Effects on cycle control and bodyweight of the combined contraceptive ring, NuvaRing, versus an oral contraceptive containing 30 μg ethinyl estradiol and 3 mg drospirenone

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BACKGROUND: The objective of this study was to compare cycle control, cycle-related characteristics and bodyweight effects of NuvaRing with those of a combined oral contraceptive (COC) containing 30 μg of ethinyl estradiol and 3 mg of drospirenone. METHODS: A randomized, multicentre, open-label trial in which 983 women were treated (intent-to-treat population) with NuvaRing or the COC for 13 cycles. RESULTS: Breakthrough bleeding or spotting during cycles 2–13 was in general less frequent with NuvaRing than that with the COC (4.7–10.4%) and showed a statistically significant odds ratio of 0.61 (95% confidence interval: 0.46, 0.80) with longitudinal analysis. Intended bleeding was significantly better for all cycles with NuvaRing (55.2–68.5%) than that with the COC (35.6–56.6%) ($P < 0.01$). Changes from baseline in mean bodyweight and body composition parameters were relatively small for both groups with no notable between-group differences. CONCLUSION: NuvaRing was associated with better cycle control than the COC, and there was no clinically relevant difference between the two groups in bodyweight.

Key words: combined contraceptive vaginal ring/combined oral contraceptive/cycle control/irregular bleeding

Introduction

Combined oral contraceptives (COCs) are a well-established method of contraception demonstrating proven efficacy for over 40 years. More recent advances in contraception have led to the development of lower dose COCs in an effort to reduce unwanted side effects such as nausea and breast tenderness. However, reducing the dose of estrogen can compromise cycle control, which is a key factor affecting contraceptive acceptability, compliance and convenience (Rosenberg *et al*., 1995, 1999).

Another factor that may affect contraceptive acceptability is concern about bodyweight increase. Many women and physicians believe that an association exists between the use of hormonal contraceptives and weight gain. However, the analysis of the literature reveals either minimal weight increases or little evidence for a causal relationship (Gupta, 2000). Furthermore,

comparative studies show no evidence of weight gain in COC users compared with non-users over a period of 6 months (Reubinoff *et al*., 1995) or 1 year (Carpenter and Neinstein, 1986). Despite the lack of conclusive evidence, user's and physician's concerns about weight gain remain and may affect decisions about the choice of contraceptive method.

NuvaRing is a flexible combined hormonal contraceptive ring that releases 15 μg of ethinyl estradiol (EE) and 120 μg of etonogestrel per day intended for a 3-week cycle use. The main advantage of NuvaRing is the convenience of once-a-month administration. In addition, NuvaRing offers the use of lower doses of contraceptive hormones (Timmer and Mulders, 2000), and its controlled-release delivery via the vaginal route avoids the daily fluctuations in hormone levels that can occur with COCs. The excellent efficacy, tolerability and acceptability of

NuvaRing have been established in large-scale studies conducted in Europe and North America (Roumen *et al.*, 2001; Dieben *et al.*, 2002; Oddsson *et al.*, 2005a,b). A combined analysis of three small-scale, open-label trials showed that cycle control was better with NuvaRing compared that with a COC containing 30 µg of EE and 150 µg of levonorgestrel (Bjarnadottir *et al.*, 2002). This result was confirmed in a recent large-scale comparative trial which demonstrated that NuvaRing produced superior cycle control compared with that by the same COC (Oddsson *et al.*, 2005b). These earlier studies have also shown that NuvaRing does not produce clinically significant changes in bodyweight, but so far, the effect of NuvaRing on bodyweight has not been compared directly with that of a COC.

The primary aims of this study were to compare the effects of NuvaRing with those of a COC containing 30 µg of EE and 3 mg of drospirenone on vaginal bleeding characteristics and weight neutrality and to demonstrate the non-inferiority of NuvaRing on bodyweight versus the COC. Secondary objectives included contraceptive efficacy, acceptability, body composition changes and cycle-related characteristics [including premenstrual syndrome (PMS) and dysmenorrhoea]. A comparison of the efficacy, acceptability and tolerability of these two contraceptives will be discussed in a separate article.

Materials and methods

This randomized, open-label, multicentre trial was conducted in gynaecological and/or general practitioner's practices in 10 European countries (Austria, Belgium, Denmark, France, Germany, Italy, Norway, Spain, Sweden and Switzerland) between May 2002 and April 2004. The study was approved by the independent ethics committee/institutional review boards of the participating centres and was conducted in accordance with the Declaration of Helsinki and the ICH Guideline for Good Clinical Practice. All subjects provided written informed consent.

Subjects

Women included in this study were ≥18 years of age, at the risk of pregnancy and seeking contraception. Exclusion criteria included the use of an injectable hormonal contraceptive within 6 months of initiation of the study; abortion or breastfeeding within 2 months before the start of trial medication; abnormal cervical smear diagnosed during screening; and any contraindication for contraceptive steroid use including the presence of, history of or predisposition to venous or arterial thrombosis.

