The combined contraceptive vaginal ring and bone mineral density in healthy pre-menopausal women

R.Massai¹, L.Mäkäräinen², A.Kuukankorpi³, C.Klipping⁴, I.Duijkers⁴ and T.Dieben⁵,6

¹Instituto Chileno de Medicina Reproductiva, Jose Victorino Lastarria 29, Depto 101, Santiago, Chile, ²Department of Obstetrics and Gynaecology, University of Oulu, SF-90220 Oulu, ³Perhesuunnitelunuevola, Satamakatu 17C, SF-33200 Tampere, Finland, ⁴Dinox Medical Investigations, Groenewoudseweg 317, 6524 TX Nijmegen, and ⁵Clinical Development Department, Contraception, NV Organon, 5340 BH Oss, The Netherlands

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BACKGROUND: Hormonal contraceptives have been associated with various effects on the bone mineral density (BMD) of pre-menopausal women. The aim of this study was to assess the effects of a vaginal contraceptive ring on BMD in pre-menopausal women and compare them with those of non-hormonal contraceptive use. METHODS: This open-label, multicentre study used dual-energy X-ray absorptiometry to measure BMD in the lumbar spine (L₂–L₄) and femoral neck regions. Subjects were assigned 3:1 to receive a contraceptive ring (n = 105) or a non-hormonal contraceptive control (n = 39) and were assessed after 13 and 26 cycles of contraceptive ring treatment or 12 and 24 months of control treatment. RESULTS: No change from baseline in BMD (Z-scores) was seen in contraceptive ring users (n = 73) at either time-point. In the control group (n = 30), BMD increased slightly from baseline resulting in significant differences (P < 0.001) between the two groups at cycle 26/month 24. These differences are not clinically relevant, although some degree of acquisition of peak bone mass might have been prevented in the contraceptive ring group. The contraceptive ring was generally well tolerated; a higher incidence of treatment-related adverse events was observed in the contraceptive ring group compared with the non-hormonal contraceptive control group. CONCLUSIONS: In healthy pre-menopausal women, 2 years of contraceptive ring use produced no changes in BMD.

Key words: bone mineral density/contraceptive/ethinylestradiol/etonogestrel/vaginal ring

Introduction

Although various studies have been conducted, the effects of oral contraceptives on bone mineral density (BMD) in pre-menopausal women are uncertain (Kuohung et al., 2000). Some studies have reported that oral contraceptives have a bone-sparing or protective effect on BMD (Corson, 1993). Others have reported that hormonal contraceptives have no effect (Reed et al., 2003) or even a negative effect on BMD (Prior et al., 2001). Differences in the amounts of contraceptive hormones used in these studies may have contributed to the discrepancies between these reports since there is evidence that the influence of estrogen upon bone is dose dependent. In post-menopausal women, doses of ethinylestradiol (EE) <15 µg have been correlated with a loss of bone whilst doses ≥25 µg have been correlated with a gain of bone (Horsman et al., 1983). Thus, although hormonal contraceptives may have a beneficial effect on BMD, this has not been firmly established and remains an area of debate. The predicted increase in the proportion of older people in the populations of industrialised nations demonstrates the need to evaluate the impact of hormonal contraceptives on bone metabolism in order to determine the potential long-term risks of increases in the prevalence of osteoporosis.

NuvaRing is a combined contraceptive vaginal ring that releases 15 µg EE and 120 µg of the progestogen etonogestrel per day. It is designed for 3 weeks continuous use followed by a 1 week ring-free period. Clinical trials have shown the ring to be an effective contraceptive with excellent cycle control and to be well tolerated, convenient and highly acceptable to users (Mulders and Dieben, 2001; Roumen et al., 2001; Dieben et al., 2002). The vaginal route of administration employed by NuvaRing offers several advantages over oral forms of hormonal contraception. These include convenient, once-monthly administration and delivery of a lower daily dose of EE than many oral contraceptives (typically ≥20 µg). Because the effect of estrogen on BMD may be dose-dependent, it is important to determine the effect of the low, daily dose of estrogen from NuvaRing on BMD. For this reason, an open-label, multicentre trial was conducted in which the effects of NuvaRing on BMD were studied in a population of healthy young women over a 2 year period.

