Society for Women's Health Research

March 16, 2021

Alex H. Krist, M.D., M.P.H.
Chairperson, U.S. Preventive Services Task Force
5600 Fishers Lane
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Rockville, MD 20857

Re: USPSTF Draft Research Plan, "Menopausal Hormone Therapy in Postmenopausal Women: Primary Prevention of Chronic Conditions"

Dear Dr. Krist:

I am writing to you on behalf of the Society for Women's Health Research (SWHR) to provide comments on the U.S. Preventive Services Task Force (USPSTF) Draft Research Plan, "Menopausal Hormone Therapy in Postmenopausal Women: Primary Prevention of Chronic Conditions."

SWHR is dedicated to promoting research on biological sex differences in disease and improving women's health through science, policy, and education. For over 30 years, SWHR has brought attention to diseases and conditions that disproportionately or differently impact women.

SWHR is pleased to see a new draft research plan to investigate the use of hormone therapy (HT) in the primary prevention of chronic conditions. There are several areas in which we encourage the USPSTF to expand upon the current draft plan to provide a more nuanced exploration of the use of HT. Please see our comments below on each of these areas in detail.

Definition of "Chronic Condition"

The current draft research plan does not include a strict definition of the term "chronic conditions." SWHR urges the USPSTF to include an operational definition of this term. It is well-known that definitions for chronic conditions vary widely, especially across settings, including academia and government agencies.

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Moreover, even seemingly minor variance in definitions may contribute to variance in outcomes.[1]

This terminology has important implications in regard to the impact of HT in perimenopausal and postmenopausal women. The genitourinary syndrome of menopause (GSM), for example, represents a chronic and progressive condition marked by a range of vulvovaginal, sexual, and lower urinary tract symptoms. GSM is well-known to affect quality of life in both peri- and postmenopausal patients.[2] Vasomotor symptoms (VMS) are considered hallmarks of the menopausal transition and affect quality of life for the 80% of individuals who experience these symptoms.[3]

We ask the USPSTF to operationalize the working definition of "chronic conditions" within its study plan. Further, we encourage the USPSTF to consider both GSM and VMS as potential chronic conditions within this definition, given the significant impact both conditions have on overall health and quality of life.

Outcomes

Bone health remains an important outcome for menopausal patients. Primary care providers would benefit from a review of the evidence on the benefits and harms of hormone therapy for the prevention of bone loss and fracture in menopausal patients at average risk. We encourage the USPSTF to include bone health as an outcome of interest within the draft plan.

Intervention

The current draft research plan includes systemic therapy interventions with both estrogen-only formulations as well as combination HT with both estrogen and progestin. Within the "Proposed Key Questions to Be Systematically Reviewed," the USPSTF plans to assess whether menopausal HT outcomes differ by subgroup. Specified subgroups include type, dose, and mode of delivery. SWHR highly suppports outcomes-based analyses that seek to determine whether estrogen-only and combined HT are statistically different with regard to improvement in outcomes. SWHR also supports a careful review of low dose vaginal estrogen therapies for the treatment of GSM, as these products generally do not increase systemic blood levels, so should not be subject to the same warnings as standard dose HT used for the treatment of VMS.

SWHR suggests that the evidence review also include progestin intrauterine devices, used in combination with estrogen, as a formulation of menopausal hormone therapy.

[1] Goodman, R. A., Posner, S. F., Huang, E. S., Parekh, A. K., & Koh, H. K. (2013). Defining and measuring chronic conditions: imperatives for research, policy, program, and practice. *Preventing chronic disease*, *10*, E66. https://doi.org/10.5888/pcd10.120239
[2] Angelou, K., Grigoriadis, T., Diakosavvas, M., Zacharakis, D., & Athanasiou, S. (2020). The Genitourinary Syndrome of Menopause: An Overview of the Recent Data. *Cureus*, *12*(4), e7586. https://doi.org/10.7759/cureus.7586
[3] Avis, N. E., Crawford, S. L., & Green, R. (2018). Vasomotor Symptoms Across the Menopause Transition: Differences Among Women. *Obstetrics and gynecology clinics of North America*, *45*(4), 629–640. https://doi.org/10.1016/j.ogc.2018.07.005

