

Clinical Applications of Estrogens in Adolescence and the Menopausal Transition

Sridhar A¹, Gemzell Danielsson K², Gaspard U³, Barriga P⁴, de Villiers T⁵

¹ David Geffen School of Medicine at University of California, Los Angeles, USA

² Department of Women's and Children's Health, Karolinska Institutet, and the Division for Gynecology and Reproductive medicine, Karolinska University Hospital, Stockholm, Sweden

³ Department of Obstetrics and Gynecology, University Hospital, Liege, Belgium

⁴ Facultad de Medicina Universidad Finis Terrae, Chile

⁵ Panorama Bone Densitometry Clinic, Clintrials Centre for Clinical Studies, South Africa

Introduction

Estrogen-containing contraceptives are vital for reproductive health across life stages, with natural, body-identical estrogens offering a safer and more metabolically favourable alternative to synthetic formulations, whose unique pharmacological properties ensure effective contraception and therapy with reduced health risks for adolescents, young, and midlife women [1-3]. In adolescents and young adults, COCs with natural estrogens (estradiol [E2] and estetrol [E4]) show benefits in managing menstrual disorders and carry a lower thrombotic risk than synthetic formulations. However, caution is warranted in individuals with a predisposition, and further age-specific research is needed. In menopausal women, E2 and E4 therapies effectively relieve vasomotor symptoms with an improved safety profile [4-8]. This section discusses the role of estrogens throughout a woman's life, reflecting the changing physiological needs at various stages. It also addresses barriers to contraception throughout the lifespan.

Adolescents and young adults

COCs are widely used by adolescents, offering effective contraception together with additional health benefits [4,9]. Beyond safety and adherence, it is essential to support confidentiality and autonomy, ensuring that adolescents feel empowered in their contraceptive decisions. Their values and preferences, including convenience, bleeding profile, and the need for privacy, are central to method choice and long-term satisfaction [4,10,11].

Safety and eligibility of CHC use

The World Health Organization (WHO), Centers for Disease Control and Prevention (CDC), and other global organisations provide Medical Eligibility Criteria (MEC) for contraceptive use, categorising methods based on safety for specific medical conditions [12-14]. While age is not a contraindication for any contraceptive method, only reversible options are recommended in adolescents. Additionally, the use of progestogen-only contraceptives, such as depot medroxyprogesterone acetate, in individuals under 18 may have a potential impact on achieving peak bone mass, although this is not a contraindication [9,15,16]. These considerations should be taken into account when prescribing contraception for adolescents.

According to the WHO MEC, adolescents without contraindications are generally eligible to use combined hormonal contraceptives (CHCs) safely [12,13]. CHCs may be particularly useful for those with conditions such as mild controlled acne, iron-deficiency anaemia, or heavy menstrual bleeding, where additional therapeutic benefits can be achieved. However, CHCs are contraindicated in all users, including adolescents and young users (<35 years), with a history of thromboembolism, migraine with aura, severe liver disease or active liver tumours, or known thrombophilia (congenital or acquired) [12,13]. Common side effects, such as unscheduled bleeding, nausea, and headaches, should be discussed to improve adherence [17].

Adolescents can take CHCs with a 4- or 7-day hormone-free interval (HFI) or use extended-cycle regimens, which may be beneficial in school, sports, or social settings. This can also be done to reduce dysmenorrhea, heavy menstrual bleeding, acne, anaemia, and conditions influenced by hormonal fluctuations,

such as migraine without aura and inflammatory bowel disease. These conditions are not an absolute contraindication for CHC use; nevertheless, caution is advised, and the decision should be individualised based on the patient's overall health, disease activity, and potential risks. Certain factors, like increased thromboembolism risk or active disease states, may influence that choice [18,19]. Extended-cycle CHC use results in either equivalent or reduced unscheduled bleeding compared to cyclic regimens, with endometrial safety well established [19]. To maintain contraceptive efficacy, HFIIs should not occur before 21 consecutive days of CHC use. Written instructions and digital resources can aid adherence, with follow-ups at one and three months [4,9].

Adolescence is a critical period for bone mass accumulation, continuing until around age 25. Evidence indicates that COCs containing ethinylestradiol (EE) may hinder bone accrual in post-menarche adolescents compared with non-users [9,20]. The impact varies by estrogen dose, progestin type, and duration, with effects most evident after more than two years of use. Findings on dose are inconsistent, with some studies showing reduced accrual at 15–20 µg EE and others at 30 µg [20,21]. A two-year trial of 30 µg EE/3 mg drospirenone (DRSP) confirmed reduced bone mass gain and lower bone formation markers [22], while a meta-analysis reported significantly decreased spinal bone mineral density (BMD) after 12–24 months [23]. A 5-year longitudinal study in South African adolescents also found that COC users (90% 30–40 µg

EE) experienced smaller gains in BMD than non-users, suggesting attenuated accrual during a key growth period (Beksinska et al., 2009). In contrast, natural estrogens such as E2 appear more bone-friendly: a recent meta-analysis found minimal changes in bone turnover markers with E2-containing COCs, compared with significant reductions under EE [24]. Limited clinical data are available for E4; however, existing analyses suggest that E4, when combined with DRSP, reduces bone turnover markers to a lesser extent than EE-containing COCs [24,25]. However, while this pattern suggests neutrality or potential benefit in adults, interpretation in younger women remains uncertain, as bone turnover markers do not reliably predict long-term BMD and pooling data across age groups, as done by Tassi et al., may obscure critical differences [24,26]. Moreover, preclinical studies in osteoporotic models have demonstrated that E4 can increase BMD, enhance bone strength, and elevate osteocalcin levels compared to untreated controls [25].

