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Matched-pairs analysis of ovarian suppression during oral versus vaginal hormonal contraceptive use

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Abstract

Background—This study was conducted to compare ovarian suppression during oral versus vaginal hormonal contraceptive use. Secondary aims included comparison of endometrial thickness and bleeding patterns.

Methods—In two open-label trials assessing ovarian suppression, 33 compliant women completed both studies. They first used OCs [randomized to either 20 mcg ethinyl estradiol (EE)/100 mcg levonorgestrel (LNG) or 30 mcg EE/150 mcg LNG] and subsequently used contraceptive vaginal rings (CVR) (daily release of 15 mcg EE/120 mcg etonogestrel), all 21/7 day regimens. Participants had at least one run-in cycle using each contraceptive method prior to evaluation. During one cycle of each method, women underwent bi-weekly transvaginal sonography to measure ovarian follicular diameters and endometrial thickness. We also noted presence of a corpus luteum or a ruptured follicle as a marker of ovulation. Participants recorded bleeding days on paper calendars. We used matched pairs analyses as appropriate.

Results—During follow-up, we identified at least one ovarian follicle ≥ 8 mm in 20/33 (61%) OC users and 12/33 (36%) CVR users (matched pairs analysis, $p=0.02$). Similar trends were seen for larger follicles; however we had limited statistical power to evaluate these differences. Median follicular diameter among OC users was larger than median follicular diameter among CVR users ($p=0.01$). We did not observe a corpus luteum or ruptured follicle in any participant during either study. Endometrial thickness was similar during OC and CVR use (mean 4.1 ± 1.4 mm versus 4.1 ± 1.6 mm, $p=0.9$) as was the number of bleeding or spotting days (mean 2.1 ± 2.4 versus 1.9 ± 2.1 , $p=0.8$). OC dose was unrelated to follicle diameter, endometrial thickness, or bleeding.

Conclusions—Ovarian follicles ≥ 8 mm were more common in 33 compliant women during OC use than during CVR use indicating CVR use results in greater ovarian suppression than OC use.

Keywords

NuvaRing®; Oral Contraception; Ovarian Suppression

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1. Introduction

Oral contraceptive pills (OCs) are effective and popular; to be most effective women must take the pill every day. A recent randomized control study by Hou et al. found that missing multiple pills per cycle is common [1]. An alternative method of hormonal contraception is the NuvaRing®, a vaginal ring with an outer diameter of 54 mm and a cross-sectional diameter of 4mm that releases 120 mcg of etonogestrel and 15 mcg of ethinyl estradiol daily. Conventional use of the contraceptive vaginal ring (CVR), as described in the product label, is insertion into the vagina for three weeks of continuous use followed by removal for a ring-free week. This method requires less user action than daily combined oral contraceptive use.

The CVR is highly effective in terms of ovarian suppression [2–4] and cycle control [5–9] and has high acceptability among users [7–9]. Most studies comparing CVR to OCs focused on evaluation of cycle control through bleeding and spotting diaries kept by participants [6, 9, 10] with little emphasis on comparative pharmacodynamic research [11].

The aim of this analysis was to compare ovarian suppression in compliant women during OC and CVR use. Our study design allowed us to compare ovarian suppression in a group of women who used both of these methods and in whom we measured compliance. Secondary aims included comparisons of endometrial thickness and bleeding patterns.

2. Patients and methods

Women were eligible for this analysis if they completed two clinical trials, the first evaluating follicular development during OC use and the second evaluating follicular development during CVR use.

