Original Article

Efficacy of Combined Contraceptive Vaginal Ring Versus Oral Contraceptive Pills in Achieving Hypothalamic-Pituitary-Ovarian Axis Suppression in Egg Donor *In Vitro* Fertilization Cycles

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Abstract

Background: Our study compares the efficacy of the combined contraceptive vaginal ring to oral contraceptive pills (OCPs) for hypothalamic-pituitary-ovarian (HPO) axis suppression in egg donor *in vitro* fertilization (IVF) cycles.

Methods: Our retrospective cohort study includes patients from the Center for Assisted Reproduction (CARE) in Bedford, Texas undergoing IVF cycles as egg donors from January 2003 through December 2009. Twenty-five and thirty-nine women were treated with OCPs and the combined contraceptive vaginal ring, respectively. Statistical analyses were performed using the SigmaStat Software package (Systat, Chicago, IL). Data were analyzed by t or Mann-whitney test and Chi-square of Fisher exact test. Statistical significance was set at $p<0.05$.

Results: Prior to gonadotropin initiation, endometrial thickness and serum estradiol were 5.6±2.6 *mm* and 33.6±19.9 *pg/ml* in the OCP group and 6.0±2.4 *mm* and 36.6±24.3 *pg/ml* in the combined contraceptive vaginal ring group, respectively (p=0.49 and p=0.33). Average serum FSH and LH were 1.7±1.9 and 1.7±2.5 *mIU/ml* in the OCP group and 1.7±1.6 and 1.2±1.4 *mIU/ml* in the combined contraceptive vaginal ring group, respectively (p=0.45 and p=0.95). No significant differences were found for gonadotropin requirement, peak estradiol, maximal endometrial thickness, number of oocytes retrieved, number of normally fertilized embryos, number of cryopreserved embryos, or live birth rates.

Conclusion: The combined contraceptive vaginal ring is effective for HPO axis suppression in egg donor IVF cycles and associated with cycle characteristics similar to those observed with OCP treatment. The combined contraceptive vaginal ring may provide an important advantage over OCPs due to improved patient compliance.

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Introduction

Coordinating egg donor *in vitro* fertilization (IVF) cycles with their recipients is vital to a successful reproductive outcome. Synchronization of the donor and recipient menstrual cycles has historically been accomplished with the use of various formulations of combined oral contraceptive pills (OCPs) (1, 2). However, this strategy relies on the donor's responsibility to remember daily administration of pills.

Each year, more than three million women in the United States experience an unintended pregnancy, and almost half occur in women who reported

using contraception (3). Although OCPs are one of the most widely used contraceptive methods, patients experience difficulty in proper use of this medication. More than one million unintended pregnancies result from OCP method failure, misuse, and discontinuation (4). In addition, the largest number of these unintended pregnancies occur among women aged 20 to 24 years (3). For these reasons, a longer lasting contraception that may be administered in the office setting, such as the combined hormonal contraceptive vaginal ring, may be more optimal for the young egg donor population as it may take several months to prepare for and coordinate donor and recipient treatment cycles.

Large-scale studies have previously demonstrated the efficacy, tolerability, and acceptability of the combined contraceptive vaginal ring, and reliable cycle control with a low daily dose of ethinyl estradiol (5–9). Several studies have suggested that cycle control with the combined contraceptive vaginal ring was superior to that with a combined OCP (10–12). This attribute may be the result of local hormone administration and concentrations or stable hormone levels from continuous dosing. Large efficacy trials have also shown that the ring is comparable with other combined hormonal contraceptive methods, with pregnancy rates less than one percent (5–7). However, the ability of the combined contraceptive vaginal ring to obtain sufficient hypothalamic-pituitary-ovarian (HPO) axis suppression for IVF cycle synchronization with egg donor recipients has not been previously described.

The objectives of this study were to evaluate the effects of the combined contraceptive vaginal ring on HPO axis suppression in egg donation IVF cycles as assessed by vaginal ultrasound imaging and serum gonadotropin levels. Reproductive outcomes of the egg donation IVF cycles, including live birth rates, were also studied.

