

## POSITION STATEMENT, Part II

# 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*. Part I appeared in our May/June 2003 issue.

### 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<sup>69</sup> and progesterone<sup>70</sup> 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, stimu-

lating 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.<sup>71-74</sup>

Clinical trial results conflict with observational study findings. In the prospective, randomized Women's Health Initiative (WHI),<sup>75</sup> 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)<sup>76,77</sup> and the Estrogen Replacement and Atherosclerosis trial (ERA).<sup>78</sup> 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.<sup>79,80</sup>

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.<sup>44</sup> 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).<sup>72</sup> However, the stroke risk was not significant with

**Table 5.**  
**Minimum progestogen dosing requirements for endometrial protection with standard estrogen dosing<sup>1</sup>**

	Cyclic (Daily, $\geq 12$ d/mo)	Continuous (Daily)
<b>Oral</b>		
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
<b>Intrauterine (IUD)</b>		
levonorgestrel (LNG)	–	20 $\mu$ g/day
<b>Vaginal</b>		
progesterone gel	4% (1 applicator every other day)	4% (1 applicator every other day)

<sup>1</sup>0.625 mg CEE or its equivalent (table includes only products available in North America).

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.

### 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*.

### Atherosclerosis

Atherosclerotic plaques are a major contributor to cardiovascular disease. Animal studies suggest that estrogen inhibits the progression of atherosclerosis.<sup>81-83</sup> Adding progestogen to ET produces varied effects on this process. Intermittent parenteral progesterone has shown no detrimental effect,<sup>81</sup> whereas continuous MPA blunted CEE benefit in one study<sup>82</sup> but not in a subsequent study.<sup>83</sup> 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.<sup>84</sup> In animals with existing arterial disease, neither ET nor EPT reduced atherosclerosis.<sup>85-87</sup>

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.<sup>88</sup> A prospective 2-year trial of unopposed 17 $\beta$ -estradiol versus placebo showed significantly reduced IMT among estrogen recipients.<sup>89</sup> In women with increased IMT, no slowing of atherosclerosis progression was seen with estradiol and gestodene after 48 weeks.<sup>90</sup> 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.<sup>87,91</sup> However, the addition of nomegestrol acetate to ET did not reverse the beneficial effects of 17 $\beta$ -estradiol on vascular dilation,<sup>92</sup> indicating that different progestins exert different effects. In another study, coronary artery vasospasm was avoided with the combination of 17 $\beta$ -estradiol plus progesterone but not with 17 $\beta$ -estradiol plus MPA.<sup>93</sup>

In women, both acute and long-term use of ET produces dilation of coronary arteries.<sup>94,95</sup> Some studies have found that use of CEE with either oral micronized progesterone or MPA improves flow-mediated dilation,<sup>96</sup> whereas others have found that MPA impairs flow-mediated dilation in a dose-dependent manner.<sup>97</sup> The combination of NETA and 17 $\beta$ -estradiol did not improve flow-mediated dilation.<sup>98</sup> In another study,<sup>99</sup> 17 $\beta$ -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 ( $\geq 80$  years) using mostly unopposed ET<sup>100</sup> or women with established angina pectoris using ethinyl estradiol and NETA<sup>101</sup> 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,<sup>102</sup> although the addition of methyltestosterone to ET does not diminish vascular reactivity in monkeys.<sup>103</sup>

### **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.<sup>21,104,105</sup> 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.<sup>75,77</sup>

In the PEPI trial,<sup>106</sup> 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,<sup>105</sup> combining norgestimate with 17 $\beta$ -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.<sup>21</sup> Concentrations of LDL-C have been lowered with both ET and EPT,<sup>106-110</sup> although higher doses of NETA (0.5 mg) enhanced LDL-C reductions.<sup>107</sup> Levels of Lp(a) are decreased with both ET and EPT.<sup>108,110</sup>

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.<sup>96</sup> 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.<sup>111,112</sup> However, the combi-

nation of transdermal 17 $\beta$ -estradiol and oral NETA decreased CRP levels in women with diabetes mellitus (DM),<sup>113</sup> 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 17 $\beta$ -estradiol reduce fibrinogen and type-1 plasminogen activator inhibitor (PAI-1) levels, beneficial changes that are not affected by the addition of MPA<sup>114</sup> or NETA.<sup>107</sup> There is evidence that oral ET is associated with a procoagulant state with adverse changes in antithrombin III and protein C.<sup>115</sup> 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.<sup>116</sup> 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.<sup>117</sup>

