Menopause Hormone Therapy

6

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6.1 Introduction

There are more than 100 years of history of providing supplemental hormones to women in the menopause transition. Given the early and ongoing assumptions, then the limited data, then a plethora of data, it is not surprising that many women and many clinicians remain either confused or overwhelmed by the nuances of menopause hormone therapy (MHT). Estrogen, and estrogen with a progestogen in women with a uterus, are indicated for relief of vasomotor symptoms and vaginal dryness, and for osteoporosis prevention [1]. Other menopausal symptoms benefit from MHT. In this volume, chapters on each menopause transition experience provide the specifics of estrogen and progestogen application and benefits if any for that symptom. This chapter summarizes international and regional guidelines and analyzes the data regarding important differences in patient profile, hormone formulation, and delivery route which impact the benefits and risk profile.

6.2 Estrogen

6.2.1 Type and Delivery Methods of Estrogen Therapy

Oral estradiol is poorly absorbed in the gastrointestinal tract. It is rapidly converted to estrone in the intestinal mucosa, then extensively metabolized in the first pass through the liver. Less than 5% of the original dose of estradiol is available unchanged in circulation. For clinical use, estradiol absorption is enhanced by micronizing. Estrogens are stabilized by conjugating or adding piperazine or an

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Table 6.1 Oral estrogens available for menopausal use. Not all doses are available in all regions

Estrogen	Low dose (mg/day)	Moderate dose (mg/day)	High dose (mg/day)
Conjugated equine estrogen (CEE)	0.3, 0.4, 0.45	0.625	1.25
Conjugated estrogen (CE)	0.15, 0.3, 0.4, 0.45	0.625	
Piperazine estrone	0.3, 0.625	1.25, 1.5	2.5
Ethinyl estradiol (EE)	<0.010	0.010	>0.010
17beta-estradiol (E2)	0.5, 1.0	1.5, 2	4
Estradiol valerate (EV)	0.5	1	2
Esterified estrogen (ESE)	0.3	0.625	1.25

Classification of orally delivered estrogen doses based on Furness et al. [5]

ester group. Addition of an ethinyl group decreases liver metabolism, increasing potency [2].

Conjugated equine estrogen (CEE) was made available as Premarin® in North America in the 1940s. With development of more sensitive assays it became clear that CEE contains at least ten equine estrogens, all of which are biologically active, with 17beta-estradiol dominant [3]. Subsequently, synthesized conjugated estrogen, micronized estradiol, and esterified estrogen became pharmaceutically available. Conjugated estrogen and 17beta-estradiol are available in oral products or topical vaginal creams from regulatory bodies. Other estrogens are available in oral and in transdermal forms as adhesive patches, creams, gels and sprays, as well as topical vaginal cream [4]. See Table 6.1. These estrogens have unique absorption and first-pass hepatic metabolism when delivered orally and unique absorption profiles dependent on the delivery matrix when used topically [5, 6]. Transdermal delivery avoids hepatic first-pass effect on lipid profile and achieves a steady state serum level. There are differences in risk profile between transdermal and oral delivery, discussed in that section.

6.3 Progesterone

Micronized progesterone, medroxyprogesterone acetate, dydrogesterone (a stereoisomer of progesterone, not available in North America) and progestins, synthetic compounds with progestational activity, are pharmaceutically available for use in MHT. Collectively all progestational activity compounds, including progesterone, are termed progestogens [7]. Progestogen dose is determined by ability to inhibit endometrial development. There are limited studies comparing progestogen side effect profiles. Differences in risk profile are discussed in that section.

The biological activity, including pharmacokinetics, potency, and efficacy are dependent upon structure. Synthetic progestins are classified as having structure similar to testosterone or structure similar to progesterone, a classification unrelated

Table 6.2 Bioavailability and half-life of progestogens

Micronized progesterone	Progesterone similar molecular structure	Testosterone similar molecular structure		Spironolactone similar molecular structure
Low <5% bioavailable Half-life oral with food 5–10 h, vaginal 14–50 h	*Medroxyprogesterone* High >90% bioavailable Half-life oral 40–60 h *Dydrogesterone* Moderate 28% bioavailable Half-life 8 h	*Norethindrone/ norethisterone family* Prodrugs norethindrone acetate, ethynodiol diacetate, lynestrenol Moderate 62–76% bioavailable Half-life 8 h	*Levonorgestrel family* Etonogestrel, Desogestrel Prodrug norgestimate to norelgestromin High >90% bioavailable Intermediate half-life	*Drosperinone* Moderate 66% bioavailable Half-life 31–32 h

to source or molecular precursor [8]. Drospirenone is structurally similar to spironolactone and synthesized to exhibit progestogenic activity. See Table 6.2. Some progestogens of the norethindrone family (norethindrone acetate, ethynodiol diacetate, and lynestrenol) and of the levonorgestrel family (desogestrel and norgestimate) are prodrugs and require hepatic metabolism into the biologically active form. Metabolism of norethindrone also results in ethinyl estradiol (EE). It is estimated that a dose of 0.5–1 mg oral norethindrone may result in an increase of 2–10 μg of EE [8].

