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REVIEW

Progestogens as a component of menopausal hormone therapy: the right molecule makes the difference

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Abstract

Optimizing menopausal hormone therapy (MHT) requires an awareness of the benefits and risks associated with the available treatments. This narrative review, which is based on the proceedings of an Advisory Board meeting and supplemented by relevant articles identified in literature searches, examines the role of progestogens in MHT, with the aim of providing practical recommendations for prescribing physicians. Progestogens are an essential component of MHT in menopausal women with a uterus to prevent endometrial hyperplasia and reduce the risk of cancer associated with using unopposed estrogen. Progestogens include natural progesterone, dydrogesterone (a stereoisomer of progesterone), and a range of synthetic compounds. Structural differences and varying affinities for other steroid receptors (androgen, glucocorticoid, and mineralocorticoid) confer a unique biological and clinical profile to each progestogen that must be considered during treatment selection. MHT, including the progestogen component, should be tailored to each woman, starting with an estrogen and a progestogen that has the safest profile with respect to breast cancer and cardiovascular effects, while addressing patient-specific needs, risk factors, and treatment goals. Micronized progesterone and dydrogesterone appear to be the safest options, with lower associated cardiovascular, thromboembolic, and breast cancer risks compared with other progestogens, and are the first-choice options for use in 'special situations,' such as in women with high-density breast tissue, diabetes, obesity, smoking, and risk factors for venous thromboembolism, among others.

Keywords: menopausal hormone therapy, progesterone, progestogen

Citation

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Introduction

Declining estrogen levels at menopause produce a wide range of signs and symptoms, including vasomotor symptoms, sleep disturbances, changes in mood and energy levels, urogenital atrophy, sexual dysfunction, and decreased bone density.[1,2] If severe, menopausal symptoms can affect a woman's daily functioning and impair her quality of life. Moreover, the timing of menopause coincides with the emergence of age-related chronic diseases.[3,4]

Menopausal hormone therapy (MHT) has been shown to have a favorable risk–benefit ratio in women without contraindications who initiate treatment between the ages of 50–59 years or within 10 years of menopause onset.[5–11] In this defined population, MHT effectively relieves vasomotor and urogenital symptoms, can prevent bone loss and fracture,[6–11] and may protect against all-cause mortality and cardiac events.[12,13]

MHT encompasses several drug classes, including estrogens, progestogens, estrogen plus progestogen combinations, synthetic steroids (e.g. tibolone), and selective estrogen receptor modulators (e.g. raloxifene, bazedoxifene, ospemifene).[5,11] The wide range of formulations and delivery systems allows for individualized treatment based on a woman's symptoms, risk factors, and treatment goals. However, because the risks and benefits of MHT differ depending on the type, dose, formulation, route of administration, duration of

use, and timing of initiation,[10,11] prescribing physicians must be well informed in order to optimize treatment.[14]

Persistent negative attitudes towards MHT following publication of the Women's Health Initiative studies in the early 2000s led to a virtual abandonment of MHT use and of medical education about menopause and MHT.[15,16] Many physicians today are not comfortable providing care to menopausal women, resulting in unnecessary suffering and wasted opportunities for better health outcomes.[16] As a step towards resolving the knowledge gap, this narrative review examines the use of MHT in menopausal women, with an emphasis on the role of progestogens in MHT. The expertise and clinical experience of the authors is supported by relevant literature (e.g. clinical guidelines) with the aim of providing practical recommendations for prescribing physicians, including in special situations such as obesity, diabetes, and others, where uncertainty may be greater.

Content-development methods

This review was developed primarily from the proceedings of an Advisory Board meeting attended by the authors held in Lisbon in October 2019, organized by Mylan Pharmaceuticals. The aims of the meeting were to differentiate between progestogens and their roles in menopause management and establish consensus recommendations to treat menopausal women in everyday practice. Published reviews of the differential actions of progestogens used in MHT formed the basis of the discussion and generated the topics to be covered in this review. Review articles were supplemented by clinical practice guidelines and other relevant materials identified through PubMed searches or known to the authors. Some content reflects the clinical experience and expert opinion of the authors.

