A prospective study of the forearm bone density of users of etonorgestrel- and levonorgestrel-releasing contraceptive implants

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BACKGROUND: The aim of the study was to compare bone mineral density (BMD) before insertion and at 18 months of use of etonorgestrel- and levonorgestrel-releasing contraceptive implants. METHODS: One hundred and eleven women, 19–43 years of age, were randomly allocated to two groups: 56 to etonorgestrel and 55 to levonorgestrel. BMD was evaluated at the midshaft of the ulna and at the distal radius of the non-dominant forearm using dual-energy X-ray absorptiometry before insertion and at 18 months of use. RESULTS: There was no difference in baseline demographic or anthropometric characteristics, or in BMD of users of either model of implant. BMD was significantly lower at 18 months of use at the midshaft of the ulna in both groups of users. However, no difference was found at the distal radius. Multiple linear regression analysis showed that the variables associated with BMD at 18 months of use in both implant groups were baseline BMD, body mass index (BMI) and difference in BMI (0 versus 18 months of use). CONCLUSIONS: Women of 19–43 years of age using either one of the implants showed lower BMD at 18 months of use at the midshaft of the ulna, however, without a difference at the distal radius.

Key words: bone mineral density/contraceptive implants/etonorgestrel/levonorgestrel.

Introduction

The role of hormonal contraceptives in BMD, bone loss, osteoporosis and fracture risk is controversial. Recently, the US Food and Drug Administration required the inclusion in the package insert of the injectable contraceptive depot medroxyprogesterone acetate (DMPA, Depo-provera®, Pfizer, USA) a black box with a warning notice that DMPA may impair BMD (United States Food and Drug Administration, 2004). This statement is in agreement with several publications showing that the use of DMPA may affect BMD (Cundy et al., 1991, 1998; Gbolade et al., 1998; Tang et al., 1999; Petitti et al., 2000); however, these findings contrast with others in which no significant effect was observed (Taneepanichskul et al., 1997; Bahamondes et al., 1999; Perrotti et al., 2001). Regarding the other progestogen-only contraceptive methods, the World Health Organization (WHO) recently published a statement on hormonal contraception and bone health to the effect that: ‘...data on levonorgestrel implants suggest no adverse effect on BMD’ and in the recommendations stated: ‘There should be no restriction on the use of other [than DMPA] progestogen-only contraceptive methods among women who are otherwise eligible to use these methods, including no restrictions on duration of use’ (World Health Organization, 2005).
Demographic and anthropometric characteristics in users of both single-rod, etonogestrel-releasing implant (Implanon®; NV Organon, Oss, The Netherlands) and 55 women received a two silicone sealed envelopes prepared at the WHO. Fifty-six women received a kind of implant using a computer-generated randomization system and sealed envelopes prepared at the WHO. Fifty-six women received a single-rod, etonogestrel-releasing implant (Implanon®; NV Organon, Oss, The Netherlands) and 55 women received a silicone rod levonorgestrel-releasing implant (Jadelle®, Schering Oy, Turku, Finland). All the insertions were performed within the first 5 days of the menstrual cycle and there was not wash-out time between the last contraceptive method used and implant insertion. Nine women (four in the Implanon group and five in the Jadelle group) were in amenorrhea at the time of insertion due to use of DMPA. The enrolment of volunteers was carried out between August 2003 and July 2004.

To be eligible, the volunteers should not have been pregnant or lactating within the 12 months preceding enrolment. Exclusion criteria included women with chronic diseases such as diabetes mellitus, chronic renal failure, hyper/hypothyroidism, hyper/hypoparathyroidism, hepatitis, cancer or pituitary diseases. In addition, women who had used calcium supplementation and/or vitamin D, anticonvulsants, any kind of corticosteroids, thiazide diuretics or drugs for the treatment of thyroid disease were also excluded.

Sample size was calculated based on the results of the study by Beerthuizen et al. (2000) assuming a difference in BMD of 0.014 g/cm² between pre-insertion and 18 months of implant use, a β of 0.20, α of 0.05, and a difference of 0.008. Therefore, a sample size of 48 women in each group would be sufficient to provide adequate power (Pocock, 1987).

Definition of variables
The dependent variable, BMD, was defined as the relationship between bone mineral content (g/cm²) and the area of the bone measured. The independent variable was the kind of implant used by the woman. The control variables included race, number of pregnancies and deliveries, time of exclusive and partial breast-feeding, body mass index (BMI, kg/m²), duration of exercise practice, smoking habits (Kanis et al., 2005a), and coffee and alcohol consumption patterns (Kanis et al., 2005b).