Treatments

Subjects received treatment for 13 consecutive cycles. Each cycle comprised a 21-day ring/pill treatment period followed by a 7-day ring/pill-free period. Women were randomized to the NuvaRing (NuvaRing®, NV Organon, Oss, The Netherlands) and COC [containing 30 µg of EE and 3 mg of drospirenone (Yasmin®, Schering AG, Berlin, Germany)] treatment groups in randomly permuted treatment blocks (1:1 NuvaRing : COC ratio). To ensure non-predictability of treatment allocation, we generated blocks of 4 and 6 positions using SAS software (version 6.12). To avoid assignment bias, we carried out randomization using an APEX (APEX Voice Communications, Woodland Hills, CA, USA), Interactive Voice Response System. Investigators contacted the server by telephone, entered the subject number and date of birth and were given a medication number that corresponded to the treatment linked to the first free block position.

Ring use and pill intake

At study entry, women received instruction on ring use, including how and when to insert and remove it. Women taking no hormonal contraception before the study inserted the ring between days 1–5 of the menstrual cycle according to the instructions in the package insert. Women with no hormonal contraceptive use in the past month started pill-taking on the first day of menstrual bleeding. For both NuvaRing and COC groups, women who had been using other methods of contraception followed the instructions in the NuvaRing or COC package inserts, respectively, according to the method they were using.

Assessments

Assessments occurred at screening (within 1 month before starting treatment) and within 1 week after the ring/pill-free period of cycles 1, 3, 6, 9 and 13 or at premature discontinuation.

Cycle control

Diary cards were issued at screening and used for daily documentation of vaginal bleeding patterns up to and including the ring/pill-free period of cycle 13. If vaginal bleeding was present, subjects indicated whether it was considered to be spotting (requiring ≤1 pad/tampon per day) or bleeding (requiring ≥2 pads/tampons per day). Withdrawal bleeding was classified as any bleeding/spotting that occurred during the ring/pill-free period. Any withdrawal bleeding starting before the ring/pill-free period and continuing into the ring/pill-free period was termed early withdrawal bleeding. Continued withdrawal bleeding was defined as any withdrawal bleeding that continued into the ring/pill-use period of the next cycle. Breakthrough bleeding/spotting was defined as any bleeding/spotting episode that occurred during the ring/pill-use period that was not early or continued withdrawal bleeding. Intended bleeding was defined as an 'ideal' bleeding pattern—i.e. a cycle without any breakthrough bleeding/spotting and in which withdrawal bleeding only occurred during the ring/pill-free week.

PMS and dysmenorrhoea

Pretreatment PMS and dysmenorrhoea were assessed by investigators who briefly interviewed subjects about their last menstrual period before screening. During study assessments, subjects were also asked about the presence and severity of PMS and dysmenorrhoea in the preceding cycle(s). No standardized process, definitions of PMS and dysmenorrhoea or questionnaire was used in these assessments, and investigators used local clinical standards and the information provided by subjects to classify PMS and dysmenorrhoea as none, mild, moderate or severe.

Bodyweight and composition

Bodyweight measurements and body composition assessments were performed at screening and at each study visit. To standardize bodyweight measurements, we measured weight while the subject was wearing underwear only, and measurements were performed at the same time of day (e.g. morning or afternoon) at each visit using a weighing scale provided to the investigator by the sponsor.

Bodyweight measurements were used to estimate the mean weight change from baseline within each treatment group and the difference in weight change in the NuvaRing group compared with that the COC group, based on the intent-to-treat (ITT) analyses.

Body composition (mass compartment, fluid compartment and metabolism) was assessed using bio-impedance analysis (BIA) (resistance and reactance). Electrodes were placed on the subject's wrist and ankle (both on the right side of the body). A small amount of electrical current (300–800 µA) was passed through the subject's body from one electrode to the other. Between the electrode and the subject, a resistor (500 Ω) was added to the circuit. Resistance and reactance were recorded to determine body fat, body water and lean body mass.

If the resistance value was less than the reactance value, if the resistance value was <100 Ω, or if the values were obtained from a non-calibrated or incorrectly calibrated BIA system, the data were not used for derivation of the body composition parameters.

Statistical methods

The ITT group consisted of all randomized subjects from the all-subject-treated group—i.e. all randomized subjects who received at least one ring/pill.

Cycle control data were analysed using descriptive statistics and tested between groups using the two-sided Fisher exact test adjusting for country for the ITT population. The sample size was based on the assumption that 500 randomized subjects per treatment arm would provide 350 evaluable ITT cycles in each of cycles 2–13 for both arms. The trial was designed to detect a statistically significant lower incidence of breakthrough bleeding/spotting episodes for the cycle 2–13 period with >80% probability. Cycle 1 was excluded from the primary efficacy analysis to prevent bias towards NuvaRing because of different starting procedures.

The occurrence of breakthrough bleeding/spotting was assessed for each cycle during cycles 2–13 using two-sided testing at the 5% significance level, corrected for multiplicity by Bonferroni's rule. This analysis implied overall superiority if a statistically significant lower incidence was reported in ≥1 cycle in the NuvaRing group versus the COC group. In addition, an explorative longitudinal analysis using the generalized estimating equations technique with a logistic link function and a general error-covariance matrix was applied, adjusting for country. Because of its longitudinal character, this analysis did not require an adjustment for multiplicity.

Where possible, secondary cycle control parameters (breakthrough/withdrawal/intended bleeding) were assessed for cycles 1–13. These parameters were analysed using the Fisher exact test adjusted for country at a 5% significance level without adjusting for multiplicity.

