Journal of the Pediatric Orthopaedic Society of North America 7 (2024) 100061

Contents lists available at ScienceDirect

Journal of the Pediatric Orthopaedic Society of North America

journal homepage: www.jposna.com

Pediatric Bone Health Update

Estrogen exposure and skeletal health: Special populations and considerations

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ARTICLE INFO

Keywords:
Estrogen
Peak bone mass
Anorexia nervosa
Primary ovarian insufficiency
Adolescent trans health
Adolescent contraception

ABSTRACT

Estrogen is critical for bone health from puberty onwards. Various clinical scenarios in adolescence can impact skeletal exposure to estrogen during this vulnerable time. Primary ovarian insufficiency, premature menopause, and anorexia nervosa necessitate prompt evaluation, treatment, and replacement of estrogen in order to optimize accrual of peak bone mass. We have much still to learn about the skeletal impact of delaying puberty and gender affirming hormones in gender diverse individuals. While the choice of hormonal contraception in adolescence is often driven by patient preference and concerns about adherence, providers and patients much take the long-term impact on bone health into consideration.

Key Concepts:

(1) Delayed, diminished or absent estrogen during adolescence has a negative impact on peak bone mass accrual.
(2) Hormone replacement therapy is essential for patients with primary ovarian insufficiency and premature menopause.
(3) Recovery from anorexia nervosa does not lead to a complete catch-up of bone density lost/not gained.
(4) Not all hormonal contraception methods are created equal for the adolescent skeleton.
(5) Skeletal health of trans youth is an emerging focus.

Background

It has been said that osteoporosis is a pediatric disease with adult consequences. This article will focus on the skeletal consequences of delayed, diminished, or absent estrogen during adolescence, a critical period of bone mass accrual.

Estrogen has an important role in bone health from puberty onwards. This is true for both males and females. Less overall skeletal exposure to estrogen throughout the life cycle increases the risk of low bone density, osteoporosis and fractures [1]. Parker et al. demonstrated an increased incidence of osteoporosis in females with less than 25 years of menstruation [2]. Low estrogen levels during puberty lead to low bone density and impaired bone mass gains [3].

In this article we will focus on hypoestrogenism in adolescents with primary ovarian insufficiency, skeletal consequences of anorexia nervosa, the impact of delayed puberty and gender-affirming hormones in gender diverse individuals, and concerns regarding hormonal contraception during adolescence.

Primary ovarian insufficiency and premature menopause

Primary ovarian insufficiency (or premature ovarian insufficiency—POI) is characterized by hypergonadotrophic (elevated follicle-stimulating hormone and luteinizing hormone) hypogonadism (low estrogen) in women younger than 40. This may be transient or variable. Premature menopause refers to permanent loss of ovarian function before the age of 40. In women under 20, the prevalence of POI is 1 in every 10,000 women [4]. Ovarian follicular dysfunction or depletion in adolescents has a myriad of possible causes—genetic (most commonly Turner Syndrome), autoimmune, metabolic, infectious, iatrogenic (chemo, radiation), surgical, and idiopathic/spontaneous [5].

Index of suspicion must be high as waiting for the classical diagnostic criteria for menopause—12 months of amenorrhea—is inappropriate and potentially harmful. The diagnosis should be considered with oligo/amenorrhea for at least 4 months and an elevated follicle-stimulating hormone level on 2 occasions more than 4 weeks apart [6]. follicle-stimulating hormone and estradiol should be

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https://doi.org/10.1016/j.jposna.2024.100061
Received 2 April 2024; Accepted 3 April 2024
Available online 16 April 2024

evaluated together—estradiol levels of less than 50 pg/mL indicate hypoestrogenism [7]. Health concerns and comorbidities among individuals with POI include sexual dysfunction, infertility, cardiovascular disease, cognitive function, dry eye syndrome, endocrine disorders (particularly hypothyroidism), and low bone mineral density (BMD)/increased fracture risk [5,8,9].

In a large 2009 study, women with POI who had an onset of irregular menses before age 20 were 2.72 times more likely to have a dual energy photon absorptiometry (DXA) with Z-scores below −2.0 as compared to those who had an onset of menstrual irregularity at age 20 or later ($P < .0001$). All subjects with POI also had BMD significantly lower at all sites (lumbar spine—luteinizing hormone, total hip—TH, femoral neck—FN) than concurrent recruited control as well as matched controls from National Health and Nutrition Examination Survey [10]. The adolescent skeleton is particularly vulnerable but low bone density is a concern in all women with POI.

Physiologic estrogen therapy has been shown to increase bone density in adolescent patients with POI secondary to hematopoietic stem cell transplantation [11], in patients with Turner syndrome particularly if initiated before age 18 [12], and in young women with spontaneous 46,XX POI [13]. In the latter study, those on continuous transdermal estradiol and a cyclic oral progestin gained 7.7% in lumbar spine BMD over 3 years and restored the mean femoral BMD to normal (Fig. 1).