6.3.1 Clinical Use of Progesterone in the Menopause Transition

Progesterone may be used alone for treatment of VMS in women who cannot use estrogen, but is most commonly used in combination with an estrogen for endometrial protection [6]. Progesterone improves sleep and has beneficial effects on endothelial function, a marker for cardiovascular risk [9]. Used alone, progestogens demonstrate limited ability to manage VMS. In small studies, progesterone at 150% of standard dose independently alleviated VMS. A systematic review of progestogen only therapy identified seven RCT with a total of 601 women using varied forms and doses of progestogen, with both oral and transdermal administration, with durations of treatment from 21 days to 12 weeks [10]. A trial of 300 mg micronized progesterone reported the most robust findings. Women within 10 years of menopause randomized to either 300 mg of micronized progesterone or placebo demonstrated improvement of VMS frequency and overall VMS score (58.9% improvement progesterone, 23.5% improvement placebo) but not in VMS severity [11]. Side effects including headaches and vaginal bleeding were significant in five of seven trials and led to discontinuation of treatment in 6–21% of participants.

None of the studies were of sufficient power or duration to identify risks in progestogen only therapy [10].

6.3.2 Type and Delivery Methods of Progesterone and Progestins

Oral Delivery Progestogen
Given significant differences in progestogens, oral delivery results in considerable variability, up to fivefold, of circulating active drug and intracellular progesterone activity. Further, in a not yet completely defined manner, dependent upon the particular progestogen-receptor combination, the bioactivity may range from partially to fully either agonistic or antagonistic within the same cell [8].

Transdermal Delivery
Two transdermal progestins, levonorgestrel and norethindrone acetate, are available as patches in combination with estradiol for use in menopause symptom management. There are no transdermal topical progesterone cream or gel products approved for menopausal use.

Intravaginal Delivery
Intravaginal progestogen delivery has been studied but is not approved for use in menopause symptom management. Compared to intramuscular, intravaginal delivery of 200 mg micronized progesterone gel (compounded, off-label) resulted in relatively low circulating progesterone (7 ng/mL vs. 16 ng/mL) but still exhibited increased progestational endometrial activity, the target organ of progestogen therapy [12]. Micronized progesterone gel 4% (45 mg/day) is available in pharmaceutical grade with regulatory body approval for uses other than menopause symptom management. This delivery method was not represented in the 2020 systematic review [10].

6.4 Combined Estrogen and Progestogen in Women with a Uterus

6.4.1 Endometrial Suppression

In women with a uterus, a progestogen or bazedoxifene, a selective estrogen receptor molecule with endometrial suppression activity, must be used in conjunction with estrogen in all stages of the menopause transition to protect from endometrial hyperplasia, atypia, and possible carcinoma [1, 6, 13–16]. Systemic oral delivery of estrogen alone in women with a uterus is associated with endometrial hyperplasia at all doses and duration of therapy between 1 and 3 years [5].

6.4.2 Combined Hormone Regimens

Continuous combined regimens use an estrogen with a progestogen (E + P) on a daily basis. The continuous combined regimen avoids withdrawal bleeding and allows for smaller though more frequent doses of progestogen than sequential regimens. Continuous combined E + P is associated with more frequent unscheduled uterine bleeding, up to 40% in the first several months after initiation, but most women (75–89%) become amenorrheic within a year due to progressive progestogen induced endometrial suppression [17].

Sequential, also known as cyclic, estrogen and progestogen regimens use daily estrogen with the addition of progestogen at an increased dose for 12–14 days each month. This is likely to be followed by monthly withdrawal uterine bleeding. Long cycle regimens, with a progestogen every 2–6 months, have insufficient evidence of endometrial safety. Long cycle regimens are not recommended in international or regional menopause symptom management guidelines [1, 6, 13–16].

Delivery of oral micronized progesterone 200 mg was shown efficacious in endometrial protection for up to 5 years when used cyclically for 12–14 days each month [18]. Maximum endometrial protection was seen in the continuous combined delivery regimen. For women with an intact uterus using continuous combined estrogen and oral progestogen, the risk of endometrial hyperplasia was not different from placebo (1 mg NETA: OR 0.04; 95% CI 0–2.8 and 1.5 mg MPA: no hyperplasia events) [5]. The recommended dose of oral progestogen for endometrial protection is based on potency studies of endometrial tissue relative to norethindrone/norethisterone dose as value of 1 [19]. See Table 6.3.

