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Efficacy, tolerability and acceptability of a novel contraceptive vaginal ring releasing etonogestrel and ethinyl oestradiol

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A novel contraceptive vaginal ring releasing etonogestrel 120 μg and ethinyl oestradiol 15 μg daily over a period of 3 weeks was tested. Each ring was used for one cycle, comprising 3 weeks of ring use followed by a 1 week ring-free period. This 1 year, multicentre study assessed the contraceptive efficacy, cycle control, tolerability and acceptability of the contraceptive. Altogether, 1145 women were exposed to the vaginal ring for 12 109 cycles (928 woman-years). Six pregnancies occurred during treatment, giving a Pearl Index of 0.65 (95% confidence interval 0.24–1.41). Cycle control was very good, since irregular bleeding was rare (2.6–6.4% of evaluable cycles) and withdrawal bleeding (mean duration 4.7–5.3 days) occurred in 97.9–99.4% of evaluable cycles. Compliance to the prescribed regimen was high with criteria being fulfilled in 90.8% of cycles. The ring was well tolerated. The majority of women considered this new contraceptive method easy to use, and it offers an effective, convenient, well-accepted and novel method for hormonal contraception.

Key words: acceptability/efficacy/ethinyl oestradiol/etonogestrel/vaginal ring

Introduction

Combined oral contraceptive (COC) products are based on the hormonal activity of a progestogen and an oestrogen. COC offer highly effective and reversible protection against pregnancy, in combination with good cycle control, but rely on daily intake of tablets.

Development of new COC has been directed towards regimens containing the lowest suitable dose of both the progestogen and oestrogen, in order to minimize steroid-associated adverse events. However, reduction of the daily oestrogen dose to <20 μg of ethinyl oestradiol (EE) has tended to compromise cycle control (Gestodene Study Group 322, 1999; Gestodene Study Group 324, 1999). Contraceptives that employ the oral route of administration have to pass through the gastrointestinal tract, resulting in a hepatic first-pass effect, and in possible diminished uptake because of vomiting.

The above-mentioned aspects initiated the development of alternative contraceptive methods using different routes of administration and/or controlled-release formulations. The potential higher bioavailability with non-oral routes of administration, as well as the constant serum concentrations that can be obtained with controlled-release formulations, offer the possibility of achieving adequate contraceptive efficacy and good cycle control with lower dosing than that given with an oral formulation.

This report presents the results obtained with a novel, controlled-release formulation for hormonal contraception using the vaginal route of administration. This formulation is a vaginal ring, NuvaRing, that releases both a progestogen and an oestrogen at almost constant release rates for a period of three consecutive weeks. NuvaRing is a flexible, soft, transparent ring with an outer diameter of 54 mm and a cross-section of 4 mm, and releases 120 μg of the progestogen etonogestrel (ENG) and 15 μg of the oestrogen EE per day. Each ring can be easily inserted and removed by the woman herself and is intended to be used for one cycle, comprising 3 weeks of continuous ring use and a 1 week ring-free period. A pharmacodynamic study with NuvaRing has demonstrated that NuvaRing use is associated with complete ovulation inhibition. Furthermore, ovarian suppression achieved with NuvaRing was comparable to that observed with a desogestrel 150 μg/EE 30 μg COC (Marvelon®) (Mulders and Dieben, 2001). A pharmacokinetic study with NuvaRing showed that, compared with a desogestrel 150 μg/EE 30 μg-containing COC, the systemic exposure to ENG was similar with both contraceptives, while exposure to EE with NuvaRing was ~50% of that with the COC (Timmer and Mulders, 2000).

This was the first large-scale study in which >1000 women were treated with NuvaRing, a combined contraceptive vaginal ring, resulting in >12 000 cycles of exposure.

Materials and methods

This 1 year, open-label, non-comparative, multicentre study was carried out at 52 centres in Austria, Belgium, Denmark, Finland, France, Germany, Israel, The Netherlands, Norway, Spain, Sweden and the UK.

The primary objectives of the study were to determine the contraceptive efficacy, cycle control and tolerability of the contraceptive vaginal ring NuvaRing. Secondary objectives were to determine user acceptability and compliance with this novel contraceptive. The study was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and with local ethical committee approval.

