Clinical Guidelines and Primary Care

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Guidelines For Postmenopausal Preventive Hormone Therapy: A Policy Review

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The clinical question of whether to recommend hormone therapy to asymptomatic women at or after the time of menopause has been a difficult and puzzling one for physicians and for their patients for decades. The complexity of the question is a function of the number of organ systems and disease processes affected by the female sex hormones, as well as the large and sometimes confusing body of literature on the subject. Cardiovascular disease, breast and endometrial cancer, osteoporosis, and sexual function are all affected by these hormones, and the changes accompanying menopause reflect the sometimes beneficial and sometimes detrimental effects of reduced estrogen and progesterone levels. Quality of life issues are associated with hormone administration as well, including the prospect of unpredictable vaginal bleeding and the need to take medication daily for many years.

Family physicians have long been involved in extensive discussions with their patients about preventive hormone therapy. With nearly 40 million women in the United States living one-third of their lives after menopause, clarification and guidance concerning preventive hormone therapy will likely be welcomed by women and their physicians alike.

In December 1992 the American College of Physicians (ACP) published clinical guidelines for counseling postmenopausal women about preventive estrogen and progestin therapy.[1] This policy document presents summary estimates of the benefits and risks of hormone therapy and issues recommendations for counseling women about the decision whether to undertake this therapy. Recommendations are made also regarding hormone regimens, as well as endometrial cancer surveillance. The purpose of this policy review is to assess critically and put into perspective the methods used and the recommendations made in the ACP clinical guideline and its accompanying background paper.[2]

The ACP guidelines deal with preventive hormone therapy — therapy administered to asymptomatic women — rather than with hormones prescribed to relieve symptoms of menopause. The distinction is important, because the considerations of the risks and benefits of prophylaxis are different from those of treating symptoms. Symptomatic women have a defined anticipated benefit (relief from symptoms), whereas asymptomatic women cannot be assured of individual benefit. It behooves us as a profession to assure that the preventive interventions we recommend to healthy people will do more good than harm. The history of medicine is replete with examples of iatrogenic epidemics.[3] Thoughtful and critical evaluation of published clinical guidelines for preventive health care is thus an important part of a family physician's task.

The Policy Development Process and Methods

The ACP Clinical Efficacy Assessment Program (CEAP) subcommittee, which recommends clinical topics for policy development, considered preventive hormone therapy to be a topic of high priority. A team, led by Dr. Deborah Grady, was assembled in San Francisco and included clinical researchers with interests in cardiovascular disease, osteoporosis, and cancer epidemiology, as well as experts in statistical analysis, computer programming, and life-expectancy analysis (telephone conversation, Linda Johnson White, Director of Scientific Policy, American College of

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Physicians, 23 October 1992). The team determined that a modified life-table approach would best suit the topic, because hormone therapy affects multiple systems and diseases. Alternative measures, such as quality-of-life values and years of life lost, were considered, but the team believed that for patients these measures could obfuscate the issues central to decision making. At the heart of this decision is whether hormone therapy changes the lifetime probabilities of developing or dying from certain diseases and how to balance these probabilities (telephone conversation, Dr. Deborah Grady, 4 September 1992).

The team reviewed the published English-language literature since 1970 concerning preventive estrogen therapy with and without the addition of a progestin and its relation to endometrial cancer, carcinoma of the breast, coronary heart disease, stroke, and osteoporotic hip fracture. Meta-analysis was used to pool estimates from studies to determine summary estimates of relative risks (Appendix 1) of each disease with preventive hormone therapy versus without hormones. The resulting pooled or summary estimates of relative risk are displayed in tabular form in the background paper,[2] and these estimates were used in life-table calculations to estimate the lifetime probabilities of developing and dying from the diseases in question.

The authors calculated the lifetime probabilities of developing disease and the resultant life expectancy with and without long-term hormonal therapy for the following groups of 50-year-old white women: women with no risk factors, women who have had hysterectomy, women with coronary heart disease, women at high risk for coronary heart disease (such as smokers), women at high risk for breast cancer (such as those with a mother or sister with breast cancer), and women at high risk for hip fracture (such as those with low bone density). These analyses were repeated for similar subgroups of black women. Calculations were not made for women of other racial or ethnic backgrounds because of limited available data.

The guidelines (Appendix 2) summarize the potential benefits and risks of preventive hormone therapy and recommend an individualized approach that involves the woman herself in the decision-making process. In addition, recommendations are made about hormone regimens, as well as regarding indications for and techniques of diagnostic endometrial evaluation. These recommendations are based on expert opinion; their background is less clearly documented than the estimates of risks and benefits.

