

More data on hormone therapy risks arrive to reshape practice

📌 It might be time to switch progestins in combination HT for menopausal symptoms

Which progestin do you most often prescribe as part of combination hormone therapy for a postmenopausal woman who has hot flashes and an intact uterus?

1. oral medroxyprogesterone acetate
2. oral micronized progesterone
3. oral norethindrone acetate
4. vaginal progesterone
5. levonorgestrel-releasing intrauterine system

Please read on, now that you've responded to this survey. I'll return to the answers later.

One reason I find the practice of medicine exciting is that new scientific data make for a direct change in the way I care for my patients. You likely feel the same way. As an example, hormone therapy (HT) generates that kind of excitement because it continues to be reshaped by research findings in menopause medicine.

Over the past 12 months, one of

What route of estrogen delivery do you prescribe for combination HT?

Instant Poll

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the most important research findings to emerge from the literature is that HT is safe during the decade after menopause because it is not associated with increased risk of adverse cardiac events, such as myocardial infarction. There was a second practice-altering discovery: Regimens of combined HT that use progesterone may be associated with a lower risk of breast cancer than other progestin-containing regimens are.

HT for menopausal symptoms is safe in the decade after menopause

Evidence strongly indicates that estrogen therapy is highly effective for treating vasomotor symptoms and vaginal dryness. But initial reports from the Women's Health Initiative (WHI) trial raised concern that both estrogen-only therapy and estrogen-progestin therapy were associated with an increased risk of cardiovascular events, such as myocardial infarction.

More recent analyses of WHI findings, however, reveal that the risk of HT-induced coronary artery disease (CAD) is lessened if therapy is started within the first decade after the menopause.¹

- For women who begin HT less than 10 years from menopause, the hazard ratio (HR) for CAD is 0.76 (95% confidence interval [CI], 0.5–1.16)

- For those who begin therapy 10 to

19 years from menopause, HR is 1.10

- For women who begin therapy 20 or more years from menopause, HR is 1.28 (*P* for trend = .02).

HT increased the risk of stroke (HR 1.32; 95% CI, 1.12–1.56), regardless of the time from onset of menopause or the subject's age.

In a substudy of the WHI, women 50 to 59 years old who received conjugated equine estrogen alone were demonstrated to have less coronary-artery calcium deposition (as determined by computed tomography) than women who had been treated with placebo.²

These studies suggest that estrogen may have a direct beneficial effect on cardiac vascular function in women who are recently menopausal. A major indication for HT is the treatment of vasomotor symptoms, which, typically, become clinically significant before, or at the same time as, menopause. Because the safety profile of HT is better if it is started more closely to the onset of menopause, these findings should offer reassurance to clinicians and patients alike.

Should we change the progestin we use?

A startling paradox of the WHI findings is that combined estrogen-progestin therapy was associated with an increased risk of both CAD and breast cancer, but that estrogen-

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TABLE The relative risk of invasive breast Ca among HT users varies by type of progestin

Progestin	Route of administration of estrogen	Person-years of data	Relative risk* of invasive breast Ca	95% confidence interval
Progesterone	Transdermal	35,513	1.08	0.89–1.31
Medroxyprogesterone acetate	Oral	7,035	1.48	1.02–2.16
Norethindrone acetate	Oral	7,401	2.11	1.56–2.86
Dydrogesterone	Transdermal	25,405	1.18	0.95–1.48
Nomegestrol acetate	Transdermal	18,826	1.60	1.28–2.01
Promegestone	Transdermal	14,910	1.52	1.19–1.96

*Compared with risk in women who never used HT.
Adapted from Fournier A et al., 2008.⁴

only therapy was not associated with these two adverse outcomes.

These results implicate progestins in the pathogenesis of breast cancer and heart disease in postmenopausal women who take estrogen.

We do not yet have high-quality data to inform clinicians fully about how to evolve their practice to provide the endometrial protection necessary for menopausal women taking estrogen while minimizing risks to the heart and breast. Two recent studies report that the type of progestin used in combination HT influences the risk of breast cancer. The studies report that progesterone is associated with a lower risk of breast cancer than progestins such as norethindrone acetate.

From Germany: Lower risk with estrogen-only HT. Consider the results of a case-control study conducted in Germany, in which 3,464 women who had breast cancer and 6,657 who did not were interviewed about their exposures and about HT.³ Just as WHI findings revealed, estrogen-only HT was associated with a lower risk of breast cancer than were estrogen-progestin regimens. In women who

took a continuous combination regimen, progesterone and medroxyprogesterone acetate treatments were associated with a lower rate of breast cancer than were norethindrone acetate or norgestrel regimens. Progesterone and medroxyprogesterone effects were not studied head-to-head by these investigators, however.

