New Options for Treating the Symptoms of Menopause

R. Mimi Secor, MS, MEd, APRN, BC and James A. Simon, MD

A variety of hormonal options are available for women seeking to alleviate symptoms associated with menopause. However, the safety of hormone therapy (HT) has been challenged by reports of increased cardiovascular risk. Recent studies show that such risk can be minimized if HT is initiated early in the menopausal transition and that transdermal estrogen products may pose lower cardiovascular risk than oral agents. Patients with an intact uterus who are prescribed estrogen should be monitored closely for signs of endometrial hyperplasia or endometrial cancer, and the addition of progestogen to their hormonal regimen is recommended. Women receiving HT should be educated thoroughly about its risks and benefits.

Approximately 45.5 million American women are postmenopausal. In the coming decades, this number is expected to rise dramatically as the US life expectancy continues to increase. Once seen as a passage to old age and physical decline, the menopausal transition is now regarded as a period during which good health, high quality of life, and vigor can be anticipated.

Estrogen therapy has been available for more than 60 years. Its generally recognized benefits include the ability to reduce or eliminate vasomotor symptoms and to ameliorate urogenital atrophy and associated symptoms. Secondary benefits include improvements in sexual function, sleep, cognition, mood, and quality of life. Additionally, estrogen is well documented to prevent osteoporosis and reduce the risk of fractures. Despite being associated with an increase in breast cancer risk, HT was generally regarded as safe based on available data at that time.

Attitudes toward HT changed dramatically following the release of the Women's Health Initiative (WHI) report in 2002. The fear generated by the WHI findings has caused many practitioners to cut back on or stop prescribing HT, potentially compromising the quality of life for women who experience moderate or severe vasomotor or urogenital symptoms.

Initial Findings of the WHI
The WHI consisted of two parallel, randomized, double-blind, placebo-controlled clinical trials of HT designed to determine whether conjugated equine estrogen (CEE) only (for women with prior hysterectomy) or CEE combined with progestin (for women with an intact uterus) would reduce cardiovascular events. The CEE plus progestin trial was halted in July 2002 after a mean follow-up of 5.2 years because health risks were found to exceed benefits. Risk of cardiovascular disease (CVD)—coronary heart disease (CHD), stroke, and venous thromboembolism (VTE)—was increased in the combination group, as was the risk of breast cancer. There was a 37% and a 24% decrease in colorectal cancer and total fractures, respectively, and no difference in all-cause mortality. In 2004, the estrogen-only trial also was halted because the risk with CEE for stroke was elevated and the other endpoints were unlikely to change with continuation of the trial.

In the wake of the WHI trial, the use of HT declined sharply among perimenopausal and postmenopausal women. According to one analysis, the number of prescriptions for oral estrogen and oral combined estrogen/progestin fell by half, from 17.5 million in 1995 to 8.9 million in 2003, the year following the release of the WHI findings.

R. Mimi Secor, MS, MEd, APRN, BC is President Emerita and Senior Advisor for the Nurse Practitioner Associates for Continuing Education (NPACE), Natick, Massachusetts, Visiting Scholar at Boston College.

James A. Simon, MD is Clinical Professor in the Division of Reproductive Endocrinology, Department of Obstetrics and Gynecology, at George Washington University School of Medicine in Washington, DC, and Past President of the North American Menopause Society.
RE-EXAMINATION OF THE WHI DATA
The atmosphere of alarm that spawned the decline in use of HT may have occurred because some critically important study data were not widely reported. For instance, although use of HT was associated with increased relative risk of CVD, absolute risk was minimal (Figure 1). In fact, there was even a suggestion of lower CHD risk with estrogen use among women who were between ages 50 and 59 at the start of the study.

In addition, other factors related to patient characteristics clearly contributed to the reported increased risk of CVD. The average age of WHI participants was 63 years at baseline and some were already diagnosed with CVD while others had significant cardiovascular risk factors. For example, 50% of study subjects were current or former smokers and the mean body mass index was 28.5 (Table 1).