The recommended dose of hormone therapy in a young patient is higher than that in traditional menopausal hormone therapy to approximate estrogen exposure during an ovulatory menstrual cycle—100 mcg patch, 1.25 of conjugated equine estrogens, or 2 mg of oral estradiol. Cyclic oral or intrauterine progestins are added in those with a uterus. Ovulation may be intermittent and unpredictable for years in patients with POI, and spontaneous pregnancies has been reported [14]; hormonal contraception can thus be considered for estrogen replacement though may not be as optimal for skeletal health as compared to hormone therapy [15,16].

Multiple medical societies including but not limited to the Menopause Society, the Endocrine Society, and the American College of Obstetricians and Gynecologists recommend the use of hormone therapy in this population until the average age of menopause, 51. Unfortunately, this true hormone *replacement* has been conflated and confused with the use of menopausal hormone therapy as studied to

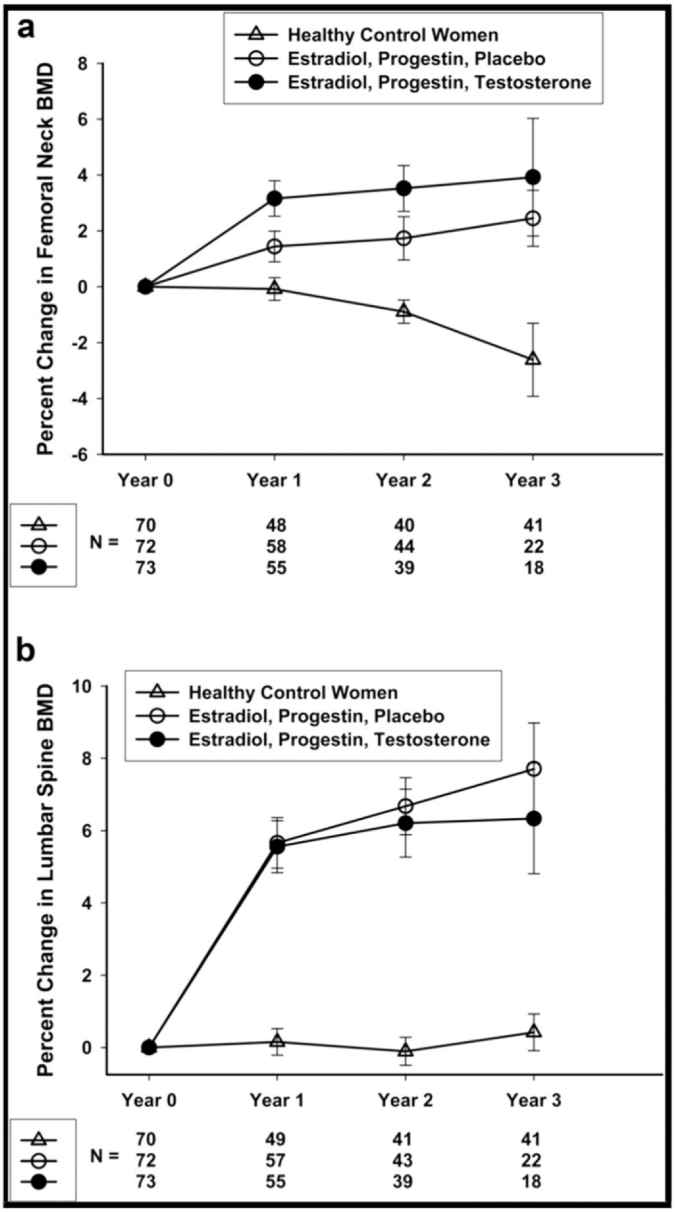


Figure 1. (A.) Mean percentage change from screening in the femoral neck BMD. (B.) Mean percentage change from screening in the lumbar spine BM.

great fanfare and dismay in the Women's Health Initiative [17]. The Women's Health Initiative is not applicable to the adolescent patient population, in whom the hypoestrogenemia should be viewed and replaced as would any other deficient hormone from other endocrine organs.

The European Society for Human Reproduction and Embryology guidelines recommend measurement of BMD at initial diagnosis of POI. With appropriate systemic estrogen replacement, repeated DXA scans in those with normal BMD is low yield while those with low bone density/osteoporosis should be rescanned every 5 years [7]. This interval may be too long in adolescents accruing peak bone mass; others have suggested yearly scans from early-mid puberty and every 2 years in late adolescence [8].

Physicians, parents, and adolescents themselves should be attuned to regular menses as a 'vital sign,' particularly during this narrow window of bone accrual.

Eating disorders and disordered eating—anorexia nervosa

The DSM-5 defines anorexia nervosa (AN) as (a) restriction of energy intake relative to requirements, leading to a significant low body weight in the context of the age, sex, developmental trajectory, and physical health and (b) intense fear of gaining weight or becoming fat or persistent behavior that interferes with weight gain [18]. Stice et al. (2012) [19] found that between 0.9% and 2.0% of females and 0.1% and 0.3% of males will develop anorexia, while subthreshold anorexia occurs in 1.1% to 3.0% of adolescent females. Severe undernutrition during a time when growth and development needs calories to fuel same can have devasting consequences; patients with anorexia between the ages of 15 and 24 have 10 times the risk of dying compared to age-matched peers [20].