Participant-related activities for the first clinical trial were conducted between July 2006 and December 2008 in New York City at the Columbia University Medical Center Division of Family Planning and Preventive Services. The Columbia University Institutional Review Board approved the study and all participants gave informed consent. In brief, eligible women were aged 18–35 years with a history of regular, spontaneous menstrual cycles who were either normal weight or obese. Eligible women had normal-appearing ovaries at baseline sonogram. We only enrolled women who were in the World Health Organization Medical Eligibility for Contraceptive Use Category 1 [12]. We randomly assigned participants to one of two OC formulations, either 30 mcg ethinyl estradiol (EE) and 150 mcg levonogestrel (LNG) or 20 mcg EE and 100 mcg LNG (both 21/7 day formulations). Randomization was done with a 1:1 treatment allocation using a random-number table constrained by the use of randomly permuted blocks. Participants completed at least two OC cycles before the study cycle. During the study cycle, women underwent biweekly vaginal sonograms. Follicles were measured in two perpendicular diameters using a Sonosite Titan with a 7.5 MHz transvaginal probe (from Sonosite in Bothell, Washington). We recorded all follicles with dimensions greater than or equal to 8 mm. We also noted presence of a corpus luteum or a ruptured follicle and we measured the anterior-posterior endometrial thickness. Participants maintained daily bleeding and spotting diaries throughout the study. We evaluated OC compliance by measuring LNG levels at each visit during the study cycle. More detailed methods of this study are published elsewhere [13].

One hundred eighty-one women completed the OC trial. We invited 40 of these women to participate in a second trial evaluating ovarian suppression during use of CVR. Of these 40 women 20 were obese and 20 were overweight; 17 had received the 20 mcg EE/100 mcg LNG OC and 23 had received the 30 mcg EE/150 mcg LNG OC. Participant-related activities for the CVR clinical trial were conducted between June 2008 and December 2008

in New York City at the Columbia University Medical Center Division of Family Planning and Preventive Services. The Columbia University Institutional Review Board approved the study and all participants gave informed consent. In brief, we distributed two CVRs to each participant at the enrollment visit. Participants inserted the first CVR and used it for 3 weeks inside the vagina followed by a ring-free week. Insertion of the second CVR marked day 1 of the study cycle and was used continuously in the vagina. The research coordinator confirmed insertion and removal of each CVR by phone and gave participants reminders before their scheduled insertion of the second ring. Investigators verified presence of the CVR at each biweekly sonogram as a compliance check. The study methods were similar to the OC trial previously described [2].

The primary measure of ovarian suppression in this analysis was the largest follicular diameter during any study sonogram of each participant [3, 4, 11]. We used the mean of two perpendicular diameters; we did not record these measurements for any follicular diameter less than 8 mm. We then calculated the proportion of women who had any follicle with a diameter ≥ 8 mm as well as other prespecified thresholds (10 mm, 13 mm, and 18 mm) selected from the literature [14–19]. We used the sign test to determine the direction of the difference between maximum follicular diameter [20]. We used McNemar's matched pairs analysis to compare follicle suppression within each woman during OC and CVR use [20].

We measured endometrial thickness and the total number of bleeding or spotting days throughout the study and compared these during OC and CVR use. We used paired t-tests to compare these variables.

3. Results

One hundred eighty-one women completed the OC trial; we invited 40 of these women to participate in the second CVR trial. Of these 40 women 20 were obese and 20 were overweight; 17 had received the 20 mcg EE/100 mcg LNG OC and 23 had received the 30 mcg EE/150 mcg LNG OC. Of the 40 women we enrolled for the second (CVR) trial, two discontinued before the CVR study cycle (one due to a motor vehicle accident and one due to a venous thromboembolism), and we excluded five from final analysis after compliance assays revealed they had been inconsistent OC users. The two women who discontinued before the CVR study cycle for medical reasons were both normal weight and had received the 20 mcg EE/100 mcg LNG OC. Among the inconsistent OC users, one was normal weight and four were obese; two had received the 20 mcg EE/100 mcg LNG OC and three the 30 mcg EE/150 mcg LNG OC. Therefore, these analyses include 16 obese women and 17 normal weight women; 13 of these women had received the 20 mcg EE/100 mcg LNG OC and 20 women had received the 30 mcg EE/150 mcg LNG OC. Baseline characteristics of the 33 women who completed both studies and were included in this analysis are presented in Table 1.

Having at least one ovarian follicle ≥ 8 mm in any of the biweekly sonograms for the two study cycles was relatively common in both trials. The proportion of OC users with at least one ovarian follicle ≥ 8 mm was 20/33 (61%) compared to 12/33 (36%) of CVR users ($p=0.02$). In a matched pairs analysis follicles at least 8 mm were more common in women while using OC than in the same women while using the CVR ($p=0.02$, Table 2). Similar trends were seen at other prespecified thresholds of 10 mm, 13 mm, and 18 mm with more women using OC consistently having at least one follicle measuring at or above the prespecified thresholds than the same women while using CVR ($p=0.5$, 0.1, and 0.2 respectively); however, we had limited statistical power to evaluate these differences (Table 3).