Weight neutrality analysis, performed on both the NuvaRing and COC groups, was considered to be demonstrated if the upper bound of the two-sided 95% confidence interval (CI) based on Student's t-distribution of the mean change from baseline in the NuvaRing or COC group at the last assessment in the ITT group was <1.5 kg. Weight non-inferiority was considered to be established if the difference in adjusted (for age and baseline bodyweight) change from baseline in bodyweight at the last assessment between the NuvaRing and the COC was <0.75 kg with 95% probability. The calculation of this adjusted treatment contrast was performed using an analysis of covariance (ANCOVA) with baseline bodyweight and age as covariates and treatment as factor. The impact of possibly different discontinuation rates on the primary results of last measurements was analysed by additional analysis, restricting the attention/analysis to completers only.

Body composition parameters were derived from the reactance, resistance, and bodyweight and height along the lines given by Kottler *et al.* (1996) as follows: mass compartment (fat-free mass, fat mass, body cell mass and extracellular mass), fluid compartment (total body water, intracellular water and extracellular water) and metabolism (basal metabolic rate). For each parameter, change and relative change from baseline for the ITT group were analysed using ANCOVA with treatment and country as factors and the respective baseline value as covariate.

Results

Subject disposition

The first subject was screened in May 2002, and the final assessment of the last subject was in April 2004. Of the 1017 randomized subjects, 34 discontinued before treatment: 7 (NuvaRing, *n* = 4; COC, *n* = 3) were pregnant at screening; 1 (COC) was lost to follow-up; 1 (NuvaRing) had no further need for contraception; 10 (NuvaRing, *n* = 6; COC, *n* = 4) were

not willing to co-operate any further; 15 (NuvaRing, *n* = 6; COC, *n* = 9) for other reasons (Figure 1). Of the 983 subjects (NuvaRing, *n* = 499; COC, *n* = 484) who were randomized and treated (ITT group), 267 [NuvaRing, *n* = 144 (28.9%); COC, *n* = 123 (25.4%)] discontinued prematurely, primarily due to adverse events (NuvaRing, *n* = 61; COC, *n* = 48) and other reasons (NuvaRing, *n* = 32; COC, *n* = 23); 716 women completed the trial [NuvaRing, *n* = 355 (71.1%); COC, *n* = 361 (74.6%)].

There were no notable differences between treatment groups in baseline demographic and clinical characteristics (Table I).
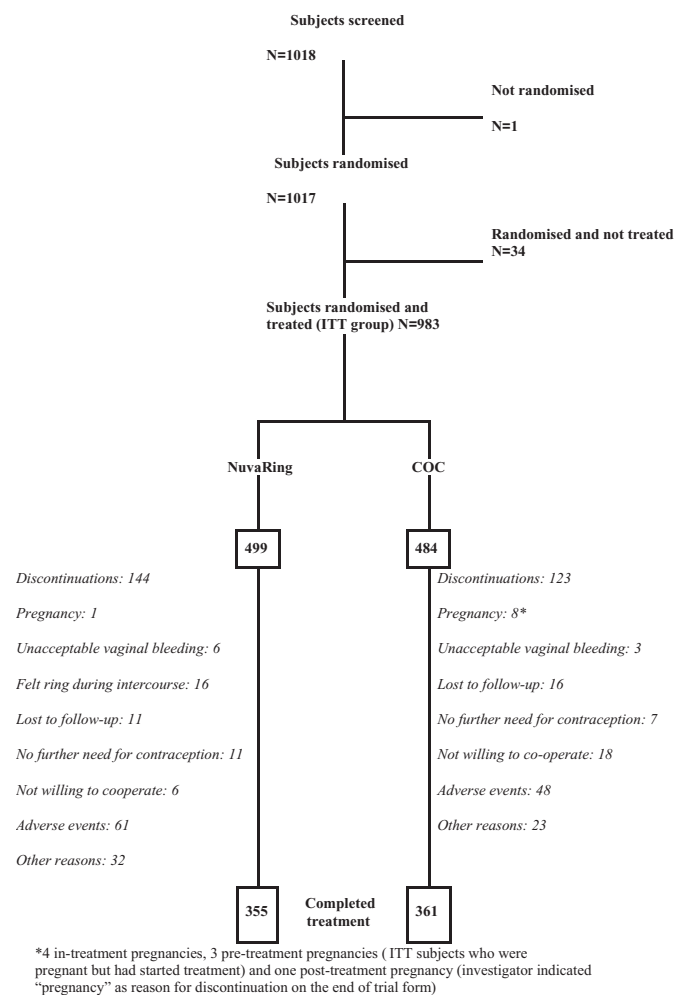

Figure 1. Subject disposition. COC, combined oral contraceptive; ITT, intent to treat.

Table I. Baseline demographic and clinical characteristics for the NuvaRing and combined oral contraceptive (COC) treatment groups [intent-to-treat (ITT) population]

	NuvaRing (*n* = 499)	COC (*n* = 484)
Age, mean ± SD (years)	26.6 ± 6.1	26.6 ± 6.2
Race, *n* (%)		
Caucasian	488 (97.8)	476 (98.3)
Weight, mean ± SD (kg)	62.4 ± 8.4	62.7 ± 8.1
Body mass index, mean ± SD (kg/m^2)	22.4 ± 2.6	22.5 ± 2.6
Nulligravid, *n* (%)	306 (61.3)	297 (61.4)
Nulliparous, *n* (%)	345 (69.1)	334 (69.0)

Efficacy and compliance

There was one in-treatment pregnancy in the NuvaRing group (Pearl Index = 0.25; 95% CI: 0.006, 1.363) and four in the COC group (Pearl Index = 0.99; 95% CI: 0.269, 2.530). Compliance rates were high in both treatment groups (89.2 and 85.5% for the NuvaRing and COC groups, respectively). These data will be described in more detail in a separate publication.