Very low BMD has been documented in adolescents with AN [21–23]. In a study of 60 adolescent girls with AN compared to 58 healthy controls [21], DXA Z-scores between −1.0 and −2.0 were noted in 41% of girls with AN (vs 23% of controls) and Z-score less than −2.0 were noted in 11% of girls with AN (vs 2% of controls) (Fig. 2). The most significant predictor of BMD at most sites—lumbar spine, total, femoral neck, total body—was lean body mass. Those with AN had lower estradiol levels and lower levels of IGF-1 compared to controls. Misra et al. [22] published a study of 17 adolescent males with AN and 17 controls, that demonstrated significantly lower Z-scores among those with AN in the lumbar spine ($P = .004$), total hip ($P = .0008$), and femoral neck ($P = .004$). Testosterone ($P = .004$) and estradiol ($P = .01$) were significantly lower those with AN. Bone turnover markers, both formation and resorption, are suppressed in adolescent girls [21,24] and boys [22] with AN.

Low bone density and diminished bone accrual in this population is also associated with an increased fracture risk that remains elevated decades after diagnosis and persists despite weight restoration and normalization of gonadal hormones [25,26]. When followed longitudinally for an average of 1.8 years, Sheperd et al. (2017) [23] reported a vertebral fracture rate of 5.9% in 68 adolescents with AN referred for bone density assessment—in the absence of local disease or high-energy trauma, a vertebral fracture is indicative of osteoporosis in adolescents irrespective of bone density [21]. Prevalence of stress and nonstress fractures was significantly higher in females 12 to 22 years old with active AN compared to controls ($P = .02$), with the relative risk of prior fracture 59.8% greater [27]. Areal BMD (amount of bone mineral divided by bone scanned area) is an imperfect predictor of fracture in this population as microarchitectural deterioration can occur in the absence of decreased areal BMD [27,28]. However, until more refined imaging modalities (eg, high-resolution peripheral quantitative computed tomography/HR) gain wider clinical use, Endocrine Society Guidelines (2017) recommend a baseline DXA for adolescents with 6 or more months of amenorrhea. Bone density should be assessed before this 6-month mark in those with severe nutritional deficiency, other energy deficient states and/or skeletal fragility [29].

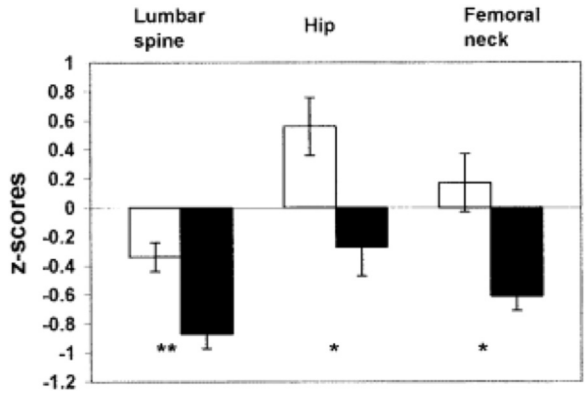


Figure 2. Z scores for lumbar spine, hip and femoral neck BMD in girls with AN (■) and healthy control subjects (▢). Girls with AN had significantly lowers z scores at each site than healthy adolescents. *$P < .01$; **$P \leq .001$.

Weight recovery and a return to spontaneous ovulatory cycles are the best markers of health in our patients with eating disorders, though the latter may lag behind the former for many months [30]. However, rates of full remission are low, and relapse is common [31]. Furthermore, bone accrual does not 'catch up' to peers even in recovery [32]. Adolescents with anorexia AN have limited time to optimize peak bone mass as they struggle with psychological aspects of the illness. As with postmenopausal osteoporosis, adequate calcium and vitamin D are necessary but not sufficient for treatment in this setting [30]. Though still widely used, the combined oral contraceptive pill (COC) does not increase BMD [33]—oral estrogen suppresses IGF-1, already impaired in AN and further decreases androgen levels. COC use for presumed bone benefits should be discouraged [29]. In a pivotal 2011 study, Misra et al. [34] demonstrated that physiologic estrogen replacement with transdermal 17-beta estradiol (100 mcg patch applied twice weekly) in adolescents with mature bone age and small, increasing oral doses of ethinyl-estradiol to girls with immature bone age, increased spine and hip BMD significantly compared to placebo. Changes in lumbar and hip BMD at 6, 12, and 18 months were comparable to normal-weight controls in those treated with estrogen (Fig. 3). Current guidelines support this regimen for adolescents with AN who have not had a return to spontaneous menses after 6 to 12 months of nutritional, psychological, and exercise-related interventions [29].

Though preliminary data using recombinant human insulin-like growth factor showed favorable increases of P1NP (a marker of bone formation), a 2021 placebo-controlled longitudinal study of adolescents and young women (ages 14-22) using concurrent recombinant human insulin-like growth factor with transdermal estrogen yielded disappointing results [35,36]. Guidelines recommend against using bisphosphonates, denosumab, testosterone, and leptin in this patient population [29]. Teriparatide has not been studied in this patient population given concerns about osteosarcoma in those with open epiphyses [37].

