EDITORIALS

Hormone Replacement Therapy and Endometrial Cancer: Are Current Regimens Safe?

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There is extensive epidemiologic evidence that postmenopausal estrogen therapy substantially increases the risk for endometrial cancer. Since 1970, more than 30 epidemiologic studies have documented the strong association between unopposed estrogen use and increased endometrial cancer risk. Risk is increased with increasing dose of estrogen and particularly with increasing duration of use, such that women with more than 10 years of unopposed use have about a 10-fold increased risk of endometrial cancer (*1*). Adding a progestin to the estrogen regimen can lower the increased risk of endometrial cancer associated with estrogen therapy, but it might also remove some of the other benefits of estrogen, such as the favorable effect on lipoproteins, coronary atherosclerosis, or vascular tone. For these reasons, questions regarding optimal dose, duration, and type of progestin are crucial. In this issue of the Journal, Pike et al. (*2*) present data from a large case–control study on the endometrial safety of currently used estrogen–progestin regimens.

Currently, two hormone replacement regimens—a cyclic and a continuous regimen—are in widespread clinical use. In the cyclic regimen, a woman is given estrogen (in the United States, usually at a dose of 0.625 mg of conjugated estrogens) daily or with a 5- to 7-day estrogen-free period at the end of the month and a progestin (in the United States, usually medroxyprogesterone acetate (MPA) at a dose of 5-10 mg) for 10-14 days of the month. The lower (5 mg) dose of medroxyprogesterone acetate is often preferred because many women experience mild dysphoria when taking higher doses and potential adverse effects on the lipoprotein profile or the cardiovascular system are likely to be minimized. In the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial, 10 mg of MPA given daily for 10 days per month (with conjugated estrogens at 0.625 mg daily) has been shown to prevent development of endometrial hyperplasia during 3 years of treatment (*3*). The case–control study by Pike et al. found a nearly twofold increased risk for endometrial cancer associated with cyclic regimens used for fewer than 10 days per month but no increased risk among women who took cyclic therapy for 10 or more days per month. In contrast, the only other large case–control study of cyclic hormone therapy found a small increase in endometrial cancer risk, even among women who took 10 mg of MPA daily for 10 or more days per month (relative risk for 5 or more years of use = 2.7; 95% confidence interval = 1.0-6.8) (*4*). In the only large trial that investigated the lower dose of cyclic MPA (5 mg daily), women were treated for 14 days per month, and no increase in endometrial hyperplasia was noted after 1 year of therapy (*5*). Because the low-dose cyclic regimen has been in widespread use for only 5 years or so, neither of the two case–control studies (*2,4*) provides data on the low-dose cyclic regimen. Both case–control studies showed that, relative to the risk in nonusers, endometrial cancer risk decreases with increasing number of days per month of progestin use.

The second hormone replacement regimen in common use is called continuous and is composed of daily estrogen (conjugated estrogens at 0.625 mg) and progestin (MPA at 2.5 or 5.0 mg). Again, the lower dose of progestin is preferred to minimize side effects. Large trials have shown no increased risk for endometrial hyperplasia among women using either 2.5 mg or 5.0 mg MPA in a continuous regimen (*3,5*). Pike et al. (*2*) also found no increased risk for endometrial cancer among women using this therapy.

In summary, both the cyclic and continuous hormone replacement regimens are associated with a much lower risk of endometrial cancer than estrogen used alone. Because the only two studies of cyclic hormone regimens and endometrial cancer risk produced conflicting results, the optimum duration of progestin use in cyclic regimens requires further study. The low-dose cyclic MPA regimen should be used for 14 rather than 10 days per month, and compliance with this complex regimen is crucial. If a woman routinely forgets to take half of her MPA tablets, her endometrium will not be adequately protected.

In an effort to minimize duration of exposure to progestins as well as the monthly withdrawal bleeding associated with cyclic therapy, investigators have evaluated quarterly regimens. In one uncontrolled trial (*6*), 214 women who had been taking monthly cyclic hormone replacement therapy were switched to therapy with conjugated estrogens at 0.625 mg daily and MPA at 10 mg added daily for 14 days only every 3rd month. The rate of endometrial hyperplasia after a year of therapy was 1.5% (95% confidence interval = 0%-3.2%), very similar to that expected in untreated women. In contrast, the Scandanavian LongCycle Study (*7*), in which 240 postmenopausal women were randomly

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assigned to monthly or quarterly cyclic hormone therapy (2 mg of estradiol on days 1-78 and 1 mg of estradiol on days 79-84, with 1 mg of norethindrone on days 69-78) was stopped after 2-3 years of the planned 5 years of treatment because of an unacceptably high rate of endometrial pathology (including one endometrial cancer) in the quarterly compared with the monthly cycle group (6.2% versus 0.8%; $P = .004$). Although this study used different hormones than those in the U.S. trial, it raises questions about the safety of quarterly cyclic therapy.

Current hormone replacement regimens might be safe, but are they optimal? For short-term treatment of menopausal symptoms, MPA appears safe and effective. However, growing evidence suggests that micronized progesterone might be a better progestin for long-term use. Neither MPA nor progesterone added to estrogen alters the beneficial effect of estrogen in preventing loss of bone density (*8*), but evidence suggests that MPA negates more of the beneficial effects of estrogen on the cardiovascular system than micronized progesterone. MPA reduces the high-density lipoprotein-increasing effect of unopposed estrogen more than micronized progesterone does (*9*) and may reduce the beneficial effect on atherosclerosis (*10*) and on coronary vascular tone (*11*,*12*). The PEPI Trial found no increased risk of endometrial hyperplasia in women who were randomly assigned to cyclic therapy with daily conjugated estrogens plus micronized progesterone given at a dose of 200 mg daily for 10 days per month, but no studies of the effect of micronized progesterone on endometrial cancer risk have been published.

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Malignant Origin of the Stromal Component of Wilms' Tumor

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In this issue of the Journal, Zhuang et al. (*1*) provide molecular evidence for an important proof of principle, mainly that the various histologic components of a tumor arise from a common clone. This principle has long been accepted in the leukemic stem cell disorder chronic myeloid leukemia, where the Philadelphia chromosome can be found in morphologically normal hematopoietic elements (*2*). However, in solid tumors, this issue has been much more controversial. Authors talk about the "benign" stromal component of a tumor, yet this component may often make up the vast bulk of the tumor. Is such an aberrantly proliferating stroma really benign?

By studying allelic loss in microdissected components, Zhuang et al. (*1*) show that, for the embryonal tumor nephroblastoma or Wilms' tumor, the stroma is clearly part of the malignant process. Wilms' tumor is renowned for its multipotent differentiation capabilities, sometimes bordering on teratomatous appearances. The classic triphasic Wilms' tumor contains blastemal, epithelial, and stromal elements, all of which are believed to be differentiation products of the primitive renal stem cell; any one of these three components may dominate. The blastemal and epithelial elements usually mimic structures seen during normal nephrogenesis, whereas the stromal component can undergo heterologous differentiation along the lines of smooth or striated muscle, cartilage, bone, or adipose tissues. These diverse histologies raise the question of whether the various types of Wilms' tumor arise from multipotent renal stem cells at various stages of commitment and how these relate to the

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