Pharmacology of progestogens

Progestogens are a class of steroid hormones that bind to and activate the progesterone receptor. In women, progesterone receptors are found in the uterus, breast, ovary, brain, bone, and other tissues. Endogenous progesterone is an essential regulator of female reproductive function and has an integral role in the normal physiology of the cardiovascular system, bone, and central nervous system.[17]

Progestogens is a collective term that encompasses natural progesterone, dydrogesterone (a stereoisomer of progesterone), and a range of synthetic compounds designed to mimic the action of endogenous progesterone.[18] Although progestogens vary widely in their molecular structures, they all derive from progesterone, testosterone, or spironolactone (Table 1).[19,20] Progestogens commonly used for MHT in clinical practice in Europe include progesterone, dydrogesterone, medroxyprogesterone acetate, norethisterone acetate (norethindrone), nomegestrol acetate, (levo)norgestrel, and dienogest.

Table 1. Classification of progestogens.[19,20]

Natural	Progesterone
Retroprogesterone	Dydrogesterone
Progesterone derivatives	Chlormadinone acetate Cyproterone acetate Demegestone Medrogestone Medroxyprogesterone acetate Megestrol acetate Nesterone Nomegestrol acetate Promegestone Trimegestone
Testosterone derivatives	Desogestrel Dienogest Ethynodiol diacetate Gestodene Levonorgestrel Lynestrenol Norethindrone Norethindrone acetate Norethynodrel Norgestimate Tibolone
Spironolactone derivatives	Drospirenone

Apart from binding to progesterone receptors, progestogens may interact to varying degrees with other steroid receptors (androgen, glucocorticoid, and mineralocorticoid receptors). The relative binding affinities and biological activities of commonly prescribed progestogens at steroid receptors are shown in Supplementary Table 1 (available at: https://www.drugsincontext.com/wp-content/uploads/2020/11/dic.2020-10-1-Suppl.pdf).[18,21,22] As differences in the chemical structures, metabolism, pharmacokinetics, and receptor affinities of progestogens confer individual biological and clinical profiles, progestogens are considered to lack a class effect.[18,19]

The specific biological profile of a progestogen can affect its tolerability, although it can also be used to achieve certain clinical effects or mitigate underlying risk factors.[21] As examples, androgenic progestogens may antagonize estrogen-induced changes in the hepatic synthesis of lipoproteins (high-density lipoprotein (HDL), very-low-density lipoprotein (VLDL), triglycerides), coagulation and fibrinolysis factors, angiotensinogen, and hormone-binding globulins.[21] Progestogens with glucocorticoid activity may increase pro-coagulatory activity in vessel walls.[21] Androgenic progestogens may attenuate estrogen-induced hypercoagulability and the risk of venous thromboembolism (VTE).[21] Progestogens with antiandrogenic effects may be useful to manage androgenic cutaneous disorders.[21] Progestogens with antimineralocorticoid properties may induce a transient reduction in aldosterone-induced water retention in predisposed patients,[21] combating fluid overload and lowering blood pressure.[23]

Selecting a progestogen for MHT requires an understanding of the differential risks and benefits associated with their metabolic profiles. Although direct clinical comparisons of progestogens are lacking, evidence for the biological and clinical effects of individual progestogens on the endometrium, breast, cardiovascular system, bone, and brain has been previously reviewed.[19–24]

Progestogens in menopause management

Role of progestogens

Estrogen is the main component of MHT that relieves the vasomotor and urogenital symptoms of menopause and protects against osteoporosis.[6–11] Administered early in menopause, estrogen also attenuates the atherosclerotic process, thus protecting women from coronary heart disease, which may be particularly important in women with early menopause.[12] Women with a uterus require a progestogen to prevent endometrial hyperplasia and the risk of endometrial cancer associated with the use of unopposed estrogen.[19,24]

Route of administration

Progestogens for use in MHT are available as single agents for concomitant use with estrogen or in fixed combinations with estradiol. Free (i.e. not fixed) combinations of estrogen and progestogen may facilitate treatment individualization in terms of dosage and formulation. Routes of administration for MHT include oral, vaginal, transdermal, and intrauterine.[19,24]

Progesterone for use in MHT is micronized to enhance its bioavailability. Progesterone is commonly administered orally, although it is also formulated for vaginal administration. Oral and vaginal (but not transdermal) micronized progesterone provide endometrial protection.[25] Dydrogesterone is administered orally. Other progestogens for use in MHT are usually administered orally, although some are available as an intrauterine device (e.g. levonorgestrel intrauterine system) for use with estrogen or may be formulated with estrogen in a transdermal patch. Treatment selection must consider the benefits and disadvantages associated with each route of administration.