Patients with anorexia should be cared for by a multidisciplinary team with expertise in and empathy for this challenging, recalcitrant, and potentially devastating condition.

Transgender and gender-diverse individuals

Given that puberty is a critical time for bone mass accrual, suppression of puberty as part of gender affirming care has raised concerns. Gender affirming hormone therapy is increasingly available to US teenagers who identify as transgender or gender nonconforming. The primary goals of medical intervention around the time of puberty are (1) prevention of unwanted and (2) development of desired secondary sex characteristics [38]. Current guidelines recommend GnRH agonists

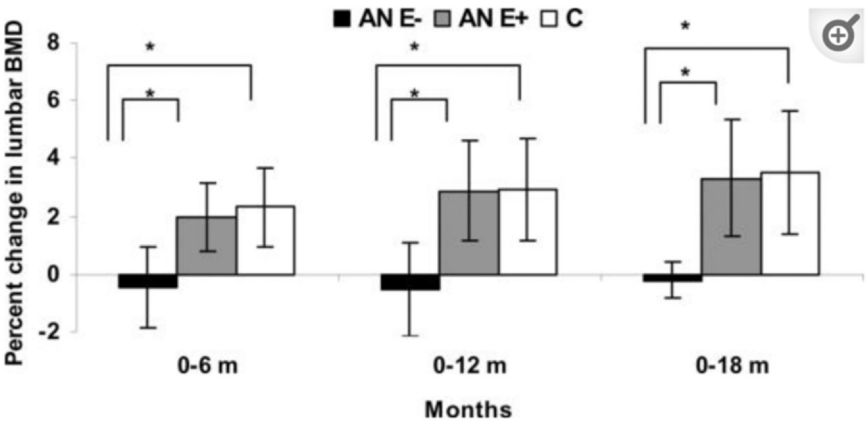


Figure 3. Percent change in lumbar bone mineral density (LBMD) in adolescent girls with anorexia nervosa (AN) randomized to placebo (AN E-) (black bars), girls with AN randomized to estrogen (AN E+) (gray bars) and normal weight controls (C) (white bars). AN E+ had significant increases in LBMD at 6, 12, and 18 months compared with AN E-. When compared with C, AN E- had significant decreases in LBMD at 6, 12, and 18 months, whereas AN E+ did not differ from C for changes in BMD over time. Analysis was performed for differences between means for pairs $*P < .05$.

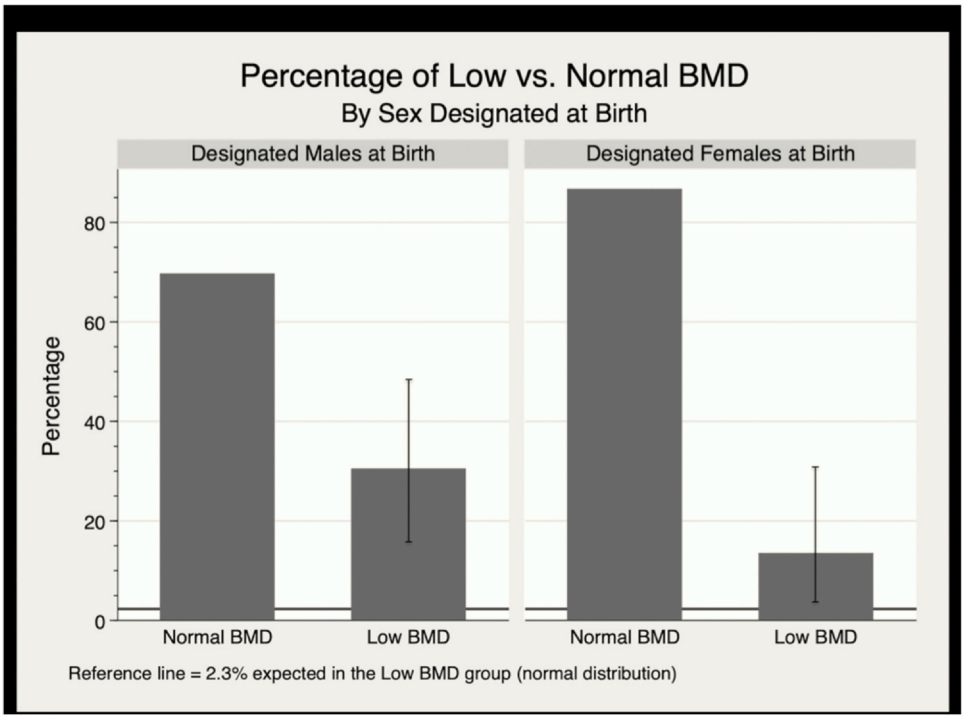


Figure 4. Percentage of low versus Normal BMD. Bar graph demonstrating markedly higher percentages of low BMD, as defined as at least one BMD z-score < -2, in our cohort of transgender/gender diverse youth. Low BMD error bars denote 95% confidence intervals. Data are stratified by sex designated at birth and show that DMAB had a higher frequency of pretreatment low BMD than DFAB youth (0.30 ± 0.47 vs 0.13 ± 0.35, $P = .0545$). Horizontal reference lines indicate the expected 2.3% to have BMD z-scores < -2 in a normal distribution. BMD, bone mineral density; DFAB, designated females at birth; DMAB, designated males at birth.