The objective of this study was to assess the effects of NuvaRing on BMD and compare them with those of a control group comprising pre-menopausal women using a non-hormonal method of contraception.
Materials and methods
This open-label trial was carried out at two study centres in Finland, and at single centres in Chile and The Netherlands. The relevant local independent ethics committees or institutional review boards approved the final study protocol and amendment. The trial was carried out in accordance with the Declaration of Helsinki, International Conference on Harmonization and Good Clinical Practice guidelines. Written, informed consent was obtained from all subjects before the start of the study. The study also assessed the effect of NuvaRing on endometrial histology and these results will be published separately.

Subjects
It was intended that the trial would recruit 135 healthy women aged 18–35 years with a normal menstrual cycle of 24–35 ± 3 days and a body weight between 80 and 130% of ideal. The subjects included NuvaRing users and a control group and were recruited in a ratio of 3:1 NuvaRing users:control subjects. The control group comprised women who did not use a hormonal method of contraception. Permissible methods included non-hormonal medicated intrauterine device (IUD) supplied as trial medication, any alternative non-hormonal method of contraception or no contraceptive method at all. Women who were already using a non-hormonal medicated IUD were also allowed to participate in the trial.

Exclusion criteria included: a family history of osteoporotic fracture at age 70 years; endocrine disorder (including controlled diabetes, thyroid or parathyroid disease, Cushing’s disease); rheumatoid arthritis; significant scoliosis; engaging in vigorous exercise; abnormal concentrations of parathyroid hormone, calcitonin, cholesterol or triglycerides; heavy smoking (>10 cigarettes per day); the use of calcium supplements in combination with supplements of vitamin D or calcitonin or fluorides).

Procedures
Upon enrolment, each subject was given a code number. As the trial was not randomized, code numbers were given to subjects according to the numerical order in which they were enrolled.

The treatment period for the NuvaRing group was 26 consecutive cycles of 28 days. Each 28 day cycle comprised 21 days of NuvaRing treatment followed by a 7 day ring-free period. The treatment period for the control group was 24 months.

Subjects in the NuvaRing group were provided with verbal and written instructions on the use of NuvaRing. They received a single NuvaRing for each cycle of use. Those who had previously been using oral contraceptives had a washout period of ≥1 month and then inserted their first ring on day 5 of their normal cycle. After insertion, the ring had to remain in place for 21 consecutive days. In the control group, IUDs were inserted on one of the first 5 days of the subject’s normal cycle.

Study assessments
Subjects visited the study centres every 3 months for the duration of the study. At the screening visit, medical and gynaecological histories were taken, physical and gynaecological examinations were carried out, cervical cytology was examined and vital signs were measured. Measurements of BMD were carried out at screening and at the cycle 13/month 12 and cycle 26/month 24 visits, or the treatment discontinuation visit if ≥6 months had elapsed since the previous assessment. The primary end-points for the study were the change from baseline to the end of cycle 26 (month 24) in BMD in the lumbar spine (L2–L4) and the proximal femur (femoral neck) and assessment of the effects of NuvaRing on endometrial histology.

The BMD measurements were performed at each study centre or reference unit by dual-energy X-ray absorptiometry (DEXA). The measurements were carried out using a protocol provided by an independent company (SYNARC, San Francisco, CA, USA) who also reanalysed the data from all centres to ensure uniformity. Changes in BMD were assessed by measuring changes in Z-score, which is the distance in standard deviations of a data-point from the mean of a data set, defined here as:

\[
Z\text{-score} = \frac{\text{BMD value} - \text{mean (reference population, age dependent)}}{\text{SD (reference population)}}
\]

The mean and SD values for the reference population were taken from the GE Lunar Corp. (Madison, WI, USA) Ref. 10/97 for Caucasian women. A decrease or increase of 1 SD (Z-score –1 or +1) is deemed clinically relevant as this difference would translate into a large difference in the risk of fracture in the older woman (World Health Organization Study Group, 1994).