Because we did not record follicular diameters measuring less than 8 mm, we could not compare mean follicular diameters. Therefore, we compared the median maximum follicular diameter for women while using OC and the same women while using the CVR. We found substantial differences such that the median follicular diameter during OC use was greater than during CVR use ($p=0.01$). We did not observe a corpus luteum or ruptured follicle in any participant during either study.

We also conducted a stratified matched pairs analysis of the 17 normal weight women and the 16 obese women, to evaluate if the differences in follicle suppression were limited to one group. In both normal weight and obese women, follicles at least 8 mm in diameter were more common in women while using OC than in the same women while using CVR. This trend was also observed at the other prespecified thresholds of 10 mm, 13 mm, and 18 mm for the separate stratified analysis (data not shown).

Endometrial thickness was similar during OC and vaginal ring use (mean 4.1 ± 1.4 mm versus 4.1 ± 1.6 mm, $p=0.9$) as was the number of bleeding or spotting days (mean 2.1 ± 2.4 versus 1.9 ± 2.1 , $p=0.8$). We counted both schedule and unscheduled bleeding or spotting days and nearly all were scheduled. Results for follicular diameter, endometrial thickness, and bleeding or spotting days did not differ after stratification by OC dose or age.

4. Discussion

This analysis compared follicle suppression during OC and CVR use in the same women, all during 21/7 day regimens. Our results indicate that in compliant users, the CVR is associated with greater follicular suppression than an OC even though this CVR has a lower EE dose than the OCs used in this study. Follicle development during hormonal contraceptive use is a necessary, although not sufficient, precedent of contraceptive failure. According to Spona, follicle development during oral contraceptive use can lead to breakthrough ovulations potentially lessening the reliability of oral contraceptives [21–22]. As described by others, less follicle suppression in women using 21/7 day formulations may result in contraceptive failure [23–24].

A recent study by Hou et al. [1] found that when using an electronic monitoring device to measure pill compliance 57% of women missed an average of 3 pills or more per cycle. Further, Hou et al. [1] found that even when given daily reminders to take their OC (through text message reminders) women in the study still missed an average of 4.7 pills per cycle. In the original OC study from which we recruited the participants in this study, 17% of women were inconsistent OC users based on multiple serum measurements of the OC hormones [13]. Inconsistent OC use is prevalent, and for these inconsistent OC users, a simpler method of contraception such as CVR may be more effective in preventing unwanted pregnancy. We are not, however, aware of any data evaluating whether inconsistent OC users use CVR more consistently.

Oral contraceptive formulations containing a progestin with a longer half life have lower failure rates than formulations containing a progestin with a shorter half life [25]. The half life of LNG (the progestin in our OC formulation) is 17 hours [26] and the half life of etonogestrel (the progestin in the CVR) is 30 hours [27]. Along with less follicular development with CVR use that we report here, the longer half life of ENG may give additional contraceptive protection to women using the CVR.

Our results are compatible with previous studies finding CVR to be highly effective in suppressing follicle growth. A recent study conducted in the Netherlands considered differences in follicular diameter between 19 OC users and 21 CVR users [11]. During the second cycle they found no difference in the geometric mean of maximum follicular

diameter (defined as the largest follicular diameter measured during a treatment cycle) between the two groups when using an analysis of variance. The authors concluded ovarian suppression was comparable between CVR and OC; but that study did not state how they assessed compliance. Because our study compared follicular development in the same women, and assessed method compliance throughout the study cycles, we provide a more powerful and novel analysis.

The reported failure rates of OC and CVR are similar in both clinical trials and typical use. Mansour reports that the Pearl Index for perfect CVR use ranges up to 1.0 and typical use up to 1.2 per 100 woman years [28]. For OC, Mansour reports that the Pearl Index for perfect use ranges up to 1.3 and typical use up to 1.8 per 100 woman years [28]. However, data from the National Survey of Family Growth in the U.S. indicate that oral contraceptive failure rates may be as high as 8% per 100 woman years during the first 12 months of use [29]. There was insufficient data on typical use of CVR in this survey to determine the failure rates for typical CVR use in the United States [29]. For women who typically remember to take their OC pill daily, OC is an effective option. CVR is similarly effective and as previously discussed requires less daily user action. Thus, clinicians can assure women who have difficulty remembering to take their OC daily (beyond what would be considered typical use) or would prefer a less intensive regimen that the CVR will provide greater ovarian suppression than an OC and be highly effective in preventing pregnancy.