Contraindications

Contraindications for MHT include unexplained vaginal bleeding; a history of stroke, transient ischemic attack, myocardial infarction, pulmonary embolism, or VTE; breast or endometrial cancer; or active liver disease.[6] Principal contraindications for progestogens are breast cancer and undiagnosed abnormal vaginal bleeding.

Adverse effects

The common adverse effects associated with progestogens in MHT are breakthrough bleeding and breast discomfort.[26] Other possible adverse effects include headache, nausea, somnolence, fatigue, weight gain, abdominal bloating, anxiety, irritability, depression, decreased libido, hirsutism and acne, back pain, and myalgia.[26]

Selecting a progestogen

As tolerability to progestogens varies considerably among women, treatment must be individualized. Treatment should begin with a progestogen that has the lowest risk profile regarding breast cancer and cardiovascular effects,[26] while addressing patient-specific needs and risk factors. Numerous opinion leaders, guideline groups, and menopause societies recommend adding either micronized progesterone or dydrogesterone to estrogen therapy as the associated cardiovascular, thromboembolic, and breast cancer risks are lower with these molecules compared with other progestogens.[5,6,8,9,11,26–31] Progesterone and its derivatives are less likely than androgenic progestogens to attenuate the beneficial effects of estrogens on lipoprotein metabolism,[32] which may be relevant for patients at higher risk for cardiovascular disease (CVD).

Progestogen dose

The recommended daily dose of progestogen varies by agent and is a reflection of its endometrial effectiveness as assessed in

studies using endometrial biopsies.[33] The dose and duration of a progestogen also depend on the estrogen dose. As estrogen doses are currently much lower than those used previously, correspondingly lower doses of progestogen are required to balance the estrogenic effects. Progestogens for use in MHT are available in numerous formulations. Dosing details for each agent and formulation can be found in the associated Summary of Product Characteristics (Europe), Prescribing Information (United States), and/or national pharmaceutical compendiums.

When and how to treat patients

Prescribing MHT

The goal of managing women through menopause is twofold: to address the initial symptoms/complaints and to reduce the long-term postmenopausal adverse outcomes. MHT is part of an overall management strategy that includes lifestyle measures aimed at promoting good health such as smoking avoidance, healthy diet, regular physical activity, moderate alcohol consumption, and weight management.[6,34]

MHT is indicated in symptomatic women without contraindications, aged 50–59 or within 10 years of menopause onset, whose menopausal symptoms are interfering with their quality of life.[6–11] General guidance is that women should be prescribed 'an appropriate type, dose, formulation, route of administration, and duration of MHT' to meet their treatment objectives.[10,11] Guidelines recommend starting with the lowest effective dose and up-titrating as required based on clinical response.[6] The fully effective dose will vary by woman according to her age, symptom type, symptom severity, body mass index, time since menopause, and endometrial thickness and may need to be adjusted at various times during the course of therapy.[10,11]

MHT regimen

An MHT regimen may be sequential or continuous combined, depending on the stage of menopause.[5,6,24]

In newly menopausal women, a sequential MHT regimen (daily estrogen with a progestogen for 12–14 days/cycle) is appropriate. Regular progestogen withdrawal bleedings (i.e. monthly menses) will occur. Spotting within the first few months after starting MHT is relatively common and should be explained to patients beforehand. If irregular bleeding occurs, a first step may be to enquire about treatment adherence (e.g. unused patches/tablets). An underlying fear of MHT can negatively affect compliance, which can be addressed through counseling and reassurance. Irregular bleeding can also occur due to concurrent antibiotic use or digestive problems. Importantly, early spotting, which is normal, differs from bleeding that develops after many years of MHT use, which must be investigated thoroughly.

