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ORIGINAL STUDY

Bone mass in women with premature ovarian insufficiency: a comparative study between hormone therapy and combined oral contraceptives

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Abstract

Objective: The aim of the study was to evaluate whether combined oral contraceptives (COCs) can be used as hormone therapy (HT) to preserve bone mineral density (BMD) in women with premature ovarian insufficiency (POI).

Methods: An observational study of women with POI comparing the use of COC (ethinylestradiol 30 μg + levonorgestrel, continuously) with: low-dose HT (continuous conjugated estrogen 0.625 mg plus medroxyprogesterone or continuous estradiol [E2] 1 mg + norethisterone), high-dose HT (continuous conjugated estrogen 1.25 mg + medroxyprogesterone or continuous E2 2 mg + norethisterone), tibolone 2.5 mg, or no treatment. Bone density scans were performed every 2 ± 1 years. The difference between final and initial (delta) BMD values was calculated for the lumbar spine, total femur, and femoral neck. Generalized estimating equations were used to analyze the effect of treatment over time. Variables without normal distribution were transformed into ranks.

Results: Overall, 420 scans (210 deltas) of 119 women were analyzed. The women were 30.3 ± 9.2 years old (mean ± SD). BMD deltas at the lumbar spine and total femur were grater in the COC and high-dose HT groups. At the lumbar spine, the differences between two scans were greater in the COC group when compared to low-dose HT group: −0.043 (95% CI −0.062 to −0.024), untreated: −0.056 (−0.080 to −0.032), and tibolone: −0.050 (−0.094 to −0.006) groups. Total femur BMD decreases and the delta were lower in the low-dose HT group −0.038 (−0.052 to −0.024) when compared to COC.

Conclusion: Continuous COC was associated with increased BMD in women with POI compared to low-dose HT, with similar improvement in the COC and high-dose HT groups.

Key Words: Bone mass – Bone mineral density – Combined oral contraceptive – Hormone therapy – Premature ovarian insufficiency.

Video Summary: http://links.lww.com/MENO/A620.

Women with premature ovarian insufficiency (POI) become estrogen-deficient at an early age, with ovarian activity ceasing before 40 years of age.[1] The condition presents with signs and symptoms such as hot flashes, vaginal dryness, altered sexual function,[1] and changes to sleep patterns.[2] In addition, there are mood swings, with an increased risk of depression[3] and more difficult psychosocial adjustment.[4] A reduction in cognitive function has also been detected, leading to an increased risk of dementia and Parkinson's disease, and causing a consequently negative impact on self-esteem and quality of life.[5,6] The repercussions of estrogen deficiency also affect fertility, the cardiovascular system, bone loss and neurological function, in addition to increasing early mortality rates.[7-10]

In the bones, estrogens play a role in homeostasis during growth and in adult life. The anabolic and anticatabolic effects of estrogens result from various mechanisms including regulation of the generation and apoptosis of osteoblasts and osteoclasts, and prolongation of the life of osteocytes.[11] During puberty, decreased estrogenic action results in a

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reduction in the bone mass peak. Although bone mass can increase up to around 30 years of age, around 90% of peak bone mass is acquired by 18 years of age.[12,13] Estrogen deficiency accelerates the modulation of bone resorption through increased osteoclastic activity, also stimulating the increase in osteoblastic activity, albeit at lower proportions.[14] In POI, estrogen deficiency is, therefore, associated with a reduction in bone mineral density (BMD) at an early age, particularly at the lumbar spine.[11,13,15]

The treatment of POI consists principally of prolonged hormone therapy (HT) aimed at reducing the effects of estrogen deficiency[14] on the young female body. Basically, two types of estrogen are used in HT: estradiol (E2) and conjugated estrogens (CEs). Ethinylestradiol (EE), a synthetic estrogen present in the majority of combined oral contraceptives (COC), has been used almost empirically to treat women with POI; however, although there is evidence of the effect of COCs on the bone mass of women with normal ovarian function[16] and in women who use them for contraception, there are few data in relation to women with POI.[17]

This study was developed to evaluate the association between the continuous use of a COC and the bone mass variation in women with POI compared to other conventional hormone therapies.

METHODS

A retrospective, observational, longitudinal cohort study was conducted using data collected from the medical records of women with a diagnosis of POI. The study was carried out using the archives from the Gynecological Endocrinology Clinic of the Department of Obstetrics and Gynecology, University of Campinas, Brazil. The institution's internal review board approved the study protocol under document CAAE 08623412.7.0000.5404.

