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Use of the novel combined contraceptive vaginal ring NuvaRing for ovulation inhibition

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Objective: To assess the effects of the combined contraceptive vaginal ring NuvaRing on ovarian function.

Design: Randomized, open-label, crossover study.

Setting: Clinical pharmacology unit.

Participant(s): Sixteen healthy female volunteers.

Intervention(s): Group 1: one cycle of combined oral contraceptive containing desogestrel (150 μg) and ethinyl estradiol (30 μg) (desogestrel/EE COC), followed by a NuvaRing treatment period. Group 2: NuvaRing treatment period followed by a cycle of desogestrel/EE COC.

Main Outcome Measure(s): Follicular diameter, serum hormone concentrations (follicle-stimulating hormone, 17β estradiol, luteinizing hormone, and progesterone), and endometrial thickness.

Result(s): NuvaRing use for the recommended period of 3 weeks resulted in complete inhibition of ovulation, as assessed by vaginal ultrasound (follicular diameter) and by serum luteinizing hormone and progesterone concentrations. Inhibition of ovulation was maintained for an additional 2 weeks of NuvaRing use. Ovarian suppression between the groups was comparable. Furthermore, ovarian suppression after 3 weeks of NuvaRing use was comparable to that on day 21 of DGS/EE COC intake. NuvaRing was well tolerated.

Conclusion(s): NuvaRing completely inhibited ovulation throughout the normal 3-week period and the extended period of use. Ovarian suppression was comparable to that with desogestrel/EE COC. (Fertil Steril® 2001;75:865–70. ©2001 by American Society for Reproductive Medicine.)

Key Words: Pharmacodynamics, contraception, follicular diameter, serum hormone levels, ovulation inhibition, etonogestrel, vaginal ring

NuvaRing (NV Organon, Oss, The Netherlands) is a novel combined-contraceptive vaginal ring containing etonogestrel and ethinyl estradiol (EE). Etonogestrel is the biologically active metabolite of desogestrel. Both desogestrel (and thus etonogestrel) and EE are steroids that are used widely in a number of established contraceptive products (1–4). NuvaRing is a flexible, colorless vaginal ring with an outer diameter of 54 mm and a cross-sectional diameter of 4 mm. On average, 120 μg of etonogestrel and 15 μg of EE per day are released. The NuvaRing regimen involves use of the ring for one cycle—in other words, 3 weeks of continuous ring use, followed by a 1-week ring-free period. A new ring is used for each cycle. The pharmacokinetic profile of NuvaRing has been described elsewhere (5).

This pharmacodynamic study assessed the inhibition of ovulation achieved using NuvaRing during the normal 3-week treatment period and during a subsequent 2-week follow-up period (i.e., up to 35 days in total). The extended period of ring use was included to determine whether inhibition of ovulation is sufficiently maintained if a woman forgets to remove the ring after the usual 3-week use period. The effect of NuvaRing on ovarian function was also compared with the established combined oral contraceptive Marvelon, containing desogestrel (150 μg) and EE (30 μg).

The objectives of this study were to evaluate the effects of etonogestrel and EE released from NuvaRing on ovarian function as assessed by vaginal ultrasound scan (USS; follicular diameter and endometrial thickness) and by serum concentrations of FSH, E_2, LH, and P.

METHODS

This open-label, randomized, cross-over study was conducted at the Kendle Clinical

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Pharmacology Unit, Utrecht, The Netherlands, between January and May 1998. The study was conducted in accordance with the Declaration of Helsinki, the International Committee for Harmonization for Good Clinical Practice, and current regulatory guidelines. The Institutional Review Board of the Academic Hospital in Utrecht, The Netherlands, approved the study protocol. All subjects entering the trial provided written informed consent.

Study Population

Sixteen female subjects aged between 18 and 35 years, in good physical and mental health, and with a body mass index between 18 and 29 kg/m^2 were enrolled. All subjects were required to have good visibility of both ovaries by vaginal ultrasound, as well as good venous accessibility. Subjects were excluded if they had any contraindications for contraceptive steroid use. There were also several specific vaginal ring–related exclusion criteria, including the presence at screening of cervicitis, vaginitis, or a bleeding cervical erosion; a diagnosis of a cervical smear of Papanicolaou class III, IV, or V; prolapse of the uterine cervix, cystocele, and/or rectocele; severe or chronic constipation; and dyspareunia or other coital problems.

