

# Hormonal treatment of endometriosis in adolescents and young adults: consequences on bone density

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## ABSTRACT

Endometriosis is a chronic disorder characterized by the finding of “endometrium-like” tissue outside the uterus. It is the leading cause of secondary dysmenorrhea in adolescents. Endometriosis is mainly an estrogen-dependent disorder, therefore current hormonal therapies aim to counteract the biological effect of estrogens, reducing cell proliferation, neuroinflammation and pain. In adolescents and young adults, in particular, treatment aims to reduce pain, prevent the development of endometrial implants, and preserve fertility.

Estrogens are main regulators of bone physiology, and hormonal therapies may therefore affect bone remodeling, both during adolescence and aging. Peak bone mineral accrual may be a concern in patients receiving long-term, low-estrogen hormonal treatment, such as for endometriosis. Here, we review crucial estrogen-related mechanisms associated with bone remodeling in adolescents and young adults and their potential role in long-term hormonal treatment of endometriosis. Early diagnosis of endometriosis is crucial, but early hormonal administration may expose young patients to bone fragility later in life.

## KEYWORDS

Endometriosis, adolescents, hormones.

## Introduction

Endometriosis is an estrogen-dependent disorder characterized by the finding of “endometrium-like” tissue outside the uterus. It affects 10% to 15% of all reproductive-age women and is present in up to 70% of women with chronic pelvic pain<sup>[1]</sup>. The majority of endometriotic implants are located in the pelvis, with the ovaries being the most frequent site<sup>[2]</sup>. These implants can cause pain, scarring, and infertility. The severity of pain originating from endometriosis is associated with the lesion location and depth of invasion, and the stretching or scarring of tissue. However, the presence of symptoms does not always correlate with the extent of endometriosis<sup>[2]</sup>. Endometriosis is the leading cause of secondary dysmenorrhea in adolescents<sup>[3]</sup>. The exact prevalence of endometriosis in this age group is unknown, but it has been estimated that among the 15% of young adults who suffer from chronic pelvic pain, in up to 97% it is due to endometriosis<sup>[2,4]</sup>. Patients with endometriosis most commonly present with both cyclic (associated with menses) and non-cyclic (not associated with menses) pain<sup>[5]</sup>. Although they often report the onset of symptoms during adolescence, the diagnosis of endometriosis is often delayed. On average, an adolescent waits one year after the onset of symptoms before seeking medical advice and two years (0-7 years) before receiving a diagnosis of endometriosis<sup>[6]</sup>.

In a recent cross-sectional longitudinal cohort study of adolescents and women (n=984) with endometriosis, DiVasta et al.<sup>[6]</sup> noted that most participants (90%) experienced moderate-severe menstrual pain. In addition, more adolescents (50%) than adults (33%) reported pain starting at menarche (P=0.002), with nausea accompanying the pain (69% vs 53%; P=0.01).

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Non-cyclic, general pelvic pain was also more prevalent in adolescents than in older women (77% vs 66%; (P=0.04)).

Treatment of endometriosis in the adolescent and young adult population aims to reduce pain, prevent the development of endometrial implants, and preserve fertility<sup>[7,8]</sup>. The rationale for the use of hormonal therapies is to reduce the biological effect of circulating and local estrogenic environment of ectopic lesions in order to reduce cell proliferation, neuro-inflammatory mediators and pain. The European Society of Human Reproduction and Embryology recommends an empirical treatment which includes non-steroidal anti-inflammatory drugs (NSAIDs) as a first-line treatment, followed by a hormonal treatment such as combined oral contraceptives (combined oral contraceptives, COCs), progestogens, gonadotropin-releasing hormone (GnRH) agonists, anti-progestogens, and aromatase inhibitors<sup>[9]</sup>.

If a symptomatic adolescent/young adult does not respond to NSAIDs for three menstrual periods, consideration should be given to prescription of hormonal agents such as combined hormonal contraceptives (CHCs) or progestogens to create a hypoestrogenic state. GnRH agonist use is limited in young people as this class of drugs downregulates the hypothalamic-pituitary axis, leading to a severe hypoestrogenic state.

Indeed, estrogens are the main regulators of bone physiology and hormonal therapies can affect bone remodeling. This applies both during adolescence and during the aging process. Peak bone mineral accrual may be a concern in situations where long-term hormonal treatment is indicated, such as endometriosis. In this article, we review the crucial estrogen-related mechanisms associated with bone remodeling in adolescents and young adults and their potential role in the long-term management of endometriosis-associated pain.