Women with POI who had undergone two or more BMD scans with an interval of 2 ± 1 years between them were included in the study. Diagnosis of POI was based on reported hormonal imbalance characterized by amenorrhea or menstrual cycles of more than 120 days occurring before 40 years of age, and at least two follicle-stimulating hormone measurements, performed with an interval of 30 days between them, showing serum levels more than 25 IU/L.[14] Once we evaluated the association between HT and the bone mass variation, we only included women with a consistent use of HT or women without any kind of HT use during the interval of BMD analysis (group without HT). Women with mobility issues and those using of any medication (eg, glucocorticoids) or with any disease (eg, malabsorption syndrome, hypothyroidism) that could have a negative impact on bone mass were excluded from the study.

The variables analyzed were age at ovarian insufficiency (rated only for women with secondary amenorrhea, in which case their age at the last menstrual period was taken into account), and age at initiation of HT. The following variables were collected from the records taken at the time the BMD scan was performed: age, height, weight, body mass index (BMI), type of HT used, and duration of HT. In addition, the results of the BMD scan at the lumbar spine (L1-L4 vertebrae), femoral neck, and total femur were collected.

In relation to the forms of HT used in the study, the COC evaluated contained 30 μg of EE together with levonorgestrel in a continuous-use regimen. The other forms of HT used were separated into three groups for comparison with the COC: (1) a low-dose estrogen/progestin combination (0.625 mg of CE used continuously together with medroxyprogesterone acetate or 1 mg E2 used continuously together with norethisterone); (2) a high-dose estrogen/progestin combination (1.25 mg of CE used continuously together with medroxyprogesterone acetate or 2 mg E2 used continuously together with norethisterone); and (3) tibolone 2.5 mg daily. A control group consisting of women who were not using HT was also included in the study.

Sample size

A convenience sample of women who had been diagnosed with POI between January 2000 and December 2016 at the Gynecological Endocrinology Clinic of the University of Campinas and who met the inclusion criteria and had none of the exclusion criteria was included in the study.

Bone mineral density

BMD was measured by dual-energy x-ray absorptiometry (Lunar Prodigy, GE Medical Systems, Madison, WI) at the lumbar spine (L1-L4), femoral neck, and total femur, and described as g/cm^2, t scores, and z scores.

Statistical analysis

Descriptive statistics were performed for the numerical variables using means, standard deviations, and medians. Changes in BMD were analyzed from the difference between two BMD scans, that is, the difference obtained by subtracting the BMD value obtained at baseline from that obtained at the end of the period for each 2-year interval (± 1) and for each treatment group, with the results being referred to as deltas.

To evaluate the effect of treatment on the BMD of the women over time, a generalized estimating equation (GEE) was calculated using the variation (delta) in BMD obtained for the women treated with COC as a reference to be compared with the deltas obtained with the other treatments. The variables without normal distribution were transformed into ranks (age, height, weight, BMI, BMD, and deltas). The significance level adopted throughout the statistical analysis was P less than 0.05. The entire statistical analysis was conducted using SAS for Windows, version 9.2.

RESULTS

The medical records of 255 women with POI were initially evaluated. Of these, 119 women were selected for the study following application of the inclusion/exclusion criteria (Fig. 1). A total of 420 BMD scans were evaluated, with analysis of the lumbar spine, femoral neck, and total femur, resulting in 210 deltas.

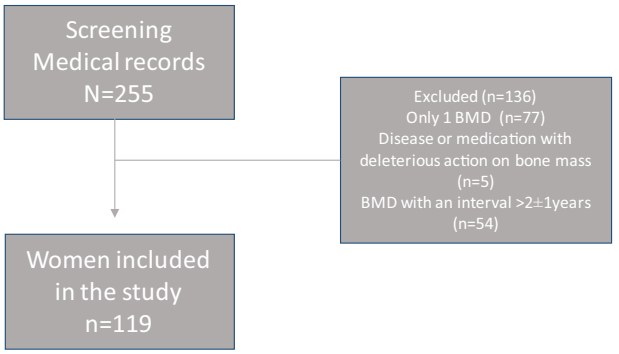

FIG. 1. Flow chart summarizes the search process with inclusion and exclusion criteria. BMD, bone mineral density.