Study Design

All trial medication was supplied by N.V. Organon (Oss, The Netherlands). All subjects received at least one pretreatment cycle of desogestrel (150 μg) and EE (30 μg) COC (Marvelon, NV Organon, The Netherlands; 21 days of pill intake followed by a 7-day pill-free period). After the pretreatment COC cycle, subjects were randomized to one of two treatment groups. Group 1 (COC $\rightarrow$ NuvaRing) received 21 days of desogestrel/EE COC intake followed by a 7-day pill-free period; this was followed by a 35-day period of NuvaRing use. Group 2 (NuvaRing$\rightarrow$ COC) received 35 days of treatment with NuvaRing, followed by a 7-day ring-free period, and then 21 days of desogestrel/EE COC intake.

Subjects were instructed to use the ring continuously for 5 weeks (3 weeks of normal ring use extended by an additional 2 weeks of continuous ring use). Each ring was inserted and removed by the subject. If considered necessary, temporary removal of the ring was permitted (e.g., before intercourse) provided it was reinserted within 3 hours. Subjects were instructed to take their desogestrel/EE COC tablets in the morning. Condoms were used as an additional protection against pregnancy if follicles with a diameter $\geq$13 mm were observed during the vaginal USS assessments.

At screening, subjects provided a medical and gynecological history and underwent a physical and gynecological examination. Immediately before insertion of NuvaRing or intake of the first desogestrel/EE COC pill, a home pregnancy test was performed, and subjects only proceeded with the study if this test was negative.

The total length of the study period was 72 days. Blood samples were collected for assay of serum hormone levels (FSH, E_2, LH, P), and vaginal USS was performed as follows: in both groups on days 1 (first day of NuvaRing use), 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20; daily on days 22–35; day 36 (ring removal day); and on day 38. In addition, in group 1 only, on days 21 (last day of desogestrel/EE intake) and 24 of the COC cycle; and in group 2 only, on days 21 and 24 of both the pretreatment and treatment COC cycles.

The vaginal USS was performed using a Toshiba Capasse SSA-220-A with a 5-MHz transvaginal transducer. The determination of follicle size was based on the measurement of follicle diameters (longitudinal and transverse planes). Only follicles with a mean diameter of $\geq$5 mm were recorded. Endometrial thickness was measured by vaginal ultrasound of the sagittal plane of the uterus and calculated by measuring the sum of both endometrial layers.

Blood samples were processed to serum and stored at -20°C until assays were performed. FSH, LH, E_2, and P levels in serum were determined by using a time-resolved fluoroimmunoassay (AutoDelfia).

Throughout the study period, subjects recorded compliance with the COC and NuvaRing treatment on diary cards. Compliance with the NuvaRing regimen was documented as the daily number of hours of ring use, whereas compliance with the pill regimen was documented by indicating whether a pill was taken or not. At screening and at completion, subjects underwent a physical and gynecological examination, an assessment of vital signs, and blood sampling for measurement of routine hematology and blood biochemistry parameters. Adverse events and the use of concomitant medications were monitored throughout the study period. In addition to the medications known to interfere with sex steroids, concomitant use of sex steroids other than the trial medication were prohibited.

Statistical Methods

Summary statistics (median, minimum, and maximum) for serum hormone levels and vaginal USS measurements (follicular diameters and endometrial thickness) were calculated for the first 3 weeks of NuvaRing use and for the extended 2-week period of ring use. Summary statistics for these parameters were also calculated for day 20 of NuvaRing treatment and for day 21 of COC use. The median values and ranges as presented apply to the maximum follicular diameter or the maximum serum hormone level for each subject and — if applicable — for each subperiod. The exposure data was summarized by listing the total number of exposure hours (NuvaRing) and days (COC) for subjects in both study groups (groups 1 and 2).