Subjects

It was planned to recruit 1200 healthy women aged 18–40 years who were at risk of pregnancy and seeking contraception. The most important exclusion criteria included: contraindications to contraceptive steroids; use of drugs that interfere with metabolism of contraceptive steroids; previous use (within 6 months) of an injectable hormonal method of contraception, or (within 2 months) an implant or hormone-medicated intrauterine device; the presence of certain conditions of relevance to vaginal ring use, like cervicitis, vaginitis or bleeding cervical erosion; Papanicolau (PAP) grade III–V cervical smear result; prolapse of uterine cervix, cystocele and/or rectocele; severe or chronic constipation, dyspareunia or other coital problems.

On study entry, women received verbal and written instructions on use of the ring, including how and when they should insert and remove it. Women were to receive 13 cycles of treatment with NuvaRing® (NV Organon, Oss, The Netherlands). Each cycle consisted of 3 weeks of continuous ring use followed by a 1 week ring-free period. A new ring was to be used for each cycle. Subjects were allowed to remove the ring if desired, e.g. in case of interference during intercourse, as long as the ring was reinserted within 3 h.

Women who had been using a combined contraceptive pill started using the first ring, at the latest, on the day following the usual tablet-free interval (or placebo-tablet interval) of their previous COC. Women who were taking a progestogen-only pill (POP) continued pill intake until the day before ring insertion. Women who were taking no hormonal oral contraceptive inserted the first ring between day 1 and day 5, but at the latest on day 5 of the menstrual cycle, and used a barrier method such as a condom during the first 7 days of use.

Study assessments

Study visits were scheduled at screening, in the first week following cycles 3, 6 and 9, and after cycle 13 or premature discontinuation.

Contraceptive efficacy

A urinary pregnancy test was performed by the subject before the first ring insertion to exclude any pregnant women. Pregnancy tests were also carried out if pregnancy was suspected during the study. A serum test for β-human chorionic gonadotrophin was performed after the last treatment cycle. Any pregnancies occurring during the study were fully documented.

Cycle control

Vaginal bleeding was recorded daily by each subject on diary cards, and classified as spotting (requiring $\leqslant$1 pad/tampon per day) or bleeding ($\geqslant$2 pads/tampons per day). Any bleeding starting or occurring during the ring-free week was defined as withdrawal bleeding; any bleeding starting before, or continuing after, the ring-free week was termed early or late withdrawal bleeding respectively. All other vaginal bleeding was defined as irregular bleeding.

Compliance

Ring use was documented daily on diary cards, and these data were used to determine exposure and compliance. Subjects were asked to document the number of hours of ring use during each of the treatment days. Regimen compliance was calculated as the proportion of cycles in which the ring was used for $21\times24 \pm 48$ h and withdrawn for $7\times24 \pm 24$ h. In addition to regimen compliance, the number of hours of temporary ring removal during each ring-period was assessed by determining the actual duration of ring usage as a proportion of the scheduled usage (21×24 h) in each ring period. The number of temporary ring removals per subject was also assessed.

Tolerability

At screening, subjects provided a medical and gynaecological history and underwent a physical and gynaecological examination. The physical examination was repeated at the last visit; the gynaecological examination was repeated at cycle 6 and at the end of the study.

Blood pressure, heart rate and body weight were assessed at screening, cycles 3, 6, 9 and 13, or on early withdrawal from the study. Adverse events and use of concomitant medication were reported and recorded throughout the trial. Any problems that were directly related to ring use, such as vaginal discomfort, coital problems, foreign body sensation and device expulsion were considered adverse events. The use of other sex steroids or drugs that interfere with steroid metabolism was prohibited.

Cervical cytology

Cervical smear tests were performed at screening, cycle 6 and at the end of the study. The smears were assessed at a central laboratory using both the Bethesda system and Papanicolaou class. Women were allowed to enter the study without the PAP smear result, since the report was often delayed, if they met all the other entry criteria. If abnormal PAP screening results were reported, subjects were to be discontinued.

Acceptability

Acceptability was evaluated by analysing discontinuation rates and the reasons for discontinuation. The user's satisfaction with NuvaRing was evaluated by use of a repeated questionnaire that comprised 21 questions. The women completed this questionnaire at the cycle 3, 6 and 13 visits, or on early withdrawal from the study.

Statistical methods

All analyses except the tolerability and cervical cytology analyses were performed on both the intent-to-treat (ITT) population (defined as all enrolled women who started treatment) and the per protocol (PP) population (defined as all treated women without protocol violations). Protocol violations included use of prohibited concomitant medication, misuse or non-availability of diary cards, serious violations of inclusion and exclusion criteria, and serious violations of the scheduled regimen of ring use.