From France: Type of progestin is implicated. In a large cohort study from France, 80,337 women were followed for 12 years; 2,354 cases of breast cancer were detected.⁴ Upon entry into the study, average age of participants was 53 years. Successful follow-up occurred for 87% of the subjects.

The study revealed:

- Estrogen-only HT was associated with a slightly increased risk of breast cancer, compared with what was seen in women who had never used hormones (relative risk, 1.28; 95% CI, 0.98–1.69)

- The type of progestin used in combination HT influenced the observed risk of breast cancer (TABLE); for example, progesterone therapy was associated with a lower risk of breast cancer than was norethin-

drone acetate therapy or medroxyprogesterone therapy.

Note that, in France, most women who use progesterone therapy receive transdermal, not oral, estrogen. In contrast, most women in France who take norethindrone acetate or medroxyprogesterone acetate use oral estrogen. It is possible that some of the differences observed are an effect of the dosage or route of estrogen, or both.

Search for answers, and inspiration for a new vehicle to deliver hormone

It's not likely that any investigator will conduct a randomized study large enough to detect a difference between the effects of progesterone and those of medroxyprogesterone acetate or norethindrone acetate on breast cancer or cardiovascular risk in symptomatic postmenopausal women. Without such high-quality

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data from clinical trials, we'll need to use epidemiologic evidence and data from small trials, with intermediate markers, to guide treatment choices. Preliminary data suggest that progesterone may be associated with a lower risk of breast cancer than 19-nor progestins appear to be.

When used in a combination HT regimen, oral progesterone can be prescribed as either:

- 100 mg nightly in a continuous regimen
- 200 mg nightly for 12 or more nights each month in a cyclic regimen.

Clinicians have proposed developing an intrauterine progestin-releasing device to fit in the small postmenopausal uterus, to reduce the risk of endometrial hyperplasia and minimize the systemic effect of progestin.

Instant Poll



HOW DO YOU DELIVER ESTROGEN?

The route of administration of estrogen that I choose most often when I prescribe combination HT for a postmenopausal woman who has hot flashes and an intact uterus is:

- oral
- transdermal patch
- transdermal spray or gel
- vaginal
- injectable

Choose your customary route in the **Instant Poll** at www.obgmanagement.com

Compare what you do with your colleagues' practices when **Instant Poll Results** are published in an upcoming issue

In the United States, available intrauterine progestin-releasing systems are large, relative to the endometrial area of the average postmenopausal uterus; a frameless⁵ or small progestin-releasing device designed to fit in the average postmenopausal uterus⁶ will, once it is developed and approved, make this approach more practical.

Is your answer in line with current thinking?

The preliminary new evidence reviewed here suggests that, for a postmenopausal woman beginning combination HT, progesterone be given consideration as the progestin component. Only the oral route of progesterone (answer #2) is FDA-approved for endometrial protection in menopausal women receiving estrogen. To repeat my beginning question: What do you prescribe?

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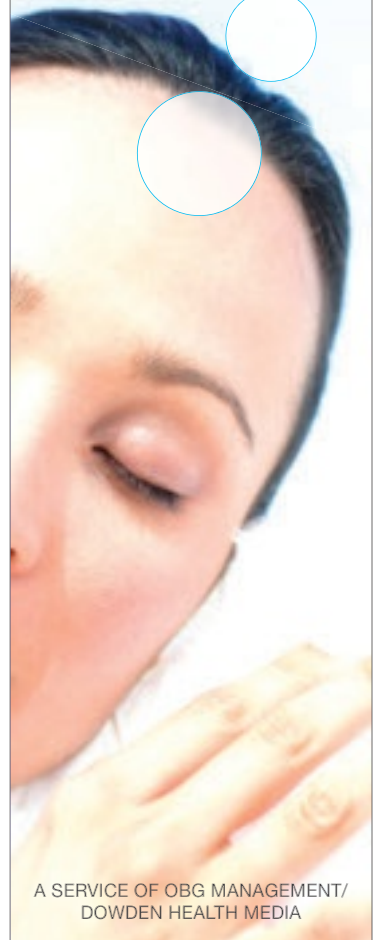
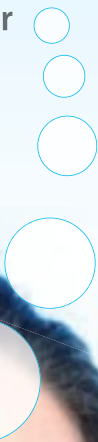
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