Women who have been postmenopausal for at least a year or those with weak or absent withdrawal bleeds can be switched to a continuous (daily) combined estrogen/progestogen regimen. Changes to MHT dosages and a wider range of progestogens have shortened this timeframe from the 2–3 postmenopausal years previously required. In patients who may wish to start MHT with continuous combined therapy, factors such as age and endometrial thickness must be considered. Bleeding-free MHT is possible in patients with an endometrial thickness less than 5 mm.[35]

In Europe, the preferred estrogen for MHT is estradiol and the preferred progestogen is usually micronized progesterone or dydrogesterone. The route of administration of estrogen can be selected according to patient preference. With regard to the progestogen component, only norethisterone acetate and norgestrel are formulated for both oral and transdermal administration. The usual approach is to begin with a low dose of estrogen and titrate gradually until symptoms are controlled. Patients with severe symptoms may need to start with a medium dose of estrogen. If symptoms persist after 4–12 weeks, the dose can be increased to achieve an adequate effect. Over time, some patients may achieve sufficient symptom control to allow for dosage reduction.

How long to maintain MHT?

Although most women will have discontinued MHT by their late 50s or early 60s, age alone is not a reason to stop.[8,10,11] Other factors that may inform a decision to continue or not to continue MHT include symptom severity with/without medication, bone mass, and the presence of risk factors for breast cancer. Symptomatic women who wish to continue MHT should not be denied treatment if there are no contraindications or changes to their risk status, although consideration should be given to using MHT formulations with the lowest risk.[8]

Women receiving MHT should be monitored regularly as treatment goals and choice of therapy may change over time. At least annual assessments are recommended to evaluate the risk–benefit balance and the patient's desire to continue with treatment.[34] Assessments may need to be more frequent in patients with concerns or risk factors. Adjustments to the dose or route of administration or switching to a different product are strategies that can be used to maintain therapy in women who wish to continue MHT.

After a period of time, possibly 3–5 years,[36] tapering from MHT may be considered. Gradual dosage reduction may limit symptom recurrence (e.g. hot flashes) in the short term.[5,37] If symptoms return, up-titrating to the original dose is an option. For women who wish to stop MHT altogether, reducing the dose over 2–3 months is preferable to stopping abruptly.[37] For practical reasons, treatment discontinuation is best not attempted during summer.

The physician's role in menopause management

In Europe, gynecologists have primary responsibility for prescribing MHT and managing menopausal women although,

Table 2. Physician's role in menopause management.

Knowledge	Physicians must have sound knowledge of: • Guideline recommendations for MHT • Choice of estrogen and progestogen (e.g. specific benefits of certain combinations) • Risk mitigation in women with risk factors • Absolute and relative contraindications for estrogens/progestogens
Communication	Physicians must be able to: • Effectively communicate the benefits and risks of MHT to patients to facilitate informed choices • Provide reassurance and support during MHT as necessary for individual patients
Monitoring	Physicians must: • Monitor women regularly to identify changes in risk factors and to confirm the need for continued or modified treatment • Schedule a follow-up within a few months (e.g. 3 months) of first prescription of MHT[36] that includes a review of tolerability and side effects, especially bleeding disorders • At least annual follow-up consultations are suggested thereafter to review and adjust MHT according to the patient's treatment goals[36]

MHT, menopausal hormone therapy.

Table 3. Symptoms of menopause.[1]

Central nervous system	Vasomotor symptoms (hot flushes, night sweats); mood disturbances (anxiety, depression); cognitive function (memory loss, cognitive difficulties); sleep disturbances (delayed onset, frequent awakenings)
Genitourinary tract	Vulvovaginal atrophy, dyspareunia; sexual dysfunction; urgency/stress incontinence; urinary frequency; recurrent urinary infection; vaginal infection
Musculoskeletal system	Joint/muscle pain; loss of muscle mass (sarcopenia); loss of bone mass (osteopenia, increased risk for fractures)

in a few countries (e.g. United Kingdom, The Netherlands), the responsibility lies with general practitioners.[38] Effective management of menopausal women receiving MHT involves three basic aspects of care delivery: knowledge (clinical skills), communication, and regular assessment (Table 2).

Initial consultation for MHT

All candidates for MHT must undergo a thorough assessment and be informed about the risks and benefits. A full menopause consult takes considerably longer than a standard consult and needs to be scheduled accordingly.

A detailed personal and family history is essential as many chronic conditions begin to emerge after menopause.[3,4] A menopause consult also provides the opportunity to counsel women about the benefits of any lifestyle changes (e.g. smoking, diet, exercise, alcohol intake) that may be required to correct or prevent risk factors.[6] Enquiring about colon cancer at the time of a menopause consult can promote participation in screening programs and is strongly advised. Some epidemiological data support a protective effect of MHT on colon cancer,[39,40] although this does not constitute an indication for initiation of MHT.