In a recent study, researchers prospectively examined the relationship between a woman's age at HT initiation and time since menopause, using postmenopausal participants in the Nurse's Health Study. In the subgroup of women demographically similar to those in the WHI, there was no significant relationship between HT and CHD among those who began therapy prior to their 10th year after menopause. However, when HT was initiated within four

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<tbody>
<tr>
<td><strong>WOMEN'S HEALTH INITIATIVE</strong></td>
</tr>
<tr>
<td><strong>The Headlines</strong></td>
</tr>
<tr>
<td>• 41% increase in strokes</td>
</tr>
<tr>
<td>• 29% increase in heart attacks</td>
</tr>
<tr>
<td>• &gt;100% increase in venous thromboembolism</td>
</tr>
<tr>
<td>• 22% increase in total CVD</td>
</tr>
<tr>
<td>• 26% increase in breast cancer</td>
</tr>
<tr>
<td>• 37% decrease in colorectal cancer</td>
</tr>
<tr>
<td>• 33% decrease in hip fracture</td>
</tr>
<tr>
<td>• 24% decrease in total fractures</td>
</tr>
<tr>
<td>• No difference in all-cause mortality (not mentioned)</td>
</tr>
<tr>
<td><strong>Not in the media about WHI</strong></td>
</tr>
<tr>
<td>• Average age 63</td>
</tr>
<tr>
<td>• Most already had silent CVD</td>
</tr>
<tr>
<td>• 50% current or former cigarette smokers</td>
</tr>
<tr>
<td>• Average BMI 28.5, many obese</td>
</tr>
<tr>
<td>• Average study participant was older, overweight/smoker</td>
</tr>
</tbody>
</table>


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**FIGURE 1**

*Women's Health Initiative*

**EPT Study Effect on Event Rates per 10,000**

<table>
<thead>
<tr>
<th>Event Category</th>
<th>Risks*</th>
<th>Benefits*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additional Events</td>
<td>+7</td>
<td>+8</td>
</tr>
<tr>
<td>CHD</td>
<td>Stroke</td>
<td>Breast Cancer</td>
</tr>
<tr>
<td>Reduced Events</td>
<td>-6</td>
<td>-5</td>
</tr>
<tr>
<td>Deaths</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Statistically significant based on 95% nominal CI on Hazard Ratios

Data adapted from Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute. WHI HT Update—2002.
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years of the last menstrual period, the risk of CHD was reduced by approximately 30%.15

One potential explanation for these age effects in both the Nurses Health Study and the WHI is related to the effect of estrogen, which has been shown to increase levels of matrix metalloproteinase (MMP) enzymes.16 These enzymes play a role in remodeling of the blood vessels which may account for the age-related window of opportunity in the initiation of hormone therapy.

Most thrombi form at sites of fissure or rupture of a plaque lesion in an artery. Coronary events and strokes may occur because collagen in the fibrous cap, which seals off the atherosclerotic lesion and its prothrombotic contents, is degraded by MMPs and becomes vulnerable to rupture and subsequent thrombosis.16,17 In perimenopausal women and those in the early stages of menopause, estrogen reduces the risk of coronary events by preventing atherosclerotic buildup and protecting against inflammation. However, in older postmenopausal women—who possibly have more significant plaque buildup and more complex atheromas and luminal narrowing—HT would not have this protective effect and may even compromise plaque stability by increasing MMP production.18-20

| TABLE 2 |
|-----------------|-----------------|-----------------|-------------------|-------------------|
| Hormone Therapy Options | Oral | Patches | Dermal | Others |
| Estrogen | Cenestin® | Alora® | EstroGel® (gel) | Estrace® (vaginal cream) |
| Estrace® | Climara® | Estrasorb® (emulsion) | Estrarin® (vaginal ring) |
| Estratab® | Esclim® | Estraderm® | Premarin® (vaginal ring) |
| Menest® | Menostar® | Vivelle® | Vagifem® (vaginal cream) |
| Premarin® | Vivelle-Dot® | | Estratest® HS 0.625/1.25 |
| Progestogen | Aygestin® | Climara Pro® | | Estratest® |
| Ayestra® | Femhrt® | CombiPatch® | | |
| Prometrium® | Ortho-Prefert® | | | |
| Combinations | Activella® | Premphase® | | |
| Fempro® | | Prempak® | | |

Source: R. Minke Sacco, MS, MEd, APRN, BC.
progestins, and combination medication regimens (Table 2). Aspects of HT regimens such as dose, duration, and delivery method should be customized for the individual patient, with patient safety and preference being critical determinants in the therapeutic decision-making process.29

COMPARING EFFICACY AND SAFETY OF HT AGENTS
A meta-analysis of 14 trials found that oral CEE and 17β-estradiol, as well as transdermal 17β-estradiol, significantly reduced hot flash frequency, severity, or both, compared with placebo.30 No evidence was found that one agent was more effective than the other.