## Estrogen regulation of bone density during adolescence

Peak bone mass (PBM) acquisition is largely regulated by endocrine factors, in particular by adequate levels of gonadal, adrenal and pituitary hormones. Numerous factors affect bone capital: genetic factors, physical activity, nutritional factors, anthropometric characteristics, calcium intake, and hormonal status. PBM acquisition during puberty, in both genders, is proportional to the increase in sex steroids. Sex steroids are therefore essential for normal pubertal development, growth, and pubertal skeletal maturation. Estrogens are major determinants of bone mass (BM) and are the key regulator of bone metabolism. Estrogens inhibit bone resorption by slowing down the process of remodeling while androgens have a greater anabolic role. Estrogen receptors are expressed by osteocytes, osteoblasts and osteoclasts <sup>[10]</sup>. Estrogen decreases bone remodeling by means of direct actions on osteoclast formation and inhibition of bone resorption, while maintaining bone formation <sup>[11]</sup>. Progesterone has receptors expressed on the surface of osteoblasts, but literature data on its effects on bone metabolism are limited. However, in partnership with estrogen, it plays an important role in the acquisition of PBM.

Although women gain most of their BM during their adolescent years — it increases by 2 to 10% per year from menarche to reach a peak at around 20 to 22 years old <sup>[12]</sup> —, bone density continues to increase after adolescence and PBM is normally reached in the third decade of life <sup>[13]</sup>. In adulthood, an annual bone remodeling rate of 0.3% is observed <sup>[14]</sup>. The age at which PBM is achieved varies by skeletal site, with hip PBM being reached at an earlier age than lumbar spine PBM in women <sup>[15]</sup>. Women reach PBM at both the femoral neck and the total hip at between 16 and 19 years of age, while lumbar spine PBM is achieved between the ages of 33 and 40 years according to prospective population-based data from the Youth and Adult CaMos cohorts <sup>[16]</sup>. The lumbar spine is an ideal site for monitoring bone mineral density (BMD) during adolescence and early adulthood because it is more sensitive to hormonal changes and pathologies. Any interference with the acquisition of PBM during adolescence and young adulthood may modulate BMD and increase the risk of osteoporosis and fractures later in life <sup>[10,17]</sup>. Epidemiological studies indicate that a 10% increase in PBM can help to decrease the risk of osteoporosis by 50% in the future <sup>[18]</sup>. Davies et al. compared 16- to 40-year-old women with a past or current history of functional amenorrhea of a median duration of three years with a control group of age-matched normal volunteers with no history of menstrual disorders. They

found that the amenorrheic group showed a mean 15% reduction in BMD compared with the controls. Bone loss was related to the duration of amenorrhea and the severity of estrogen deficiency <sup>[19]</sup>. Several clinical conditions associated with hypogonadism are associated with BMD reduction, supporting the hypothesis that chronic hypoestrogenism affects bone health. Conditions such as hypothalamic-pituitary insufficiency (functional hypothalamic amenorrhea, anorexia nervosa, Kallmann syndrome, hyperprolactinemia), ovarian failure (gonadal dysgenesis, premature ovarian failure), and iatrogenic treatment (surgery, chemotherapy, radiotherapy, contraception) can cause hypoestrogenism <sup>[11,20]</sup>. However, diagnostic guidelines used in adults cannot be directly extrapolated to pediatric subjects for two reasons: the effect, in the latter, of growth and hormonal development as seen on densitometric measurements; and the difference in fracture epidemiology between children, adolescents and adults <sup>[21]</sup>.

Some years ago, some clinical reviews described “the estrogen threshold hypothesis”. According to this hypothesis, tissues vary in their sensitivity to estradiol and a “concentration of estradiol [between 30 and 45 pg/ml] that will partially prevent bone loss may not stimulate endometrial growth” and therefore the development of endometrial lesions <sup>[7]</sup>. The estrogen threshold hypothesis has been proposed for adults, but no studies have been conducted in adolescents during the period of PBM accrual. Specifically, the threshold concentration of estradiol associated with a decline in estrogen-mediated bone acquisition in adolescents is currently unknown.

## Lowering estrogens for endometriosis may impair bone health: hormonal treatment for endometriosis affects BMD

Biological and clinical data show that reducing concentrations of estrogens and/or antagonizing their biological effects by means of progestogens results in considerable improvements in endometriosis-related pain symptoms. Different hormonal regimens showing effectiveness are: CHCs (administered in different forms: pill, contraceptive patch or vaginal ring), progestin-only pills, etonogestrel subdermal implants, intramuscular depot medroxyprogesterone acetate (DMPA), the levonorgestrel-releasing intrauterine system, and GnRH agonist therapy. Although there is agreement that low-dose estrogenic regimens are preferable over high-dose treatments, which carry a thromboembolic risk, the potential consequences of low-dose regimens on bone density and strength in adolescents and young adults have so far been overlooked.

