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MENOPAUSE

Management of perimenopause disorders: hormonal treatment

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ABSTRACT

Perimenopause represents a transition period of a woman's life during which physiological, affective, psychological, and social changes mark progression from a woman's fertile life to menopause, with wide sexual hormones fluctuations until the onset of hypergonadotropic hypogonadic amenorrhea. Contraception during menopause should not only avoid unwanted pregnancies, but also improve quality of life and prevent wide range of condition affecting this population. Hormonal contraceptives confer many noncontraceptive benefits for women approaching menopause: treatment of abnormal uterine bleeding, relief from vasomotor symptoms, endometrial protection in women using estrogen therapy, musculoskeletal protection, and mood disorders protection. The main point remains selecting the most adequate contraceptive option for each woman, considering her risk factor, comorbidities, and keeping in mind the possibility of continuing contraception until reaching menopause and even further, creating a bridge between perimenopause and menopause hormonal therapy. Correct perimenopause management should rely on individualized medical therapy and multidisciplinary approach considering lifestyle and food habits as part of general good health of a woman.

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Introduction

Perimenopause represents a delicate transition period of a woman's life during which physiological, affective, psychological, and social changes mark progression from a woman's fertile life to climaterium, with wide sexual hormones fluctuations until the onset of hypergonadotropic hypogonadic amenorrhea [1]. This phase begins with the onset of menstrual irregularities and ends after one year of amenorrhea, defining the final menstrual period (FMP). Three stages of perimenopause have been described: the early transition is defined by almost regular cycles and only occasionally skipped cycles; the late menopausal transition is characterized by greater menstrual irregularity, with periods of amenorrhea lasting over 60 days until reaching FMP; and the early postmenopause [2]. These changes have been well documented and related to specific hormonal event and consequent different clinical signs [3].

Although neuroendocrine changes in the menopausal transition are various and complex, the central biological event of this period is gradual ovarian failure, both in the number of follicles and in the quality of oocytes. The serum levels of follicle-stimulating hormone (FSH), estrogen and progesterone fluctuate around menopause; increases in both FSH and LH levels occur in response to diminished negative feedback on the FSH/LH release due to loss of inhibin B and progesterone. An increase in FSH levels not only stimulates accelerated ovarian folliculogenesis until the onset of menopause, but also increases the risk of multiple pregnancies. The increased folliculogenesis causes a greater production of estrogens, which may contribute to irregular bleeding and symptoms such as bloating and breast tenderness [4]. Each woman experiments menopause differently, so that frequency, intensity and duration of symptoms varies widely from one to another.

Perimenopause-related symptoms include a variety of gynecological conditions and many women complain hot flushes, menstrual irregularities and many other symptoms described after-menopause (such as poor sleep, irritability, premenstrual syndrome (PMS), mood changes, skin changes, musculoskeletal disorders, balance disorders, vaginal dryness, and bladder symptoms). Although perimenopause affects most of the women, it has been estimated that quality of life is significantly affected only in 20% of them [5]. Hot flash is experienced by most women, and is moderately problematic for about 1/3 of women. While most women will have an experience of hot flashes limited to just a year or two, others will experience them for a decade or more, and a small proportion of women will never be free of them [6]. Poor sleep becomes more common during perimenopause not only in association with the menopausal transition but also in relation to aging.

Depressed mood and anxiety also increase during this period, with an abrupt rise in prevalence when women approach the later stages of the menopausal transition and have longer periods of amenorrhea. These common symptoms often interact with one another enhancing themselves such that depressed women tend to experience worse hot flashes and worse sleep [6]. During the latest stage of the transition, about 1/3 of the population will experiment vaginal dryness and dyspareunia and those vaginal symptoms will not go away without treatment [6].

Recently, the importance of ovarian function cessation in depression and cardiovascular disease (CVD) risk was assessed, and it seems to exist a bi-directional relationship between these two conditions and menstrual cycle alteration [4]. Although various neuroendocrine mechanisms are involved in this process, the link that unites these conditions seems to be the ovarian dysfunction. From this perspective, women in the menopausal

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transition period experience greater mood changes, even more than during the subsequent period, when, on the other hand, the cardiovascular risk increases [7].