(GnRHa) as early as Tanner stage 2 to pause puberty, prevent gender incongruent physical changes, and allow time for gender exploration [39]. If no contraindications exist, gender-affirming sex steroid treatment is initiated at approximately 16 years; however, there is some controversy around this given that this is a late age at which to initiate puberty.

The International Society for Clinical Densitometry guidelines recommend calculating Z-score using the normative database that matches the gender identity of the individual. If requested by the provider, Z-score may be calculated using the normative database that matches the sex recorded at birth [40]. Assessment of BMD is recommended at baseline and every 1 to 2 years during suppression and induction of puberty. Thereafter, screening for osteoporosis in transgender males is recommended if testosterone treatment is stopped or inconsistent, and/or if the patient develops risks for bone loss. Baseline screening is recommended for transgender females; if low risk, this is repeated at age 60 or is nonadherent to hormone therapy [39]. Trans youth may have risk factors for low BMD predating medical intervention Consistent with prior studies from Europe [41], Lee et al. [42] reported a high prevalence of low BMD—defined as a Z-score < -2.0—at baseline in those designated male at birth (30%) and designated female at birth (13%), prior to initiation of puberty blockade. Selected determinates of bone health were analyzed between those with low versus normal BMD with the only statistically significant difference determined to be the Physical Activity Questionnaire for Older Children ($P = .01$). This isolated significant difference was also seen comparing designated male at birth with designated female at birth ($P = .04$) with the former reporting higher activity scores (Fig. 4).

In a survey by Bishop et al., transgender and gender-nonconforming students were less like likely to participate in sports ($P < .0001$), be physically active at least 60 minute/day ($P < .0001$) and more likely to have body mass index outside the normal range ($P < .0001$), miss lunch ($P < .0001$), and be bullied for weight or size ($P < .0001$) as compared to cisgender students [43]. The identification of and correction for disparities in healthy behaviors and bone density that are present before starting GnRH therapy may help to mitigate the expected decrease in BMD with treatment.

Schagen et al. [44] studied bone mass development in 51 transgirls and 70 transboys receiving GnRHa and 36 transgirls and 42 transboys receiving GnRHa and gender-affirming hormones, subdivided into