After a 1½-year effort that included discussions with the CEAP subcommittee, the guidelines and their accompanying background paper were sent to 25 reviewers, including members of the American Academy of Family Physicians and the American College of Obstetricians and Gynecologists, 2 members of the CEAP panel, and experts in cardiovascular epidemiology, cancer epidemiology, and statistics. After revision, it was forwarded to the full CEAP subcommittee, who then recommended its approval to the ACP Health and Public Policy Committee and the Board of Regents. This review strategy invites the comments of many potential users of the policy and then subjects the policy to full peer review (telephone conversations with Linda Johnson White, ACP, 23 October 1992, and Dr. Deborah Grady, 4 September 1992).

Discussion

Presentation

The policy is presented as a set of guidelines (Appendix 2), accompanied by a scientific paper in traditional format that describes the methods and findings of the policy team.[2] The guidelines take the form of summary statements (labeled General Recommendations) in which certain groups of patients are addressed. This is followed by a section entitled Management Strategy that summarizes the estimation of benefits and risks of hormone therapy and presents a set of recommendations for dosage regimens and follow-up.

The introduction to the background paper defines the clinical problem and delineates the methods used to select the relevant literature. Tables of the epidemiologic studies used in the meta-analyses and a summary table of the "best" estimates of relative risk of the considered conditions are presented. The background paper also contains tables of the projected lifetime probabilities of the various conditions, as well as projected net changes in life expectancy for women in various risk situations who receive long-term hormone therapy. The methods used to pool estimates from studies to estimate relative risk will be unfamiliar to most physicians, as will the life-table methods.

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Even with the summary estimates, the recommendations of the policy are complex and potentially confusing. For example, the life expectancy of a woman at high risk for breast cancer is calculated to increase slightly with combination estrogen-progestin therapy under optimistic assumptions about the effect of added progestin but to decrease slightly under pessimistic assumptions. For many patients, the concept of relative risk and the meaning of changes in life expectancy that seem small for an individual, for example, could represent large differences from an epidemiologic point of view. Moreover, the method for combining the risk status in several categories is not clear, and the weight to be given to quality-of-life issues is not specified. Unfortunately, the organization of the guidelines paper is difficult to discern. Some subheadings were omitted, and the placement of the table and the exhibits make it somewhat difficult to follow the text. The organization and presentation of the background paper, however, is clear.

The terminology used in this policy is carefully chosen. The authors avoid the use of the word "replacement" and instead use the expression "preventive hormone therapy." Estrogen administration with or without progestins after menopause is an intervention that differs from the natural course of things; estrogen is not replaced as it would be for a castrated premenopausal woman. The word "replacement" does appear, however, in Tables A through H and in some sections of the background paper; the expression has appeared in the literature so commonly that its use is often routine.

Validity Issues: Limitations of the Data

It is essential for physicians to recognize the limitations of the data that were used in the calculations for this policy. As the authors point out, their estimates are based entirely on observational epidemiologic studies. Randomized controlled trials, which are essential to test cause-and-effect relations with regard to both benefits and risks, are not yet accomplished.

Unfortunately, epidemiologic case-control and cohort studies are subject to important potential biases that could affect their results. For example, estrogen users could, as a group, be more health conscious than women who do not take estrogen. If estrogen users have healthier lifestyles, they might be at lower risk of heart disease independent of their estrogen use. On the other hand, women receiving estrogen might undergo more intensive surveillance, including breast examinations and mammography, and thus have more of their asymptomatic breast cancers detected. Such a "detection bias" could make it appear that estrogen use is responsible for an increase in the risk of breast cancer.[4] Clearly even the most complex and sophisticated calculations and meta-analyses cannot correct for these potential biases. Randomized controlled trials are necessary to measure directly the risks and benefits of hormone administration. Additionally, there could be unanticipated effects of hormones that only a controlled trial would reveal.

Some technical issues arise about the calculations of benefits and risks. First, the authors apparently included in their meta-analyses some subjects who were surgically menopausal.[2p1031] The validity of including these women is questionable, because they might not be comparable to women undergoing natural menopause. Second, population-based estimates of disease incidence and mortality were used to calculate the lifetime probabilities of developing the various diseases and the resultant life expectancy. Such populations include both high-risk and low-risk women, and applying these estimates to groups of low-risk women could overestimate both the benefits and the risks of hormone therapy.