TABLE 1

Baseline demographics for women randomized to group 1 (n = 8) and 2 (n = 8).

	Group 1		Group 2	
Parameter	Mean (SD)	Range	Mean (SD)	Range
Age (y)	26.5 (3.2)	22–30	23.0 (2.9)	18–26
Body weight (kg)	66.8 (8.3)	51–76	62.3 (9.1)	51–79
Body height (cm)	172.1 (5.9)	160–179	166.0 (5.1)	159–174
BMI (kg/m^2)	22.5 (1.8)	20–85	22.5 (2.4)	19–27

Note: BMI = body mass index.

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The safety analysis was restricted to summary statistics.

RESULTS

Patient Characteristics

Sixteen women were randomized to treatment groups 1 (n = 8) or 2 (n = 8). There were no differences between the two groups in baseline demographic characteristics (Table 1). The physical and gynecological examinations revealed no abnormalities, and all pregnancy tests were negative.

On account of the temporary ring removal by some subjects, ring exposure was 6,704 and 6,715 hours in groups 1 and 2, respectively, instead of the ideal 6,720 hours for the 35-day period. All subjects were exposed to desogestrel/EE COC for 21 days, with the exception of one subject who forgot to take her first desogestrel/EE COC tablet and was therefore exposed for 20 days.

Efficacy

Ovulation, as assessed by follicular diameter and serum hormone levels, was not observed in any subject during the study. The ovarian suppression achieved was comparable in both groups.

The largest follicles were observed between days 1 to 4 of NuvaRing use in all except 2 subjects (subjects 08 and 13; Table 2). Follicular diameters were small (medians of <6.4 mm) in the second and third weeks of NuvaRing use. Follicular size remained small during the extended period of NuvaRing use (Figure 1). In total, two subjects (subjects 10 and 13) were instructed (on days 3 and 30 of NuvaRing use, respectively) to use condoms because of the presence of follicles of ≥13 mm diameter. These follicular diameters subsequently decreased in size by the following day. Overall, the follicular diameters were small (ranging between <5 mm and 7.3 mm) and were comparable between NuvaRing (day 20) and desogestrel/EE COC (day 21) users.

FSH concentrations were generally low throughout the study period (Table 3). The highest FSH concentrations occurred in the first week of NuvaRing use, coinciding with the period of largest follicular diameters. Similarly, serum concentrations of estradiol were low and generally below the detection limit (49.9 pmol/L). The highest levels of estradiol were also observed during the first week of NuvaRing use (Figure 1), consistent with the follicular diameter results.

The inhibition of ovarian activity indicated by vaginal USS measurements was confirmed by serum LH and P concentrations (Table 3). LH and P levels were fully suppressed throughout the entire study period. Hormone concentrations after 3 weeks of NuvaRing use (day 20) were comparable to those observed on day 21 of desogestrel/EE COC intake.

Measurements of endometrial thickness showed that the endometrium was suppressed in all subjects during NuvaRing treatment. The endometrial thickness observed on day 21 of desogestrel/EE COC intake was comparable to that observed after 3 weeks of NuvaRing use (day 20; Table 4).

Safety Assessments

NuvaRing and desogestrel/EE COC treatments were well tolerated. All adverse events reported were mild to moderate