ET/EPT has been shown to lower fasting glucose and insulin concentrations and improve insulin sensitivity in some studies,<sup>118,119</sup> but not in others.<sup>120,121</sup> One study reported improvement in women using transdermal NETA but deterioration in women using oral LNG,<sup>121</sup> 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,<sup>122-124</sup> as well as C-reactive protein levels.<sup>113</sup> Also, ET/EPT has been found to increase 2-h postprandial glucose, a parameter that correlates better with CVD than fasting glucose.<sup>108</sup>

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 women with DM, are not increased further with transdermal ET/EPT.<sup>109,125</sup> 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.<sup>126</sup> 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<sup>127</sup> 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<sup>128</sup> 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).<sup>127</sup>

It has been suggested for many years that 19-nortestosterone derivatives (eg, NETA) have greater skeletal effects than 17 $\alpha$ -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,<sup>21</sup> recently postmenopausal women (average age, 52 years; 1-4 years beyond menopause) received ethinyl estradiol (1.0, 2.5, 5.0, and 10  $\mu$ g/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  $\mu$ g) seemed to have greater spinal BMD increases than those receiving 5 and 10  $\mu$ g 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  $\mu$ g 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%.<sup>75</sup> 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 non-glandular tissue increase during the luteal phase under the influence of endogenous progestogen, enlarging breast size.<sup>129-131</sup> 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.<sup>132</sup> Also, normal breast tissue placed into an athymic nude mouse model did not proliferate when exposed to progestogen.<sup>133</sup>

In vitro studies evaluating the effects of progesterone on breast tissue proliferation have yielded mixed results, reporting both increases and decreases.<sup>134-137</sup> 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.<sup>138,139</sup> Also, even though progesterone decreases the tumor-suppressor protein p53, leading potentially to increased proliferation,<sup>140</sup> the induction of proliferation caused by an increase of growth factors<sup>141</sup> is followed by an inhibitory effect.<sup>142</sup> Relating to the synergistic influence of growth factors in breast cell proliferation, there is some concern that exogenous progestogen may have proliferative influences.<sup>143</sup> 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.<sup>144</sup> 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.<sup>136</sup>

Clinical studies demonstrate that a larger proportion of women develop increased mammographic density when progestogen is added to ET.<sup>145</sup> 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.<sup>146,147</sup> 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,<sup>148</sup> 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<sup>149</sup> 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.<sup>150</sup> In a randomized, placebo-controlled study of postmenopausal women,<sup>151</sup> 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.<sup>152</sup> Several retrospective, case-control studies,<sup>153-157</sup> 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.<sup>158</sup>

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.<sup>75</sup> 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<sup>153,154</sup> 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,<sup>159</sup> 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.<sup>160-162</sup> In some women, progestogen may have a negative effect on mood.

In the brain, progesterone metabolites can elicit hypnotic, anxiolytic, anesthetic, or antiepileptic effects.<sup>163,164</sup> These metabolites do not interact with classical intracellular steroid receptors but bind stereo-selectively 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.<sup>165</sup>

Micronized progesterone taken orally has sedative and anesthetic properties, primarily because of hepatic conversion to its 5 $\alpha$ - and 5 $\beta$ -reduced metabolites, the neurosteroids allopregnanolone and pregnanolone.<sup>165</sup> Vaginal administration decreases conversion to allopregnanolone and may reduce central nervous system (CNS)-associated side effects attributed to these metabolites.<sup>166</sup> At

pharmacologic doses of oral micronized progesterone, these two metabolites may have anesthetic effects.<sup>164</sup> 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.<sup>167</sup> Very high doses of oral micronized progesterone (1,200 mg) have been associated with fatigue, confusion, and a reduction in immediate recall.<sup>168</sup> 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 5 $\alpha$ - and 5 $\beta$ -reduced specific metabolites and may not have the same effects, although CNS-type effects do occur with certain progestins in some women.<sup>102</sup> In one study,<sup>160</sup> 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.<sup>169</sup> Both progestins induced strong negative mood symptoms in women with a history of premenstrual syndrome (PMS). In 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 thera-

py 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 discon-

tinuance correlates with uterine bleeding.<sup>170</sup> 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.<sup>171,172</sup>

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.<sup>173</sup> 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 occurring mostly with 19-nortestosterone derivatives (eg, NET, LNG). Mood swings, dizziness, and fatigue may be encountered with very high doses of oral progesterone,<sup>10</sup> 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 pre-

ferred 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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