Explicitness

The meta-analytic method used to estimate the relative risks is not described in the paper, but it is referenced.[5] The use of MEDLINE and manual literature searches is noted, but literature search strategies are not described. The relation between the evidence and the recommendations is quite clear. The problems with the available evidence and gaps in evidence are clearly noted in the background paper. The authors state specifically that they do not include quality-of-life assessment in the analysis, leaving the clinician to include a discussion of the effects of menopause and of hormone therapy on quality of life with each patient.

Flexibility

The ACP guidelines do not state specifically that a certain treatment is preferred but instead presents the relative risk estimates for the treatment

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options, indicating that physicians and patients should decide based on these estimates. This approach differs from the method described by Eddy,[6] which incorporates cost information and patients' preferences into a policy and then rates the relative strength of a policy as a standard, guideline, or option. This nomenclature has been adopted by the American Academy of Family Physicians' Task Force on Clinical Policies for Patient Care. The policy under review here cannot be classified using this scheme, but to do so is functionally an option, because the policy paper alludes that there is not consensus from patients about the preferences for certain outcomes (side effects and changes in relative risks of disease) and that the probabilities of the various outcomes are not yet known.

The policy allows clinical flexibility and does not at all approach a "cookbook" format to which many clinicians object. The many clinical scenarios that are possible with regard to this issue are considered, and those situations are described for which data are not sufficient to allow analysis of risk. Some readers will be disappointed that no clear universal recommendation is made about whether preventive hormone therapy should be prescribed. On the other hand, the policy allows — and even requires — individualization of the decision regarding prophylactic hormone therapy. Because women differ in their background risks of disease and in their values about potential side effects and benefits, each will have a unique situation to consider.

Comprehensiveness

The policy reviews virtually all of the relevant data and appropriately omits consideration of studies of premenopausal women, studies lacking relevant outcome measures, and opinion literature. No information is included on the dollar costs of preventive therapy, of treating complications of therapy, or of treating the various medical outcomes with and without therapy. There is no estimate of the relation between medication prescribed and the likelihood that medication is taken by patients in actual practice.[7] Patient preference is not quantified, but its importance is acknowledged in the design of the recommendations. Quality-of-life issues, which can be as important to women as quantity of life, are not addressed formally to the degree that mortality risks are. For example, some women consider the prospect of the return of vaginal bleeding to be intolerable, while others do not. Finally, the guidelines consider only the situation of a 50-year-old woman; the risk and benefits for women years after the menopause are not calculated.

The authors did not address the contraindications to estrogen administration, some of which can be confusing to physicians. In the past, stroke and myocardial infarction were considered contraindications to estrogen administration.[8] The American College of Obstetricians and Gynecologists lists as a contraindication "recent vascular thrombosis,"[9] which could be interpreted to include arterial as well as venous events. Hypertension and hyperlipidemia are also often considered relative contraindications to hormone therapy. Estrogen therapy appears, however, to improve the lipid profile and reduce the risk of myocardial infarction — and not to increase the blood pressure or risk of stroke. Thus there could be reasons to consider giving hormones, rather than avoiding them, in women with stroke, myocardial infarction, hypertension, or hyper lipidemia. Unlike oral contraceptives, postmenopausal hormone therapy is not uniformly contraindicated in all women with a history of venous thromboembolism. Clarification of which patients could take postmenopausal doses of estrogen safely would be helpful to physicians. Other contraindications to estrogen administration are not controversial: known or suspected pregnancy, breast or endometrial cancer or other estrogen-dependent malignancy, undiagnosed abnormal genital bleeding, and active thromboembolic disorders.[10]

Hormone Regimens and Endometrial Monitoring

The ACP guidelines also include recommendations on hormone regimens and endometrial monitoring, some of which deserve comment. The authors recommend that estrogen administration be continuous, without 5 to 6 days per month off estrogen. Continuous estrogen administration has the advantages of being less confusing for patients and of avoiding hot flashes during the last few days of the month. There is little evidence, however, to support a recommendation that women currently taking the commonly prescribed regimen of estrogen on days 1 to 25 of the month with progestin on days 13 or 16 to 25 need change their regimen.

