

**A three-year longitudinal evaluation of the forearm bone density of users of
etonogestrel- and levonorgestrel-releasing contraceptive implants**

Running title: Bone density on users of contraceptive implants

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Abstract

BACKGROUND: The aim of this study was to evaluate bone mineral density (BMD) at baseline and at 18 and 36 months of use of etonogestrel (ENG)- and levonorgestrel (LNG)-releasing contraceptive implants. This is a continuation of a previous study in which BMD was evaluated at baseline and at 18 months of use. **METHODS:** A total of 111 women, 19–43 years of age, were randomly allocated to use one of the two implants. At 36 months of follow-up, only 36 and 39 women were still using the ENG- and LNG-releasing implants, respectively. BMD was evaluated at the distal and at the ultra-distal radius of the non-dominant forearm using dual-energy X-ray absorptiometry. **RESULTS:** There was no difference in the BMD of users of either implant at 18 and at 36 months. BMD was significantly lower at 18 and at 36 months at the distal radius in both groups of users compared to pre-insertion values; however, no difference was found at the ultra-distal radius. **CONCLUSIONS:** Women 19–43 years of age using either one of these two contraceptive implants for 36 months had lower BMD values at the distal radius compared to pre-insertion values; however, no difference was found at the ultra-distal radius.

Key words: bone mineral density/contraceptive implants/etonogestrel/levonorgestrel

Background

Although hormonal contraceptive methods are in use worldwide, their effect on bone mineral density (BMD) is a controversial issue, particularly with reference to the use of progestogen-only (p-only) methods [1]. Users of hormonal contraceptives include women of different ethnic groups and ages, ranging from adolescence through the final reproductive years. The impact of these contraceptive methods on BMD may be measured during use, after discontinuation or in the postmenopause, and may also be evaluated according to bone loss or risk of osteoporotic fracture [1].

It has been well-established that hypo-estrogenism is one of the most important factors related to bone formation and resorption during a woman's lifetime [2,3] and it is also known that the use of some of the p-only contraceptive methods, mainly the injectable depot-medroxyprogesterone acetate (DMPA), affects serum levels of estradiol [4,5]. For this reason and based on several publications showing that the use of DMPA may affect BMD [4,6-8], the US Food and Drug Administration [9] and the United Kingdom Committee on the Safety of Medicines [10] required inclusion in the package insert of DMPA of a warning that the drug may impair BMD.

Although a recommendation issued by the World Health Organization (WHO) also established some restrictions to the use of DMPA, principally in adolescents and in women in the menopausal transition [11], it has also established that the data on levonorgestrel (LNG)-releasing implants suggest no adverse effect on BMD and recommended no restriction on the use of other p-only contraceptive methods by women who are eligible to use them [11].

Since data on BMD in users of etonogestrel (ENG)- and LNG-releasing contraceptive implants is scarce [8,12-15], this study was conducted with the aim of evaluating BMD prior to insertion and following 36 months of use in women who opted to use ENG- and LNG-releasing subdermal contraceptive implants.

Methods

This is a continuation of a previous study in which data was presented on BMD levels prior to insertion and at 18 months of use of these two types of contraceptive implant [15]. A total of 111 women, 19–43 years of age, were evaluated at the Human Reproduction Unit, Department of Obstetrics and Gynecology, School of Medicine, Universidade Estadual de Campinas (UNICAMP), Campinas, Brazil. The Ethical Committee of the institution approved the study, and all participants signed an informed consent form prior to admission.

The methods of this study have been published previously [15], together with the results of BMD at baseline and at 18 months of use. Briefly, the women comprised a subset of participants from a larger study conducted by the UNDP/UNFPA/World Bank/WHO Special Programme in Research Training in Human Reproduction, World Health Organization. Women requesting an implant as a contraceptive method were randomly allocated to one of the two kinds of implant using a computer-generated randomization system and sealed envelopes. Fifty-six women received a single-rod, ENG-releasing implant (Implanon[®], NV Organon, Oss, The Netherlands) and 55 women received a two-silicone-rod, LNG-releasing implant (Jadelle[®], Bayer-Schering Pharma Oy, Turku, Finland). All the insertions were performed within the first 5 days of the menstrual cycle

and there was no 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 the use of DMPA.

