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Review Article

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An endocrine perspective on menstrual suppression for adolescents: achieving good suppression while optimizing bone health

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Abstract: Suppression of menstruation and/or ovarian function in adolescent girls may be desired for a variety of reasons. Numerous medical options exist. The choice of the appropriate modality for an individual patient depends on several factors based on differences in the efficacy of achieving menstrual suppression as well as in their side effect profiles. Adolescence is also a period of bone mass accrual in girls, and several of these modalities may negatively influence peak bone mass. This review focuses on the efficacy of achieving menstrual suppression and the effect on bone health of the various options through an overview of the current literature and also highlights areas in need of further research.

Keywords: adolescents; amenorrhea; bone health; contraception; ethics; menstrual suppression; osteoporosis.

Background

Menstrual suppression in adolescents may be desirable for multiple clinical conditions, including transgender and gender-nonconforming youth with dysphoria secondary to menses, intellectual disability with difficulty coping

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secondary to psychological immaturity and difficulty with self-care, heavy or prolonged menstrual bleeding, or dysmenorrhea [1–3]. Options for menstrual suppression have varying efficacy for the reduction in bleeding. Some of these options may suppress ovarian estrogen secretion and have adverse effects on bone mass.

In females, although bone mass continues to increase past age 20 years, peak accrual occurs during puberty and three years following menarche [4]. Nearly half of adult bone mass is attained during the four years surrounding the pubertal growth spurt [5]. Although bone mineral density (BMD) has not been validated in adolescents as a predictor of future risk of fracture, a 5–10% lower BMD in a postmenopausal woman is associated with an approximately 50% increased fracture risk [4].

This review provides a contemporary perspective on the options for menstrual management in adolescents with a focus on their efficacy for menstrual suppression and their effect on bone health. Literature from adolescent studies is cited when available; however, in the absence of robust pediatric data, pertinent literature from studies in adult women is cited, thereby highlighting the need for further research. Of note, this review does not cover acute management of heavy menstrual bleeding, nor does it serve as a comprehensive prescribing reference. Readers are referred to the Centers for Disease Control U.S. Medical Eligibility Criteria for Contraceptive Use, prescribing information, and other resources for comprehensive information regarding contraindications, contraceptive efficacy, and complete side effect profile of each formulation discussed [6]. We discuss several strategies for menstrual suppression below; for each, we will review available formulations and relevant physiology, summarize the literature on the efficacy for this indication, effects on bone health, and briefly discuss other key clinical considerations that may influence prescribing decisions.

Content

Combined estrogen and progestin preparations

Combinations of estrogen and progestin are available as oral tablets, transdermal patches, and vaginal rings. These preparations are not only marketed and approved as contraceptives but also are frequently used off-label for menstrual suppression in both adolescent and adult women. The form of estrogen most commonly used in combined oral contraceptives (COCs) is ethinyl estradiol (EE, different from 17β-estradiol [E2] secreted by the ovaries). EE is more potent than E2 and has a longer half-life [7]. Oral forms of E2 are available as micronized estradiol (for increased absorption) or estradiol valerate (metabolized to estradiol in the liver). All oral estrogens undergo substantial hepatic first-pass metabolism, exerting significant estrogenic effects on the liver that include increased production of sex hormone binding globulin (SHBG), as well as the decreased synthesis of insulin-like growth factor-1 (IGF-1) [7].

Just as EE differs from E2 secreted by the ovaries, the progestins in COCs are distinct from progesterone secreted by the ovary. Progestins are usually synthetic derivatives of progesterone or testosterone which primarily act on the progesterone receptor but may have differing actions from progesterone on other steroid hormone receptors [8]. In contrast, micronized progesterone, available in oral, vaginal, and intramuscular preparations, is bioidentical to progesterone secreted by the ovary, but not typically used in COCs.

Progestins are classified as first through the fourth generation based on the date they were introduced for clinical use (Table 1). They are also classified by their chemical structure (estranes, gonanes, pregnanes, and spironolactone derivatives) and have varying venous thromboembolism (VTE) and androgenicity risk [9]. Neither classification, however, adequately cohorts all clinical effects.

The first three generations of progestins are mainly derivatives of testosterone and have some androgenic activity, with third-generation progestins having lower androgenic potential. The fourth-generation progestins were specifically developed to possess anti-androgenic properties (Table 1). Despite these differences, circulating concentrations of androgens typically decrease with the use of any COC. This occurs through several mechanisms: inhibition of LH (lowering ovarian testosterone), stimulation of SHBG production (lowering free testosterone), lowering of adrenal androgens, and inhibition of androgen-binding to the androgen receptor [10].

Combined oral contraceptive preparations used for menstrual suppression

Available COCs contain varying doses of estrogens (typically EE) and types of progestins (most commonly norethindrone, levonorgestrel, and norgestimate) (Table 1). Whereas traditional use of COCs for contraception includes the use of placebo days to induce withdrawal bleeding, continuous use of COCs with the exclusion of the placebo days has similar efficacy for contraception and is safe and effective for

Table 1: Oral estrogen and progestin formulations.

Progestin-Only Oral preparations
Norethindrone "mini-pill": 0.35 mg, 28-pill packs
Desogestrel "mini-pill": 0.75 mg, 28-pill packs
Norethindrone acetate: 5 and 10 mg
Medroxyprogesterone acetate: 2.5 mg, 5 mg, and 10 mg
Combined estrogen and progestin oral contraceptives (COCs):
Estrogen component: Most commonly ethinyl estradiol 20–35 μg; 10 and 50 μg also available
Progestin component:
First-generation progestins:
Estranes derived from testosterone
Norethindrone: 0.4 mg, 0.5 mg, 0.8 mg, 1 mg; biphasic (0.5 mg, 1 mg); triphasic (0.5 mg, 0.75 mg, 1 mg), (0.5 mg, 1 mg, 0.5 mg)
Norethindrone acetate: 1 mg, 1.5 mg
Ethynodiol diacetate: 1 mg
Pregnane derived from 17-hydroxyprogesterone
Chlormadinone acetate: 2 mg, 5 mg, 10 mg, 25 mg (not available in the US or Canada)
Second-generation progestins (gonanes derived from testosterone):
Norgestrel: 0.3 mg, 0.5 mg
Levonorgestrel: 0.1 mg, 0.15 mg; triphasic (0.05 mg, 0.075 mg, 0.125 mg); extended cycle 0.09 mg, 0.1 mg, 0.15 mg
Third-generation progestins (gonanes derived from levonorgestrel):
Norgestimate: 0.25 mg, triphasic (0.18, 0.215, 0.25 mg)
Desogestrel: 0.15 mg, triphasic (0.1 mg, 0.125 mg, 0.15 mg)
Gestodene: 0.6 mg, 0.75 mg (not available in the US or Canada)
Fourth-generation progestins/anti-androgenic progestins:
Non-ethinylated estrane
Dienogest: 2 mg; in combination with estradiol valerate (2 mg, 3 mg)
Spironolactone derivative
Drospirenone: 3 mg
Pregnane derived from 19-norprogesterone
Nomegestrel acetate: 2.5 mg with 17β-estradiol (not available in the US or Canada)
Pregnane derived from 17-hydroxyprogesterone
Cyproterone acetate: 2 mg (not available in the US)
Other COC preparations
Estradiol valerate quadriphasic (3 mg, 2 mg, 2 mg, 1 mg) + dienogest (none, 2 mg, 3 mg, none, respectively)
17β-estradiol 1.5 mg + nomegestrol acetate 2.5 mg
Dosing regimens for COCs
Mono or multiphasic preparations
Cyclic or continuous use preparations

achieving menstrual suppression in the majority of cases with prolonged use [11–14]. The concentration of EE in combined pills is typically 20–35 μg (range 10–50 μg). Intermittent bleeding is more likely to occur in users of COCs containing 20 μg or less of EE [7], correlating with a higher rate of discontinuation [15, 16]. COCs are available in monophasic combinations (same dose EE and progestin over 21–24 days), biphasic (two different concentrations of EE and/or progestin), and triphasic (three concentrations of EE and/or progestin). A quadriphasic COC formulation that contains estradiol valerate (1–3 mg) rather than EE and the progestin dienogest is also available. The biphasic and triphasic pills were developed to more closely mimic the normal hormonal fluctuations of a menstrual cycle and to reduce total hormone doses, thereby potentially limiting side effects. However, two 2006 Cochrane reviews [17, 18] and two 2011 Cochrane reviews comparing these various combinations all failed to find sufficient evidence of differences in contraceptive efficacy, irregular bleeding, and discontinuation rates [19, 20]. In the absence of proven superiority, the authors of the Cochrane review suggested choosing a monophasic preparation for greater simplicity and lower cost [19]. For menstrual suppression using COCs continuously, only monophasic preparations are directly supported by the literature [12–14, 21]. From a physiological standpoint, the continuous progestin effect to thin the endometrium underlies the safety of continuous COC use with regard to endometrial health [11, 21]. Potential advantages of the formulation containing estradiol valerate may include decreased adverse effects on blood pressure and lipids compared to combinations containing EE [22, 23].

