New KEEPS data on hormone therapy and atherosclerosis

Despite improving some markers of CVD risk, 4 years of early hormone therapy did not affect progression of atherosclerosis


Summary. In order to determine the effect of early postmenopausal initiation of hormone therapy (HT) on atherosclerosis progression and cardiovascular disease (CVD) risk factors, researchers for the Kronos Early Estrogen Prevention Study (KEEPS) recruited healthy postmenopausal women (aged 42-58 y) between 6 and 36 months from their last menses without prior CVD events and with a coronary artery calcium (CAC) score below 50 Agatston units. They received 0.45 mg/d of oral conjugated equine estrogens (CEE) or 50 mcg/d of transdermal 17β-estradiol, each with 200 mg of oral progesterone for 12 days per month, or placebo for 48 months. The primary end point of this randomized, controlled trial was annual change in carotid artery intima-media thickness (CIMT). In 727 women, 89.3% had at least one follow-up CIMT test, and 79.8% had a CIMT test after 48 months. Increases in mean CIMT and CAC scores were similar across all groups. There were no observed changes in blood pressure with CEE or transdermal 17β-estradiol. With CEE, low- and high-density lipoprotein cholesterol levels improved and C-reactive protein, triglycerides, and sex hormone-binding globulin (but not interleukin-6) increased. With 17β-estradiol, insulin resistance decreased. Unexpected uterine bleeding was three to four times higher in HT groups compared with placebo.

Comment #1. The rationale for KEEPS is that menopausal HT initiated early may reduce CVD, supporting the timing hypothesis and the importance of timing as a modifier of disease outcome. This theory has been supported by large observational studies, beneficial effects on CVD risk factors, and benefits of early HT in primates and rodents. Additionally, subset data analyses of the Women’s Health Initiative (WHI) support the trend for reduced CVD. The mean age in this study was 52.7 years, which is substantially lower than the entire WHI cohort.

The changes in risk factors, blood pressure, cholesterol, triglycerides, insulin resistance, CIMT, and CAC are reported in the study. Less than 13% of the participants had CAC scores at baseline, with most being between 0 and 10. Four percent had CAC scores greater than 10, and women with scores greater than 50 were excluded from the study. Women who had an
existing CAC score were more likely to progress.

Compared with placebo, both the transdermal and oral estrogen groups showed fewer women with increased scores. This is supportive of the timing hypothesis because it suggests, but does not prove, that estrogen may protect against an increase in the CAC scores of higher-risk women.

The authors provide an excellent discussion of why no apparent effect of HT on CIMT was found. Because numbers were small, the findings are not statistically significant. The findings are consistent with the WHI follow-up CACs. KEEPS selection criteria have minimized the ability to observe effects of treatment during the limited duration of the study. Further study, with longer follow-up time, will be required to show statistical significance.

Marla Shapiro, MDCM, CCFP, MHSc, FRCP(C), FCP, NCMP
Associate Professor
Department of Family and Community Medicine
University of Toronto
Toronto, Ontario, Canada

Comment #2. KEEPS is the latest randomized, controlled trial to evaluate the effect of postmenopausal HT on CVD—in this case, on the development or progression of atherosclerosis. KEEPS is unique in evaluating the HT timing hypothesis to see whether giving it early in the postmenopausal period would decrease atherosclerosis.

Results show that 4 years of HT did not affect progression of atherosclerosis, despite improving some markers of CVD risk. The results also showed a substantial reduction in vasomotor symptoms, such as hot flashes and night sweats, as well as some improvement in bone mineral density. The trial was not powered to assess effects on clinical outcomes such as heart attacks, strokes, or cardiovascular death.

From a cardiologist’s perspective, these results are not surprising. The characteristic biomarker changes seen in earlier HT trials were also seen in this study. It is not surprising that the effects on CIMT were null in this population of young women, who would have very small CIMTs anyway. And although this study was not powered for hard cardiovascular outcomes, the low level of adverse events and apparent safety of the therapy are comforting.