Though off-label, use of the 52 mg levonorgestrel intrauterine system (LNG-IUS) as a menopause progestogen to suppress estrogen effect on the uterine endothelium is included in the recommended options of the Korean Society of Menopause, North American Menopause Association clinical care guidelines, the Society of Obstetricians and Gynecologists of Canada and the Indian Menopause Society Guidelines [6, 13, 14, 16]. The 52 mg, 20 μg/day, LNG-IUS used with various estrogen types and doses demonstrated strong endometrial suppression in clinical trials and observational studies of women in postmenopause followed for 5 and 10 years [20–23]. There was no difference in intrauterine and systemic progestin in symptom relief in a 2011 systematic review of the LNG-IUS that included six trials with 518 participants. Intrauterine progestin had less endometrial proliferation than sequential oral MPA [24].

Vaginal micronized progesterone gel 4% (45 mg/day) used sequentially at least 10 days/month or every other day at 100 mg/day for up to 3–5 years provided endometrial protection [18]. This indication is not approved by pharmaceutical regulatory bodies.

Table 6.3 Minimum progestogen dosing for endometrial suppression when used with standard dose of estrogen

	Continuous combined mg/day	Sequential (12–14 days/month progestogen with daily estrogen) mg/dose
Oral		
Micronized progesterone	100 mg	200 mg
Medroxyprogesterone acetate	2.5 mg	5 mg
Norethindrone/norethisterone	0.35 mg	0.35–0.7 mg
Norethindrone/norethisterone acetate	0.5–1 mg	2.5 mg
Dydrogesterone	5 mg	10 mg
Transdermal (available only as patches in combination with estrogen)		
Norethindrone/norethisterone acetate	0.14–0.25 mg	
Levonorgestrel	0.015 mg	
Dienogest	2 mg	
Vaginal		
Progesterone gel[a]	45–100 mg twice to three times weekly	45–200 mg
Intrauterine system		
Levonorgestrel[a]	20 μg/day or 52 mg device	

[a]Not approved for endometrial suppression in MHT. Based on Pinkerton [17], Meeta et al. [14], Mueck and Römer [20]

6.5 Bioidentical Estrogen and Progesterone

The definition of bioidentical hormone therapy (BHT) is "having the same molecular structure as a substance produced in the body" with a first known use of the term in 1997 [25, 26]. Sometimes the term body-identical is substituted. All hormone products are synthesized or changed in some manner with the exception of the Class A steroid conjugated equine estrogens, which while native to the horse, are not to the woman. Although technically of questionable accuracy, bioidentical terminology has slowly become accepted in the scientific realm and typically applies to estradiol and micronized progesterone. Many BHTs are available via approved regulatory bodies. Thus bioidentical is a distinct concept from custom compounded hormone therapy.

Superiority of Micronized Progesterone Micronized progesterone (MP) is available from regulated pharmaceutical sources. Evidence for the superiority, if any, of MP over synthetic progestins is limited to observational studies and physiological data. Micronized progesterone may provide a clinical benefit beyond endometrial protection with a mild sedative effect in women with sleep issues [27, 28].

Micronized progesterone appears to convey the best safety profile in breast cancer risk as seen in the E3N longitudinal observational study [29]. Physiological data demonstrate that MP with transdermal estradiol is less mitogenic in breast tissue than CEE with MPA [30]. Medroxyprogesterone acetate and androgenic progestins negated the endothelial cell protection, improved lipid profile, and improved glucose metabolism imparted by estrogen while MP and drospirenone (available in one combination estrogen/progestin product for menopause therapy use) did not [31–34]. The American Association of Clinical Endocrinologists and American College of Endocrinology guidelines call for preferential use of micronized progesterone over progestins [35].

Superiority of Estradiol Estradiol is available from regulated pharmaceutical sources. There are very few comparison studies of different estrogens' efficacy. There is no strong evidence of estradiol superiority over CEE in management of VMS [36]. The increase in hepatic stimulation with oral dosing, indicated by increase in sex hormone binding globulin, is twofold for oral CEE over oral estradiol [37]. Oral estrogens are largely converted to estrone via hepatic metabolism. CEE, composed of many estrogens, contains a higher dose of estrone via the tablet and as a result of metabolism than estradiol. Estrone is the most prothrombotic of the three adult human estrogens [27, 28, 38]. The effect of this in outcome studies is difficult to determine. Risk of estradiol and CEE have been assessed in large population studies and smaller nested case control designs, but there are few direct comparisons. CEE studies report either no higher rate or an increased rate of CVD over reports in estradiol studies [39, 40].