Use of extended-cycle vs. monthly COCs for menstrual suppression

COCs can be taken for extended periods of time so that a withdrawal bleed occurs every three months to once-yearly to indefinite menstrual suppression. The majority of extended-cycle COCs are monophasic preparations using EE and levonorgestrel over 84 days followed by seven days of placebo or 10 μg EE. Theoretically, any monophasic COC preparation can be used for an extended duration or continuously to increase the interval between menses. Extended cycling of COCs may be a preferred option for adolescents requiring menstrual suppression as the total amount of menstrual bleeding is much less than with monthly cycling.

A 2014 Cochrane review of randomized controlled trials of extended-cycle contraceptives vs. conventional 28-day formulations found comparable adherence [11]. Menstrual symptoms such as headache, dysmenorrhea, and fatigue were improved. Although overall bleeding/spotting was similar or lesser in the extended-cycle group, discontinuation rates were similar or higher and patient satisfaction was similar or lower potentially due to greater unscheduled bleeding in this treatment group [11]. Endometrial assessment performed in four trials by ultrasound and/or endometrial biopsy revealed no endometrial hyperplasia.

Endometrial quiescence and atrophy has been documented as early as four months after continuous COC use [24].

Combined estrogen and progestin transdermal patch and vaginal ring

Although less commonly used in adolescents, both transdermal patches and vaginal rings with combinations of EE and progestin are available. The combined hormone patch is applied once weekly for three weeks. With conventional use for contraception, no patch is applied for the fourth week to achieve withdrawal bleeding. Compared with COCs, the patch achieves fewer fluctuations in serum EE level and a lower peak level, but an overall higher area under the curve [25–27]. The combined hormone vaginal rings include a flexible latex-free vinyl polymer ring and a reusable silicone ring that is inserted vaginally by the patient and left in place for three weeks of every four-week cycle. Similar to the patch, the vaginal ring achieves steady serum levels of EE compared to a 30 μg EE-containing COC, but cumulative systemic EE exposure is much lower with ring use compared to either the patch or COC [27].

Once-weekly application with the patch, or once monthly with the vaginal ring, has the potential for increased adherence and relative ease of achieving perfect use compared to COCs. In addition, they may be useful options in adolescents who cannot or will not swallow pills. However, patches have relatively high detachment rates and overall higher rates of user discontinuation than COCs, as demonstrated in Cochrane reviews [26] and in studies specifically in adolescents and young adults [28–30]. The vaginal ring may be inappropriate for younger children requiring menstrual suppression and has shown mixed results with regard to acceptability among sexually active adolescents, although adherence is superior to COC for those willing to continue with its use [31–33].

Efficacy of combined estrogen and progesterone preparations for menstrual suppression

Up to 70% of patients can achieve menstrual suppression by one year with continuous use of COC [12–14]. Though there is an initial increase in spotting days, the number tends to decrease as the year progresses.

Studies evaluating extended regimens of the contraceptive vaginal ring and patch are limited. In a study among 28 adolescents on the patch, 14% experien ced breakthrough bleeding, half experienced a shorter duration of bleeding while 4% experienced longer menses, and a third reported lighter flow [30]. In another small study, almost half of adolescents reported less menstrual bleeding on the patch compared to baseline [28]. Data on extended ring use in adolescents is lacking. In adults, postponement of the withdrawal bleeding (ring-free week) for up to one year allowed reduction in bleeding days, but days with spotting increased [34].

The efficacy of combined hormonal preparations may be decreased by some co-morbidities or concomitant medical therapies. For example, anti-epileptic drugs that enhance cytochrome P450 and/or uridine-diphosphate-glucoronosyltransferase activity reduce the efficacy of combined hormone preparations by increasing the metabolism of estrogen and progestin. A recent opinion piece by the American College of Obstetricians and Gynecologists (ACOG) provides further guidance [35].

Effects of combined estrogen and progestin preparations on bone health

Estrogen inhibits bone resorption, reducing both osteoclast number and activity [36], whereas physiologic levels of progesterone promote osteoblast differentiation and maturation [37]. Although studies in adult women have been reassuring regarding the effects of COC on bone health [38], data are mixed regarding the effects of COC on bone mineral accrual and bone mass acquisition in adolescence, during which rising levels of estradiol, growth hormone (GH), and IGF-1, along with the initiation of ovulatory menstrual cycles, contribute to evolving bone geometry and bone deposition [39–41]. EE prevents hypothalamic-pituitary stimulation of endogenous estradiol production, such that lower dose COC formulations that do not provide adequate estrogenic replacement may increase bone resorption and lower bone formation [40]. Alternatively, COC formulations with supraphysiologic EE levels may result in excessive suppression of bone resorption, impairing bone remodeling [40]. EE may also interfere with other anabolic bone actions including reduced androgen receptor binding and suppressed IGF-1 production [5, 42].

Bone turnover markers are typically high in adolescents and young adults secondary to high rates of bone remodeling [43]. COC use appears to decrease bone turnover, but studies on BMD and fracture risk with COCs have yielded variable results [43]. A longitudinal study of 110 women up to age 33 years with serial BMDs since childhood (67 of whom had COC exposure at varying doses of EE), found a benefit on BMD if COC was used within five years following peak height velocity. However, beyond this period, COC use adversely affected BMD. The authors theorized that after completion of growth, bone formation and resorption are more tightly coupled and

continued estrogenic suppression of resorption would negatively affect adult bone formation [5]. Other reports show detrimental effects of COC on bone mineral content and/or density in adolescents [44–46], particularly with the use of lower (≤20 μg) doses of EE [47–49]. Importantly, a prospective cross-over study of 56 adolescents pointed to greater impairment in BMD increase in low-dose (≤20 μg) EE users compared to those taking higher doses [49]. The frequency of placebo days may be another determinant of effects on BMD. In a study of 829 adolescents, those randomized to an extended regimen of 84 days of levonorgestrel (150 μg) plus 30 μg EE followed by seven days of 10 μg EE had similar changes in BMD compared to an untreated reference group, whereas those randomized to 21 days of levonorgestrel (100 μg) plus 20 μg EE followed by seven days of placebo had reduced gains in BMD compared to the reference group [50]. A 2014 Cochrane review concluded that COCs do not appear to negatively affect BMD, but studies were in adult women and the overall quality of evidence was rated as low [51]. A 2019 meta-analysis of nine prospective studies assessing the effect of COC on bone mass in a total of 1535 adolescents (age 12–19 years) suggested a small reduction in BMD in COC users over 1 and 2 years, with an effect size of −0.2 g/cm^2, the clinical significance of which is unclear [52].

Bone accrual and bone masses are important predictors and surrogate markers of present and future fracture risk [53]. However, this association is best studied in postmenopausal women. Fragility fractures are fortunately quite rare in premenopausal women; thus, data on the association between COCs and fracture risk are limited and conflicting [43, 54, 55]. Cochrane reviews (2011, 2012, and 2014) were unable to determine if COC exposure affects fracture risk as none of the included trials assessed fractures as an outcome [51, 56, 57]. Subsequently, a large retrospective study of 12,970 women suggested that the use of COCs decreased the risk of fracture with the strongest effect in the 18–25 and 26–35-year-old groups [58]. Since only women with fractures at age ≥18 years were included, these results cannot be generalized to the use of COC in younger adolescents.

A potential mechanism by which COCs could impact bone health is that oral estrogen metabolism by the liver decreases IGF-1 production and bioavailability [40, 42]. IGF-1 has important bone trophic effects as it binds to the IGF-1 receptor on osteoblasts, promoting their differentiation and bone formation [42]. This implies a potential benefit to transdermal delivery of contraceptive formulations, which avoids hepatic first-pass metabolism. Consistent with this hypothesis, COC users have lower IGF-1 levels than controls [59], while the contraceptive patch appears to have no effect on IGF-1 concentration [60]. The comparative effects of oral vs. transdermal estrogen have been well-studied in adolescents with functional hypothalamic amenorrhea (FHA). The E2 patch (with cyclic oral micronized progesterone) in adolescents with FHA is superior to COCs or no estrogen replacement in increasing BMD [61]. Similarly, in 110 adolescent girls with anorexia nervosa, the E2 patch plus cyclic oral progestin increased BMD compared to nonusers [62].