The cumulative discontinuation rate was estimated with the Kaplan-Meier method. Contraceptive efficacy was estimated by calculation of the Pearl Index (i.e. the expected number of pregnancies per 100 woman-years of exposure) and its 95% confidence interval (CI). Cycle control was analysed for evaluable cycles using descriptive statistics only. Cycle control was also analysed separately for switchers (defined as women who had used any form of hormonal contraception within 2 months of starting study treatment) or starters (defined as women who had not used any hormonal contraception within 2 months of starting study treatment).

Tolerability and cervical cytology analyses were limited to the ITT population and were performed using summary statistics and

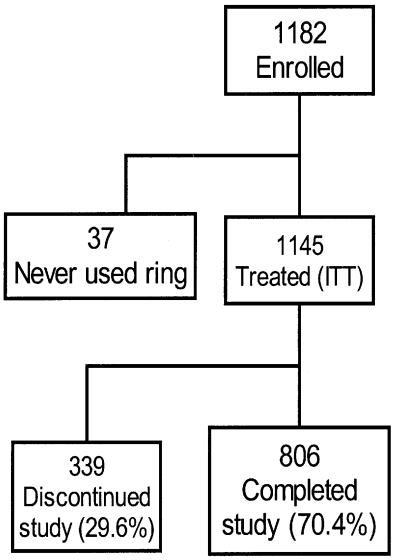

Figure 1. Subject disposition.

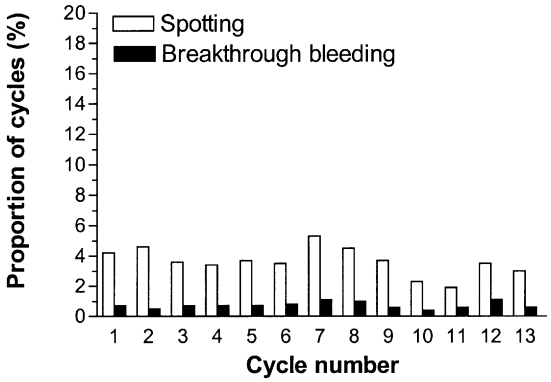

Figure 2. Incidence of irregular bleeding in the intent-to-treat (ITT) population.

frequency tables. The latter illustrate shifts from baseline (screening) to post-baseline assessments.

Results

Subject disposition and baseline demographics

A total of 1182 women were enrolled, of whom 37 did not take any study medication. The ITT population therefore consisted of 1145 women (Figure 1). Of the ITT population, 1049 subjects had no major protocol violation and so comprised the PP population. From the ITT population (1145 women), 339 women (29.6%) discontinued treatment prematurely. Total drug exposure was 12 109 cycles (928.3 woman-years) for the ITT population, and 9880 cycles (757.4 woman-years) for the PP population. In total, 706 of the 1145 participants were classified as switchers from another hormonal contraceptive.

The baseline demographics of the ITT population are presented in Table I.

Efficacy

A total of six pregnancies occurred during treatment, giving a Pearl Index for the ITT population of 0.65 (95% CI 0.24–1.41). Three out of these six women appeared to have substantially violated compliance to NuvaRing in the cycle of conception. Details of all the in-treatment pregnancies, and the type of compliance violation in the women with non-PP pregnancies, are presented in Table II.

Table I. Baseline characteristics of the intent-to-treat (ITT) population[a]

Parameter	ITT population (n = 1145)
Starters[b] (%)	38
Switchers (%)	62
Age (years)	28.2 ± 5.7
Caucasian race (%)	99
Other race (%)	1
Body mass index (kg/m^2)	22.3 ± 2.7
Nulligravid (%)	46
Nulliparous (%)	55
Contraceptive method ever used[c], n (%)	
Oral contraceptive	771 (74)
Barrier method	235 (21)
Intrauterine device	84 (7)
None	35 (3)
Other	23 (2)

[a]Continuous variables are presented as mean ± SD.
[b]Women were classified as switchers (those who had used any hormonal contraception within 2 months of starting study treatment), or starters (who had not done so).
[c]These percentages do not necessarily correspond with those for starters and switchers because of the above-mentioned definition. Note that some women also reported having used more than one method.