Methods

We conducted a retrospective cohort study of all patients from the Center for Assisted Reproduction (CARE) in Bedford, Texas undergoing *in vitro* fertilization cycles as egg donors from January 1st, 2003 through December 31st, 2009. This time frame was chosen because CARE transitioned from using combined OCPs to combined contraceptive vaginal ring for egg donor IVF cycles in 2006. Ninety-nine women participated in initial cycles as egg donors during the seven year time period, and all of these women were considered for our study in an effort to reduce selection bias. Eight women were excluded from the study due to IVF monitoring outside of our facility. An additional two women were excluded because they were treated with the Ortho Evra patch (Janssen, Antwerp, Belgium) and intramuscular depot provera prior to initiation of gonadotropins. Of the remaining 89 patients, 45 women were treated with the combined contraceptive vaginal ring (NuvaRing; Merck, New Jersey, U.S.) and 44 women received various combined OCPs prior to the initiation of gonadotropins. Unfortunately, archived serum samples were unavailable for six of the women using the combined contraceptive vaginal ring and 19 women using the combined OCPs. Archived serum samples prior to 2003 were also largely unavailable. Therefore, 39 women who received the combined contraceptive vaginal ring and 25 women who received combined OCPs were included in the study. Institutional Review Board approval at the University of Texas Southwestern Medical Center was obtained for our research study.

Combined OCPs administered to the patients included the following: desogestrel 0.15 *mg/ethinyl* estradiol 0.03 *mg*, desogestrel 0.15 *mg/ethinyl* estradiol 0.02 *mg*, desogestrel 0.15 *mg/ethinyl* estradiol 0.03 *mg*, ethynodiol diacetate 1 *mg/ethinyl* estradiol 0.035 *mg*, drospirenone 3 *mg/ethinyl* estradiol 0.03 *mg*, norgestimate 0.25 *mg/ethinyl* estradiol 0.035 *mg* and norethindrone 1 *mg/ethinyl* estradiol 0.05 *mg*. Only the combined OCPs with active medication were taken in preparation for the IVF process.

The combined contraceptive vaginal ring administered in the office was the NuvaRing (Merck, New Jersey, U.S.). NuvaRing is a flexible vaginal ring with an outer diameter of 54 *mm* and a cross-section of 4 *mm*. The ring releases 120 μg of etonogestrel and 15 μg of ethinyl estradiol per day, and insertion should occur between day one and five of the menstrual cycle. The contraceptive ring is designed for use during one cycle, comprising a three week period of continuous use followed by a one week ring-free period. Therefore, when necessary, a new vaginal ring was administered every three weeks in the women using the combined contraceptive vaginal ring of this study.

Egg donors participated in a gonadotropin releasing hormone (GnRH) antagonist IVF protocol. The combined contraceptive vaginal ring or combined OCPs were used for a minimum of two

weeks until the day prior to gonadotropin initiation. The gonadotropin medications used during the treatment cycles included follitropin beta injection (Follistim; Merck, New Jersey, U.S.), follitropin alpha injection (Gonal-f; EMD Serono, Geneva, Switzerland), and/or menotropins for injection (Menopur; Ferring, Saint-Prex, Switzerland). Ultrasonographic and laboratory evaluation was conducted at the CARE, and all decisions were made by three senior physicians. Final follicle maturation was triggered with either hCG (Novarel; Ferring, Saint-Prex, Switzerland) or a GnRH agonist (Lupron; Abbott, Illinois, U.S.). Ultrasound-guided oocyte retrievals were performed under anesthesia approximately 36 *hr* following Novarel or Lupron administration. Embryo transfers were performed under ultrasound guidance using day 5 blastocysts. Although the majority of embryos were cyropreserved on day 5, cryopreservation of the remaining embryos was performed on days 5 through 7.

The electronic medical record at the CARE was utilized to obtain the majority of data for the study, including history and physical exams, ultrasound reports, laboratory reports, and IVF flowsheets. Previously stored blood samples drawn prior to gonadotropin initiation were analyzed onsite at the CARE for evaluating serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels.