Karol E. Watson, MD, PhD
Professor of Medicine/Cardiology
Co-director, UCLA Program in Preventive Cardiology
Director, UCLA Barbra Streisand Women’s Heart Health Program
Los Angeles, California

In breast cancer survivors, lidocaine reduces vulvar vestibular tenderness

Because study only covers pain on insertion, it does not apply to all types of dyspareunia


Summary. To test the hypothesis that genital tenderness in survivors of breast cancer not using estrogen and experiencing dyspareunia is limited to the vulvar vestibule rather than the vagina and is reversed by topical anesthetic, researchers recruited 49 postmenopausal breast cancer survivors (aged 37-69 y) with moderate and severe dyspareunia to a randomized, double-blind intervention using topical aqueous 4% lidocaine or normal saline for 3 minutes on the tender areas. All women had tenderness in the vulvar vestibule and vulvovaginal atrophy. One had vaginal mucosal tenderness, and two had pelvic floor myalgia. The lidocaine reduced the vestibular tenderness of all painful sites.

Commentary. Breast cancer survivors are a growing group of women, diagnosed at younger ages, with expectations of healthy sexuality. They are often free of disease for long periods of time, exposed to years of induced meno-
pause, hypoestrogenism, and antiestrogen treatments, with a devastating effect on urogenital function, sexual health, and intimacy.\textsuperscript{1} Goetsch and colleagues investigated the location of sexual pain in such women. The vestibule was the primary location for pain rather than the vagina, which had minimal to no pain in response to touch with cotton swabs. By systematically mapping out the most painful genital areas, they were able to demonstrate the ability of lidocaine to significantly eliminate pain in response to touch compared with normal saline. A randomized, at-home intervention study of the group followed and confirmed a reduction of pain with penetrative intercourse.\textsuperscript{2}

The authors write that “assumptions that vaginal dryness and vaginal atrophy cause tenderness [and] old concepts attributing pain to vaginal dryness and atrophic vaginitis deserve reconsideration.” Many menopause clinicians, as well as The North American Menopause Society and the International Society for the Study of Sexual Health, agree that there has been undue focus on vulvovaginal atrophy in regard to this condition. Recently, a joint nomenclature consensus conference coined the term \textit{genitourinary syndrome of menopause} (GSM), which includes vestibular, introital, clitoral, and vaginal structures as critical to sexual and urogenital health in menopause.

That said, a conclusion cannot be drawn from this small cohort regarding the role of vaginal tissue and dryness in menopausal dyspareunia because women with pelvic pain and deep dyspareunia were excluded from the study—only women suffering from pain on insertion were studied. Pain from an inelastic, narrowed, dry, and shortened vagina, all commonly seen in an untreated woman with severe and chronic pain, can present as deep dyspareunia and complaints of dryness. The most bothersome symptom in 44\% of patients in a large clinical trial of 310 women was dryness.\textsuperscript{3} It would be helpful to know whether lidocaine applied to the vestibule helps these other sufferers with more advanced anatomic and functional impairment.

Novel approaches to menopausal dyspareunia are critically important because many breast cancer survivors are likely to avoid local vaginal estrogens. Patients have understandable fears of recurrence, even though no controlled or observational data has associated minimally absorbed local vaginal estrogen with a worsened prognosis. Fortunately, many (but not enough) menopause clinicians and oncologists are comfortable informing patients with debilitating symptoms that such treatments can be justified with benefit-risk and quality-of-life analyses.

The use of selective estrogen-receptor modulators (SERMs) in this population (including ospemifene, approved for menopausal dyspareunia and with preclinical effects similar to tamoxifen on breast cancer models), deserves further study.\textsuperscript{4,5} Lasofoxifene, a SERM approved in Europe that improved vulvovaginal symptoms, also showed an 80\% reduction in breast cancer incidence in a large trial.\textsuperscript{6} Tissue-selective estrogen complexes, intravaginal dehydroepiandrosterone, testosterone, and estriol are options to improve symptoms, reverse tissue changes, and safeguard breast health and risk.\textsuperscript{7}

Lidocaine in the present study demonstrably reduced scores of pain on touch; however, it is likely masking the progressive and potentially irreversible long-term problems these patients experience. Although successful penetration is important to sexuality, the absence of pain does not necessarily imply the presence of pleasure. After all, the vulvar and clitoral areas contain sensory nerves and vasculature that respond to touch, pressure, fullness, and movement with engorgement, arousal, desire, and orgasm. Local anesthetics in this context likely desensitize normal sexual response and fail to restore and reverse progressive, detrimental tissue changes.

