Why Individualizing Hormone Therapy Is Crucial: Putting the Results of the WHI Trial Into Perspective

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Introduction

Dr. Morris Notelovitz is a consultant in adult women's medicine. He spoke with Ursula Snyder, Site Editor/Program Director, Medscape Women's Health, on the clinical implications of the findings from the estrogen/progestin arm of the Women's Health Initiative. What follows is a transcript of the conversation.

The first thing is to put the whole issue into perspective. The term hormone replacement therapy is a misnomer. Menopausal women are hormone deficient but not hormone depleted. How much endogenous estradiol an individual menopausal woman produces will determine whether or not she needs hormonal therapy for quality-of-life purposes. Her risk factors for osteoporosis, cardiovascular disease, and cognitive dysfunction will determine whether she will need additional therapy (and possibly hormone therapy) for those indications.

It is most important that physicians distinguish between the symptomatic and the asymptomatic menopausal woman. It is also important to appreciate that there is a sound biological rationale for the use of estrogens and androgens for treatment of the menopausal woman. In every single tissue in the body there are estrogen and androgen receptors that respond to estrogen and androgen to protect against conditions and diseases associated with hormone deficiency.

The problem--for reasons that escape me--is that when it comes to treatment of the menopausal woman, all women are regarded as being equal, and most women are being treated generically--that is, with the same dosage and, to a large extent, with the same type of hormone therapy. This is exemplified by the WHI trial. More than 8000 women were randomized to receive *Prempro* (0.625 mg conjugated equine estrogens and 2.5 mg medroxyprogesterone acetate). Whether these women were truly eligible candidates for this particular formulation of hormone therapy is not known. *Prempro* is only one of many formulations of hormone therapy. This must be taken into account when one is confronted with the WHI report of increased risk of adverse events. It also must be emphasized that relative and not absolute risks are being publicized in the media.

For example, what does the reported 29% increase in heart attacks in the hormone therapy group compared with the placebo group mean? It means that per 10,000 person-years, there would be 37 women who used hormone therapy compared with 30 women who used placebo who would have a heart attack -- 7 more women out of 10,000 in a year. In other words, the risk for any individual woman is very, very small. The study reports a 41% increase in strokes in the treatment group -- that sounds scary, doesn't it? -- but this translates into 29 cases of stroke in the hormone group vs 21 in the placebo group per 10,000 person-years. Again, only 8 more women in 10,000. Moreover, what is not measured at

all in the WHI study is the quality of life of women on hormone therapy vs women on placebo, and this is why the majority of menopausal women elect to take hormones.

It's really time that physicians understand that one needs to prescribe hormone therapy to treat menopause-related conditions in exactly the same way as one prescribes thyroid therapy for a woman with hypothyroidism or diabetic medications for a diabetic. The point is we that we need to tailor the therapy to the patient; we need to measure the levels of the therapeutic agents we prescribe so that we can determine whether we are giving too much, too little, or just the right amount; and we need to monitor the patient on a regular basis and adjust treatment as needed.

So, the message I would like to convey is this: Hormone therapy, if indicated, if individualized, and if monitored, is safe.

In determining the type of hormone therapy, one should take into consideration the age of the individual and what her risks are at the time of her examination for some of the adverse conditions that have been associated with hormone therapy, ie, cardiovascular events, stroke, breast cancer. If those risk factors are absent, and if one treats a woman with 17beta estradiol (the natural estrogen that her body was producing prior to menopause) at the lowest effective dosage for whatever the particular indication is for hormone therapy -- for her individually -- not only is the therapy safe, but it should enhance her quality of life. On the basis of numerous observational studies, early hormone therapy will also reduce her risk for cardiovascular disease, osteoporosis, and possibly cognitive functioning.

The problem arises when physicians treat the older woman with established heart disease with estrogen. Again, we must put the clinical issues into perspective: If she is 65 or older (an age at which every woman has some degree of heart disease whether symptomatic or not), and certainly if she has had a myocardial infarction or stroke, she must be evaluated more carefully to determine whether there really *is* an indication for estrogen therapy. If there is, use of low-dose transdermal estrogen is prudent because it has a minimal effect on stimulating coagulation factors, C-reactive protein, and other proinflammatory factors.

