [3]. Progesterone vaginal gel 90 mg (Crinone® 8%; Actavis Pharma, Inc.) is indicated for infertile women with progesterone deficiency as part of an assisted reproductive technology (ART) treatment to supplement or replace progesterone [5]. Compared with oral or intramuscular progesterone, progesterone vaginal gel may improve efficacy and tolerability because it is transported directly to the endometrium, potentially reducing systemic exposure [2,6,7].

However, literature on the use of estrogen with vaginal progesterone gel in donor oocyte cycles is limited, older and prone to biases due to outdated ART methodologies such as slow freeze and cleavage stage embryo transfer. Moreover, due to the fact that ovum donation cycles are significantly more costly and complicated, clinicians are more apprehensive to change from the dogmatic approach of intramuscular progesterone (IMP).

The efficacy of vaginal progesterone gel (Crinone 8%) in combination with transdermal estradiol previously was demonstrated in a prospective randomized trial of patients in an oocyte donor program undergoing fresh transfers [8]. In a retrospective study, Berger et al. [9] assessed pregnancy outcomes from 2004-2006 with progesterone vaginal gel vs. intramuscular progesterone in 225 donor oocyte recipients also receiving estradiol tablets and estradiol transdermal

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patch in a single, large ART center. In this series, comparable results were reported among fresh transfers. A recent retrospective study by Kaser et al. [10] observed day three frozen embryo transfer cycles with vaginal progesterone gel compared to IMP had lower odds of clinical pregnancy and live birth rate. Thus, the current status of available data with respect to ART replacement cycles are conflicting, not contemporary and extremely limited with respect to ovum donation cycles, both fresh and frozen.

The present study was conducted to detect any differences in pregnancy rates between vaginal progesterone only as compared to IM and vaginal progesterone among fresh and frozen donor oocyte cycles between two separate practitioners in a large regional ART center.

## Methods

### Study design and patients

This retrospective analysis was conducted using data from a large regional ART center. The protocol was approved by Shulman Associates institutional review board. All women aged <55 years who were oocyte recipients in a contemporary oocyte anonymous donor program from January 1, 2009 to June 30, 2013, and who did not have severe pelvic factor infertility were included in the analysis. The study consisted of 255 cycles, among two clinicians, from separate IVF labs. Recipients in this data set include cycles in which PGS was performed and also includes transfers to Gestational Surrogates. Oocyte donors were prescreened in the standard manner and had a normal basal antral follicle count and normal follicular stimulating hormone and estradiol levels on day 3 of the menstrual cycle.

In this ART protocol, clinician A oocyte recipients in both fresh and frozen cycles, received oral estradiol 2 mg 2-3 times daily in a step-up protocol followed by vaginal progesterone gel (Crinone 8%) 90 mg twice daily for 5 completed. On the sixth day Blastocyst transfer was completed. Clinician B oocyte recipients prepared the endometrium in a similar fashion with respect to oral estradiol, followed by IMP 50 mg once daily for 5 days prior to transfer and subsequently a progesterone 200 mg vaginal capsule was administered. An ultrasound was performed and estradiol and progesterone levels were assessed before the administration of progesterone. Patients with residual ovarian function also received a gonadotropin-releasing hormone agonist. Embryo transfers were performed with a soft catheter using ultrasound guided assistance. Serum human chorionic gonadotropin (hCG levels) were determined eight to ten days after embryo transfer to confirm pregnancy.

Baseline oocyte donor ages were reported. In addition, baseline recipient clinical characteristics were reported, including age, number of embryos transferred, and serum estradiol and progesterone levels. Estradiol and progesterone serum levels at midcycle and at the time of pregnancy testing, endometrial thickness at midcycle, and pregnancy rates were assessed. A positive pregnancy was defined as having a positive serum hCG. A clinical pregnancy was confirmed by ultrasound and determined based on fetal cardiac activity at 10 weeks gestation.

### Statistical analysis

Pregnancy outcome rates were calculated as the number and percentage of recipients with positive serum hCG, and clinical pregnancy. Chi-square ($\chi^2$) tests of independence are conducted when the independent and dependent variables are categorically coded.

## Results

A total of 255 recipients were included in the analysis. Of the 255 recipients, 47 (75.8%) were aged >35 years. Results from the chi-square ($\chi^2$) test of independence are presented in Table 1. Results showed that the fertility interventions did not significantly differ with regard to number of positive pregnancy tests, $\chi^2(3)=4.41$, $p=0.220$.

Results from the chi-square ($\chi^2$) test of independence are presented in Table 2, showing that the fertility interventions did not significantly differ with regard to number of clinical pregnancies, $\chi^2(3)=4.68$, $p=0.196$. The fertility interventions resulted in similar percentages of participants having a positive heartbeat on ultrasound. These percentages are reported in Table 2.