Further safety parameters included physical and gynaecological examinations and measurement of haematological and biochemical parameters, which were carried out at the cycle 13/month 12 and cycle 26/month 24 visits. At the 3-monthly visits, vital signs were monitored and information on adverse events was collected through questioning or examination of the subject.

Statistical analyses were carried out using the following subject populations: all-subjects-allocated (ASA), all-subjects-treated (AST), intent-to-treat (ITT) and per-protocol (PP). The ASA group consisted of all subjects allocated to a treatment group and given an identification number. The AST group consisted of all subjects who used at least one vaginal ring plus all the subjects in the control group. The ITT group was a subset of the AST group, consisting of subjects for whom at least one BMD result was available. The PP group comprised all subjects from the ITT group without any major protocol violations.

The primary analysis for both BMD parameters, L2–L4 and the femoral neck, was the change from baseline in Z-scores for 2 year completers. Analyses were performed on the ITT and PP populations for cycle 13/month 12 and cycle 26/month 24 (or the last assessment) using analysis of covariance (ANCOVA) with centre and treatment group as factors and baseline Z-score as covariate. Analyses were corrected for longitudinal analysis, scanner movements and cross-calibration.

Study group sizes were based on power calculations that used the anticipated change from baseline to 2 years in Z-scores of BMD measurements for the lumbar spine and the femoral neck. Based on observations from a previous study (Beerthuizen et al., 2000), it was anticipated that 100 NuvaRing users and 35 control subjects would need to be enrolled. After 2 years, this would give 50 and 31 completers in the NuvaRing and control groups respectively. Based on an SD of change from baseline for Z-scores ranging from 0.20 to 0.45, these numbers of completers would allow detection of a difference in mean change from baseline in Z-scores after 2 years of δ = 0.3 (detectable difference) with a power of >80%.

Results
Demographics and baseline characteristics
A total of 144 subjects was enrolled into the study (the ASA population, Figure 1) which ran between October 1999 and June 2003. Of the 105 women in the NuvaRing group, two did not receive treatment. Of the 39 women in the control group, 18 were already fitted with an IUD, 16 received a Multiload 375 device as study treatment and only five used an alternative, non-hormonal method of contraception or no contraception at all. This left 142
subjects in the AST population. A further 15 subjects missed either an endometrial biopsy and/or a BMD measurement and were excluded, leaving 127 subjects in the ITT population (NuvaRing = 93; control = 34). Since there were no major protocol violations, there were also 127 subjects in the PP population.

All subjects who entered the study were confirmed as healthy after physical and laboratory examinations had been performed and medical histories had been taken. Baseline demographics and characteristics are shown in Table I. The two groups were similar in their baseline characteristics apart from a small difference in age (26.6 years in the NuvaRing group versus 29.1 years in the control group) and a difference in previous oral contraceptive use (44.7% in the NuvaRing group versus 2.6% in the control group). Also, the proportion of women who were either nulligravid or nulliparous was greater in the NuvaRing group (54.4 and 57.3%, respectively) compared with the control group (15.4% for both).

In the NuvaRing group, 27 women (26.2%) discontinued, 16 due to an adverse event (15.5%): four women experienced depression, two experienced vaginal discomfort, two had leukorrhoea, two had acne, and there were single cases of headache, pruritus, vaginitis and leukorrhoea. All were considered possibly or probably related to treatment except for the cramped legs and paraesthesia, cervical HPV infection and positive smear test, which were considered not to be treatment-related. Eight women (20.5%) discontinued in the control group, two (5.1%) due to adverse events; these were single cases of hypothyroidism (not treatment-related) and menstrual disorder (treatment-related).