TABLE 2

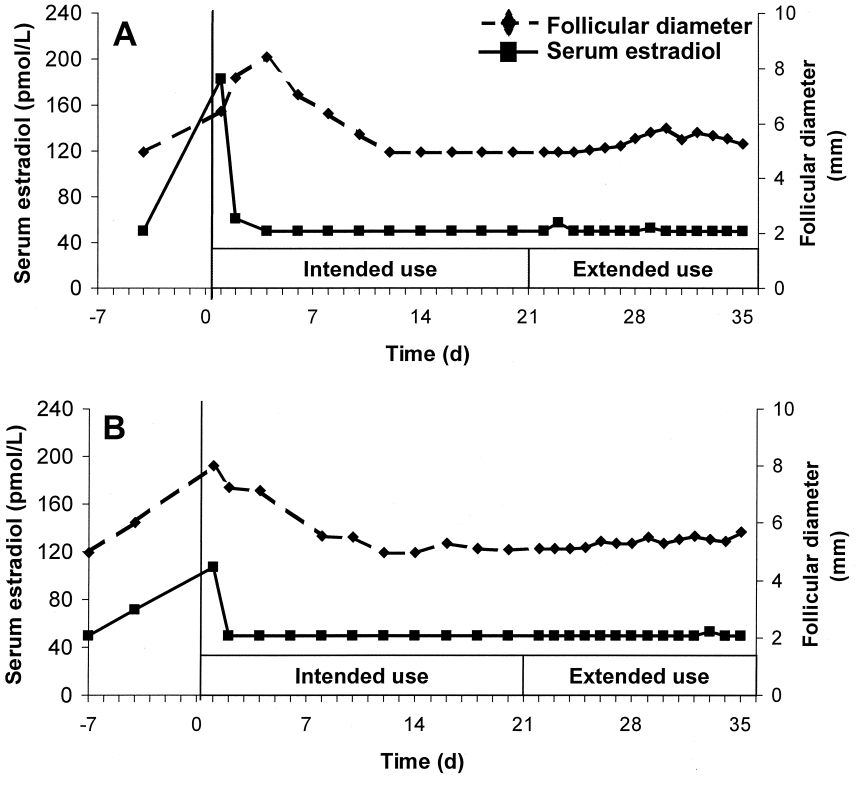
Diameter of largest follicle by subject during NuvaRing treatment.

Group 1 (COC → NuvaRing)			Group 2 (NuvaRing → COC)		
Subject no.	Diameter of largest follicle (mm)	NuvaRing treatment day	Subject no.	Diameter of largest follicle (mm)	NuvaRing treatment day
02	6.6	2	01	9.7	2
03	12.7	2	04	8.0	1
06	10.1	4	05	7.2	2
07	6.7	4	08	6.7	35
10	15.7	4	09	6.5	1 + 4
12	6.7	1	11	8.1	1
13	13.3	31	14	8.2	2
15	6.2	4	16	9.2	4

Mulders. Ovulation inhibition of NuvaRing. Fertil Steril 2001.

FIGURE 1

Median follicular diameter (in millimeters) and serum 17β-estradiol concentrations (in picomoles per liter) for (**A**) group 1 (n = 8) and (**B**) group 2 (n = 8) during treatment with NuvaRing (days 1–35). Median values have been calculated for the diameter of the largest follicle and the peak serum hormone level per subject per day.



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in intensity, and none of the subjects discontinued treatment on account of adverse events.

Results from the physical and gynecological examinations and the hematology and blood biochemistry analyses performed at baseline and the end of the study were comparable.

DISCUSSION

NuvaRing is a novel combined-contraceptive vaginal ring that releases etonogestrel (120 μg) and EE (15 μg) at a continuous daily rate. This study assessed the effects of NuvaRing on ovarian function during both a normal (3-week) and an extended (additional 2-week) period of ring use. Analysis over the extended period allowed assessment of likely ovarian activity in the event of failure to remove the ring after 3 weeks.

During the normal 3-week period of use, NuvaRing completely inhibited ovulation. Extended use of NuvaRing for a further 2 weeks did not compromise ovarian suppression, and inhibition of ovulation was maintained. The largest follicular diameters and also the highest concentrations of serum estradiol were observed during the first week of NuvaRing use. This finding is a result of follicular growth initiated during the preceding 1-week steroid-free period.

In the present study, the effects of NuvaRing on ovarian activity were assessed over a 5-week period. However, assessments for the COC cycle were limited to the last day of pill intake (day 21). Therefore, comparisons between NuvaRing and the desogestrel/EE COC are valid only for this time point. Evaluation of follicular diameter and serum hormone concentrations on day 21 of COC use indicated that ovarian suppression was similar to that observed after 3 weeks of NuvaRing use (day 20).