Menopausal symptoms affect the central nervous system, musculoskeletal system, and genitourinary tract (Table 3). Symptoms such as sleep disorders, memory, or concentration difficulties ('brain fog') are not always recognized as menopausal. Conversely, some women may present with symptoms that are part of the menopause constellation (e.g. depression, insomnia) but are in fact attributable to other causes. It is important to establish a clear association between symptoms and menopause before prescribing MHT.[6]

A risk evaluation to identify comorbidities is appropriate for all MHT candidates. The extent of the assessment will depend

on the presence and type of risk factors (e.g. obesity, smoking, hypertension, diabetes). Risk assessment tools have been developed for osteoporosis (e.g. FRAX®), breast cancer (e.g. IBIS Risk Assessment Tool), CVD (e.g. Systematic COronary Risk Evaluation; SCORE), and diabetes (QDiabetes®). Evaluating comorbidities can inform product selection and route of administration to minimize risk.

All candidates for MHT must be assessed for contraindications. MHT is contraindicated in women with known, suspected, or a history of breast cancer.[6] Although observational evidence suggests that MHT does not further alter risk in women with a family history of breast cancer[10] and, in some countries (e.g. Belgium and Switzerland), a family history is not a contraindication, it is prudent to not prescribe MHT for women at high risk of breast cancer. Clinical judgment is warranted by taking into consideration the number of cases and age at diagnosis within a given family history. Breast cancer risk calculators can also be of value.

Examination and investigations

All MHT candidates must undergo a physical examination, including a blood pressure check. Blood tests (e.g. fasting lipid profile, blood glucose level) are optional and can be selected based on the clinical picture that emerges during personal and family history taking.

In some countries (e.g. Belgium), mammography is generally performed before prescribing MHT. In other countries, results from government breast-screening programs, which are typically recommended every 2–3 years for women aged 50–70 years, may be used to inform the appropriateness of MHT for candidate patients.

Although some countries (e.g. Germany, Switzerland) perform endometrial ultrasound for candidate patients, systematic screening of asymptomatic patients for the early detection of endometrial cancer is not recommended due to the number of false positives.[41] Endometrial ultrasound is not necessary for not-at-risk, non-obese, non-diabetic patients with regular bleeding. Conversely, abnormal vaginal bleeding before or during MHT should prompt consideration of an ultrasound to check endometrial thickness (cut-off <4 mm) and exclude pathologies.

A dual energy x-ray absorptiometry (DEXA) bone density scan is performed routinely in some countries (e.g. Belgium) but not in others (e.g. UK). Procedure cost and DEXA availability are among the factors influencing local practice habits. DEXA is not mandatory for women with no risk factors who are candidates for or already receiving MHT, although it may be indicated in women at risk for osteoporosis.

Special situations

All women should be characterized before starting MHT, as each may have personal risk factors or a relevant family history (e.g. CVD, VTE, breast cancer) to consider. Identifying risk factors assists in individualizing treatment to minimize risk.[6]

Age

Women who enter the menopause before the age of 40 years have premature ovarian insufficiency. MHT is indicated to provide symptom relief and lower the risk of osteoporosis (and CVD).[42,43] The strongest evidence for endometrial protection is with cyclical combined treatment. Patient preference for route of administration of each MHT component must be considered when prescribing.[42,43] MHT should be continued at least until the natural age of menopause (~51–52 years), then reassessed.[42–44] As spontaneous ovarian activity may resume in women with premature ovarian insufficiency, some form of contraception may be required.[45]

Menopause between the ages of 40 and 45 years is considered early-onset menopause. The risk of CVD and mortality is higher in this group compared with women who enter menopause after the age of 50 years.[46] MHT is indicated for early menopause to control symptoms and prevent diseases associated with estrogen deficiency. Transdermal or oral estrogen therapy plus cyclical progestogen is generally considered first-line therapy for women with early menopause.[44]

The usual age for menopausal transition is between 45 and 55 years. Within this group, women aged 45–50 years are managed similarly to women aged >50 years. Women aged 50–59 years are the main target population for MHT. Initiating MHT is an option for symptomatic women aged ≥60 years,[10] although careful assessment is required to confirm that symptoms are indeed menopausal and to identify risk factors. Transdermal or ultra-low dose oral formulations may be most appropriate for use in this patient population.[10]

