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Short Communication

Could Hormonal Contraception Affect Mineral Bone Density in Women?

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Abstract

Hormonal contraception represents the main form of contraception worldwide. During the different stages of life, estrogens fulfill a fundamental function for the acquisition of peak bone mass in adolescence and the maintenance of mineral density in adult life. In general, combined hormonal contraceptives induce a reduction in estrogen and serum progesterone, this effect, being dose dependent. During adolescence, low dose oral contraceptives are associated with lower bone gain and decrease in bone formation markers. In perimenopause where hormonal fluctuation negatively impacts the bone, the 20μg dose of ethinylestradiol has been beneficial in preventing bone loss. The use of DMPA is associated with a decrease in bone mineral density, although it is reversible after discontinuation of its use. In conclusion, the contraceptive choice, the stages of the user's life and the individual´s bone risk factors must be taken into account.

Keywords: Bone Mineral Density; Hormonal Contraceptive; Adolescence; Menopause

Introduction

In the world, hormonal contraception represents the main form of contraception, being used for a long time and from early ages. Estrogens play a fundamental role in both the formation and maintenance of bone mass and bone metabolism. In adolescence they are essential for the acquisition of peak bone mass and in adulthood for the regulation of bone mineral density (BMD) [1]. All cells present in bone tissue (osteoblasts, osteoclasts and osteocytes) have estrogenic receptors. In the trabecular bone; present in vertebrae and forearms; estrogenic beta receptors (REβ) predominate, and in cortical bone; present in extremities and hip; estrogen receptors alpha (REα) predominate. Osteoblasts and osteoclasts also have receptors for progesterone. Estradiol performs its action through multiple mechanisms, to name a few: decreases the expression of lysosomal enzymes (osteoclasts), regulates the production of cytokines (interleukin-1 and 6) and the nuclear factor activating receptor kappa-b (RANK), stimulates production of the Osteoprotegerin (OPG) locally, decreases the depth of the resorption lagoons, (the rate of bone remodeling- (osteoblasts), and suppresses osteoclastogenesis and osteoblastogenesis. In combination with progesterone they have a synergistic action in cell proliferation. Combined hormonal contraceptives (AHC) induce a reduction in serum estrogen and a suppression of endogenous progesterone. This reduction is dose dependent; therefore, if the dose is insufficient to ensure appropriate levels of sex steroids, bone tissue metabolism could be affected. This is particularly important during adolescence, when the hypothalamus-pituitary-ovary axis is not fully mature and during the perimenopausal period, when circulating estrogen and progesterone levels may be reduced. Studies that evaluate the impact of contraceptives on BMD seem to suggest that AHC would not have negative effects.

All studies showed changes in BMD but did not modify the incidence of fracture, which is definitely the real gold standard for measuring the impact of ACH use on bone. Variations in BMD might not accurately reflect the actual risk of fracture and its value in the context of the use of steroidal contraceptives is unknown [1-4]. Making an analysis of the impact of hormonal contraceptives

on bone mass is difficult, since there are currently different doses, schedules and combinations, and there are factors that could influence the results such as the age of the user, the time of use, the inheritance, food, exercise and smoking. Vestergaard et al. [5], evaluated the risk of fractures in users of AHC in 64548 women with previous fractures. In users of low doses of combined hormonal contraceptives (AHC) a small increase in risk was found, which disappears when considering comorbidities. When comparing two formulations, nomegestrol acetate (NOMAC) 2.5mg and 17β-estradiol (E2) 1.5mg in a 24/4 regimen with levonorgestrel 150 µg and ethinylestradiol 30 µg in a 21/7day regimen, in 110 healthy women between the ages of 20 and 35, a clinically relevant effect or significant difference in BMD [6] was not present after 2 years of use.

A retrospective study of 12970 women, with an average age of 37-8 years old, compared the risk of bone fracture in AHC users with women who never used it and found that the use of AHC for more than 1 year is associated with a significantly lower risk of fractures [7]. Another review assessing the impact on BMD and AHC containing lower doses of EE, 20 or 15mcg [8], showed no differences between users and non-users, although there was an increase in bone formation markers and a reduction in the reabsorption markers in the group taking AHC. Currently there is a wide range of AHC, with different routes of administration. The vaginal ring is a vaginal release system that contains 11.7mg of etonogestrel and 2.7mg of ethinyl estradiol and releases on average 0.120mg of etonogestrel and 0.015mg of ethinyl estradiol daily for a period of 3 weeks. The transdermal contraceptive patch contains 6mg of norelgestromin (NGMN) and 600 micrograms of EE which releases on average 203mcg of NGMN and 33.9mcg of EE every 24 hours. Massaro et al. [9] evaluated the effects of the vaginal ring and contraceptive patch on bone turnover (measurement of serum osteocalcin and urinary excretion of pyridinoline and deoxypyridinoline) and BMD in fertile young women.

After 12 months, they found no changes in the BMD of the spine, while the biochemical markers showed positive changes for bone health. Nappi et al. [1], in a systematic review that included 129 studies, analyzed the effect on BMD and fracture risk of AHCs, progestogen contraceptives alone, transdermal and vaginal ring, and concluded that AHCs have no significant effect on BMD in the general population. Although in adolescents, the consequences on BMD seem to be determined by the dose of estrogen and in perimenopausal women it seems to reduce bone demineralization and could significantly increase BMD, even with a dose of 20 mcg.

