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PII: S0301-2115(17)30115-X
DOI: http://dx.doi.org/doi:10.1016/j.ejogrb.2017.03.011
Reference: EURO 9815

To appear in: *EURO*

Received date: 23-11-2016
Revised date: 22-2-2017
Accepted date: 5-3-2017

Please cite this article as: Seo Jong-Wook, Lee Dong-Yun, Yoon Byung-Koo, Choi DooSeok.Effects of long-term postoperative dienogest use for treatment of endometriosis on bone mineral density.*European Journal of Obstetrics and Gynecology and Reproductive Biology* http://dx.doi.org/10.1016/j.ejogrb.2017.03.011

Effects of long-term postoperative dienogest use for treatment of endometriosis on bone mineral density

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ABSTRACT

Objective: This study was conducted to evaluate the effects of long-term postoperative dienogest (DNG) use for the treatment of endometriosis on bone mineral density (BMD).

Study design: Sixty reproductive-aged women who underwent conservative surgery for endometriomas and received postoperative DNG (2 mg/day) for at least 12 months to prevent recurrence were analyzed. BMD was measured before and after DNG treatment by using dual energy X-ray absorptiometry, and changes in BMD were evaluated.

Results: Mean patient age was 30.5 years, and mean duration of DNG treatment was 18.6 months. BMD at the lumbar spine significantly decreased after the first 6 months (-2.2%), and 1 year (-2.7%) of DNG treatment, compared to baseline. The proportion of women who had significantly decreased BMD at the lumbar spine after 1 year was 75% (45/60). In addition, BMD at the femur neck also decreased significantly after 1 year (-2.8%). BMDs after 2 years were not different from those after 1 year at both sites in 24 women who received DNG for ≥ 2 years. In addition, there were no differences in baseline characteristics between women who had significantly reduced BMD at the lumbar spine after 1 year (N = 45) and women who did not (N = 15).

Conclusion: This study suggests that long-term postoperative DNG treatment might have an adverse effect on BMD in reproductive-aged women. Bone loss mostly occurs during the first 6 months of treatment with DNG. A clinical trial is warranted to establish the effects of long-term DNG treatment on bone mass.

Keywords: endometriosis, dienogest, bone mineral density

Introduction

Endometriosis is a chronic, recurrent, and debilitating disease which affects at least 10% of reproductive-aged women [1], and may be found in 40% of infertile women [2] and 90% of women with pelvic pain [3]. Since endometriosis is now considered a progressive disease in certain aspects [4], the current treatment strategy for endometriosis includes the long-term post-operative use of medications after surgery to prevent the recurrence of symptoms and lesions [5-7].

Various medications are recommended to prevent the recurrence of endometriosis [8] according to the specific manifestations of disease as well as the underlying patient characteristics [9]. Among them, dienogest (DNG) is an orally active, synthetic 19-nortestosterone derivative that exhibit selective binding to the progesterone receptor [10], and is currently approved to treat endometriosis in many countries. Several clinical trials have demonstrated the efficacy, safety and tolerability of DNG for the treatment of endometriosis [11-14].

As DNG doses ≥ 2 mg inhibits ovulation [15], there could be concern about its negative effect on bone health, especially with long-term use. Although this issue has been addressed in some clinical trials, the results have not been consistent and the duration of DNG use was only 24 weeks [12,16]. In addition, although some studies have assessed longer effects [14], long-term data regarding the effects of DNG on bone mineral density (BMD) are still limited.

Because there is currently no cure for endometriosis, and it is a chronic disease that requires long-term management [17], careful consideration should be given not only to the efficacy of treatment but also to potential adverse effects accompanied by long-term medical treatment. In this context, this study was performed to evaluate the effects of long-term DNG treatment for endometriosis on BMD.

Materials and methods

The Endometriosis Cohort at Samsung Medical Center (ES-SMC cohort) began July 2012 to assess the effects of postoperative medical treatment for the prevention of endometriosis recurrence. All reproductive-aged women who underwent surgeries for endometriosis at the Endometriosis Clinic at Samsung Medical Center in Seoul, Korea, were advised to participate in the ES-SMC cohort.

Among the 72 participants from the ES-SMC cohort who started DNG treatment between July 2013 and June 2015, only patients who received DNG (Visanne®, Bayer, Korea) at a dose of 2 mg/day for at least 12 months were selected for this analysis. Patients were excluded from the analysis if they (1) underwent an oophorectomy or hysterectomy during the operation, (2) had a history of previous pelvic surgery for endometriosis, (3) had a history of preoperative hormonal treatment, (4) stopped DNG treatment or were lost to follow-up before completing the 1-year assessment, and (5) had a history of disease or took other medications which could affect bone density. Finally, a total of 60 patients completed the 1-year assessment, and 24 completed the 2-year follow-up assessment. The study protocol was approved by the institutional review board at Samsung Medical Center, and informed consent was obtained from all participants.

