Comments on Women, hormones, and clinical trials: a beginning, not an end

To the Editor: We wish to compliment Dr. Virginia Miller and colleagues on their timely Invited Editorial “Women, hormones, and clinical trials: a beginning, not an end” (4). Their clear and succinct summary of the controversies surrounding observational and clinical trial research on estrogen and hormone replacement therapy in postmenopausal women was both insightful and engaging. We also applaud the call for a need to bring together basic and clinical scientists to address issues of such clear importance to women’s health.

We were excited to learn more about the goals of the Kronos Early Estrogen Prevention Study (KEEPS), including the differences between this clinical trial and the Heart and Estrogen Replacement Study (HERS) and the Women’s Health Initiative (WHI) clinical trial. Clearly, time since menopause and the initiation of hormone therapy is a key difference in these studies and is likely important in the prevention of atherosclerotic lesions. Other major differences between the clinical trials were mentioned, but we believe that they are deserving of further discussion. First, we find it of great importance to highlight that in KEEPS, all women in the two experimental groups will be administered progesterone, whereas in the WHI trial, the women receiving combined hormone treatment were administered the synthetic progestin medroxyprogesterone acetate (MPA). Second, we find it important that route of estrogen administration will be investigated in the two experimental groups in KEEPS (oral conjugated equine estrogen vs. weekly transdermal estradiol). The authors commented that the procoagulant effects of oral estrogen may not be present if estrogen is delivered via a transdermal route.

These two key differences bring forth our primary reason for responding to the Invited Editorial. Specifically, we would like to raise the question: How do we translate messages about risks and benefits of hormonal therapy in postmenopausal women to the millions of young women taking exogenous hormones for contraceptive therapy and treatment for gynecological disorders? Despite the very large numbers of young women taking exogenous hormones, there is very little information available regarding potential cardiovascular outcomes with long-term use. The lack of consensus in the literature on exogenous sex hormone use and potential cardiovascular risk stems largely from our lack of research focus in young women.

Complicating this issue is that the numerous forms of progestins vary greatly, not only in type, formulation, and route of administration but also in their bioactivity across different hormone-sensitive tissues in women’s bodies. Furthermore, progestins can be administered cyclically with estrogen (e.g., 12 days per month) or continuously. In others, progestins may be administered without estrogen, such as with Depo-Provera, an MPA-only injectable contraception that suppresses fluctuations in natural estrogen (3). It may be that certain progestins carry increased or decreased risk or that exogenous progesterone is a much safer alternative to synthetic progestins. This could imply that millions of young women are unnecessarily compromising their long-term cardiovascular health. Although we feel the KEEPS clinical trial is pushing researchers to acknowledge the importance of looking at hormone therapy across different stages of women’s lives, the information to be gained may not improve our understanding of the effects of these hormones on the long-term health of young women.

In addition to the timing of hormone use in women’s lives, the route of administration appears to be very important, especially with regard to estrogen. There have been recent media reports that the transdermal combined hormone “patch” used for contraception may be associated with an increased risk of thrombotic complications in young women compared with oral contraceptives (2). This finding challenges the previous concept that transdermal estrogen is safer than oral estrogen. It is likely that the disparity between reports in young women vs. older women may be due to differences in the dose of transdermal estrogen. However, they highlight the lack of studies, particularly randomized clinical trials, investigating the potential risks of exogenous hormone use in young women.

We suspect that prior contraceptive use and degree of atherosclerotic lesion formation at enrollment will be considered in the KEEPS study, but this may not hold much relevance to young women currently taking exogenous hormones, because the specific form, concentration, and route of administration of hormones currently in use likely differ significantly from those taken by women who will enroll in the KEEPS clinical trial. Dr. Barbara Alving, director of the Women’s Health Initiative, recently highlighted in her National Institutes of Health report that oral contraceptive use has not been previously linked to lowering cardiovascular risk in users, but rather the evidence suggests that oral contraceptive use may be linked to increasing the risk for future cardiovascular events in older women and smokers (1).

The HERS, WHI, and KEEPS trials are all important investigations helping us to better understand the complexities of hormone use in women. Although we are excited about new information to be learned from the KEEPS trials, we believe there needs to be a better understanding regarding certain exogenous hormones and risk of cardiovascular disease, bone loss, and cancer in young women as well. This research will likely span basic research and clinical trials because different hormonal combinations will need to be considered alongside multiple patient populations.

REFERENCES


Christopher T. Minson
Paul Kaplan
Jessica R. Meendering
Britta N. Torgenson
Nicole P. Miller
1Department of Human Physiology
2University of Oregon Health Center

University of Oregon
Eugene, Oregon
e-mail: minson@uoregon.edu