At the time of inclusion in the study, the mean age of the women was 30.34 ± 9.24 years; mean BMI was 24.4 ± 4.52 kg/m^2; and mean BMD measurements at the lumbar spine (L1-L4), femoral neck, and total femur were 0.97 ± 0.17, 0.87 ± 0.16, and 0.90 ± 0.15 g/cm^2, respectively (Table 1). Median ± SD for each HT group is also included.

To evaluate response to the different treatments, 90 BMD scans (45 deltas) were analyzed for the continuous COC group (30 μg EE), 184 (92 deltas) for the low-dose HT group (0.625 mg CE or 1 mg E2), 90 (45 deltas) for the high-dose HT group (1.25 mg CE or 2 mg E2), 16 (8 deltas) for the tibolone 2.5 mg group, and 40 scans (20 deltas) for the group of women not in use of HT. Positive values show bone mass gain, and negative values indicate loss of bone mass.

In the group of women treated with a COC, an increase in bone mass was found at the lumbar spine and total femur. Likewise, the group treated with high-dose HT also showed an improvement in bone mass at the lumbar spine and total femur, although this positive impact was less pronounced than that found in the COC group. At the lumbar spine, there was a loss of BMD in the untreated group, in the low-dose HT group, and in the group of women using tibolone. BMD at the femoral neck decreased in all the treatment groups with the exception of the tibolone group. For the total femur, there was a reduction in BMD only in the low-dose HT group (Table 2).

When the differences between the two scans (delta, g/cm^2) were compared, taking the COC group as a reference, results

TABLE 1. *Characterization of women with premature ovarian insufficiency*

	Total $N = 119$	COC	Low-dose	High-dose	Tibolone	No treatment
Age	30.34 ± 9.24	27.60 ± 6.33	38.27 ± 8.71	30.98 ± 7.40	42.38 ± 3.02	41.90 ± 8.66
Height	60.94 ± 12.72	63.93 ± 11.64	67.12 ± 13.62	60.53 ± 17.01	63.19 ± 9.68	64.92 ± 16.92
Weight	1.58 ± 0.09	1.61 ± 0.09	1.59 ± 0.08	1.55 ± 0.12	1.60 ± 0.02	1.55 ± 0.08
BMI	24.43 ± 4.52	24.74 ± 4.33	26.59 ± 4.78	24.84 ± 4.87	24.77 ± 3.18	26.90 ± 5.91
BMD LS (L1-L4), g/cm^2	0.97 ± 0.17	0.89 ± 0.11	0.96 ± 0.15	0.93 ± 0.11	0.95 ± 0.14	0.95 ± 0.11
BMD LS (L1-L4) *z* score	−1.48 ± 1.30	−1.44 ± 0.92	−1.12 ± 1.16	−1.31 ± 0.85	−0.69 ± 1.06	−1.42 ± 1.03
BMD LS (L1-L4) *t* score	−1.38 ± 1.26	−1.57 ± 0.98	−1.28 ± 1.15	−1.43 ± 0.89	−1.04 ± 1.07	−1.51 ± 0.86
BMD femoral neck, g/cm^2	0.87 ± 0.16	0.78 ± 0.10	0.86 ± 0.13	0.83 ± 0.11	0.81 ± 0.10	0.81 ± 0.13
BMD femoral neck *z* score	−0.55 ± 1.14	−0.73 ± 0.93	−0.21 ± 1.04	−0.46 ± 0.96	−0.11 ± 0.64	−0.66 ± 0.83
BMD femoral neck *t* score	−0.60 ± 1.29	−0.83 ± 0.93	−0.39 ± 1.05	−0.54 ± 0.97	−0.49 ± 0.66	−0.97 ± 0.92
BMD total femur, g/cm^2	0.90 ± 0.15	0.84 ± 0.08	0.91 ± 0.13	0.86 ± 0.10	0.88 ± 0.06	0.89 ± 0.12
BMD total femur *z* score	−0.70 ± 1.17	−0.83 ± 0.72	−0.40 ± 1.04	−0.71 ± 0.79	−0.31 ± 0.48	−0.56 ± 0.88
BMD total femur *t* score	−0.66 ± 1.22	−0.90 ± 0.75	−0.48 ± 1.05	−0.75 ± 0.82	−0.59 ± 0.44	−0.75 ± 0.98

BMD, bone mineral density; BMI, body mass index; COC, combined oral contraceptive; LS (L1-L4), lumbar spine in the L1-L4 segment.

