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REVIEW

Counseling in menopausal women: How to address the benefits and risks of menopause hormone therapy. A FIGO position paper

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Menopause marks the end of menstrual cyclicity and, depending on individual vulnerability, has several consequences related to gonadal steroid deprivation, especially if it is premature. Menopause may be more burdensome for some women than for others. Individual factors, such as personal history, socioeconomic status, ethnicity, and current health conditions, affect symptomatology and, thereby, the menopausal experience. In addition, some menopausal symptoms, such as severe hot flashes, sleep disorders, and depression, are markers of future health risks. Counseling is a fundamental part of health care in the peri- and postmenopause periods. It must include an assessment of the patient's symptoms, needs, desires, and risk profile to address the benefits and risks of menopausal hormone therapy (MHT) on an individual basis and promote a healthy lifestyle. Indeed, healthcare practitioners can and must protect the health and lives of mid-life women by increasing awareness of menopausal symptoms and ensuring healthcare options, especially MHT. The type and duration of MHT should be tailored based on the patient's history, menopausal age, physical characteristics, and current health status so that the benefits always outweigh the risks. This FIGO position paper focuses on the benefits and risks of MHT on health domains, target organs, and systems, and on systemic and vaginal MHT regimens, to provide indications that can be used in the clinical practice for menopausal counseling. Moreover, it offers insights into what FIGO considers the mainstay for the healthcare management of women in peri- and postmenopause, worldwide.

Keywords: bioidentical hormones, counseling, hormone therapy, menopausal hormone therapy benefits, menopausal hormone therapy regimens, menopausal hormone therapy risks, menopausal symptoms, menopause

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Background

Menopause represents an opportunity for healthcare practitioners to comprehensively audit a woman's physical and psychological condition and to ensure due attention is given to any symptoms or risks she may present that could harm her future health.

With the increase in longevity and extensive research in recent decades, there has been a greater understanding of the impact and health implications that menopause has on women's lives.

Menopause marks the end of menstrual cyclicity and entails several consequences related to gonadal steroid deprivation. In most women, symptoms of menopause substantially affect their quality of life and arise at a time when they still occupy an essential role in the family and society. Early symptoms, such as hot flashes and sweats, mood swings, disturbed sleep, migraine, and poorer cognitive performance, are disruptive and may occur as early as a few years before the final menstrual period (FMP).[1]

Late-onset manifestations, such as central body fat distribution, metabolic and cardiovascular consequences, urogenital atrophy and sexual dysfunction, osteoporosis, and an increased risk of disabling fractures, are frequently insidious.[1] Moreover, menopause accelerates biological aging, especially if severely symptomatic.[2,3]

Natural menopause, secondary to the physiological depletion of ovarian reserve, involves a transition from the reproductive to the post-reproductive phase, termed perimenopause, that may occur over several years.[4] Perimenopause encompasses three stages: early menopausal transition, characterized by persistent cycle irregularity; late menopausal transition, characterized by an interval of amenorrhea of 60 days or more in the prior 12 months; and early postmenopause, the first year after the FMP (Box 1).[4]

Surgical menopause, due to surgical removal of the ovaries, or chemotherapy-/radiotherapy-induced ovarian failure produce

much more abrupt changes.[1] These conditions raise the risk of premature death, cardiovascular disease (CVD), dementia, parkinsonism, and Parkinson's disease significantly more than natural menopause.[5–8]

Worldwide, most women experience their FMP between the ages of 45 and 55 years.[9] Late-onset menopause, occurring after the age of 55 years, bears some health risks, such as an increase in estrogen-sensitive tumors such as breast cancer, as well as benefits, mainly a reduced cognitive decline and risk of CVD,[10–12] due to the more prolonged lifetime exposure to ovarian hormones.[11,12] On the other hand, premature ovarian insufficiency occurs before the age of 40 years, implies a short lifetime exposure to ovarian hormones, and has the worst impact in terms of morbidity and mortality, with a significant increase in cognitive deterioration, cardiovascular events, and osteoporosis-related fractures.[11–13]

Menopause may be more burdensome for some women than for others. In addition, individual factors, such as personal history, socioeconomic status, ethnicity, and current health conditions, especially obesity, affect the menopausal experience.[1]

Vasomotor symptoms, the most disrupting manifestations affecting nearly 75% of women, may last an average of 7.4 years.[14,15] The prevalence of vasomotor symptoms is still significant in older women. Indeed, 39% of women aged 65–69 years, 31% 70–74 years, and 24% aged 75–79 years still report hot flashes.[16] Moreover, vasomotor symptoms, especially nocturnal symptoms, may cluster with other disturbances, such as sleep disruption, fatigue, depression, memory loss, and poor concentration.[17–19]

Women transitioning through menopause often experience problems with memory, concentration, and learning,[20] recently termed brain fog,[21] which causes considerable distress. Small but significant declines in processing speed and verbal memory occur over the long-term in postmenopausal women.[22–24] However, most difficulties are limited to perimenopause.[20] Surgical menopause has more severe consequences on cognitive functions than natural menopause[6] and increases the risk of full-blown dementia, mainly if it occurs before the age of 45 years.[25]

Mood disorders, depression, and anxiety may relapse or worsen during perimenopause, especially in vulnerable women.[26–28] In addition, migraine frequency may also increase in susceptible women.[29] Aging-related weight gain combined with the menopause-related central distribution of fat leads to increased visceral fat, responsible for inducing the metabolic syndrome.[30–32] This phenomenon is accelerated in women who have had surgical menopause.[5]