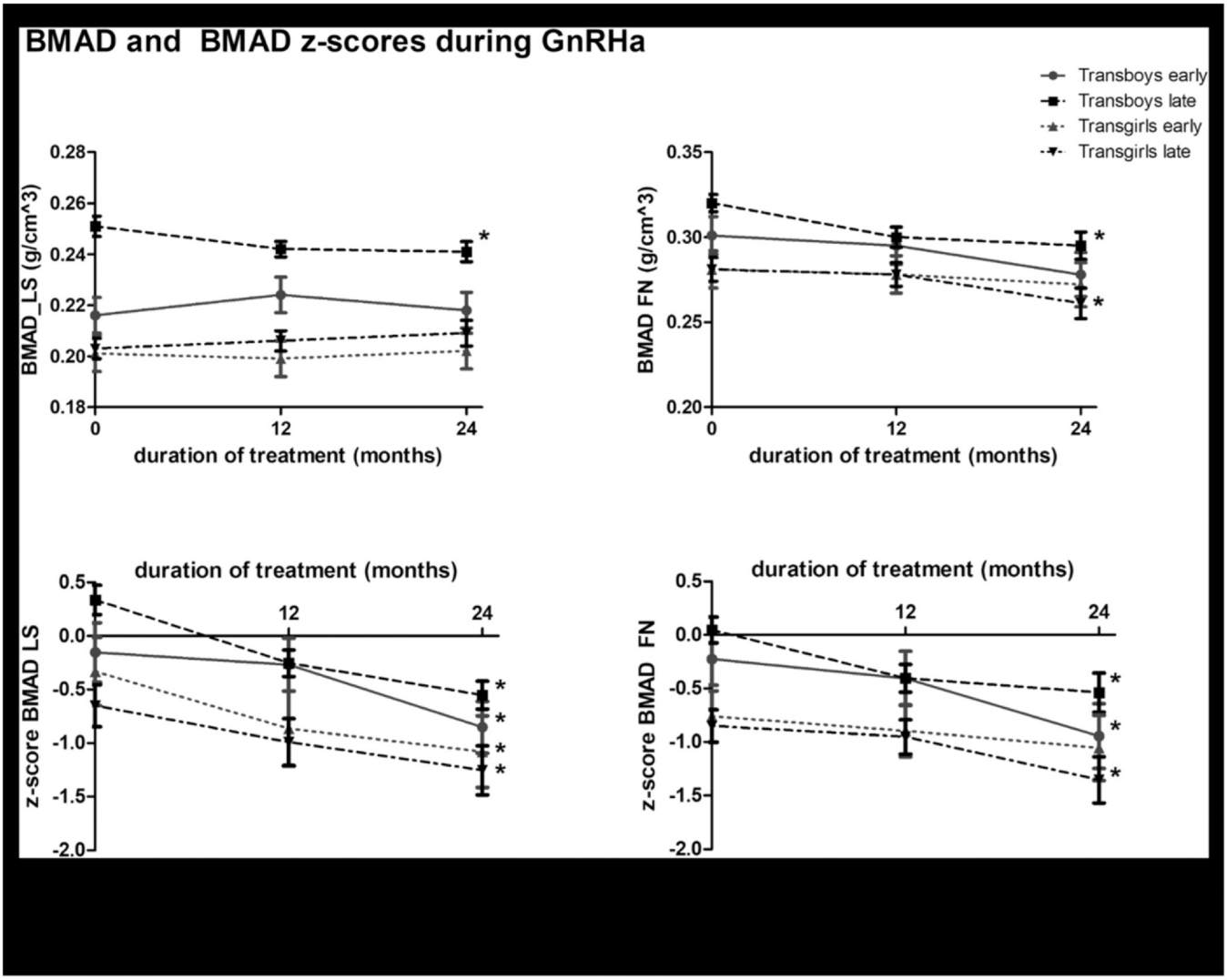


Figure 5. Estimated marginal means and standard error of the mean of BMAD prior to and during 2 years of GnRHa administration in transgirls and transboys. Significant changes during the 2 years of GnRHa administration are indicated by an asterisk. Abbreviations: BMAD, bone mineral apparent density; FM, femoral neck; LS, lumbar spine.

early- and late-pubertal groups. During 2 years of GnRHa treatment, bone mineral apparent density (BMAD) an adjustment made to compensate for altered growth during treatment [45], of the lumbar spine did not change in transgirls or early pubertal transboys. Late-puberal (Tanner stage 4 or 5 at start of treatment) transboys showed a small but significant decrease in lumbar spine BMAD ($P < .05$). BMAD of the femoral neck significantly decreased in late-pubertal transgirls ($P = .007$), early-pubertal transboys ($P = .015$), and late-pubertal ($P < .001$). Bone mineral apparent (BMAD) density Z-scores of the lumbar spine decreased in all 4 groups ($P \leq .001$). Only early-puberal transgirls were spared a significant decline in the BMAD z-scores of the femoral neck (Fig. 5).

Reassuringly, after an average of 1.89 years of GnRHa treatment, BMAD of the lumbar spine increased significantly in all four groups ($P < .001$) and did BMAD Z-scores of the lumbar spine with 3 years of gender-affirming hormone treatment. The BMAD of the femoral neck ($P < .05$) and BMAD Z-scores of the femoral neck in increased significantly all groups save for late-pubertal transboys (Fig. 6). For this population, the proandrogenic progestin may be preferred over GnRHa [46].

Peak bone mass acquisition, differences in bone quality, fracture risk throughout the lifecycle, and outcomes of orthopedic procedures remain unanswered questions in this growing population—both as individuals and a group [47].

Hormonal contraception—skeletal concerns

The United States has one of the highest known rates of adolescent pregnancy and birth in developed regions [48]. Fortunately, this has declined significantly over the last 30 years—the 2020 birth rate of 15.4 births for every 1,000 females 15 to 19 is 75% lower than the 1991 peak [49]. This decline is almost entirely driven by improved contraceptive use as levels of teen sexual activity remain stable [50]. While a highly desirable outcome for maternal and infant health as well as broader societal and socioeconomic concerns, the impact of hormonal manipulation during adolescence is not without challenges and concerns.

Depot Medroxyprogesterone Acetate (DMPA) is a highly effective injectable progestin-only contraceptive, administered 4 times per year. It has carried an FDA "black box" warning since 2004 [51] regarding loss of bone mineral density. Specific to adolescents, it reads as follows, "It is unknown if use of Depo-Provera contraceptive injection during adolescence or early adulthood, a critical period of bone accretion, will reduce peak bone mass and increase risk for osteoporotic fracture in later life." A prospective study of 98 healthy females aged 12 to 18 followed BMD after DMPA initiation, demonstrated declines from baseline of 2.7% (LS), 4.1% (TH), and 3.9% (FN) ($P < .001$ at all three sights, with the magnitude of loss increasing with duration of use). BMD recovered to baseline after discontinuation by 60 weeks in the spine, 180 weeks in the femoral neck