Cycle control

Breakthrough bleeding/spotting

The incidence of breakthrough bleeding/spotting during cycles 2–13 ranged from 3.6 to 6.2% in the NuvaRing group and from 4.7 to 10.4% in the COC group (Figure 2). The incidence of breakthrough bleeding/spotting was lower with NuvaRing than that with the COC for all cycles, except cycles 11 and 12. Statistical analysis revealed a trend towards superiority with NuvaRing ($P = 0.068$), but as this did not achieve statistical significance, superiority could not be demonstrated. This trend towards a lower occurrence of breakthrough bleeding/spotting was confirmed by the exploratory longitudinal analysis that
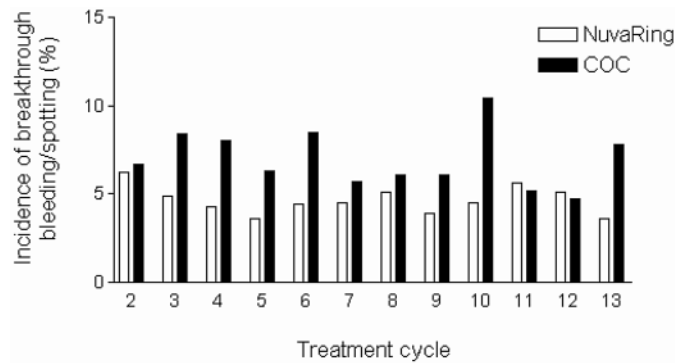

Figure 2. The incidence of breakthrough bleeding and spotting during the ring/pill period in subjects receiving NuvaRing or a combined oral contraceptive (COC) during cycles 2–13.

resulted in a statistically significant odds ratio of 0.61 (95% CI: 0.46, 0.80). In addition, when NuvaRing was compared with the COC on the basis of individual cycles (i.e. without the correction for multiplicity), there were statistically significant lower incidences of breakthrough bleeding/spotting with NuvaRing in cycles 4 ($P = 0.046$), 6 ($P = 0.038$) and 10 ($P = 0.006$). The mean number of bleeding/spotting days in a single episode ranged from 1.4 to 4.5 days over cycles 2–13 for the NuvaRing group and from 1.8 to 3.3 days for the COC group (Table II).

The incidence of breakthrough bleeding alone ranged from 0.3 to 1.8% for the NuvaRing group and from 0.3 to 2.8% for the COC group over cycles 1–13 (Figure 3). Fewer occurrences of breakthrough bleeding were observed in the NuvaRing group during cycle 1 ($P < 0.05$). This statistically significant effect was most likely due to the difference in starting procedures.

The incidence of breakthrough spotting alone ranged from 2.6 to 8.5% for NuvaRing and from 4.4 to 16.9% for the COC over cycles 1–13 (Figure 3). Significantly fewer breakthrough spotting episodes were observed in the NuvaRing group during cycles 1, 3, 4, 6 and 10 ($P < 0.05$).

Withdrawal bleeding

The mean number of withdrawal bleeding days ranged from 2.2 to 2.8 days for the NuvaRing group and from 2.6 to 3.0 days for the COC group (Table II). Further information on withdrawal bleeding characteristics is presented in Table III. The incidence of cycles (1–13) without withdrawal bleeding ranged from 0.2 to 3.2% for NuvaRing- and from 0.5 to 1.7% for COC-treated subjects, with no statistically significant differences between the groups in any cycle.

Significantly more early withdrawal bleedings were observed in the NuvaRing group compared with those in the COC group during cycles 1, 5, 8 and 12 ($P < 0.05$). Between-group differences for continued withdrawal bleeding were statistically significant in each of cycles 1–12 in favour of NuvaRing ($P < 0.0001$). In both groups, early and continued withdrawal bleeding consisted mainly of days of spotting

Table II. Number of breakthrough bleeding/spotting days and withdrawal bleeding days [intent-to-treat (ITT) population]