In addition, the loss of anti-atherogenic and vasodilatory effects of estrogen on the endothelium increases hypertension and atherosclerosis after menopause.[33–35] Together, these factors increase the risk of cardiovascular and cerebrovascular events, such as myocardial infarction and stroke, especially in women with premature ovarian insufficiency.[36]

Box 1: Stages of menopause according to Stages of Reproductive Aging Workshop (STRAW) criteria164

***Menopausal transition*:**
- *Early* menopausal transition (*Stage –2*) lasts a variable number of years and is characterized by a persistent ≥7- day difference in length of consecutive cycles
- *Late* menopausal transition (*Stage –1*) is estimated to last on average 1–3 years before the FMP and is character- ized by an interval of amenorrhea of ≥60 days

***Perimenopause* means the time around the menopause and includes:**
- Early menopausal transition (*Stage –2*)
- Late menopausal transition (*Stage –1*)
- The first year after the FMP (early postmenopause *Stage +1a*)

Postmenopause:
- *Early* postmenopause lasts approximately 5–8 years and includes the following stages:
  - *Stage +1a* lasts 1 year. It marks the end of the 12- month period of amenorrhea required to define that the FMP has occurred and corresponds to the end of the "perimenopause"
  - *Stage +1b* lasts 1 year. It includes the remainder of the
  - period of rapid changes in mean FSH and estradiol levels
  - *Stage +1c* is estimated to last 3–6 years. It represents the period of stabilization of high FSH levels and low estradiol values
- Late postmenopause (Stage +2) includes the remain- ing lifespan. It represents the period in which further changes in the reproductive endocrine function are more limited and processes of somatic aging become of paramount concern.

Abbreviations: FMP, final menstrual period; FSH, follicle- stimulating hormone.

In its early stages, menopause is commonly associated with decreased sexual libido[37] and, later on, vulvovaginal atrophy and dyspareunia, which can lead to sexual dysfunction[38,39] and interfere with social and psychological well-being. Genitourinary syndromes will also include dysuria and recurrent urinary tract infections.[38] Urinary incontinence is probably related to weight gain and an increase in waist-to-hip ratio during this period of life.[40]

Menopause is directly responsible for the never-ending decrease in bone mineral density, which is rapid within the first 3–5 years from the FMP.[41] As a result, osteoporosis, initially in trabecular bone and then in cortical bone, increases the risk of fractures, which occur most frequently in the spine, hip, and wrist.[41] In addition, sarcopenia and the loss of muscle tone that ensue after menopause are facilitating factors for fractures.[42]

Healthcare practitioners should also bear in mind that some symptoms of menopause are markers of future health risks. Severe vasomotor symptomatology and poor sleep quality are associated with an increased risk of CVD[43,44] and depression.[45] Moreover, vasomotor symptoms, sleep disorders, and depression might increase the susceptibility to develop cognitive dysfunction.[46,47] Severe hot flashes have also been associated with an increased risk of osteoporosis and bone fracture.[48]

There may be an individual vulnerability, whereby some women have more symptoms and more significant morbidity related to the loss of exposure to estrogen.

Box 2: Contraindications to menopausal hormone therapy

Personal history of:
- Breast cancer
- Severe active liver disease
- Coronary heart disease
- Stroke
- Venous thromboembolic event

These contraindications do not apply to transvaginal-based estrogen therapies, as the serum concentration of estrogen from this route is extremely low.

FIGO position on the issue

Healthcare practitioners can, and must, protect the health and lives of mid-life women by increasing awareness of the symptoms of menopause, providing healthcare options, namely menopausal hormone therapy (MHT), and promoting healthy lifestyle changes. Modifications made before or during the menopausal transition have the most significant impact, even at an older age.

In women with bothersome symptoms of menopause, namely vasomotor and urogenital, and absence of contraindications (Box 2), MHT is the first line of treatment. However, MHT should be personalized based on the patient's history, chronological and menopausal age, physical characteristics, and current health status so that the benefits always outweigh the risks.

To obtain the most significant benefits, MHT should be started as soon as possible after menopausal symptoms appear and continued while the risk–benefit ratio is favorable.

MHT benefits and risks on health domains, target organs, and systems

Longevity

Overall mortality in estrogen-progestogen users is decreased.[49–51] Women with premature menopause who start MHT before the age of 50 years achieve the most significant benefit in terms of longevity.[50]

Central nervous system

Vasomotor symptoms

MHT effectively alleviates vasomotor symptoms, even at low doses.[52,53] Estrogen-progestogen preparations and the bazedoxifene/conjugated estrogens (BZA/CE) combination are the most successful.[54] Tibolone is also a valid option to provide relief from hot flashes.[55] Whatever the composition, it is advisable to begin any hormone treatment at the lowest effective dose and titrate until control of symptoms is achieved.[52–55]

Sleep

The benefits of estrogen-progestogen therapy (EPT) include improved sleep quality.[56–58] All improvements in sleep domains correlate with a reduction in vasomotor symptoms, except for sleep latency and sleep efficiency,[56,57] demonstrating that the positive effect of EPT on subjective sleep cannot be fully explained by decreased bothersome vasomotor or depressive symptoms.[57] The explanation may lie in additional underlying biological mechanisms for EPT-mediated improvements in self-reported sleep, such as a reduction in the hypothalamus-pituitary–adrenal axis sensitivity and reactivity.[57] Progesterone alone is also beneficial for sleep.[59]