Importantly, there is no evidence to date that changes in BMD or CHC use increase the risk of bone fractures, suggesting that the observed changes in bone biomarkers and density may not translate into clinically relevant harm [22–24,26–28] (see also Section 9). In women with impaired ovarian function, it seems that COCs have a positive influence on BMD [29]. Furthermore, CHCs are not indicated for osteoporosis prevention, but non-oral combined hormonal formulations (injectables, patches, or rings) could be an option that may reduce bone loss in anorexia nervosa [30–33].



Optimising regimens and adherence

In real-world settings, adherence to daily oral contraceptive regimens is generally lower than that observed in clinical trials, with adolescents and young users typically being less compliant.

Data on the impact of missed pills from clinical studies are limited. A pooled analysis of phase 3 trials, published by Creinin et al., assessed the effectiveness of E4 combined with DRSP (E4/DRSP) under conditions of imperfect adherence [34]. Among 2,837 participants, pregnancy rates increased with missed pills: 0.09% with full adherence, 0.25% with one missed pill, 0.83% with two missed pills, and 1.6% with more than two missed pills. Nonetheless, no pregnancies occurred when missed-pill instructions were correctly followed. All pregnancies linked to missed pills happened within the first three cycles of use. These results show that this COC option maintains very high contraceptive effectiveness, with a significant degree of forgivability, which is likely due to the long half-life and distinctive pharmacology of E4 (see Section 4) [34,35].

Although less extensively studied, COCs containing E2 or E2 valerate (E2V) have also shown reliable contraceptive efficacy and favourable adherence outcomes. Trials with E2 norgestrel acetate (E2/NOMAC) and E2V combined with dienogest DNG (E2V/DNG) report reasonable cycle control, low rates of unscheduled bleeding, and consistent symptom relief, even when used in extended or flexible regimens [3,36,37]. While data on missed-pill management are not as detailed as for E4 combined with DRSP, available evidence suggests that contraceptive reliability is preserved with appropriate use, making these natural-estrogen COCs a practical option for adolescents and young women [3,36,37].

In contrast to natural estrogens, evidence from EE-containing COCs shows that efficacy is highly dependent on strict daily adherence. Missed pills are common, particularly among adolescents: up to 47% of users report missing at least one pill per cycle and around 22% miss two or more, which is linked to an increased risk of unintended pregnancy [38,39]. Discontinuation rates in this age group can reach 50% within the first three months of use [38,40]. Missed pills are also a major contributor to unscheduled bleeding, which further undermines continuation [38]. Escape ovulation is most likely during the HFI or when pills are missed, but studies show that shortening the HFI in EE-based regimens (e.g. 24/4 vs 21/7) improves ovarian suppression and reduces follicular development [38,41,42]. Taken together, these findings indicate that EE-containing COCs are less forgiving under typical use than natural-estrogen regimens, underscoring the importance of adherence counselling and the consideration of regimen modifications to mitigate risks [9].

In conclusion, unlike EE or E2, which have shorter half-lives and are metabolised more quickly, E4 offers sustained estrogenic activity and is not subject to CYP450 metabolism [35] (see Section 4). These pharmacological characteristics are likely to contribute to a more favourable profile for contraceptive forgiveness during typical use, positioning E4 as distinct among natural estrogens.

Clinical profile of estrogens in COCs in adolescents

E2/NOMAC and E2V/DNG have been studied in adult women and some younger users, demonstrating good tolerability, effective cycle control, and reductions in menstrual-related symptoms. Pharmacokinetic data for E2/NOMAC show similar systemic exposure in adolescents and adults [43]. Although long-term data in adolescents are limited, preliminary evidence for these natural-estrogen COCs suggests that they have less negative impact on haemostatic and metabolic markers than many EE-based formulations [1,44,45] (see Section 8). Importantly, as already mentioned, data also suggest that E2-containing COCs cause only minimal suppression of bone formation markers compared with EE, indicating a potentially more favourable profile for bone health during adolescence [24]. However, whether they completely prevent reduced bone accrual or definitively lower the risk of venous thromboembolism (VTE) in adolescent populations remains to be confirmed.

E4, like E2 and E2V, also seems to have a less negative impact on haemostatic and metabolic markers than many EE-based formulations [1,44,45]. E4 combined with DRSP has been evaluated for safety, tolerability, bleeding profile, and effect on dysmenorrhoea in adolescents aged 12-17 years. It was safe for use, leading to a predictable bleeding pattern and a reduction in dysmenorrhoea by over 30% and decreased use of pain medication occurred after three cycles of use and remained until the conclusion of the study [46].

