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POSITION STATEMENT

Role of progestogen in hormone therapy for postmenopausal women: position statement of The North American Menopause Society

ABSTRACT

Objective: To create an evidence-based position statement regarding the role of progestogen in postmenopausal hormone therapy (estrogen plus a progestogen, or EPT) for the management of menopause-related symptoms.

Design: NAMS followed the general principles established for evidence-based guidelines to create this document. Clinicians and researchers acknowledged to be experts in the field of postmenopausal hormone therapy were enlisted to review the evidence obtained from the medical literature and develop a position statement for approval by the NAMS Board of Trustees.

Results: The primary role of progestogen in postmenopausal hormone therapy is endometrial protection. Unopposed estrogen therapy (ET) is associated with a significantly increased risk of endometrial hyperplasia and adenocarcinoma. Adding the appropriate dose and duration of progestogen to ET has been shown to lower that risk to the level found in never-users of ET. The clinical goal of progestogen in EPT is to provide endometrial protection while maintaining estrogen benefits and minimizing progestogen-induced side effects, particularly uterine bleeding. EPT discontinuance correlates with uterine bleeding—women with more days of amenorrhea have higher rates of continuance. All US Food and Drug Administration-approved progestogen formulations will provide endometrial protection if the dose and duration are adequate. Progestogens may diminish the beneficial effects of ET on cardiovascular risk factors. However, no EPT (or ET) regimen should be initiated for the primary or secondary prevention of cardiovascular heart disease. Some progestogens may negatively affect mood. Adding progestogen to ET does not decrease the breast cancer risk, although it does not seem to increase mortality. Progestogen increases mammographic density, which is reversed after discontinuation of use. Progestogen has limited effect on the bone-enhancing action of ET. In general, the side effects of added progestogen are mild, although they may be severe in a small percentage of women.

Conclusions: Progestogen should be added to ET for all postmenopausal women with an intact uterus to prevent the elevated risk of estrogen-induced endometrial hyperplasia and adenocarcinoma. There is no consensus on a preferred regimen for all women. By changing the progestogen type, route, or regimen, clinicians can individualize therapy to minimize side effects, especially uterine bleeding, and limit any effects on ET benefits while providing adequate endometrial protection.

Key Words: Menopause – Progestogen – Progestin – Progesterone – Hormone therapy – Estrogen – Estrogen plus progestogen.

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The benefits and risks of adding progestogen to estrogen as part of hormone therapy for postmenopausal women have been debated for years. In North America, progestogen is typically added to reduce the increased risk of endometrial hyperplasia and cancer associated with estrogen therapy (ET). Unopposed ET is generally recommended only for women who do not have a uterus. A wide variety of progestogen types, routes of administration, and dosage regimens are available, each having distinct side effects, as well as different actions on the endometrium and other organ systems.

In response to the need to define standards of clinical practice in North America, The North American Menopause Society (NAMS) has created this position statement on the role of progestogens in hormone therapy for postmenopausal women. An editorial board composed of experts from both clinical practice and research was enlisted to review the published data and compile supporting statements and conclusions. If the evidence was contradictory or inadequate to form a conclusion, a consensus-based opinion was made. (The NAMS consensus-building process was described in a previous article.[1])

For this position statement, a search was performed of the medical literature on progestogen use in postmenopausal women using the database MEDLINE. Priority was given to evidence from randomized, controlled clinical trials and meta-analyses of such trials followed by evidence from controlled observational studies, using criteria described elsewhere.[2-4] Conclusions from other evidence-based guidelines also were reviewed. The NAMS Board of Trustees was responsible for the final review and approval of this document. Additional updates to this position statement will be published as developments in scientific research occur that substantially alter the conclusions.

Terminology

Terminology related to postmenopausal hormone therapy and to progestational compounds is inconsistent. To clarify, the terms *estrogen therapy* and *unopposed estrogen therapy* both refer to regimens using only estrogen; these are abbreviated ET. Regimens combining estrogen plus progesterone are abbreviated EPT. The term *hormone therapy* refers to either ET or EPT or both. The term *progestogen* is an inclusive term that encompasses both *progesterone* and the synthetic progestational compounds referred to as *progestins.*

The intent of this position statement is to provide an update on clinical information relating to progestogens and offer a reasonable approach regarding their use in combination with estrogen in postmenopausal women. This review will not address the use of progestogens in contraceptives or the use of progestogens in pre- or perimenopausal women. Although the information regarding progestogen use is relevant internationally, the focus is limited to products available in North America.

CLASSIFICATION OF PROGESTOGENS

Progestogens can be divided into two types: natural and synthetic. The term *natural* is defined as native to living organisms (plant or animal). Based on this definition, there is only one natural progestogen that is used therapeutically: progesterone. Progesterone is a compound identical to that secreted by the human ovary after ovulation and by the placenta during pregnancy. It can be chemically synthesized in the laboratory for therapeutic use. Relatively recent advances have allowed progesterone crystals to be micronized, resulting in improved oral absorption.

Before micronization, the rapid inactivation and poor bioavailability of orally administered progesterone led to the development in the 1950s of progestins, synthetic steroids that mimic endogenous progesterone effects. Progestins obtained from a plant-derived precursor (eg, diosgenin, which is found in plants such as the wild yam or soybean) should not be referred to as natural progestogens because they undergo multiple chemical reactions during synthesis. Only part of the carbon skeleton of the precursor remains in the final product.

Progestins can be classified as those that more closely resemble either progesterone or testosterone in chemical structure (see Table 1).

MODE OF ACTION

Several factors play a role in determining the biologic response of a progestogen. Prerequisites for progestational activity include the number and presence of progesterone receptors, adequate affinity for the progesterone receptor, induction of conformational change of the steroid-receptor complex, and duration of binding to DNA. The number of receptors occupied by the steroid is a function of its concentration in the target cell. Intracellular steroid concentration is related to the quantity of steroid that enters the cell and is metabolized and stored. The extent to which the steroid enters the cell is, in turn, dependent on its circulating level in a bioavailable form (ie, not bound to sex

TABLE 1. *Classification of progestogens*

Progesterone (identical to endogenous progesterone)

Progestins (not identical to endogenous progesterone)
- A. *Structurally related to progesterone*
  - 1. pregnane derivatives:
    - a. *acetylated* (also called 17α-hydroxyprogesterone derivatives): medroxyprogesterone acetate, megestrol acetate, cyproterone acetate, chlormadinone acetate
    - b. *nonacetylated:* dydrogesterone, medrogestone
  - 2. 19-norpregnane derivatives (also called 19-norprogesterone derivatives):
    - a. *acetylated:* nomegestrol acetate, nestorone
    - b. *nonacetylated:* demegestone, trimegestone, promegestone
- B. *Structurally related to testosterone* (also called 19-nortestosterone derivatives)
  - 1. ethinylated:
    - a. *estranes:* norethindrone (also called norethisterone), norethindrone acetate, norethynodrel, lynestrenol, ethynodiol diacetate
    - b. *18-ethylgonanes:* levonorgestrel, norgestrel, desogestrel, gestodene, norgestimate
  - 2. nonethinylated: dienogest, drospirenone

hormone-binding globulin). The serum level of the steroid depends on its pharmacokinetics (ie, its absorption, metabolism during the hepatic first pass, rates of distribution and elimination, and excretion).

In the human, two progestogen receptor (PR) proteins, PR A and PR B, have been identified.[5] Whether the available progestogen therapies preferentially bind to PR A or PR B is unclear. Selective progestogens are in an early stage of development.