The BZA/CE combination favors sleep in postmenopausal women with moderate to severe vasomotor symptoms.[60]

Cognition and mood

In women aged 75 years or older, a long duration of past MHT exposure, either with estrogen alone or with estrogen-progestogens, is positively associated with cognitive status, especially when MHT is started within 5 years from the FMP.[11]

Indeed, the notion of a "critical window" of MHT has arisen whereby MHT may improve cognition when started in the perimenopausal period but become deleterious if started too far from the FMP.[61]

The evidence suggests that the use of MHT, particularly in women who have had surgical menopause, especially when young, is protective against cognitive impairment.[61,62]

Likewise, MHT is likely to be more efficacious on mood when started at a younger age. Furthermore, MHT and antidepressants seem to have a positive cumulative effect on clinical depression.[61]

In addition, in women who are APOE4 carriers and therefore at high risk for Alzheimer's disease, early MHT may represent an effective targeted strategy to mitigate their higher lifetime risk of Alzheimer's disease.[63,64]

Further investigation in this area is still warranted, as data from the literature are somewhat contradictory. Indeed, recent North European Finnish/Danish case–control studies, based on national registries, have pointed towards a relationship between MHT and the risk of developing Alzheimer's disease and/or late-onset dementia.[65,66]

However, these studies have several essential biases. First, they are not randomized controlled trials. Second, the women were prescribed MHT because of vasomotor symptoms, often associated with sleep and mood disorders, which make them intrinsically more prone to developing cognitive dysfunction.[67,68] Women with a predisposition for dementia may also have been prevalent in the Danish trial population as, during the study years, MHT was prescribed to prevent cognitive deterioration. Finally, in the Danish report, an increase in the risk of dementia was present for a duration of therapy as small as less than 1 year, suggesting the presence of confounding factors (alcohol, smoking, social isolation) that weaken the hypothesis of a direct causation.

Sexuality

In early postmenopause, transdermal estradiol-based treatment significantly improves overall female sexual function, whereas oral conjugated equine estrogens (CEE)-based treatment has less effect.[69] Tibolone is the most effective therapy for restoring sexual function, including desire, sexual interest, and

satisfaction, which may be attributed to its combined estrogenic and androgenic properties.[70]

In women who develop hypoactive sexual desire disorder, transdermal testosterone treatment can be used to restore sexual function, bearing in mind that proper dosing should both attain and maintain total testosterone levels in the premenopausal physiological range and that safety data are not available beyond 2 years of treatment.[71–73] Moreover, it should be stopped if there is no response within 6 months of treatment.[69] Women with premature and early surgically induced menopause are potential candidates for testosterone therapy because of their experience of abrupt loss of ovarian androgen and substantial prevalence of hypoactive sexual desire disorder.[72,74]

Dehydroepiandrosterone (DHEA) oral supplementation may be used in women with low sex drive associated with low levels of circulating dehydroepiandrosterone.[75,76]

Prasterone (vaginal DHEA) may be used efficiently to improve all sexual domains in women with vulvovaginal atrophy and moderate to severe dyspareunia.[76,77]

Osteo-skeletal system

Menopausal EPT significantly reduces the risk of hip, vertebral, and total fractures, with a parallel increase in bone mineral density (BMD),[78] and this benefit persists well after MHT cessation.[79–81] Likewise, tibolone increases BMD and reduces fracture risk, even at low doses (1.25 mg/day).[82]

Cardiovascular system

The effect of MHT differs according to age at initiation of MHT and time since menopause.

Women starting treatment under the age of 60 years and/ or earlier, or at most within 10 years from their FMP, have a lower risk of death from cardiovascular causes and non-fatal myocardial infarction.[83–87] It is noteworthy that those benefits persist years after the cessation of MHT.[77,82] Indeed, the first 10 years from FMP offer a "window of opportunity" due to the anti-atherogenic and vasodilatory effects estrogens have on healthy cardiovascular structures.[83–87]

In the second decade after the FMP, estrogens have a fairly neutral effect, and therefore, women may still enjoy the benefits of MHT without fearing an increase in cardiovascular events.[83] When more than 20 years have passed from the FMP, MHT should not be started as this could significantly increase cardiac thrombo-occlusive events due to a vascular disease that has developed over time.[83] Generally speaking, lifetime cumulative estrogen exposure decreases the risk of ischemic and hemorrhagic stroke.[88] This is in line with the finding that transdermal estrogens[89–92] and oral estradiol[92] tend to decrease the risk of stroke, whereas the use of oral CEE, at intermediate and high doses, increases the risk of ischemic stroke.[89] Time of oral CEE initiation from FMP may play a role, as the longer the time lapse from FMP, the higher the risk.[92]

Transdermal estrogens do not increase the risk of venous thromboembolism (VTE),[93–95] while oral estradiol, and particularly CEE, do.[94]

Another critical determinant of thrombotic risk is the type of progestogens associated with estrogens used by women with an intact uterus. Indeed, micronized progesterone and dydrogesterone do not increase the risk, but norpregnanes, namely nomegestrol acetate and promegestone, norethisterone, as well as MPA, do increase the risk.[89,93–95]

Therefore, the use of transdermal estrogens and, where indicated, micronized progesterone or dydrogesterone should be preferred in women who have an increased baseline thrombotic risk.[96]