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Population Subgroups

SWHR commends the USPSTF for its inclusion of patients with surgical and premature menopause within the draft research plan. It is crucial to disaggregate outcomes data based on type of menopause. Women experiencing early surgical or natural menopause, for example, are recommended to use HT until the age of natural menopause — those who do not use HT during this time have been shown to be at higher risk of both cardiovascular disease and dementia. Type of menopause also impacts treatment recommendations. For example, given a more favorable balance of benefits and risks for estrogen-alone therapy, longer durations of estrogen-only treatment are often very appropriate for women without a uterus.[4]

Additionally, SWHR wants to reiterate the importance of age as related to disease prevention for women who start treatment before the age of 60 years, and especially for those who begin using HT before the age of 50 years. The majority of women who have a surgical menopause have the procedure by age 50, in which case the use of hormone therapy can be of substantial benefit. Any conclusions regarding outcomes, risks, and benefits should take appropriate care to avoid painting with too broad a stroke as factors such as type of menopause and age at menopause are crucial to take into account, especially given results from the Women's Health Initiative data that suggest significant decreases in deaths due to cardiovascular disease, breast cancer, and Alzheimer's disease in women who initiate HT between 50 and 59 years of age.[5]

SWHR encourages the USPSTF to consider the various ways in which a woman may enter into the menopausal transition as well as the ways treatment recommendations may differ based on these factors. Careful consideration of the complex interactions of these variables will be of the utmost importance in order to provide clear guidance for both patients and their providers.

Risk for Chronic Conditions

Finally, SWHR encourages further consideration into individual risk for chronic conditions. For patients pursuing menopausal HT, risk of breast cancer and/or cardiovascular disease can and should be factored into decision-making, and we support the inclusion of risk for chronic conditions into consideration by subgroups.

One-Year Intervention Duration

The draft research plan indicates duration of intervention will be one year, with interventions that include less than one year of treatment excluded from consideration. Interventions of less than one year may still provide useful data to inform recommendations. It is unclear why one year is the cut-off point for inclusion. SWHR encourages the USPSTF to reconsider the one-year minimum in order to avoid

[4] Shifren, J.L., Crandall, C.J., & Manson, J.E. (2019). Menopausal hormone therapy, *JAMA Insights, 321*(24), 2458-2459.
[5] Sarrel, P. M., Njike, V. Y., Vinante, V., & Katz, D. L. (2013). The mortality toll of estrogen avoidance: an analysis of excess deaths among hysterectomized women aged 50 to 59 years. *American journal of public health*, *103*(9), 1583–1588. https://doi.org/10.2105/AJPH.2013.301295

unecessary limitations to the inclusion criteria. We encourage consulting with an expert in this area to determine whether and how to best consider an evidence-based intervention duration inclusion and/or exclusion criterion.

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The aforementioned items are known to affect patient risk, outcome, and response to therapy, both individually and in interaction. We appreciate the USPSTF's consideration of these areas in greater depth in the formulation of its research plan. Given the complexity of these topics, SWHR strongly recommends that an OB/GYN(s) with specific expertise in menopause and a menopause patient advocate(s) participate in the development and/or in the expert review of the evidence reports.

SWHR appreciates the opportunity to comment on this important work and looks forward to working with the USPSTF throughout the process of updating the "Menopausal Hormone Therapy in Postmenopausal Women: Primary Prevention of Chronic Conditions" recommendations.

If you have any questions, please do not hesitate to reach out to SWHR's Director of Public Policy & Government Affairs, Melissa Laitner, PhD, MPH, at melissa@swhr.org.

Sincerely,

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