Compared to the large number of publications on COCs and bone health, studies evaluating the effects of the nonoral combined hormonal preparations are limited, particularly in adolescents. Although studies in adult women using the vaginal ring or patch suggest no effect on BMD [63, 64], these data cannot necessarily be extrapolated to adolescents. One small study of five girls using an estrogen/progestin patch suggested lower gains in BMD compared to controls, but conclusions were limited by sample size [60]. Data are not available regarding the effects of the vaginal ring on BMD in adolescents.

In summary (Table 2), current literature in adolescents suggests that COCs, particularly at lower doses of EE ≤ 20 μg, may be detrimental to bone mineral acquisition, although data on effects on fracture risk are lacking. Further data evaluating effects based on EE dose, age of COC initiation, and the risk of fracture with BMD change are needed. Even less is known regarding the BMD effects of the combined hormonal patch and vaginal ring during adolescence, and large-scale randomized controlled trials are needed. Current data, although extremely limited, suggest that choosing a COC with ≥30 μg EE and decreasing the number of placebo days may minimize potential adverse effects on bone [41, 65].

Other clinical considerations

Common side effects of combined estrogen/progestin preparations include spotting or breakthrough bleeding, particularly in the first few cycles of use, breast tenderness, headache, nausea, acne, and emotional lability. COC users may also note lipid abnormalities, hypertension, and cholelithiasis. Compared to COCs, contraceptive patches are associated with more side effects, including skin reaction at the patch site in up to 20% of users leading to discontinuation in up to 3% [26]. About 2/3 of adolescents reported mild site reactions and 13% reported a rash [28, 30]. The vaginal ring causes less nausea, acne, and emotional lability, compared to the patch and COCs, but can cause vaginal irritation and discharge [26].

Table 2: Summary of hormonal options for menstrual suppression.

	Rate of amenorrhea	Contraceptive efficacy	Effects on BMD and/or fracture risk	Risk of venous thromboembolism (VTE)
COC, taken continuously	70% by one year	>99% (with correct use) 91% (with typical use in the first year)	Mild detrimental effect on BMD possible; more studies needed	Though absolute risk remains low, the risk for VTE increased compared to non-users (relative risk 3.5). Risk varies by type of progestin and dose of EE. Risk may be mildly increased with extended cycle COCs compared with cyclic use. Estradiol valerate-containing COCs may have a lower risk of VTE and metabolic side effects
Transdermal patch and vaginal ring	Insufficient data. Bleeding days decreased with the postponement of withdrawal bleeding, but spotting increased (vaginal ring)	Similar to COCs	Very limited literature. Bone turnover appears to be decreased, but no significant effect on BMD	VTE risk with patches is twice that of COCs
Progesterone "mini-pill"	<10%	87–100% in the first year of use though needs to be consistently taken within a short time window and efficacy significantly varies with compliance	Very limited literature	Minimal to no risk of VTE
Norethindrone acetate or medroxyprogesterone acetate, taken continuously	Up to 76% by end of the second year; success rates increase with dose up-titration	Not known (not indicated for use as a contraceptive)	No data	Minimal to no risk of VTE
Depot medroxyprogesterone acetate	50% by one year, up to 80% with longer-term use	>99%	Decreased BMD and increased fracture risk	Minimal to no risk of VTE
Etonogestrel subdermal implant	Up to 22%	>99%	Literature sparse. No apparent decrease in BMD. No data on fracture risk	Minimal to no risk of VTE
Progesterone-containing IUDs	52 mg: 20% by one year, 40–60% with longer-term use. May be less in lower-dose preparations	>99%	Appears neutral, but more studies needed	No increased risk of VTE compared to non-users
Pregnancy	(N/A)	(N/A)	BMD loss during pregnancy; eventual recovery to baseline	Four to five-fold increased risk of VTE compared to non-pregnant state; > 20-fold increased risk in the six-week postpartum period

BMD, bone mineral density; COC, combined oral contraceptive (estrogen/progestin); IUD, intrauterine device; VTE, venous thromboembolism.

A 2010 prospective study in adolescents did not find weight gain among COC users compared with nonusers [66]. A 2013 Cochrane Review was also unable to find an association between COC use and weight gain, or an increased rate of discontinuation due to weight gain [67].

VTE risk is increased over two-fold with the use of combined hormonal contraceptives compared with nonuse, and certain formulations may pose a higher risk [68, 69]. Nevertheless, the absolute risk is low (8–10 events per 10,000 women years) and the overall risk is

lower than the VTE risk of pregnancy and the postpartum period [70]. However, patient factors must be carefully considered. Obesity may independently increase VTE risk up to ten times in COC users compared to nonusers [71, 72]. Current evidence does not support that combined hormonal contraceptive use (oral, patch, or ring) increases seizures in patients with a seizure disorder, hence epilepsy is not a contraindication. However, EE may enhance the metabolism of some drugs, altering their efficacy, and therefore as an example, COCs should be used with caution in lamotrigine users [35].

Oral progestins

Depending on the specific formulation, dose, and schedule, oral progestin preparations can be used for menstrual suppression and may, when used continuously over time, induce amenorrhea. Progestin-only pills (POPs), also known as mini-pills, contain either 35 µg norethindrone, 75 µg desogestrel, or 4 mg drospirenone [73]. POPs can be an alternative contraceptive method for adolescents who have contraindications to estrogen-containing medications, such as an increased risk of VTE [74, 75]. However, they are not typically used for menstrual suppression due to a low rate of achieving amenorrhea and high rate of irregular bleeding.

Other oral progestins such as norethindrone acetate (NETA) and medroxyprogesterone acetate (MPA), when used continuously, may offer an alternative therapeutic option for menstrual suppression. Of note, a fraction of NET or NETA is converted to EE *in vivo* (5 mg of NETA gives rise to about 10 µg of EE) while MPA is not metabolized to EE [73].

Efficacy of oral progestin preparations for menstrual suppression

POP formulations can be used daily to attempt menstrual suppression, but efficacy is dependent on dose and adherence to taking the hormone as close to the same time each day as possible. Since they do not effectively inhibit ovulation, up to half of the POP users will have monthly menses [76, 77] and will have more unpredictable bleeding in comparison to COC users. The rate of menstrual suppression in studies of the mini-pill is quite low, sometimes <10% [76–78].

Oral NETA at doses 2.5–15 mg or MPA at doses 5–20 mg per day, or even higher in cases of acute heavy menstrual bleeding, can be used for menstrual suppression or as therapy for abnormal or irregular bleeding and endometriosis [73]. Whereas high doses and thrice-daily administration may be required for suppression of acute heavy menstrual bleeding, continuous once-daily use of lower doses of NETA or MPA is often effective for achieving long-term menstrual suppression and represents an easier regimen for compliance. Improved rates of menstrual suppression can be achieved with up-titration of NETA or MPA with reports citing up to 76% rates at two-year follow-up [78, 79]. Although there are no randomized controlled trials in adolescents supporting continuous once-daily use of NETA at doses of 2.5–15 mg, there are reports of its successful use in adolescents who have endometriosis [80] or who desire menstrual suppression to affirm male gender identity [2]. The authors of this piece share a similar experience with its successful use, although clinical research is needed to better characterize its comparative effectiveness.

Effects of oral progestin preparations on bone health

In theory, oral progestins may affect bone by decreasing the production of estrogen by the ovaries via an anti-gonadotropin effect [81]. No longitudinal data are available regarding oral progestins on BMD in adolescents. However, a retrospective cohort study of over 50,000 females age 12–45 years who started progestin-only pills from 2005 to 2015, showed a slightly reduced risk of fracture of 0.88; this reduced risk was not significant in the group with >2 years of use [82]. Due to the lack of studies evaluating this, it is also unclear if the differential metabolism of oral NETA and MPA to EE has a bearing on their skeletal effects.

Other clinical considerations

Oral progestin formulations may be useful for adolescents who have contraindications to oral estrogens, such as migraines with aura, increased VTE risk, or use of cert ain anti-epileptic medications. Bleeding irregularity (including prolonged bleeding), acne, and breast tenderness can be associated with POPs, and higher doses of oral progestin in NETA or MPA may be associated with bloating, mood changes, and increased appetite and weight gain [77, 83–85].

Long-acting progestin formulations

These are effective contraceptives and include implants (formulations with the sustained release of a progestin) and

depot medroxyprogesterone acetate (DMPA). However, not all patients achieve menstrual suppression and breakthrough bleeding is common [86, 87]. Formulations include intramuscular DMPA (150 mg) and a subcutaneous formulation (104 mg/0.65 mL), both effective as contraceptives for 13 weeks and administered every three months. A subdermal implant containing 68 mg of etonogestrel is another depot progestin formulation that can be placed in the upper arm and is effective as a contraceptive for three years. Outside of the US and Canada, a subdermal implant (consisting of two rods) with 75 mg levonorgestrel is available for effective contraception up to five years.