Tibolone does not increase the risk of VTE[94] but does increase the risk of stroke in women aged 60–85 years.[97] Therefore, it should not be used in elderly women or those with stroke risk factors, such as hypertension, tobacco smoking, diabetes, and/or atrial fibrillation.[97]

The cardiovascular risk profile is acceptable for the BZD/CE combination.[98]

Endocrine system

Estrogen and EPT improve insulin resistance and lower progression to diabetes in postmenopausal women.[99,100] The tissue-selective estrogen complex (BZD/CE) has neutral effects on glucose metabolism,[101] while tibolone reduces insulin sensitivity and should not be used in women with prediabetes or diabetes.[102]

Female reproductive and genitourinary systems

Breast

According to randomized clinical trials, CEE-only therapy is associated with a lower incidence and mortality of breast cancer incidence,[103] and estradiol-only therapy carries no risk for breast cancer.[104]

EPT in women with an intact uterus has a variable impact on the risk of breast cancer, depending on the type of progestogens used in combination with estrogens: medroxyprogesterone acetate (MPA),[103–107] norethisterone (NETA),[104–106] and levonorgestrel (LNG)[104–106] increase the risk of breast cancer, whereas dydrogesterone[101,104] and especially progesterone,[104,106] do not.

Due to their neutral effect on the risk of breast cancer, natural progesterone or its isomer, dydrogesterone, should be considered the first choice for endometrial protection in women with an intact uterus.[104,106,107]

During CEE + MPA treatment, the risk of breast cancer increases with the duration of use,[105] but it drops substantially in the early post-treatment phase (within 2.7 years), although the relative risk remains higher than 1 through 5.5 years (median) of additional follow-up.[105,108]

Nevertheless, in the Finnish population, the risk of breast cancer mortality was reported to be reduced not only in women using estradiol-only therapy but also in those using estradiol-progestogen regimens (43% NETA, 30% MPA), especially in the age groups of 50–59 and 60–69 years.[109]

Indeed, neither unopposed estrogen nor estrogen-progestogen regimens used after surgical menopause or premature ovarian insufficiency are associated with an increased risk of young-onset breast cancer before the age of 50 years.[110]

Tibolone has a neutral effect on the risk of breast cancer only with a short duration of use (<5 years). Thereafter, the risk increases.[104,106] However, in the Korean population, tibolone has been shown to lower the risk of breast cancer, both after short and long duration of use.[111]

Although the literature is scant, BZA/CE appears to have a favorable breast-related safety profile as it does not increase mammographic breast density[111] and has been shown to have a neutral effect on the risk of breast cancer over follow-up periods of 5 and 7 years.[112,113]

Uterus

Systemic estrogen-only therapy can cause endometrial hyperplasia or cancer in women with an intact uterus and should, therefore, always be combined with a progestogen.[114] Continuous combined EPT is associated with a decreased risk of endometrial cancer, especially in obese women.[115,116]

Tibolone is associated with an increased risk of endometrial cancer, particularly for type 1 endometrial cancer and especially with a long duration of use (10+ years).[117]

Ovary

Both estrogen-only and estrogen-progestogen hormone therapies are associated with an increased risk of serous and endometrioid ovarian cancer.[118] Likewise, tibolone is associated with an increased risk of epithelial ovarian cancer overall, particularly serous ovarian cancer, especially with a long duration of use (10+ years).[117]

Women with a history of endometriosis must be informed of the possibility of disease recurrence with MHT. In these women, even when subjected to hysterectomy, continuous combined preparations and tibolone should be considered instead of unopposed estrogens.[119] Moreover, recent data suggest that in women with a history of endometriosis or de novo endometriosis, the risk of epithelial ovarian cancer appears to be increased after estrogen-only treatment, whereas EPT and tibolone therapy are neutral.[120]

Vulva, vagina and urinary tract

Estrogen, estrogen-progestogen, and tibolone therapy reduce bothersome symptoms of vulvovaginal atrophy.[121,122]

The effect of MHT on urinary symptoms depends on the type used. Systemic MHT may cause urinary incontinence[123] or worsen existing urinary symptoms, while vaginal estrogens improve dysuria, frequency, urge and stress incontinence, and recurrent urinary tract infections.[124]

Moreover, it is advisable to inform women with pre-existing pelvic organ prolapse that exposure to systemic estrogen-progestogen regimens might negatively affect this problem.[125]

Orally administered ospemifene is an effective non-estrogen systemic treatment specifically for vulvovaginal atrophy with a good cardiovascular safety profile.[126,127]

Gastrointestinal system

Estrogen, estrogen-progestogen. and tibolone therapy lower the risk of colorectal cancer in women.[128,129]

MHT Regimens

When deciding to begin MHT, the route of delivery, dose, and type of estrogens or estrogen-progestogens should be carefully pondered based on a woman's characteristics (Table 1).