Cycle	Breakthrough bleeding/spotting days				Withdrawal bleeding days			
	NuvaRing		COC		NuvaRing		COC	
	Mean (SD)	Median (range)	Mean (SD)	Median (range)	Mean (SD)	Median (range)	Mean (SD)	Median (range)
1	3.8 (3.8)	2.0 (1–14)	3.8 (3.0)	3.0 (1–13)	2.8 (1.8)	3.0 (0–13)	3.0 (2.0)	3.0 (0–20)
2	1.8 (1.3)	1.0 (1–7)	2.6 (1.9)	2.0 (1–7)	2.6 (1.8)	3.0 (0–19)	2.9 (2.0)	3.0 (0–28)
3	2.3 (2.0)	1.0 (1–7)	2.3 (1.7)	2.0 (1–8)	2.5 (1.6)	3.0 (0–12)	2.8 (1.5)	3.0 (0–8)
4	2.0 (1.6)	1.0 (1–6)	2.0 (1.5)	1.5 (1–8)	2.5 (1.9)	2.0 (0–18)	2.8 (1.5)	3.0 (0–8)
5	1.4 (0.8)	1.0 (1–4)	3.3 (2.6)	2.5 (1–10)	2.5 (1.7)	2.0 (0–11)	2.7 (1.5)	3.0 (0–8)
6	4.5 (4.5)	2.0 (1–15)	2.5 (1.8)	2.0 (1–7)	2.4 (1.6)	2.0 (0–12)	2.7 (1.6)	3.0 (0–10)
7	2.2 (1.5)	2.0 (1–6)	2.1 (1.5)	2.0 (1–6)	2.4 (1.5)	2.0 (0–8)	2.7 (1.5)	3.0 (0–7)
8	2.5 (2.6)	1.0 (1–11)	2.1 (1.5)	1.5 (1–7)	2.4 (1.6)	2.0 (0–8)	2.7 (1.5)	3.0 (0–7)
9	2.3 (1.4)	2.0 (1–6)	2.7 (1.6)	3.0 (1–6)	2.3 (1.5)	2.0 (0–7)	2.7 (1.6)	3.0 (0–7)
10	2.3 (1.8)	1.0 (1–7)	2.8 (2.1)	2.0 (1–8)	2.4 (1.5)	2.0 (0–7)	2.7 (1.6)	3.0 (0–8)
11	2.7 (2.4)	2.0 (1–9)	1.8 (1.0)	1.5 (1–4)	2.3 (1.6)	2.0 (0–11)	2.7 (1.5)	3.0 (0–8)
12	2.5 (1.5)	2.0 (1–5)	1.9 (1.1)	1.5 (1–4)	2.2 (1.4)	2.0 (0–6)	2.7 (1.5)	3.0 (0–7)
13	2.7 (1.9)	2.0 (1–6)	2.8 (1.9)	2.0 (1–7)	2.4 (1.8)	2.0 (0–16)	2.6 (1.4)	3.0 (0–7)

COC, combined oral contraceptive.

during the ring/pill period (Table III). The mean number of withdrawal bleeding days ranged from 2.2 to 2.8 days and from 2.6 to 3.0 days over cycles 1–13 for the NuvaRing and COC groups, respectively.

Intended bleeding

The incidence of intended bleeding was significantly higher in the NuvaRing group (55.2–68.5%) than that in the COC group (35.6–56.6%) for each of the cycles 1–12 ($P < 0.01$) (Figure 4).
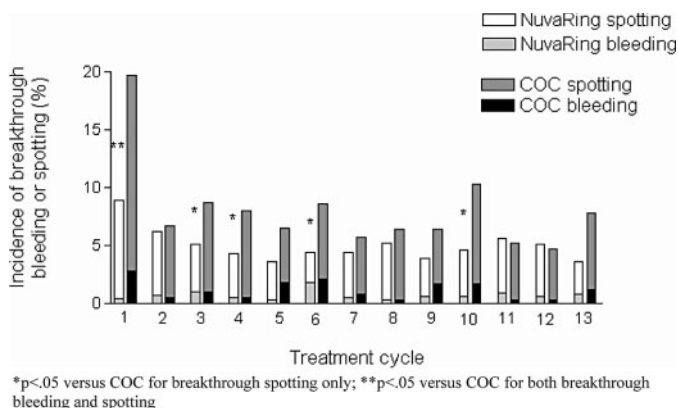

*p<.05 versus COC for breakthrough spotting only; **p<.05 versus COC for both breakthrough bleeding and spotting

Figure 3. The incidence of breakthrough bleeding or spotting during the ring/pill period in subjects receiving NuvaRing or a combined oral contraceptive (COC) during cycles 1–13.

Table III. Incidence (%) of withdrawal bleeding parameters (cycles 1–13 unless otherwise stated)

Cycle control parameter	NuvaRing	COC
Absence of withdrawal bleeding	0.2–3.2	0.5–1.7
Early withdrawal bleeding	2.0–11.8	0.8–7.0
Early withdrawal bleeding/spotting only	0.8–8.3	0.8–4.4
Continued withdrawal bleeding (cycles 1–12)	22.9–28.5	37.7–49.1
Continued withdrawal bleeding/spotting only (cycles 1–12)	19.4–23.2	28.0–38.4

COC, combined oral contraceptive.
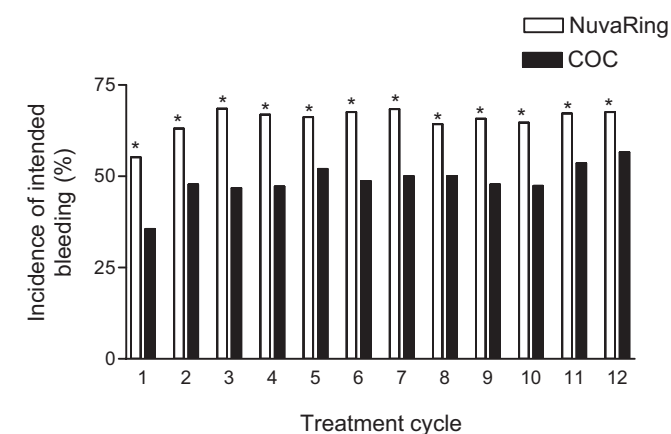
*p<.01 versus COC

Figure 4. The incidence of intended bleeding in subjects receiving NuvaRing or a combined oral contraceptive (COC) during cycles 1–12.