As an aside, at the 10th World Congress on Menopause in Berlin in June, a British group presented results of their evaluation of the effect of 17beta-estradiol and norethindrone acetate vs a placebo in women who had just recently had myocardial infarctions. It was a small study, but they did not find any significant increase of repeat heart attacks in the hormone-treated group vs the placebo-treated group; in fact, the risk of heart attack was slightly reduced in the hormone-treated group. The important point is that these investigators used a different estrogen and progestin from that used in the WHI.

In women for whom breast cancer is a risk, the issue is not so much the type of estrogen (although the safest form of estrogen would be low-dose transdermal estrogen because it is less likely to stimulate the synthesis of metabolites that could be potentially oncogenic), but the type of the progestin that is used and whether it is used cyclically or continuously.

It is possible to determine a breast cancer risk profile that allows for the differentiation between low-risk and high-risk individuals. Key factors include the following: a family history of breast cancer, increased

breast density on mammogram prior to initiating hormone therapy, obesity, and mature-onset diabetes. The single most important factor is the pretreatment mammogram. Dense breast tissue identified on pretreatment mammogram is indicative of a lot of estrogen being endogenously synthesized in the woman's breast tissue. Women with very high bone density also synthesize excess estrogen in the breast. So, the relative risk of breast cancer for a woman with dense breasts or high bone density is actually greater than that associated with hormone therapy as reported in the WHI study. The risk is also greater for obese women.

What kind of progestin should one use in a woman with an intact uterus and who is at risk for breast cancer? Natural micronized progesterone -- the progesterone that the breast has seen throughout the premenopausal reproductive life. Again, one would use a low dose together with low-dose transdermal estrogen. With this combination, it is highly unlikely that a woman will suffer any ill effect. There is also a new progesterone-medicated intrauterine device on the market called *Mirena* (levonorgestrel-releasing intrauterine system) that provides progesterone primarily to the endometrium and relatively little to the circulation. This ensures minimal exposure to the breast on the one hand and protection of the endometrium on the other.

Every year that a menopausal or postmenopausal woman visits her physician, she should be asked whether she is on hormone therapy. If so, why? And if not, why not? This is especially important for women who have just entered menopause. Many physicians start women on hormone therapy too late in their lifecycle. This is one of the problems with the WHI study (The ages of women who initiated hormone therapy in this study ranged from 50 to 79 years, with a mean age at initial screening of 63.2 years; 66.6% of the women in the hormone group were between 60 and 79 years.)

Provided there is an indication for hormone therapy, it is crucial to start when the woman is in early menopause and to start with low dosages. Re-evaluate on an annual basis to determine whether the original indication is still relevant and whether there are any adverse side effects. If she takes 17beta estradiol, her treatment can be monitored by measuring 17beta estradiol blood levels to determine whether the appropriate estrogen level for the particular indication has been achieved. Remember, progestin is only used to protect the endometrium.

Although we might have anticipated the results of the WHI study, we need to consider the applicability of randomized clinical trials to clinical practice. We do not practice medicine in a randomized fashion -- or we shouldn't. We do not just assign a woman to hormone therapy arbitrarily. We should decide what form of hormone therapy a woman needs and then prescribe the lowest effective dosage, be it oral or transdermal. (My preference has always been 17beta estradiol because that is what the body produces and blood levels can be reliably measured.) Studies have shown that estrogen in lower doses than the equivalent of 0.625 mg conjugated equine estrogens have positive clinical effect without the adverse effects. We have had the same experience with oral contraceptives -- lower doses are effective and safer.

I'd like to add a scholastic note to this brief interview. I am not a student of history, but I am aware of a very famous physician and scholar, Moses Ben Maimon, who is better known by the name of Maimonides. He was born in Spain in 1135 but moved to the Middle East, where he served as the

physician to the Sultan of Egypt in the 12th century. He stated in one of his doctrines of treatment of patients that one should always consider the particular patient, the particular time in the patient's life, and the patient's particular constitution. Eight hundred years ago this man made the point: Do not treat everybody as if they are the same! Physicians need to consider each woman at the particular point in her life that she is seeking treatment; try to understand her particular constitution, *why* she is seeking treatment, and how she differs from another woman of the same age seeking similar treatment. If we practice medicine intelligently, by understanding normal biology and the pathophysiology of diseases, we will be less likely to make mistakes or have patients experience adverse effects from our prescribed therapy.

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