EE-containing COCs have been extensively studied in adolescents and shown to be highly effective, with contraceptive efficacy comparable to that observed in adults. Their safety profile in this age group is broadly consistent with older users, with common side effects including unscheduled bleeding, headaches, and nausea [4,9]. International guidelines, including WHO and CDC MEC, consider EE-containing COCs safe for use in healthy adolescents without contraindications such as venous thromboembolism, migraine with aura, liver disease, or thrombophilia [12,13]. Beyond contraception, EE-containing COCs also provide non-contraceptive benefits such as improved cycle regulation, relief of dysmenorrhea, and reduced menstrual blood loss. However, their haemostatic profile seems less favourable compared with natural estrogens, contributing to

a relatively higher risk of venous thromboembolism [44,45].

Regional barriers to effective contraception in adolescents

Adolescents across Europe, Asia, Africa, Latin America, and North America encounter a range of barriers to effective contraception. These challenges are shaped by cultural, structural, legal, and interpersonal factors unique to each region [47,48].

Sub-Saharan Africa faces significant challenges, including limited availability of contraceptive methods, high costs, and inadequate healthcare infrastructure [49,50]. Cultural and religious beliefs often discourage contraceptive use, and myths about side effects are prevalent. Adolescents, particularly girls, may also encounter gender-based barriers and lack autonomy in making reproductive health decisions. Additionally, healthcare providers may exhibit biases against providing contraceptives to unmarried adolescents, further restricting access [51].

In South and Southeast Asia, cultural norms often prioritise early marriage and childbearing, especially for girls, which can discourage contraceptive use among adolescents. Married adolescents may face familial pressure to conceive immediately, while unmarried youths often lack access to reproductive health services due to societal taboos and limited youth-friendly healthcare facilities [52]. Moreover, misconceptions about contraceptive methods and limited comprehensive sex education further impede effective contraceptive use [53,54].

In Latin America, adolescents often face legal and societal barriers to accessing contraception. In some countries, laws restrict access to specific contraceptive methods, and cultural stigmas around adolescent sexuality can deter youths from seeking reproductive health services. Fear of judgment or gossip within communities may prevent adolescents from obtaining contraception, even when services are available [55-57]. Moreover, the inconsistent implementation of sexual education programs across the region contributes to misinformation and low contraceptive use among teenagers.

In North America, disparities in contraceptive access persist, particularly among marginalised communities. In the United States, Hispanic and African American adolescents face higher rates of unintended pregnancies, partly due to limited access to affordable contraceptive services and comprehensive sex education [58]. Confidentiality concerns, especially for minors, and lack of transportation or insurance coverage can also hinder adolescents from obtaining

contraception [59,60]. Additionally, political debates and policy changes regarding reproductive health services can create uncertainty and restrict access for young people.

In parts of Eastern Europe, restrictive laws and limited access to youth-friendly services hinder adolescents' contraceptive use [61-63]. For example, countries like Poland and Hungary have seen increasing limitations on reproductive health services, including contraception, due to political and religious influences. Additionally, stigma surrounding adolescent sexual activity and inadequate sexual education contribute to low contraceptive uptake among teenagers.

Menopausal transition

Hormonal and reproductive changes during perimenopause

The menopausal transition, also referred to as perimenopause, represents the period preceding menopause and corresponds to stages -1 and -2 of the STRAW+10 Staging System for Reproductive Ageing in Women [64]. It typically begins 5–10 years before menopause, around the age of 40, and is characterised by increasing menstrual cycle variability, with a difference of at least seven days between consecutive cycles [65]. Late perimenopause is characterised by cycles that exceed 60 days in length [66].

During the menopausal transition, hormonal alterations occur due to a decline in the number of primordial follicles, resulting in lower levels of inhibin B and anti-Müllerian hormone [67]. Consequently, E2 levels decrease, disrupting the negative feedback mechanism that regulates the secretion of follicle-stimulating hormone and luteinizing hormone (LH) [68]. The inability of low E2 levels to trigger an LH surge results in anovulatory cycles and irregular menstrual patterns [68,69]. These hormonal changes can result in symptomatic outcomes as well as contribute to reduced fertility in women over 40, although unintended pregnancies remain a concern. While the annual pregnancy risk declines from 10% at ages 40–44 to 2–3% at ages 45–49, the rate of elective abortion is higher in this age group, highlighting the continued need for effective contraception [70]. In the United States, for instance, unintended pregnancies accounted for 49% of all pregnancies in 2006, with 48% occurring among women aged 40–44, underscoring the importance of reproductive health management in this population [71].

Role of CHCs in symptom relief and menstrual regulation

Several menopausal transition conditions may be effectively managed with modern hormonal contraceptives, which not only prevent unintended pregnancies but also offer additional non-contraceptive benefits [72]. Given the increased variability in ovulation and

menstrual cycles during menopausal transition, fertility awareness-based methods are considered unreliable and, therefore, are not recommended as a method of contraceptive use in this population [72].