Physician reporting of PMS and dysmenorrhoea

After 1 year of treatment, the reporting of moderate or severe PMS or dysmenorrhoea decreased in both groups with no apparent differences between the treatments. The proportion of subjects reporting moderate or severe PMS symptoms decreased from 12.6 to 4.5% in the NuvaRing group and from 14.7 to 4.7% in the COC group (screening versus cycle 13). The proportion of subjects reporting moderate or severe dys- menorrhoea also decreased at study end compared with screen- ing (decreasing from 17.4 to 5.9% in the NuvaRing group and from 19 to 6.4% in the COC group).

Bodyweight

Weight neutrality

The mean bodyweight per cycle of assessment is summarized in Table IV and was similar for NuvaRing and COC groups. For the NuvaRing ITT group, the estimated mean bodyweight change from baseline to the last assessment was 0.37 kg (two- sided 95% CI: 0.10, 0.64; Table V). For the COC ITT group, the estimated mean bodyweight change from baseline was – 0.03 kg (two-sided 95% CI: –0.29, 0.23). In both cases, the upper limit of the two-sided 95% CI was below the pre-speci- fied 1.5 kg; therefore, it was concluded that weight neutrality of both the NuvaRing and the COC was demonstrated. Results for the study completers were similar.

Weight non-inferiority

The estimated adjusted mean difference (NuvaRing – COC) in change from baseline in bodyweight in the ITT group at the last assessment was 0.38 kg lower in the COC group as com- pared with the NuvaRing group. As the upper limits of the 95% CIs of the adjusted mean differences were above the pre-speci- fied 0.75 kg (0.76), the non-inferiority of NuvaRing versus COC could not be demonstrated. Results of the study compl- eters were similar.

Body composition

At the end of the trial (after cycle 13), no clear changes from baseline in body composition were observed for both treatment groups. The changes from baseline in all body composition parameters were relatively small for both NuvaRing and the COC (Tables VI and VII). Overall no clear differences were

Table IV. Bodyweight (mean ± SD) per assessment for NuvaRing and combined oral contraceptive (COC) groups [intent-to-treat (ITT) population]

Assessment	Bodyweight, mean ± SD	
	NuvaRing ($n = 499$)	COC ($n = 484$)
Baseline	62.4 ± 8.4 (494)	62.8 ± 8.1 (474)
After cycle 1	62.2 ± 8.4 (462)	62.6 ± 8.0 (450)
After cycle 3	62.1 ± 8.5 (428)	62.7 ± 8.0 (430)
After cycle 6	62.4 ± 8.5 (390)	62.7 ± 8.0 (390)
After cycle 9	62.5 ± 8.5 (366)	62.9 ± 8.2 (365)
After cycle 13	62.7 ± 8.8 (301)	63.3 ± 8.5 (294)
Last assessment	62.8 ± 8.8 (477)	62.8 ± 8.2 (461)

Data in parentheses denote the population (*n*).

Table V. Bodyweight neutrality analyses (mean ± SD) for NuvaRing and combined oral contraceptive (COC) groups [intent-to-treat (ITT) population]

Analysis group	Weight (kg)			Estimate (95% CI)
	Baseline (actual values)	Last measurement (actual values)	Last measurement (change from baseline)	
NuvaRing	62.4 ± 8.4 (494)[a]	62.8 ± 8.8 (477)[a]	0.4 ± 3.0 (477)[a]	0.37 (0.10, 0.64)
COC	62.8 ± 8.1 (474)[a]	62.8 ± 8.2 (461)[a]	−0.0 ± 2.8 (460)[a]	−0.03 (−0.29, 0.23)

[a]Data in parentheses denote the population (n).

Table VI. Change from baseline in body mass parameters for NuvaRing and combined oral contraceptive (COC) groups [intent-to-treat (ITT) population]

Parameter	Visit	n	Mean (SD)		Adjusted mean difference (NuvaRing – COC)	
			NuvaRing	COC	Estimate	95% CI
Fat-free mass (kg)	Baseline	484	45.0 (5.4)	45.1 (5.2)		
	After cycle 6	381	−0.2 (3.7)	−0.1 (3.4)	−0.32	(−0.85, 0.22)
	After cycle 13	297	−0.1 (3.6)	0.0 (4.1)	−0.13	(−0.80, 0.53)
	Last	467	0.0 (3.7)	−0.2 (3.9)	0.15	(−0.38, 0.69)
Fat mass (kg)	Baseline	484	17.4 (7.2)	17.7 (7.1)		
	After cycle 6	381	0.2 (4.2)	−0.3 (4.0)	0.70*	(0.03, 1.37)
	After cycle 13	297	0.6 (4.7)	0.1 (4.6)	0.54	(−0.33, 1.42)
	Last	467	0.3 (4.6)	0.1 (4.6)	0.25	(−0.44, 0.93)
Body cell mass (kg)	Baseline	484	21.7 (3.7)	21.7 (3.7)		
	After cycle 6	381	−0.1 (3.0)	0.0 (2.8)	−0.17	(−0.58, 0.25)
	After cycle 13	297	0.0 (3.0)	0.2 (3.2)	−0.11	(−0.64, 0.42)
	Last	467	0.1 (3.0)	0.0 (3.2)	0.10	(−0.32, 0.52)
Extracellular mass (kg)	Baseline	484	23.3 (2.3)	23.5 (2.2)		
	After cycle 6	381	−0.1 (1.7)	−0.1 (1.6)	−0.14	(−0.39, 0.11)
	After cycle 13	297	−0.2 (1.6)	−0.2 (1.5)	0.00	(−0.28, 0.28)
	Last		−0.0 (1.6)	−0.2 (1.6)	0.04	(−0.18, 0.27)

*$P = 0.042$ versus baseline.