Efficacy of long-acting progestin formulations for menstrual suppression

About 55% of those using DMPA will achieve menstrual suppression after one year and up to 80% after five years of use [87–90]. With DMPA, breakthrough bleeding rates are high at 50–60% during the first year and 32% the second year [6, 87], while subcutaneous preparation bleeding rates are even higher at 78% [87, 89].

Etonogestrel implants have a higher rate of unscheduled light bleeding with greater than 75% of users reporting some form of irregular bleeding over a three-month period. Menstrual suppression during any 90-day period was only achieved by 22% of women. Though a favorable bleeding pattern in the first three months of use may predict the pattern for the rest of the use period, the bleeding pattern can remain random and unpredictable for the three years of use. Although there is limited data in adolescents, a study of 116 adolescents using etonogestrel implant in the U.S. noted that 17% became amenorrheic over a 36 month period [6, 91, 92].

Effects of long-acting progestin formulations on bone health

Depot medroxyprogesterone acetate

Unlike other forms of progestin-containing preparations, the dose of DMPA is high enough to cause significant suppression of the hypothalamic-pituitary-ovarian axis thereby lowering endogenous estradiol. However, DMPA users were also shown to have higher IGF-1, which may be beneficial to bone [93].

One prospective study of new adolescent users of DMPA found BMD decreased by 6.81% in 58 DMPA users vs. 19 controls after two years [94]. Similar results have been reported by others for DMPA [95–99]. DMPA likely has a dose-related effect on BMD. A randomized 48 week trial of 34 adolescents showed a significant decrease in BMD with the 104 and 150 mg preparations, but no change with 75 mg [100]. A retrospective review of 83 adolescents showed that DMPA users for >15 months were more likely to have low BMD [99]. A longitudinal study of 178 adult women starting DMPA showed that BMD continues to decrease at the hip and spine after up to 48 months of use though the rate of decline is slower [101]. The presence of other risk factors such as eating disorders, weight loss, and excessive exercise can exacerbate the bone-health effects [102, 103].

The effects of DMPA on BMD may be reversible. A multicenter observational study followed 98 new adolescent users of DMPA for up to 240 weeks of use and up to 300 weeks following cessation of DMPA. Those who discontinued DMPA increased their BMD, with a mean recovery time of 60 weeks for their spine BMD to return to baseline, and continued increases thereafter [104, 105]. Mean recovery of total hip and femoral neck BMD to baseline was much slower at 240 and 180 weeks, respectively [105]. Lastly, an individually matched case-control study investigated differences in BMD by age of DMPA initiation among 50 pairs of women aged 18–25 years (started DMPA before age 20 years) and 35–45 years (started DMPA after age 34 years). The mean duration of DMPA use was three years. Only the younger matched cohort demonstrated significant negative differences in BMD at the lumbar spine, lumbar lateral areal BMD (bone size), and BMD at the hip in DMPA users compared to nonusers, suggesting that initiating DMPA prior to achievement of peak bone density and bone size may have greater detrimental effects [93]. Fracture occurrence is the primary clinical outcome of a concern. High-quality data about long-term risk of fracture with DMPA use in adolescents and young adults is lacking, and data from observational studies are mixed. A retrospective cohort study of females age 12–45 years who started DMPA, COC, progestin-only pills, copper, or levonorgestrel IUDs from 2005 to 2015 showed an increased risk for fracture in those who had used DMPA within the past two years, with the greatest adjusted hazard ratio (1.42) for those with >2 years' exposure, but not with past use >2 years prior. A major limitation is the hazard ratio was not presented by age group and DMPA use [82]. Conversely, a retrospective study of 83 adolescents who had received at least three DMPA injections did not experience increased fracture; however, use was of shorter duration (median 15 months) [99].

The concern over the risk of decreased BMD with DMPA use led the FDA to issue a black box warning in November 2004. Though the concerns of decrease in BMD at a time of bone mass accrual and slow/lack of complete BMD recovery in some anatomical sites up to five years

following two or more years of DMPA use are legitimate, several of these findings were based on studies with small sample size. The warning recognizes that it is unclear if the decrease in BMD leads to lower peak bone mass or an increase in the risk of future osteoporotic fractures, yet it states that DMPA use beyond two years should be considered only if other contraceptive methods are inadequate. Therefore, DMPA may not be optimal to use for menstrual suppression in young adolescents who are at the peak of their active bone mineralization. Before selecting this method, additional individual risk factors for low BMD should be considered. Routine use of bone densitometry for BMD is currently not recommended in adolescent DMPA users, though additional longer-term studies are needed to understand the utility of BMD monitoring in these patients [106]. Also, measures that improve general bone health including regular weight-bearing exercises, smoking cessation, and age-appropriate calcium and vitamin D intake should be encouraged for all DMPA users though it is unclear if these measures offset BMD loss during DMPA use [106].

Etonogestrel subdermal implant

Progestin-releasing implants suppress gonadotropins and inhibit ovulation, but have a lesser effect on estradiol, with estradiol levels declining to early follicular phase levels after insertion [107]. Studies in adults comparing the etonogestrel implant with IUD use or the levonorgestrel implant with nonuse have shown no detrimental effect on BMD at the lumbar spine, femoral neck, or distal radius, though these studies were small [108–110]. In a very small study in adolescents comparing a change in BMD after two years of DMPA or levonorgestrel implant vs. controls, seven DMPA users experienced a 3.12% decrease, three implant users a 9.33% increase, and four controls a 9.49% increase in lumbar spine BMD [97]. Thus, although the literature on progestin implant use and effect on BMD is small, the evidence to date suggests no significant decrease in BMD effect, while no studies on fracture incidence have been reported (Table 2).

Other clinical considerations

DMPA has been associated with increased risk for menstrual irregularities (as above), abdominal pain (11%), weight gain >10 lbs at two years (38%), headache (17%), dizziness (6%), nervousness (11%) as well as postmarketing reports of thromboembolism, decreased glucose tolerance, and osteopenia (described above) [111].

Progestin-containing intrauterine devices

The American Academy of Pediatrics (AAP) [112] and the ACOG [113] consider intrauterine devices (IUDs) to be first-line contraceptive option for adolescents. Where as copper-containing IUDs may increase menstrual bleeding, progestin-containing IUDs reduce menstrual bleeding significantly and may result in menstrual suppression. Four levonorgestrel-releasing intrauterine systems (LNG-IUS) for contraception are currently available: two 52-mg preparations (both approved for up to six years for contraceptive use), a 19.5-mg LNG-IUS (approved for a 5–6 year duration), and a 13.5-mg LNG-IUS (approved for a 3 year duration). Although the prescribing information for one of the 52-mg levonorgestrel products recommends the device only for parous women, the safety and efficacy of all LNG-IUS are well-established in nulliparous women [114]. The lower-dose LNG-IUS have narrower insertion tubes and smaller T-frames than the 52-mg products.

Efficacy of progestin containing IUDs for menstrual suppression

Compared to short-acting contraceptives in the adolescent population, IUDs have higher efficacy, higher continuation rates, and better patient satisfaction [113]. IUDs are particularly suitable for adolescents with disabilities based on convenience, duration of action, and limited interaction with other medications, although placement usually requires sedation in this population [115–117].

One of the 52-mg LNG-IUSs (Mirena® in the US) is approved for the treatment of heavy menstrual bleeding, and all LNG-IUS devices generally lighten menstrual bleeding and reduce dysmenorrhea, mainly by direct effects on the endometrium rather than hypothalamic-pituitary-ovarian axis suppression [41, 118]. Following a transient increase in a number of days with menstrual bleeding in the first few months following placement, menstrual bleeding steadily decreases. Though there could be up to a 97% reduction in menstrual blood loss after 12 months of LNG-IUS use in patients with heavy menstrual bleeding (based on a study of 20 women using 46 mg LNG-IUS), achievement of menstrual suppression is less common [119]. About 20% of 52-mg LNG-IUS users progress to menstrual suppression during at least one 90-day interval by one year of use, with rates approaching 40–60% with longer-term use [79, 120–122]. Lower-dose devices may have lower rates of menstrual suppression [113, 123] though other studies did not find a difference [124].