The primary actions of progestogens have been characterized in most detail in the uterus. In this target tissue, progestogen functions primarily as an antiestrogen, decreasing the number of nuclear estrogen receptors, most likely through down-regulation of estrogen receptors.[6] In the endometrium, progestogen increases the activity of 17β-hydroxysteroid dehydrogenase, resulting in conversion of estradiol to estrone, a biologically weaker estrogen.[7] These changes result in less estrogen-induced endometrial stimulation.

POTENCY OF PROGESTOGENS

Assessment of progestogen potency is problematic because of the large number of variables and assumptions in both laboratory and animal (in vivo) progestogen potency tests. Difficulties arise when potency estimates from animal tests are extrapolated to humans, as profound differences in progestational activity are often observed between human and animal tissues. Limitations to in vitro receptor-binding assays include not adding estrogen to the progestogen being tested and testing progestogens at higher doses than those currently prescribed in estrogen plus progestogen therapy (EPT).

Although several in vitro and in vivo tests have been used to determine progestational potency, androgenic potency, and antiestrogenic potency, very few clinical trials have evaluated the relative potencies of progestogens. A 1985 review of published human data,[8] obtained from studies that assessed progestogen effects on delay of menses, subnuclear vacuolization, glycogen deposition, and levels of lipids/lipoproteins, concluded that norethindrone (NET), norethindrone acetate (NETA), and ethynodiol diacetate are approximately equivalent in potency. Norgestrel and levonorgestrel (LNG) are about 5 to 10 and 10 to 20 times, respectively, more potent than NET.

Another approach used in determining progestogen potency is analyzing biochemical and morphologic features of endometria from estrogen-primed postmenopausal women. Using this approach, effects of at least three different doses of five orally administered progestogens—progesterone, medroxyprogesterone acetate (MPA), NET, LNG, and dydrogesterone—were assessed after 6 days of cyclic progestogen treatment during the last 6 to 12 days of the month.[9] Relative to a value of 1 for NET, LNG was 8 times more potent, whereas MPA, dydrogesterone, and progesterone were 10, 50, and 500 times less potent, respectively. The NETA prescribing information states that, on a weight basis, it is twice as potent as NET, but in clinical terms, these progestogens are probably equipotent.

The conclusions regarding potency are not based on blood levels of progestogens, which vary significantly because of hepatic first-pass metabolism. However, certain generalizations regarding potency can be made. Progestins structurally related to testosterone are more potent than progesterone and pregnane derivatives, although some 19-norprogesterone derivatives are more potent than the 19-nortestosterone compounds. Among the progestins structurally related to progesterone, MPA is more potent than dydrogesterone, which is more potent than progesterone. Among the progestins structurally related to testosterone, LNG is more potent than norgestimate, whereas NET and NETA are considerably less potent.

The progestogen potencies demonstrated in these evaluations are consistent with the oral progestogen doses typically prescribed for endometrial protection (ie, 1 mg for NET and NETA, 2.5-10 mg for MPA, and 100-300 mg for micronized progesterone),[10] although the dose used depends on whether the progestogen is given for 10 to 14 days per month or continuously, as well as on the type of estrogen administered.

ROUTES OF ADMINISTRATION

Progestogens may be administered through several routes, some approved by the US Food and Drug Administration (FDA) and others custom-compounded: oral (tablet, capsule, liquid), transdermal (topical patch, gel, cream), vaginal (gel), intrauterine device (IUD), sublingual, intramuscular injection, rectal suppository, and subcutaneous implant. Formulations used for EPT are oral, transdermal, and IUD (Tables 2 and 3). Some oral and transdermal products offer the convenience of combined estrogen plus progestogen.

Progestogen therapy has been used for decades to oppose the effects of ET on the endometrium. However, the FDA approval of this indication is relatively recent. All oral and transdermal combined estrogen-progestin products and some oral progestins have FDA approval for use in EPT. In the late 1990s, oral micronized progesterone was FDA-approved for EPT use, although custom-compounded oral micronized progesterone formulations have been used for much longer.

ENDOMETRIAL EFFECTS

The primary role of progestogen in hormone therapy is endometrial protection. Progestogen added to ET results in significant histologic changes in the endometrium. Although a secretory pattern is frequently found, other findings (eg, atrophic, inactive or progestogen-dominant, insufficient tissue) have been described in hormone therapy trials.

Postmenopausal women with an intact uterus who use unopposed ET have an increased risk of endometrial carcinoma. Use of oral ET for at least 1 or 2 years has a relative risk of endometrial cancer of approximately 2.4, which increases to 8.0 after 10 years.[11-16] Increased risk declines upon discontinuation of ET, although risk is still significantly elevated 5 or more years after last use.

Endometrial hyperplasia is a surrogate marker for the development of endometrial cancer. The histologic classification of endometrial hyperplasia shows it transitions from simple hyperplasia (a benign lesion) to atypia to adenomatous hyperplasia. In most clinical trials of ET, simple hyperplasia is the predominant form of adverse histologic change. However, adenomatous cases can be detected when the size of the study population is sufficiently large.

Clinical trials have found that oral ET has an annual incidence of endometrial hyperplasia from 8% to 53%, depending on the type and dose of estrogen and the duration of the trial.[17-22] In one study,[23] transdermal ET had a higher rate of endometrial hyperplasia than transdermal EPT. The 1-year incidence with unopposed transdermal 17β-estradiol (50 μg/day) was 37.9% versus 0.8% to 1.1% with continuous-combined transdermal 17β-estradiol plus NETA at 140, 250, and 400 μg/day.

Lower doses of ET may not induce endometrial hyperplasia, although long-term data are not available. In clinical trials, 1-year endometrial hyperplasia rates were similar to placebo (≤ 1%) for oral conjugated equine estrogen (CEE; 0.3 or 0.45 mg/day), oral esterified estrogens (0.3 mg/day), and oral ethinyl estradiol (5 μg/day).[17,20,21] However, in one case-control study,[24] oral CEE (0.3 mg/day) was associated with increased endometrial cancer risk. The risk was highest (odds ratio, 9.2) in women using ET for more than 8 years. Various low-dose preparations of vaginal ET

TABLE 2. *Progestogens used for EPT in North America*

Composition	Proprietary name	Available dosages
Progesterone (micronized)		
Oral capsule	Prometrium	100, 200 mg
Vaginal gel	Prochieve[1] (45 mg/dose)	4% gel
Progestin		
Oral tablet		
medroxyprogesterone acetate	Provera, Gen-Medroxy,[2] Alti-MPA,[2] Novo-Medrone,[2] various generics	2.5, 5.0, 10.0 mg
norethindrone (norethisterone)	Micronor, Nor-QD[1]	0.35 mg
norethindrone acetate	Aygestin,[1] Norlutate,[2] generic	5.0 mg
norgestrel	Ovrette[1]	0.075 mg
Intrauterine system		
levonorgestrel	Mirena	20 μg/day approx release rate (52 mg/device; 5-y use)

[1]Available only in the United States.
[2]Available only in Canada.
Products not marked are available in both the United States and Canada.