Fertility and perimenopause

Perimenopause is characterized by profound hormonal and reproductive changings that are related to low fecundity rate, because of anovulatory cycles as well as reduced quality of eggs. Likelihood of pregnancy declines with age and women over 40 have lower fecundity rate compared with their younger cohort [8]. A study conducted on family growth in the US in 2013 observed that nulliparous women between 40 and 44 years were 2.5 times more likely to experience impaired fecundity versus women aged 24–29 years [9].

In a study on women undergoing insemination with donor sperm, fecundity rate was 0.2 for women less than 35 years of age versus 0.06 for women over the age of 40 [10]. Anyway, although fertility rate is reduced, pregnancy is not uncommon in older reproductive age women: the pregnancy rate has been estimated approximately 26 births per 1000 women aged 40 and older and about a third of them are unintended [11]. Compared to younger women, pregnancies in older reproductive women are associated with an increased risk of adverse events. The risk of spontaneous abortion and chromosomal abnormalities increases markedly after the age of 40 [12], with spontaneous abortion rate of 34% in women from 40 to 44 age and a rate of 53% in women aged 45 and older [13]. In addition, a significant proportion (approximately one-third) of these pregnancies is likely to be medically or surgically terminated compared to one-fifth in younger women [14].

Advanced maternal age is also linked to an increased risk of developing gestational diabetes, hypertensive disorders of pregnancy, intrauterine growth restriction, placenta pathologies, preterm delivery, and increasing of cesarean delivery [15]. It seems clear that the higher incidences of maternal and perinatal mortality and morbidity (including that associated with preterm delivery and low birth weight) are consequences of advanced maternal age and this is why it is important to perform counseling with women about age-related pregnancy risks [16].

Guidelines for contraceptive use

In 2010, the 'Centers for Disease Control and Prevention' (CDC) published the first document that provides practical recommendation, evidence-based, for a safe and effective use of different contraceptive options [17]. This document, updated in 2016, weighs risks and benefits associated with the use of the various contraceptive method considering medical comorbidities and patient characteristic [18]. There is no single contraceptive choice contraindicated based on age alone, because there is no evidence to suggest that age itself is a risk factor for contraceptive-related complications [18]. However, aging is associated with increased risk of developing medical conditions, including obesity, hypertension, diabetes, and cancer. In particular, the incidence of cardiovascular complications increases with age and therefore age should be considered when assessing the safety of combined hormonal contraceptive (CHCs) methods in patients who have other preexisting cardiovascular risk factors. The use of CHCs in patients aged 35 or older is contraindicated if they are heavy smokers (15 or more cigarettes/die) and cautioned against if they are light smokers (less than 15 cigarettes/die). Furthermore, CHCs are contraindicated or recommended with caution in older women with multiple cardiovascular risks factors, including hypertension (controlled and otherwise) and diabetes [18].

Contraception during perimenopause

Extending the use of CHCs in healthy, nonsmoker women until the age of 50 significantly improved contraception choice in perimenopause. CHCs are available as a daily pill, weekly transdermal patch, and monthly vaginal ring. Combined oral contraceptive (COC) containing 30/35 mcg estrogen ethinylestradiol supply a useless higher dose for this group of women than those containing lower dose (20 mcg) which could reduce the risk of estrogen-mediated side effects and risk of venous thromboembolism (VTE) without reducing contraceptive efficacy. On the other hand, irregular bleeding appears to be more likely with COCs with lower dose of ethinylestradiol and this can decrease compliance [19]. Based on recent data, women that switch to menopausal replacement therapy from CHCs use can be encouraged from recent data that shows no significant higher risk of breast cancer after previous use of CHCs [20]. CHCs with 17 β-estradiol appear to have less metabolic impact on procoagulant factors than CHCs with ethinylestradiol. The shorter half-life of estradiol reduces first-pass hepatic effects on coagulation. Estradiol pills may be particularly suitable for women over 40 years, bridging the gap between contraception and hormone therapy. This would provide an excellent solution for women who currently have to stop COCs at 50 years [14]. Third- and fourth-generation COCs vary according to their progestogen component and may provide additional health benefits for women. COCs with progestins such as drospirenone, cyproterone acetate, and dienogest are authorized in many countries for their anti-androgenic action and consequent non-contraceptive benefits: they have a positive therapeutic impact on acne, premenstrual dysphoric disorder, and heavy menstrual bleeding; this is especially important for women over 40 who commonly experience these problems.