No pregnancies occurred in the NuvaRing group during the treatment period. In the control group, two pregnancies occurred during the treatment period, both in subjects using an IUD.

For study completers in the ITT population, the mean Z-scores for lumbar spine and femoral neck in the NuvaRing group did not show any significant change from baseline after 2 years of treatment (Table II). In the control group, the mean Z-scores for lumbar spine and femoral neck increased slightly from baseline over 2 years. This increase in the control group was within 1 SD (Z-score of 1). Similar results were observed for the PP population (data not shown).

The ANCOVA analysis of the NuvaRing and control groups showed that at month 12/cycle 13, there was a significant difference in the change in Z-scores from baseline for lumbar spine (P = 0.003) but not for femoral neck. At cycle 26/month 24 there was a statistically significant difference in the Z-score change from baseline for both lumbar spine and femoral neck (P < 0.0001 for both, Table III). These differences were caused by the increases in mean Z-scores seen in the control group. The difference between the two treatments did not reach 1 SD. The results for the PP population were similar (not shown).

In the NuvaRing group, 81.6% of subjects experienced an adverse event; in the control group, 76.9% experienced an adverse event. More subjects in the NuvaRing group (51.5%) had method-related adverse events than in the control group, who were not using hormonal contraception (20.5%). The most frequently reported NuvaRing treatment-related adverse events were headache, pruritus, vaginitis and leukorrhoea.

There were no clinically relevant findings relating to haematological and biochemical values. Physical, pelvic and breast examinations showed no clear differences between treatments. No clinically significant changes in blood pressure were observed in either group. In the NuvaRing group, 31 subjects (30.7%) had a relative increase in body weight from baseline.

### Table I. Demographics and baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>NuvaRing (n = 103)</th>
<th>Control (n = 39)</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>26.6 (4.9)</td>
<td>29.1 (4.1)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64.2 (7.8)</td>
<td>63.9 (7.7)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>167.7 (7.2)</td>
<td>166.0 (6.9)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.8 (2.3)</td>
<td>23.2 (2.8)</td>
</tr>
<tr>
<td>Femoral neck Z-Score</td>
<td>0.109 (0.087)</td>
<td>0.277 (0.123)</td>
</tr>
<tr>
<td>Lumbar spine Z-Score</td>
<td>1.233 (0.123)</td>
<td>1.235 (0.127)</td>
</tr>
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Data presented are for the all-subjects-treated group.
The change in bone mineral density (BMD) with age has been well documented. BMD increases until the age of 20–25 years, reaching a peak at around 30 years of age. After peaking, BMD remains constant for several decades until the menopause, after which the rate of loss increases dramatically. The increase in BMD with age is seen as the addition of bone mass during the third decade of life. This increase is followed by a relative decrease in body weight from baseline ≥7%, whereas in the control group, seven subjects (17.9%) experienced such an increase. Nine subjects (8.9%) in the NuvaRing group and four (10.3%) in the control group had a relative decrease in bone mass from baseline ≥7%.

### Discussion

This study showed that 2 years of treatment with NuvaRing did not change BMD in the lumbar spine or femoral neck regions of healthy pre-menopausal women. However, in the control group, BMD increased slightly from baseline to the end of treatment. This increase produced a statistically significant difference in the change in BMD from baseline to the end of the 2-year treatment period between the NuvaRing and control groups. Because this difference was <1 SD, it could be argued that this is not clinically relevant (World Health Organization Study Group, 1994). One could also say that some degree of acquisition of peak bone mass might have been prevented in the NuvaRing group.

BMD in women varies according to age and hormonal status. Although by the age of 17 or 18 years the vast majority of peak bone mass has already been achieved, small increases in bone mass during the third decade of life have been demonstrated in several studies, reaching a peak at age 20–25 years (Burkman, 2001). After peaking, BMD remains constant for 10 years and then declines gradually until the menopause, after which the rate of loss increases dramatically. The increased risk of osteoporosis in older women has been associated with the post-menopausal decrease in estrogen (Compston, 2001). Estrogen deficiency in younger women, caused by hypothalamic–pituitary disorders such as late menarche or premenopausal amenorrhea (e.g. anorexia nervosa, excessive exercise and hyperprolactinaemia), is also associated with reduced BMD (Compston, 2001). Thus, there is a close association between BMD and estrogen concentrations.