TABLE 2. *Difference between two bone densitometries (delta, in g/cm^2) for lumbar spine, femoral neck, and total femur for the different treatments used in women with premature ovarian insufficiency*

HT (*N*)	BMD	Mean ± SD (95% CI)	Median
COC ($n = 45$)	Lumbar spine (L1-L4)	0.018 ± 0.056 (0.001-0.035)	0.023
	Femoral neck	−0.008 ± 0.075 (−0.031 to 0.015)	0.005
	Total femur	0.019 ± 0.037 (0.007-0.031)	0.017
Low-dose HT ($n = 92$)	Lumbar spine (L1-L4)	−0.021 ± 0.093 (−0.041 to −0.002)	−0.004
	Femoral neck	−0.022 ± 0.117 (−0.047 to 0.003)	−0.005
	Total femur	−0.016 ± 0.057 (−0.029 to −0.003)	−0.004
High-dose HT ($n = 45$)	Lumbar spine (L1-L4)	0.012 ± 0.093 (−0.016 to 0.040)	0.022
	Femoral neck	−0.010 ± 0.080 (−0.035 to 0.014)	0.008
	Total femur	0.005 ± 0.053 (−0.012 to 0.022)	0.013
Tibolone ($n = 8$)	Lumbar spine (L1-L4)	−0.024 ± 0.060 (−0.074 to 0.026)	−0.018
	Femoral neck	0.005 ± 0.049 (−0.036 to 0.047)	0.009
	Total femur	0.020 ± 0.029 (−0.004 to 0.044)	0.018
No treatment ($n = 20$)	Lumbar spine (L1-L4)	−0.034 ± 0.055 (−0.060 to −0.009)	−0.034
	Femoral neck	−0.020 ± 0.071 (−0.050 to 0.010)	−0.005
	Total femur	0.000 ± 0.031 (−0.013 to 0.013)	0.007

Data shown as mean (95% confidence interval).
BMD, bone mineral density; COC, combined oral contraceptive-etinilestradiol 30 μg; high-dose, conjugated estrogen 1.25 mg or estradiol 2 mg; HT, hormone therapy; low-dose, conjugated estrogen 0.625 mg or estradiol 1 mg; SD, standard deviation.

TABLE 3. *Differences in bone mineral density means between treatments with the combined oral contraceptive group as a reference, without adjustment and adjusted for age, body mass index, and hormone therapy duration covariates, through Generalized Estimating Equations*

	Without adjustment Mean differences (95% CI)	Adjusted Mean differences (95% CI)
Lumbar spine		
COC	0.000 ————	0.00 ————
Low-dose	−0.043 (−0.062 to −0.024); $P < 0.001$	0.024 (−0.046 to −0.002); $P = 0.037$
High-dose	−0.009 (−0.030 to 0.012); $P = 0.412$	−0.003 (−0.025 to 0.020); $P = 0.824$
Tibolone	−0.050 (−0.094 to −0.006); $P = 0.026$	−0.026 (−0.072 to 0.021); $P = 0.277$
No treatment	−0.056 (−0.080 to −0.032); $P < 0.001$	0.032 (−0.062 to −0.003); $P = 0.031$
Femoral neck		
COC	0.000 ————	0.000 ————
Low-dose	−0.021 (−0.045 to 0.003); $P = 0.085$	−0.020 (−0.047 to 0.007); $P = 0.143$
High-dose	−0.009 (−0.028 to 0.011); $P = 0.395$	−0.006 (−0.026 to 0.015); $P = 0.593$
Tibolone	0.012 (−0.025 to 0.048); $P = 0.538$	0.022 (−0.018 to 0.062); $P = 0.282$
No treatment	−0.020 (−0.047 to 0.007); $P = 0.143$	−0.015 (−0.053 to 0.024); $P = 0.455$
Total femur		
COC	0.000 ————	0.000 ————
Low-dose	−0.038 (−0.052 to −0.024); $P < 0.001$	−0.029 (−0.046 to −0.012); $P = 0.001$
High-dose	−0.015 (−0.029 to −0.001); $P = 0.038$	−0.012 (−0.026 to 0.002); $P = 0.100$
Tibolone	−0.001 (−0.021 to 0.018); $P = 0.893$	0.012 (−0.012 to 0.035); $P = 0.328$
No treatment	−0.018 (−0.032 to −0.004; $P = 0.014$	−0.009 (−0.029 to 0.011); $P = 0.357$