TABLE 3. *Combination estrogen-progestin products for postmenopausal use*

Composition	Product name	Available dosages
Oral continuous-cyclic regimen		
conjugated equine estrogens (E) + medroxyprogesterone acetate (P) (E alone for days 1–14, followed by E+P on days 15–28)	Premphase[1]	0.625 mg E + 5.0 mg P (2 tablets: E; E + P in dispenser)
Oral continuous-combined regimen		
conjugated equine estrogens (E) + medroxyprogesterone acetate (P)	Prempro[1]	0.625 mg E + 2.5 or 5.0 mg P (1 tablet)
	Premplus[2]	0.625 mg E; 2.5 or 5.0 mg P (2 tablets: E; P)
ethinyl estradiol (E) + norethindrone acetate (P)	Femhrt	5 μg E + 1 mg P (1 tablet)
17β-estradiol (E) + norethindrone acetate (P)	Activella	1 mg E + 0.5 mg P (1 tablet)
Oral intermittent-combined regimen		
17β-estradiol (E) + norgestimate (P) (E alone for 3 days, followed by E+P for 3 days; repeated continuously)	Ortho-Prefest[1]	1 mg E + 0.09 mg P (2 tablets: E; E + P in dispenser)
Transdermal continuous-combined regimen		
17β-estradiol (E) + norethindrone acetate (P)	CombiPatch[1] Estalis[2]	50 μg E + 140 or 250 μg P
Transdermal continuous-cycle regimen		
17β-estradiol (E) + norethindrone acetate (P)	Estalis Sequi[2]	50 μg E + 140 or 250 μg P (2 patches: E; E + P in dispenser)
	Estracomb[2]	50 μg E + 250 μg P (2 patches: E; E + P in dispenser)

[1]Available only in the United States.
[2]Available only in Canada.
Products not marked are available in both the United States and Canada.

have not been clearly associated with increased risk.[25] Until longer trials corroborate these results, use of unopposed low-dose systemic ET in clinical practice is not recommended.

Adding the proper dose and duration of progestogen to ET may lower the risk of endometrial cancer to that found in never-users of ET.[11-15,26] No EPT regimen has been found to be completely protective, as endometrial cancer is a risk for all women, including those who use no hormone therapy.

Clinical trials have determined that the relative risk for endometrial cancer is lower in women using progestogen for 10 or more days each month than in women using progestogen for fewer days.[25-27] A review of published studies[28] found that both the dose and the duration of progestogen therapy are important. Most cases of simple endometrial hyperplasia regress after one cycle of progestogen (eg, MPA 10 mg for at least 10 days).[19,29,30]

In studies demonstrating the effects of progestogen on ET-stimulated endometrial hyperplasia, most have been conducted with oral progestins. Other progestogens and routes of administration are available, although clinical trial data (especially long-term data) supporting their use for endometrial protection are limited. The only FDA-approved transdermal EPT product available in North America, a combination of NETA and 17β-estradiol, demonstrated endometrial safety in a 1-year trial.[23]

At standard doses, vaginal progesterone avoids systemic effects, making it an attractive option. Measurement of tissue levels of progesterone after vaginal administration suggests selective uptake by the uterus.[31] In 31 postmenopausal women using either 45 mg or 90 mg of vaginal bioadhesive progesterone gel every other day over 12 days of the month (six applications per month), no hyperplasia was observed after 3 months.[32] However, trial duration of 3 months is considered inadequate for hyperplasia evaluation.

Transdermal (topical) progesterone cream or gel preparations obtained either over-the-counter or custom-compounded by prescription may not exert sufficient activity to protect the endometrium from unopposed estrogen.[33,34] These products should not be used for this purpose until optimal therapeutic doses and serum levels of topical progesterone are established and long-term trials are conducted that document endometrial protection.

Conclusions

Progestogen should be added to ET in all postmenopausal women with an intact uterus to prevent the elevated risk of estrogen-induced endometrial hyperplasia and adenocarcinoma. All FDA-approved

progestogen formulations will provide endometrial protection if the dose and duration are adequate. Evidence is lacking to recommend topical progesterone preparations for preventing estrogen-induced endometrial hyperplasia.

EPT REGIMENS

Many types of regimens are used when prescribing EPT, and descriptive terminology is often inconsistent. The clinical goal of these EPT regimens is to provide uterine protection, maintain estrogen benefits, and minimize side effects (particularly uterine bleeding, which is annoying to many women and often reduces compliance), although there is no consensus on how to accomplish this goal. Regimens may be classified into the following types: cyclic, cyclic-combined, continuous-cyclic, continuous long-cycle, continuous-combined, and intermittent-combined (Table 4).

Cyclic EPT

In this regimen, estrogen is taken from day 1 to day 25 of the calendar month, with progestogen added the last 10 to 14 days. This allows for a hormone-free interval of 3 to 6 days and is designed to mimic the normal premenopausal ovulatory cycle. Progestogen therapy should be used for 10 days or more.

Using standard EPT dosing with this regimen, about 80% of women have withdrawal uterine bleeding after the progestogen cycle. This bleeding usually begins 1 to 2 days after the last progestogen dose and continues a few days during the therapy-free interval. Estrogen should be resumed at the beginning of the next month, irrespective of whether bleeding has stopped.

Some women will experience vasomotor symptoms during the therapy-free interval, caused by the relatively short half-life of estrogens (eg, the half-life of oral 17β-estradiol has been reported to be 15-20 hours).[35]

This is the oldest of the regularly used EPT regimens. It is decreasing in popularity in North America, primarily because newer regimens have lower uterine bleeding rates.

TABLE 4. *Terminology defining types of EPT regimens*

Regimen	Estrogen	Progestogen
Cyclic	Days 1–25	Last 10–14 days of ET cycle
Cyclic-combined	Days 1–25	Days 1–25
Continuous-cyclic (sequential)	Daily	10–14 days every month
Continuous long-cycle	Daily	14 days every 3–6 months
Continuous-combined	Daily	Daily
Intermittent-combined (pulsed-progestogen; continuous-pulsed)	Daily	Repeated cycles of 3 days on, 3 days off

Cyclic-combined EPT

For this regimen, estrogen and progestogen are taken on days 1 to 25, followed by a hormone-free interval of approximately 5 days. In studies using oral micronized progesterone,[36,37] this EPT regimen had a low rate of uterine bleeding and a high rate of tolerability. In one trial,[36] endometrial biopsies performed before and after 4 months of cyclic-combined EPT (2 mg/day 17β-estradiol plus 50, 100, or 200 mg/day oral micronized progesterone) confirmed an atrophic endometrium in all women receiving 200 mg/day oral micronized progesterone and in most women receiving 100 mg/day. Uterine bleeding occurred in the first few cycles, but decreased with time. However, the trial duration of 4 months is considered inadequate to evaluate the regimen's effect on endometrial hyperplasia.

Continuous-cyclic EPT

In this regimen (sometimes referred to as *sequential*), estrogen is used every day, with progestogen added cyclically for 10 to 14 days during each month. As with the cyclic regimen, uterine bleeding occurs in about 80% of women when progestogen is withdrawn, although bleeding can begin 1 or 2 days earlier, depending on the type and dose of progestogen used. The primary advantage of the continuous-cyclic regimen compared with cyclic EPT is the absence of an estrogen-free period during which vasomotor symptoms can occur.[38]

In a typical continuous-cyclic regimen, progestogen is started on day 1 or day 15 each month. Starting on the first day of the month may facilitate tracking uterine bleeding episodes, as the cycle day corresponds with the day of the month.

Continuous long-cycle EPT

To lessen the incidence of uterine bleeding, a modified continuous-cyclic EPT regimen of daily estrogen with cyclic progestogen (eg, 10 mg/day MPA for 14 days during the month) added every 3 to 6 months has been evaluated. Although this long-cycle regimen reduces the number of withdrawal bleeding episodes, bleeding that occurs may be heavier and last for more days per episode than withdrawal bleeding with progestogen added monthly.

The effect of long-cycle EPT on endometrial protection is undetermined. Two studies did not find evidence of endometrial hyperplasia after 1 year in women using

estrogen at standard (0.625 mg/day CEE) or one-half standard (0.3 mg/day CEE) doses with MPA administered either quarterly or every 6 months.[39,40] However, the Scandinavian Long Cycle Study,[41] which used 2 mg/day of 17β-estradiol (ie, twice the standard dose) with a progestin administered quarterly, was stopped after 3 of 5 scheduled years because of an increased incidence of hyperplasia compared with a monthly progestogen regimen. Until more data are available, the continuous long-cycle EPT regimen is not recommended as standard therapy.