High-density breast tissue

High-density breast tissue is associated with an increased risk of breast cancer.[47,48] Progesterone in combination with estradiol appears less likely than other progestogens to increase mammographic density.[30] Evidence suggesting that breast cancer risk is lower with micronized progesterone or dydrogesterone than with other progestogens[8,26–28] supports their use in women with high breast density concerns. Tibolone has been shown to increase breast density to a lesser extent than estradiol/norethisterone acetate in postmenopausal women during 6 months of treatment.[49]

Endometriosis

In menopausal women with a history of endometriosis, MHT may reactivate residual disease or cause new lesions, although evidence is not sufficiently strong to deny treatment to women with severe menopausal symptoms.[50] An initial step in selecting treatment may be to differentiate between women with active lesions and those with a history of lesions. For patients with current symptomatic endometriosis who require MHT, a continuous combined estrogen plus progestogen

regimen or tibolone is appropriate.[51,52] In patients with a history of endometriosis, including those who have undergone hysterectomy, the possibility of residual endometrial tissue (e.g. lesions on the bowel) is frequently unknown. A pragmatic approach in hysterectomized women may be to begin MHT using estrogen (except in patients with known residual endometriosis or a history of deep infiltrating endometriosis) and, if symptoms return (e.g. abdominal pain), add a progestogen. Continuous combined MHT is also appropriate in this setting and tibolone can be considered.[52]

Metabolic disorders

All postmenopausal women with metabolic disorders, such as diabetes and dyslipidemia, should receive appropriate lifestyle, dietary, and pharmacological measures for the prevention of CVD. In women aged 50–59 years who require MHT for relief of menopausal symptoms, MHT has the potential to improve the cardiovascular risk profile by modifying certain metabolic parameters.[8] Estrogen is associated with beneficial effects on blood glucose levels, insulin sensitivity, low-density lipoprotein-cholesterol (LDL-C) and HDL-C levels.[53,54] As progestogen type can determine the differential effects of estrogen-induced changes in lipid and lipoprotein levels, the choice of agent is important. The least to greatest effect on metabolic parameters has been reported with dydrogesterone and medrogestone, progesterone, cyproterone acetate, medroxyprogesterone acetate, transdermal norethindrone acetate, norgestrel, and oral norethindrone acetate.[50]

Diabetes

The complete metabolic profile, including glucose and lipids, should be considered when selecting MHT for women with diabetes.[53] In diabetic women at low CVD risk, oral estrogen may be preferred given its stronger benefit on glucose and lipid profiles compared with transdermal estrogen.[55] In obese diabetic women and in those with a higher CVD risk, transdermal estrogen offers benefits in terms of triglyceride levels and coagulation factors.[55] In either case, progestogens with neutral effects on glucose metabolism, such as micronized progesterone or dydrogesterone, should be used in women with insulin resistance or diabetes.[55]

Dyslipidemia

Triglyceride and HDL-C levels are important considerations given their greater impact on CVD risk in postmenopausal women compared with men.[56] Dietary modifications and specific pharmacological therapy should be implemented as needed to correct dyslipidemia in postmenopausal women.

Although all estrogen preparations reduce LDL-C and increase HDL-C levels, a large pooled analysis showed that triglycerides are increased by oral estrogen (due to an increase in hepatic triglyceride synthesis) but are decreased by transdermal estradiol.[54] As such, transdermal MHT may be most appropriate in women with hyperlipidemia and hypertriglyceridemia, whereas oral MHT may be more suitable in women with low HDL-C levels. Among progestogens commonly prescribed for MHT in Europe, progesterone, dydrogesterone, and nomegestrol acetate have neutral effects on estrogen-induced modifications to blood lipids; norethisterone acetate attenuates the beneficial effect of estradiol on HDL-C but has favorable effects on triglyceride levels, LDL-C, and VLDL; and drospirenone has favorable effects.[32] In a longitudinal analysis, metabolic parameters (lipid and glucose levels) were similarly improved among women treated for a least 2 years with transdermal estrogen with or without dydrogesterone, indicating no attenuation by dydrogesterone of estrogen-induced beneficial effects.[57]