COC, combined oral contraceptive; *P* values, comparison of each treatment with COC.

were poorer, with a loss of BMD at the lumbar spine, in the untreated group ($P < 0.001$), in the group of women receiving low-dose HT ($P < 0.001$), and in the group treated with tibolone ($P = 0.026$). For the total femur, compared to the group of women using COC, results were also poorer, with a reduction in BMD, in the untreated group ($P = 0.014$), in the low-dose HT group ($P < 0.001$), and in the high-dose HT group ($P = 0.038$). For the femoral neck, no statistically significant differences were found in the response of BMD to the different treatments (Table 3 and Fig. 2). The results adjusted for age, BMI, and HT duration are also shown in Table 3. A similar analysis was performed to compare the *z* scores and *t* scores between the group of women using the COC and the groups using other treatments or no treatment (Fig. 2).

For the women using COC continuously for 2 years, there was a mean increase in BMD at the lumbar spine of $2.5\% \pm 6.5\%$ compared to an increase of $1.8\% \pm 9.9\%$ in the group of women using the high-dose HT. For the other groups, there was a loss of BMD of $-1.3\% \pm 11.5\%$ in the low-dose HT group, of $-2.2\% \pm 5.3\%$ for the tibolone group, and of $-3.3\% \pm 5.4\%$ for the untreated group. For the total femur, there was an increase in BMD of $2.4\% \pm 4.6\%$ in the group of women treated with COC compared to an increase of $0.9\% \pm 5.8\%$, $2.2\% \pm 3.3\%$, and $0.02\% \pm 0.02\%$, respectively, for those treated with high-dose HT and tibolone, and those untreated.

DISCUSSION

The present study analyzed the difference in BMD in response to hormonal treatment in women with POI, comparing the association of the continuous use of a COC containing 30 μg of EE to other conventional hormonal treatments. Treatment with COC proved effective, generating an increase in BMD at the lumbar spine and total femur. As expected, an improvement in BMD at the lumbar spine and total femur (although smaller in magnitude) was also obtained with treatment using high doses of natural estrogen, that is, E2 at a dose of 2 mg or CE at a dose of 1.25 mg, both used continuously. On the contrary, the COC was unquestionably more effective than the use of these estrogens at lower doses. The small sample size of women using tibolone limits the conclusions that can be drawn with respect to this form of HT. These results, however, need to be considered preliminary in clinical practice.

It is known that the repercussions of estrogen on bone mass require time to produce measurable changes in densitometry and that different parts of the skeleton respond in different ways to estrogen. The lumbar spine, formed predominantly by trabecular bone, is more metabolically active and a larger proportion is undergoing remodeling compared to the femur, formed predominantly by cortical bone.[18] Thus, agents such as estrogen, which affect bone formation and resorption, influence it to a much greater extent and more quickly,[19,20] which leads us to assume that the lumbar spine, being more sensitive to estrogen, has changed faster in response to treatment than the femur. This may also be an explanation for the femoral neck not showing bone mass gain in any group, except the group treated with tibolone, but having a very small number of women limits any conclusions. Perhaps analysis with intervals between densitometry for a period longer than 2 years could also reveal bone mass gain in the femoral neck.

Studies show that HT containing E2 has beneficial effects on bone mass density. It acts by inhibiting osteoclasts and reducing the rate of bone remodeling.[21,22] In women with POI, depending on the age at which ovarian function ceases, prolonged estrogen deficiency may affect peak bone mass or be responsible for early bone loss. Both situations may be associated with an increased fracture risk.[23] There is evidence that better compliance with HT is associated with better preservation of bone mass, with BMD loss having been