Based on a previous study [14], sample size was estimated at 48 women in each group assuming a difference in BMD of 0.014 g/cm^2 between pre-insertion and 18 months of implant use, an α of 0.20, β of 0.05, and a difference of 0.008 [16].

Definition of variables

The dependent variable, BMD, was defined as the relationship between bone mineral content (g/cm) 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/m^2), duration of exercise practice, smoking habits [17], and coffee and alcohol consumption patterns [18].

Bone mineral density measurement

BMD was measured in three opportunities in the non-dominant forearm at distal and ultra-distal radius with the same equipment of dual-energy X-ray absorptiometry (DXA) (DTX-200; Osteometer Meditech A/S Co., Rodovre, Denmark). Two measurements of BMD were taken in each woman: at the distal radius (where cortical bone predominates), at the point where the radius is 8 mm from the ulna; and at the ultra-distal radius near the articulation with the carpal bones (where trabecular bone predominates [65%]). The equipment identified the 8 mm distance between ulna and radius. This ensured that the

same area was assessed every time. The equipment was calibrated by twice-daily phantom measurements with a device provided by the manufacturer. The calibration, positioning, assessment and calculation were performed automatically in order to minimize the operator errors. The in vivo accuracy is >97% and precision >99% and the coefficient of variation (CV) was 0.8%

Statistical analysis

Comparison of demographic, anthropometric and obstetric variables and BMD between the two groups was performed using Pearson and Yates' χ^2 tests as appropriate. To compare BMD at baseline and at 36 months, Wilcoxon's non-parametric test or Student's *t*-test was used [19]. The data are presented as mean \pm standard deviation (SD).

Results

Of the 111 women who underwent BMD measurement prior to insertion and at 18 months of implant use, only 39 and 36 women were still in use of Jadelle[®] and Implanon[®], respectively, at 36 months of evaluation. The decrease in the number of cases was due to premature removals. In our previous publication [15], selected demographic, anthropometric and some obstetric characteristics were presented for the two study groups, confirming that the two groups were similar on the day of implant insertion. Mean BMI (kg/m²) for Jadelle[®] and Implanon[®] users was 24.8 ± 0.5 and 24.0 ± 0.5 , respectively, at baseline, increasing to 25.4 ± 0.6 and 24.4 ± 0.6 in the two groups of users, respectively, at 36 months of use. Only two women in the Implanon[®] group were in amenorrhea at 36 months of evaluation.

The BMD at the distal radius was significantly lower at 18 and at 36 months of use compared with baseline measurements in both Implanon[®] users (-5.90%) ($P < 0.001$) and Jadelle[®] users (-4.44%) ($P < 0.002$). However, at the ultra-distal radius, there were no significant differences in BMD at 18 and 36 months compared with baseline values in either group of implant users (Table). Moreover, there were no significant differences in BMD between users of Implanon[®] and Jadelle[®] at baseline or at 18 and 36 months of use.

Discussion

Our results show that there were no statistically significant differences in BMD at ultra-distal radius between the users of the two types of subdermal contraceptive implants prior to implant insertion or at 18 and at 36 months of use, and these results were almost identical to those found at pre-insertion and at 18 months of use [15]. Although there was a significant reduction in BMD at the distal radius in both groups of women, no significant changes were found at the ultra-distal radius where trabecular bone predominates. These results are in agreement with those reported from a previous study [14] in which BMD was evaluated in Implanon[®] users at pre-insertion and at 2 years of use at the spine, femoral neck, Ward's triangle, trochanter, and distal radius. They reported BMD to be similar prior to insertion and at 24 months of use, although a slight decrease in BMD was observed at the femoral neck; however, this decrease was less than one SD [20].

With respect to the group that used Implanon[®], in theory our results were to be expected because although this implant inhibits ovulation, estrogen only decreased to early follicular phase levels at the beginning of use. Moreover, estrogen levels show a tendency to increase over the years of use and amenorrhea has been reported in ~20% of users, a

higher proportion than the ~5% observed in our study group, although due to endometrial effect [21]. However, the present data is important, since we evaluated ENG-releasing implant users at the end of the approved time of use of this implant (3 years), albeit evidence suggests that the duration of the use of Implanon[®] may be extended without replacement up to 5 years [22].