Effects of progestin containing IUDs on bone health

Effects of LNG-IUS on BMD are presumed to be minimal to none because these devices release progestin locally with limited systemic hormonal effects. Serum levels of levonorgestrel achieved with the highest-dose (52 mg) LNG-IUS are roughly 25 times less than those achieved by a low-dose levonorgestrel-containing COC [125]. At all three doses of LNG-IUS, most women continue to ovulate [125], and estradiol levels in women on all doses of LNG-IUS fall within the typical range of women with normal menstrual cycles [125]. With regard to data on BMD, the Phase 3 study of 13.5-mg and 19.5-mg LNG-IUS products reported no change in BMD at the hip or lumbar spine after three years of treatment compared to baseline [126]. Smaller studies comparing adult users of the 52-mg LNG-IUS to users of a copper IUD showed no differences in BMD, suggesting no detrimental effects of LNG-IUS [127, 128]. A retrospective cohort study of females age 12–45 years comparing new users of DMPA, COC, progestin-only pills, copper or levonorgestrel IUDs, found no increased risk for fracture in the 80,000 IUD users (including 12,000 adolescents), although the copper and progestin-IUDs were grouped together in the analysis [82].

Other clinical considerations

IUD expulsion rates are 2–10% among all women, with most studies suggesting adolescents have similar risks [113, 117, 118, 124]. There is a very small increase in the risk of pelvic inflammatory disease in the first 20 days after placement and minimal risk of uterine perforation [113]. IUDs do not increase the risk of ectopic pregnancy and do not have long-term effects on fertility following removal [113, 118]. Both copper- and progestin-containing IUDs reduce the risk of endometrial cancer [118]. LNG-IUS also does not appear to increase the risk of VTE compared to nonusers [129].

Surgical options and related ethical considerations

Surgical approaches for the management of abnormal menses are typically permanent and hence only used in adolescents as a last resort. Options for long-term menstrual suppression by surgical means used in adults include endometrial ablation, hysterectomy, and/or oophorectomy. Endometrial ablation is not recommended in adolescents, but hysterectomy may be permissible and may be in the best interests of the patient in certain circumstances where all other options, including pharmacotherapy, have been exhausted [130–133]. There are significant ethical issues associated with surgical menstrual suppression in adolescents [131, 132]. In adolescents with disabilities, it may be especially challenging or impossible to obtain informed assent and to allow the patient to express her autonomy, due to the inability to understand the potential outcomes or complications of surgical menstrual suppression [133]. There is a sordid history of forced sterilization and eugenics in individuals with physical and intellectual disabilities and any association with irreversible sterilization in this population brings up the specter of that history [132, 134]. Before a potential sterilizing procedure is undertaken, a professional assessment of the patient's decisional capacity, maturity, and competence must be completed, the potential reproductive outcomes discussed, alternative options laid out, and state and federal laws examined [130–133, 135]. In order to obtain informed assent/consent, the clinician must discuss the potential risks of any menstrual suppression therapy [133].

Adolescents with disabilities may not be sexually active, may be incapable of offering consent, and may be at risk of sexual abuse. Hysterectomy effectively prevents pregnancy and menstruation, but it comes with a risk of morbidity and mortality and does not protect the child from sexual abuse or from sexually transmitted infections [130]. Families with girls who have undergone permanent sterilization still require ongoing vigilance for sexual abuse or sexually transmitted infections, a necessary point of discussion.

Ethics committee and legal considerations

In instances involving minors and considerations of permanent sterilization, involvement of a local ethics committee is highly recommended and likely required by most institutions. In addition, local jurisdictions may require the appointment of an independent guardian *ad litem* to advocate for the best interest of the patient before a court.

Summary and outlook

Menstrual suppression in adolescent girls may be desirable in a wide variety of situations. There are several medical options for menstrual suppression, and no single method is universally superior to the others (see Table 2

for the summary). While each option may differ in efficacy and side-effect profile, individual patient, family, and social factors may further influence the efficacy and should be taken into consideration. Additionally, failure of one method generally does not preclude successful trials of another. The options with the highest rate of success achieving menstrual suppression are COCs, used continuously (70% in the first year of use), and DMPA (80% by five years of use). Continuous once daily use of progestin-only preparations, NETA or MPA also has ≥70% success of achieving menstrual suppression with upward dose titration. Of these options, DMPA has the most significant adverse effects on BMD during use, most of which is reversible with cessation of use. Hence DMPA could still be considered as an effective option for menstrual suppression in adolescents though benefits must be weighed against skeletal side-effects with prolonged use. COCs may have modest adverse effects on bone, particularly at lower EE doses, and more data are needed for the effects of oral NETA and MPA. Progestin-containing IUDs reduce bleeding in almost all users, up to 60% achieve menstrual suppression over long-term use, and have the most definitive data with regard to neutrality on bone health. Balancing minimal side effects with moderate efficacy in achieving menstrual suppression, progestin-containing IUDs can be considered a first-line option for adolescents who can tolerate both IUD insertion and some breakthrough bleeding. Progestin-containing IUDs also have the best performance with regard to contraceptive efficacy. DMPA or etonogestrel implants provide the second-best option for contraceptive efficacy, although breakthrough bleeding is likely in the first several months. For adolescents in whom breakthrough bleeding is highly distressing, e.g., adolescents with intellectual disability, continuous COC may be considered the first line, followed by continuous oral NETA or MPA, all of which have the advantage of being able to up-titrate dosing or switch to an alternative regimen if breakthrough bleeding occurs. Of note, contraceptive efficacy of oral NETA and MPA is not well-defined, and other agents should be used when contraception is required. Additional large-scale studies aimed at assessing safety outcomes and skeletal effects with long-term use of these modalities are needed to provide conclusive evidence and allow better-informed decisions for patients.

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References

1. Albanese A, Hopper NW. Suppression of menstruation in adolescents with severe learning disabilities. Arch Dis Child 2007;92:629–32.
2. Carswell JM, Roberts SA. Induction and maintenance of amenorrhea in transmasculine and nonbinary adolescents. Transgend Health 2017;2:195–201.
3. Sachedina A, Todd N. Dysmenorrhea, endometriosis and chronic pelvic pain in adolescents. J Clin Res Pediatr Endocrinol 2020;12:7–17.
4. Tremollieres F. Impact of oral contraceptive on bone metabolism. Best Pract Res Clin Endocrinol Metab 2013;27:47–53.
5. Jackowski SA, Baxter-Jones ADG, McLardy AJ, Pierson RA, Rodgers CD. The associations of exposure to combined hormonal contraceptive use on bone mineral content and areal bone mineral density accrual from adolescence to young adulthood: a longitudinal study. Bone Rep 2016;5:e333–e41.
6. Curtis KM, Tepper NK, Jatlaoui TC, Berry-Bibee E, Horton LG, Zapata LB, et al. U.S. Medical eligibility Criteria for contraceptive use, 2016. MMWR Recomm Rep 2016;65:1–103.
7. Stanczyk FZ, Archer DF, Bhavnani BR. Ethinyl estradiol and 17beta-estradiol in combined oral contraceptives: pharmacokinetics, pharmacodynamics and risk assessment. Contraception 2013;87:706–27.
8. Sitruk-Ware R. Pharmacological profile of progestins. Maturitas 2004;47:277–83.
9. Sitruk-Ware R. New progestagens for contraceptive use. Hum Reprod Update 2006;12:169–78.
10. Martin KA, Anderson RR, Chang RJ, Ehrmann DA, Lobo RA, Murad MH, et al. Evaluation and treatment of hirsutism in premenopausal women: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2018;103:1233–57.
11. Edelman A, Micks E, Gallo MF, Jensen JT, Grimes DA. Continuous or extended cycle vs. cyclic use of combined hormonal contraceptives for contraception. Cochrane Database Syst Rev 2014:CD004695. https://doi.org/10.1002/14651858.CD004695.pub3.
12. Machado RB, de Melo NR, Maia H Jr. Bleeding patterns and menstrual-related symptoms with the continuous use of a contraceptive combination of ethinylestradiol and drospirenone: a randomized study. Contraception 2010;81:215–22.
13. Teichmann A, Apter D, Emerich J, Greven K, Klasa-Mazurkiewicz D, Melis GB, et al. Continuous, daily levonorgestrel/ethinyl estradiol vs. 21-day, cyclic levonorgestrel/ethinyl estradiol: efficacy, safety and bleeding in a randomized, open-label trial. Contraception 2009;80:504–11.
14. Archer DF, Jensen JT, Johnson JV, Borisute H, Grubb GS, Constantine GD. Evaluation of a continuous regimen of levonorgestrel/ethinyl estradiol: phase 3 study results. Contraception 2006;74:439–45.
15. Moreau C, Bouyer J, Bajos N, Rodriguez G, Trussell J. Frequency of discontinuation of contraceptive use: results from a French population-based cohort. Hum Reprod 2009;24:1387–92.