Continuous-combined EPT

With this regimen, fixed doses of estrogen and progestogen are administered every day. Women using currently available continuous-combined EPT preparations do not have a significant rate of endometrial cancer, based on short-term studies usually no longer than 1 year.[42] Because of its low incidence of uterine bleeding, the continuous-combined regimen has become the predominant regimen used in North America.

Various EPT doses in continuous-combined regimens have demonstrated a low incidence of endometrial hyperplasia. Combined oral CEE plus MPA regimens (CEE 0.625/MPA 2.5 mg/day; CEE 0.45/MPA 2.5 mg/day; CEE 0.45/MPA 1.5 mg/day; CEE 0.3/MPA 1.5 mg/day) produced hyperplasia rates equal to those found in the placebo arms of clinical trials (< 1%).[20] Oral continuous-combined regimens of 17β-estradiol (1 mg/day) with NETA (0.1, 0.25, or 0.5 mg/day),[18] as well as oral ethinyl estradiol (1.0, 2.5, 5.0, or 10 μg/day) combined with NETA (0.2, 0.5, 1.0, or 1.0 mg/day, respectively),[21] also produced hyperplasia rates less than 1%. Transdermal 17β-estradiol (50 μg/day) combined with NETA (0.14 or 0.25 mg/day) did not result in any measurable hyperplasia after 1 year of treatment.[23] A continuous-combined transdermal patch delivering 17β-estradiol (25 μg/day) and NETA (0.125 mg/day) provided endometrial protection and maintained a high rate of amenorrhea in a 2-year clinical trial.[43]

Intermittent-combined EPT

This regimen (also called *pulsed-progestogen* or *continuous-pulsed EPT*) uses estrogen daily with the progestogen dose administered intermittently in cycles of 3 days on and 3 days off, which is then repeated without interruption. This regimen is designed to lower the incidence of uterine bleeding while avoiding down-regulation of progesterone receptors that continuous progestogen can produce, a mechanism that may not fully protect the endometrium. By interrupting the progestogen for 3 of every 6 or 7 days, up-regulation of progesterone receptors occurs intermittently.[44,45]

In one study,[45] women using 17β-estradiol (1 mg/day) with a pulsed regimen (3 days on, 3 days off) of norgestimate (90 μg/day) had improved bleeding control. During month 1, 69% of the women experienced only spotting; after 1 year, 80% were free of uterine bleeding. The incidence of endometrial hyperplasia after 1 year was less than 1%. In another study,[46] no cases of endometrial hyperplasia were detected in nearly 500 women after 12 months of continuous estrogen (1 mg/day) plus norgestimate (90 or 180 μg/day) pulsed 3 days on and 3 days off. Other pulsed regimens have demonstrated similar effects: continuous piperazine estrogen sulfate (0.75 mg/day) with pulsed NET (0.35 mg/day);[47] transdermal 17β-estradiol (50 μg/day for 1 week) followed by transdermal combined 17β-estradiol (50 μg/day) plus NETA (250 μg/day) for 3 days.[48]

Trial duration for almost all of these intermittent-combined regimens was only 1 year. Longer-term surveillance of endometrial effects will be needed to fully ascertain efficacy and safety.

Comparing regimens: endometrial hyperplasia

A 1999 Cochrane review[42] concluded that the addition of oral progestin to ET, administered either continuous-cyclic or continuous-combined, is associated with reduced rates of hyperplasia. Cyclic progesterone added to ET also has been shown to inhibit the development of endometrial hyperplasia.[49-52] In the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, combining oral CEE (0.625 mg/day) with oral micronized progesterone (200 mg/day for 12 days/month) did not increase endometrial hyperplasia rates after 3 years.[19]

It has been suggested that continuous-combined EPT may not be as protective as continuous-cyclic EPT, citing the possibility that some buildup of the endometrium may not be shed and that continuous progestogen may completely down-regulate progesterone receptors, thereby reducing endometrial protection.[28,47] However, epidemiologic studies of continuous-combined EPT indicate no increased risk and may even suggest some added protection against endometrial cancer.[25,53] A 9-month study of postmenopausal women using estrogen plus cyclic progestin for 10 to 13 days a month found incidences of complex endometrial hyperplasia and atypical hyperplasia of 5.3% and 0.7%, respectively.[54]

Comparing regimens: uterine bleeding

Many postmenopausal women dislike having episodes of uterine bleeding, and this progestogen-related side effect decreases EPT continuance. Various regimens have been designed to lessen or eliminate bleeding.

The term *withdrawal* uterine bleeding refers to the predictable bleeding that often results from progestogen cessation (or withdrawal). In contrast, the term *breakthrough* uterine bleeding refers to the unpredictable and irregular bleeding associated with regimens using continuous progestogen.

Retrospective trials[55,56] have suggested that withdrawal uterine bleeding occurring after day 11 of a cyclic 12-day progestogen course reflects a normal secretory pattern of the endometrial tissue. However, prospective trials[42,57] have not confirmed these findings, and no correlation has been established between day of bleeding onset and histologic findings. Nevertheless, most studies with cyclic administration of progestogen have shown a high percentage of regular withdrawal uterine bleeding in women with a normal secretory endometrium.[42,58] Bleeding pattern is a less reliable indicator of endometrial safety when continuous-combined regimens are used.[56,59,60]

Breakthrough uterine bleeding has been observed in 40% of women on a continuous-combined regimen during the first 3 to 6 months.[58] The probability of achieving amenorrhea is greater if EPT is started 12 months or more after menopause; women who are recently postmenopausal exhibit more breakthrough bleeding.[58,61] Most women (75%-89%) who continue therapy become amenorrheic within 12 months. However, bleeding may persist intermittently for months or years. Persistent breakthrough bleeding with continuous-combined EPT may necessitate switching to another regimen.

A study comparing two continuous-combined regimens—CEE 0.625 mg/day plus MPA 2.5 mg/day and 17β-estradiol 1 mg/day plus NETA 0.5 mg/day—found that, within 3 months, 71.4% of the estradiol-NETA users reached amenorrhea compared with 40.0% of the CEE-MPA users.[38] After 6 months, the differences were not statistically significant. This study confirmed other findings that recently postmenopausal women (within 1-2 years of last menses) experienced more bleeding than women more than 3 years postmenopause.

The 19-nortestosterone derivatives (eg, NET, NETA, LNG, norgestimate) tend to produce less breakthrough uterine bleeding during the first few months of use because of atrophy resulting from increased progestational activity. Conversely, micronized oral progesterone when given cyclically may lead to quantitatively less uterine bleeding than progestins. In this setting, the endometrium is weakly proliferative and does not exhibit a strong progestational effect.

Among women using EPT beyond 2 years, those using a continuous-combined regimen have lower rates of breakthrough uterine bleeding and endometrial biopsies than those using the cyclic regimen.[62] These findings confirm other studies that show decreased breakthrough uterine bleeding over time in women using the continuous-combined regimen. Nevertheless, continuance rates at 3 years are slightly higher in cyclic EPT users than in continuous-combined EPT users.[63]

Intrauterine-administered progestogen is an option to avoid systemic side effects. Although the levonorgestrel intraduterine device (IUD; Mirena) was developed for contraception, not EPT use, this preparation (which releases LNG at a rate of 20 μg/day) seems to be effective in postmenopausal women in opposing the proliferative effects of ET on the endometrium.[64,65] Similar effects had been observed with the progesterone IUD (Progestasert), now withdrawn from the market.[66,67] A lower-dose LNG-containing IUD (10 μg/day), which is under FDA review, also seems to protect the endometrium and produces minimal uterine bleeding.[68] However, more experience and longer duration of use are required before conclusions can be reached regarding the clinical endometrial response profile of the lower-dose IUD.