Statistical analyses were performed using the SigmaStat Software package (Systat, Chicago, IL). Numerical data were analyzed for normality followed by either the t-test or Mann-Whitney test, and categorical data were analyzed using either the chi-square test or Fisher's exact test. Statistical significance was set at $p<0.05$.

Results

Patient characteristics, including age, parity, race, body mass index, menstrual cycle length, and ovarian volume on ultrasound, were compared between the combined contraceptive vaginal ring and combined OCP groups (Table 1). There were no significant differences among any of the patient characteristics.

Prior to gonadotropin initiation, the endometrial thickness and serum estradiol were 5.6±2.6 *mm* and 33.6±19.9 *pg/ml* in the OCP group and 6.0±2.4 *mm* and 36.6±24.3 *pg/ml* in the combined contraceptive vaginal ring group, respectively (p=0.49 and p=0.33). Average serum FSH and LH were 1.7±1.9 and 1.7±2.5 *mIU/ml* in the OCP group and 1.7±1.6 and 1.2±1.4 *mIU/ml* in the combined contraceptive vaginal ring group, respectively (p=0.45 and p=0.95). No significant differences were found for gonadotropin requirement, peak estradiol, maximal endometrial thickness, number of oocytes retrieved, number of normally fertilized embryos, or number of cryopreserved embryos (Table 2). The average numbers of embryos transferred to the egg donor recipients during the fresh IVF cycle were 1.8±0.4 and 1.9±0.4 (p=0.31) in the OCP group and combined contraceptive vaginal ring group, respectively.

Table 1. Patient characteristics for comparing two methods of HPO axis suppression in egg donation IVF cycles

	OCP	Contraceptive vaginal ring	p-value
Patients (*n*)	25	39	
Age (years) *	25.5±3.7	25.0±3.1	0.82
Parity (median, range)	1 (0-3)	1 (0-4)	0.64
Race (*n, %*)			
Caucasian	17 (68%)	24 (62%)	0.80
African American	3 (12%)	7 (18%)	0.73
Hispanic	4 (16%)	8 (21%)	0.75
Asian	1 (4%)	0 (0%)	0.39
Body mass index (kg/m^2) *	24.7±4.1	23.7±3.8	0.36
Menstrual cycle length (days) *	29.0±3.7	28.6±2.5	0.90
Ovarian volume (*ml*) *			
Right ovary	7.5±4.0	7.3±3.9	0.74
Left ovary	6.9±5.1	6.4±2.6	0.80

* Mean±SD

Table 2. IVF cycle data of women in comparing two methods of HPO axis suppression in egg donation IVF cycles

	OCP (M±SD)	Contraceptive vaginal ring (M±SD)	p-value
Baseline endometrial thickness (*mm*)	5.6±2.6	6.0±2.4	0.49
Baseline FSH level (*mIU/ml*)	1.7±1.9	1.7±1.6	0.45
Baseline LH level (*mIU/ml*)	1.7±2.5	1.2±1.4	0.95
Baseline estradiol level (*pg/ml*)	33.6±19.9	36.6±24.3	0.33
Maximal endometrial thickness (*mm*)	10.7±1.9	11.1±2.5	0.49
Peak estradiol level (*pg/ml*)	2627.2± 1071.1	3079.9±1710.0	0.41
Total gondotropin dosage (*IU*)	2279.0±1037.4	1855.3±739.1	0.06
Oocytes (*n*)	17.4±8.2	16.9±8.2	0.63
2PN (*n*)	10.2±4.8	11.4±7.4	0.98
Cryopreserved embryos (*n*)	3.9±3.8	5.3±5.1	0.28
Embryos transferred (*n*)	1.8±0.4	1.9±0.4	0.31