To avoid cycle-related symptoms, COCs can be taken as continuous regimen. Reduction or avoidance of the hormone-free interval increases contraceptive efficacy by maximizing endogenous cycle suppression. Tolerability is further enhanced through reduction of hormone withdrawal symptoms and reduction of dysmenorrhea and menorrhagia. Further combinations, involving the addition of androgens to combined pill preparations to enhance sexuality, should be particularly targeted to the perimenopausal age group who are at greatest risk of low sexual desire [14].

The position statement approved by the International Menopause Society in 2019 states that testosterone therapy, in doses that approximate physiological testosterone concentrations for premenopausal women, exerts a beneficial effect on sexual function including increases of an average of one satisfying sexual event per month, and increases in sexual desire, arousal, orgasmic function, pleasure, and sexual responsiveness, together with a reduction in sexual concerns including sexual distress (level I, grade A) [21]. As the majority of studies reporting on sexual function recruited women assessed as having hypoactive sexual desire disorder/dysfunction (HSDD) or generalized female sexual disorder (FSD), these recommendations cannot be generalized to other subtypes of FSD or women without sexual dysfunction [21].

The progestogen-only pill (POP) can be easily suggested to women in their forties and older to minimize VTE risk. The drawback with the low-dose POP is that its mechanism of action

relies on very careful administration with only a 3-h window each day. The higher-dose desogestrel POP has two main advantages compared to low-dose POPs: reliable ovulation inhibition in over 99% of cycles and a 12 h intake window. Although ovulation is suppressed, endogenous estradiol levels are maintained within the physiological range. However, the main drawback with any POP is the high incidence of breakthrough bleeding which is particularly problematic in the perimenopause. There is no proven benefit of POPs for cycle-related symptoms and they may induce continuous PMS, typical of progestogenic side effects [14].

The levonorgestrel intrauterine system (IUS) is an excellent choice for women requiring contraception around forties. It provide not only a reliable contraceptive cover, but it grants benefits also on metrorrhagia and can be used as the progestogen component of hormone therapy. However, there can be initial irregular bleeding and systemic PMS-type side-effects.

The recent development of a smaller and lower releasing levonorgestrel system (14 µg rather than 20 µg) is a significant option for the perimenopausal woman. It is easy to fit, with no discomfort, and reduces the risk of systemic progestogenic side effects. However, it is not as effective at producing amenorrhea and is not licensed for use as the progestogen component of hormone therapy [22].

Depot progestogens are not currently recommended for women over fifties because of concern that the prolonged hypoestrogenic state will increase the risk of osteoporosis. However, the development of preparations with 'add back' estrogen will enhance prospects for using these preparations as both contraception and hormone therapy in perimenopausal women [14].

Implantable etonogestrel progestogen rods provide excellent contraception but, like POPs, have the drawback of inducing irregular bleeding patterns in more than 50% of users. Perimenopausal fluctuation of hormone levels makes it more likely that these women will have bleeding problems with this method. The advantage is that estradiol levels are not suppressed despite ovulation being inhibited and therefore do not expose the user to additional risk of osteoporosis [14] (Table 1).

Potential health risks with hormonal contraception in perimenopause

The impact of CHCs on cancer risk is of clinical importance for older women. For CHCs, user has been found a 12% reduction in risk of any cancer and a 29% risk reduction of gynecologic cancers [23]. CHCs use reduce risk for endometrial and ovarian cancer and this benefit persists 15 years after discontinuation. The risk for endometrial cancer is significantly decreased by 56%

Table 1. Hormone therapy during perimenopause.