Conclusions

Standard EPT regimens provide adequate endometrial protection. There is less long-term experience with intermittent-combined and continuous long-cycle regimens, and more study is required to fully ascertain efficacy and safety. Some cyclic regimens may be less effective than continuous regimens in inhibiting the development of uterine cancer. With cyclic and continuous-cyclic regimens, withdrawal uterine bleeding occurs in about 80% of women when progestogen is stopped, although many women on continuous-cyclic regimens become amenorrheic within 12 months. Continuous-combined regimens avoid withdrawal bleeding, but breakthrough uterine bleeding occurs in nearly 40% of women during the first 6 months. Nearly 90% of women on this regimen become amenorrheic within 12 months. Persistent breakthrough bleeding with continuous-combined EPT may necessitate switching to another regimen. Pulsed regimens have 1-year amenorrhea rates of nearly 80%. Some women using a cyclic

ET regimen experience hot flashes during the estrogen-free period; regimens with continuous estrogen administration usually avoid hot flashes.

EFFECTS ON OTHER ORGAN SYSTEMS

Progestogens exhibit effects on organ systems other than the endometrium. These effects vary depending on the progestogen type, dose, and route of administration, and the EPT regimen.

Cardiovascular system

Cardiovascular disease (CVD), which includes both coronary heart disease (CHD) and stroke, is the leading cause of mortality in women. The incidence of CVD increases after age 50. A number of cardiovascular effects are known to be mediated by both estrogen[69] and progesterone[70] receptors.

Although a substantial body of evidence (basic science, observational studies, and small clinical trials) has suggested that estrogen has a beneficial effect on CVD, larger randomized, prospective clinical trials have not confirmed these findings. The purported benefits of estrogen—improving lipids and lipoprotein concentrations, stimulating vasodilation, and decreasing the progression of atherosclerosis—may be confounded by progestogen exposure, although data are mixed. How progestogen influences these ET effects is complex.

Observational studies, using primarily data from the Nurses' Health Study, have shown reductions in CHD risk of approximately 35% to 40% for both ET and EPT.[71-74]

Clinical trial results conflict with observational study findings. In the prospective, randomized Women's Health Initiative (WHI),[75] which enrolled apparently healthy postmenopausal women, results indicate that continuous-combined oral EPT (0.625 mg/day CEE and 2.5 mg/day MPA) does not decrease the risk of heart disease and causes an increase in CHD events during the first few years of exposure in susceptible women. Lack of treatment benefit also has been documented in two secondary prevention studies: the Heart and Estrogen/progestin Replacement Study (HERS)[76,77] and the Estrogen Replacement and Atherosclerosis trial (ERA).[78] Both used CEE either alone or with MPA. Based on these results, NAMS (as well as other groups) recommends that ET/EPT should not be initiated for the primary or secondary prevention of CHD.[79,80]

The discrepancy between these randomized studies and observational studies showing benefits with ET/EPT may be related to the extent of arterial damage present when ET/EPT was initiated. Older women, even in the absence of a history of cardiovascular events, most likely have undiagnosed disease. The use of continuous progestogen administration, resulting in continuous down-regulation of estrogen receptors, may also account for the differences.[44] However, there are no definitive data on this point, and the observational studies showing benefit were equally protective for ET and EPT. Data on the ET-arm of the WHI are not expected until 2005.

Regarding stroke risk, results from the Nurses' Health Study suggest that current use of ET/EPT has a borderline increase on the overall risk of stroke (relative risk, 1.13).[72] However, the stroke risk was not significant with low-dose estrogen alone (0.3 mg/day CEE), although it was significantly increased with the 0.625- and 1.25-mg doses. The WHI reported a significant relative risk of 1.41 with EPT (CEE 0.625 mg/day plus 2.5 MPA). Whether progestogen affects stroke risk is not known.

Although this position statement relies on specific endpoint data for recommendations, the following sections present the current knowledge regarding EPT effects that are based on surrogate markers of CVD.

Atherosclerosis

Atherosclerotic plaques are a major contributor to cardiovascular disease. Animal studies suggest that estrogen inhibits the progression of atherosclerosis.[81-83] Adding progestogen to ET produces varied effects on this process. Intermittent parenteral progesterone has shown no detrimental effect,[81] whereas continuous MPA blunted CEE benefit in one study[82] but not in a subsequent study.[83] In rabbits, estradiol reduced aortic intimal area by about one-half, with higher doses of added progesterone inhibiting that benefit in a dose-dependent manner.[84] In animals with existing arterial disease, neither ET nor EPT reduced atherosclerosis.[85-87]

In women, the effects of estrogen on atherosclerosis have been mixed. In one trial, ET/EPT was associated with decreased intima-medial thickness (IMT) but only after 1 year's use.[88] A prospective 2-year trial of unopposed 17β-estradiol versus placebo showed significantly reduced IMT among estrogen recipients.[89] In women with increased IMT, no slowing of atherosclerosis progression was seen with estradiol and gestodene after 48 weeks.[90] Differences observed between these trials may indicate that ET/EPT does not inhibit atherosclerosis in women with existing CVD, but ET/EPT may have that effect in healthier women who do not have significant atherosclerosis.

Vasodilation

In animal studies, cyclic high-dose MPA (equivalent to 10 mg/day in humans) and continuous low-dose MPA (equivalent to 2.5 mg/day in humans) diminished the beneficial effect of CEE on acetylcholine-induced coronary vascular dilation.[87,91] However, the addition of nomegestrol acetate to ET did not reverse the beneficial effects of 17β-estradiol on vascular dilation,[92] indicating that different progestins exert different effects. In another study, coronary artery vasospasm was avoided with the combination of 17β-estradiol plus progesterone but not with 17β-estradiol plus MPA.[93]

In women, both acute and long-term use of ET produces dilation of coronary arteries.[94,95] Some studies have found that use of CEE with either oral micronized progesterone or MPA improves flow-mediated dilation,[96] whereas others have found that MPA impairs flow-mediated dilation in a dose-dependent manner.[97] The combination of NETA and 17β-estradiol did not improve flow-mediated dilation.[98] In another study,[99] 17β-estradiol increased nitrous oxide levels, but the addition of NETA did not significantly increase these levels. Two studies assessing flow-mediated dilation in either older women (≥ 80 years) using mostly unopposed ET[100] or women with established angina pectoris using ethinyl estradiol and NETA[101] found no vasodilatory benefit from ET or EPT. Some have postulated that both MPA and NETA may exert some androgenic action that partially reverses the benefit of estrogen effects on vasomotion in women,[102] although the addition of methyltestosterone to ET does not diminish vascular reactivity in monkeys.[103]

Other cardiovascular risk factors

A number of cardiovascular risk factors are improved with both ET and EPT, which could be expected to reduce CHD. Oral ET improves low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and lipoprotein(a) [Lp(a)]. The addition of progestogen may or may not affect lipid concentrations, depending on the type of progestogen used. Some progestogens can modify the estrogen-induced increase in triglycerides.[21,104,105] Although the effects of ET/EPT on lipids and lipoproteins are considered to be important, they have not been found to modify risk factors in clinical trials. In HERS and WHI, the beneficial changes with EPT, especially in HDL-C, did not protect against an increase in CHD events.[75,77]

In the PEPI trial,[106] the most favorable effect on HDL-C concentrations was observed in women taking unopposed estrogen (CEE). Adding MPA (2.5 or 10 mg/day for 12 days/month) blunted much of estrogen's benefit, although oral micronized progesterone (200 mg/day) still resulted in beneficial changes in HDL-C. In another study,[105] combining norgestimate with 17β-estradiol resulted in HDL-C improvement similar to CEE plus micronized progesterone but caused less of an increase in triglyceride levels. Another EPT combination, ethinyl estradiol and NETA, lowered HDL-C but had little effect on triglyceride levels.[21] Concentrations of LDL-C have been lowered with both ET and EPT,[106-110] although higher doses of NETA (0.5 mg) enhanced LDL-C reductions.[107] Levels of Lp(a) are decreased with both ET and EPT.[108,110]

The beneficial effects of ET on other cardiovascular risk factors, including a number of atherogenic and inflammation markers, do not seem to be blunted by the addition of progestogen.[96] Whereas a number of inflammation markers associated with increased CVD risk are decreased with ET/EPT, C-reactive protein (CRP) levels are increased with both ET and EPT.[111,112] However, the combination of transdermal 17β-estradiol and oral NETA decreased CRP levels in women with diabetes mellitus (DM),[113] suggesting that hepatic metabolism associated with oral therapies may be involved with the increase.