Table 3. Pregnancy outcomes in donor recipients from fresh IVF cycles

	OCP	Contraceptive vaginal ring	p-value
Not pregnant (*n, %*)	9 (36%)	11 (28%)	0.70
Missed abortion (*n, %*)	1 (4%)	3 (8%)	1.00
Biochemical pregnancy (*n, %*)	2 (8%)	2 (5%)	0.64
Ectopic pregnancy (*n, %*)	0 (0%)	0 (0%)	1.00
Singleton pregnancy (*n, %*)	9 (36%)	5 (13%)	0.06
Twin pregnancy (*n, %*)	4 (16%)	16 (41%)	0.07
Triplet pregnancy (*n, %*)	0 (0%)	1 (3%)	1.00
Live births (*n*)	13	22	0.93

Pregnancy outcomes in the egg donor recipients from fresh IVF cycles are shown in table 3. There were no significant differences for any of the pregnancy outcomes, including live birth rates, between the OCP group and combined contraceptive vaginal group.

Discussion

The combined contraceptive vaginal ring has been shown to produce mean serum ethinyl estradiol concentrations of 19 *pg/ml* and maximum serum concentrations of 35 *pg/ml* (13). Pharmacokinetic evaluation revealed that after reaching maximum serum concentrations of etonogestrel and ethinyl estradiol, levels decreased linearly over time, in contrast to daily peaks of the combined OCP (13). The maximum serum concentrations of etonogestrel and ethinyl estradiol were approximately 40 and 30 μg, respectively, compared to the levels with a combined OCP containing 150 μg desogestrel and 30 μg ethinyl estradiol (13). Exposure to ethinyl estradiol from the combined contraceptive vaginal ring was on average 2.1 times lower than those using combined OCPs containing 150 μg levonorgestrel and 30 μg ethinyl estradiol (14). Variations in individual serum ethinyl estradiol levels were far greater with either the combined OCP compared to the combined contraceptive vaginal ring (14). A number of other studies have reported similar pharmacokinetic results (13, 15, 16) Treatment with the combined contraceptive vaginal ring or combined OCP containing 150 μg desogestrel and 20 μg ethinyl estradiol resulted in comparable tissue concentrations of ethinyl estradiol and etonogestrel in samples from the upper myometrium, mid myometrium, and cervical region of the uterus; however, the combined contraceptive vaginal ring group showed lower concentrations of both hormones in the endometrium (17). Therefore, the combined contraceptive vaginal ring is not associated with elevated uterine concentrations of ethinyl estradiol or etonogestrel compared with a combined OCP (17). Overall, differences exist between the phar-

macokinetics of the combined contraceptive vaginal ring and combined OCPs which could potentially result in variations between their treatment outcomes.

The combined contraceptive vaginal ring has consistently been shown to have good cycle control in several large studies (5, 7, 10, 11). Furthermore, cycle control with the combined vaginal contraceptive ring has been shown to be superior to that with a combined OCP containing 30 *μg* ethinyl estradiol and 150 *μg* levonorgestrel (10, 11) or 3 *mg* drospirenone (12). The incidence of irregular bleeding with the combined contraceptive vaginal ring is approximately five percent in all cycles (5, 7, 8, 10). With combined OCPs, 15 *μg/day* dosage of ethinyl estradiol results in irregular bleeding in approximately 29 percent of women during the initial six cycles (18, 19). Continuous vaginal ring use also resulted in an acceptable bleeding profile in most patients with a reduction in flow, a reduction in pelvic pain, and a high continuation rate (20). The good cycle control achieved with the combined contraceptive vaginal ring may be the result of the continuous release of steroids from the ring, avoiding daily fluctuations in the hormone levels.