Evidence suggests that CHCs play a role in alleviating vasomotor symptoms, including hot flashes, which can emerge during the premenopausal period. Studies indicate that CHC use effectively reduces these symptoms, with combined oral contraceptive (COC) therapy being a more widely accepted option than menopausal hormone therapy (MHT) for women experiencing early menopausal symptoms [73]. In a clinical study, an alternative estrogen exposure regimen during the placebo week of COC use was evaluated. One group received 10 µg of EE for five days, followed by two days of placebo, while the other group received a traditional seven-day placebo regimen. Both groups reported a reduction in somatic, anxiety, and depressive symptoms, with a more pronounced improvement in vasomotor symptoms, depression, and sexual dysfunction in the estrogen-supplemented group [73]. In women with non-iatrogenic premature ovarian insufficiency who wish to maintain contraception, using the combined oral contraceptive is recommended to be taken in a continuous or extended regimen to provide ongoing estrogen therapy and prevent bone loss [74]. Additionally, Sørđal et al. confirm that COCs used for two years do not affect BMD in premenopausal women. They also note that there is no difference when using a monophasic COC containing 2.5 mg E2/NOMAC or EE 30 µg/LNG 150 µg [75].

Migraine considerations and CHC safety

Menopausal transition is also associated with an increase in migraine frequency and severity, particularly in women with menstrual migraine, likely due to more frequent menstruation as the cycle length shortens [76]. Women with migraines are at higher risk for vasomotor symptoms, anxiety, depression, and sleep disturbances, further contributing to morbidity.

In postmenopausal women, the prevalence of migraines without aura declines, while migraines with aura remain unaffected by menopause, with headache intensity diminishing with age [76]. Theoretically, continuous COC use, which suppresses ovarian activity and menstrual bleeding, may mitigate hormonal migraine triggers. However, clinical trial data on migraine management with COCs remain limited. The European Headache Federation and the European Society of Contraception and Reproductive Health recommend COCs for women requiring contraception, experiencing estrogen-withdrawal headaches, or benefiting from COC therapy for other medical reasons [77]. Continuous COC use is advised to prevent estrogen-withdrawal migraines, with shortened breaks (four days) if necessary to manage unscheduled bleeding. Migraine, including menstrual migraine, is a MEC category 2, whereby the advantages outweigh the risks [13]. However, migraine with aura is a MEC category 4,

meaning COCs pose an unacceptable risk and should not be recommended.

Transition and perimenopausal women have an increased risk of stroke, as a function of advancing age, hypertension, and smoking, and these risks are increased by oral contraceptive use and migraine aura [12,13,77,78]. Accordingly, administration of EE-containing COCs, which increase VTE and stroke risk, should be avoided. During this transitional period and perimenopause, COCs containing E2, E2V, or E4 are advisable, rather than EE-containing COCs [45].

Cultural differences in managing fertility and symptoms during menopausal transition

Cultural perspectives significantly influence how women across different continents manage fertility and symptoms during menopausal transition, particularly regarding contraceptive use [79]. In Western cultures, such as North America and parts of Europe, menopause is often medicalised, with a focus on symptom management through hormone therapy and contraceptives [80]. However, disparities exist; for instance, women from lower socioeconomic backgrounds or certain ethnic minorities may have less access to these treatments and may experience more severe symptoms due to stress and limited healthcare access [81,82]. Furthermore, increased media attention around menopause and menopausal transition also impacts awareness and ultimately management strategies. Conversely, in many Asian cultures, menopause is perceived as a natural life transition rather than a medical condition [83]. Japanese women, for example, report fewer vasomotor symptoms like hot flashes, possibly due to dietary factors and cultural attitudes that view menopause as a positive stage of life. African women's experiences with menopause vary widely across the continent. In some regions, menopause is associated with increased social status, while in others, it may be stigmatised. Access to contraceptives and hormone therapy is often limited, influencing how symptoms are managed. In Latin America, cultural norms and limited healthcare infrastructure can impact hormonal contraceptive use during perimenopause. Users may rely more on traditional methods or have limited access to hormonal treatments, especially oral combined with E2 or E2V, and E4 [84]. This ultimately affects the management of menopausal symptoms due to estrogen deficiency or abnormal uterine bleeding due to ovulatory dysfunction.

Conclusion

The evolving role of estrogens across the reproductive life course highlights the importance of tailoring contraceptive and therapeutic choices to women's changing physiology, priorities, and contexts. Advances in natural estrogen formulations, such as E2 and E4, offer an opportunity to balance efficacy with safety, particularly in adolescents, where EE-containing COCs may impair bone accrual, and in perimenopausal women, where thrombotic risk is a concern. Beyond clinical outcomes, attention to cultural norms, structural barriers, and individual preferences remains essential for ensuring equitable access and adherence to treatment.

Current gaps and future directions

Long-term data on adolescent bone accrual are limited; more studies are needed comparing EE with natural estrogens.

Comparative trials in perimenopause should establish the benefits and safety of E2/E4 vs EE formulations.

Implementation research is required to overcome cultural, structural, and regional barriers to equitable contraceptive access.