Systemic MHT

In healthy, normal-weight early postmenopausal women (approximately 5–8 years from the FMP), the following regimens are generally suitable: oral estrogens or transdermal estradiol at medium doses combined with cyclic or continuous progestogens for endometrial protection;[130] tibolone at low to standard doses;[55] and tissue selective estrogen complex at the standard dose.[101]

In healthy late postmenopausal women, MHT may be continued but seldom begun,[86,87] with the following regimens:[130] low doses of transdermal estradiol[89,91] or low doses of oral estrogens,[89] associated with micronized progesterone or its isomer, dydrogesterone, administered continuously, where there is an indication for endometrial protection;[130] and low-dose tibolone.[55]

In overweight (body mass index [BMI, calculated as weight in kilograms divided by the square of height in meters] >25) early postmenopausal women (approximately 5–8 years from the FMP), the following regimen is generally suitable: transdermal estrogens[87,89] combined with cyclic or continuous progestogens.[130]

In women who have had surgical removal of the ovaries before the age of 50 years, the following regimens are generally suitable: medium to high doses of oral estrogens or transdermal estradiol, in combination with appropriate doses of progestogens, where indicated;[130] transcutaneous testosterone therapy may be necessary when hypoactive sexual desire disorder is diagnosed at a dose that achieves the normal premenopausal range of circulating testosterone levels.[71]

In women with primary ovarian insufficiency (POI) needing contraception, the following regimens are generally suitable for the first few years after diagnosis: low-dose estrogen-progestogen contraceptives; and estrogen associated with a levonorgestrel (LNG) intrauterine system.[75]

Women transitioning through perimenopause with contraceptive needs may also use the abovementioned regimens.

In women with POI without contraceptive needs, the following may be used: medium to high doses of oral or transdermal estradiol, combined with appropriate doses of progestogens, where indicated.[130]

In women with symptoms of fatigue, depression, and/or a reduced sexual desire associated with low endogenous DHEA

Table I: Systemic MHT regimens.

Formulation	Route	Regimen	Dose/day
Early postmenopause (within 5–8 years from the FMP), healthy, normal weight			
Estrogens-progestogens	Oral	Combined sequential[a]	• E2 2 mg + dydrogesterone 10 mg • E2 1 mg + dydrogesterone 10 mg • CEE 0.625 mg + oral/vaginal MP 200 mg
		Combined continuous[b]	• E2 1 mg + oral/vaginal MP 100 mg • E2 1 mg + dydrogesterone 5 mg • E2 1 mg + DRSP 2 mg • E2 1 mg + NETA 1 mg • CEE 0.625 mg + oral/vaginal MP 100 mg
	Transdermal (patch)	Combined sequential[a]	• 17βE2 50 µg + LNG 150 µg • 17βE2 50 µg + NETA 250 µg • 17βE2 25–50 µg + oral/vaginal MP 100–200 mg • 17βE2 25–50 µg + oral dydrogesterone 5–10 mg
		Combined continuous[b]	• 17βE2 25–50 µg + oral/vaginal MP 100–200 mg • 17βE2 25–50 µg + oral dydrogesterone 5–10 mg • 17βE2 25–50 µg + 20 µg LNG-IUS
	Transcutaneous (gel, spray)	Combined sequential[a]	• 17βE2 1–2 mg + oral/vaginal MP 100–200 mg • 17βE2 1–2 mg + oral dydrogesterone 5–10 mg
		Combined continuous[b]	• 17βE2 1–2 mg + oral/vaginal MP 100–200 mg • 17βE2 1–2 mg + oral dydrogesterone 5–10 mg • 17βE2 1–2 mg + 20 µg LNG-IUS
Tissue selective estrogen complex	Oral	Continuous	• Bazedoxifene 20 mg + CEE 0.45 mg
Selective tissue estrogenic activity regulator	Oral	Continuous	• Tibolone 1.25–2.5 mg (low-standard dose)
Androgens	Transdermal (cream)	Continuous	• Testosterone cream 1% 300 µg/day (1/10th standardmale dose)
	Oral	Continuous	• DHEA 10–25 mg
Late postmenopause (after 5–8 years from the FMP), healthy, normal weight			
Estrogens-progestogens	Oral	Combined continuous[b]	• E2 1 mg + oral/vaginal MP 100 mg • E2 1 mg + dydrogesterone 5 mg • E2 1 mg + DRSP 2 mg • CEE 0.3–0.45 mg + oral/vaginal MP 100 mg
	Transdermal (patch)	Combined continuous[b]	• 17βE2 25 µg + oral/vaginal MP 100 mg • 17βE2 25 µg + oral dydrogesterone 5 mg
	Transcutaneous (gel, spray)	Combined continuous[b]	• 17βE2 0.50–1 mg + oral/vaginal MP 100 mg • 17βE2 0.50–1 mg + oral dydrogesterone 5 mg
Selective tissue estrogenic activity regulator	Oral	Continuous	• Tibolone 1.25 mg
Androgens	Oral	Continuous	• DHEA 10–25 mg
Early postmenopause (within 5–8 years from the FMP) and overweight (BMI > 25)			
Estrogens-progestogens	Transdermal (patch)	Combined sequential[a]	• 17βE2 25–50 µg + oral/vaginal MP 200 mg • 17βE2 25–50 µg + oral dydrogesterone 10 mg
		Combined continuous[b]	• 17βE2 25–50 µg + oral/vaginal MP 100–200 mg • 17βE2 25–50 µg + oral dydrogesterone 5–10 mg • 17βE2 25–50 µg + 20 µg LNG-IUS
	Transcutaneous (gel, spray)	Combined sequential[a]	• 17βE2 1–1.5 mg + oral/vaginal MP 200 mg • 17βE2 1–1.5 mg + oral dydrogesterone 10 mg
		Combined continuous[b]	• 17βE2 1–1.5 mg + oral/vaginal MP 100–200 mg • 17βE2 1–1.5 mg + oral dydrogesterone 5–10 mg 20 µg • 17βE2 1–1.5 mg + 20 µg LNG-IUS