16. Murphy PA, Brixner D. Hormonal contraceptive discontinuation patterns according to formulation: investigation of associations in an administrative claims database. Contraception 2008;77: 257–63.
17. Van Vliet HA, Grimes DA, Helmerhorst FM, Schulz KF. Biphasic versus monophasic oral contraceptives for contraception. Cochrane Database Syst Rev 2006;3:CD002032.
18. van Vliet HA, Grimes DA, Lopez LM, Schulz KF, Helmerhorst FM. Triphasic versus monophasic oral contraceptives for contraception. Cochrane Database Syst Rev 2006;3:CD003553.
19. Van Vliet HA, Grimes DA, Lopez LM, Schulz KF, Helmerhorst FM. Triphasic versus monophasic oral contraceptives for contraception. Cochrane Database Syst Rev 2011;11:CD003553.
20. Van Vliet HA, Raps M, Lopez LM, Helmerhorst FM. Quadriphasic versus monophasic oral contraceptives for contraception. Cochrane Database Syst Rev 2011;11:CD009038.
21. Johnson JV, Grubb GS, Constantine GD. Endometrial histology following 1 year of a continuous daily regimen of levonorgestrel 90 micro g/ethinyl estradiol 20 micro g. Contraception 2007;75: 23–6.
22. Grandi G, Piacenti I, Volpe A, Cagnacci A. Modification of body composition and metabolism during oral contraceptives containing non-androgenic progestins in association with estradiol or ethinyl estradiol. Gynecol Endocrinol 2014;30:676–80.
23. Grandi G, Xholli A, Napolitano A, Piacenti I, Bellafronte M, Cagnacci A. Prospective measurement of blood pressure and heart rate over 24 h in women using combined oral contraceptives with estradiol. Contraception 2014;90:529–34.
24. Miller L, Hughes JP. Continuous combination oral contraceptive pills to eliminate withdrawal bleeding: a randomized trial. Obstet Gynecol 2003;101:653–61.
25. Galzote RM, Rafie S, Teal R, Mody SK. Transdermal delivery of combined hormonal contraception: a review of the current literature. Int J Womens Health 2017;9:315–21.
26. Lopez LM, Grimes DA, Gallo MF, Stockton LL, Schulz KF. Skin patch and vaginal ring versus combined oral contraceptives for contraception. Cochrane Database Syst Rev 2013:CD003552. https://doi.org/10.1002/14651858.CD003552.pub4.
27. van den Heuvel MW, van Bragt AJ, Alnabawy AK, Kaptein MC. Comparison of ethinylestradiol pharmacokinetics in three hormonal contraceptive formulations: the vaginal ring, the transdermal patch and an oral contraceptive. Contraception 2005;72:168–74.
28. Rubinstein ML, Halpern-Felsher BL, Irwin CE Jr. An evaluation of the use of the transdermal contraceptive patch in adolescents. J Adolesc Health 2004;34:395–401.
29. Raine TR, Foster-Rosales A, Upadhyay UD, Boyer CB, Brown BA, Sokoloff A, et al. One-year contraceptive continuation and pregnancy in adolescent girls and women initiating hormonal contraceptives. Obstet Gynecol 2011;117:363–71.
30. Harel Z, Riggs S, Vaz R, Flanagan P, Dunn K, Harel D. Adolescents' experience with the combined estrogen and progestin transdermal contraceptive method ortho evra. J Pediatr Adolesc Gynecol 2005;18:85–90.
31. Stewart FH, Brown BA, Raine TR, Weitz TA, Harper CC. Adolescent and young women's experience with the vaginal ring and oral contraceptive pills. J Pediatr Adolesc Gynecol 2007;20:345–51.
32. Maheux-Lacroix S, Leboeuf M, Dufresne A, Dodin S. Adolescents' willingness to use the contraceptive vaginal ring. J Obstet Gynaecol Can 2011;33:353–60.
33. Gill K, Happel AU, Pidwell T, Mendelsohn A, Duyver M, Johnson L, et al. An open-label, randomized crossover study to evaluate the acceptability and preference for contraceptive options in female adolescents, 15 to 19 years of age in Cape Town, as a proxy for HIV prevention methods (UChoose). J Int AIDS Soc 2020;23: e25626.
34. Miller L, Verhoeven CH, Hout J. Extended regimens of the contraceptive vaginal ring: a randomized trial. Obstet Gynecol 2005;106:473–82.
35. American College of Obstetricians and Gynecologists (ACOG). Gynecologic management of adolescents and young women with seizure disorders: ACOG committee opinion, number 806. Obstet Gynecol 2020;135:e213–e20. https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2020/05/gynecologic-management-of-adolescents-and-young-women-with-seizure-disorders.
36. Riggs BL. The mechanisms of estrogen regulation of bone resorption. J Clin Invest 2000;106:1203–4.
37. Seifert-Klauss V, Prior JC. Progesterone and bone: actions promoting bone health in women. J Osteoporos 2010;2010: 845180.
38. Kuohung W, Borgatta L, Stubblefield P. Low-dose oral contraceptives and bone mineral density: an evidence-based analysis. Contraception 2000;61:77–82.
39. Weaver CM, Gordon CM, Janz KF, Kalkwarf HJ, Lappe JM, Lewis R, et al. The National Osteoporosis Foundation's position statement on peak bone mass development and lifestyle factors: a systematic review and implementation recommendations. Osteoporos Int 2016;27:1281–386.
40. Bachrach LK. Hormonal contraception and bone health in adolescents. Front Endocrinol 2020;11:603.
41. Golden NH. Bones and birth control in adolescent girls. J Pediatr Adolesc Gynecol 2020;33:249–54.
42. Southmayd EA, De Souza MJ. A summary of the influence of exogenous estrogen administration across the lifespan on the GH/IGF-1 axis and implications for bone health. Growth Horm IGF Res 2017;32:2–13.
43. Herrmann M, Seibel MJ. The effects of hormonal contraceptives on bone turnover markers and bone health. Clin Endocrinol 2010; 72:571–83.
44. Hartard M, Kleinmond C, Wiseman M, Weissenbacher ER, Felsenberg D, Erben RG. Detrimental effect of oral contraceptives on parameters of bone mass and geometry in a cohort of 248 young women. Bone 2007;40:444–50.
45. Pikkarainen E, Lehtonen-Veromaa M, Mottonen T, Kautiainen H, Viikari J. Estrogen-progestin contraceptive use during adolescence prevents bone mass acquisition: a 4-year follow-up study. Contraception 2008;78:226–31.
46. Brajic TS, Berger C, Schlammerl K, Macdonald H, Kalyan S, Hanley DA, et al. Combined hormonal contraceptives use and bone mineral density changes in adolescent and young women in a prospective population-based Canada-wide observational study. J Musculoskelet Neuronal Interact 2018;18:227–36.
47. Agostino H, Di Meglio G. Low-dose oral contraceptives in adolescents: how low can you go? J Pediatr Adolesc Gynecol 2010;23:195–201.
48. Biason TP, Goldberg TB, Kurokawa CS, Moretto MR, Teixeira AS, Nunes HR. Low-dose combined oral contraceptive use is associated with lower bone mineral content variation in adolescents over a 1-year period. BMC Endocr Disord 2015;15:15.