Goetsch and associates demonstrate that lidocaine applied to the vestibule may be an option to make penetration and sexual activity possible, particularly for those breast cancer survivors and clinicians unwilling to use local estrogen or other treatments that maintain...
genitourinary function and integrity. Our goals as clinicians and researchers should be to help improve sexuality and intimacy every way we can for this group of women who deserve both quality and quantity of life.

David J. Portman, MD
Director, Columbus Center for Women’s Health Research
Board of Directors, International Society for the Study of Women’s Sexual Health
Co-Chair, ISSWSH/NAMS Vulvovaginal Atrophy Terminology Consensus Conference
Columbus, Ohio

References


Lifetime surgery risk for stress urinary incontinence or pelvic organ prolapse

Women aged 80 years have 20% risk of surgery for either problem


Summary. Using a US claims and encounters database (2007-2011), researchers examined women aged 18 to 89 years and estimated age-specific incidence rates and cumulative incidence of stress urinary incontinence (SUI) surgery, pelvic organ prolapse (POP) surgery, and either incontinence or prolapse surgery with 95% confidence intervals (CIs). They evaluated 10,177,480 adult women who were followed for 24,979,447 person-years. Overall, there was a lifetime risk of any primary surgery for SUI or POP of 20.0% (95% CI, 19.9-20.2) by the age of 80 years (risk for SUI surgery was 13.6%, and risk for POP surgery was 12.6%).

Comment. In this study of claims data, Wu and colleagues found a 20% lifetime risk of surgery for SUI or POP in women aged 80 years. This represents a more current and probably more accurate risk than the commonly quoted lifetime risk of 11.1%, which is based on the Kaiser population in the Pacific Northwest in 1995.

This study was conducted using the MarketScan Commercial Claims and Encounters Database. Researchers conducted several sensitivity analyses to determine the robustness of their findings, and indeed the estimates did not change significantly. A minor limitation of the study was that they were not able to evaluate the uninsured or the Medicaid population, thus the rate may be other than 20%. Nevertheless, this study represents the best to date on the lifetime risk of a woman needing incontinence or prolapse surgery and should be the new reference standard for prevalence of lifetime prolapse or incontinence surgery risk.

Charles W. Nager, MD
Professor of Clinical Reproductive Medicine
UC San Diego Health System
Division Director, Female Pelvic Medicine and Reconstructive Surgery
La Jolla, California

Reference

How effective is cervical cytology screening in reducing deaths from cervical cancer?

Researchers estimate that screening of US women aged 55 to 79 years could prevent 630 annual deaths


**Summary.** Researchers in a case-control study sought to quantify the efficacy of cervical cytology screening to reduce death from cervical cancer by comparing Papanicolaou (PAP) test screening histories of women (aged 55-79 y) who died of cervical cancer between 1980 and 2010 (cases) to those of women at risk of cervical cancer (controls). Of these women, 80 eligible controls were matched 2:1 to 39 eligible cases based on health plan, age, and enrollment duration. After adjustment for matching characteristics, smoking, marital status, and race/ethnicity using logistic regression, the odds ratio of death from cervical cancer associated with screening was 0.26 (95% CI, 0.10-0.63). Researchers estimated that screening US women aged 55 to 79 years could avert 630 deaths annually.

**Comment.** Changing cervical cancer screening guidelines have significantly altered the practice of gynecologic care. The Pap test has long been equated with and has served as a driving force for the annual gynecologic visit, which served many functions beyond screening for cervical disease. The visit reinforces the patient-physician relationship and provides the opportunity to address a myriad of age-appropriate, health-related issues, including screening for cancer and chronic disease. Based on guidelines published by the American Society for Colposcopy and Cervical Pathology and the American Congress of Obstetricians and Gynecologists, women aged older than 65 years with a history of prior adequate screening (and no history of cervical intraepithelial neoplasia ≥ grade II) no longer require cervical cancer screening. Undoubtedly, there now exists a great need for patient education because, for many women, this policy will be misinterpreted to imply that there is no longer a need at this age for routine, well-woman gynecologic care.