Treatments	Drugs	Doses	Regimes	Side effects and risks
Oral combined contraceptives	Ethinyl estradiol (or 17 β-estradiol or estradiol valerate)+norethindrone or levonorgestrel or drospirenone or cyproterone acetate or dienogest	0.02 mg ethinyl estradiol or 1–2 mg 17 β-estradiol or 0.5–2 mg estradiol valerate + norethindrone 0.5–1 mg or 0.1 mg levonorgestrel or 3 mg drospirenone or 2 mg cyproterone acetate or 2 mg dienogest	Daily ingestion of pill; most regimens still 21/7 though more with 24/4 and 26/2 and some continuous use regimens	Irregular bleeding; venous thromboembolism
Oral progestin	MPA Micronized progesterone Desogestrel	5 and 10 mg/d 100 or 200 mg/d 75 mcg/d	Daily ingestion of pill	Breakthrough bleeding; PMS
Intrauterine system (LNG-IUS)	Levonorgestrel	13.5 or 19.5 mg/d	Inserted at time when pregnancy is not likely (e.g. menses). Left *in situ* for prescribed period of effectiveness. Removed and replaced if further contraception is desired	Initial irregular bleeding; PMS
Transdermal patch	17b-estradiol 17b-estradiol + norethindrone 17b-estradiol + levonorgestrel	0.025, 0.0375, 0.05, 0.075, and 0.1 mg/d 0.05 mg estradiol + 0.14 or 0.25 mg norethindrone 0.045 mg estradiol + 0.015 mg levonorgestrel	Transdermal patch placement applied weekly or twice weekly, depending on the brand. Patch is then removed and replaced with new patch. Repeated for 3 weeks and then followed by a patch-free week before re-initiation	Venous thromboembolism
Vaginal ring	Estradiol hemihydrate Etonogestrel + ethinyl estradiol	7.5 mcg/d 0.120 mg etonogestrel + 0.015 ethinyl estradiol	Vaginal placement of ring and left *in situ* for 3 weeks; removed for 1 week ring-free interval before replacing new ring. For estradiol only vaginal ring insert 1 ring every 90 d	Venous thromboembolism
Injectables	Etonogestrel implant Depo MPA[a]	68 mg 150 mg	Intramuscular or subcutaneous initiation for prescribed time period. Reinjection at end of time period if continued contraception is desired	Irregular bleeding; bone mineral density reduction

MPA: medroxyprogesterone acetate; LNG-IUS: levonorgestrel intrauterine system; PSM: premenstrual syndrome.
aAdd-back estrogen preparations will improve the prospects of using these preparations both as contraception and as hormone therapy in perimenopausal women.

after only 4 years of use and by 72% after 12 years of use [24, 25]. CHCs may also offer a modest colorectal cancer protection: it has been estimated 18% risk reduction for colorectal cancer among CHCs users versus nonusers [26]. A case-control study funded by the National Institutes of Health and conducted by the CDC found no statistically increased risk of breast cancer in CHC users (RR of 0.9 and 0.9, respectively (95% CI 0.8–1.0 and 0.8–1.0, respectively)) regardless of estrogen dose, duration of use, or CHCs formulation [27]. In a recently published prospective cohort of 1.8 million Danish women from 15 to 49 years, it has been estimated that current and recent users of any hormonal contraception (with the vast majority utilizing CHCs) had an RR of 1.20 (95% CI 1.14–1.26, $P < 0.002$) for breast cancer compared with never-users [28].

In a recent meta-analysis exploring oral contraceptive use among BRCA1/2 carriers, breast cancer risk was not significantly increased by CHCs use with formulations containing 35 mcg or less EE [29]. Furthermore in both BRCA1 and BRCA2 carriers, use of COCs is associated with protection against ovarian cancer (RR of 0.51 and 0.50, respectively (95% CI 0.40–0.65 and 0.29–0.89, respectively)) and for these reasons carriers of BRCA1/2 with no personal history of breast cancer may reasonably use CHCs for contraception [30].

A systemic review [31] found an elevated risk of invasive cervical cancer with long-term oral contraceptive use (RR 1.6, 95% CI 1.4–1.7) and DMPA (RR 1.2, 95% CI 1.0–1.6) after 5 years of use. A later Lancet reanalysis of 24 similar studies reaffirmed this finding. The risk dissipated with time since last use [32].

