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July 22, 2015

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To Whom It May Concern:

The Society for Women's Health Research (SWHR) appreciates the opportunity to comment on the U.S. Preventive Services Task Force's (USPSTF) draft research plan for *Menopausal Hormone Therapy: Primary Prevention of Chronic Conditions*. SWHR, a national non-profit organization based in Washington, D.C., is widely recognized as the thought leader in research on sex differences and is dedicated to improving women's health through advocacy, education, and research. SWHR is submitting comments to support the draft research plan with several recommendations. These recommendations include USPSTF development of consensus definitions and distinctions between the menopausal stages, subgroups, and hormone replacement therapy dosages, types, and delivery methods. In addition, SWHR requests USPSTF include "arthritis" and "systemic lupus erythematosus" as additional chronic conditions for review.

SWHR is greatly concerned with the issue of menopausal hormone therapy because of its significant impact on women. All menstruating women naturally undergo menopause as their ovaries stop producing estrogen and progesterone. Hormone replacement therapy (HT) has been one, among many, options for treating menopausal symptoms including hot flashes/night sweats, vaginal dryness, mood swings, and attention problems. However, conflicting research evidence both supports and refutes claims that HT reduces risks of developing chronic conditions such as coronary heart disease and certain cancers.

SWHR applauds USPSTF for undertaking a new systematic review of its previous recommendation, including subgroup analysis of hormone replacement therapy benefits/risks. The benefits and harms of HT may differ depending on duration of use, type, dose, and mode of delivery, age, and/or menopausal stage. An extensive review of the available literature focusing on the subgroups outlined in the research plan should provide clarity to clinicians and consumers regarding these mixed messages.

To assist in alleviating this issue, SWHR recommends USPSTF develop a working definition for each of the subgroups proposed and share this definition with researchers and clinicians in the evidence reviews and recommendation statements. As it stands, definitions for the timing and duration of "premature," "peri-," and "post-" menopausal stages may vary depending on the research cited. In addition, distinctions between the specific types, doses, and mode of delivery of HT should be developed and examined throughout the research review process.

In 2012, SWHR convened a Roundtable on Menopausal Hormone Therapy to provide clarification on the effects of hormone therapy on five chronic conditions: cardiovascular disease, osteoporosis, cognitive aging and Alzheimer's disease, cancer, and quality of life. At the conclusion of this meeting, participants found HT is more favorable for younger, newly menopausal women as well as specific populations such as early postmenopausal women at increased fracture risk to prevent osteoporosis.¹

New evidence points to a relationship between HT use among women with arthritis or systemic lupus erythematosus (lupus). As a result, SWHR recommends the inclusion of "arthritis" (inclusive of rheumatoid and osteoarthritis) and "systemic lupus erythematosus" as additional chronic conditions studied under this research plan. Growing evidence supports improved symptoms and bone density in arthritic women using HT and establishes a relationship between estrogen levels and osteoarthritic diagnoses.²⁻⁸ However, a better understanding of the role that estrogen plays in arthritis is needed, and a systematic review of the available evidence and research gaps by USPSTF will greatly assist in this effort.

Research focused on the benefits and harms of HT use among lupus patients appears to be conflicting, as several studies suggest an increased risk of lupus flares while taking HT.^{2,9} Meanwhile, other studies suggest no increased risk of flares.⁸ Yet others recommend individual clinical judgement in prescribing HT to lupus patients meeting certain criteria.¹⁰⁻¹² Similar to arthritis in women taking HT, further USPSTF examination into the available literature could greatly assist with clarifying mixed messages to the public.

Given the significant confusion and mixed messages regarding the benefits and harms of HT to specific populations of postmenopausal women, an in-depth systematic review of the topic by USPSTF is warranted. SWHR looks forward to a new recommendation statement eliciting further details for health professionals on any additional benefits HT may provide in the prevention and treatment of chronic conditions.

Sincerely,



Phyllis Greenberger, MSW
President & CEO

¹Davies E, Mangongi NP, Carter CL. Is timing everything? A meeting report of the Society for Women's Health Research roundtable on menopausal hormone therapy. *J Womens Health (Larchmt)*. 2013 Apr;22(4):303-11. 2

²Holroyd CR, Edwards CJ. The effects of hormone replacement therapy on autoimmune disease: rheumatoid arthritis and systemic lupus erythematosus. *Climacteric*. 2009 Oct;12(5):378-86.

³Hussain SM, Cicuttini FM, Bell RJ, et al. Incidence of total knee and hip replacement for osteoarthritis in relation to circulating sex steroid hormone concentrations in women. *Arthritis Rheumatol*. 2014 Aug;66(8):2144-51.

⁴Prieto-Alhambra D, Javaid MK, Judge A, et al. Hormone replacement therapy and mid-term implant survival following knee or hip arthroplasty for osteoarthritis: a population-based cohort study. *Ann Rheum Dis*. 2015 Mar;74(3):557-63.

⁵Martin-Millan M, Castaneda S. Estrogens, osteoarthritis, and inflammation. *Joint Bone Spine*. 2013 Jul;80(4):368-73.

⁶Yang JH, Kim JH, Lim DS, Oh KJ. Effect of combined sex hormone replacement on bone/cartilage turnover in a murine model of osteoarthritis. *Clin Orthop Surg*. 2012 Sep;4(3):234-41.

⁷Roman-Blas JA, Castaneda S, Largo R, Herrero-Beaumont G. Osteoarthritis associated with estrogen deficiency. *Arthritis Res Ther*. 2009;11(5):241.

⁸Bove R. Autoimmune diseases and reproductive aging. *Clin Immunol*. 2013 Nov;149(2):251-64.

⁹Lateef A, Petri M. Hormone replacement and contraceptive therapy in autoimmune diseases. *J Autoimmun*. 2012 May;38(2-3):1170-6.

¹⁰Gompel A, Piette JC. Is there a place for postmenopausal hormone therapy use in women with lupus? *Painman Med*. 2008 Sep;50(3):247-54.

¹¹Cravioto MD, Durand-Carbajal M, Jimenez-Santana L, et al. Efficacy of estrogen plus progestin on menopausal symptoms in women with systemic lupus erythematosus: a randomized, double-blind, controlled, trial. *Arthritis Care Res (Hoboken)*. 2011 Dec;63(12):1654-63.

¹²Li RH, Gebbie AE, Wong RW, et al. The use of sex hormones in women with rheumatological diseases. *Hong Kong Med J*. 2011 Dec;17(6):487-91.