Effects of the etonogestrel contraceptive implant (Implanon®) on bone metabolism during lactation: a prospective study

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ABSTRACT

Aim To evaluate the effects of the etonogestrel contraceptive implant (Implanon®) on bone metabolism in lactating women using markers for bone formation and resorption.

Study design This single-centre, prospective cohort study was conducted in Turgut Ozal University Medical Faculty Obstetrics and Gynecology Department with healthy lactating women aged between 24 and 38 years to compare the effect on bone metabolism of 6 months' use of either the implant or a non-hormonal contraceptive method. The **s**tudy group (n=25) used an implant and the control group (n=25) used a non-hormonal contraceptive intrauterine device inserted 40 days' postpartum. Bone metabolism differences at the time of insertion and after 6 months were assessed quantitatively by biochemical analysis of serum and urine samples.

Results At baseline, serum levels of bone metabolism parameters were similar for the two groups. In the implant group, serum alkaline phosphatase (ALP) levels decreased (p=0.004) and total protein levels increased (p=0.045) at 6 months. In the control group, serum levels of bone metabolism parameters did not change at 6 months compared to baseline. However, serum levels of phosphorus (p=0.013) and ALP (p=0.003) decreased at 6 months compared to baseline.

Conclusion Six months' postpartum use of Implanon was found to have no deleterious impact on bone turnover in healthy lactating women.

Key message point

Six months' postpartum use of Implanon® was found to have no deleterious impact on bone turnover in healthy lactating women.

INTRODUCTION

Contraception for breastfeeding women is an important public health issue with regard to postponing subsequent pregnancies. Non-hormonal formulations are the first-choice contraceptives for lactating women; however, progestogen-only methods can be used by women for whom non-hormonal methods are contraindicated.[1] The World Health Organization has published recommendations regarding the use of contraceptives in breastfeeding women in three categories according to postpartum week.[1] The choice of contraceptive is determined by its effects on the quality and quantity of milk production, and on infant growth, as a result of the hormones present in the mother's milk. In this regard, progestogen-only contraceptives (POCs) seem not to affect the mother's milk or the infant, and can be used by breastfeeding women from 6 weeks' postpartum.[1–3]

Implanon® (Organon, The Netherlands) is a single-rod, long-acting, progestogenic contraceptive implant containing 68 mg etonogestrel in an ethylene vinyl acetate copolymer cover. Etonogestrel is the active metabolite of the progestogen prodrug desogestrel (19-nortestosterone derivative).[4] It provides contraception for 3 years by inhibiting ovulation.[4]

Maternal bone metabolism and density alter during lactation.[5] Some studies have reported that bone turnover increases

and transient bone loss completely resolves after termination of breastfeeding; however, other studies show that bone mineral density (BMD) is not associated with breastfeeding.[6] Apart from breastfeeding, hormonal contraceptives are also reported to be associated with bone metabolism during the reproductive period. The most obvious example of BMD deterioration linked to a progestogen-only contraceptive is attributed to depot medroxyprogesterone acetate (DMPA), which has received a US Food & Drug Administration (FDA) Black Box Warning.[7] However, data on the effect of POCs on bone mass and turnover during breastfeeding is limited.[8 9] The effect of progestogen-only pills on lactation is relatively better studied compared to other hormonal contraceptives, although there are few randomised controlled trials.[2] To the best of our knowledge, no data exist on the effect of Implanon on bone metabolism during the breastfeeding period.

The aim of our study was to investigate the effects of the etonogestrel implant on bone metabolism in lactating women, and to compare the effects with those found in non-hormonal contraceptive users.

METHODS

Study design

An open, prospective, comparative study was conducted in Turgut Ozal University Medical Faculty Obstetrics and Gynecology Department between 2009 and 2011, with healthy lactating women aged between 24 and 38 years, to assess the effects of the etonogestrel contraceptive implant on bone metabolism by biochemical analysis of serum and urine samples. Institutional ethical committee approval of the study protocol was obtained, and written informed consent was taken from the study participants.

Participants and data collection

Inclusion criteria for the study participants were: having a body mass index (BMI) between 20 and 30 kg/m^2, haemoglobin level >10 g/dl, first delivery >20 years of age, smoking <20 cigarettes/week, no alcohol intake, absence of a chronic illness that affects BMD, and not using drugs such as glucocorticoids, anticonvulsants, thiazides, calcium, or thyroid hormones.

All participants were regularly cohabiting, urban-dwelling women of low-to-middle socioeconomic status, who were not planning a pregnancy for the next 2 years. Participants also had no contraindications to the contraceptive methods used in the study.