Table VII. Change from baseline in fluid compartment parameters and basal metabolic rate for NuvaRing and combined oral contraceptive (COC) groups [intent-to-treat (ITT) analyses]

Parameter	Visit	n	Mean (SD)		Adjusted mean difference (NuvaRing – COC)	
			NuvaRing	COC	Estimate	95% CI
Total body water (l)	Baseline	484	34.1 (4.5)	34.2 (4.3)		
	After cycle 6	381	−0.2 (3.1)	−0.1 (2.9)	−0.22	(−0.67, 0.23)
	After cycle 13	297	−0.1 (3.0)	0.0 (3.4)	−0.06	(−0.62, 0.50)
	Last	467	0.1 (3.1)	−0.1 (3.3)	0.17	(−0.28, 0.62)
Intracellular water (l)	Baseline	484	0.259 (0.034)	0.260 (0.033)		
	After cycle 6	381	−0.001 (0.024)	−0.001 (0.022)	−0.0016	(−0.0051, 0.0018)
	After cycle 13	297	−0.001 (0.023)	0.000 (0.026)	−0.0005	(−0.0047, 0.0038)
	Last	467	0.000 (0.023)	−0.001 (0.025)	0.0013	(−0.0021, 0.0047)
Extracellular water (l)	Baseline	484	33.9 (4.5)	34.0 (4.3)		
	After cycle 6	381	−0.2 (3.1)	−0.1 (2.8)	−0.21	(−0.66, 0.23)
	After cycle 13	297	−0.1 (3.0)	0.0 (3.4)	−0.06	(−0.61, 0.49)
	Last	467	0.1 (3.0)	−0.1 (3.3)	0.17	(−0.27, 0.62)
Basal metabolic rate (kCal)	Baseline	484	1469.2 (239.8)	1464.9 (233.6)		
	After cycle 6	381	−9.4 (216.1)	1.3 (194.4)	−10.14	(−39.09, 18.81)
	After cycle 13	297	0.9 (213.1)	14.0 (224.9)	−2.83	(−39.28, 33.62)
	Last	467	5.1 (211.3)	0.2 (221.2)	8.85	(−20.00, 37.71)

found between the treatment groups in the mass compartment and fluid compartment parameters and metabolic rate.

Discussion

The results of this randomized multicentre, open-label, trial demonstrate that NuvaRing produced better cycle control than a COC containing 30 µg of EE and 3 mg of drospirenone and that there was no clinically relevant difference in bodyweight change between the two treatments.

Good cycle control is a key factor influencing compliance and acceptability. Because of the vaginal route of administration, good cycle control with NuvaRing is especially important because breakthrough or prolonged withdrawal bleeding may

particularly be of inconvenience to the user. With a low daily dose of 15 µg EE, NuvaRing has consistently been shown to have excellent cycle control in several large studies (Roumen *et al*., 2001; Bjarnadottir *et al*., 2002; Dieben *et al*., 2002; Oddsson *et al*., 2005b). Furthermore, cycle control with NuvaRing has been shown to be superior to that with a COC containing 30 µg of EE and 150 µg of levonorgestrel (Bjarnadottir *et al*., 2002; Oddsson *et al*., 2005b). In the present study, NuvaRing once again displayed cycle control characteristics that were better than those of the COC in almost all aspects.

The incidence of breakthrough bleeding/spotting in cycles 2–13 was lower in the NuvaRing group than that in the COC group in the majority of cycles. This difference approached statistical significance in the per-cycle analysis and was statistically significant in the more appropriate longitudinal analysis. The discrepancy between the two analyses may come from the fact that the longitudinal analysis uses the within-subject correlation between the different cycles to provide more precise estimates. This may lead to more power than in the per-cycle analysis where the Bonferroni adjustment for multiplicity does not take these correlations into account. The incidence of intended bleeding patterns, which provides an overall measure of several cycle control parameters, was significantly higher with NuvaRing than that with the COC throughout cycles 1–12 and provides evidence that cycle control was better with NuvaRing than that with the COC. The low incidence of breakthrough bleeding/spotting in cycles 2–13 with NuvaRing was similar to that previously reported [e.g. 2.6–6.4% of cycles 1–13 (Roumen *et al*., 2001) and 2.0–6.4% of cycles 2–13 (Oddsson *et al*., 2005b)]. In addition, the majority of this bleeding was restricted to spotting, with an incidence of breakthrough bleeding of ≤1.8%. The low incidence of breakthrough bleeding with NuvaRing may be explained by NuvaRing's continuous release of contraceptive hormones, which is in contrast to the situation with COCs, in which circulating concentrations of contraceptive hormones fluctuate daily. The incidence of irregular bleeding/spotting with the COC in cycles 2–13 in our study (4.7–10.4%) was also similar to that reported with another COC containing 30 µg of EE and 150 µg of levonorgestrel (range 3.5–12.6%) in a previous comparison with NuvaRing (Oddsson *et al*., 2005b).