Estradiol use may be cardioprotective in specific groups (see Chap. 5). Age of initiation and the type of progestogen used affected outcome. Stronger CVD protection was seen with initiation close to the age of menopause, use of estrogen alone in women without a uterus, or with use of estradiol but not CEE combined with micronized progesterone or NETA rather than MPA [27, 28]. In a direct observational study, comparison of CEE current users showed a doubling of risk of thromboembolic events over current estradiol use (RR 2.08, 95% CI 1.02–4.07) [41]. As discussed later in this chapter, transdermal delivery of estradiol does not appear to convey risk of increased gallbladder disease, thromboembolic events, stroke, or of CVD when used close to the age of menopause. The American Association of Clinical Endocrinologists and American College of Endocrinology guidelines call for preferential use of transdermal estrogen delivery but do not stipulate a preference for either CEE or estradiol in other routes of administration [35].

6.5.1 Compounded Bioidentical Hormone Therapy

Compounding is the process of mixing, combining, or altering ingredients to create a medication tailored to the needs of a patient [42]. Compounding is initiated by a health care clinician's order, then fulfilled by a licensed clinician, most often a

pharmacist, who may or may not have special training and certification [43]. Compounding plays a role in menopause hormone therapy but there is confusion in terminology. In this chapter, bioidentical hormones, as already defined, are hormones having molecular structure the same as the human body. Compounded bioidentical hormones (cBHT) meet bioidentical criteria, but are obtained from a compounder rather than a pharmaceutical manufactured source. The term *natural*, employed in popular literature, is without scientific precision or accuracy.

Following the publication of the Women's Health Initiative study of CEE with or without MPA, there was a popular push away from synthesized hormones and toward cBHT worldwide, with the largest impact in the United States. Tracking of compounded prescriptions and post-marketing is done on a state level, making it difficult to determine the impact and safety of cBHT use [44]. In the USA, an estimated 1–2.5 million women aged 40 years or older use cBHT, accounting for 28–68% of all hormone use. Of women using cBHT, 86% of women were unaware that the products are not FDA approved [45]. In an internet survey of women ages 40–84 years, 28% of responders were ever-users of MHT with cBHT representing 31% of all ever-users and an even higher 41% of ever-users among the younger women aged 40–49 years [44]. In contrast, in Australia, data published in 2016 showed current use of MHT in a population survey of women age 50–69 years was 13%, similar to the number reported in 2004–2005 following the 55% decrease in use seen after publication of the WHI. The estimated population weighted prevalence of ever use cBHT in Australia was 6% and was 2% for use at the time of the survey [46].

A qualitative analysis identified women's decision-making process in choosing a cBHT over an approved product. Themes of fear of the safety of FDA-approved hormone products, aversion to CEE specifically, and distrust of the medical and pharmaceutical industries emerged. In contrast, women were attracted by a belief of superior safety and efficacy in cBHT, as well as cBHT being more tailored to an individual's needs while accompanied by enhanced clinical care and attention [47]. Analysis of the regulatory gaps in cBHT with in the United States can identify fallacies in these beliefs.

Compounded products are not tested for safety or efficacy or required to be labeled with the warnings imposed on regulatory approved medications using the same active ingredients. The lack of data and labeling do not imply safety, though the public may be led to believe it does so. Compounding pharmacies have much less stringent regulatory supervision. They are not required to report adverse drug events [43]. Pharmacies, regardless of size, that do not provide more than 5% of their product across state lines are exempt from registration, from new drug applications including the standard process of dose determination, efficacy and safety, from providing medication labels with instructions for use, and from current good manufacturing practice procedures, all of which create challenges in patient understanding of cBHT use [43].

The National Academy of Science, Engineering, and Medicine (NASEM) of the United States released a comprehensive report on the Clinical Utility of Compounded Bio-identical Hormones in 2020. Large gaps in data were identified. Their report states that the absence of data does not imply safety [43].

- There were no studies of compounded progesterone with estrogen related to risk of endometrial cancer.
- In assessing effectiveness of cBHT in meeting the approved indications for MHT, studies of estradiol were largely limited to manufactured products sponsored by pharmaceutical companies rather than individually compounded products.
- There were no studies of osteoporosis prevention (see Chap. 13).
- Only one study of compounded progesterone cream was identified, indicating effectiveness in managing VMS but limited by difficulty in replication of the product studied [48].
- Data on estriol, limited to approved manufactured products from outside the United States rather than compounded products, failed to demonstrate superiority to estradiol in meeting MHT indications.
- There were no studies on effectiveness of compounded estradiol, estriol, or progesterone in improving symptoms associated with genitourinary syndrome of menopause (see Chap. 11).
- There were no studies allowing conclusions on the safety, either superior or inferior, of cBHT products compared to BHT products approved by regulatory bodies.

Endometrial cancer protection using compounded progesterone is reliant on the least bioavailable of the progestogens, and a form possibly ineffective in transdermal but not transvaginal delivery. There is no identified safe and effective dosage of topical progesterone cream or gel. There is no long-term data demonstrating lasting suppression or prevention of endometrial neoplasia [8, 18].