Results
Selected demographic, anthropometric and some obstetric characteristics of the two study groups are shown in Table I. The mean age of patients at implant insertion was 27.9 ± 0.7 and 27.1 ± 0.6 years for Implanon and Jadelle users, respectively. There were no significant differences in the pre-insertion characteristics of women in the two groups. In both groups, almost 40% of the women were housewives, 45% worked in retail or services, while 15% were professional workers. Seventy-seven percent of Implanon users and 82% of Jadelle users were white. Almost an equal proportion of women had used hormonal or non-hormonal contraceptive methods as their last method before the insertion of the implant in both groups, including DMPA used by four and five women in the Implanon and Jadelle groups, respectively. Fourteen women in the

### Table I. Demographic and anthropometric characteristics in users of both models of contraceptive implants pre-insertion

<table>
<thead>
<tr>
<th>Variables</th>
<th>Study group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Implanon users (n = 56)</td>
<td>Jadelle users (n = 55)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>27.9 (0.7)</td>
<td>27.1 (0.6)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.8 (1.2)</td>
<td>64.1 (1.4)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160.3 (0.8)</td>
<td>160.7 (0.8)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.0 (0.5)</td>
<td>24.8 (0.5)</td>
</tr>
<tr>
<td>No. of pregnancies</td>
<td>1.2 (0.8)</td>
<td>1.3 (0.7)</td>
</tr>
<tr>
<td>No. of deliveries</td>
<td>1.1 (0.7)</td>
<td>1.2 (0.7)</td>
</tr>
<tr>
<td>Race (White women)</td>
<td>77%</td>
<td>82%</td>
</tr>
<tr>
<td>Smokers</td>
<td>14%</td>
<td>22%</td>
</tr>
<tr>
<td>Last contraceptive method</td>
<td>48%</td>
<td>56%</td>
</tr>
<tr>
<td>IUD/condom/withdrawal</td>
<td>48%</td>
<td>56%</td>
</tr>
<tr>
<td>COC/CIC</td>
<td>45%</td>
<td>35%</td>
</tr>
<tr>
<td>DMPA</td>
<td>7%</td>
<td>9%</td>
</tr>
</tbody>
</table>

IUD = intrauterine device; COC = combined oral contraceptives; CIC = combined injectable contraceptives; DMPA = depot medroxyprogesterone acetate.

aPearson $r^2$ test.

bMann–Whitney test for independent samples.

c$\chi^2$ test with Yates correction.

dIUD/condom/withdrawal versus COC/CIC/DMPA: $P = 0.372$. 

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Implanon group and 10 in the Jadelle group were amenorrhoeic at 18 months of evaluation Mean BMI (kg/m²) at insertion was 24.0±0.5 and 24.8±0.5 for Implanon and Jadelle users, respectively. At 18 months of use, BMI increased significantly to 24.7±0.5 in Implanon users (P<0.021) and 25.6±0.5 in Jadelle users (P<0.001).

The BMD at the midshaft of the ulna was significantly lower at 18 months of use compared with baseline in Implanon users (−3.75%) (P<0.001) and Jadelle users (−3.36%) (P<0.002). However, at the distal radius, there were no significant differences at 18 months when compared with baseline values in either group of implant users (Table II). Moreover, there were no significant differences in BMD between users of Implanon and Jadelle at baseline and at 18 months of use. Multiple linear regression analysis showed that the variables significantly associated with lower BMD at 18 months of use of both implants and at both evaluation sites (midshaft of the ulna and distal radius) were the corresponding baseline BMD, initial BMI (P<0.001), and the difference in BMI between baseline and 18-months (Table III). Although a few women were using DMPA before the implant insertion, we explored whether the multiple linear regression analysis identified this variable as associated with lower BMD at 18 months of use, when compared with previous use of the other contraceptive methods. No relationship was observed.

### Discussion

Our results showed that at 18 months of use, Implanon users presented a significant reduction in BMD (−3.75%; −0.5 SD) at the midshaft of the ulna; however, there was no significant change at the distal radius (−2%; −0.3 SD). As far as we know, there is only one study in which BMD was evaluated in users of Implanon (Beerthuizen et al., 2000). The authors studied BMD at the spine, femoral neck, Ward’s triangle, trochanter and distal radius of 44 users and 29 non-users up to 2 years, and BMD was similar at baseline and 24 months. Moreover, there were no differences in measurements between Implanon users and non-users. However, this study showed a slight decrease in BMD at the femoral neck, but the magnitude of this decrease failed to reach significance of 1 SD (World Health Organization, 1994).