Obesity

The risk–benefit ratio of MHT differs in obese women (body mass index >30 kg/m^2) due to an inherently higher risk of breast cancer[58] and CVD.[59] Dietary measures as well as hypertensive and diabetes control, where applicable, should be implemented to counteract cardiovascular risk in obese women. Transdermal MHT, at low doses, may be preferable for obese women, mainly because it does not increase the risk of VTE.[5,6] Micronized progesterone and dydrogesterone are appropriate progestogens given their neutral effects on cardiovascular risk factors and lower associated risk of breast cancer.[60,61] To minimize risk, women who have undergone gastric bypass surgery for extreme obesity should receive a transdermal estrogen/progestogen or transvaginal progesterone.

Hypertension

Hypertension is not a contraindication for MHT; however, blood pressure should be controlled to minimize cardiovascular risk. Transdermal MHT, at low doses, may be preferable in patients with hypertension.[6]

Smoking

Smoking is not a contraindication for MHT but is regarded as a morbidity. Cessation should be advised in postmenopausal women who smoke. Oral estrogen is metabolized more rapidly than transdermal estrogen in smokers, supporting the use of the transdermal route in these women.[62] As smoking increases cardiovascular risk, low-dose transdermal estrogen and micronized progesterone or dydrogesterone may be preferred in view of their neutral effect on cardiovascular risk factors.[55,63]

Venous thromboembolism

Transdermal estrogen is associated with a lower risk of VTE than oral estrogen.[64] Separately, there is evidence that VTE risk varies by type of progestogen. In patients with a history of deep vein thrombosis, saphenectomy, or those at risk of VTE, transdermal

estrogen plus micronized progesterone or dydrogesterone is recommended, as these combinations are associated with the lowest risk of VTE.[64–66]

Migraine

The association between MHT use and migraine in postmenopausal women is unclear. Migraine attacks may be improved by MHT if they appear after menopause or may be worsened by MHT if they improve after menopause. In view of the link between fluctuating estrogen levels and menstrual attacks of migraine, maintaining a stable estrogen environment using non-oral routes may be an appropriate strategy.[67] Women with a history of migraine should receive the lowest dose of transdermal estrogen necessary to control menopause symptoms.[67] Continuous formulations (e.g. continuous combined transdermal preparations or levonorgestrel intrauterine system) are preferred to avoid the adverse effect of cyclical progestogens on migraine.[67] As migraine with aura is a risk factor for stroke, women with a past or current history should receive non-oral MHT.[67]

Surgery

The need to discontinue MHT prior to elective surgery depends on the type of surgery (e.g. day surgery *versus* a more complex procedure requiring immobilization and prolonged hospitalization). In patients not at risk of VTE who will be mobilized soon after surgery, discontinuing MHT before surgery is likely unnecessary. In patients receiving oral MHT who are at high risk of VTE after surgery, a therapeutic window or change to transdermal MHT prior to surgery can be considered.

Miscellaneous conditions

Certain patients (e.g. those with autoimmune diseases) may react adversely to MHT or experience deterioration in their condition during hormone therapy. In patients with systemic lupus erythematosus, the risk–benefit ratio of MHT must be weighed carefully due to the increased risk of VTE, cardiovascular events, and disease flare.[68] Conversely, as rheumatoid arthritis is a risk factor for osteoporosis, its presence may be an added consideration in symptomatic women who are candidates for MHT.

The safety of MHT in patients with a given disease, especially a rare disease, is not always known. With some exceptions, a general approach may be that premenopausal women who have had bilateral oophorectomy as part of the management plan for a given disease are not candidates for MHT. Otherwise, MHT may be appropriate. In women with *BRCA1* or *BRCA2* mutations who have had risk-reducing bilateral salpingo-oophorectomy, MHT can be used in the absence of a personal history of breast cancer.[42]

Conclusions

In suitable candidates, MHT is an important tool to treat menopausal symptoms and maintain bone health. Progestogens are added to estrogens to provide endometrial protection in women with a uterus. When a progestogen is required, micronized progesterone and dydrogesterone appear to be the safest options for minimizing cardiovascular, thromboembolic, and breast cancer risks compared with other progestogens. MHT, including the choice of progestogen, should be individualized according to the patient's medical history and treatment goals.

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