Table II. Demographics of women with in-treatment pregnancies

Subject	Age	Gravidity	Parity	Estimated cycle of conception	PP/non-PP pregnancy
1	29	2	2	Cycle 9	PP
2	27	0	0	Cycle 2	Non-PP[a]
3	27	3	2	Cycle 5	PP
4	33	2	0	Cycle 11	PP
5	33	1	1	Cycle 8	Non-PP[b]
6	37	1	0	Cycle 1	Non-PP[c]

[a,b,c]Type of violation resulting in the exclusion of women from the per protocol (PP) population: [a]A ring period of 15 days in cycle 2: the estimated date of conception was 1 day after last ring removal; the woman was reported to have discontinued the study because of a desire to conceive. [b]A ring-free period of 8.5 days for cycle 7 in combination with multiple, temporary ring removals. [c]Several days without ring use in cycle 1; it is believed the woman lost the ring whilst removing a tampon.

Cycle control

As the bleeding patterns for the ITT cycles appeared to be very similar to those of PP cycles, i.e. bleeding patterns did not improve substantially by excluding cycles with protocol violations, the description of the cycle control data was limited to the ITT analysis. Furthermore, bleeding patterns between starters and switchers were very similar; consequently, the results for all the ITT cycles combined are presented unless stated otherwise.

Irregular bleeding was rare throughout the whole treatment period, occurring in only 2.6–6.4% of the cycles (Figure 2, Table III). The irregular bleeding that did occur consisted

Table III. Incidences (percentages) of bleeding as a proportion of intention-to treat evaluable cycles[a]

Irregular bleeding (breakthrough bleeding/spotting):	2.6–6.4
Withdrawal bleeding	
Absence	0.6–2.1
Early	5.4–7.7
Early with spotting only	2.8–5.4
Late	20.4–27.3
Late with spotting only	16.5–21.4

[a]Percentages apply to cycles 1–12 for incidences of late withdrawal bleeding, and to cycles 1–13 otherwise.

mostly of spotting only: breakthrough bleeding was reported in only 0.4–1.1 % of the cycles.

Withdrawal bleeding occurred in almost all cycles; the proportion of cycles where withdrawal bleeding was absent ranged between 0.6 and 2.1% over cycles 1–13 (Table III). Overall, the mean duration of withdrawal bleeding ranged over cycles 1–13 from 4.7–5.3 days (SD 1.7–2.5).

In 5.4–7.7% of the cycles, withdrawal bleeding started in the preceding ring period (early withdrawal bleeding). In most women, this bleeding was restricted to spotting. It was notable that women who were switchers reported less early withdrawal bleeding (3.7–6.0%) than starters (7.1–12.4%), ranging over cycles 1–13.

Withdrawal bleeding continued beyond the ring-free week in 20.4–27.3% of the evaluable cycles. In the majority of these cycles (16.5–21.4% of all evaluable cycles), late withdrawal bleeding was limited exclusively to spotting.

Of the 250 women who did not use hormonal contraception after the treatment period, 91.9% reported normal menstruation by the fourth week following removal of the last ring.

Compliance

Compliance to the prescribed regimen was high, with criteria being fulfilled in 90.8% of cycles. Prolonged ring-free periods occurred in 4.1% of the cycles: in the majority of these cycles, the ring-free period was not extended by more than 24–48 h than the recommended 1 week.

Temporary ring removal during a ring period only occurred on 1% of all ring days. About 90% of all subjects never removed the ring during any of the ring periods of cycles 1–13.

Tolerability

Medical assessments performed before, during and after the study did not show any clinically relevant changes from baseline. In addition, no clinically relevant changes from baseline were observed in blood biochemistry, haematology, blood pressure, heart rate or body weight. Mean body weight increased by 0.43 $\pm$ 3.35 kg over the 13 cycles of treatment. A decrease in body weight from screening to the last visit of $\geqslant$7% was reported for 8% of the women while an increase in body weight of $\geqslant$7% was reported for 10% of women.

Throughout the 1 year study period, 41% of the women did not report any adverse events. Of the remaining 59%, 32% reported adverse events that were considered by the investigator to be possibly, probably or definitely related to the study treatment.