One of the main advantages of vaginal rings as a choice of contraception is their convenience. NuvaRing is easy to insert and remove by the woman herself. If a woman forgets to remove the ring after the recommended 3-week period of use, contraceptive efficacy might theoretically be compromised. The results of this study indicate that inhibition of ovulation was maintained for up to 2 weeks after the rec-

TABLE 3

Peak serum FSH, LH, and progesterone levels during treatment with NuvaRing and desogestrel/EE COC (maximum individual levels during each subperiod).

Subperiod		Group 1 (COC → NuvaRing, (n = 8)		Group 2 (NuvaRing → COC), (n = 8)	
Parameter	Treatment day	Median	Range	Median	Range
Serum FSH levels (U/L)					
NuvaRing					
Normal use	1–7	6.6	4.0–10.5	5.3	3.7–6.6
	8–14	2.9	1.4–7.1	4.2	<1.0–5.9
	15–21	2.2	<1.0–8.1	1.7	<1.0–6.4
Extended use	22–28	1.9	<1.0–9.0	2.2	<1.0–6.7
	29–35	2.6	<1.0–10.0	4.3	<1.0–9.4
Desogestrel/EE COC	21	<1.0	<1.0–3.3	<1.0	<1.0–2.3
NuvaRing	20	1.4	<1.0–7.9	1.7	<1.0–6.0
Serum LH levels (U/L)					
NuvaRing					
Normal use	1–7	7.3	3.0–11.0	4.2	2.5–11.3
	8–14	3.7	1.3–7.3	2.8	<0.60–8.7
	15–21	2.0	0.6–6.6	1.2	<0.60–9.9
Extended use	22–28	1.7	<0.60–6.2	1.3	<0.60–9.9
	29–35	2.2	<0.60–7.1	2.9	<0.60–11.6
Desogestrel/EE COC	21	<0.60	<0.60–2.1	<0.60	<0.60–1.5
NuvaRing	20	1.1	<0.60–6.3	<0.60	<0.60–8.0
Serum progesterone levels (nmol/L)					
NuvaRing					
Normal use	1–7	1.3	1.0–1.6	1.2	<0.99–2.7
	8–14	1.2	<0.99–1.6	1.5	<0.99–2.4
	15–21	1.2	<0.99–1.6	1.5	<0.99–2.6
Extended use	22–28	1.5	1.2–2.2	1.4	<0.99–2.7
	29–35	1.5	<0.99–1.7	1.4	<0.99–2.8
Desogestrel/EE COC	21	1.0	<0.99–1.9	1.2	<0.99–1.8
NuvaRing	20	1.2	<0.99–1.3	1.325	<0.99–2.6

Mulders. Ovulation inhibition of NuvaRing. Fertil Steril 2001.

TABLE 4

Endometrial thickness in millimeters during treatment with NuvaRing and desogestrel/EE COC.

Subperiod		Group 1 (n = 8)		Group 2 (n = 8)	
Substance	Treatment day	Median (SD)	Range	Median (SD)	Range
NuvaRing treatment period					
Normal use	1–7	3.5 (1.1)	2.6–5.2	2.8 (1.5)	1.5–6.1
	8–14	2.5 (1.2)	1.0–4.7	3.3 (1.0)	1.9–4.8
	15–21	2.0 (0.65)	1.2–3.0	2.9 (1.2)	1.7–5.2
Extended use	22–28	4.0 (0.76)	2.6–5.0	3.3 (0.66)	2.3–4.3
	29–35	5.0 (0.91)	3.6–5.9	4.0 (1.6)	2.6–6.5
COC	21	2.1 (0.71)	1.0–3.3	3.1 (1.2)	1.9–5.4
NuvaRing	20	1.8 (0.55)	1.2–2.7	2.4 (0.65)	1.5–3.5

Mulders. Ovulation inhibition of NuvaRing. Fertil Steril 2001.

ommended 3-week period of NuvaRing use. Extended use of NuvaRing was not associated with any unfavorable safety concerns.

In conclusion, NuvaRing use was associated with complete inhibition of ovulation during the normal 3-week period of use and during an additional 2-week period. Ovarian suppression achieved with NuvaRing was comparable to that observed with a low-dose combined oral contraceptive.

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