Key messages

In adolescents, CHCs are safe and effective, providing contraception and non-contraceptive benefits such as relief from dysmenorrhea and heavy bleeding. EE-containing COCs may impair bone accrual, while E2 and E4 formulations show more favourable profiles for bone health and overall safety. E4/DRSP also appears more forgiving when pills are missed. Nevertheless, cultural and regional barriers, such as stigma, provider bias, and limited youth-friendly services, continue to restrict access and influence method choice.

In perimenopause, CHCs help prevent unintended pregnancies and alleviate symptoms such as hot flushes and migraines. Continuous use benefits women with migraines without aura, but is contraindicated in those with aura. Natural estrogen-containing COCs are preferable to EE-based formulations due to their lower thrombotic risk and favourable metabolic profile.

Cultural views on menopause vary, whereby some cultures are tolerant to MHT, while in other cultures there is limited access and acceptability.

Personalised, age- and context-sensitive counselling is key to optimising contraceptive care throughout a woman's life.

References

- [1] Chabbert-Buffet N, Diaz Yamal IJ, Douxfils J, et al. Body-identical estrogens in combined hormonal contraceptives: A safer path forward. *Int J Gynaecol Obstet*. 2025.
- [2] Frisendahl C, Kallner HK, Gemzell-Danielsson K. The clinical relevance of having more than one estrogen in combined hormonal contraception to address the needs of women. *Best Pract Res Clin Obstet Gynaecol*. 2025;98:102571.
- [3] Fruzzetti F, Machado RB, Lete I, et al. A review of the pharmacology, clinical outcomes, and real-world effectiveness, safety, and non-contraceptive effects of NOMAC/E2. *Eur J Obstet Gynecol Reprod Biol X*. 2024;21:100283.
- [4] Todd N, Black A. Contraception for Adolescents. *J Clin Res Pediatr Endocrinol*. 2020;12(Suppl 1):28-40.
- [5] Gaspard U, Taziaux M, Mawet M, et al. A multicenter, randomized study to select the minimum effective dose of estetrol (E4) in postmenopausal women (E4Relief): part 1. Vasomotor symptoms and overall safety. *Menopause*. 2020;27(8):848-857.
- [6] Gaspard U, Taziaux M, Jost M, et al. A multicenter, randomized, placebo-controlled study to select the minimum effective dose of estetrol in postmenopausal participants (E4Relief): part 2-vaginal cytology, genitourinary syndrome of menopause, and health-related quality of life. *Menopause*. 2023;30(5):480-489.
- [7] Graham S, Archer DF, Simon JA, et al. Review of menopausal hormone therapy with estradiol and progesterone versus other estrogens and progestins. *Gynecological Endocrinology*. 2022;38(11):891-910.
- [8] Panay N, Nappi RE, Stute P, et al. Oral estradiol/micronized progesterone may be associated with lower risk of venous thromboembolism compared with conjugated equine estrogens/medroxyprogesterone acetate in real-world practice. *Maturitas*. 2023;172:23-31.
- [9] Ott MA, Sucato GS, Leroy-Melamed M, et al. Contraceptive Counseling and Methods for Adolescents: Clinical Report. *Pediatrics*. 2025;156(1).
- [10] Lassi Z, Abdul Rahim K, Stavropoulos A, et al. Use of contraceptives, empowerment and agency of adolescent girls and young women: a systematic review and meta-analysis. *BMJ Sexual & Reproductive Health*. 2024;50:bmjsrh-2023.
- [11] Ti A, Soin K, Rahman T, et al. Contraceptive values and preferences of adolescents and young adults: A systematic review. *Contraception*. 2022;111:22-31.
- [12] World Health Organization. Medical Eligibility Criteria for Contraceptive Use. 5th ed. World Health Organization: Geneva, Switzerland. 2015.
- [13] Curtis KM, Tepper NK, Jatlaoui TC, et al. U.S. Medical Eligibility Criteria for Contraceptive Use, 2016. *MMWR Recomm Rep*. 2016;65(3):1-103.
- [14] Faculty of Sexual & Reproductive Healthcare. UK Medical Eligibility Criteria for Contraceptive Use (UKMEC) 2016 [Accessed 26 September 2025]. Available from: <https://www.fsrh.org/Public/Public/Standards-and-Guidance/uk-medical-eligibility-criteria-for-contraceptive-use-ukmec.aspx>
- [15] American College of Obstetricians and Gynecologists. Committee Opinion No. 602: Depot medroxyprogesterone acetate and bone effects. *Obstet Gynecol*. 2014;123(6):1398-1402.
- [16] Scholes D, LaCroix AZ, Ichikawa LE, et al. Change in bone mineral density among adolescent women using and discontinuing depot medroxyprogesterone acetate contraception. *Arch Pediatr Adolesc Med*. 2005;159(2):139-144.
- [17] Mack N, Crawford TJ, Guise JM, et al. Strategies to improve adherence and continuation of short-term hormonal methods of contraception. *Cochrane Database Syst Rev*. 2019;4(4):CD004317.
- [18] Ott MA, Sucato GS, Committee on Adolescence. Contraception for adolescents. *Pediatrics*. 2014;134(4):e1257-1281.
- [19] Edelman A, Micks E, Gallo MF, et al. Continuous or extended cycle vs. cyclic use of combined hormonal contraceptives for contraception. *Cochrane Database Syst Rev*. 2014;2014(7):CD004695.
- [20] Lim LM, Said WB, Latthe P. Effects of Combined Hormonal Contraceptives (CHC) on Bone Health in Adolescent Girls - a Systematic Review. *J Pediatr Adolesc Gynecol*. 2025.
- [21] Golden NH. Exogenous Hormones and Bone Health in Adolescent Girls. *J Pediatr Adolesc Gynecol*. 2025;38(4):445-446.
- [22] Caldeirao TD, Orsolini LR, da Silva CC, et al. Effect of two combinations of low-dose oral contraceptives on adolescent bone mass: A clinical trial with 2 years follow-up. *Medicine (Baltimore)*. 2022;101(37):e30680.
- [23] Goshtasebi A, Subotic Brajic T, Scholes D, et al. Adolescent use of combined hormonal contraception and peak bone mineral density accrual: A meta-analysis of international prospective controlled studies. *Clin Endocrinol (Oxf)*. 2019;90(4):517-524.
- [24] Tassi A, Londero AP, Xholli A, et al. Hormonal Contraception and Bone Metabolism: Emerging Evidence from a Systematic Review and Meta-Analysis of Studies on Post-Pubertal and Reproductive-Age Women. *Pharmaceuticals (Basel)*. 2025;18(1).