The effects of ET/EPT on hemostasis and fibrinolysis have been mixed. In addition to lowering Lp(a) with ET/EPT, both CEE and oral 17β-estradiol reduce fibrinogen and type-1 plasminogen activator inhibitor (PAI-1) levels, beneficial changes that are not affected by the addition of MPA[114] or NETA.[107] There is evidence that oral ET is associated with a procoagulant state with adverse changes in antithrombin III and protein C.[115] In vitro evidence suggests that some progestogens with glucocorticoid activity (eg, MPA) may potentiate the procoagulant effects of thrombin by increasing the availability of thrombin receptors in smooth muscle cells.[116] Some have proposed that there may be susceptible subgroups of women who are more prone to thrombotic events, such as those with low baseline Lp(a) levels[110] or prothrombotic genetic variants.[117]

ET/EPT has been shown to lower fasting glucose and insulin concentrations and improve insulin sensitivity in some studies,[118,119] but not in others.[120,121] One study reported improvement in women using transdermal NETA but deterioration in women using oral LNG,[121] a difference attributed to the strong androgenicity of LNG. However, in women with type-2 DM, both ET and EPT have improved a number of CHD risk factors, including lipid and lipoprotein parameters, glycemic control, and thrombotic indices,[122-124] as well as

C-reactive protein levels.[113] Also, ET/EPT has been found to increase 2-h postprandial glucose, a parameter that correlates better with CVD than fasting glucose.[108]

Thus, ET/EPT seems to have mixed effects on most cardiovascular risk factors in women with DM, and the specific agent, dose, regimen, and route of administration of ET/EPT are especially important. Transdermal ET/EPT may offer advantages over the oral route in women with DM. Serum triglyceride levels, which are often increased in woman with DM, are not increased further with transdermal ET/EPT.[109,125] If oral EPT is required for women with DM, continuous-cyclic therapy is recommended, rather than continuous-combined therapy, to minimize exposure to progestogen. The use of low-dose, oral micronized progesterone is recommended, although vaginal or intrauterine progesterone formulations may also minimize the potential for negative metabolic effects.

The effects of standard and lower doses of both oral CEE (0.625, 0.45, 0.3 mg/day) and MPA (2.5, 1.5 mg/day) on CHD risk factors were evaluated in healthy postmenopausal women.[126] A dose-dependent decrease in total- and LDL-C was observed with CEE that was not affected by MPA. HDL-C levels were increased with all doses of CEE, and MPA attenuated this effect in a dose-dependent manner. Changes in carbohydrate metabolism were minimal with all treatments. Beneficial decreases in fibrinogen and PAI-1 were seen with all treatments, although MPA reduced the benefit. Adverse effects on antithrombin III and protein S were observed with higher doses of CEE, but these procoagulant effects were not apparent with the lower-dose EPT regimens.

Conclusions

Because of clinical trials (primarily WHI and HERS) reporting significantly increased risks with EPT, NAMS recommends not initiating any ET or EPT regimen for the primary or secondary prevention of CHD, although the effect of ET on CHD is not yet clear. However, observational studies have shown that ET has beneficial effects on atherosclerosis, vasodilation, plasma lipids, arterial response to injury, and insulin sensitivity. Although adding some progestogens may diminish these beneficial effects, in general, they do not eliminate them. Selecting a metabolically neutral progestogen for EPT, such as micronized progesterone or norgestimate, is recommended to maintain higher plasma HDL-C. In animal studies, progestins with a higher androgenic potency reduce more of the beneficial effects of estrogens on vasodilation; progesterone and 19-norpregnane derivatives have less of an adverse effect. For women with DM who are using EPT to treat acute menopausal symptoms, continuous-cyclic EPT regimens are recommended to minimize progestogen exposure; low-dose oral micronized progesterone is also recommended.

Skeleton

Three large, placebo-controlled, clinical trials have provided the best evidence for possible additional bone-preserving effects of progestogen when used in combination with estrogen for early postmenopausal women without osteoporosis.

The PEPI trial[127] examined the effects in postmenopausal women (average age, 56 years; 1-10 years beyond menopause) of CEE (0.625 mg/day), unopposed and opposed by various progestogen regimens: continuous-combined with MPA (2.5 mg/day) and continuous-cyclic with either MPA (10 mg added 12 days per month) or oral micronized progesterone (200 mg added 12 days per month). Bone mineral density (BMD) was measured over 3 years using dual energy x-ray absorptiometry (DXA) at both hip and spine. Among adherent women, the average 3-year increase in spinal BMD was 5.1%. No differences were observed in BMD changes at the spine or hip between estrogen alone and any of the EPT regimens.

The Women's Health, Osteoporosis, Progestin, Estrogen (HOPE) study[128] compared skeletal effects of various daily doses of CEE (0.3, 0.45, and 0.625 mg), either alone or opposed by continuous-combined MPA (1.5 and 2.5 mg daily), in recently postmenopausal women (average age, 52 years; 1-4 years beyond menopause). BMD was measured for the spine, hip, and total body during the 2 years of treatment. Adding 2.5 mg MPA increased the 2-year spinal BMD about 1% over that observed with CEE alone, but this reached statistical significance only for the 0.625-mg CEE dosage. Hip and total body BMD changes observed with CEE were not enhanced by adding either 1.5 mg or 2.5 mg MPA. Thus, these data confirmed the PEPI results: continuous-combined EPT with CEE and 2.5 mg/day MPA has slightly greater effects than estrogen alone on spinal BMD, but MPA has no impact on hip BMD.

Measurement of bone turnover markers were included in the PEPI and HOPE studies; however, only the latter compared the antiresorptive effects of estrogen alone versus estrogen combined with MPA. Whereas estrogen showed dose-related decreases in N-telopeptide and osteocalcin, there were no significant differences in bone turnover markers between unopposed ET and ET-MPA. This is especially important

given the hypothesis put forth by PEPI investigators that MPA combined with estrogen might have greater antiresorptive effects when combined with lower doses (ie, < 0.625 mg CEE).[127]

It has been suggested for many years that 19-nortestosterone derivatives (eg, NETA) have greater skeletal effects than 17α-hydroxyprogesterone derivatives (eg, MPA). In the only well-designed clinical study examining the impact of added NETA on estrogen, the Continuous Hormones as Replacement Therapy (CHART) study,[21] recently postmenopausal women (average age, 52 years; 1-4 years beyond menopause) received ethinyl estradiol (1.0, 2.5, 5.0, and 10 μg/day) either unopposed or opposed with continuous-combined NETA (0.2, 0.5, 1.0, and 1.0 mg/day, respectively) for 2 years. Although not statistically significant, women receiving 1.0 mg NETA plus ethinyl estradiol (5 or 10 μg) seemed to have greater spinal BMD increases than those receiving 5 and 10 μg ethinyl estradiol alone. No enhancement of BMD was observed with the addition of 0.2 or 0.5 mg NETA among women receiving 1.0 or 2.5 μg ethinyl estradiol.