49. Cibula D, Skrenkova J, Hill M, Stepan JJ. Low-dose estrogen combined oral contraceptives may negatively influence physiological bone mineral density acquisition during adolescence. Eur J Endocrinol 2012;166:1003–11.
50. Gersten J, Hsieh J, Weiss H, Ricciotti NA. Effect of extended 30 mug ethinyl estradiol with continuous low-dose ethinyl estradiol and cyclic 20 mug ethinyl estradiol oral contraception on adolescent bone density: a randomized trial. J Pediatr Adolesc Gynecol 2016;29:635–42.
51. Lopez LM, Grimes DA, Schulz KF, Curtis KM, Chen M. Steroidal contraceptives: effect on bone fractures in women. Cochrane Database Syst Rev 2014;6:CD006033.
52. Goshtasebi A, Subotic Brajic T, Scholes D, Beres Lederer Goldberg T, Berenson A, Prior JC. Adolescent use of combined hormonal contraception and peak bone mineral density accrual: a meta-analysis of international prospective controlled studies. Clin Endocrinol 2019;90:517–24.
53. Li Z, Chines AA, Meredith MP. Statistical validation of surrogate endpoints: is bone density a valid surrogate for fracture? J Musculoskelet Neuronal Interact 2004;4:64–74.
54. Barad D, Kooperberg C, Wactawski-Wende J, Liu J, Hendrix SL, Watts NB. Prior oral contraception and postmenopausal fracture: a Women's Health Initiative observational cohort study. Fertil Steril 2005;84:374–83.
55. Vestergaard P, Rejnmark L, Mosekilde L. Fracture risk in very young women using combined oral contraceptives. Contraception 2008;78:358–64.
56. Lopez LM, Chen M, Mullins S, Curtis KM, Helmerhorst FM. Steroidal contraceptives and bone fractures in women: evidence from observational studies. Cochrane Database Syst Rev 2012;8: CD009849.
57. Lopez LM, Grimes DA, Schulz KF, Curtis KM. Steroidal contraceptives: effect on bone fractures in women. Cochrane Database Syst Rev 2011;7:CD006033.
58. Dombrowski S, Jacob L, Hadji P, Kostev K. Oral contraceptive use and fracture risk-a retrospective study of 12,970 women in the UK. Osteoporos Int 2017;28:2349–55.
59. Blackmore KM, Wong J, Knight JA. A cross-sectional study of different patterns of oral contraceptive use among premenopausal women and circulating IGF-1: implications for disease risk. BMC Wom Health 2011;11:15.
60. Harel Z, Riggs S, Vaz R, Flanagan P, Harel D, Machan JT. Bone accretion in adolescents using the combined estrogen and progestin transdermal contraceptive method Ortho Evra: a pilot study. J Pediatr Adolesc Gynecol 2010;23:23–31.
61. Ackerman KE, Singhal V, Baskaran C, Slattery M, Campoverde Reyes KJ, Toth A, et al. Oestrogen replacement improves bone mineral density in oligo-amenorrhoeic athletes: a randomised clinical trial. Br J Sports Med 2019;53:229–36.
62. Misra M, Katzman D, Miller KK, Mendes N, Snelgrove D, Russell M, et al. Physiologic estrogen replacement increases bone density in adolescent girls with anorexia nervosa. J Bone Miner Res 2011;26:2430–8.
63. Massai R, Makarainen L, Kuukankorpi A, Klipping C, Duijkers I, Dieben T. The combined contraceptive vaginal ring and bone mineral density in healthy pre-menopausal women. Hum Reprod 2005;20:2764–8.
64. Massaro M, Di Carlo C, Gargano V, Formisano C, Bifulco G, Nappi C. Effects of the contraceptive patch and the vaginal ring on bone metabolism and bone mineral density: a prospective, controlled, randomized study. Contraception 2010;81:209–14.
65. Nappi C, Bifulco G, Tommaselli GA, Gargano V, Di Carlo C. Hormonal contraception and bone metabolism: a systematic review. Contraception 2012;86:606–21.
66. Beksinska ME, Smit JA, Kleinschmidt I, Milford C, Farley TM. Prospective study of weight change in new adolescent users of DMPA, NET-EN, COCs, nonusers and discontinuers of hormonal contraception. Contraception 2010;81:30–4.
67. Gallo MF, Lopez LM, Grimes DA, Carayon F, Schulz KF, Helmerhorst FM. Combination contraceptives: effects on weight. Cochrane Database Syst Rev 2014:CD003987. https://doi.org/10.1002/14651858.CD003987.pub5.
68. de Bastos M, Stegeman BH, Rosendaal FR, Van Hylckama Vlieg A, Helmerhorst FM, Stijnen T, et al. Combined oral contraceptives: venous thrombosis. Cochrane Database Syst Rev 2014: CD010813. https://doi.org/10.1002/14651858.CD010813.pub2.
69. Committee on Gynecologic Practice. ACOG Committee Opinion Number 540: risk of venous thromboembolism among users of drospirenone-containing oral contraceptive pills. Obstet Gynecol 2012;120:1239–42.
70. Dragoman MV, Tepper NK, Fu R, Curtis KM, Chou R, Gaffield ME. A systematic review and meta-analysis of venous thrombosis risk among users of combined oral contraception. Int J Gynaecol Obstet 2018;141:287–94.
71. Practice Committee of the American Society for Reproductive Medicine. Electronic address Aao, Practice Committee of the American Society for Reproductive M. Combined hormonal contraception and the risk of venous thromboembolism: a guideline. Fertil Steril 2017;107:43–51.
72. Woods GM, Kerlin BA, O'Brien SH, Bonny AE. A review of hormonal contraception and venous thromboembolism in adolescents. J Pediatr Adolesc Gynecol 2016;29:402–8.
73. Shoupe D. The Progestin Revolution: progestins are arising as the dominant players in the tight interlink between contraceptives and bleeding control. Contracept Reprod Med 2021;6:3.
74. Hall KS, Trussell J, Schwarz EB. Progestin-only contraceptive pill use among women in the United States. Contraception 2012;86: 653–8.
75. Tepper NK, Whiteman MK, Marchbanks PA, James AH, Curtis KM. Progestin-only contraception and thromboembolism: a systematic review. Contraception 2016;94:678–700.
76. Broome M, Fotherby K. Clinical experience with the progestogen-only pill. Contraception 1990;42:489–95.
77. McCann MF, Potter LS. Progestin-only oral contraception: a comprehensive review. Contraception 1994;50:S1–195.
78. Hillard PA. Menstrual suppression: current perspectives. Int J Wom Health 2014;6:631–7.
79. Pradhan S, Gomez-Lobo V. Hormonal contraceptives, IUDs, GnRH analogues and testosterone: menstrual suppression in special adolescent populations. J Pediatr Adolesc Gynecol 2019;32:S23-9.
80. Kaser DJ, Missmer SA, Berry KF, Laufer MR. Use of norethindrone acetate alone for postoperative suppression of endometriosis symptoms. J Pediatr Adolesc Gynecol 2012;25:105–8.
81. Sarfati J, de Vernejoul MC. Impact of combined and progestogen-only contraceptives on bone mineral density. Joint Bone Spine 2009;76:134–8.
82. Raine-Bennett T, Chandra M, Armstrong MA, Alexeeff S, Lo JC. Depot medroxyprogesterone acetate, oral contraceptive,

