The Role of Preparatory Cycles in Ovum Donation Recipients: A Retrospective Study¹

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Purpose: To determine whether preparatory cycles affect in vitro fertilization (IVF) outcome in ovum donation.

Methods: Medical records of 98 ovum donation recipients undergoing their first egg donation cycle were analyzed retrospectively. Preparatory cycles were performed in 50 patients with leuprolide acetate, estrogen, and progesterone. An endometrial biopsy was performed on day 10–12 of progesterone supplementation, to determine adequacy of the preparatory cycle.

Results: Pregnancy rates in women with and without preparatory cycles were 42.0% and 43.8%, respectively. Among ovum donation recipients who underwent preparatory cycles, the percentages of adequate endometrial biopsies in pregnant versus nonpregnant groups were 76.2% and 84.3%, respectively. No results showed statistical significance.

Conclusions: Preparatory cycles do not increase pregnancy rates in ovum donation recipients. In addition, no correlation was noted between adequate endometrial biopsies and higher pregnancy rates.

KEY WORDS: Assisted reproduction; egg donation; IVF; ovum donation; preparatory cycles.

INTRODUCTION

Oocyte donation has become a well-established method for treatment of infertility in women with or without ovarian function (1). Appropriate endometrial preparation with exogenous ovarian hormones prior to implantation as well as careful synchronization of both donor and recipient are crucial factors in achieving higher pregnancy rates (2).

To ensure proper endometrial development in the recipient, preparatory cycles often are performed before the actual egg donation cycle. The exact same protocol designed for the egg donation cycle is used

for the preparatory cycle, during which an endometrial biopsy is performed. Once adequate endometrial maturation is confirmed, the patient undergoes the egg donation cycle using the regimen tested in the preparatory cycle.

Recently, due to its noninvasiveness, ultrasonography has become popular as an alternative to endometrial biopsy (3). A few studies have already correlated ultrasonographic characteristics of the endometrium with either morphologic features of the biopsies or pregnancy outcome in ovum recipients (4–7). Hofmann *et al.* demonstrated that all women with endometrial thickness <7 mm had out-of-phase biopsies, whereas all women with ≥7 mm had in-phase biopsies (5). Another study found higher pregnancy rates in recipients with an endometrial thickness >7.5 mm compared with those with <7.5 mm and noted no pregnancies among women with an endometrial thickness <5 mm (7).

The purpose of our study was to determine whether or not preparatory cycles had a positive effect in pregnancy outcome for ovum donation recipients.

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MATERIALS AND METHODS

Medical records of ovum donation recipients undergoing their first egg donation cycle at Brigham and Women's Hospital (BWH) between January 1998 and September 2000 were analyzed retrospectively. This study was approved by the Partner's Healthcare System Human Research Committee for medical records review. Of the 118 patients initially reviewed, 20 were excluded from the study because their outcomes were associated with gestational carriers, cancelled cycles, or cycles in which all embryos were cryopreserved. Of the remaining 98 ovum recipients, 50 underwent preparatory cycles. The decision to undergo these cycles was made by the individual physicians. In general, physicians either utilized or did not utilize preparatory cycles. The main outcome measure was an ongoing pregnancy of at least 12 weeks or a live birth.

Preparatory cycles were carried out with leuprolide acetate (Lupron, TAP Pharmaceuticals, Deerfield, IL), estrogen, and progesterone. Typically, leuprolide acetate was begun in the mid-luteal phase, as determined by a day 21 serum progesterone level of ≥ 4 ng/mL or 7 days after a documented luteinizing hormone (LH) surge. After 10 days, the leuprolide dosage was halved, usually from 1.0 to 0.5 mg daily. If the serum estrogen and progesterone levels confirmed downregulation, estrogen was begun using patches (Estraderm, Vivelle, Novartis Pharmaceuticals, Summit, NJ) and Estrace pills (Bristol-Myers-Squibb, Princeton, NJ) and continued for 18–21 days. Administration of progesterone, either as an intramuscular injection, 50 mg daily, or as vaginal suppositories, typically 200 g three times daily, was then begun. An endometrial biopsy was performed on day 10–12 of progesterone supplementation following the course of estrogen. The first day of progesterone administration was normalized to cycle day 15. This length of progesterone exposure would therefore be expected to result in a day 25–27 endometrium ± 2 days (8). We considered a dating of day 23 endometrium to be the earliest acceptable preparatory cycle biopsy result based on these predictions. The endometrial stripe was measured by a transvaginal ultrasound on day 18–21 of estrogen therapy in 44 of 50 patients who underwent preparatory cycles. The decision to order an ultrasound was made by the individual physician.