Implanon inhibits ovulation, and estrogen was reduced to early follicular phase levels at the beginning of implant use. Although estrogen levels show a tendency to increase over the years of use, there are no cyclical peaks of estrogen. Levels are, however, higher than those observed in users of DMPA (Makarainen et al., 1998), and amenorrhoea occurs in only ~20% of users (Croxatto et al., 1999). Consequently, we did not expect a reduction in BMD because the levels of estradiol were similar to those of non-users.

Users of Norplant or Jadelle showed, at the first year of use, only 14% of the cycles with luteal activity, and this rate increased over the years of use, with declining serum levonorgestrel. In addition, mean estradiol levels were very similar between users and non-user controls; however, cases with low and high levels mainly among those women with menstrual irregularities were observed (Croxatto et al., 1988; Croxatto, 2002). Consequently, as stated with Implanon, due to unaffected estradiol levels, Jadelle could not influence the BMD. The users of Jadelle showed similar results to those of Implanon users, and at 18 months of exposure those women presented a significant reduction in BMD at the midshaft of the ulna (−3.36%; −0.4 SD), although there were no significant changes at the distal radius (−1%; −0.2 SD). Although there is no information regarding BMD in users of Jadelle, this implant releases a similar daily amount of levonorgestrel to Norplant and results may therefore be comparable (Croxatto, 2002; Meirik et al., 2003). However, our results may be biased by the fact that the increase in BMI between baseline and 18 months of use may have protected the women against bone loss.

The results of cross-sectional and longitudinal studies in Norplant users have shown no significant differences (Naessen et al., 1995; Taneepanichskul et al., 1997) or increase in BMD (Di et al., 1999; Diaz et al., 1999) compared with non-users. In addition, the larger study conducted by the WHO (Petitti et al., 2000) in 610 Norplant users observed that BMD was lower at the midshaft of the ulna when compared with measurements taken in non-users. However, the difference was only within 1 SD of the mean of the non-users. Nevertheless, no study, with the exception of that conducted by the WHO (Petitti et al., 2000), has evaluated women for >24 months of use.

There are concerns about the use of progestogen-only contraceptives and their impact on BMD, osteopenia, osteoporosis and fracture risk, mainly during the post-menopausal years.

### Table I. Bone mineral density according to type of implant use and section of the forearm

<table>
<thead>
<tr>
<th></th>
<th>Midshaft ulna</th>
<th>Distal radius</th>
<th>P-value</th>
<th>P-valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implanon</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.479 (0.005)</td>
<td>0.409 (0.005)</td>
<td>0.001</td>
<td>0.177</td>
</tr>
<tr>
<td>18 months</td>
<td>0.461 (0.006)</td>
<td>0.401 (0.008)</td>
<td>0.002</td>
<td>0.694</td>
</tr>
<tr>
<td>Jadelle</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.475 (0.006)</td>
<td>0.396 (0.007)</td>
<td>0.002</td>
<td>0.694</td>
</tr>
<tr>
<td>18 months</td>
<td>0.459 (0.007)</td>
<td>0.400 (0.008)</td>
<td>0.002</td>
<td>0.694</td>
</tr>
</tbody>
</table>

aWilcoxon test.

### Table III. Multiple linear regression coefficients of variables influencing bone mineral density at both sections of the forearm evaluated in both groups of users

<table>
<thead>
<tr>
<th>Variable</th>
<th>Linear regression coefficient</th>
<th>SE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midshaft of the ulna</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline BMI</td>
<td>0.833</td>
<td>0.059</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline BMI</td>
<td>0.006</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Difference in BMI (0 versus 18 months of use)</td>
<td>0.004</td>
<td>0.001</td>
<td>0.002</td>
</tr>
<tr>
<td>Constant</td>
<td>−0.097</td>
<td>0.033</td>
<td>0.004</td>
</tr>
<tr>
<td>Distal section</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline BMI</td>
<td>0.784</td>
<td>0.083</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline BMI</td>
<td>0.008</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Difference in BMI (0 versus 18 months of use)</td>
<td>0.006</td>
<td>0.002</td>
<td>0.004</td>
</tr>
<tr>
<td>Constant</td>
<td>−0.104</td>
<td>0.041</td>
<td>0.010</td>
</tr>
</tbody>
</table>