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The policy recommends the oral route of administration of estrogen. Estrogen absorbed through the gastrointestinal tract is delivered directly to the liver through the portal circulation, potentially maximizing the hepatic effects, including those on lipid metabolism. Nonoral routes of estrogen delivery might not provide the same degree of beneficial effect on the lipid profile as does oral hormone.[11]

The recommended dose of cyclic progestin therapy is 5 to 10 mg of medroxyprogesterone acetate or equivalent, and the recommended duration is 10 to 14 days per month. The "best" dose of progestin to prescribe is not yet clearly supported by evidence. Theoretically one should minimize the progestin dose to protect the lipid profile but also prescribe enough progestin to adequately prevent endometrial hyperplasia and cancer. There is some evidence that superior protection from endometrial hyperplasia is achieved with the higher dose (i.e., 10 mg/d),[8,12] as well as with the longer duration of progestin administration (i.e., 12 or more days per month).[13] There is still little information whether the higher dose and longer duration of progestins affect the risk of ischemic heart disease. Thus, the optimal dose and duration of progestin therapy is not clear.

There is less experience with the continuous estrogen-progestin regimen than there is with the cyclic-progestin regimen, although the former appears to protect women well from endometrial hyperplasia. The continuous-progestin regimen is attractive to many physicians and patients because it minimizes long-term withdrawal bleeding. Unpredictable bleeding is common in the first year, however.[14]

The policy document offers welcome guidance about the indications for endometrial evaluation for women on combined estrogen and progestin and for those on estrogen alone. Because experience is still limited with bleeding patterns on the continuous-progestin regimen, these recommendations could change with additional experience. (It should be noted that the policy document has an internal inconsistency concerning the indications for endometrial evaluation with both the cyclic and the continuous regimen recommendations.[1pp1040-1])

Finally, the guidelines introduce the option of transvaginal ultrasound examination for evaluation of the endometrium. This relatively new procedure appears to be quite useful in distinguishing endometrial hyperplasia and carcinoma.[15,16] Vaginal ultrasonography is less invasive than office endometrial biopsy and thus will be a welcome option to both physicians and patients. Experience with vaginal ultrasonography is still relatively limited, however, and its performance in distinguishing serious endometrial disease in large populations of postmenopausal women should be monitored.

Conclusion

This clinical policy represents a tremendous amount of work and a well-designed strategy for analyzing a potentially confusing topic. The authors have done an admirable job of compiling, organizing, and analyzing the available data on risks and benefits of preventive hormone therapy. The meta-analysis and life-table techniques are sophisticated and appropriate. The summary estimate of relative risk and net change in life expectancy will be extremely useful for physicians in counseling patients. In effect, the guidelines offer a formalized method for risk-benefit assessment — the best our current knowledge has to offer — to clarify and update our discussions with patients.

This policy on hormone therapy in postmenopausal women does not, to the chagrin of some, simplify the situation to the point of making a single recommendation. It does, however, state clearly the relative risk associated with use of these hormones in various clinical situations, allowing women to make an informed decision with guidance from their physicians. The authors also remind us of the dangers of coming to conclusions before sufficient evidence is available. The background paper points out the gaps in the evidence and refrains from stating a relative risk when such an estimate would be inappropriate.

As family physicians, we find that we must continue to do what most of us did before this policy emerged: tell postmenopausal women about the available evidence, explain that there is no absolute right or wrong answer, and work with our patients to find the best treatment for each. The ACP guidelines give us specific risk estimates and a structured approach to use in our discussions with patients. The authors of the policy have served our patients well by evaluating in detail

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the published studies and making specific recommendations only when sufficient evidence is available. They also provide compelling guidance to research planners at the national level as they plan funding of studies of women's critical health issues.

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Appendix 1: Relative Risk

Relative risk estimates the magnitude of an association between use of hormone replacement and the development of one of the studied clinical outcomes and reflects the likelihood of developing the outcome in those women who take hormone replacement therapy versus those who do not.[17] When the risk is equal in these two groups, the relative risk is 1.0. A relative risk greater than 1.0 indicates that the exposed group has a greater risk of developing the outcome than does the unexposed group (e.g., endometrial cancer), but a relative risk less than 1.0 indicates that the exposed group has a lower risk than the unexposed group (e.g., hip fracture). A relative risk of 1.8 reflects a risk that is 1.8 times as great, which is the same as a risk that is 80 percent greater.

Confidence intervals for relative risks are generally interpreted as significant if they do not include 1. For example, a relative risk of 1.3 with a confidence interval of 0.9–1.7 is considered to include the possibility that there is no increase in risk in the exposed group, but a relative risk of 1.3 with a confidence interval of 1.1–1.5 would reflect a high likelihood that the risk is increased for the exposed group. A relative risk of 0.7 with a confidence interval of 0.6–0.8 reflects a high likelihood that risk is decreased for the exposed group, but a relative risk of 0.7 with a confidence interval of 0.3–1.1 includes the possibility that there is no decrease in risk for the exposed group.

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