Table I: Continued

Formulation	Route	Regimen	Dose/day
Late menopause (after 5–8 years from the FMP) and overweight (BMI > 25)			
Estrogens-progestogens	Transdermal (patch)	Combined continuous[b]	• 17βE2 25 µg + oral/vaginal MP 100 mg • 17βE2 25 µg + oral dydrogesterone 5 mg
	Transcutaneous (gel, spray)	Combined continuous[b]	• 17βE2 0.50–1 mg + oral/vaginal MP 100 mg • 17βE2 0.50–1 mg + oral dydrogesterone 5 mg
Surgical menopause			
Intact uterus			
Estrogens-progestogens	Oral	Combined sequential[a]	• E2 2 mg + dydrogesterone 10 mg • E2 1 mg + dydrogesterone 10 mg • CEE 0.625 mg + oral/vaginal MP 200 mg • E2 1–2 mg + MP 100–200 mg
		Combined continuous[b]	• E2 1 mg + MP 100 mg • E2 1 mg + dydrogesterone 5 mg • E2 1 mg + DRSP 2 mg • E2 1 mg + NETA 1 mg • CEE 0.625 + oral/vaginal MP 100 mg
	Transdermal (patch)	Combined sequential[a]	• 17βE2 50 µg + LNG 150 µg • 17βE2 50 µg + NETA 250 µg • 17βE2 50–100 µg + oral/vaginal MP 200 mg • 17βE2 50–100 µg + oral dydrogesterone 10 mg
		Combined continuous[b]	• 17βE2 50 µg + oral/vaginal MP 200 mg • 17βE2 50 µg + oral dydrogesterone 10 mg • 17βE2 50 µg + 20 µg LNG-IUS
	Transcutaneous (gel, spray)	Combined sequential[a]	• 17βE2 1.5–2 mg + oral/vaginal MP 200 mg • 17βE2 1.5–2 mg + oral dydrogesterone 10 mg
		Combined continuous[b]	• 17βE2 1.5 mg + oral/vaginal MP 200 mg • 17βE2 1.5 mg + oral dydrogesterone 10 mg
Androgens	Transdermal (cream)	Continuous	• Testosterone 1% cream 300 µg (1/10th standard male dose)
	Oral	Continuous	• DHEA 10–25 mg
Hysterectomized			
Estrogens	Oral	Continuous	• E2 1–2 mg • CEE 0.625 mg
	Transdermal (patch)		• 17βE2 50–100 µg
	Transcutaneous (gel, spray)	Continuous	• 17βE2 1.5–2 mg
Androgens	Transdermal (cream)	Continuous	• Testosterone 1% cream 300 µg (1/10th of standard male dose)
	Oral	Continuous	• DHEA 10–25 mg
Premature ovarian insufficiency			
Contraceptive needs			
Estrogens-progestogens	Oral	Continuous	• E2 hemihydrate 1.5 mg + NOMAC 2.5 mg • E2 valerate 1–3 mg + DNG 2–3 mg
Non-contraceptive needs			
Estrogens-progestogens	Oral	Combined sequential[a]	• E2 2 mg + dydrogesterone 10 mg • CEE 0.625 + oral/vaginal MP 200 mg
	Transdermal (patch)	Combined sequential[a]	• 17βE2 50 µg + LNG 150 µg • 17βE2 50 µg + NETA 250 µg • 17βE2 50–100 µg + oral/vaginal MP 200 mg • 17βE2 50–100 µg + oral dydrogesterone 10 mg
		Combined continuous[b]	• 17βE2 50–100 µg + oral/vaginal MP 200 mg • 17βE2 50–100 µg + oral dydrogesterone 10 mg • 17βE2 50–100 µg + 20 µg LNG-IUS
	Transcutaneous (gel, spray)	Combined sequential[a]	• 17 βE2 1.5–2 mg + oral/vaginal MP 200 mg • 17 βE2 1.5–2 mg + oral dydrogesterone 10 mg
		Combined continuous[b]	• 17 βE2 1.5–2 mg + oral MP 100–200 mg • 17 βE2 1.5–2 mg + oral dydrogesterone 10 mg
Androgens	Transdermal	Continuous	• Testosterone 1% cream 300 µg (1/10th standard male dose)
	Oral	Continuous	• DHEA 10–25 mg

Abbreviations: 17βE2, 17 beta-estradiol; CEE, conjugated equine estrogens; E2, estradiol; DHEA, dehydroepiandrosterone; DNG, dienogest; DRSP, drospirenone; FMP, final menstrual period; LNG-IUS, levonorgestrel intrauterine system; MHT, menopausal hormone therapy; MP, micronized progesterone; NETA, norethisterone acetate; NOMAC, nomegestrol acetate.

[a] Progestogen is administered for 12–14 days/cycle.

[b] Progestogen is administered daily.

Box 3: Vaginal menopausal hormone therapy formulations

- E2 10 µg vaginal tablets
- E2 7.5 µg/24 h, vaginal ring
- Estriol 500 µg/day cream
- Estriol 50 µg/day gel
- Promestriene 10 mg vaginal capsules
- Prasterone (DHEA) 6.5 mg vaginal suppositories

Abbreviations: DHEA, dehydroepiandrosterone; E2, estradiol.

levels, supplemental DHEA may be considered at a starting dose of 10 mg/ day up to 25 mg/day alone or as an adjunct to systemic MHT.[75,76] Table I lists standard systemic MHT regimes.