Patient demographics and baseline clinical characteristics are presented in Table 3. The mean oocyte donor age was 25.6 years and the mean recipient age was 40.4 years. Midcycle estradiol and progesterone levels and endometrial thickness before progesterone application are presented in Table 4. Estradiol and progesterone levels at the time of pregnancy testing are presented in Table 5. Positive pregnancy rates were similar between patients ≥35 years (78.7%) and <35 years old (73.3%).

## Discussion

This current analysis is one of a few studies assessing the efficacy of preparing the endometrium with oral estradiol and vaginal progesterone gel, in recipients participating in a contemporary donor oocyte program with respect to both fresh and frozen ART cycles. Recipients received oocytes from anonymous donors who were aged

| | Yes | No | Total |
|---|---|---|---|
| **Fresh cycles with vaginal crinone only and estrogen** | 80 (73.3%) | 29 (26.7%) | 109 (100.0%) |
| **FET cycles with vaginal crinone only and estrogen** | 40 (77.0%) | 12 (23.0%) | 52 (100.0%) |
| **Fresh cycles with vaginal and intra-muscular progesterone and estrogen** | 27 (73.0%) | 10 (27.0%) | 37 (100.0%) |
| **FET cycles with vaginal and intra-muscular progesterone and estrogen** | 45 (78.9%) | 12 (21.1%) | 57 (100.0%) |

**Table 1:** Chi-square ($\chi^2$) Test of Independence: Four fertility interventions and positive pregnancy test (Yes/No) outcomes.

| | Yes | No | Total |
|---|---|---|---|
| **Fresh cycles with vaginal crinone only and estrogen** | 75 (68.8%) | 34 (31.2%) | 109 (100.0%) |
| **FET cycles with vaginal crinone only and estrogen** | 34 (65.3%) | 18 (34.7%) | 52 (100.0%) |
| **Fresh cycles with vaginal and intra-muscular progesterone and estrogen** | 27 (73.0%) | 10 (27.0%) | 37 (100.0%) |
| **FET cycles with vaginal and intra-muscular progesterone and estrogen** | 43 (75.4%) | 14 (24.6%) | 57 (100.0%) |

**Table 2:** Chi-square ($\chi^2$) Test of Independence: Four fertility interventions and clinical pregnancy (Yes/No) outcomes.

| | FRESH VAGINAL PROG | FROZEN V AGINAL PROG | FRESH IM/VAG PROG | FROZEN IM/VAG PROG |
|---|---|---|---|---|
| **MEAN RECIPIENT AGE YEARS** | 40.4 | 38.9 | 41.2 | 35.9 |
| **MEAN NO. OF EMBRYOS TRANSFER** | 2 | 2.2 | 1.8 | 1.9 |
| **PGS** | 25/109 (23%) | 14/52 (27%) | 30/57 (53%) | 7/37 (19%) |
| **GESTATIONAL CARRIER** | 40/109 (37%) | 19/52 (37%) | 21/57 (37%) | 16/37 (43%) |

**Table 3:** Patient demographics.

| | FRESH VAGINAL PROG | FROZEN VAGINAL PROG | FRESH IM/VAG PROG | FROZEN IM/VAG PROG |
|---|---|---|---|---|
| **Mid Cycle Mean EEC mm** | 10.1 | 10.0 | 8.8 | 8.5 |
| **Mid cycle Mean E2 pg/mL** | 521.3 | 704.2 | 509.4 | 417.0 |
| **Mid cycle Mean P4 ng/dL** | 0.49 | 1.06 | 0.71 | 0.80 |
| **Pregnancy test Mean E2 pg/mL** | 491.1 | 545.4 | 545.0 | 356.0 |
| **Pregnancy test Mean P4 ng/dL** | 10.3 | 8.4 | 34.3 | 36.1 |

**Table 4:** Midcycle estradiol and progesterone levels and endometrial thickness before progesterone application.

| | FRESH VAGINAL PROG | FROZEN VAGINAL PROG | FRESH IM/VAG PROG | FROZEN IM/VAG PROG |
|---|---|---|---|---|
| **Week 5 Mean E2 pg/mL** | 651.6 | 571.5 | 431.7 | 447.9 |
| **Week 5 Mean P4 ng/dL** | 11.8 | 10.7 | 33.1 | 35.6 |
| **Week 6 Mean E2 pg/mL** | 911.0 | 679.9 | 583.7 | 616.0 |
| **Week 6 Mean P4 ng/dL** | 15.9 | 11.4 | 37.44 | 37.4 |

**Table 5:** Estradiol and progesterone levels at the time of pregnancy testing.

≤ 32 years. Findings showed that combining oral estradiol and vaginal progesterone gel was highly effective in this study population, with positive pregnancy test and clinical pregnancy outcomes similar to that of intramuscular progesterone and oral estradiol.