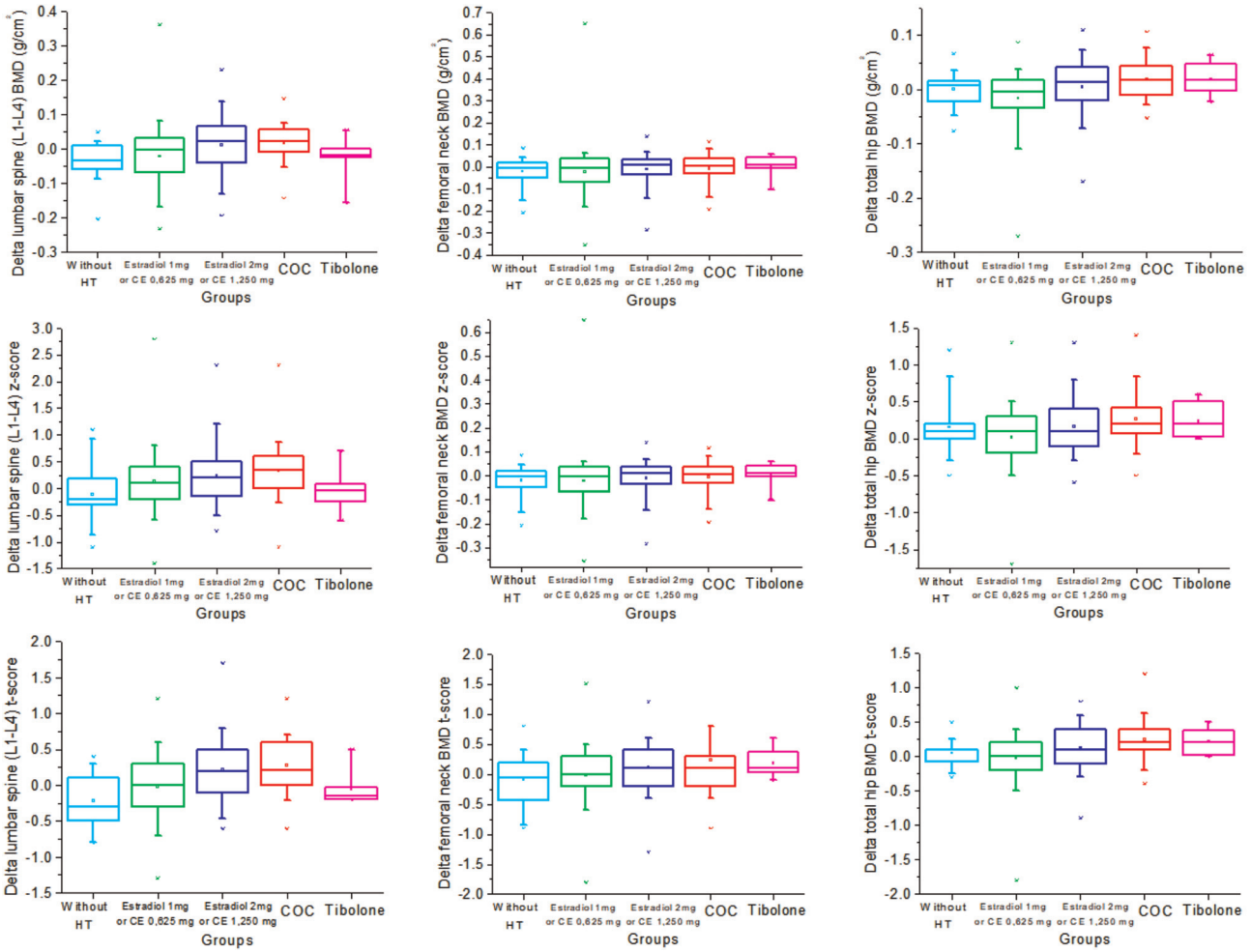

FIG. 2. Comparison between deltas of densitometry in relation to treatments, using the COC group as a reference. BMD, bone mineral density; COC, combined oral contraceptive.

documented in women who interrupt treatment.[24] Due to the heterogeneity of the formulations used insofar as dosage, routes of administration, and schedules of use are concerned, a systematic review concluded that there are insufficient data to allow any conclusions to be reached regarding the optimal HT to maximize results on bone mass density.[25]

Considering that the response of BMD to estrogen is dose-dependent, in the case of early ovarian insufficiency, the relevant medical societies around the world have suggested the use of higher doses of estrogen than those used in standard HT for the menopause.[22] The recommendations of the European Society for Human Reproduction and Embryology are that HT for adult women with POI should contain E2 at the dose of 2 to 4 mg/d.[14] In addition, with a view to maintaining physiological estradiol levels in women of reproductive age, some studies have suggested that the dose of choice for the transdermal route should be 100 μg.[14,26]