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References

1. Hou MY, Hurwitz S, Kavanagh E, Fortin J, Goldberg AB. Using daily text-message reminders to improve adherence with oral contraceptives: A randomized controlled trial. *Am J Obstet and Gynecol.* 2010; 116:633–640.
2. Torgal A, Mayeda E, Dragoman M, Linker D, Westhoff C. Ovarian follicular development during extended use of NuvaRing® in normal weight and obese women. *Contraception.* 2010; 82:199.
3. Mulders T, Dieben T. Use of the novel combined contraceptive vaginal ring NuvaRing® for ovulation inhibition. *Fertil Steril.* 2001; 75:865–870. [PubMed: 11334895]
4. Mulders T, Dieben T, Bennink H. Ovarian function with a novel combined contraceptive vaginal ring. *Hum Reprod.* 2002; 17:2594–2599. [PubMed: 12351535]
5. Dieben T, Roumen J, Apter D. Efficacy, cycle control, and user acceptability of a novel combined contraceptive vaginal ring. *Am J Obstet Gynecol.* 2002; 100:585–593.
6. Brache V, Faundes A. Contraceptive vaginal rings: a review. *Contraception.* 2010; 82:418–427. [PubMed: 20933115]
7. Novak A, Loge C, Abetz L, Van der Meulen E. The combined contraceptive vaginal ring, NuvaRing®: and international study of user acceptability. *Contraception.* 2002; 67:187–194. [PubMed: 12618252]
8. Brucker C, Karck U, Merkle E. Cycle control, tolerability, efficacy and acceptability of the vaginal contraceptive ring, NuvaRing®: results of clinical experience in Germany. *Eur J of Contracept Reprod Health Care.* 2008; 13:31–38. [PubMed: 17853162]
9. Roumen F. The contraceptive vaginal ring compared with the combined oral contraceptive pill: a comprehensive review of randomized controlled trials. *Contraception.* 2007; 75:420–429. [PubMed: 17519147]
10. Bjarnadottir R, Tuppurainen M, Killick S. Comparison of cycle control with a combined contraceptive vaginal ring and oral levonorgestrel/ethinyl estradiol. *Am J Obstet Gynecol.* 2002; 186:389–395. [PubMed: 11904596]