Both estrogen gel and estrogen emulsion have demonstrated efficacy in treatment of hot flashes. Simon et al31 compared twelve weeks of treatment with estrogen emulsion (3.45 g micellar nanoparticle containing 86 mg estradiol) with placebo in 200 postmenopausal women with seven or more moderate to severe hot flashes daily. This study found that the emulsion was significantly superior to placebo in reducing the mean frequency of moderate to severe vasomotor symptoms ($P < 0.0001$).

Archer et al32 conducted a 12-week, double-blind, placebo-controlled study of 221 postmenopausal women to determine efficacy and tolerability of two strengths of percutaneous 17β-estradiol gel (1.25 g containing 75 mg estradiol, and 2.5 g containing 15 mg estradiol) versus placebo gel in controlling vasomotor symptoms. Women in the treatment groups experienced a significant reduction ($P < 0.05$) in the mean frequency of moderate to severe hot flashes and mean frequency of all hot flashes, compared with controls.

POTENTIAL ADVANTAGES OF NON-ORAL DELIVERY METHODS
An important treatment goal is to maximize safety of the hormone therapy regimen chosen, whether unopposed

![FIGURE 2](image-url)
Stable Estrogen Levels are Maintained by Transdermal Delivery System

![FIGURE 3](image-url)
Oral and Transdermal Estrogen Therapy Pharmacokinetic Comparison

Adapted from Minkin. J Reprod Med. 2004.19

Women's Health Oi-Gyn Edition  July-August 2006  47
estrogen or a combination of estrogen and progesterone. The route of administration plays an important role in this decision-making process.

Transdermal estrogen delivery systems have been shown to be safer than oral delivery systems in reducing markers of cardiovascular risk, such as coagulation factors, and in reducing actual clinical events—stroke, VTE, and myocardial infarction. In addition, since the hormones are absorbed directly into the bloodstream, bypassing the liver, transdermal delivery systems are more effective in maintaining stable blood levels of estrogen. This avoids “peaks” that have been associated with increased risk of adverse effects, including cardiovascular events (Figure 2).14,33

Furthermore, since transdermal estrogen is absorbed directly into the body, first-pass metabolism by the gastrointestinal tract and liver is avoided (Figure 3).14,35 When given orally, larger estradiol doses are needed to achieve therapeutic levels and to counter metabolism by the liver and inactivation by the gut wall. Eliminating this first-pass hepatic metabolism also allows lower doses of estrogen to be administered.14,36

Godsland37 conducted a meta-analysis of 248 studies comparing the effects of various types of HT regimens on lipid levels. The results showed that all estrogen-only regimen raised HDL levels and lowered total and LDL cholesterol. However, while oral estrogens raised triglycerides, transdermal administration of 17β-estradiol had the effect of lowering triglyceride levels.37

Other studies have shown that, while oral estrogen increases markers (such as C-reactive protein) associated with risk of CVD and plaque rupture, transdermal formulations have no impact on these markers.38,39

Oral estrogen therapy has been shown to increase the risk of VTE, compared with transdermal formulations. In a multicenter case-control study, Scarabin et al.40 compared the effect of oral and transdermal estrogen in 155 postmenopausal women with a first documented episode of idiopathic VTE versus 381 age-matched controls. They found that 21% of patients with VTE were current users of oral estrogen (vs 7% of controls) and 19% of patients with VTE were current users of transder-