Fracture endpoints were not used in PEPI, HOPE, and CHART. Although lower BMD levels, in general, indicate higher fracture risk, other factors also influence risk, such as frailty, falls, and previous fractures. Results from the WHI have confirmed that continuous-combined CEE (0.625 mg/day) and MPA (2.5 mg/day) significantly decreases both spine and hip fractures by 36%.[75] Comparative data on fracture reduction for the ET-arm of the WHI are not expected until 2005.

Conclusions

Although adding 2.5 mg MPA or 1 mg NETA to ET slightly enhances estrogen's ability to prevent BMD loss in early postmenopausal women, estrogen alone is adequate to maintain BMD. EPT reduces spine and hip fractures, but the role of progestogen in this effect is not known. The decision to add progestogen to ET should not be based on its skeletal impact.

Breast

In the endometrium, proliferation and mitotic activity are inhibited during the luteal phase under the influence of endogenous progesterone. In contrast, in the breast, mitotic activity and DNA production of both glandular and nonglandular tissue increase during the luteal phase under the influence of endogenous progestogen, enlarging breast size.[129-131] However, this increase in activity does not lead to hyperplasia in a normal breast, as it might in the endometrium. Instead, it is followed by apoptosis, suggesting that the significance of increased mitotic activity in the breast may be different.

Proliferation of breast tissue from exogenous progestogen influence also varies under different experimental conditions. Inhibition of exogenous estrogen-induced proliferation in the human breast has been demonstrated by applying high concentrations of micronized progesterone gel (2.5 mg progesterone) locally to the breast.[132] Also, normal breast tissue placed into an athymic nude mouse model did not proliferate when exposed to progestogen.[133]

In vitro studies evaluating the effects of progesterone on breast tissue proliferation have yielded mixed results, reporting both increases and decreases.[134-137] Results in breast cancer cell lines have also been conflicting, depending on PR status. Although progesterone may induce proliferation in certain PR-positive cell lines, it inhibits the T47D cell line, related to differentiation and gene expression.[138,139] Also, even though progesterone decreases the tumor-suppressor protein p53, leading potentially to increased proliferation,[140] the induction of proliferation caused by an increase of growth factors[141] is followed by an inhibitory effect.[142] Relating to the synergistic influence of growth factors in breast cell proliferation, there is some concern that exogenous progestogen may have proliferative influences.[143] Some oral progestogens with androgenic properties (LNG and gestodene) have been shown to increase cell proliferation in MCF-7 breast cells, an effect mediated via the estrogen receptor.[144] In a monkey model in which breast tissue was removed at necropsy after several years of exposure to estrogen with progesterone or MPA, exposure to MPA was associated with greater breast cell proliferation.[136]

Clinical studies demonstrate that a larger proportion of women develop increased mammographic density when progestogen is added to ET.[145] Most studies have not been able to distinguish between type of progestogen or EPT regimens and the extent of mammographic density changes, although two studies suggested that breast density is highest with the continuous-combined regimen.[146,147] Mammographic density increases are reversed approximately 3 weeks after discontinuing EPT. Although increased mammographic density has been shown to be associated with an increased risk of breast cancer,[148] it is unclear if density changes induced by ET/EPT carry the same significance as density changes observed when not using hormones.

The results of studies evaluating the effect of progestogen on breast cancer risk are inconsistent. A trial measuring proliferation of MCF-7 breast cancer cells in

vitro[149] showed that MPA inhibited the estradiol-induced growth of those cells. Some clinical studies in premenopausal women with benign breast disease have suggested that progestogen has an antiproliferative effect on breast tissue.[150] In a randomized, placebo-controlled study of postmenopausal women,[151] micronized progesterone gel applied daily to the breast for 14 days reduced the estradiol-induced proliferation of normal breast epithelial cells. A large, population-based study did not demonstrate an increased risk of breast cancer when progestogen was added to ET, even with long-term use.[152] Several retrospective, case-control studies,[153-157] however, suggest that progestogen may increase breast cancer risk in postmenopausal women, although these studies have not consistently linked any specific progestogen or EPT regimen with greater risk. A recent case-control study has suggested that the risk is greatest with continuous-combined therapy.[158]

Results from the prospective, randomized WHI trial suggest that continuous-combined CEE (0.625 mg/day) plus MPA (2.5 mg/day) may increase the risk of breast cancer.[75] This led, at least in part, to the early termination of the EPT-arm of the trial. The increased risk (26% after 5.2 years) was of borderline significance (95% CI, 1.00-1.59) and is similar to observational data. At 5.2 years, the ongoing ET-arm did not show a statistical increase in breast cancer.

Two case-control studies[153,154] suggested that progestogen use increases the incidence of the relatively rare lobular cancers, but not the more common ductal cancers.

Breast discomfort and pain may be increased when progestogen is added to ET. In one study,[159] adding MPA (1.5, 2.5 mg/day) to CEE (0.3, 0.45, 0.625 mg/day) doubled the proportion of women complaining of breast pain. MPA has glucocorticoid-like activity that induces water retention and bloating, which may account for these symptoms.

Conclusions

Breast cancer risk is not decreased when progestogen is added to hormone therapy, and emerging data suggest that there may be an increased risk with standard doses. However, the overall risk (approximately 30% increase) does not seem to affect mortality. Mammographic density is increased with progestogen use, although this effect will reverse with discontinuation of use. Breast discomfort and pain may increase with progestogen use.

Central nervous system

A number of clinical studies report an improvement in depressive mood changes in postmenopausal women using ET, an effect that may be separate from estrogen's relief of vasomotor disturbances.[160-162] In some women, progestogen may have a negative effect on mood.

In the brain, progesterone metabolites can elicit hypnotic, anxiolytic, anesthetic, or antiepileptic effects.[163,164] These metabolites do not interact with classical intracellular steroid receptors but bind stereoselectively and with high affinity to receptors for the major inhibitory neurotransmitter in the brain, gamma-amino-butyric acid (GABA), and have effects similar to benzodiazepines.[165]

Micronized progesterone taken orally has sedative and anesthetic properties, primarily because of hepatic conversion to its 5α- and 5β-reduced metabolites, the neurosteroids allopregnanolone and pregnanolone.[165] Vaginal administration decreases conversion to allopregnanolone and may reduce central nervous system (CNS)-associated side effects attributed to these metabolites.[166] At pharmacologic doses of oral micronized progesterone, these two metabolites may have anesthetic effects.[164] At lower doses (in animal models), anxiolytic effects have been observed.

In clinical trials, intramuscular administration of up to 100 mg of progesterone to healthy postmenopausal women increased allopregnanolone levels, but with modest, sedative-like effects.[167] Very high doses of oral micronized progesterone (1,200 mg) have been associated with fatigue, confusion, and a reduction in immediate recall.[168] However, at lower doses (300-600 mg) and doses typically used in EPT (100-300 mg), these effects were not significantly different from placebo.

Progestins are not converted to the same 5α- and 5β-reduced specific metabolites and may not have the same effects, although CNS-type effects do occur with certain progestins in some women.[102] In one study,[160] adding 5 mg/day of MPA to daily CEE (either 0.625 mg or 1.25 mg) attenuated the mood-enhancing effect of estrogen, particularly in the group receiving the lower, standard estrogen dose.