Table IV. Incidence of adverse events

Adverse event[a]	Related[b], *n* (%)	Total, *n* (%)
Headache	76 (6.6)	135 (11.8)
Leukorrhea	61 (5.3)	68 (5.9)
Vaginitis	57 (5.0)	157 (13.7)
Device-related event[c]	44 (3.8)	47 (4.1)
Nausea	32 (2.8)	52 (4.5)
Weight increase	25 (2.2)	34 (3.0)
Vaginal discomfort	25 (2.2)	27 (2.4)
Breast pain	22 (1.9)	32 (2.8)
Dysmenorrhoea	21 (1.8)	30 (2.6)
Depression	19 (1.7)	28 (2.4)
Abdominal pain	8 (0.7)	31 (2.7)
Cystitis	1 (0.1)	42 (3.7)
Pharyngitis	0 (0.0)	51 (4.5)
Sinusitis	0 (0.0)	43 (3.8)
URTI	0 (0.0)	37 (3.2)
Influenza-like symptoms	0 (0.0)	36 (3.1)

[a]Adverse events occurring in $\geqslant$2% of the 1145 treated subjects.
[b]Possibly, probably or definitely treatment-related, as judged by investigator.
[c]Comprising 'foreign body sensation', 'coital problems' and 'device expulsion'.
URTI = upper respiratory tract infection.

The most frequently reported adverse events were vaginitis (13.7%), headache (11.8%), and leukorrhoea (5.9%). When the investigator's opinion of the relationship with NuvaRing treatment was taken into account, both the incidences and ranking of these events changed: i.e. headache (6.6%), leukorrhoea (5.3%), and vaginitis (5.0%) (Table IV).

In total, 15.1% of women decided to discontinue the study because of an adverse event. The most frequently reported events leading to discontinuation from the study were device-related events (2.6%), headache (2.1%), vaginal discomfort (1.0%) and nausea (1.0%). Except for nausea, all these events were considered to be possibly, probably or definitely related to the trial medication by the investigator. For nausea, 10 of the 12 events were considered to be related to the trial medication.

Cervical cytology

At screening, a cervical cytology grading of PAP IIIa [low-grade squamous intraepithelial lesion (SIL)] or higher was diagnosed in 34 subjects (2.8%), of whom three had a PAP IIIb [high-grade SIL (moderate to marked dysplasia)] and 2 had a PAP IV [high-grade SIL (carcinoma in situ)]. In agreement with the exclusion criteria, 28 of these 34 subjects were withdrawn once the cytology results became available, while six women (all having a PAP IIIa result) remained in the study. Repetitive follow-up smears were performed, and the cervical cytology grade did not subsequently worsen in any of these six women.

Twenty-one women with normal cervical cytology at screening experienced shifts to abnormal (i.e. PAP IIIa or higher) at the last clinic visit: 18 subjects shifted to PAP IIIa (low-grade SIL), two subjects shifted to a PAP IIIb and one subject shifted to a PAP IV.

Acceptability

A total of 339 women (29.6%) of the ITT population discontinued treatment prematurely, mainly because of adverse