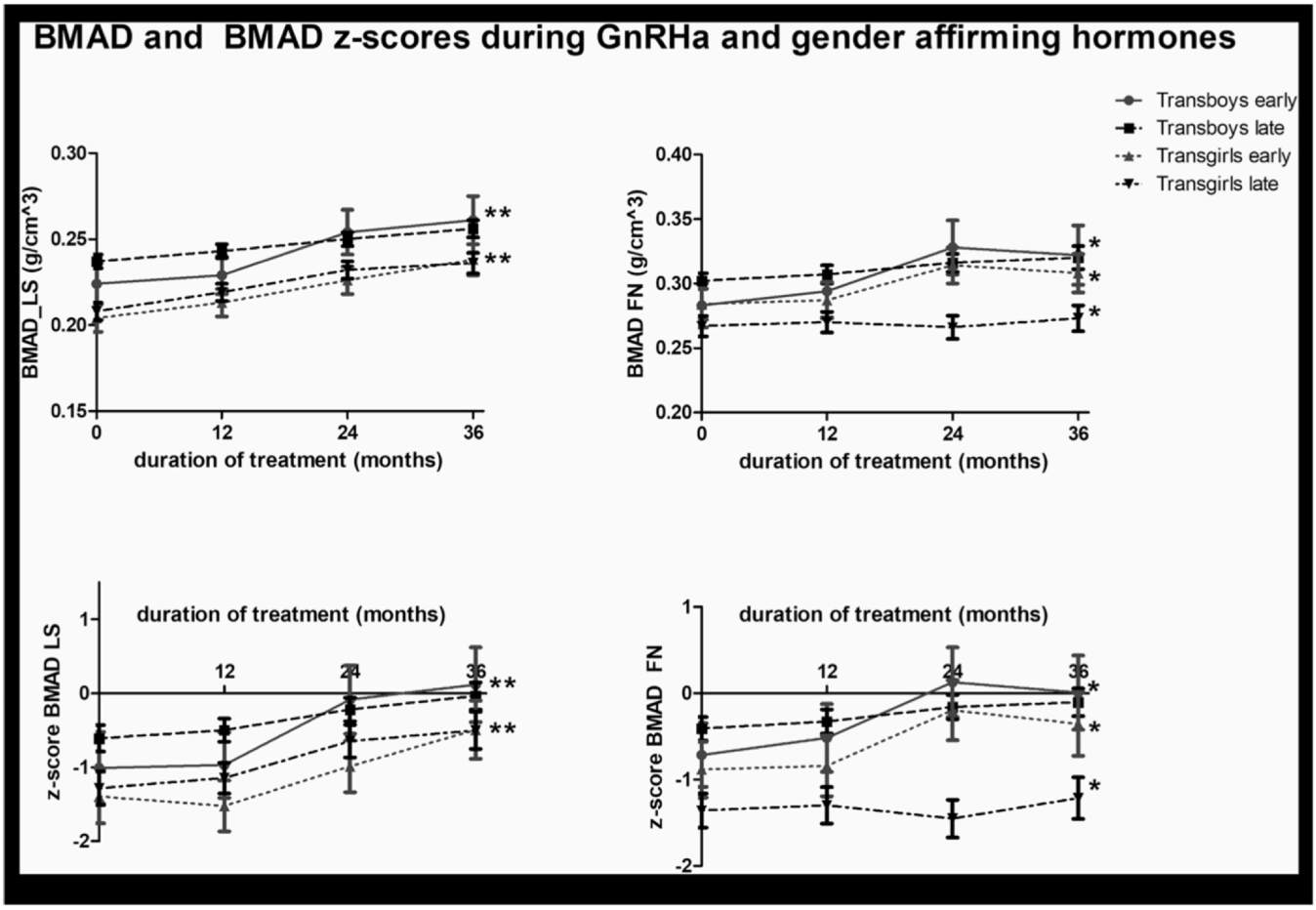
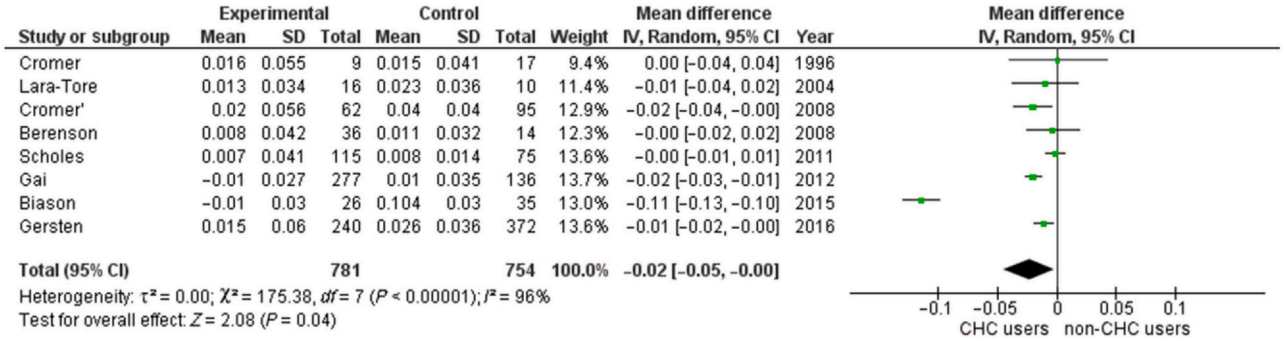


Figure 6. Estimated marginal mean and standard error of the mean of BMAD prior to and during 3 years of GnRHa + gender-affirming treatment in transgirls and transboys. Significant changes during the 3 years of GnRHa + gender-affirming treatment are indicated by an asterisk.