Reports of the lack of effect of hormonal contraceptives on BMD continue to appear, as illustrated by recent reports of two randomized, prospective studies. One showed that 3 years treatment with a low dose 20 µg EE/100 µg levonorgestrel formulation and a standard formulation containing 30 µg EE/150 µg levonorgestrel had no effect on BMD (Endrikat et al., 2004). The other study involved a 1-year comparison of ultra-low and low-dose formulations containing EE and gestodene (15 µg/60 µg and 20 µg/75 µg respectively) and also found no difference in BMD with either formulation (Nappi et al., 2003). Several cross-sectional studies have also been published recently, including one that involved 2472 subjects. All of these reported that hormonal contraceptives (oral or depot injection) had no effect on BMD (Petitti et al., 2000; Ferro et al., 2001; Wannischetal, 2002). These reports cast doubt on the association of hormonal contraceptives with improvements in BMD, and agree with the findings of the present study.

The literature also contains a few reports of associations between hormonal contraceptives and loss of BMD. A crosssectional study of 524 pre-menopausal women in Canada found that women who had ever used oral contraceptives had

<table>
<thead>
<tr>
<th>Table II. Change in Z-scores from baseline for study completers in the intent-to-treat group</th>
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<td>-----------------------------------------------</td>
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<tr>
<td>Lumbar spine (L2–L4)</td>
</tr>
<tr>
<td>Cycle 13/month 12</td>
</tr>
<tr>
<td>Cycle 26/month 24</td>
</tr>
<tr>
<td>Last measurement</td>
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<tr>
<td>Femoral neck</td>
</tr>
<tr>
<td>Cycle 13/month 12</td>
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<tr>
<td>Cycle 26/month 24</td>
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<tr>
<td>Last measurement</td>
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Cycles 13 and 26 were used in the NuvaRing group calculations and months 12 and 24 were used in the control group calculations.
lower BMD values than those who had never used them (Prior et al., 2001). Furthermore, the use of depot injections of medroxyprogesterone, in a prospective, 12 month controlled study of 155 women aged 18–33 years was associated with a decrease in BMD compared with women who had not used hormonal contraceptives (Berenson et al., 2001). However, a 2 year, comparative study of the etonogestrel contraceptive implant (Implanon) in 73 women aged 18–40 years found no effect on BMD (Beerthuizen et al., 2000). The difference in effect on BMD of these two progestogen-only methods may be dose-related: endogenous estrogen levels during implanted etonogestrel use may be higher compared with depot injections of medroxyprogesterone acetate because of lower daily exposure to progestogen.

Our study possessed several strengths. The inclusion and exclusion criteria were carefully designed to control various factors that have been shown to affect BMD. These include smoking, BMI and exercise (Mazess and Barden, 1991; Corson, 1993). Also, the 2 year duration of our study was sufficient to allow detectable changes in BMD to occur and, unlike many other studies of the effects of hormonal contraceptives on BMD, the design of this study was prospective. The open-label design was a weakness of our study. This is linked to the difficulties involved in attracting women to participate in any study in which they would be unsure about their contraceptive status and consequent risk of pregnancy. In addition, a woman’s contraceptive choice needs to be respected. Many published studies in this area have not used a randomized design, as illustrated in the review Kuohung et al. (2000).

In conclusion, the findings of the present study demonstrate that long-term use of NuvaRing produced no changes in BMD in pre-menopausal women.

Acknowledgements

We are grateful to M.Kepers for help with the statistical analysis. This study was supported by NV Organon, Oss, The Netherlands.

References


Submitted on January 4, 2005; resubmitted on April 18, 2005; accepted on April 22, 2005.