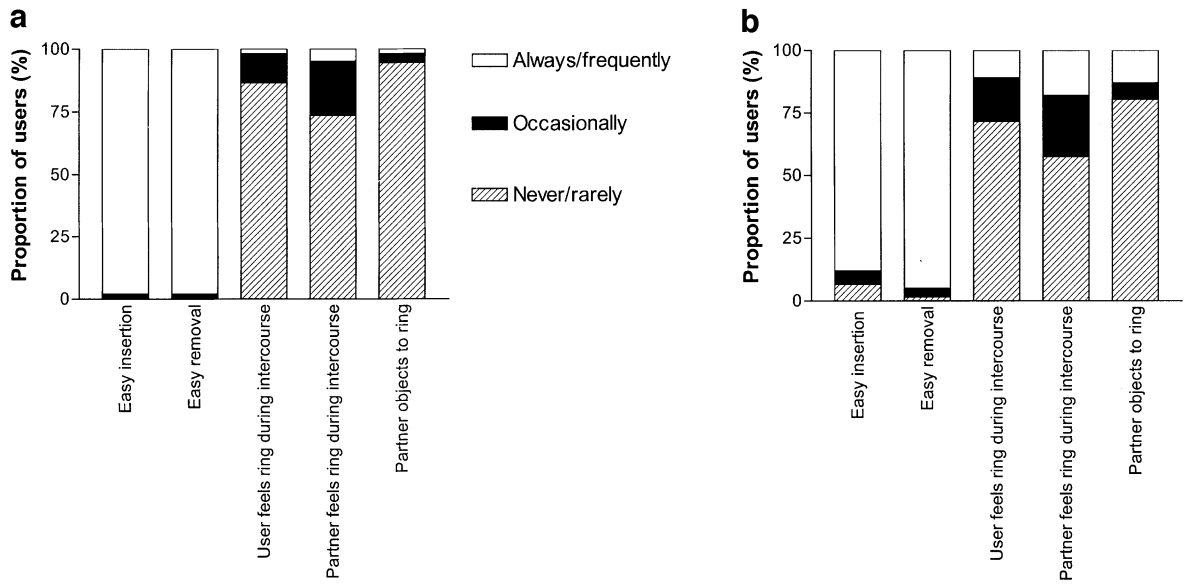

Figure 3. NuvaRing acceptability data in women who (**a**) completed or (**b**) discontinued the study (800 completers and 280 discontinuers completed a questionnaire).

events (15.1%; see also Tolerability section) or 'other reasons' (13.4%). Only nine women discontinued because of irregular bleeding. Most of the women who discontinued the study because of an adverse event did so during the first three or four cycles of NuvaRing use. The 'other reasons' category mostly consisted of women who wished to conceive or had no further need for contraception, non-acceptance of the vaginal ring by the woman or her partner, an abnormal cervical cytology result at screening, and subjects lost to follow-up.

Figure 3 shows the responses gained from subjects, who completed or discontinued the study, to five of the questions asked in the acceptability questionnaire. The data presented were collected at the cycle 13 visit, or at early discontinuation from the study; the responses obtained at the cycle 3 and 6 visits are similar and are not presented.

Insertion and removal of the ring was considered to be easy by the majority of women, even by those who discontinued the study. In addition, the majority of the women (87% of 'completers' versus 72% of 'non-completers') as well as their partners (74% of 'completers' versus 58% of 'non-completers') did not report feeling the ring during intercourse. Even if a partner reported feeling the ring during intercourse, the majority reported not minding that the subject was using this contraceptive method (95% of 'completers' versus 80% of 'non-completers'). Almost all women who completed the study were very satisfied with NuvaRing and would recommend this method to others (96 and 98% of the women respectively). The same opinions were even expressed by the majority of women who discontinued the study (59 and 67% of the women respectively).

Discussion

This 1 year, phase III study demonstrated that NuvaRing is a highly effective contraceptive method with an exceptionally good cycle control. It is well tolerated and accepted by users.

Contraceptive efficacy is reflected in the ITT Pearl Index of 0.65 with a 95% CI of 0.24–1.41. Three out of the six women with in-treatment pregnancies appeared to have substantially violated compliance to NuvaRing in the cycle of conception. This confirms that, as for any other method of contraception, compliance to the prescribed regimen is a prerequisite for adequate contraceptive efficacy.

Cycle control is one of the key factors contributing to the acceptability of a contraceptive method to its users. Cycle control with the ENG/EE ring was excellent as virtually all users experienced withdrawal bleeding in each ring-free week, and irregular bleeding barely occurred during any of the ring periods. The latter is substantiated by the fact that cycle control did not improve substantially by excluding cycles with protocol violations. Furthermore, bleeding patterns between starters and switchers were also very similar.

Irregular bleeding was rare, occurring in only 2.6–6.4% of cycles. The incidence of irregular bleeding was already low in the first cycle of use (4.9%), and continued to be low during the subsequent cycles. Both the pattern and incidence of irregular bleeding of NuvaRing are different from that for low dose COC. Up to ~20% of women starting with low-dose COC experience some degree of irregular bleeding during the first cycle of use, and this percentage decreases markedly with continued use (Brill *et al*., 1991; Endrikat *et al*., 1995; Bannemerschult *et al*., 1997; Serfaty and Vree, 1998). Furthermore, the incidence of irregular bleeding with NuvaRing was lower than that generally observed for low-dose COC, even those containing EE 30 μg (Rabe *et al*., 1987; Corson, 1990; Brill *et al*., 1991; Fotherby, 1995). The latter is remarkable since the daily EE dosage with NuvaRing is 15 μg, of which only 50% is systemically available (Timmer and Mulders, 2000). It is likely that the continuous release of steroids contributes to the exceptionally good cycle control as observed with NuvaRing.