In multiple studies, pharmaceutical grade progesterone cream at doses of 30–80 mg/day applied to keratinized skin and administered with estrogen, found serum levels of progesterone remained very low (>4 ng/mL) though with evidence of endometrial suppression and high salivary levels of progesterone. However at 20 mg/day dose, endometrial suppression was seen in only a limited number of participants. Efficacy of topical progesterone cream in endometrial suppression cannot be based on serum progesterone level but must rely on endometrial evidence of suppression [49].

Further compromising patient safety, prescriptions for combined estradiol progesterone capsules and creams from 15 compounding pharmacies showed up to 27% and 35% variation in dose for capsules and up to 14% and 18% in creams [50]. Many creams available over the counter and labeled progesterone did not actually contain progesterone but rather contained wild yam extract. Diosgenin, a precursor for progesterone, is present in wild yam extract but the necessary conversion to an active ingredient is not possible in vivo [8]. Cases of endometrial cancer have been reported in women taking cBHT [51].

The National Academy of Science, Medicine and Engineering concluded that the majority of marketing claims about the safety and effectiveness of cBHT preparations are not supported by evidence from well-designed, properly controlled studies [43]. The International Menopause Society, the American College of Obstetricians and Gynecologists, the Endocrine Society, the North American Menopause Society

(NAMS), the United States Food and Drug Administration, the American College of Clinical Pharmacology, the Society of Obstetricians and Gynaecologists of Canada, and the Australian Menopause Society have all released statements advising against the use of compounded therapy until evidence is produced with regard to efficacy and safety. As the Australian Menopause Society statement acknowledges, "with such diverse content mix, production sites and methods, that is unlikely to be forthcoming" [1, 6, 16, 26, 42, 52–54].

A role for compounding menopause hormone therapy continues in the provision of products addressing dose and allergies, particularly peanut allergy. In most of the world except the USA, peanut oil in micronized progesterone capsules has been replaced by safflower oil. Safflower oil is not a registered drug component in the USA [28]. Women allergic to peanuts require a compounded product to use oral micronized progesterone.

6.6 Risks in Estrogen Only and Estrogen with Progestogen Menopause Hormone Therapy

The most common therapy associated risks for MHT use are venous thromboembolism (VTE) and gallbladder disease. There is a less robust but consistent risk of stroke within specific patient profiles. There is some increase in risk of breast cancer with long duration estrogen and progestin use and much less to no increase in breast cancer with estrogen alone. The type of estrogen, the delivery route, and the timing and duration of use impact risk. See Table 6.4.

6.6.1 Venous Thromboembolism

Estrogen plus progestogen menopause therapy is associated with a doubling of risk of VTE across all age groups (RR 1.92; CI 1.24–2.99. 33,477 in six studies). The assumed risk increased from 10:1000 to 20:1000 users. There is slightly less risk in women less than 10 years from menopause (RR 1.74, CI 1.11–2.73), with an increase in assumed risk from 6:1000 to 11:1000 users. The majority of events occur in the first 1–2 years of MHT use [55].

Route of delivery affects the increase in risk of VTE. Estrogen delivered orally causes significant hepatic stimulation [56]. Transdermal delivery, avoiding first-pass liver metabolism, has decreased risk of VTE over oral delivery of estrogen. Transdermal delivery of estrogen demonstrated no significant increase in VTE in a meta-analysis of seven population-based studies including 26,471 VTE cases [57].

6.6.2 Gallbladder Disease

Estrogen alone and estrogen with progestogen increased risk of gallbladder disease measured as occurrence of cholecystectomy (HR 1.10, 95% CI 1.01–1.20)

Table 6.4 Summary of hormonal management of VMS

	Indications	Contraindications and cautions	Risk → Risk amelioration
			Absolute Risk Uncommon 1/100–1/1000[a]
Estrogen and progestogen (E+P) Estrogen alone in women w/o a uterus (E)	Moderate to severe VMS Osteoporosis prevention GSM	*Contraindications*: History CVD Hormone-dependent cancer Active or history of thromboembolic event Severe active liver disease w/abnormal LFT Undiagnosed vaginal bleeding History of breast cancer *Cautions* History of gallbladder disease Prothrombotic mutations	VTE across all age groups → No increase risk with transdermal estrogen Gallbladder disease Risk E > E+P → Less increase risk with transdermal estrogen Dementia *only when initiated 65+ years age.* Risk E+P > E → No increase risk initiated close to age of FMP Consider nonhormonal management options 65+ years age
			Absolute Risk Rare 1/1000–1/10,000
			Stroke, CVD *when initiated 60+ years age* → No increase risk initiated close to age of FMP No increase risk with transdermal estrogen Less increase risk with estrogen dose <oral estradiol 1 mg, CEE 0.0625 mg, transdermal estradiol 0.05 mg Less increase risk with micronized progesterone Increased incidence breast cancer *when initiated close to FMP and used for long duration.* Risk E+P > E → Less increase risk with micronized progesterone Assess use regularly Consider nonhormonal management after long duration of use
CEE and bazedoxifene	Moderate to severe VMS Osteoporosis prevention	Same as E/E+P with addition of Contraindicated Prothrombotic mutations	Limited data. Unable to draw conclusions
Tibolone		Same as E/E+P	