Rustagi and colleagues found that the rate of death was lower by 74% in those women who were screened within 7 years of the index date or the date of diagnosis of invasive cervical cancer in the case patient. By analyzing the data grouped into those aged more than and less than 65 years, they found that there was a lesser but still significant reduction in risk of dying from cervical cancer in women aged 65 years and older with screening. Using population data, the authors estimated that using cytology screening in women aged 55 years and older in the United States could prevent 630 deaths per year.

The cervical cancer screening guidelines are complicated. Although this study does not incorporate high-risk human papillomavirus (HPV) testing, the results do support a potential life-saving benefit for periodic screening in this population. Perhaps an ideal study would incorporate HPV testing and capture the critical social history question of whether the woman remains sexually active, notably with a new partner. Millions of American women aged 65 years and older remain sexually active and at risk for sexually transmitted infections. For now, this study could be used as a reference point to make clinical judgments for a woman aged older than 65 years in lieu of evidence-based guidelines because she could live another 30 years. This study could also be taken as encouragement to not let the routine gynecologic visit be a relic of the past but instead to incorporate gender-specific and
lifestyle-based screening around issues of menopause and sexuality in addition to screening for cancer and chronic disease.

Diana L. Bitner, MD, NCMP
Attending Physician and Surgeon
Division of Obstetrics and Gynecology and Women’s Health
Medical Director, Women’s Health Network
Spectrum Health Medical Group
Adjunct Clinical Professor
Michigan State University Medical School
Grand Rapids, Michigan

References


Menopause Editor’s picks from July 2014

NAMS spotlights selections from the most recent issue of the Society’s official journal, Menopause, chosen by its editor in chief, Isaac Schiff, MD.

Health characteristics of women beginning postmenopausal hormone therapy: have they changed since the publication of the Women’s Health Initiative?
Agnes Fournier, PhD; Xavier Fritel, MD, PhD; Henri Panjo, MSc; Marie Zins, MD, PhD; and Virginie Ringa, MD, PhD.

Cigarettes, genetic background, and menopausal timing: the presence of single nucleotide polymorphisms in cytochrome P450 genes is associated with increased risk of natural menopause in European-American smokers.
Samantha F. Butts, MD, MSCE; Mary D. Sammel, ScD; Christine Greer, BS; Timothy R. Rebbeck, PhD; David W. Boorman, MS; and Ellen W. Freeman, PhD.

Relationship between circulating serum osteoprotegerin and total receptor activator of nuclear K-B ligand levels, triglycerides, and coronary calcification in postmenopausal women.
Indu G. Poornima, MD; Rachel H. Mackey, PhD, MPH; Alhaji M. Buhari, MA, MSIE; Jane A. Cauley, DrPH; Karen A. Matthews, PhD; and Lewis H. Kuller, MD, DrPH.

First to Know® is a registered trademark of The North American Menopause Society
Copyright © 2014 The North American Menopause Society
All rights reserved
5900 Landerbrook Drive, Suite 390 • Mayfield Heights, OH 44124 • USA
Tel 440/442-7550 • Fax 440/442-2660 • info@menopause.org • www.menopause.org

The level of evidence indicated for each study is based on a grading system that evaluates the scientific rigor of the study design, as developed by the US Preventive Services Task Force. A synopsis of the levels is presented below.

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level I</td>
<td>Properly randomized, controlled trial.</td>
</tr>
<tr>
<td>Level II-1</td>
<td>Well-designed controlled trial but without randomization.</td>
</tr>
<tr>
<td>Level II-2</td>
<td>Well-designed cohort or case-control analytic study.</td>
</tr>
<tr>
<td>Level II-3</td>
<td>Multiple time series with or without the intervention (eg, cross-sectional and uncontrolled investigational studies).</td>
</tr>
<tr>
<td>Level III</td>
<td>Meta-analyses; reports from expert committees; descriptive studies and case reports.</td>
</tr>
</tbody>
</table>
New Member Forum on www.menopause.org

What are your clinical challenges with dyspareunia? Post on our Member Forum to discuss July’s *First to Know* papers:
www.menopause.org/member-login?ReturnUrl=%2fforum