Operations were performed by the same surgeon. All recognized lesions were treated with excision or fulguration, and restoration of normal anatomy was achieved in all cases.

Baseline and follow-up assessment consisted of a structured questionnaire and interview. Pain was evaluated on a visual analog scale (VAS; 0=no pain to 10=extreme pain). Patients were asked about adverse events on every visit. Pelvic ultrasound was performed for determining endometrioma recurrence at 6 months after surgery and then annually. BMD was

measured at the lumbar spine and hip using dual-energy X-ray absorptiometry (Delphi Q, Hologic Inc., Bedford, MA, USA) before and after 6, 12, and 24 months of DNG treatment. The *in vivo* coefficient of variation in our center was 1.3% for the lumbar spine and 1.4% for the hip.

Statistical analyses were performed with IBM SPSS ver. 21.0 (IBM Corp., Armonk, NY, USA). Data are presented as mean ± standard deviation or number (%). The Mann-Whitney test was used to compare non-parametric continuous variables including age, age at menarche, body mass index and duration of DNG treatment, and Student's or paired t-test were used to compare other parametric continuous variables. Chi-square test was used to compare categorical data as indicated. P-values of less than 0.05 were considered statistically significant.

Results

Baseline patient characteristics are shown in Table 1. Mean age was 30.5 years, and mean body mass index (BMI) was 20.5 kg/m^2. The mean duration of DNG treatment was 18.6 months (range: 12-36 months). Baseline BMD at the lumbar spine and femur neck was 0.967 ± 0.115 g/cm^2 (Z-score; -0.2 ± 1.0) and 0.746 ± 0.097 g/cm^2 (Z-score; -0.2 ± 0.8) respectively, which were all within the expected range.

BMD at the lumbar spine decreased significantly after the first 6 months (-2.2 ± 4.5%; p = 0.001), and 1 year (-2.7 ± 5.4%; p = 0.001) of DNG treatment, compared to the baseline. BMD at the femur neck also decreased significantly after 1 year of DNG treatment (-2.8 ± 5.5%, p = 0.001). BMD changes at both sites were not significantly different between 6 months and 1 year of DNG treatment (Fig. 1). Among the 24 patients who received DNG for more than 2 years, BMD after 2 years of DNG treatment was not statistically different compared to BMD

after 1 year of DNG treatment at both sites (data not shown).

BMD decreased at the lumbar spine after the first year of treatment with DNG in 45 out of 60 (75%) patients. There were no significant differences in patient characteristics between women who had reduced BMD at the lumbar spine after 1 year of DNG use (N = 45) and women who did not (N = 15) (Table 2).

In addition, pain assessed by the mean VAS score decreased significantly at 6 months (1.3) and 12 months (1.1), compared to baseline (6.6), and no cases of pain recurrence were reported after DNG treatment. Also, no patient experienced endometrioma recurrence during DNG treatment (data not shown).

Comment

This study evaluated the effects of long-term postoperative DNG treatment for endometriosis on BMD, and showed that long-term DNG treatment might have an adverse effect on BMD in reproductive-aged women.

Postoperative DNG treatment for at least 12 months in the current study reduced mean BMD at the lumbar spine. This finding is consistent with two studies in Japanese women which demonstrated a decrease in BMD at the lumbar spine over 24 weeks (-1.0%) [16] and at 52 weeks of DNG treatment (-1.7%) [14]. In contrast, a study in Caucasian women reported that BMD did not decrease with DNG treatment for 24 weeks [12]. Racial and ethnic differences may explain these inconsistent findings. Because Asians usually have lower BMDs and smaller bone size than Caucasians, DNG treatment at a dose of 2 mg per day might have greater effects on BMD in Asian women.

In the present study, BMD decrease at the lumbar spine (-2.8%) with 1 year of DNG

treatment was more prominent compared to findings from a Japanese study over the same time period (-1.7%) [14]. The difference in dosage (1 mg twice daily in the Japanese study and 2 mg once daily in the current study) may have led to the difference in BMD change, since the latter dosage could have a greater effect on the level of sex hormones. As BMD decreased rapidly with DNG treatment similar to accelerated bone loss during the menopause transition or early menopause [18], a milieu of low estrogen could be involved. Indeed, a study evaluating the pharmacodynamics of DNG showed that the mean estradiol concentration was 39 ± 11 pg/mL, which was not much different from the estradiol level during menopause [15].

If we can predict which women will lose bone mass more after DNG treatment, individualized treatment and follow-up could be possible. However, we did not find any differences in patient characteristics when comparing women with and without a decrease in BMD at the lumbar spine after 1 year of DNG use. More efforts are needed to determine the factors associated with BMD decrease during long-term DNG treatment.

The present study showed that DNG reduced the recurrence of pain as well as endometriomas. These findings are in line with other studies that have reported DNG effectively prevents endometriosis or endometrioma recurrence [11-14,16,19].