Study or subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI	Year
Cromer	0.016	0.055	9	0.015	0.041	17	9.4%	0.00 [-0.04, 0.04]	1996
Lara-Tore	0.013	0.034	16	0.023	0.036	10	11.4%	-0.01 [-0.04, 0.02]	2004
Cromer'	0.02	0.056	62	0.04	0.04	95	12.9%	-0.02 [-0.04, -0.00]	2008
Berenson	0.008	0.042	36	0.011	0.032	14	12.3%	-0.00 [-0.02, 0.02]	2008
Scholes	0.007	0.041	115	0.008	0.014	75	13.6%	-0.00 [-0.01, 0.01]	2011
Gai	-0.01	0.027	277	0.01	0.035	136	13.7%	-0.02 [-0.03, -0.01]	2012
Biason	-0.01	0.03	26	0.104	0.03	35	13.0%	-0.11 [-0.13, -0.10]	2015
Gersten	0.015	0.06	240	0.026	0.036	372	13.6%	-0.01 [-0.02, -0.00]	2016
Total (95% CI)			**781**			**754**	**100.0%**	**-0.02 [-0.05, -0.00]**	

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 175.38$, $df = 7$ ($P < 0.00001$); $I^2 = 96\%$
Test for overall effect: $Z = 2.08$ ($P = 0.04$)

Figure 7. This random-effects forest plot assessed the 24-mo weighted mean difference in mean absolute change from baseline in g/cm^2 for spinal areal bone mineral density (BMD) in adolescent-combined hormonal contraceptives (CHC) users and nonusers/controls.

and 240 weeks in the total hip; however, baseline is not our BMD goal in a growing skeleton [52]. Long-awaited fracture data was published in 2017 [53], with a case-control study demonstrating increased fracture risk in current and past users of DMPA, most dramatically in young patients (< 30 years) with longer DMPA exposure (10 or more prescriptions; odds ratio 3.04, 95% CI). Lowering of mean serum estradiol level [54] and a partial glucocorticoid effect are the proposed mechanisms [55].

For other progestin-only contraceptives, the data to date is reassuring, albeit limited in this population. Progestin-only mini pills are generally avoided due to high failure rate but long-acting reversible contraception are increasingly preferred in teens. Long-acting reversible contraceptions include hormonal intrauterine device (levonorgestrel) or implants (etonogestrel). With the levonorgestrel intrauterine device (LNg-IUD) there is little systemic absorption of the progestin and consequently less suppression of endogenous estrogen production [56]. As compared to copper IUD users, etonogesterel-releasing implant users did not show significant differences in lumbar or femoral neck BMD at 12 months of use, ergo it is similar to a nonhormonal method with no expected impact on skeletal health [57].

Combined oral contraceptives are the most used method of hormonal contraception in this age group—multiple formulations and regimens exist, with varying amounts of estrogen, various types and/or variable doses of progestogens. Adolescents aged 12 to 18 in a 2004 study [57] demonstrated a 1.4% loss of LS BMD on DMPA, gain of 2.3% on a 20 mcg ethinyl estradiol COC, and a gain of 3.8% in controls. While not as dramatic as the impact of the injectable progestin, the difference between COC and controls was significant ($P = .03$). A meta-analysis of prospective changes in spinal BMD in healthy adolescents (12-19) confirmed significantly less 24-month accrual in those on COCs (Fig. 7)

[58]. Proposed mechanisms for this attenuation include relative hypoestrogenemia [59], suppression of bone resorption and consequent remodeling [58], and inhibition of IGF-1 [60]. Current consensus is that COC preparations with doses of ethinyl estradiol $=/>$ 30 mcg should be used preferentially to low dose [61–63], particularly if started within 3 years of menarche [59,63,64].

Though there is reassuring data in postadolescent woman for both the contraceptive patch and ring [65], data in adolescents is limited. In a small study of 5 teenagers (ages 16-18), the transdermal ethinyl estradiol/norelgestromin patch did not lower IGF-1 compared to non-user controls, but nonusers gained whole body BMD (3.9%), hip BMD (2.7%), and spine BMD (2.8%) while these parameters in users remained stable [66].

While peak bone mass acquisition is certainly a consideration and worry in this population, the adherence to/acceptance of contraceptive method and prevention of unwanted pregnancy is of paramount importance.

Conclusion

In summary, the growing skeleton can present challenges to the pediatric orthopedic surgeon outside of the operating room and beyond injury care. Awareness of conditions and treatments that impact peak bone mass accrual in adolescent patients is critical for those caring for this population. To paraphrase the American Orthopaedic Association's admonition, pediatric orthopedic surgeons must own the growing bone.

Author contributions

Alana Serota: Writing – original draft. **Giavanna D'Erasmo:** Writing – review & editing.

Declarations of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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