- [25] Coelingh Bennink HJ, Heegaard AM, Visser M, et al. Oral bioavailability and bone-sparing effects of estetrol in an osteoporosis model. *Climacteric*. 2008;11 Suppl 1:2-14.
- [26] Douxfils J, Foidart J-M. Critical Considerations in the Interpretation of Bone Turnover Marker Data in Hormonal Contraceptive Users. Comment on Tassi et al. Hormonal Contraception and Bone Metabolism: Emerging Evidence from a Systematic Review and Meta-Analysis of Studies on Post-Pubertal and Reproductive-Age Women. *Pharmaceuticals* 2025, 18, 61. *Pharmaceuticals*. 2025;18(9).
- [27] Lopez LM, Chen M, Mullins Long S, et al. Steroidal contraceptives and bone fractures in women: evidence from observational studies. *Cochrane Database Syst Rev*. 2015;2015(7):CD009849.
- [28] Scholes D, LaCroix AZ, Hubbard RA, et al. Oral contraceptive use and fracture risk around the menopausal transition. *Menopause*. 2016;23(2):166-174.
- [29] Ampatzis C, Zervoudis S, Iatrakis G, et al. Effect of Oral Contraceptives on Bone Mineral Density. *Acta Endocrinol (Buchar)*. 2022;18(3):355-360.
- [30] Faculty of Sexual & Reproductive Healthcare. Contraceptive choice for young people 2019 [Accessed 26 September 2025]. Available from: <https://www.fsrh.org/Common/Uploaded%20files/documents/fsrh-guideline-contraception-young-people-may-2019.pdf>
- [31] Di Meglio G, Crowther C, Simms J. Contraceptive care for Canadian youth. *Paediatr Child Health*. 2018;23(4):271-277.
- [32] Gersten J, Hsieh J, Weiss H, et al. Effect of Extended 30 mcg Ethinyl Estradiol with Continuous Low-Dose Ethinyl Estradiol and Cyclic 20 mcg Ethinyl Estradiol Oral Contraception on Adolescent Bone Density: A Randomized Trial. *J Pediatr Adolesc Gynecol*. 2016;29(6):635-642.
- [33] Maimoun L, Renard E, Lefebvre P, et al. Oral contraceptives partially protect from bone loss in young women with anorexia nervosa. *Fertil Steril*. 2019;111(5):1020-1029 e1022.
- [34] Creinin MD, Jensen JT, Chen MJ, et al. Combined Oral Contraceptive Adherence and Pregnancy Rates. *Obstet Gynecol*. 2023;141(5):989-994.
- [35] Stanczyk FZ, Winer SA, Foidart JM, et al. Comparison of estrogenic components used for hormonal contraception. *Contraception*. 2024;130:110310.
- [36] Christin-Maitre S, Serfaty D, Chabbert-Buffet N, et al. Comparison of a 24-day and a 21-day pill regimen for the novel combined oral contraceptive, norgestrel acetate and 17beta-estradiol (NOMAC/E2): a double-blind, randomized study. *Hum Reprod*. 2011;26(6):1338-1347.
- [37] Mansour D, Verhoeven C, Sommer W, et al. Efficacy and tolerability of a monophasic combined oral contraceptive containing norgestrel acetate and 17beta-estradiol in a 24/4 regimen, in comparison to an oral contraceptive containing ethinylestradiol and drospirenone in a 21/7 regimen. *Eur J Contracept Reprod Health Care*. 2011;16(6):430-443.
- [38] Chabbert-Buffet N, Jamin C, Lete I, et al. Missed pills: frequency, reasons, consequences and solutions. *Eur J Contracept Reprod Health Care*. 2017;22(3):165-169.
- [39] Rosenberg M, Waugh MS. Causes and consequences of oral contraceptive noncompliance. *Am J Obstet Gynecol*. 1999;180(2 Pt 2):276-279.
- [40] Balassone ML. Risk of contraceptive discontinuation among adolescents. *J Adolesc Health Care*. 1989;10(6):527-533.
- [41] Spona J, Elstein M, Feichtinger W, et al. Shorter pill-free interval in combined oral contraceptives decreases follicular development. *Contraception*. 1996;54(2):71-77.
- [42] Willis SA, Kuehl TJ, Spiekerman AM, et al. Greater inhibition of the pituitary-ovarian axis in oral contraceptive regimens with a shortened hormone-free interval. *Contraception*. 2006;74(2):100-103.
- [43] Post TM, Gerrits M, Kerbusch T, et al. Prediction of norgestrel acetate pharmacokinetics in healthy female adolescents and adults by whole-body physiology-based pharmacokinetic modelling and clinical validation. *Contraception*. 2016;93(2):133-138.
- [44] Didembourg M, Locquet M, Raskin L, et al. Lower reporting of venous thromboembolisms events with natural estrogen-based combined oral contraceptives compared to ethinylestradiol-containing pills: A disproportionality analysis of the Eudravigilance database. *Contraception*. 2025;142:110727.
- [45] Douxfils J, Raskin L, Didembourg M, et al. Are natural estrogens used in contraception at lower risk of venous thromboembolism than synthetic ones? A systematic literature review and meta-analysis. *Front Endocrinol (Lausanne)*. 2024;15:1428597.
- [46] European Medicines Agency. Drovelis: Summary of Product Characteristics. Available from: https://www.ema.europa.eu/en/documents/product-information/drovelis-epar-product-information_en.pdf
- [47] Li Z, Patton G, Sabet F, et al. Contraceptive Use in Adolescent Girls and Adult Women in Low- and Middle-Income Countries. *JAMA Netw Open*. 2020;3(2):e1921437.
- [48] Burchett HED, Kneale D, Griffin S, et al. Which Structural Interventions for Adolescent Contraceptive Use Have Been Evaluated in Low- and Middle-Income Countries? *Int J Environ Res Public Health*. 2022;19(18).

