

## POSITION STATEMENT, Part I

# Role of Progestogen in Hormone Therapy for Postmenopausal Women: Position Statement of the North American Menopause Society

### Editor's note

This position statement defines the most current scientific evidence as it relates to the role of progestogen in estrogen therapy. The position statement was published in the March-April 2003 issue of *Menopause* and appears in *Menopause Management* with the permission of The North American Menopause Society and the editors of *Menopause*. The statement will be published here in two parts. The second part will run in the July/August issue.

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 enlist-

ed 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.<sup>1</sup>)

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.<sup>2-4</sup> 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.

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

**Table 1.**  
**Classification of progestogens**

Progesterone (identical to endogenous progesterone)

Progestins (not identical to endogenous progesterone)

A. Structurally related to progesterone

- pregnane derivatives:
  - acetylated* (also called 17 $\alpha$ -hydroxyprogesterone derivatives): medroxyprogesterone acetate, megestrol acetate, cyproterone acetate, chlormadinone acetate
  - nonacetylated*: dydrogesterone, medrogestone
- 19-norpregnane derivatives (also called 19-norprogesterone derivatives):
  - acetylated*: norgestrel acetate, norgestrel
  - nonacetylated*: demegestone, trimegestone, promegestone

B. Structurally related to testosterone (also called 19-nortestosterone derivatives)

- ethinylated:
  - estrans*: norethindrone (also called norethisterone), norethindrone acetate, norethynodrel, lynestrenol, ethynodiol diacetate
  - 18-ethylgonanes: levonorgestrel, norgestrel, desogestrel, gestodene, norgestimate
- nonethinylated*: dienogest, drospirenone

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).

### 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*.

### 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 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.<sup>5</sup> 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.<sup>6</sup> In the endometrium, progestogen increases the activity of 17 $\beta$ -hydroxysteroid dehydrogenase, resulting in conversion of estradiol to estrone, a biologically weaker estrogen.<sup>7</sup> 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,<sup>8</sup> 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.<sup>9</sup> 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),<sup>10</sup> 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-

**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 <sup>1</sup> (45 mg/dose)	4% gel
Progestin		
Oral tablet		
medroxyprogesterone acetate	Provera, Gen-Medroxy, <sup>2</sup> Alt-MPA, <sup>2</sup> Novo-Medrone, <sup>2</sup> various generics	2.5, 5.0, 10.0 mg
norethindrone (norethisterone)	Micronor, Nor-QD <sup>1</sup>	0.35 mg
norethindrone acetate	Aygestin, <sup>1</sup> Norlutate, <sup>2</sup> generic	5.0 mg
norgestrel	Ovrette <sup>1</sup>	0.075 mg
Intrauterine system		
levonorgestrel	Mirena	20 µg/day approx release rate (52 mg/device; 5-y use)

<sup>1</sup> Available only in the United States.

<sup>2</sup> Available only in Canada.

Products not marked are available in both the United States and Canada.

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 pro-

tection. 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.<sup>11-16</sup> 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

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

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

<sup>1</sup> Available only in the United States.

<sup>2</sup> Available only in Canada.

Products not marked are available in both the United States and Canada.

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.<sup>17-22</sup> In one study,<sup>23</sup> 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).<sup>17,20,21</sup> However, in one case-control study,<sup>24</sup> 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 have not been clearly associated with increased risk.<sup>25</sup> 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.<sup>11-15,26</sup> 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.<sup>25-27</sup> A review of published studies<sup>28</sup> 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).<sup>19,29,30</sup>

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 17 $\beta$ -estradiol, demonstrated endometrial safety in a one-year trial.<sup>23</sup>

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.<sup>31</sup> 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 three months.<sup>32</sup> However, trial duration of three 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.<sup>33,34</sup> 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

Progesterone 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 progesterone 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

**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-progesterone; continuous-pulsed)	Daily	Repeated cycles of 3 days on, 3 days off

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. Progesterone 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 17 $\beta$ -estradiol has been reported to be 15–20 hours).<sup>35</sup>

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.

