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## For Hormone Replacement Therapy, One High-Dose Size May Not Fit All

By KATHLEEN MCAULIFFE

NOWADAYS, it seems as if only people with a Ph.D. in epidemiology -- and preferably circus experience -- can juggle all the pros and cons of hormone replacement therapy (H.R.T.), much less make sense of all the conflicting reports.

As if the choices the treatment itself poses weren't complicated enough, now medical researchers are challenging the popular notion that the same-size dose fits all women. That means the million-dollar question facing women of menopausal age -- do I or don't I? -- may soon be eclipsed by an even trickier one: how much is right for me? The answer to the latter question could determine the response to the former, for dose has a direct bearing on the treatment's side effects, long-term safety and likely benefits.

Think back to the birth control pill, circa 1960 -- the one that caused a massive outbreak of swollen breasts, bloating and depression and even triggered life-threatening complications like blood clots. It is now common knowledge that the high doses of hormones were to blame for this epidemic. Today's birth control pill, which contains 5 times less estrogen and 10 times less progestin, is generally considered safe and is tolerated by most women.

Hormone therapy may be evolving along a similar path. Despite its sizable health perks -- relief from menopausal symptoms, stronger bones and possible cardiovascular benefits -- as many as two-thirds of women who start H.R.T. stop the treatment within two years. Side effects are the major reasons that women cite, with many complaining of mood swings, tender breasts, water retention, irregular bleeding or just plain feeling "crummy." Concern that long-term use of hormones might raise the risk of breast cancer has further dampened women's enthusiasm for hormone therapy.

What is clearly needed "is a safer, gentler, more acceptable form of H.R.T.," said Dr. Bruce Ettinger, an endocrinologist and senior investigator at Kaiser Permanente Medical Program in Oakland, Calif. To that end, Dr. Ettinger and researchers nationwide have been studying how women on hormone therapy respond to reductions of 50 percent or more in the standard prescription of estrogen (typically 0.625 milligrams of Premarin). Less progestin is also given because its sole purpose in the treatment is to counter estrogen's tendency to promote cancer in the uterus.

The picture that is emerging from this research is intriguing, suggesting that a woman's need for estrogen shifts as she ages. As the investigators acknowledge, women experiencing a turbulent change of life frequently do require full-strength H.R.T. for symptom relief. But women whose symptoms have subsided or who are not bothered by menopause may be able to gain long-term benefits with fewer side effects by switching to a half-dose regimen. This approach appears to maintain sufficient bone mass to stave off fractures of osteoporosis, an often crippling disease that affects 22 million American women. More tentatively, low-dose regimens may help lower cholesterol and improve other parameters of cardiovascular health.

Still, the research is new, and critical questions remain unanswered. It is not known whether low-dose H.R.T. will offer any protection against heart disease. Indeed, new research has raised questions about the cardiovascular benefits of full-dose H.R.T. At currently prescribed doses, hormone therapy dramatically increases coronary blood flow, which is normally viewed as a positive change. But in some susceptible individuals, it can trigger blood clots, strokes or heart attacks. A reduced dose of estrogen, clinicians theorize, would be less likely to overload the cardiovascular system and trigger the coronary

events that the therapy was to prevent.

Similarly, more conservative doses are expected to carry less risk of breast cancer than full-dose H.R.T., but it could take decades to determine this.

It does appear, though, that low-dose hormone therapy can often provide relief from the symptoms of menopause. In a study conducted by Dr. Ettinger, 138 women who had been using the standard amount of H.R.T. for an average of nine years were switched to a half-strength dose of estrogen and were given progestin less frequently (for 14 days once every six months rather than monthly). Only 7 percent of subjects experienced a surge in hot flashes, leading them to drop out of the trial. The majority reported complete or substantial relief from menopausal symptoms, and 85 percent preferred the lower dose.

Studies exploring the effects of low-dose hormone therapy on bone density are also encouraging. In a three-year trial involving 108 women age 65 and older, researchers at Creighton University in Omaha gave participants half-strength H.R.T. with a daily supplement of calcium and vitamin D. Subjects' spine bone mass increased by an average of 5 percent. "That rivals the results you get at high doses of Premarin," said Dr. Robert Recker, director of Creighton's Osteoporosis Research Center and the lead investigator.

Reported side effects in the women, many of whom were using hormone therapy for the first time in their 70's and 80's, were so mild as to be virtually indistinguishable from a placebo group. That is noteworthy. Clinicians, Dr. Recker said, "were told without adequate data that the minimum dose for protecting bones was .625 milligrams of estrogen, yet at the same time such a high dose was not tolerated in the elderly." The addition of calcium may be the secret to why less estrogen can be so effective. Dr. B. Lawrence Riggs, a professor of medicine at Mayo Clinic in Rochester, Minn., and an expert on hormone replacement therapy, said estrogen boosts bones' absorption of calcium and prevents its leakage through the kidneys.

As doctors revise basic concepts, Dr. Ettinger warns, it is possible that doses will come down even further. Ultra-low dose H.R.T. is currently being tested and makes the half-dose look large by comparison.

WITH investigators at the University of California in San Francisco, Dr. Ettinger is overseeing a trial of these tiny doses (less than one-millionth the standard dose of estrogen) in women over 60. The rationale for the trial stems from a surprising finding from the research team led by Dr. Steven Cummings, assistant dean for clinical research at the University of California, San Francisco. Using new, more sensitive assays to measure estradiol (the key estrogen produced after change of life), the group discovered that postmenopausal women fall into two distinct clusters: roughly 70 percent produce 5 to 20 picograms of estradiol per milliliter of blood serum, but about 30 percent make none at all. And the difference between producing a little versus none is significant.

Osteocytes, which are cells critical for maintaining bone health, die off in women who cease making the hormone. And they are three times more prone to devastating hip and vertebral fractures. Dr. Cummings suspects that the loss of estrogen may cause cells in other parts of their body to atrophy as well, perhaps accelerating cardiovascular decline or degenerative conditions like Alzheimer's disease. On the plus side, women who produce no estradiol have the lowest incidence of breast cancer.

"This finding challenges what a normal menopause means," Dr. Cummings said. "The key question is, do women who produce no estradiol have a bleaker clinical picture overall? And what happens if we give estrogen at levels to raise older women into the normal range for their age?"

This is the goal of the ultra-low dose trial. Estrogen will be administered in such tiny quantities that investigators suspect that no progestin will be needed to prevent hyperplasia -- something they will carefully monitor. At the same time, they will look to see whether the ultra-low dose improves bone mass, mood, memory, cholesterol, vaginal dryness, libido and urinary incontinence.

Until then, what should a woman do? Half-dose H.R.T., say the investigators, is an option that women who are open to taking hormones may want to discuss with their doctors. As for ultra-low doses, stay tuned. Medical experts have as yet a fragmentary understanding of hormone therapy, and the conventional wisdom about it seems to shift as often as the wind. Women must be ready to change course as new findings emerge.

Kathleen McAuliffe writes a column on women's health for More magazine.