Withdrawal bleeding is generally considered a desirable feature, as it helps reassure women of the absence of pregnancy. In the present study, almost all women in both treatment groups had withdrawal bleeding. Early withdrawal bleeding (mainly spotting) was slightly more frequent with NuvaRing than with the COC (incidence 2–11.8% versus 0.8–7.0%). Bleeding problems including heavy or extended withdrawal bleeding can contribute to poor compliance (Rosenberg *et al*., 1995). In our study, continued withdrawal bleeding was significantly less frequent with NuvaRing than that with the COC in cycles 1–12. This confirms previous reports of a lower incidence of continued withdrawal bleeding with NuvaRing compared with that with a COC (Oddsson *et al*., 2005b). The results are reassuring because ring insertion during continued withdrawal bleeding may be a nuisance for some women, although this bleeding was comprised mainly of spotting.

PMS and dysmenorrhoea are common cycle-related disorders of menstruating women (Jamieson and Steege, 1996; Dickerson *et al*., 2003), and in a small proportion of women, symptoms can be disabling or incapacitating (Dickerson *et al*., 2003) or associated with significant distress and life disruption (Durain, 2004). Oral contraceptives are widely prescribed for the management of PMS, although they have not been shown to be consistently effective (Dickerson *et al*., 2003). There is some evidence of the beneficial effects of oral contraceptives in dysmenorrhoea (French, 2005), although a systematic review found insufficient evidence to draw conclusions about their effectiveness in treating this condition (Proctor *et al*., 2001). In our study, the proportions of women with PMS and dysmenorrhoea decreased in both groups, and there were also reductions in the proportions of women with moderate or severe PMS or dysmenorrhoea. The respective proportions of women with PMS in the NuvaRing and COC groups at screening were 34.5 and 38.8%, but at cycle 13, these values had decreased to 20.6 and 22.4%, respectively. The proportions with moderate or severe PMS at screening in the NuvaRing and COC groups were 12.6 and 14.7%, respectively, and after cycle 13, this had decreased to 4.5 and 4.7%, respectively. The respective proportions of women in the NuvaRing and COC groups with dysmenorrhoea at screening were 41.7 and 42.4%, and by cycle 13, these proportions had fallen to 21.7 and 23.0%, respectively. The proportions with moderate or severe dysmenorrhoea at screening were 17.4 and 19.0%, respectively, and these proportions had fallen to 5.9 and 6.4%, respectively, by cycle 13.

In the present study, both contraceptives achieved weight neutrality, but the non-inferiority of NuvaRing versus the COC for change in bodyweight could not be demonstrated. To have sufficient power to detect a non-inferior change in bodyweight at the last assessment, we required 500 subjects per group. However, fewer than 500 subjects (477 in NuvaRing and 460 in COC group) in each group had a change from baseline assessment. This is consistent with the upper limit of the 95% CI being just above 0.75 kg and may have resulted in or contributed to the failure to demonstrate the non-inferiority of NuvaRing.

In the NuvaRing group, the observed mean change in bodyweight of +0.37 kg was similar to that previously reported (+0.43 kg) in a large (*n* = 1145 women) European 1-year efficacy trial of NuvaRing (Roumen *et al*., 2001). The current data are also comparable with a report that combined the European data with those from a North American study and reported an increase of 0.84 kg over 1 year (Dieben *et al*., 2002). In addition, a slight decrease in bodyweight has also been reported with NuvaRing (–0.13 kg) over a shorter duration of use (6 cycles) (Bjarnadottir *et al*., 2002). With the COC, there was a slight decrease (–0.03 kg) in bodyweight after 13 cycles. This decrease is less than the weight loss reported in earlier trials with this COC over the same treatment period (–0.46 kg over a 13-cycle treatment period; Huber *et al*., 2000) or shorter (–0.78 kg over 6 cycles; Oelkers *et al*., 1995) time frames. In contrast, another study demonstrated a slight increase in bodyweight using the same COC over 26 cycles, although bodyweight was below baseline for the majority of the study (Foidart *et al*.,

2000). Thus, it appears that the precise role of NuvaRing or COCs in bodyweight changes in women still has to be defined.

One of the strengths of this trial is that bodyweight was evaluated as a primary outcome using rigorous methods for assessing weight over a study duration of 1 year. Weight gain can occur as a result of increases in a combination of factors, including fat deposition, fluid retention or muscle mass. In this trial, changes in all body composition parameters, including fat and fat-free mass, body cell and extracellular mass, and total body water were relatively small for both groups with no obvious differences between treatments. This lack of difference is interesting because drospirenone exerts an antimineralocorticoid effect on the renin-angiotensin-aldosterone system (Foidart, 2000), which is said to oppose the increase in water retention caused by estrogen (Keam and Wagstaff, 2003). Because other synthetic progestogens lack this antimineralocorticoid activity, the drospirenone-containing COC used in the present study is believed to offer an advantage over COCs due to reduced water retention (Parsey and Pong, 2000). However, in the present study, the absence of any significant difference between the COC and NuvaRing groups in water retention was notable. This may suggest that EE-related fluid retention can be avoided by using a contraceptive with a low EE dose (15 µg) such as NuvaRing; alternatively, these results may indicate that the antimineralocorticoid effect of drospirenone is not notable when administered in the dose used for contraceptive purposes.

In conclusion, NuvaRing was associated with reduced irregular bleeding and improved cycle control and did not show clinically relevant weight changes compared with a COC containing 30 µg of EE and 3 mg of drospirenone.

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