VMS vasomotor symptoms, *GSM* genitourinary syndrome of menopause, *CVD* cardiovascular disease, *VTE* venous thromboembolic event, *E* estrogen, *P* progestogen, *LFT* liver function tests, *FMP* final menstrual period, *CEE* conjugated equine estrogen

[a]Definitions of frequency of adverse drug reactions (CIOMS): uncommon (infrequent) ≥1/1000 and <1/100, rare ≥1/10,000, and <1/1000 from World Health Organization definitions https://www.who.int/medicines/areas/quality_safety/safety_efficacy/trainingcourses/definitions.pdf

in the French E3N observational study of 70,928 women. The largest increase in risk was seen in the estrogen only group. When adjusted for age, body mass index, parity, diabetes, and hypercholesterolemia, the oral estrogen only group demonstrated an increase in risk (HR 1.16, 95% CI 1.06–1.21) with an assumed risk of 1:150 incidence of cholecystectomy over 5 years of oral estrogen only use [58].

As in VTE, transdermal, rather than oral, delivery of estrogen ameliorates increased risk of gallbladder disease. In a prospective review of hospital records in women in the United Kingdom, the Million Women Study, current users of oral estrogen had increased risk of gallbladder disease (RR 1.64, 95% CI 1.58–1.69) which decreased after discontinuing estrogen (RR 1.27, 95% CI 1.22–1.32) compared to never users. Current transdermal estrogen therapy was associated with significantly lower increase in risk of gallbladder disease (RR 1.17, 95% CI 1.10–1.24) [59].

6.6.3 Stroke and Cardiovascular Disease

Dose of estrogen, timing of MHT initiation, and delivery method influence risk of stroke. Women in the Women's Health Initiative (WHI) with and without modifying risk factors such as hypertension, history of CVD, previous hormone use, statin use, and aspirin use had increased risk of ischemic stroke in the CEE plus MPA group (RR 1.49, 95% CI 1.02–1.90) and the CEE group (RR 1.39, 95% CI 1.10–1.77) with MHT initiation mean 12 years postmenopause. The risk is categorized as rare with an absolute risk of 0.8:1000 and 1.2:1000, respectively [60, 61]. In large epidemiological studies and in the WHI observational trial there was no increased risk of stroke when MHT was initiated close to the age of menopause [60, 62]. Doses of estrogen lower than 1 mg estradiol and 0.625 mg CEE were not associated with increased risk of stroke [60]. Transdermal delivery of estrogen, with and without progestin, at doses 50 mcg and lower did not have any increased risk of stroke in a nested case control study of over 15,000 women (RR 0.95, 95% CI 0.75–1.20) [63].

Initiation of MHT in healthy women conveys no to minimal increased CVD risk. The timing of MHT use in the menopause transition effects MHT and CVD interaction. A large systematic review analyzed the timing hypothesis of MHT and CVD [55]. A collection of observational, case-controlled, and epidemiological studies of women using MHT published in the 1990s and involving over 90,000 women followed for a range of 2–16 years indicated a 30–50% reduction in cardiac events with use of MHT when initiated close to the age of final menstrual period [55, 64]. These findings were in agreement with the WHI analysis of women starting MHT <10 years after the final menstrual period and with the Danish Osteoporosis Prevention Study (DOPS) which included women aged 45–58 years age within ≤24 months of final menstrual period [65–68].

MHT for secondary prevention of future CVD events in women with existing CVD demonstrated increased events in the first year of use, a risk that ameliorated with continued use [69]. A systematic review and meta-analysis of MHT and cardioprotection shows no impact of MHT on CVD mortality in women with preexisting CVD (Risk 45 per 1000 placebo and MHT) [55]. The International Menopause Society along with regional menopause societies state that MHT has no role in secondary prevention of CVD. Nonhormonal methods should be used for VMS management in women with existing CVD [6, 13–16, 70].

6.6.4 Breast Cancer

Summary of risk The Revised Global Consensus statement representing multiple regional scientific societies concluded that the increased risk of breast cancer associated with MHT in women over 50 years age is complex, and seems to be primarily, but not exclusively, associated with the use of estrogen with progestin. The increased incidence of <1.0 case of breast cancer per 1000 women per year of E + P use meets the definition of a rare event. Further, the consensus statement points out that the relative risk of breast cancer with MHT use is akin to that of the risk of breast cancer from sedentary lifestyle, obesity, and alcohol consumption [1].