### Combined hormonal contraceptives

CHCs suppress the pituitary production of gonadotropins, which subsequently prevents ovarian production of estradiol. The circulating levels of estrogen are mainly determined by the dosages present in the CHC formulation. Different CHC formulations may have different effects in younger women, who have not yet reached PBM, as compared with women who have.

If the pill formula of the CHC does not guarantee sufficient circulating levels of sex steroids, bone metabolism may be neg-

actively affected, especially during adolescence. Indeed, using a low-dose CHC may result in a reduced, suboptimal BMD, as a low plasmatic estrogen concentration might not be sufficient to achieve maximal PBM. The low-dose formulations provide estrogen concentrations similar to those recorded during the early follicular phase. Both age at first CHC use and cumulative estrogen dose appear to be important factors in determining skeletal development in adolescents<sup>[22]</sup>. Moreover, initiation of CHC use within the first three years after menarche appears to be of particular concern because of the decrease of androgens<sup>[23]</sup>. Some studies suggest that long-term use of a low-dose oral monophasic contraceptive formulation [ethinyl estradiol (EE) 20 mg + desogestrel 0.150 mg] may result in suboptimal PBM. A cross-sectional study of 606 women aged 14–40 years (50% were adolescents aged 14–18 years) examined both contraception duration and estrogen dose, and their association with BMD at the hip, spine and whole body<sup>[24]</sup>. Among the COC users, 38% used “low-dose” OCs (<30 mcg EE). In adolescents, mean BMD differed neither by COC duration nor by EE dose. However, mean BMD in the women aged 19–30 years was lower with longer COC use for the spine and whole body ( $p=0.004$ ,  $p=0.02$ , respectively) and lowest for >12 months of low-dose COC for the hip, spine and whole body ( $p=0.02$ , 0.003 and 0.002, respectively). Scholes and colleagues concluded that “prolonged use of today’s OCs, particularly <30 mcg EE, may adversely impact young adult women’s bone density”<sup>[25]</sup>. A recent meta-analysis showed that significantly less spinal bone mineral density accrual occurred in adolescent women who were first taking combined hormonal contraceptives compared with those not using them. This evidence for potential impairment of peak spinal bone mineral density accrual is of concern and suggests a potential public health problem<sup>[26]</sup>.

### GnRH agonists

GnRH agonist therapy is a highly effective, non-surgical treatment option for adolescents with endometriosis, but it is accompanied by side effects such as bone loss and menopausal symptoms<sup>[27]</sup>. These side effects may be decreased by introducing appropriate add-back therapy as add-back does not worsen endometriosis-associated pain and decreases the adverse side effects of therapy<sup>[27]</sup>.

Adding norethindrone acetate (NETA) (5 mg/d) + conjugated quine estrogens (CEE) (0.625mg/d) preserved BMD in young women with endometriosis treated for one year with a GnRH agonist, although no increase in BMD was clearly shown. *In vivo*, NETA is converted into EE after oral ingestion, such that 20 mg NETA may be equivalent to taking a pill containing 30 µg of EE. Moreover, the presence of CEE further increases the estrogenic environment far beyond values indicated in the “estrogen threshold hypothesis” mentioned above<sup>[28]</sup>. Spinal BMD has been shown to decrease by between 5 and 8% after 3–6 months of GnRH agonist treatment<sup>[29,30]</sup>. BMD may not return to baseline after cessation of treatment<sup>[31]</sup>. Loss of BMD is more pronounced if add-back therapy is delayed<sup>[32]</sup> and monitoring of bone density by dual-energy X-ray absorptiometry every six months is recommended in adolescents if GnRH agonist use is prolonged<sup>[27]</sup>. Early diagnosis of endometriosis could translate into prolonged exposure to the GnRH ag-

onist, therefore this treatment is not currently recommended as a first-line treatment for adolescents/young adults and should not be used for more than 12 months<sup>[33]</sup>.

### Progestogen-only agents

Progestin-only agents can also be used in the treatment of endometriosis. Progestins suppress the hypothalamic-pituitary-ovarian axis, a process that induces anovulation and reduces estrogen levels. The use of progestin-only agents leads to decidualization and atrophy of ectopic endometrial tissue and endometriotic lesions, although the biological response of endometriosis may be affected by progesterone resistance (because of the chronic inflammation) and by the type of progestogen used<sup>[34]</sup>.