There is low clinical evidence on the effects of HA on bone metabolism in adolescents. Data derived from longitudinal cohort studies are contradictory [10,11]. Some studies suggest a beneficial effect on BMD and others failed to find any detectable effect. Rizzo et al. [12] evaluated the effects and possible differences between the use of AHC containing 20 µg of EE + 150µg of desogestrel vs. 30µg of EE+3mg of drospirenone in the bone metabolism of adolescents during a one year of follow-up compared to non-users. No significant differences were found for lumbar BMD, total body, lumbar bone mineral content and total body in both groups with AHC. Both groups with AHC showed a reduction in bone markers (bone alkaline phosphatase and osteocalcin). There was a significant difference between the AHC groups with a higher bone mineral content in the 30µg EE group + 3mg drospirenone. Therefore, they conclude that the use of low-dose AHC during adolescence is associated with lower bone gain and decreased markers of bone formation. When the effect on BMD of the lumbar spine was analyzed in adolescents after 12 months of an extended regime of 84/7 of LNG 150mcg +EE 30mcg and with a traditional regime of 21/7 of LNG 100mcg /EE 20mcg with a control group of adolescents who do not use AHC it was found that the 3 groups had an increase in BMD, however, adolescents users of the traditional LNG / EE regime 20mcg 21/7 had a statistically significant (1.05%; 95% CI, 0.61% -1.49%) lower increase in BMD of the lumbar spine than those of the control group [13]. According to WHO data, adolescents who use less AHC than EE 30mcg have a lower BMD compared to non-users [14].

On the other hand, the majority of cross-sectional studies indicate that the use of AHC is not associated with differences in the values of BMD in postmenopausal women, compared to women who never used AHC, but there is also no evidence that the use of AHC reduce the risk of fracture before menopause. During perimenopause there is a decrease in BMD, possibly associated with the decrease in the production of ovarian estrogens that leads to an activation of bone turnover, even greater in women with oligomenorrhea. When the effect of low-dose AHC on BMD and bone metabolism in perimenopausal women with oligomenorrhea was compared, the dose of 20mcg of EE accompanied by any gestagens was found to have a beneficial effect on prevention [15]. The use of gestagens alone has been a reliable and safe contraceptive tool for those women to whom the use of estrogen is contraindicated according to the WHO eligibility criteria [15]. Depending on the gestagen used, there will be ovulation inhibition (desogestrel, medroxyprogesterone, subdermal implant with etonorgestrel) and/or thickening of the cervical mucus (levonorgestrel), thus hindering the rise of sperm to the uterine cavity. When considering the effect of gestagens on bone mass, the impact of the use of intramuscular medroxyprogesterone (DMPA) on BMD [16] was evaluated in a prospective study in women between 25 and 35 years of age. It was found found that BMD in DMPA-IM users had decreased by 5.16% in the total hip and 5.38% in the lumbar spine after 7 years. However, after suspending its use, recovery of BMD was observed towards the reference values. Equally, in a comparative cross-sectional study [17], which evaluated BMD in the lumbar spine and femoral neck, after 10 years of use, they found low bone mass and osteoporosis. Among DMPA users who had been using the method for 10 years, 11-15 years or 16-23 years, BMD was found to decrease as the number of years of DMPA use increased. Therefore, it can be concluded that the longer is used, the greater the loss of bone mass. Additionally, Nappi et al. published that the use of DMPA is associated with a decrease in BMD, although it is reversible after discontinuation of its use [1].

Another study also conducted in adolescents, reveals that, after 2 years, BMD increased by 9.3% in users of levonorgestrel-based subdermal implant (Norplant ®) and 9.5% in the control group, but decreased by 3.1% in DMPA users (p <0.000 I) [18]. Dienogest

(DNG), a molecule derived from nortestosterone that lacks androgenic activity, suppresses the trophic effects of estradiol, both in the eutopic and ectopic endometrium. The administration of dialogist continuously results in a hypoestrogenic environment. Although its indication in clinical practice is for patients with endometriosis, the results of Seo et al. [19], which evaluated in 60 women of reproductive age who previously underwent conservative endometriosis surgery, are of long interest term of this molecule in BMD. They found that long-term DNG treatment could have an adverse effect on BMD in women of reproductive age.

Conclusion

Hormonal contraceptives are the most commonly used forms of contraception and probably the first choice. However, the impact on bone mass and its metabolism differs when comparing formulations and doses. Adolescence is a stage of formation of the bone mass peak. Evidence suggests that this group should be indicated combined hormonal contraceptives in doses of 30μg of EE. In contrast, in perimenopause, where hormonal fluctuation negatively impacts bone, even doses of 20μg of EE have been shown to be beneficial in preventing bone loss. In this age group it would not be advisable to use DMPA, because of its negative impact on both the spine and the hip. Although reversible, it is a critical and short period for the perimenopausal woman to recover bone mass. If it is necessary to indicate progestogens alone, the recommendation would be levonorgestrel-based subdermal implants that have proven beneficial for the bone.

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