Participants were recruited around the 40th postpartum day while they were fully breastfeeding. After enrolment, the participants were informed about both contraceptive methods, and were allowed to choose their preferred method. The women who chose the implant formed the study group (n=25), and the remaining women who chose the non-hormonal intrauterine device ((IUD;) Copper T 380A) formed the control group (n=25). Follow-up visits were scheduled 6 months after insertion of the chosen contraception method.

If infants were only breastfed during the first 6 months, and if breast milk was their only milk source after 6 months, they were considered to be fully breastfed. If infants were breastfed less than once a day, this was defined as weaning. The end of amenorrhoea due to lactation was defined as the first postpartum bleed (at least 1 day of normal bleeding or 3 days of consecutive spotting) that was followed by a second bleeding episode within the next 60 days.

Exclusion criteria were defined as: early weaning (before 6 months' postpartum), premature removal of a contraceptive device, and not attending follow-up visits. Accordingly, nine patients were excluded from the study. Two women in the control group failed to complete the study for personal reasons, and three women in the implant group were excluded from the study as they participated only in the first evaluation.

Biochemical analyses

Biochemical measurements were performed at baseline and 6 months after contraceptive method insertion. A 30 ml blood sample was taken between 0800 and 0900 after 12 hours of fasting and at least 2 hours after the last breastfeeding episode. Biochemical profiles of calcium, phosphorus, blood urea nitrogen, glucose, total proteins, and albumin were determined in a SMA-II autoanalyser. Parathyroid hormone (PTH) and osteocalcin were measured by a chemiluminesence method, and 25-hydroxy vitamin-D (25-OHD) was determined by high-performance liquid chromatography (HPLC). The intra-assay coefficients for the PTH, vitamin D and osteocalcin were 2.0%, 3.7% and 3.5%, respectively, and the inter-assay coefficients for the same tests were 3.8%, 5.8% and 4.7%.

Urine samples were also taken between 0800 and 0900, after 12 hours of fasting and 24 hours of hydroxyproline-free diet to measure hydroxyproline (OH-proline) and creatine. Urinary OH-proline was measured with an amino acid analyser, and the values were expressed as the hydroxyproline/creatinine ratio.

Statistical analysis

Normal distribution of numerical data was evaluated by the Shapiro–Wilk test, and if assumptions were met the data were presented as mean±standard deviation (SD). Otherwise, descriptive statistics were presented as median (25th–75th) percentiles. Comparisons between independent groups were performed either using Student's t-test or Mann–Whitney U-test according to the normal distribution of the dependent variable. Similarly, the differences between dependent groups of baseline and 6-month measurements were

evaluated by paired samples *t*-test or Wilcoxon Signed Rank test, as appropriate. A Type I error level less than 5% was considered to denote statistical significance. All analyses were performed using SPSS V.21® software (IBM Inc., Armonk, NY, USA).

RESULTS

Baseline investigations

Comparisons of the general characteristics of the two study groups are presented in Table 1. There were no statistically significant differences between the study groups as regards age ($p=0.498$), gravida ($p=0.068$), parity ($p=1$), BMI ($p=0.084$), menarche age ($p=1$) and daily calcium intake ($p=0.621$).

Baseline biochemical evaluations are presented in Table 2. The comparisons revealed that none of the biochemical parameters at insertion were significantly different for women who used the implant or IUD ($p>0.05$ for all).

Six-month investigations

None of the women reported changes in diet or intake of vitamins, minerals, calcium or other drugs that could potentially interfere with bone metabolism, or reported the occurrence of factors that interfere with creatinine renal excretion. Bone turnover marker values did not vary in either group.

In the implant group, serum levels of PTH, osteocalcin, 25-OHD, estradiol, calcium, phosphorus, albumin and urinary OH-proline were unchanged whereas alkaline phosphatase (ALP) decreased ($p=0.004$) and total protein increased ($p=0.045$) at 6 months (Table 3).

In the control group, serum levels of PTH, osteocalcin, 25-OHD, estradiol, calcium, total protein, albumin and urinary OH-proline did not change compared to the first visit. However, phosphorus ($p=0.013$) and ALP ($p=0.003$) decreased at 6 months (Table 3).

The percentile changes of serum PTH, osteocalcin, 25-OHD, estradiol, calcium, phosphorus, ALP, total protein, albumin and urinary OH-proline did not differ ($p>0.05$) between the groups (Table 4).

The implant was generally well tolerated; a higher incidence of treatment-related adverse events was not observed in the etonogestrel contraceptive implant group compared with the non-hormonal contraceptive control group.