In an open-label study from Finland conducted in 73 women aged 18 to 40 years, BMD was compared at baseline and after two years’ use of etonogestrel implant and a levonorgestrel intra-uterine device. BMD values at the lumbar spine, femur, or radius were found to be similar between the two groups<sup>[35,36]</sup>.

On 17 November 2004, the Food and Drug Administration issued a warning about DMPA, stating that its prolonged use may result in significant loss of BMD, that the loss is greater with increasing duration of use, and that BMD loss may not be completely reversible. Nonetheless, it is not clear whether the use of DPMA during adolescence or early adulthood reduces PBM and increases the risk of osteoporotic fracture in later life.

Dienogest (DNG) is a progestin widely prescribed for endometriosis-associated pain in adults. Highly selective for the progesterone receptor, it combines the pharmacological properties of 19-norprogestins and progesterone derivatives, exhibiting strong progestational effects and moderate antigonadotrophic effects, with limited androgenic, glucocorticoid, or mineralocorticoid activity<sup>[37,38]</sup>. DNG suppresses estradiol levels only moderately and in a six-month study in adults it did not alter mean lumbar spine BMD<sup>[39,40]</sup>. The safety and efficacy of DNG for providing pain relief in the adult population have been confirmed in several clinical trials, differing in design and ethnicity of populations<sup>[41,42]</sup>.

After an open-label, randomized, multicenter, 24-week comparative dose-finding trial, 2 mg of DNG once daily was recommended as the optimal dose. Women with histologically confirmed endometriosis were assigned to 1, 2, or 4 mg of DNG. The efficacy of DNG was evaluated by second-look laparoscopy and patient-reported symptoms. The 1-mg dose arm was discontinued due to insufficient bleeding control. DNG at 2 and 4 mg/day was associated with symptom improvement in a substantial proportion of the 54 women who completed the study<sup>[43]</sup>.

As the use of DNG may lead to relative estrogen deficiency, concern has been expressed regarding its effect on BMD, particularly when used during adolescence, a critical period for bone mineral accrual. During the development of DNG, the Pediatric Committee (PDCO) of the European Medicines Agency requested a pediatric investigational plan for the indication of endometriosis in symptomatic patients after menarche (age 12 to younger than 18 years). The primary objective of this study (VISADO) was to evaluate the long-term effects of DNG 2 mg per day on BMD of the lumbar spine in adolescents with

confirmed or clinically suspected endometriosis. The VISADO study was a 52-week, open-label, single-arm study conducted between March 2011 and June 2014. It concerned adolescents aged 12 to younger than 18 years from 21 study centers in six European countries. DNG was associated with a decrease in lumbar BMD (1.2%) at the end of treatment (EOT), followed by partial recovery after treatment discontinuation. Lumbar spine BMD was lower at EOT than at baseline in 73 of 103 patients (70.9%; mean change, 2.3%). Follow-up measurement six months after EOT in the subgroup with decreased BMD at EOT (n = 60) showed partial recovery of lumbar BMD (mean change from baseline: 2.3% at EOT, 0.6% at six months after EOT)<sup>[44]</sup>.

## Conclusion

Adolescence and early adulthood are critical periods of bone accretion in women. Loss of BMD following hormonal treatment is of particular concern. Optimal BMD may be decreased as a result of prolonged use of low-dose CHC or a progestogen with a strong anti-gonadotropic action. GnRH agonists with add-back treatment preserve BMD in adolescents at one-year follow-up, but as endometriosis is identified at earlier ages, GnRH agonist exposure is likely to last longer.

Specifically, the current estrogen threshold values are likely not applicable to this specific population of young women and the ideal hormonal range for avoiding negative consequences on bone accrual is currently unknown. In addition, while the bone densitometry score does bear some relationship to bone strength, it is not a sufficient surrogate marker in many cases, especially in young women; this makes the clinical picture more complex to investigate. Young bone and older bone are qualitatively different in strength, even with similar bone density. No osteoporosis risk assessment test, such as the FRAX<sup>®</sup> tool, has been developed for people younger than 40 years.

While early diagnosis of endometriosis is crucial, early hormonal management may expose young patients to bone fragility later in life. More longitudinal studies are needed to clarify the role of exogenous estrogens during peak bone accrual and their impact on the long-term management of this estrogen-related and invalidating disease. Hormonal treatment is a pillar in endometriosis care. Based on current knowledge, the specific consequences on bone health should be evaluated and discussed if a hormonal treatment is suggested in adolescents and young adults, in order to properly tailor the medical strategy.

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