- [49] Ahinkorah BO, Seidu AA, Appiah F, et al. Individual and community-level factors associated with modern contraceptive use among adolescent girls and young women in Mali: a mixed effects multilevel analysis of the 2018 Mali demographic and health survey. *Contracept Reprod Med.* 2020;5:27.
- [50] Ross JA. Contraceptive Use, Access to Methods, and Program Efforts in Urban Areas. *Front Glob Womens Health.* 2021;2:636581.
- [51] Mpunga DM, Chenge FM, Mambu TN, et al. Determinants of the use of contraceptive methods by adolescents in the Democratic Republic of the Congo: results of a cross-sectional survey. *BMC Womens Health.* 2022;22(1):478.
- [52] Najafi-Sharjabad F, Zainiyah Syed Yahya S, Abdul Rahman H, et al. Barriers of modern contraceptive practices among Asian women: a mini literature review. *Glob J Health Sci.* 2013;5(5):181-192.
- [53] Zevallos-Roberts E, Cunningham K, Adhikari RP, et al. Beyond the mother-child dyad: Is co-residence with a grandmother associated with adolescent girls' family planning knowledge? *PLoS One.* 2022;17(3):e0265276.
- [54] Bell S, Wong S, Habito M, et al. Can youth-centred sexual and reproductive health self-care and contraceptive innovation address unintended pregnancy among girls and young women? Some reflections from Asia and the Pacific. *BMJ Glob Health.* 2024;9(12).
- [55] Alonso JP, Cejas C, Berrueta M, et al. Barriers to advancing the sexual and reproductive health agenda in Latin America: a qualitative study of key informants' perspectives. *Reprod Health.* 2024;21(1):187.
- [56] Pons JE. Contraceptive services for adolescents in Latin America: facts, problems and perspectives. *Eur J Contracept Reprod Health Care.* 1999;4(4):246-254.
- [57] Davila F, Cala-Vitery F, Gomez LT. Determinants of Access to Sexual and Reproductive Health for Adolescent Girls in Vulnerable Situations in Latin America. *Int J Environ Res Public Health.* 2025;22(2).
- [58] Dehlendorf C, Rodriguez MI, Levy K, et al. Disparities in family planning. *Am J Obstet Gynecol.* 2010;202(3):214-220.
- [59] Batek LM, Leblanc NM, Alio AP, et al. Facilitators and barriers to contraception access and use for Hispanic American adolescent women: An integrative literature review. *PLOS Glob Public Health.* 2024;4(7):e0003169.
- [60] Galloway CT, Duffy JL, Dixon RP, et al. Exploring African-American and Latino Teens' Perceptions of Contraception and Access to Reproductive Health Care Services. *J Adolesc Health.* 2017;60(3S):S57-S62.
- [61] Rights CfR. Millions of European Women Struggle to Access Contraception 2012 [Accessed 27 September 2025]. Available from: <https://reproductiverights.org/millions-of-european-women-struggle-to-access-contraception/>
- [62] Morris JL, Rushwan H. Adolescent sexual and reproductive health: The global challenges. *Int J Gynaecol Obstet.* 2015;131 Suppl 1:S40-42.
- [63] Chandra-Mouli V, Akwara E. Improving access to and use of contraception by adolescents: What progress has been made, what lessons have been learnt, and what are the implications for action? *Best Pract Res Clin Obstet Gynaecol.* 2020;66:107-118.
- [64] Harlow SD, Gass M, Hall JE, et al. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. *J Clin Endocrinol Metab.* 2012;97(4):1159-1168.
- [65] Keith Edmonds D. Dewhurst's Textbook of Obstetrics & Gynaecology: Blackwell Publishing; 2007 [Accessed 26 September 2025]; 7th:[Available from: <https://download.e-bookshelf.de/download/0000/5790/96/L-G-0000579096-0002359643.pdf>
- [66] Soules MR, Sherman S, Parrott E, et al. Executive summary: Stages of Reproductive Aging Workshop (STRAW). *Fertil Steril.* 2001;76(5):874-878.
- [67] Bacon JL. The Menopausal Transition. *Obstet Gynecol Clin North Am.* 2017;44(2):285-296.
- [68] Shaaban MM. The perimenopause and contraception. *Maturitas.* 1996;23(2):181-192.
- [69] Joo JK, Shin JH, Lee JR, et al. Levonorgestrel-Releasing Intrauterine System Use in Perimenopausal Women. *J Menopausal Med.* 2021;27(2):49-57.
- [70] Chandra A. Infertility and impaired fecundity in the United States, 1982-2010: data from the National Survey of Family Growth. *Natl Health Stat Report.* 2013;14(67):1-18.
- [71] Finer LB, Zolna MR. Unintended pregnancy in the United States: incidence and disparities, 2006. *Contraception.* 2011;84(5):478-485.
- [72] Grandi G, Di Vinci P, Sgandurra A, et al. Contraception During Perimenopause: Practical Guidance. *Int J Womens Health.* 2022;14:913-929.
- [73] Blumel JE, Castelo-Branco C, Binfa L, et al. A scheme of combined oral contraceptives for women more than 40 years old. *Menopause.* 2001;8(4):286-289.