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**TABLE 3**

**ORAL VERSUS TRANSDERMAL HORMONAL DELIVERY SYSTEMS**

<table>
<thead>
<tr>
<th>Oral</th>
<th>Transdermal (Patch)</th>
<th>Transdermal (Gel or emulsion)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADVANTAGES</strong></td>
<td>No first-pass metabolism</td>
<td>No first-pass metabolism</td>
</tr>
<tr>
<td>Familiar</td>
<td>Less impact on clotting factors</td>
<td>Less impact on clotting factors</td>
</tr>
<tr>
<td>Discreet</td>
<td>Lower SHBG</td>
<td>Lower SHBG</td>
</tr>
<tr>
<td>Versatile (many options)</td>
<td>Minimal impact on triglycerides</td>
<td>Minimal impact on triglycerides</td>
</tr>
<tr>
<td>Well-researched</td>
<td>Low GI side effects</td>
<td>Low GI side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Two options</td>
</tr>
<tr>
<td><strong>DISADVANTAGES</strong></td>
<td>Skin irritation (20%-40%) (erythema/pruritis)</td>
<td>Skin irritation (less than patches, 1% to 4%)</td>
</tr>
<tr>
<td>First-pass metabolism in liver</td>
<td>Less beneficial to HDL</td>
<td>Less beneficial to HDL</td>
</tr>
<tr>
<td>Increased risk of venous thromboembolism</td>
<td>Not discreet</td>
<td>Must apply properly</td>
</tr>
<tr>
<td>GI side effects</td>
<td>Variable adhesion</td>
<td>Must add progestogen</td>
</tr>
<tr>
<td></td>
<td>Residual adhesive/lint rings on skin after removal</td>
<td>Longer time to onset of action</td>
</tr>
<tr>
<td></td>
<td>Longer time to onset of action</td>
<td></td>
</tr>
</tbody>
</table>

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ormal estrogen therapy (vs 24% of controls). The researchers concluded that the estimated risk of VTE in current users of oral estrogen was four times greater than the risk for those using transdermal estrogen.

In a follow-up study, Straczek et al. showed that even among women who had an existing prothrombotic mutation, transdermal estrogen did not confer additional risk of VTE, in contrast to oral estrogen.

Despite disadvantages associated with oral therapy, there may be important reasons for choosing it, including patient familiarity and convenience. However, risks versus benefits must always be carefully considered. A comparison of oral and transdermal formulations is found in Table 3.35,37,38,43

There are no large head-to-head trials comparing the relative advantages and disadvantages of different transdermal formulations. The patch is significantly more irritating to the skin than either gel or emulsion, with rates as high as 40% reported.42 In addition, the gel and emulsion are more discrete than the patch. The emulsion is applied to the complete surface of both legs once daily, meaning that a higher quantity is absorbed (both in number of applications and in surface area), while gel is applied once daily to one upper arm and shoulder. Gel is flammable until it dries, but once it is dry, sunscreen can be used. The emulsion may have slightly different estradiol absorption when used together with sunscreen. General instructions for application are listed in Table 4.

ComPOUNDED EstrostENS
Because there are no exact equivalencies between the various formulations of HT (ie, patch, gel, emulsion), dosage adjustment can be challenging. Compounded medications are prepared by specialized compounding pharmacies in an effort to provide highly individualized in dosing. Many of the components of compounded preparations are FDA-approved, but the actual formulations are not. Considerable variability exists between compounding pharmacies and their products. Moreover, monitoring serum hormone levels is usually recommended when using compounded products, but is both controversial and expensive.

Compounded products are usually dispensed without a package insert and thereby may appear to have lower risk profiles compared with FDA-approved preparations. In its Committee Opinion #322, the American College of Obstetrics and Gynecology states that “given lack of well-designed and well-conducted clinical trials of compounded hormones, ACOG recommends that all of them should be considered to have the same safety issues” as FDA-

| TABLE 4 |
| GENERAL PATIENT INSTRUCTIONS FOR TRANSDERMAL NON-PATCH PRODUCTS |

- **Gel and Emulsion**
  - Apply same time each day, preferably in morning
  - Apply to clean, dry, intact skin
  - Avoid applying to red, irritated skin
  - Avoid contact with eyes, vulva, or breasts
  - Wash hands after application
  - Use lowest dose to relieve symptoms
  - Patience required: four to 12 weeks before symptom relief
  - Use for shortest possible period of time
  - Follow up within three months, discuss adding progestogen at that point

Source: R. Mimi Secor, MS, Med, AFRN, BC.

| TABLE 5 |
| RELATIVE POTENCIES OF HT PRODUCTS (ESTIMATED) |

- Premarin oral 0.3 mg = Estrogen gel TD.75 mg (1/25 gm)
- 17β-estradiol patch 0.0375 mg = Estrogen gel 0.75 mg estradiol
- Premarin oral 0.625 mg = 17β-estradiol oral 1.0 mg
- Premarin oral 0.625 mg = 17β-estradiol patch 0.05 mg