This is the first prospective study to focus mainly on bone density among the various safety issues of long-term DNG treatment. Although some studies already have addressed this point, the number of patients who were eligible for analysis of BMD was small in each clinical trial (mostly fewer than 40 patients), and the duration of DNG treatment was less than 1 year [12,16]. Moreover, the current study measured BMD at the hip as well as the lumbar spine.

There are also some limitations. First, this study was not a randomized controlled trial and had no control group. However, since the efficacy of postoperative medical treatment for endometriosis has already been established, the allocation of patients into a no treatment group could be unethical. Second, some factors that could influence bone density, such as physical

activity, diet, or family history, were not assessed. In addition, serum levels of estradiol or bone turnover markers were not measured since this study was not an intervention, but rather an observational study. Therefore, low estradiol level as a plausible explanation for the BMD decrease with DNG treatment could not be confirmed.

Although BMD decreased with long-term DNG treatment in our study, caution is necessary when interpreting our results. The present study included women who were young and healthy with very low risk for clinical fractures, and BMDs were still within the normal range for age after long-term DNG treatment. Considering the benefit of this medication to prevent endometriosis recurrence and avoid repetitive surgeries, the use of DNG should not be decided solely based on BMD changes in clinical practice.

In conclusion, this study suggests that long-term DNG treatment might have an adverse effect on BMD in reproductive-aged women. Bone loss occurs in 75% of women treated with DNG, mostly during the first 6 months of DNG treatment. A further clinical trial would aid in establishing the effects of long-term DNG treatment on bone mass.

The authors report no conflict of interest

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Figure legend

Fig. 1. Bone mineral density at the lumbar spine (A) and femur neck (B) at baseline, after 6 months and after 1 year of dienogest treatment.

* p = 0.001 vs. baseline, by paired *t*-test.

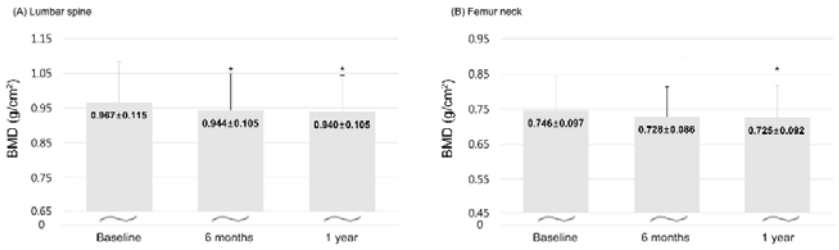

Table 1

Clinical Characteristics.

		N = 60
Age (years)		30.5 ± 6.8
Age at menarche (years)		13.8 ± 1.3
Parity (n)		
0		50 (83.3)
1+		10 (16.7)
Body mass index (kg/m^2)		20.5 ± 3.0
Pain symptom		53 (89.8)
CA-125 (U/mL)		48.5 ± 178.3
ASRM stage		
III		28 (45.8)
IV		32 (54.2)
Ovarian endometrioma		
Size of cyst (cm)		4.7 ± 1.6
Bilaterality		19 (32.2)
Baseline BMD		
Lumbar spine	g/cm^2	0.967 ± 0.115
	Z-score	-0.2 ± 1.0
Femur neck	g/cm^2	0.746 ± 0.097
	Z-score	-0.2 ± 0.8

Data are expressed as means ± standard deviation or number (%)

ASRM, American Society of Reproductive Medicine; BMD, Bone Mineral Density

Table 2

Clinical Characteristics According to BMD Change in the Lumbar Spine After 1 Year of DNG Treatment.

		Decreased BMD (n = 45)	No decreased BMD (n = 15)	p-value
Age (years)		31.2 ± 7.1	28.5 ± 5.6	NS
Age at menarche (years)		14.0 ± 1.4	13.4 ± 1.1	NS
Parity (n)				
0		37 (82.2)	13 (86.7)	NS
1+		8 (17.8)	2 (13.3)	
Body mass index (kg/m^2)		20.5 ± 3.3	20.7 ± 2.3	NS
ASRM stage				
III		22 (48.9)	6 (40.0)	NS
IV		23 (51.1)	9 (60.0)	
Ovarian endometrioma				
Size of cyst (cm)		4.8 ± 1.6	4.4 ± 1.9	NS
Bilaterality		14 (36.8)	5 (23.8)	
Baseline BMD				
Lumbar spine	g/cm^2	0.984 ± 0.117	0.925 ± 0.102	
	Z-score	-0.1 ± 0.9	-0.5 ± 0.9	NS
Femur Neck	g/cm^2	0.743 ± 0.095	0.757 ± 0.108	
	Z-score	-0.3 ± 0.7	-0.1 ± 1.0	
Duration of DNG treatment (months)		18.4 ± 6.5	16.3 ± 3.4	NS

Data are expressed as means ± standard deviation or number (%); NS, not significant

ASRM, American Society of Reproductive Medicine; BMD, Bone Mineral Density; DNG, Dienogest