However, all progestins do not have the same effect on mood. A 6-month Swedish study of postmenopausal women receiving 2 mg of estradiol daily compared the mood effects of adding MPA (10 mg/day) or NET (1 mg/day) for 12 days each month.[169] Both progestins induced strong negative mood symptoms in women with a history of premenstrual syndrome (PMS). In

TABLE 5. *Minimum progestogen dosing requirements for endometrial protection with standard estrogen dosing*[1]

	Cyclic (Daily, ≥12 d/mo)	Continuous (Daily)
Oral		
medroxyprogesterone acetate (MPA)	5 mg	2.5 mg
norethindrone (NET)	0.35–0.7 mg	0.35 mg
norethindrone acetate (NETA)	2.5 mg	0.5–1.0 mg
micronized progesterone	200 mg	100 mg
custom-compounded micronized progesterone	100 mg	50 mg
Intrauterine (IUD)		
levonorgestrel (LNG)	—	20 μg/day
Vaginal		
progesterone gel	4% (1 applicator every other day)	4% (1 applicator every other day)

[1]0.625 mg CEE or its equivalent (table includes only products available in North America).

women with no PMS history, MPA was associated with more positive and fewer negative mood symptoms than NET.

Conclusions

Negative effects on mood can occur when progestogen is added to hormone therapy. Data are inadequate to recommend specific progestogens or EPT regimens for minimal adverse effects.

THERAPEUTIC MANAGEMENT

The clinical goal of progestogen therapy when added to ET is to provide endometrial protection while minimizing unwanted side effects. As with any pharmaceutical agent, therapy should be tailored to a woman's individual needs. The only menopause-related indication for chronic progestogen use seems to be endometrial protection from unopposed estrogen therapy. NAMS recommends that clinicians prescribe adequate progestogen for all postmenopausal women with an intact uterus who are using ET; postmenopausal women without a uterus should not be prescribed a progestogen.

Studies have better defined the necessary dose and duration of the progestogen course to oppose the estrogen-induced risk of endometrial hyperplasia and adenocarcinoma. All of the FDA-approved progestogen formulations will provide endometrial protection if the dose and duration are adequate. Table 5 lists the minimal dosing requirements for endometrial protection when combined with standard estrogen doses (eg, 0.625 mg CEE or equivalent). Larger or smaller estrogen doses may require larger or smaller progestogen doses, respectively. However, the risk for endometrial cancer is never eliminated in women with a uterus, as women not using hormones can develop this disease. Long-term surveillance is necessary, even in women receiving appropriate doses of progestogen. Because of concern that adding progestogen may increase breast cancer risk and may attenuate some benefits of ET, the lowest appropriate dose of progestogen should be used. Use of EPT should be limited to the shortest duration consistent with treatment goals, benefits, and risks for the individual woman.

Side effects

Despite the increased incidence of endometrial hyperplasia when unopposed estrogen is used, EPT has not been universally adopted because of side effects associated with progestogens. Trial data show that EPT discontinuance correlates with uterine bleeding.[170] Women with more days of amenorrhea had significantly higher rates of continuance than women with more days of bleeding.

While using EPT, some women may experience uterine bleeding for months or years. Bleeding may be partially due to anatomic conditions (eg, polyps, fibroids). If bleeding on continuous-combined or pulsed EPT persists beyond 6 months, endometrial cancer must be ruled out through tissue evaluation and/or hysteroscopy. Endometrial thickness measured by ultrasonography does not always correlate with histology of the endometrium obtained from a biopsy, although an endometrial thickness of less than 4 mm on vaginal ultrasound can be reassuring if endometrial biopsy cannot be performed.[171,172]

Known adverse reactions from using progestogen alone include edema, breast effects (eg, mastalgia, increased breast size), skin and hair effects (eg, rash, melasma, acne, hirsutism, alopecia), headache, and psychological effects (eg, mood swings, irritability, fatigue, depression).

In general, the side effects of adding progestogen to estrogen therapy are mild, although they may be severe in a small percentage of women. By tailoring progestogen type, dosage, or rate of administration, or the EPT regimen, most women who require therapy can obtain benefits with minimal side effects.

Little is known about side effects for specific progestogens used in EPT. One crossover trial has shown that adverse reactions are not more frequent when MPA is added to ET.[173] Mastalgia and edema may be more common with progestogens that have glucocorticoid-like activity, such as MPA and gestodene. Acne, hirsutism, and alopecia are androgen-related side effects oc-

curring mostly with 19-nortestosterone derivatives (eg, NET, LNG). Mood swings, dizziness, and fatigue may be encountered with very high doses of oral progesterone,[10] but at the lower doses typically used in EPT (100-300 mg), these effects are not significantly different from placebo.

Hormone-related headaches may be lessened or eliminated by reducing estrogen fluctuation (eg, switching from a cyclic to a continuous-combined regimen or switching from an oral to a transdermal product). In women whose headaches are exacerbated by progestogen, a better choice may be progesterone or a 19-norpregnane.

Low doses of transdermal, vaginal, or intrauterine progestogen formulations may have metabolic advantages over higher doses or oral progestogens, especially progestins derived from 19-nortestosterone. If oral therapy is preferred, the 19-norpregnanes seem to be free from metabolic side effects.

During initial progestogen therapy (particularly with oral micronized progesterone), bedtime dosing is advised to avoid the dizziness and/or drowsiness that some women experience.

Contraindications and precautions

Contraindications for progestogen therapy in a postmenopausal woman, as stated in FDA prescribing information, include thromboembolic disorders, impaired liver function, breast or genital carcinoma, undiagnosed uterine bleeding, and hypersensitivity to the drug. Some of these contraindications stem from oral contraceptive studies. There is no evidence that progestogen alone increases the risk of thrombosis. The micronized progesterone capsule (Prometrium) is contraindicated for women who are allergic to peanuts because the active ingredient is suspended in peanut oil. As with all therapies, the contraindications may not be absolute, provided that the potential benefits outweigh the potential risks, and an informed decision is made regarding acceptance of therapy.

Precautions in product labeling include careful observation of women who have a history of depression or diabetes, or when preexisting disease may be influenced by fluid retention (eg, epilepsy, migraine, asthma, cardiac or renal dysfunction). Fluid retention has not been observed with progesterone and 19-norpregnane derivatives.

SUMMARY

The primary role of progestogen in hormone therapy is to protect the endometrium from hyperplasia and adenocarcinoma associated with unopposed ET. Adding the appropriate dose and duration of progestogen (either as progestin or progesterone) to ET has been shown to lower that risk to the level found in never-users of ET. The clinical goal of progestogen in hormone therapy is to provide endometrial protection while maintaining estrogen benefits and minimizing progestogen-induced side effects, particularly uterine bleeding. All FDA-approved progestogen formulations will provide endometrial protection if the dose and duration are adequate. There are not enough data to recommend topical progesterone for this use.

A wide variety of progestogen types, routes of administration, and dosage regimens are available, each having distinct side effects, as well as different actions on the endometrium and other organ systems. Some progestogens may diminish the beneficial effects of ET on coronary heart disease and may negatively affect mood. Data on the association between progestogen use and an increased risk of breast cancer are inconsistent and controversial, but it is clear that adding progestogen to ET does not decrease breast cancer risk. Progestogen has limited effect on the bone-enhancing action of ET.

Uterine bleeding is the primary adverse effect associated with EPT. Higher rates of EPT discontinuance correlate with more uterine bleeding, and women with more days of amenorrhea have higher rates of continuance. In general, the other side effects of added progestogen are mild, although they may be severe in a small percentage of women.

There is no consensus on the preferred regimen; however, by changing the progestogen type, route, or regimen, clinicians can help minimize any attenuation of estrogen's benefits, decrease side effects, and lessen uterine bleeding while providing adequate endometrial protection.

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