In the group of users of the LNG-releasing implant (Jadelle[®]), the results were also as expected, since luteal activity was found to increase over the years of use as serum LNG declined. Moreover, serum estradiol levels were very similar between users and non-user controls [23,24]. Additionally, our results were in agreement with those of previous longitudinal and cross-sectional studies which showed no significant differences in BMD [8,12,13, 25,26]. Also, our results on BMD were similar to those observed in adolescent users of LNG-releasing implants [27].

The strengths of our study are the fact that the users were evaluated in a longitudinal manner at preinsertion and at 18 and 36 months of use and that Implanon[®] was compared with Jadelle[®]. The limitations of the study include the fact that BMD was measured only at the forearm, which is less predictive of fracture risk than the lumbar spine or the femoral neck, although forearm BMD also provides a good predictive value [28]. BMD evaluated at the forearm, mainly at the ultra-distal radius (which contains more trabecular bone) is predictive of fractures [29]; however, it is less predictive than BMD at the hip for hip fractures and less accurate at predicting vertebral fractures than hip or spine BMD. The relative risk (95% Confidence Interval) of fracture per SD when BMD was measured at distal radius was 1.5 (1.3-1.8), 1.7 (1.5-1.9), and 1.7 (1.4-2.0) for hip, vertebral, and forearm, respectively [28]. BMD measured at the femoral neck or total hip is a strong

predictor of hip fracture and predicts risk of all fractures in comparison to peripheral BMD measure [28]. Peripheral measurements could be used as an initial screening test and those women with low BMD will need to be referred for BMD of the hip or spine.

Additionally, the participating women were young and, consequently, the possibility of BMD being affected was very low. BMD must be considered a continuous risk factor during lifetime and the lower the BMD the higher the risk of fracture. The estimates percentage of lifetime risk of hip fracture for white women at the age of 50 at T-score of zero, -2.0, and -3.5 was 10%, 27%, and 49%, respectively. However, these estimates were different for BMD at forearm or spine [30].

In addition, 36 months of use may be too short a time, since the effects of hormonal contraceptives may be observed over many years of use and following discontinuation, although it has been suggested that the effect of the past use of p-only contraceptives on BMD may be eliminated following discontinuation of use [8,31].

Conclusions

Our data do not allow conclusions to be drawn about the effect of these implants on adolescents or in women in the menopausal transition. The reduction observed at the distal radius, although within the limit of 1 SD, must be analysed with caution because it is not possible to conclude whether this loss has any clinical significance over long-term use or if it has any effect on postmenopausal fracture risk [32]. In conclusion, BMD was significantly lower at 18 and at 36 months of use compared to pre insertion values in users of both contraceptive implants at the distal radius; however, no differences were found at the ultra-distal radius. These results could be indicating apparently a non severe impact on

BMD. This cohort of women is currently being followed-up and BMD will be measured again at 60 months of use if the number of users remains adequate at that time.

List of abbreviations

BMD: Bone mineral density

BMI: Body mass index

CV: Coefficient of variation

DEXA: Double X-ray absorptiometry

DMPA: Depot medroxyprogesterone acetate

ENG: Etonogestrel

LNG: Levonorgestrel

UNDP: United Nations Development Programme

UNFPA: United Nations Fund for Population Affairs

UNICAMP: Universidade Estadual de Campinas

SD: Standard deviation

WHO: World Health Organization

Competing interests: The authors declare that they have no competing interest’.

Authors contributions:

CM-D, XE-A, JFL-F, AMF, IM, LB: contributed equally because all made substantive intellectual contributions to conception and design, acquisition of data, analysis, and interpretation and have been involved in the writing of the manuscript and have given final approval of the version submitted for publication.

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Table 1. Bone mineral density according to the type of implant used, section of the forearm and duration of use.

	BMD (g/cm ²)			
	Distal radius	<i>P</i> -value	Ultra-distal radius	<i>P</i> -value
<i>Implanon (n = 36)</i>				
Baseline	0.475 (0.032)		0.406 (0.057)	
18 months	0.454 (0.040)	<0.0001	0.390 (0.034)	0.1041
36 months	0.447 (0.038)	<0.0001	0.396 (0.048)	0.2491
<i>Jadelle (n = 39)</i>				
Baseline	0.474 (0.002)		0.395 (0.015)	
18 months	0.459 (0.040)	<0.0001	0.398 (0.028)	0.7087
36 months	0.453 (0.058)	0.0022	0.401 (0.072)	0.4705

All values are mean ± SD