11. Duijkers I, Klipping C, Verhoeven C, Dieben T. Ovarian function with the contraceptive vaginal ring or an oral contraceptive: a randomized study. *Hum Reprod.* 2004; 19:2668–2673. [PubMed: 15333593]
12. World Health Organization Department of Reproductive Health and Research. Medical eligibility criteria for contraceptive use. 3rd edition. Geneva (Switzerland): World Health Organization; 2004.
13. Westhoff CL, Torgal AH, Mayeda ER, et al. Ovarian suppression in normal-weight and obese women during oral contraceptive use. *Obstet Gynecol.* 2010; 116:275–283. [PubMed: 20664386]
14. Broome M, Clayton J, Fotherby K. Enlarged follicles in women using oral contraceptives. *Contraception.* 1995; 52:13–16. [PubMed: 8521709]
15. Hoogland HJ, Skouby SO. Ultrasound evaluation of ovarian activity under oral contraceptives. *Contraception.* 1993; 83:29–34.
16. Grimes DA, Goodwin AJ, Rubin A, Smith JA, Lacarra M. Ovulation and follicular development associated with three low-dose oral contraceptives: a randomized controlled trial. *Obstet Gynecol.* 1994; 83:29–34. [PubMed: 8272303]
17. Endrikat J, Gerlinger C, Plettig K, Wessel J, Schmidt W, Grubb G, Dusterberg B. A meta-analysis on the correlation between ovarian activity and the incidence of intermenstrual bleeding during low-dose oral contraceptive use. *Gynecol Endocrinol.* 2003; 17:107–114. [PubMed: 12737671]
18. Klipping C, Duijkers I, Trummer D, Marr J. Suppression of ovarian activity with a drospirenone-containing oral contraceptive in a 24/4 regimen. *Contraception.* 2008; 78:16–25. [PubMed: 18555813]
19. Endrikat J, Parke S, Trummer D, Schmidt W, Duijkers I, Klipping C. Ovulation inhibition with four variations of a four-phasic estradiol valerate/dienogest combined oral contraceptive: results of two prospective, randomized, open label studies. *Contraception.* 2008; 78:218–225. [PubMed: 18692612]
20. Siegel S. Non parametric statistics for the behavioral sciences. McGraw Hall Book Company. 1956
21. Spona J, Binder N, Höschen K, Feichtinger W. Suppression of ovarian function by a combined oral contraceptive containing 0.02 mg ethinyl estradiol and 2 mg chlormadinone acetate given in a 24/4-day intake regimen over three cycles. *Fertil Steril.* 2010; 94:1195–1201. [PubMed: 19709656]
22. Spona J, Elstein M, Feichtinger W, Sullivan H, Lüdike F, Müller U, Düsterberg B. Shorter pill-free interval in combined oral contraceptives decreases follicular development. *Contraception.* 1996; 54:71–77. [PubMed: 8842582]
23. Vandevan M, Kuel T, Sulak P, Witt I, Coffee A, Winckel T, Reape K. Evaluation of pituitary-ovarian axis suppression with three oral contraceptive regimens. *Contraception.* 2008; 77:162–170. [PubMed: 18279685]
24. Killick SR. Ovarian follicles during oral contraceptive cycles: their potential for ovulation. *Fertil Steril.* 1989; 52:580–582. [PubMed: 2680616]
25. Dinger J, Minh TD, Buttmann N. Effectiveness of oral contraceptive pills in a large U.S. cohort comparing progestogen and regimen. *Am J Obstet Gynecol.* 2011; 117:33–40.
26. Levonorgestrel. [Accessed April 10 2011] <http://www.drugs.com/ppa/levonorgestrel.html>.
27. Etonogestrel. [Accessed April 10 2011] <http://www.drugs.com/ppa/etonogestrel.html>.
28. Mansour D, Inki P, Gemzell-Danielsson K. A review of contraceptive failure rates. *Eur J of Contracept Reprod Health Care.* 2010; 15:4–16. [PubMed: 20136566]
29. Kost K, Singh S, Vaughan B, Trussel J, Bankole A. Estimates of contraceptive failure from the 2002 National Survey of Family Growth. *Contraception.* 2008; 77:10–21. [PubMed: 18082661]

Table 1

Baseline characteristics of participating women

Variable	Overall group N=33	Normal weight group N=17	Obese group N=16
Body Composition			
Height (cm)	164.5 ± 5.8	162.5 ± 5.4	166.6 ± 5.7
Weight (kg)	75.1 ± 20.2	57.1 ± 5.6	94.2 ± 9.0
BMI	27.4 ± 6.6	21.6 ± 1.2	33.9 ± 2.7
Demographics			
Age	26.8 ± 4.6	27.3 ± 4.7	26.3 ± 4.6
Race	9 (27)	3(18)	6(38)
Hispanic	13(40)	6(35)	7(44)
Non-Hispanic Black	9 (27)	6(35)	3(18)
Non-Hispanic White	2 (6)	2(12)	0(0)
Asian			

Continuous variables shown as mean ± standard deviation.

Categorical variables shown as n (%).

Table 2Matched pair analysis for number of women with follicles ≥ 8 mm

Oral contraception	CVR	
	< 8 mm	≥ 8 mm
< 8 mm	12	1
≥ 8 mm	9	11

McNemar's Test $p=0.02$

Table 3

Maximum follicular diameter during study cycle by type of contraception

Maximum follicular diameter	Type of contraception	
	Oral contraception	CVR
≥ 8 mm	20 (61)	12 (36)
≥ 10 mm	11 (33)	8 (24)
≥ 13 mm	8 (24)	4 (12)
≥ 18 mm	6 (18)	2 (6)

Values shown as n (%).