VTE represents one of the major risk with CHC use among women of every age. Among women of reproductive age, the risk is doubled in CHCs users versus nonusers (8–10 per 10,000 woman-years in CHCs users versus 4–5 per 10,000 woman-years in nonusers) [8]. The greatest risk occurs within the first 3 months of initiation (OR 12, 95% CI 7.1–22.4) and it is dose-related, with higher incidence with CHCs formulated with 50 or more mcg of EE [33]. Risk of VTE increases significantly with age and CHCs users aged between 45 and 49 years have a VTE risk of 20.8 per 10,000 woman years [33]. Pills containing 30–35 μg estrogen ethinylestradiol combined with gestodene, desogestrel, drospirenone, and cyproterone acetate seem to confer a higher VTE risk than those containing levonorgestrel [34]. Furthermore, there may be an increased risk of VTE in patch users and vaginal ring users versus those using comparable COC formulations. However, limited evidence (good to limited quality) has demonstrated conflicting results on whether women using these methods have a higher risk of VTE than women using COCs. CHCs is generally contraindicated women who are obese, immobile, or have a personal or family history of VTE [8]. The risk of myocardial infarction and stroke also rises with age (annual incidence of ischemic stroke of 2.4 per 10,000 for women aged 45 and 54 years) and there is a greater incidence of thrombotic stroke and heart attack among CHCs users than non-users (RR about 1.5e2.2), varying with estrogen ethinylestradiol dose and progestogen. Moreover, smoke and hypertension are independent risk factors for cardiovascular event [33].

Noncontraceptive benefits of hormonal therapy during perimenopause

Hormonal contraceptives also confer many noncontraceptive benefits especially for women approaching menopause: treatment of abnormal uterine bleeding (AUB), relief from vasomotor symptoms, endometrial protection in women using estrogen therapy, musculoskeletal protection.

Treatment of abnormal uterine bleeding

Over 90% of women will experience AUB in the 4–8 years until the final menstrual bleed [35]. AUB may include menstrual cycle irregularity (increased or decreased frequency) or heavy menstrual bleeding and several hormonal contraceptive methods are effective in their overall reduction. CHCs formulations may be used cyclically or continuously and this last use is associated with higher rates of amenorrhea and reduction of vasomotor symptomatology. CHCs with EE doses higher than 20 mcg provide a more reliable bleeding pattern with less breakthrough bleeding [36]. Also POP use could reduce AUB and can be suggested in perimenopause, although unscheduled bleeding may occur [8]. In 2009, the US Food and Drug Administration (FDA) approved the 52-mg levonorgestrel-IUS (LNG-IUS) for treatment of AUB. The high concentration of progestin causes decidualization of the endometrium, resulting in a reduction of the amount (from 79% to 97%) and the duration of menstrual bleeding [8, 37]. In a randomized controlled trial of 571 women with AUB assigned to either LNG-IUS or other medical treatments (e.g. tranexamic acid, mefenamic acid, CHCs, and POP), the LNG-IUS outperformed the others on menorrhagia treatment, quality of life improvement, and compliance [38]. The LNG-IUS is also as effective in treating AUB as endometrial ablation, providing patients with an alternative to surgery [39]. Further application on LNG-IUS is for patients with heavy menstrual bleeding related to uterine leiomyoma or adenomyoma. Depending on the number, size, and location of fibroids, the LNG-IUS can help with reduction of menstrual bleeding. However, leiomyoma size remains relatively unchanged and there may be incrementally increased risk of IUS expulsion [40].

Relief from vasomotor symptoms

Approximately, 75% of women will experience vasomotor disturbances during the menopausal transition [41]. CHCs can provide vasomotor symptom relief – especially for severe symptoms – in addition to effective contraception. About 40% of CHCs users versus 90% of nonusers reported vasomotor symptoms [42]. Continuous use regimens of CHCs are more likely to prevent the recurrence of hot flushes and night sweats [43].

Endometrial protection during hormone therapy

The 52-mg LNG-IUS is approved for endometrial protection for peri/postmenopausal women receiving estrogen hormonal therapy [44]. The concentrated progestin action of LNG-IUS, in combination with estrogen therapy, in the symptomatic perimenopausal women is highly practical as it combines the benefits of prevention of endometrial proliferation and treatment of menorrhagia and hyperplasia, if present [45, 46]. This endometrial protection has been established for up to 5 years of LNG-IUS use [47]. Placement of LNG-IUS during the menopausal transition provides midlife patients effective contraception and provides endometrial protection for patients who transition to menopausal estrogen therapy. There are no data assessing the efficacy of the 13.5 and 19.5 mg LNG-IUS for endometrial protection [8].