Source: R. Mimi Secor, MS, Med, AFRN, BC, and James A. Simon, MD.
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approved HT] and may also have additional risks unique to the compounding process.44,45

PREVENTING ENDOMETRIAL CANCER

Another important and surprising finding of the WHI is that use of combination estrogen/progestin carries greater cardiovascular risk than use of unopposed estrogen—especially when progestin acetate is used.44,45 However, it should be noted that the primary role of progestin in HT is to protect the endometrium from hyperplasia and adenocarcinoma associated with unopposed ET.

Adding an appropriate dosage of progestogen (either as progestin or progestrone) to estrogen has been shown to lower endometrial cancer risk to the levels found in never-users of HT.46 Individual regimens and formulations differ and include synthetic and natural formulations. Each route and type of progestogen is associated with different effects, risks, and benefits. Estrogen-progestrone combinations are available in both oral and transdermal patch formulations. Table 6 contains a list of oral progestogens.

A 14-day course of medroxyprogesterone acetate (MPA) (Provera®) administered quarterly has been shown to be preferred by women over monthly use. Ettinger et al47 found that 10 mg MPA taken orally for 14 days per quarter—a regimen that can enhance adherence—was associated with less than a 2% risk of endometrial hyperplasia. However, this approach was also associated with a higher rate of instrumentation (eg, biopsies) and major surgeries (eg, hysterectomies) than monthly therapy. Despite this research, “long-cycle” progestogen use is not yet a widespread practice. Oral micronized progesterone (Prometrium®), a natural formulation derived from yam roots, is more bioavailable and has fewer reported adverse effects than synthetic progestins.48

Progesterone (Prometrium®) is administered 200 mg orally for 12 days per month or quarterly; or 100 mg orally at bedtime every day. The common therapeutic side effect of drowsiness may be considered helpful for women with insomnia, a common problem in menopause.49

Even when progestogen is added to HT, it is important to exercise vigilance in monitoring for symptoms of endometrial cancer for all patients who use estrogen. Ninety percent of patients with endometrial cancer have a history of abnormal vaginal bleeding. This usually presents as menometrorrhagia in perimenopausal women, and as menstrual-like bleeding in postmenopausal women.50 Any abnormal vaginal bleeding during menopause should be taken seriously and followed up with an endometrial biopsy, which remains the gold standard of diagnosis for uterine cancer. Ultrasound is unreliable, especially in women who are still of reproductive age, because endometrial thickness varies during the cycle. In menopausal women an endometrial stripe 4 mm or less suggests that the diagnosis is unlikely to be uterine cancer, but this is still not a substitute for biopsy. Menopausal women may present with cervical stenosis, making endometrial biopsy challenging. Cervical dilation may be needed to expand and open the os to obtain a specimen of the endometrium.50

PATIENT COUNSELING AND INFORMED CONSENT

HT should be used at the lowest effective dose for relief of vasomotor symptoms.14 Some women may experience symptoms of such severity that they are willing to accept increased risk in order to obtain relief.51 HT should not be withheld from them.29 It is essential to engage in sufficient patient education and counseling to allow the patient to weigh the benefits against the risks. Patients should be provided with

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medroxyprogesterone acetate (MPA) (Provera®)</td>
<td>5 mg to 10 mg/d for 12 to 14 days per month; or 2.5 mg daily</td>
</tr>
<tr>
<td>Norethindrone acetate (Aygestin®)</td>
<td>5 mg to 15 mg/d for 14 days per month</td>
</tr>
<tr>
<td>Micronized progesterone (Prometrium®)</td>
<td>200 mg/d for 12 days per month</td>
</tr>
</tbody>
</table>

Source: R, Mimi Secor, MS, MSed, APRN, BC.
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up-to-date information and must agree to adhere to regimens that will minimize risks.\textsuperscript{52} The process of counseling and obtaining informed consent should be conducted in clear, accessible language individualized for each patient, free of statistical jargon and designed to educate, not merely to provide medical/legal protection for the clinician.\textsuperscript{53} Additionally, patients must be provided with appropriate understanding of the instructions for use of the medication, efficacy, time of onset of symptom relief, and possible adverse effects and risks. Initial follow-up is recommended within three months, then every six months or as appropriate for each patient.