Concern arose regarding the effect of combined E + P in menopause treatment from the WHI. The study demonstrated increased risk of breast cancer with use of CEE and MPA (RR 1.26; 1.0–1.59 later revised to RR 1.24; 1.01–1.53) but not CEE used alone in women without a uterus [71]. Risk was primarily in women who initiated MHT close to the final menstrual period and continued for prolonged duration. Risk of breast cancer with use of CEE + MPA for this group has an estimated hazard ratio of 1.64 (95% CI 1.00–2.68) with 5 years use and 2.19 (95% CI 1.56–3.08) with 10 years use [72].

6.6.4.1 Effect of Progestogen Formation on Breast Cancer Risk

No studies of progestogens alone at power sufficient to detect breast cancer and other risks have been done. Progesterone and progestins have differential affinity for PR-A and PR-B receptors in breast tissue, raising the question of a possible differential breast cancer risk [8]. There are no sufficiently powered RCTs of any progestin with estrogen other than CEE/MPA use in the WHI. A meta-analysis of observational studies including 86,881 women in postmenopause with a mean age of 59 years and followed for a range from 3 to 20 years compared cancer risk in MP and synthetic progestins. Micronized progesterone with estrogen was associated with lower breast cancer risk compared to progestin and estrogen use (RR 0.67, 95% CI 0.55–0.81) [73].

A subsequent systematic review of MP and breast cancer risk concluded that estrogens combined with oral MP or vaginal MP (off-label) do not increase breast cancer risk for up to 5 years of use. Further, there is very limited evidence that oral MP combined with estrogens for more than 5 years of use is associated with increased breast cancer risk.

The review identified 19 studies of varied design, type of estrogen, inclusion of progestins as well as use of MP, duration of follow-up (4.0–11.2 years), and sample size (643–80,391) [74]. Findings in the studies ranged from that of no difference in breast cancer risk among E + P use regardless of progestogen [75] to the Etude Epidemiologique de femmes e la Mutuelle Generale d l'education Nationale E3N report of 2354 cases of breast cancer among 80,377 women in postmenopause with no increase in risk of breast cancer in less than 6 years use of estradiol with MP (RR 0.9; 95% CI 0.7–1.2) while use of estradiol with

synthetic progestins did incur risk (RR 1.4; 95% CI 1.2–1.7) [76, 77]. The third report of the E3N demonstrated increased breast cancer risk with MP use mean 6.1 years (RR 1.22; 95% CI 1.11–1.35) and increased risk using synthetic progestins for more than 5 years (RR 1.98; 95% CI 1.73–2.26) [29]. This increase risk of breast cancer dissipated after discontinuation of MP (3 months to 5 years since last use, RR 1.15; 95% CI 0.93–1.42) but remained elevated 5–10 years after discontinuation when synthetic progestins were used for at least 5 years (RR 1.34; 95% CI 1.04–1.73) [29]. That said, counseling on breast cancer risk with use of E + P should be provided to all women regardless of progestogen used [74].

6.6.5 Dementia

The interaction of MHT use with cognitive function and with risk of Alzheimer's disease appears to differ between the cognitive condition investigated, the type of estrogen used, the type of progestogen used, and the use of unopposed estrogen [78]. Multiple national and international guidelines caution against MHT initiation in women over age 65 years due to risk of Alzheimer's disease but do not generalize this increased risk to younger women. No guidelines support the use of MHT for prevention of dementia [1, 13–16].

A meta-analyses of observational studies prior to 2001 linked MHT use to reduced risk of Alzheimer's disease. These primarily included younger women, close to the age of menopause, and identified a larger benefit from 17beta-estradiol than from CEE [79]. The WHI Memory Study (WHIMS), a randomized trial of CEE + MPA or CEE alone, found increased risk of probable dementia but not minor cognitive impairment (MCI) in women starting MHT after age 65. Probable dementia was determined by universal screening for cognitive function, followed by neuropsychological testing and diagnostic procedures. The small number of identified cases limited statistical power. The CEE + MPA active treatment group demonstrated doubling of risk, with an absolute risk of 12 additional dementia cases for 1000 treated women over 5 years. The CEE alone group had a relative risk of 1.5 that was not statistically significant [80, 81]. Observational data has also looked into the effect of current use compared to past use and the age and timing of use. Younger women who used hormone therapy were at reduced risk of Alzheimer's disease. Current users were at higher risk than past users. These findings may be subject to unidentified variables including a health bias [78].

The risk of a deleterious MHT effect on cognitive function has not been widely analyzed. The WHI Study of Cognitive Aging (WHISCA) explored the effect on cognitive functioning measured by standardized tests with current use of MHT in women with a mean age of 74 years. Current use of CEE + MPA but not of CEE alone worsened verbal memory over placebo and the effect was not age dependent [78].