Vaginal MHT

Vaginal estrogen therapy is the first-line treatment for the symptoms of vulvovaginal atrophy, such as dryness, dyspareunia, itching, and/ or burning.[131] Moreover, it has been proven efficient in ameliorating dysuria, urinary frequency/urgency, and recurrent lower urinary tract infections.[132,133] Vaginal estrogen therapy is more effective than systemic estrogen therapy in this domain[121] and has an excellent safety profile.[106,134–136] Moreover, it may be used alone, in which case there is no need for endometrial protection or in association with systemic MHT (Box 3).

Prasterone (vaginal DHEA) treatment alleviates vulvovaginal atrophy, difficult lubrication, dyspareunia, and arousal.[76,77]

Because of their neutral effect on the risk of breast cancer and very low systemic absorption, both low-dose vaginal estrogens and prasterone may be considered an off-label treatment in women with breast cancer when symptoms of genitourinary menopausal persist after trials of non-hormonal interventions and quality of life is adversely affected.[137] Box 3 lists standard vaginal MHT formulations.

Compounded bioidentical hormone formulations

Bioidentical hormones have been defined as "substances that have the same chemical and molecular structure as hormones that are produced in the human body".[138] However, this definition does not address the manufacturing, source, or delivery methods of the products and, therefore, may be misleading as it can cover both Food and Drug Administration (FDA)-approved formulations as well as non–FDA-approved custom-compounded products that are prepared for an individual patient by a pharmacist in response to a licensed practitioner's prescription.[139]

Compounded bioidentical hormone products have often been promoted as a "safe"/"safer", "natural", and more effective alternative to manufactured FDA-approved hormone therapies to relieve symptoms of menopause.[138] However, there is little or no scientific evidence to support the marketing myth of such a claim.[140]

Indeed, there are major concerns about compounded bioidentical hormone products that may consist of untested and unapproved combinations of multiple hormones and be used through nonstandard or untested routes of administration, such as subdermal implants, pellets, or troches.[141] Concerns include insufficient randomized trials to assess their efficacy or safety in treating symptoms of menopause, as well as their purity, potency, overall quality, and lack of labeling outlining risks.[140–142]

Moreover, pharmacokinetic studies have reported that their bioavailability, bioactivity, and potency differ from batch to batch.[140] The variable absorption of compounded estrogens and progesterone may lead to under- or overdosing, which could increase the risk of estro- gen-stimulated cancers, especially endometrial cancers.[140] Therefore, although there are some exceptions where compounded bioidentical hormone preparations may be acceptable, such as in cases of allergy to ingredients or dosages not available in FDA-approved products,[140,141] FIGO recommends the use of approved, regulated, and monitored bioidentical systemic and vaginal hormone therapies.

Follow-up and re assessment

Regular reassessment of the woman's health status is mandatory. Once optimal control of symptoms has been achieved, women should be checked annually, especially if they are on MHT.

Body weight and blood pressure should be monitored. Moreover, menopausal women must undergo timely screening for breast cancer by mammography, which hormone therapy does not interfere with.[143] Ultrasound examination of the endometrium in women on MHT, by any route, that reports bleeding is mandatory and may prompt hysteroscopic endometrial sampling if the thickness is over 4 mm.[144] Recurrent bleeding should always be investigated by endometrial biopsy, whatever the endometrial thickness assessed by ultrasound.[144] The monitoring of endometrial thickness in asymptomatic women is less specific and the ideal cutoff for invasive procedures has not been investigated thoroughly. Therefore, the need for further investigation should be based on the individual risk factors for endometrial cancer.[145,146]

MHT may be continued as long as women maintain their health status and contraindications do not develop. The benefits must always outweigh the risks.[130]

Lifestyle

Well-tailored MHT should not preclude healthy lifestyle changes, which are the mainstay of primary prevention.

Moderate-intensity physical activity for 150–300 min per week or vigorous-intensity physical activity for 75–150 min per week is recommended to reduce cardiovascular and cancer morbidity and mortality in all adults.[147] Breaking up prolonged sitting with standing or walking for 5 min every 20 min also has a positive impact on cardiovascular risks.[148] High-intensity exercise increases lumbar spine BMD.[149] Although evidence on the effects of multicomponent exercise programs in postmenopausal and older women remains conflicting, combining resistance training using high-intensity loads and impact-aerobic activities may be the best strategy to enhance muscle and bone mass.[150]

Healthy eating, such as that of the Mediterranean diet, and physical activity are pivotal in containing cardiovascular and cancer risks at mid-life and beyond.[151–155]

Maintaining alcohol consumption that meets public health recommendations and avoiding smoking are also key to reducing such risks.[156,157]

Last but not least, engaging in leisure activities, such as visiting art exhibitions, reading, listening to music, singing, and painting, is positively associated with a lower risk of depression, dementia, and death by any cause. Therefore, it can be considered a health and well-being resource to help middle-aged and older women.[158–163]

Summary of key points

- Post-reproductive health is a global priority as menopause comes at a time when women still occupy an essential role in the family and society. Counseling on the benefits and risks of MHT and lifestyle education is a must.
- Type and duration of MHT should be tailored based on patient history, menopausal age, physical characteristics, and current health status so that the benefits always outweigh the risks.
- Menopausal women should undergo regular reassessment of their health conditions, especially if they are on MHT.

Longevity

- Women on MHT to relieve their symptoms of menopause will benefit from a significant increase in longevity.
- Women who develop POI and start MHT before the age of 50 years achieve the most significant benefit in terms of longevity.