The occurrence of withdrawal bleeding is generally considered a positive attribute, as it reassures the user of continued absence of pregnancy. In this respect, the fact that absence of withdrawal bleeding occurred in only 0.6–2.1% of the cycles is a very positive finding. However, in view of the vaginal route of

administration, early and late withdrawal bleeding may be of relevance because of the need to remove or insert a ring during a bleeding/spotting event. The incidence of early withdrawal bleeding was low. Late withdrawal bleeding occurred more frequently but consisted mainly of spotting days only. Irrespective of whether a woman reported early or late withdrawal bleeding, the duration of withdrawal bleeding for all users was very similar to their situation before entering the study and ranged between 4.7 and 5.3 days over cycles 1–13.

As with any contraceptive method, compliance to the recommended regimen is crucial for its reliability. In particular, the scheduled ring-free period should not be prolonged since this may result in an increased risk of pregnancy. Compliance with the NuvaRing regimen was high. Nevertheless, prolonged ring-free periods occurred in 4.1% of cycles. The majority of these ring-free periods were at most 2 days longer than the recommended 1 week. Apart from regimen compliance, women could also have removed the ring during each insertion period of 3 weeks. Although it was allowed by protocol to remove the ring, e.g. if desired for intercourse, temporary ring removal was surprisingly infrequent as it occurred on only 1% of all ring days.

The incidence of side-effects with a contraceptive method is, in addition to cycle control, a major determinant of the overall acceptability of the method (Newton, 1995). No unexpected adverse events were experienced during use of NuvaRing, and the incidence of treatment-related complaints was generally low. All specific vaginal ring-related events, such as so-called device-related events (i.e. coital problems, foreign body sensation, and device expulsion) and vaginal discomfort were also captured as adverse events. These events were reported by a total of 4.1 and 2.4% of the women, respectively. Other complaints of interest concerned breast pain, nausea and vomiting. Breast pain occurred in only 2.8% of women and 1.9% of these pains were considered to be related to NuvaRing treatment. As this complaint is considered to be at least partly related to the oestrogen content of the combined contraceptive preparation, it is likely that the low incidence as reported in this study is related to the low dose of EE with the ring.

One of the most prominent side-effects as reported for users of a combined contraceptive vaginal ring releasing norethisterone acetate and EE was nausea, often associated with vomiting, particularly in the first cycle of ring use (Ballagh *et al*., 1994; Weisberg *et al*., 1999). This was ascribed to being probably due to release of accumulated EE near the ring surface during storage. The incidences of nausea and vomiting for users of NuvaRing were low during the whole treatment period; this suggests that high incidences of these events may be specific for users of the norethisterone acetate-EE vaginal ring.

During the study, a shift from normal cervical cytology at screening to abnormal (PAP grade III-IV) at the last visit was reported for a total of 21 women. It should be noted that the frequency of cervical cytology sampling was higher than in normal practice, thereby increasing the likelihood of detecting an abnormal result. In addition, the study was designed to include only women with normal results at screening, so it was not possible to detect improvements. In view of these factors, these data would not suggest an increased risk for cervical abnormalities with NuvaRing use. The latter is further supported by the observed incidence of ~2.8% (34 women) for a population of 1200 women as screened for this study with abnormal cervical cytology (PAP grade III–IV). Furthermore, previous investigations with a prototype Silastic vaginal ring releasing etonogestrel 120 μg/EE 15 μg detected no causative adverse changes in the cytological or bacteriological profiles of the vagina with 20 cycles of use (Roumen *et al*., 1996); this is in keeping with the low incidence of cervical abnormalities observed in the current study.

The most frequent causes for premature study discontinuation (3.6% of women) were, as expected, device-related events (such as foreign body sensation, coital problems, and device expulsion) and vaginal discomfort. As in previous observations with non-medicated rings (Roumen *et al*., 1990), these events decreased in frequency after the first cycles of use. Hardly any women discontinued because of bleeding problems. This is most probably related to the excellent cycle control as observed with NuvaRing. The overall discontinuation profile shows that NuvaRing is a highly acceptable method of contraception.

The acceptability data as collected via the questionnaire confirm that the majority of users were very satisfied with the vaginal ring as a contraceptive method. The women who completed, and also the majority of the women who discontinued the study, considered NuvaRing insertion and removal easy and did not experience interference between use of the ring and intercourse. Although the women who discontinued were less satisfied with the ring than those who completed the study, the majority (67%) would nevertheless recommend NuvaRing use to other women.

In conclusion, this study has demonstrated that NuvaRing is an effective contraceptive with excellent cycle control. It is an easily reversible, well-tolerated and well-accepted hormonal contraceptive that is convenient to use.

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