[74] European Society of Human Reproduction and Embryology. Premature Ovarian Insufficiency (POI). Healthcare professional toolkit based on the ESHRE Guideline on Premature Ovarian Insufficiency 2024 [Accessed 16 September 2025]. Available from: <https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Premature-ovarian-insufficiency>

[75] Sordal T, Grob P, Verhoeven C. Effects on bone mineral density of a monophasic combined oral contraceptive containing nomegestrol acetate/17beta-estradiol in comparison to levonorgestrel/ethinylestradiol. *Acta Obstet Gynecol Scand.* 2012;91(11):1279-1285.

[76] Grandi G, Imbrogno MG, Cainazzo MM, et al. Easy tools to screen Italian women suffering from migraine with and without aura in early reproductive age. *Eur J Obstet Gynecol Reprod Biol.* 2019;242:63-67.

[77] Sacco S, Merki-Feld GS, KL AE, et al. Effect of exogenous estrogens and progestogens on the course of migraine during reproductive age: a consensus statement by the European Headache Federation (EHF) and the European Society of Contraception and Reproductive Health (ESCRH). *J Headache Pain.* 2018;19(1):76.

[78] Uddenberg ER, Safwan N, Saadedine M, et al. Menopause transition and cardiovascular disease risk. *Maturitas.* 2024;185:107974.

[79] Vohra RLL. Should menopause management differ between ethnic groups? 2022 [Accessed 27 September 2025]. Available from: <https://pharmaceutical-journal.com/article/research/should-menopause-management-differ-between-ethnic-groups>

[80] Panay N, Palacios S, Davison S, et al. Women's perception of the menopause transition: a multinational, prospective, community-based survey. *GREM.* 2021;2-3.

[81] Jones EK, Jurgenson JR, Katzenellenbogen JM, et al. Menopause and the influence of culture: another gap for Indigenous Australian women? *BMC Womens Health.* 2012;12:43.

[82] Kaunitz AM, Burkman, R. T. Transitional Management: The Use of Oral Contraceptives in Perimenopause 2011. Available from: <https://www.contemporaryobgyn.net/view/transitional-management-use-oral-contraceptives-perimenopause>

[83] Im EO, Seung Hee L, Chee W. Subethnic differences in the menopausal symptom experience of Asian American midlife women. *J Transcult Nurs.* 2010;21(2):123-133.

[84] Melby MK, Sievert LL, Anderson D, et al. Overview of methods used in cross-cultural comparisons of menopausal symptoms and their determinants: Guidelines for Strengthening the Reporting of Menopause and Aging (STROMA) studies. *Maturitas.* 2011;70(2):99-109.