Taking these recommendations into consideration, although conventional HT was used in the present study in women with POI, few long-term evaluations on the repercussions on bone mass density have been conducted. One study in which women with POI using different HT formulations similar to those analyzed in the present study were followed up for 8 years reported that associations of CE and medroxyprogesterone acetate, E2 and norethisterone, and EE and levonorgestrel were effective in preserving bone mass density; however, they were insufficient to reduce the percentage of women with low BMD or osteoporosis.[27] Those findings could, however, have been affected by the fact that many women had used lower doses of estrogen (1 mg of E2 or 0.625 mg of CE daily) than those currently recommended. In this respect, the findings of the present study show that the women using the lower dose of HT had a loss of BMD at the lumbar spine, femoral neck, and total femur.

Based on current evidence in women with POI, there is a movement toward the physiological replacement of hormones via transdermal,[28] which has the advantage of avoiding the hepatic first-pass effect of oral estrogen in clotting factors.[29] Despite the advantage, it is a treatment that is usually more expensive when compared to oral therapies. COCs are generally prescribed for women with ovarian insufficiency who nevertheless run a certain risk of ovulation and who do not wish to conceive. Furthermore, it is important to also take into consideration the fact that in Brazil the COC used here are

supplied free of charge within the public healthcare system or are cheaper to purchase than other hormonal treatments. In addition, when prescribed as a form of HT, they are generally well accepted by young women. The literature reports that COC tend to be seen by women as a simpler and more socially acceptable form of medication.[30] Although these reasons may influence their use, it must be recognized that there is little evidence of their effectiveness in preserving bone mass. In contrast to the findings of the present study that show an improvement in bone mass with COC that was similar to that found with high-dose HT, a randomized clinical trial conducted with a small sample of women with POI treated with 2 mg of oral E2 associated with levonorgestrel daily or a COC containing 30 μg of EE associated with levonorgestrel for 21 days a month followed by a 7-day pause (21/7 schedule) showed that the increase in bone mass at the lumbar spine was greater in the group treated with E2.[31] Another study that compared a daily dose of 100 to 150 μg of transdermal E2 together with cyclic progestogens and treatment with a COC containing 30 μg of EE associated with norethisterone on a 21/7 schedule reported that bone mass protection was better after 12 months of follow-up with the E2 treatment.[19] The authors found a significant increase in bone formation markers with transdermal estradiol, but for the oral contraceptive regimen, this was not shown. An important point, however, is that those results involve a prescribed COC schedule in which the women remained hypoestrogenic during the 7-day pause, that is, for around 25% of the time. Therefore, the use of COC on a continuous schedule could be associated with improvement in bone mass, as reflected in the results of the present study in which there was an increase in bone mass at least similar to that found with the higher dose of HT.

In agreement with the results of the present study, a study on a COC prescribed for young women with anorexia nervosa showed recovery of bone mass, with bone resorption markers returning to normal levels.[32] Also in women with hypogonadotropic hypogonadism, COCs containing 20 or 30 μg of EE resulted in an improvement in bone mass.[33] In those studies, however, results were not compared with conventional HT using natural estrogen.

A strongpoint of the present study was the fact that the COC was compared with different formulations of HT, including the most used forms. Another strength is the number of women in the sample. In addition, all the women included in the study were followed up in the same tertiary unit, thus guaranteeing the uniformity of the sample and use of the recommended treatment. A further strength refers to the importance of the results, which, by suggesting that COC is effective in preserving bone mass, may encourage physicians to prescribe this form of therapy and women to comply with treatment. Limitations of the study that must be mentioned include the convenience sampling and the fact that it was conducted retrospectively through an analysis of health records and that the variation in bone density was evaluated over a relatively short period of time (2 ± 1 years). Further prospective studies, in different centers, with a randomized clinical trial design will, therefore, be required to control for possible risks of bias regarding the different treatments, thus providing a better level of evidence.

CONCLUSION

Continuous use of a COC can be considered as an option for HT in women with POI, according to the preliminary results of this study. Indeed, the formulation containing 30 μg of EE together with 150 mg of levonorgestrel, used continuously, was found to be as effective on BMD at the lumbar spine as HT containing estradiol at a dose of 2 mg or CE at a dose of 1.25 mg, also for continuous use, together with progestogens, and better than these with respect to total femur BMD measurements.

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