CONCLUSION

HT is a valuable asset for treating vasomotor symptoms in menopause, but unfortunately has been found to be associated with risks of stroke and endometrial cancer. New hormonal formulations increase the array of options for administering estrogen safely. Transdermal formulations may reduce risks associated with estrogen therapy by bypassing first-pass liver metabolism, thereby enabling lower dosages of estrogen to be prescribed. The addition of progesterone to unopposed estrogen helps protect the endometrium. Further research may help refine hormonal therapy regimens and provide new options to maximize efficacy and minimize adverse effects.

REFERENCES

33. Scott RT Jr, Ross B, Anderson C, Archer DF. Pharmacokinetics of percutaneous estradiol: a crossover study using a gel and a transder-
Menopause

1. Patient characteristics that may have skewed results of the Women's Health Initiative (WHI) studies include:
   a. overweight, nonsmoker, under age 45
   b. overweight, smoker, ages 45 to 50
   c. underweight, nonsmoker, ages 55 to 60
   d. overweight, smoker, over age 60

2. A recent analysis of the WHI results showed that coronary heart disease risk:
   a. was not affected by timing of hormone therapy (HT) initiation
   b. was reduced when HT was initiated within four years of last menstrual period
   c. was reduced when HT was initiated within 10 years of last menstrual period
   d. was increased when HT was initiated within four years of last menstrual period

3. Estrogen's effects of increasing matrix metalloproteinases (MMPs) may pose more of a risk for older women receiving HT because:
   a. greater buildup of arterial plaque is more likely to become unstable in the presence of MMPs
   b. the increase in MMPs causes stiffer arteries in older women
   c. older women have a natural increase in MMPs unrelated to estrogen
   d. none of the above

4. Vasomotor complaints are most prevalent:
   a. 10 years before the final menstrual period
   b. 10 years after the final menstrual period
   c. immediately before and during the 12 months after the final menstrual period
   d. 15 years after the final menstrual period

5. Compared with oral formulations, transdermal estrogen:
   a. allows for more stable blood levels of estrogen
   b. avoids first-pass hepatic metabolism
   c. decreases the risk of venous thromboembolism
   d. all of the above

6. Estrogen gel is applied to the:
   a. arms
   b. legs
   c. breast
   d. torso

7. Transdermal estrogen formulations begin to relieve symptoms:
   a. immediately
   b. within 1–2 weeks
   c. within 2–3 weeks
   d. within 4–6 weeks

8. Risk of endometrial hyperplasia and adenocarcinoma is increased by use of:
   a. unopposed estrogen
   b. unopposed progesterone
   c. unopposed testosterone
   d. none of the above

9. Compared with synthetic progesterone, oral micronized progesterone:
   a. is less bioavailable and has fewer adverse effects
   b. is less bioavailable and has more adverse effects
   c. is more bioavailable and has fewer adverse effects
   d. is more bioavailable and has more adverse effects

10. How soon after start of HT should initial follow-up occur?
    a. three months
    b. six months
    c. nine months
    d. one year
New Options for Treating the Symptoms of Menopause

Directions: Select one answer for each question in the exam and evaluation by completely darkening the appropriate circle. An identifier is required to process your exam.

Educational grant is provided by Ascend Therapeutics, which covers the cost of grading this exam.

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Evaluation

<table>
<thead>
<tr>
<th>1 = Very well</th>
<th>2 = Well</th>
<th>3 = Fair</th>
<th>4 = Poorly</th>
<th>5 = Very poorly</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Review findings of the Women's Health Initiative (WHI) and its effects on hormone therapy (HT) strategies.</td>
<td></td>
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</tr>
<tr>
<td>2. Discuss the rationale for HT, including risks and benefits, in light of more recent WHI analyses.</td>
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<tr>
<td>3. Evaluate appropriate candidates for HT, considering factors such as symptom severity, medical risk factors, patient preferences, and duration of therapy.</td>
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<tr>
<td>4. Compare efficacy and safety of HT preparations, including discussion of hormone content and transdermal versus oral delivery systems.</td>
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Rate the effectiveness of how well the activity:

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16. Related to your practice needs.
17. Will help you improve patient care.
18. How well did the faculty convey the subject matter?
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