BMD = bone mineral density; BMI = body mass index.
This concern is greater in users of DMPA due to the transient and profound hypoestrogenism observed during use of this contraceptive method that has been well documented, especially in amenorrhoeic women (Gbolade et al., 1998; Bahamondes et al., 2000). However, even in these users, the effect on BMD is inconsistent, with results from some studies showing a lower BMD compared with non-users (Cundy et al., 1991, 1998; Gbolade et al., 1998; Tang et al., 1999; Petitti et al., 2000), while others show no significant effect (Bahamondes et al., 1999; Perrotti et al., 2001). Most of the studies show a reduction within the limits of 2.5 SD compared with controls. Former users of DMPA could have a lower BMD than former users of other contraceptive methods (Cundy et al., 1991, 1998; Gbolade et al., 1998; Tang et al., 1999; Petitti et al., 2000); however, we did not evaluate these women separately due to the number of cases in each group. Nevertheless, the BMD was not different either at baseline or at 18 months of use in former users of DMPA and of the other contraceptives.

The medical community has other issues still to be resolved regarding the use of hormonal contraceptives and BMD, such as the effect of past use on the future life of women; the effect of use in adolescence and during the pre-menopausal years; and the effect of their use on fracture risk.

Regarding the effect of past use on the future life of women, unfortunately there are few studies in the literature on former users of progestogen-only methods. The exception are data on former users of DMPA which have reported no significant differences between former users and controls controlled for age at start of use and years between cessation of use and the menopause. The explanation could be that the effect of DMPA on BMD is reversible with the cessation of hypoestrogenism (Orr-Walker et al., 1998). In addition, the study by Petitti et al. (2000) showed no differences between past users of Norplant implants and never users of this contraceptive.

The effect of the use of Norplant implants on the BMD of adolescents was evaluated in one study (Cromer et al., 1996). BMD was assessed at baseline and after 1 and 2 years of use, and showed an increase of 2.5 and 9.3% at 1 and 2 years of use, respectively, without a significant difference when compared with non-users. There are no data on the effect of implants during the menopausal transition, and the majority of studies have been carried out in women ≤40 years of age. Our data do not permit us to draw conclusions about the effect of these implants on adolescents or in women over 40 years of age because only three women in our sample population were under 20 or over 40 years old.

There is no information available on the effect of progestogen-only implant use on fracture risk. There is only one study (Lappe et al., 2001) which used ultrasonography to evaluate stress fracture in female military recruits and found that current use of DMPA at baseline presented an increased risk [relative risk (RR) 1.7; 95% confidence interval (CI) 1.01–2.90]. The other significant variables were current or past smoking, alcohol drinking of >10 drinks/week, corticosteroid use and lower adult weight.

Our study showed a significant reduction in BMD at the midshaft of the ulna; however, this reduction remained within the limit of 1 SD. These results must be interpreted with caution because we do not know whether this loss is of clinical significance during long-term use or whether these women may return to pre-treatment BMD values following discontinuation of the method. In addition, although the reduction in BMD was small (World Health Organization, 1994), we do not know whether it has the same effect as the reduction that occurs during breast-feeding (Diaz et al., 1999; Karlsson et al., 2001) or whether it has any significant effect on fracture risk after the menopause (Cefalu, 2004).

This study used a larger sample size than that in a previous study carried out with Implanon (Beethuizen et al., 2000). Moreover, it is the first study in which Implanon is compared with Jadelle, and the study was carried out independently of the manufacturer of either contraceptive implant (Smith, 2003). The limitations to our study are that we measured BMD only at the forearm, whereas the lumbar spine and the femoral neck are the anatomical sites most predictive of fracture risk, although forearm BMD also provides a good predictive value (Marshall et al., 1996). Moreover, BMD was evaluated only at 18 months of use, whereas the effects of hormonal contraceptives may be observed over many years of use and even after discontinuation. However, it has been suggested that the effect of the past use of progestogen-only contraceptives on BMD may be eliminated following discontinuation of use (Orr-Walker et al., 1998; Petitti et al., 2000). In addition, although BMD is one of the best indicators of bone health, risk of fracture is a better indicator but one that cannot be evaluated.

In conclusion, users of both contraceptive implants showed lower BMD at midshaft of the ulna but similar BMD at the distal radius at 18 months of use when compared with baseline. This cohort of women is currently being followed-up and we will measure BMD again at 36 months of use.

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