intrauterine device use, and fracture risk. Obstet Gynecol 2019; 134:581–9.
83. Mainwaring R, Hales HA, Stevenson K, Hatasaka HH, Poulson AM, Jones KP, et al. Metabolic parameter, bleeding, and weight changes in U.S. women using progestin only contraceptives. Contraception 1995;51:149–53.
84. Speroff LD, Philip D. A clinical guide for contraception. Philadelphia, PA: Lippincott Williams & Wilkins; 2010.
85. Worly BL, Gur TL, Schaffir J. The relationship between progestin hormonal contraception and depression: a systematic review. Contraception 2018;97:478–89.
86. Winner B, Peipert JF, Zhao Q, Buckel C, Madden T, Allsworth JE, et al. Effectiveness of long-acting reversible contraception. N Engl J Med 2012;366:1998–2007.
87. Zigler RE, McNicholas C. Unscheduled vaginal bleeding with progestin-only contraceptive use. Am J Obstet Gynecol 2017;216: 443–50.
88. Arias RD, Jain JK, Brucker C, Ross D, Ray A. Changes in bleeding patterns with depot medroxyprogesterone acetate subcutaneous injection 104 mg. Contraception 2006;74:234–8.
89. Hubacher D, Lopez L, Steiner MJ, Dorflinger L. Menstrual pattern changes from levonorgestrel subdermal implants and DMPA: systematic review and evidence-based comparisons. Contraception 2009;80:113–8.
90. Fritz M, Speroff L. Long-acting methods of contraception. In: Fritz M, Speroff L, editors. Clinical Gynecologic Endocrinology and Infertility, 8th ed. Philadelphia, PA: Wolters Kluwer; 2011:1059–93 pp.
91. Obijuru L, Bumpus S, Auinger P, Baldwin CD. Etonogestrel implants in adolescents: experience, satisfaction, and continuation. J Adolesc Health 2016;58:284–9.
92. Villavicencio J, Allen RH. Unscheduled bleeding and contraceptive choice: increasing satisfaction and continuation rates. Open Access J Contracept 2016;7:43–52.
93. Walsh JS, Eastell R, Peel NF. Effects of Depot medroxyprogesterone acetate on bone density and bone metabolism before and after peak bone mass: a case-control study. J Clin Endocrinol Metab 2008;93:1317–23.
94. Lara-Torre E, Edwards CP, Perlman S, Hertweck SP. Bone mineral density in adolescent females using depot medroxyprogesterone acetate. J Pediatr Adolesc Gynecol 2004;17:17–21.
95. Busen NH, Britt RB, Rianon N. Bone mineral density in a cohort of adolescent women using depot medroxyprogesterone acetate for one to two years. J Adolesc Health 2003;32:257–9.
96. Cromer BA. Bone mineral density in adolescent and young adult women on injectable or oral contraception. Curr Opin Obstet Gynecol 2003;15:353–7.
97. Cromer BA, Blair JM, Mahan JD, Zibners L, Naumovski Z. A prospective comparison of bone density in adolescent girls receiving depot medroxyprogesterone acetate (Depo-Provera), levonorgestrel (Norplant), or oral contraceptives. J Pediatr 1996;129: 671–6.
98. Gai L, Zhang J, Zhang H, Gai P, Zhou L, Liu Y. The effect of depot medroxyprogesterone acetate (DMPA) on bone mineral density (BMD) and evaluating changes in BMD after discontinuation of DMPA in Chinese women of reproductive age. Contraception 2011;83:218–22.
99. Pitts SA, Feldman HA, Dorale A, Gordon CM. Bone mineral density, fracture, and vitamin D in adolescents and young women using depot medroxyprogesterone acetate. J Pediatr Adolesc Gynecol 2012;25:23–6.
100. Lange HL, Manos BE, Gothard MD, Rogers LK, Bonny AE. Bone mineral density and weight changes in adolescents randomized to 3 doses of depot medroxyprogesterone acetate. J Pediatr Adolesc Gynecol 2017;30:169–75.
101. Clark MK, Sowers M, Levy B, Nichols S. Bone mineral density loss and recovery during 48 months in first-time users of depot medroxyprogesterone acetate. Fertil Steril 2006;86:1466–74.
102. Babatunde OO, Forsyth JJ. Association between depot medroxyprogesterone acetate (DMPA), physical activity and bone health. J Bone Miner Metab 2014;32:305–11.
103. Nieves JW, Ruffing JA, Zion M, Tendy S, Yavorek T, Lindsay R, et al. Eating disorders, menstrual dysfunction, weight change and DMPA use predict bone density change in college-aged women. Bone 2016;84:113–9.
104. Scholes D, LaCroix AZ, Ichikawa LE, Barlow WE, Ott SM. Change in bone mineral density among adolescent women using and discontinuing depot medroxyprogesterone acetate contraception. Arch Pediatr Adolesc Med 2005;159:139–44.
105. Harel Z, Johnson CC, Gold MA, Cromer B, Peterson E, Burkman R, et al. Recovery of bone mineral density in adolescents following the use of depot medroxyprogesterone acetate contraceptive injections. Contraception 2010;81:281–91.
106. Committee Opinion No. 602. Depot medroxyprogesterone acetate and bone effects. Obstet Gynecol 2014;123:1398–402.
107. Makarainen L, van Beek A, Tuomivaara L, Asplund B, Coelingh Bennink H. Ovarian function during the use of a single contraceptive implant: implanon compared with Norplant. Fertil Steril 1998;69:714–21.
108. Modesto W, Dal Ava N, Monteiro I, Bahamondes L. Body composition and bone mineral density in users of the etonogestrel-releasing contraceptive implant. Arch Gynecol Obstet 2015;292:1387–91.
109. Beerthuizen R, van Beek A, Massai R, Makarainen L, Hout J, Bennink HC. Bone mineral density during long-term use of the progestagen contraceptive implant Implanon compared to a non-hormonal method of contraception. Hum Reprod 2000;15: 118–22.
110. Pongsatha S, Ekmahachai M, Suntornlimsiri N, Morakote N, Chaovisitsaree S. Bone mineral density in women using the subdermal contraceptive implant Implanon for at least 2 years. Int J Gynaecol Obstet 2010;109:223–5.
111. Depot Provera CI. [Drug Inser]. New York, NY: Pfizer Pharmacia and Upjohn Co.; 2017.
112. American Academy of Pediatrics (AAP). Contraception for adolescents. Pediatrics 2014;134:e1244-56.
113. ACOG Committee Opinion No. 735. Adolescents and long-acting reversible contraception: implants and intrauterine devices. Obstet Gynecol 2018;131:e130–e9.
114. Lohr PA, Lyus R, Prager S. Use of intrauterine devices in nulliparous women. Contraception 2017;95:529–37.
115. Pradhan S, Gomez-Lobo V. Hormonal contraceptives, intrauterine devices, gonadotropin-releasing hormone analogues and testosterone: menstrual suppression in special adolescent populations. J Pediatr Adolesc Gynecol 2019;32:S23–9.
116. Leeks R, Bartley C, O'Brien B, Bagchi T, Kimble RMN. Menstrual suppression in pediatric and adolescent patients with disabilities ranging from developmental to acquired conditions: a population study in an Australian quaternary pediatric and adolescent gynecology service from January 2005 to December 2015. J Pediatr Adolesc Gynecol 2019;32:535–40.

117. Schwartz BI, Alexander M, Breech LL. Intrauterine device use in adolescents with disabilities. Pediatrics 2020;146. https://doi.org/10.1542/peds.2020-0016.
118. Black A, Guilbert E, Costescu D, Dunn S, Fisher W, Kives S, et al. Canadian contraception consensus (Part 3 of 4): chapter 7–intrauterine contraception. J Obstet Gynaecol Can 2016;38:182–222.
119. Andersson JK, Rybo G. Levonorgestrel-releasing intrauterine device in the treatment of menorrhagia. Br J Obstet Gynaecol 1990;97:690–4.
120. Jensen J, Mansour D, Lukkari-Lax E, Inki P, Burock K, Fraser IS. Bleeding patterns with the levonorgestrel-releasing intrauterine system when used for heavy menstrual bleeding in women without structural pelvic pathology: a pooled analysis of randomized controlled studies. Contraception 2013;87:107–12.
121. Heikinheimo O, Inki P, Schmelter T, Gemzell-Danielsson K. Bleeding pattern and user satisfaction in second consecutive levonorgestrel-releasing intrauterine system users: results of a prospective 5-year study. Hum Reprod 2014;29:1182–8.
122. Sergison JE, Maldonado LY, Gao X, Hubacher D. Levonorgestrel intrauterine system associated amenorrhea: a systematic review and metaanalysis. Am J Obstet Gynecol 2019;220:440–8.
123. Gemzell-Danielsson K, Schellschmidt I, Apter D. A randomized, phase II study describing the efficacy, bleeding profile, and safety of two low-dose levonorgestrel-releasing intrauterine contraceptive systems and Mirena. Fertil Steril 2012;97:616–22 e1-3.
124. Parks MA, Zwayne N, Temkit M. Bleeding patterns among adolescents using the levonorgestrel intrauterine device: a single institution review. J Pediatr Adolesc Gynecol 2020;33:555–8.
125. Apter D, Gemzell-Danielsson K, Hauck B, Rosen K, Zurth C. Pharmacokinetics of two low-dose levonorgestrel-releasing intrauterine systems and effects on ovulation rate and cervical function: pooled analyses of phase II and III studies. Fertil Steril 2014;101:1656–62.e1-4.
126. Nelson A, Apter D, Hauck B, Schmelter T, Rybowski S, Rosen K, et al. Two low-dose levonorgestrel intrauterine contraceptive systems: a randomized controlled trial. Obstet Gynecol 2013;122:1205–13.
127. Bahamondes MV, Monteiro I, Castro S, Espejo-Arce X, Bahamondes L. Prospective study of the forearm bone mineral density of long-term users of the levonorgestrel-releasing intrauterine system. Hum Reprod 2010;25:1158–64.
128. Yang KY, Kim YS, Ji YI, Jung MH. Changes in bone mineral density of users of the levonorgestrel-releasing intrauterine system. J Nippon Med Sch 2012;79:190–4.
129. van Hylckama Vlieg A, Helmerhorst FM, Rosendaal FR. The risk of deep venous thrombosis associated with injectable depot-medroxyprogesterone acetate contraceptives or a levonorgestrel intrauterine device. Arterioscler Thromb Vasc Biol 2010;30:2297–300.
130. American College of O, Gynecologists' Committee on Adolescent Health C. Committee Opinion No. 668: Menstrual manipulation for adolescents with physical and developmental disabilities. Obstet Gynecol 2016;128:e20–5.
131. Acharya K, Lantos JD. Considering decision-making and sexuality in menstrual suppression of teens and young adults with intellectual disabilities. AMA J Ethics 2016;18:365–72.
132. Burgart AM, Strickland J, Davis D, Baratz AB, Karkazis K, Lantos JD. Ethical controversy about hysterectomy for a minor. Pediatrics 2017;139. https://doi.org/10.1542/peds.2016-3992.
133. Quint EH, O'Brien RF, Committee On A, North American Society for Pediatric and Adolescent Gynecology. Menstrual management for adolescents with disabilities. Pediatrics 2016;138. https://doi.org/10.1542/peds.2016-0295.
134. Reilly PR. Eugenics and involuntary sterilization: 1907-2015. Annu Rev Genomics Hum Genet 2015;16:351–68.
135. Sterilization of minors with developmental disabilities. American Academy of pediatrics. Committee on Bioethics. Pediatrics. 1999;104:337-40.