Vasomotor symptoms

- Women experiencing menopausal vasomotor symptoms, with no contraindications for systemic hormone therapy, should be offered MHT to relieve their symptoms.

Sleep

- Women with sleep disorders prescribed MHT to relieve their symptoms of menopause will benefit from a significant improvement in sleep.

Cognition and mood

- Women who have had surgical menopause, especially when young, should be offered MHT to reduce their lifetime risk of cognitive impairment.
- Women who begin MHT close to the FMP to relieve their symptoms of menopause will benefit from a significant reduction in risk of cognitive deterioration.

Sexuality

- Tibolone is the most effective therapy in terms of restoration of sexual function.
- In early postmenopause, transdermal estradiol-based treatment is associated with a significant improvement in overall female sexual function, whereas oral CEE-based therapy is less effective.
- Women with hypoactive sexual desire disorder, whose sexual function does not improve under MHT, can be offered a short trial of transdermal testosterone.

Osteo-skeletal system

- Women on MHT to relieve their symptoms of menopause will benefit from a significant reduction in osteoporosis-related fracture risk, which persists well after the cessation of MHT.

Cardiovascular system

- Women on MHT to relieve their symptoms of menopause will benefit from a significant reduction in the risk of CVD if it is begun within 10 years from the FMP.
- Transdermal estrogens and, where indicated, micronized progesterone or dydrogesterone should be the first choice MHT, especially in women with a baseline increased thromboembolic risk.

Endocrine system

- Women with prediabetes or diabetes on estrogen or estrogen-progestogen MHT to relieve their symptoms of menopause will benefit from a significant improvement in metabolic compensation.
- Women with prediabetes or diabetes should not be offered tibolone to improve their symptoms of menopause.

Breast

- Women with premature ovarian insufficiency on MHT will not increase their risk of young-onset breast cancer before the age of 50 years.
- Women on estrogen-only MHT to alleviate symptoms of menopause will not increase their risk of breast cancer.
- Women with an intact uterus should be offered natural progesterone or dydrogesterone for endometrial protection to avoid increasing their risk of breast cancer.
- Tibolone should be used for a short period of time (<5 years) to avoid increasing the risk of breast cancer.

Uterus

- Women with an intact uterus on continuous combined estrogen-progestogen MHT to relieve their symptoms of menopause will benefit from a significant reduction in the risk of endometrial cancer.
- Women with an increased baseline risk for endometrial cancer due to individual factors should not be offered tibolone to relieve their symptoms of menopause.

Ovary

- Women at risk of ovarian cancer must be informed that both estrogen-only and estrogen-progestogen hormone therapies, as well as tibolone treatment, increase the risk of epithelial ovarian cancer.
- Women with a history of endometriosis can be offered combined estrogen-progestogen or tibolone to relieve their symptoms of menopause.

Gastrointestinal system

- Women on MHT to relieve their symptoms of menopause will benefit from a significant reduction in the risk of colorectal cancer.

Vulva, vagina and urinary tract

- Vaginal estrogen therapy is the first-line treatment for symptoms of vulvovaginal atrophy.
- Prasterone (vaginal DHEA) treatment alleviates vulvovaginal atrophy, difficult lubrication, and/or arousal.
- Women on systemic MHT to relieve their symptoms of menopause will benefit from a significant reduction in vulvovaginal atrophy.
- Orally administered ospemifene is an effective non-estrogen systemic treatment for vulvovaginal atrophy.
- Women experiencing dysuria, frequency, urinary frequency/urgency, and recurrent lower urinary tract infections should be offered vaginal estrogen therapy.

Lifestyle

- Healthy eating and physical activity are pivotal in containing cardiovascular and cancer risks. Maintaining alcohol consumption that meets public health recommendations and avoiding smoking are also key to reducing such risks.
- Leisure activities can reduce the risk of depression, dementia, and death by any cause.

FIGO's commitments

With this position paper, FIGO recognizes the vital role women play well after childbearing age and the need for all physicians working in women's health to further develop the necessary knowledge to sustain women in post-reproductive life.

FIGO commits itself to:

1. Educational interventions in primary care settings for general practitioners and gynecologists aimed at improving physicians' knowledge on menopause so as to be prepared to provide reassurance on symptoms, and counseling on a healthy lifestyle and, where indicated, on hormone therapy to improve women's quality of life;
2. Promoting the study of menopausal medicine in the core curriculum of university medical graduate and postgraduate programs;
3. Interventions to increase social awareness of menopause and its impact on women to promote understanding in the home and work environment;
4. Promote reimbursement policies for officially approved indications of MHT, which may impact healthcare costs for age-related pathologies, including osteoporotic fractures, cardiovascular events, and colorectal cancer.

FIGO supports preventive medicine and the appropriate use of MHT as they have the potential to increase disability-free life expectancy for menopausal women.

Author contributions

All authors made substantial contributions to the conception or design of the work; drafting the work or reviewing it critically for important intellectual content; and gave final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest statement

Andrea R. Genazzani reports consulting fees from Mithra; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Organon, Exeltis, Gedeon Richter, Theramex, and Mithra. Tommaso Simoncini reports consulting fees from Abbott, Intuitive Surgical, Johnson and Johnson, Medtronic, Shionogi, and Astellas; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Abbott, Intuitive Surgery, Applied Medical, Gedeon Richter, Theramex, Shionogi and Vichy. All other authors report no conflicts of interest.

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