Protection on bone tissue

Gradual ovarian failure during perimenopause has a great impact on woman's bone health. Bone mineral density (BMD) loss speeds up 1–2 years before menopause, together with longer amenorrhea periods typical of late stage of transition. The period that runs between one year before and two years after the occurrence of menopause is the most critical for women bone tissue health [48]. Low-dose CHCs (20 and 35 mcg of estrogen) among perimenopausal women who have become hypo-estrogenic, protects against loss of BMD. For these women, BMD increases with the use of CHCs compared with control groups taking calcium only [49]. Insufficient data are available to confirm whether this would result in a reduction in future post-menopausal osteoporotic fractures. A Cochrane review looking at all women rather than just hypoestrogenic perimenopausal women found no difference in BMD between CHCs users and non-users, not reporting increased fracture risk for CHCs users [50]. DMPA users may have an increased fracture risk, unlike IUD use may be associated with decreased risk [50].

Hormonal fluctuation during perimenopause could lead to headache, often complained by perimenopausal women. Hormonal therapy could prevent headache during transition: insufficient data are available to defy which kind or regimen is the most effective. Patch use may show better efficacy profile on headache, unlike oral formulation, because of the insurance of more constant estrogen level [51]. Perimenopausal women also shows increased risk for mood swings: the causes of this association are not completely clear, but a main role seems to be played by hormonal fluctuation and complex relations between steroids, neurotransmitters, and their receptors. CHCs use seems to add benefit on those disturbances, improving vasomotor symptoms and anxiety related symptoms [52]. Furthermore, perimenopause represents a period of vulnerability for the development or relapse of the eating disorder: in fact, these disorders seem to have an endocrine basis, probably due to hormonal changes that occur during the transition phase. Further studies are needed to better understand the relationship between the development of eating disorder and hormonal fluctuation, also in view of a potential CHC therapy [53].

When to stop contraception in perimenopause patient?

The main scientific society, like the Centers for Disease Control and Prevention, American College of Obstetricians and Gynecologists, and The North American Menopause Society give information about when to stop contraception in perimenopause patient and recommend use of contraception until menopause is reached [18]. Non-hormonal methods, like copper IUS, can easily be used until menopause is reached, defining menopause after one year of amenorrhea [54]. With the use of progestin-only methods, or CHCs in continuous, amenorrhea is a common occurrence; accordingly, the absence of unscheduled bleeding may not accurately signal the onset of menopause. Patients may continue their use until they are 50–55 if they have no contraindications and it is on clinicians to reassess the actual safety of contraceptive options if a woman's risk factor changes and suggest other option whether needed [18]. When menopause is presumptively established, women can choose to discontinue hormonal contraception and initiate menopausal hormonal therapy. For some patients, stopping their hormonal contraceptive method for a period of 1 or 2 months to allow the resumption of menses may be a reasonable test of menopausal status if an acceptable nonhormone contraceptive option is available and used consistently [55]. Contraception may not be necessary in patients of menopausal age who have FSH levels greater than or equal to 30 IU/L on two occasions 6–8 weeks apart over the age of 50 [55]. However, in perimenopausal women, FSH levels can vary at any given moment and should not be relied upon to diagnose the transition to menopause. The FSH levels may be slightly elevated in LNG-IUS users, while etonogestrel implants have little impact on FSH levels, even at 3 years of use [8]. FSH levels are not substantially suppressed by DMPA use [56]. However, FSH levels are significantly suppressed in CHCs and POP users, and FSH testing to determine if menopause is present in those patients should occur 14 days after last use of a CHC. DMPA users may test on the first day of injection, with menopause confirmed if FSH levels are consistently greater than 30 IU/L at intervals of at least 90 days [57].

Discussion

Perimenopause transition represents a very important and delicate phase of a woman's life, it is characterized not only by sudden hormonal changes but also social, psychological, and physical changes. Contraception during menopause should not only avoid unwanted pregnancies but also improve quality of life and prevent wide range of condition affecting this population. The main point remain selecting the most adequate contraceptive option for each woman, considering her risk factor, comorbidities and keeping in mind the possibility of continuing contraception until menopause is reached and even further, creating a bridge between perimenopause and menopause hormonal therapy. The correct management of perimenopause must be based on personalized medical therapy, which takes into account also the extraconceptive benefits and tumor prevention of the hormonal therapy. A multidisciplinary approach that considers lifestyle and food habits as an integral part of woman's overall good health must be achieved.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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