In the actual synchronized egg donation cycle, the endometrium was prepared according to regimen found in an adequate preparatory cycle when applicable. Controlled ovarian stimulation of the donor consisted of leuprolide acetate for luteal downregu-

lation, purified FSH (Fertinex, Serono Laboratories, Norwell, MA) or recombinant FSH (Follistim, Organon, West Orange, NJ; or Gonaf, Serono Laboratories) for initial stimulation, and human chorionic gonadotropin (Profasi, Serono Laboratories) for triggering ovulation. Transvaginal oocyte retrieval was performed 36 h after hCG injection, and embryos were cultured 3 or 5 days prior to embryo transfer.

Clinical pregnancy was defined as an increase in serum hCG level with ultrasound confirmation of intrauterine gestation with normal fetal heart activity.

All data were analyzed by chi-square test. Statistical significance was set at $p < 0.05$. Results are reported as mean $\pm$ standard deviation of the mean.

RESULTS

Among women receiving oocyte donation, no statistical differences were observed between those who did and those who did not undergo a preparatory cycle, regardless of either the age of the donors (30.3 ± 4.3 years versus 30.8 ± 5.6 years, respectively) or the age of the recipients (40.5 ± 4.8 years versus 40.6 ± 4.6 years, respectively).

Among the study population, the pregnancy rates in women with and without preparatory cycles were 42.0% (21/50) and 43.8% (21/48), respectively ($p = \text{NS}$). In women who underwent preparatory cycles, the percentage of adequate endometrial biopsies in pregnant versus nonpregnant groups were 76.2% (16/21) and 86.2% (25/29), respectively ($p = \text{NS}$). In patients with endometrial stripes ≥ 7 mm by transvaginal ultrasound, 83.8% (26/31) of the biopsies were considered adequate; in those with stripes < 7 mm, 61.5% (8/13) were considered adequate ($p = \text{NS}$).

DISCUSSION

The main purpose of this study was to determine whether preparatory cycles had a positive effect on pregnancy outcome in women receiving donated eggs. Although the practice of performing preparatory cycles on ovum recipients is based on the assumption that confirmation of endometrial adequacy may result in improved pregnancy rates, we found no statistical difference in pregnancy outcome between patients with and without preparatory cycles.

Interestingly, our results also found no correlation between adequacy of the endometrial biopsies and

pregnancy rates. Although in some cases the initial preparatory cycle regimen may have been modified after the endometrial biopsy in an effort to improve pregnancy outcome, biopsy with or without protocol changes did not affect outcome overall. Initial studies of egg donation have shown a correlation between histologic integrity and functional capacity (1,9). Younis *et al.*, however, have noted that endometrial receptivity is not always demonstrated by appropriate morphologic findings (10). Several explanations for these inconsistencies have been offered. Endometrial biopsies are often difficult to date. Some areas of the endometrium may have responded well to the exogenous hormones, whereas others may have not, depending on the biopsy. In addition, varying locations within the endometrium may have been sampled (11). Last, inter-observer variation of 22–39% in dating endometrial samples has been noted (12).

Our study also showed no significant association between histologic findings and endometrial thickness in women who underwent both biopsy and ultrasound. In ovum donation, an endometrial thickness ≥ 7 mm is usually considered adequate for implantation (3,10,13). Endometrial thickness as a predictor of pregnancy in ovum recipients is still controversial. Although some studies have correlated adequate endometrial thickness with successful pregnancy outcome (3,10), others have failed to do so (14,15), highlighting the need for more sensitive methods to detect uterine receptivity. Preliminary reports assessing serum estradiol concentrations (16), endometrial integrins (17), and ultrasonography measuring blood pattern and flow (6) all hold promise in this regard.

To our knowledge, no studies to date have examined the role of preparatory cycles in ovum recipients. Our results failed to demonstrate higher pregnancy rates in women who underwent preparatory cycles. However, the findings of this study may have been limited by some or all of the following: 1) the retrospective nature of the study; 2) small sample size resulting in a low power of 14.9%; 3) variability in endometrial dating and measurement of endometrial thickness; and 4) differences in embryo quality.

In addition, the results as described depend on appropriate dating of the endometrium and on endometrial measurements. There is known observer variation among pathologists who interpret endometrial biopsies, and known observer variation among ultrasonographers who measure endometrial thickness. These differences could have influenced the results.

In conclusion, this small retrospective study found no evidence that preparatory cycles in ovum donation

recipients improve pregnancy rates. A definitive conclusion, however, must await the result of larger randomized studies.

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