6.7 Discontinuation of Menopause Hormone Therapy

Guidelines do not stipulate an age at which hormone therapy should be discontinued [6, 13–16]. As menopause symptoms are largely transitional, and as underlying health risks and some risks associated with use of MHT increase with age and duration of use, women should be assessed and educated regularly to share in decision-making regarding continuation of therapy. Women tolerated MHT discontinuation equally well when hormones were either stopped abruptly or tapered over 4 weeks to 6 months [82, 83]. There is limited data and a lack of consistency in stage of menopause, age of participants, and duration of therapy among hormone discontinuation studies [84–86]. In a follow-up of women with mean age at discontinuation of 56.8 ± 3.7 years and mean duration of use of 6.9 ± 2.3 years using the Menopause Rating Scale (MRS), a large number were lost to follow up (23%) and 93% of remaining women experienced recurrence of symptoms, including vaginal dryness. Twenty-three percent resumed systemic hormone use and 62% initiated vaginal estrogen [87]. Inclusion of vulvovaginal symptoms in the MRS likely contributed to the high rate of symptom recurrence. Separate data on VMS was not reported. Resumption of systemic hormones in 23% of women concurs with other observational studies [88].

6.8 Tibolone

Tibolone is a product with both estrogenic and progestogenic activity but is supported by less extensive research than estrogens and progestogens. It is available in Europe, Korea, Australia, and India, but not approved in the United States or Canada. Recommended dose is 2.5 mg orally. Tibolone has been shown effective in managing VMS, reducing bone fracture, and improving sexual dysfunction related to the menopause transition [89–92]. Tibolone may have an improved breast cancer and endometrial cancer risk profile over E + P [93]. As breast cancer is a rare to infrequent event after prolonged duration of exposure to E + P, the small sample sizes and limited duration of tibolone studies make interpretation of actual risk difficult. In women with a history of breast cancer, use of tibolone was associated with increased risk of recurrence [90].

Tibolone is a progestogen of the norethindrone family with low affinity to the progesterone and androgen receptors in its own form. Tibolone is metabolized rapidly into three metabolites, two of which bind to estrogen receptors, and the third of which binds to progesterone receptors [8].

In a small trial (n = 140 in 3 arms), tibolone was equally effective as CEE with MPA except in the Female Sexual Function Index, where tibolone demonstrated superiority [92]. In a systematic review of use of tibolone in Asian women, combined MHT was more effective in VMS management than tibolone in nine RCTs with 1336 women. When studies with a high risk of attrition bias were eliminated, the resulting effect was if 7% of women taking MHT experience VMS,

8–14% of women taking tibolone will do so. Unscheduled bleeding was more likely on MHT than tibolone, with a suggested comparison of unscheduled bleeding in 47% of women taking MHT to 18–27% of women taking tibolone [91]. See Table 6.4.

A Cochrane Database systematic review included 46 RCTs comparing tibolone to placebo, estrogens, or combined estrogen and progestogen (E + P), and involved almost 20,000 women. In the placebo comparison group, fewer women continued to experience VMS, 35–45% tibolone versus 67% placebo, and more women experienced unscheduled bleeding, 31–44% tibolone versus 18% placebo. Among women with no history of breast cancer, there was no increased risk of new onset breast cancer in follow-up ranging from 3 months to 3 years (OR 0.52, 95% CI 0.21–1.25; four RCTs; 5500 women; very low-quality evidence). Among women with history of breast cancer, there was increased risk of recurrence with tibolone (OR 1.5; 95% CI 1.21–1.85; 2 RCTs; 3165 women; moderate quality evidence). There was no difference in cerebrovascular events, endometrial cancer, cardiovascular events, VTE, or mortality from any cause [90].

6.9 Tissue Selective Estrogen Complex: Conjugated Estrogen and Bazedoxifene

The revised global consensus statement on menopausal hormone therapy (2016) places the tissue selective estrogen complex (TSEC) product of conjugated estrogen (CE) 0.045 mg and selective estrogen receptor modulator (SERM) bazedoxifene 20 mg with estrogen and progestogen as first line therapies for VMS [1]. Conjugated estrogen with bazedoxifene is approved worldwide. Each SERM product has unique tissue selection and activity. Bazedoxifene is used in MHT because of the anabolic action on bone tissue while having an antagonistic action in the breast and endometrium. It is effective in reducing VMS, relieving genitourinary syndrome of menopause, increasing bone mass, and improving sleep disruption [94–99]. Though the physiologic activity and the mammographic evidence of no increase in breast density may indicate protective breast action, it is important to note that there is not yet any breast cancer outcome data [100, 101]. See Table 6.4.

6.10 Conclusion

Counseling patients on the use of menopause hormone therapy in symptom management requires an understanding of the importance of analyzing individual benefits and risks. A patient health history is a critical indicator for risk. Age of initiation, duration of use, and specific hormone formulation and delivery route complete the profile necessary for action. Further, the clinician must clearly communicate these concepts to each individual patient so that shared decision-making may take place.

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