### 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,<sup>36,37</sup> this EPT regimen had a low rate of uterine bleeding and a high rate of tolerability. In one trial,<sup>36</sup> endometrial biopsies performed before and after four months of cyclic-combined EPT (2 mg/day 17 $\beta$ -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 four 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.<sup>38</sup>

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 one 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 six months.<sup>39,40</sup> However, the Scandinavian Long Cycle Study,<sup>41</sup> which used 2 mg/day of 17 $\beta$ -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 one year.<sup>42</sup> 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%).<sup>20</sup> Oral continuous-combined regimens of 17-estradiol (1 mg/day) with NETA (0.1, 0.25, or 0.5 mg/day),<sup>18</sup> as well as oral ethinyl estradiol (1.0, 2.5, 5.0, or 10  $\mu$ g/day) combined with NETA (0.2, 0.5, 1.0, or 1.0 mg/day, respectively),<sup>21</sup> also produced hyperplasia rates less than 1%. Transdermal 17 $\beta$ -estradiol (50  $\mu$ g/day) combined with NETA (0.14 or 0.25 mg/day) did not result in any measurable hyperplasia after one year of treatment.<sup>23</sup> A continuous-combined transdermal patch delivering 17 $\beta$ -estradiol (25  $\mu$ g/day) and NETA (0.125 mg/day) provided endometrial protection and maintained a high rate of amenorrhea in a two-year clinical trial.<sup>43</sup>

### 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.<sup>44,45</sup>

In one study,<sup>45</sup> women using 17-estradiol (1 mg/day) with a pulsed regimen (3 days on, 3 days off) of norgestimate (90  $\mu$ g/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,<sup>46</sup> 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  $\mu$ g/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);<sup>47</sup> transdermal 17-estradiol (50  $\mu$ g/day for one week) followed by transdermal combined 17 $\beta$ -estradiol (50  $\mu$ g/day) plus NETA (250  $\mu$ g/day) for 3 days.<sup>48</sup>

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<sup>42</sup> 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.<sup>49-52</sup> 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 three years.<sup>19</sup>

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.<sup>28,47</sup> However, epidemiologic studies of continuous-combined EPT indicate no increased risk and may even suggest some added protection against endometrial cancer.<sup>25,53</sup> A nine-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.<sup>54</sup>

### 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<sup>55,56</sup> 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<sup>42,57</sup> 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.<sup>42,58</sup> Bleeding pattern is a less reliable indicator of endometrial safety when continuous-combined regimens are used.<sup>56,59,60</sup>

Breakthrough uterine bleeding has been observed in 40% of women on a continuous-combined regimen during the first 3 to 6 months.<sup>58</sup> 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.<sup>58,61</sup> 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 17 $\beta$ -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.<sup>38</sup> After six 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 three 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 two years, those using a continuous-combined regimen have lower rates of breakthrough uterine bleeding and endometrial biopsies than those using the cyclic regimen.<sup>62</sup> These findings confirm other studies that show decreased breakthrough uterine bleeding over time in women using the con-

tinuous-combined regimen. Nevertheless, continuance rates at three years are slightly higher in cyclic EPT users than in continuous-combined EPT users.<sup>63</sup>

Intrauterine-administered progestogen is an option to avoid systemic side effects. Although the levonorgestrel intrauterine device (IUD; Mirena) was developed for contraception, not EPT use, this preparation (which releases LNG at a rate of 20  $\mu$ g/day) seems to be effective in postmenopausal women in opposing the proliferative effects of ET on the endometrium.<sup>64,65</sup> Similar effects had been observed with the progesterone IUD (Progestasert), now withdrawn from the market.<sup>66,67</sup> A lower-dose LNG-containing IUD (10  $\mu$ g/day), which is under FDA review, also seems to protect the endometrium and produces minimal uterine bleeding.<sup>68</sup> 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.

### Conclusion

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 six 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. ■

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(continued on page 34)

## NAMS Position Statement

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