DISCUSSION

This study compared the effects of an etonogestrel-releasing implant (Implanon) to those of an IUD on bone turnover in women during the early lactational period. To the best of our knowledge, this is the first study to investigate the effects of Implanon on bone metabolism in lactating women by measuring bone turnover markers.

A cohort of 50 breastfeeding women was followed for 6 months following device insertion, and a comparison of bone turnover markers in users of a non-hormonal contraceptive method (Copper T 380A IUD) and Implanon were conducted.

Few studies to date have evaluated the effects of Implanon on bone health. Pongsatha *et al.* reported that long-term (≥2 years) implant use negatively affected the BMD of the distal radius and ulna.[10] Similarly, Monteiro-Dantas *et al.*[11] reported that etonogestrel contraceptive implants in women aged 19–43 years may reduce BMD in the radius after 36 months. However, an open-label Finland study conducted in women aged 18–40 years that compared etonogestrel implant with IUD at baseline and 2 years reported no significant BMD changes in the lumbar spine, femur or radius.[12] These results were confirmed

Table 1 Demographic characteristics of the two study groups

Demographic characteristic	Implanon® (*n*=25)	Control (*n*=25)	*p*
Age (years)	30.4±3.5	31.1±3.8	0.498
Gravida (*n*)	2.1±1.2	1.6±0.6	0.068
Parity (*n*)	1.7±0.7	1.7±0.6	1
Body mass index (kg/m^2)	24.9±3.4	23.3±3.0	0.084
Menarche age (years)	12.8±0.6	12.9±0.6	1
Daily cacium intake (mg)	500±125	521±170	0.621

Table 2 Baseline comparisons of biochemical analyses in the two study groups

Biochemical parameter	Control	Implanon®	*p*
Parathyroid hormone	66.1 (46.3–106.0)	53.2 (45.3–86.2)	0.755
Osteocalcin	24.9±6.9	30.3±13.6	0.299
Vitamin D	15.7±10.4	15.1±8.6	0.929
Estradiol	10.4 (5.0–181.7)	10.6 (10.1–50.0)	0.857
Serum calcium	9.1 (8.7–9.4)	9.4 (9.1–9.8)	0.072
Serum phosphorus	3.9±0.5	3.7±0.4	0.415
Alkaline phosphatase	91.0±13.7	89.9±15.1	0.508
Total protein	7.5±0.5	7.5±0.6	0.915
Albumin	4.4±0.4	4.4±0.3	0.922
Hydroxyproline (24 hours)	12.5 (7.1–23.5)	17.9 (10.8–23.2)	0.529

Table 3 Changes in biochemical parameters during follow-up in the two study groups

	Control			Implanon®		
Biochemical parameter	**Baseline**	**6 months**	***p***	**Baseline**	**6 months**	***p***
Parathyroid hormone	66.1 (46.3–106.0)	73.3 (59.4–83.8)	0.505	53.2 (45.3–86.2)	59.4 (51.5–94.5)	0.875
Osteocalcin	24.9±6.9	23.4±7.6	0.574	30.3±13.6	26.8±8.4	0.249
Vitamin D	15.7±10.4	28.2±20.7	0.118	15.1±8.6	45.8±17.0	0.063
Estradiol	10.4 (5.0–181.7)	128.8 (28.9–276.5)	0.068	10.6 (10.1–50.0)	54.1 (15.7–59.8)	0.109
Serum calcium	9.1 (8.7–9.4)	9.2 (8.8–9.5)	0.284	9.4 (9.1–9.8)	9.5 (9.2–9.7)	0.807
Serum phosphorus	3.9±0.5	3.5±0.7	0.013	3.7±0.4	3.5±0.4	0.252
Alkaline phosphatase	91.0±13.7	70.2±18.6	0.003	89.9±15.1	77.2±11.7	0.004
Total protein	7.5±0.5	7.5±0.4	0.538	7.5±0.6	7.7±0.4	0.045
Albumin	4.4±0.4	4.4±0.3	0.909	4.4±0.3	4.5±0.2	0.240
Hydroxyproline (24 hours)	12.5 (7.1–23.5)	10.9 (8.5–15.4)	0.575	17.9 (10.8–23.2)	19.5 (11.0–34.2)	0.445

by pharmacokinetic studies of the etonogestrel implant, which demonstrated that the implant does not affect ovarian estradiol production or BMD in adolescents.[13 14] Nevertheless, all these studies investigated the effects of Implanon on bone density, not bone metabolism, and none of them investigated bone health in lactating women using bone turnover markers.