A decade-old study conducted by Gibbons et al. [8] compared the efficacy of vaginal progesterone (Crinone 8%) 90 mg with intramuscular progesterone 100 mg, in 72 patients receiving transdermal estradiol in an oocyte donor program. In the study, vaginal progesterone gel was administered twice-daily starting from the evening of day 14 for two weeks (until pregnancy testing was performed [8]. The positive pregnancy rate, clinical pregnancy rate, and ongoing pregnancy rate in the patient group using progesterone gel and transdermal estradiol were 54%, 48%, and 31%, respectively [8]. These rates were substantially lower than the respective rates reported in the present study.

Similarly, a recent study conducted by Berger et al. [9] compared pregnancy outcomes of vaginal progesterone gel 90 mg, with intramuscular progesterone 50 mg in 225 patients. Recipients received oral estradiol 2 mg twice daily, starting four days before the donor expected menses and transdermal estradiol 0.1 mg every three days [9]. Patients received vaginal progesterone gel 90 mg twice daily or intramuscular progesterone 50 mg once daily starting the afternoon of donor oocyte retrieval and continuing until a negative pregnancy test or 10 weeks gestational age if pregnant [9]. In the patients who received progesterone gel, the positive pregnancy rate and clinical pregnancy rate were 62% and 58%, respectively [9]. Findings from the present study are consistent with results reported by Berger et al. However, all patients in the present study used only oral estradiol tablets, not oral estradiol tablets or transdermal estradiol. This trial is the second trial that observed similar findings in a contemporary IVF oocyte donor program among fresh transfers.

Estrogen plus progesterone has been shown to improve fertility outcomes compared with progesterone alone in some studies for women undergoing IVF/ET with impaired or suppressed ovarian function [3]. Estrogen can be given orally or as a transdermal patch [1]. Pregnancy rates are similar with either route of delivery [1], which is consistent with findings taken together from Berger et al. [9] and the present study. However, there are advantages and disadvantages to both forms. One benefit of transdermal delivery is that it leads to estrogen levels similar to those observed in a natural cycle [1,10]. In addition, transdermal estrogen is not associated with changes in clotting factors and renin substrates or increases in serum lipoproteins [1]. However, some patients may find wearing a patch bothersome [11] or the patch may lead to skin irritation [12]. Besides skin irritation, the adverse events associated with equivalent doses of oral and transdermal estrogen generally are similar [12]. Therefore, the decision to prescribe either transdermal or oral estrogen or both depends on a patient's medical history and personal preference [11-13].

Similar to estrogen, progesterone can be administered via vaginal administration or intramuscular injection. Both routes of administration lead to adequate progesterone concentrations for preparing the endometrium [1]. However, vaginal progesterone may be the preferred route of administration [14]. Vaginal progesterone leads to a secretory endometrium that more closely resembles that of a natural cycle compared with intramuscular progesterone [15]. Vaginal progesterone administration is also associated with better patient adherence to medication [14]. Findings from a study of women undergoing IVF or controlled ovarian hyperstimulation (COH)/ intrauterine insemination (IUI) at 16 centers showed that 94% and 84% of women thought vaginal progesterone was easier and preferable, respectively, compared with intramuscular progesterone they had used in the past [14]. In addition, when acceptability was evaluated in women undergoing regular IVF, donor oocyte IVF, or COH/ IUI, 94% found vaginal progesterone very easy to administer and 75% found it not messy [14]. Moreover, intramuscular injections can be painful and can lead to serious adverse events [16]. Although rare, abscess formation at the injection site, hematoma formation, and persistent nodularity have been associated with intramuscular injections [16]. Therefore, progesterone administered via the vaginal route may be preferred over the intramuscular route. With respect to frozen cycles there is still a paucity of data among donor IVF cycles. Recently, Shapiro et al. [17] reported luteal support with vaginal progesterone gel or intramuscular results in comparable implantation and pregnancy rates in IVF patients receiving vitrified blastocyst. However, this data set was primarily autologous embryos; only 25 % of the embryos were derived from donor oocytes. Once again, our study independently validates for the first time these findings with respect to frozen donor IVF cycles.

This study is limited by its retrospective design and by its lack of randomization to the type of luteal support. In addition, because no a priori expected rates of success could be provided for this retrospective investigation, it was not possible to estimate statistical power with the various outcomes presented. The advantage of a regional ART center study is that patient selection criteria, laboratory results, and procedural techniques were consistent and in each case the same protocol was followed.

## Conclusions

In recipients participating in a contemporary donor oocyte program, preparing the endometrium with oral estradiol and vaginal progesterone is highly successful for pregnancy outcome, and not significantly different from utilizing oral estradiol with intramuscular and vaginal progesterone in fresh and frozen transfers. Future prospectively designed studies are warranted to add to the limited body of literature on the use of oral estradiol with vaginal progesterone in patients receiving oocyte donations.

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