Ovarian suppression achieved with the combined contraceptive vaginal ring is comparable to that observed with low-dose combined OCPs (21). During the normal three week period of use, the combined contraceptive vaginal ring completely inhibited ovulation as assessed by vaginal ultrasound and serum concentrations of FSH, 17β estradiol, LH, and progesterone (21). Extending its use for an additional two weeks did not compromise ovarian suppression and inhibition of ovulation was maintained (21). Irrespective of the length of a second cycle with the combined contraceptive vaginal ring (three weeks versus three days), a new cohort of follicles needed to be recruited and the time to ovulation after ring removal was similar (19 versus 17 days) (22). The median time needed to develop a 13 *mm* follicle was 11 days, and none of these women ovulated after insertion of a second contraceptive ring (22). Therefore, ovulation, at least until the stage of a 13 *mm* follicle, is prevented and as little as three consecutive days of combined contraceptive vaginal ring use interferes with follicle growth (22). In contrast, the generally acknowledged requirement for combined oral contraceptive pills to suppress the HPO axis is seven days (23). Although, in comparing the first cycle of combined contraceptive vaginal ring to combined OCPs, there was a tendency towards slightly higher maximum follicular diameters, FSH, and LH levels in the combined contraceptive vaginal ring group (24). However, the observed difference could be due to chance, differences in pharmacokinetic parameters, or differences in the timing of initiation (combined contraceptive vaginal rings were inserted on cycle day five and combined OCPs were initiated on cycle day one of menses) (24). Women with shorter cycles and early ovulations in the pretreatment cycle developed larger follicles during treatment with the combined contraceptive vaginal ring compared to those with longer cycles and late ovulations (25). Overall, the combined contraceptive vaginal ring is a very effective and reversible method of hormonal contraception for women.

Combined contraceptive vaginal ring users experience many of the same side effects commonly described with the use of other combined hormonal contraceptives (26, 27); however, the combined contraceptive vaginal ring has higher incidences of vaginal discomfort, vaginitis, and ring-related events (5, 7, 10, 28). Although, a high level of user and partner acceptability for the combined contraceptive vaginal ring has been reported (5, 7, 29-32). 96 percent of women using the combined contraceptive vaginal ring for 13 consecutive cycles were satisfied with their method of contraception (29). Reasons for liking the combined contraceptive vaginal ring included not having "to remember anything" and ease of use (17, 29). A one-year, open-label, randomized controlled trial compared the safety of the combined contraceptive vaginal ring with a combined oral contraceptive containing 30 *μg* ethinyl estradiol and 150 *μg* levonorgestrel 6 or 3 *mg* drospirenone (9). These studies demonstrated that the combined contraceptive vaginal ring exhibits tolerability and safety equivalent to that of an oral contraceptive (6, 9).

Our study is a retrospective study and the disadvantages include selection bias and information bias as well as the reliance on accurate record-keeping. It would be beneficial to pursue a prospective study in the future. However, in an effort to minimize potential bias, all women were considered for inclusion in the study during the specified timeline and any exclusion was clearly defined. In addition, the electronic medical record at the CARE assisted in the retrieval of patient data. Another disadvantage to our study is the transition

from the use of combined OCPs to the combined contraceptive vaginal ring in egg donor IVF cycles. Clinical and laboratory protocols continuously evolve over time, and this could potentially alter the outcomes studied.

Conclusion

Effective contraception is important in preventing unplanned pregnancy in the selected egg donors preparing for the process of IVF. Overall, studies have demonstrated that use of the combined contraceptive vaginal ring successfully inhibits ovulation with a good safety profile and high levels of patient satisfaction. However, there is a paucity of information regarding the utility of this contraceptive in achieving HPO axis suppression in egg donation IVF cycles. As assessed by transvaginal ultrasound and serum gonadotropin levels, we have now demonstrated that the combined contraceptive vaginal ring blunts activity of the HPO axis to a degree that is comparable to the use of OCPs in egg donation cycles. In addition, both methods of contraception are associated with similar reproductive outcomes in IVF cycles, including live birth rates. Thus, our data suggest that synchronization of the egg donor and embryo recipient cycles can be achieved effectively with either mode of hormonal delivery. Nevertheless, the combined contraceptive vaginal ring provides a substantial benefit as it may be placed in the office and, therefore, does not depend on reliable daily self-administration of pills. Improving compliance with medications during egg donation IVF cycles facilitates optimal outcomes for the recipients.

Conflict of Interest

The authors declare that they have no conflict of interest.

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