There is currently no evidence on the effects of Implanon on bone metabolism in either the lactating or non-lactating period. Our study investigated the effects of Implanon on bone metabolism during lactation using bone turnover markers.

Implanon provides highly effective contraceptive protection with no negative effects on breastfeeding or infant growth and development.[2 3 15] Many studies have investigated the metabolic effects of Implanon during the lactating period but none of them specifically evaluated its effects on bone.[16 17]

The effects of other progestogen-only contraceptives on bone metabolism/density have been studied in breastfeeding women. For example, Díaz *et al.*[8] investigated the effects of Norplant® implants and progesterone vaginal rings on bone turnover and density during lactation and after weaning. These two progestogen-only contraceptives (progesterone and levonorgestrel) appeared to have no deleterious effect on bone density and metabolism in healthy lactating women. In another study, Costa *et al.* evaluated BMD in breastfeeding postpartum women using DMPA, progestogen-only pills (POPs) or the levonorgestrel-releasing intrauterine system (LNG-IUS) for 6 months, and compared the results with women using non-hormonal contraceptives. Their results suggest that progestogen-only methods have a preventive effect on postpartum bone loss in breastfeeding women.[9]

Many studies have investigated the impact of progestogen-only contraceptive methods on bone density,[18] however none of them (except one designed by Massaro *et al.*) have investigated the effects of Implanon on bone turnover in either lactating nor non-lactating women.

In their study Massaro *et al.*[19] investigated the effects of the contraceptive patch and the vaginal ring on bone metabolism and BMD, and they reported that both contraceptive systems exerted a similar positive influence on bone turnover in young postadolescent women. The vaginal ring contains both ethinylestradiol and etonogestrel (120 µg daily), and the results could have been due to the combined effect of both hormones; consequently the Massaro *et al.* study can not be compared with the present study (i.e. an implant releasing 60 µg etonogestrel daily).

At the end of our study, ALP levels (an index of bone formation) were decreased in both study groups. These changes in bone turnover may have been a result of the response to the hormonal milieu of lactation, independent from the effects of implant insertion. Carneiro *et al.* assessed bone formation in lactating women using the most current bone turnover markers with serum CTX (carboxy-terminal telopeptide of collagen-1) and P1NP (amino-terminal telopeptide of procollagen-1) levels. This study demonstrated a significant two-fold increase in bone resorption as assessed by CTX during the first 2–3 months of lactation, as might be expected.[20]

Table 4 Comparison of changes in the biochemical parameters in the two study groups

Biochemical parameter	**Control**	**Implanon®**	***p***
Parathyroid hormone	−14.5 (−21.0–17.3)	5.7 (−31.6–18.4)	0.713
Osteocalcin	−1.5±7.4	−3.5±9.0	0.595
Vitamin D	12.6±14.1	30.7±21.3	0.168
Estradiol	60.8 (18.3–158.1)	9.8 (5.6–43.5)	0.400
Serum calcium	0 (−0.1–0.4)	0.07 (−0.5–0.4)	0.776
Serum phosphorus	−0.4±0.4	−0.2±0.6	0.330
Alkaline phosphatase	−20.9±17.8	−9.7±8.5	0.073
Total protein	−0.1±0.2	0.2±0.3	0.057
Albumin	0.01±0.3	0.1±0.3	0.449
Hydroxyproline (24 hours)	−0.6 (−14.3–6.0)	0.7 (−6.2–23.2)	0.529

In healthy lactating women, 6 months of etonogestrel contraceptive implant use resulted in no changes in bone metabolism. When Implanon was inserted for contraception in healthy lactating women, bone metabolism did not significantly change compared to the control group during this period. One weakness of the present study was that the treatment period was rather short in which to perform a complete evaluation of bone health, and we only used biochemical serum analyses of indices for bone resorption and formation. We did not evaluate bone density using BMD measurements.

CONCLUSION

Implanon use 6 months' postpartum appears to have no deleterious impact on bone turnover in healthy lactating women, and it has been demonstrated that it is safe to use in fully breastfeeding women during lactation.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval Ethics committees of Turgut Ozal University.

Provenance and peer review Not commissioned; externally peer reviewed.

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In memory of John Newton – former Faculty President

Professor John Newton, President of the Faculty of Family Planning and Reproductive Healthcare (since 2007 the Faculty of Sexual and Reproductive Healthcare) from 1997 to 2001, died from cardiac failure, aged 78, on 11 March 2017. In an obituary on the Faculty's website, Sarah Randall pays tribute to John's role as President of the Faculty (http://www.fsrh.org/news/professor-john-newton-obituary/).