Ideal cardiovascular health metrics and risk of incident early-onset vasomotor symptoms among premenopausal women

Hye Rin Choi 1 2, Yoosoo Chang 1 3 4, Yejin Kim 1, Yoosun Cho 5, Jeonggyu Kang 1, Min-Jung Kwon, et al.

Context: The relationship of ideal cardiovascular health (CVH) behaviors with preventing early-onset vasomotor symptoms (VMSs) is unknown. Objective: We investigated the association between CVH metrics and the development of early-onset VMSs in premenopausal women. Design: This cohort study included 2,541 premenopausal women aged 42-52 years without VMSs at baseline. Methods: CVH metrics were defined according to the American Heart Association Life Simple 7 metrics. Due to the limited availability of dietary information, CVH metrics were scored from 0 (unhealthy) to 6 (healthy) and classified into three groups: poor (0-2), intermediate (3-4), and ideal (5-6) CVH. VMSs, including hot flashes and night sweats, were assessed using the Menopause-Specific Quality of Life questionnaire. Moderate/severe VMSs was defined as a score of ≥ 3 points (range: 0 to 6, 6 being most bothersome). Results: During a median follow-up of 4.5 years, 1,241 women developed VMSs prior to menopause. After adjustment for age, parity, education level, and alcohol consumption, the hazard ratio (95% confidence interval [CI]) for developing early-onset VMSs comparing poor CVH group to the ideal group was 1.41 (1.07-1.86). CVH scores were also inversely associated with moderate/severe VMSs in a dose-response manner (P for trend = 0.004); specifically, multivariate-adjusted hazard ratios comparing intermediate and poor CVH groups to the ideal group were 1.20 (95% CI: 1.02-1.43) and 1.57 (95% CI: 1.08-2.29), respectively. Conclusion: Unfavorable CVH metrics were significantly associated with an increased risk of early-onset VMSs and its more severe forms among premenopausal women.

Concerns About Compounded Bioidentical Menopausal Hormone Therapy

JoAnn V Pinkerton 1

Following the release of the Women's Health Initiative data, women began to use compounded bioidentical hormone therapy (cBHT) in the misguided belief of greater safety and efficacy than traditional hormone therapy. New guidelines recommend government-approved hormone therapy for symptomatic healthy menopausal women younger than 60 years or within 10 years of menopause at the time of initiation. For women requesting bioidentical hormones, those similar to the hormones present before menopause, there are many government-approved hormone therapies with extensive pharmacokinetic, safety, and efficacy data provided with package inserts delineating efficacy, safety, and potential risks. For women requesting non-Food and Drug Administration-approved (cBHT), these cBHTs lack data on pharmacokinetics, safety, and efficacy and are not provided a label detailing risk. Their use should be restricted to women with allergies or dosing or formulations not available in government-approved therapies. Pellet therapy providing women with supraphysiologic hormone dosing raises even more safety concerns.

Menopausal Hormone Replacement Therapy and Reduction of All-Cause Mortality and Cardiovascular Disease: It Is About Time and Timing

Howard N Hodis, Wendy J Mack

The totality of evidence indicates menopausal hormone replacement therapy (HRT) effects are determined by timing of initiation according to age and/or time since menopause, underlying health of target tissue, and duration of therapy. Initiated in women at younger than 60 years and/or at or near menopause, HRT significantly reduces all-cause mortality and cardiovascular disease (CVD), whereas other primary CVD prevention therapies such as lipid-lowering fail to do so. The magnitude and type of HRT-associated risks, including breast cancer, stroke, and venous thromboembolism, are rare (<10 events/10,000 women), not unique to HRT, and comparable with other medications. Hormone replacement therapy is a sex-specific and time-dependent primary CVD prevention therapy that concomitantly reduces all-cause mortality, as well as other aging-related diseases with an excellent risk profile. Keeping in mind that prevention...
strategies must be personalized, health care providers and patients can use cumulated HRT data in making clinical decisions concerning chronic disease prevention including CVD and mortality reduction.

Hormone Replacement Therapy After Breast Cancer: It Is Time
Avrum Zvi Bluming 1
This article reviews the decades of evidence supporting the reproducible benefits of HRT for menopausal symptom control, improved cardiac health, prevention of hip fracture, reduction in the risk and pace of cognitive decline, and enhanced longevity. It quantifies the increased risk of thromboembolism associated with oral, though not transdermal, HRT. It evaluates the repeated claims that HRT is associated with an increased risk of breast cancer development, and, when administered to breast cancer survivors, an increased risk of breast cancer recurrence. Twenty-five studies of HRT after a breast cancer diagnosis, published between 1980 and 2013, are discussed, as are the 20 reviews of those studies published between 1994 and 2021. Only 1 of the 25 studies, the HABITS trial, demonstrated an increased risk of recurrence, which was limited to local or contralateral, and not distant, recurrence. None of the studies, including HABITS, reported increased breast cancer mortality associated with HRT. Even in the HABITS trial, the absolute increase in the number of women who had a recurrence (localized only) associated with HRT administration was 22. It is on the basis of these 22 patients that HRT, with its demonstrated benefits for so many aspects of women's health, is being denied to millions of breast cancer survivors around the world.

Management of Postmenopausal Osteoporosis: ACOG Clinical Practice Guideline No. 2
Purpose: To provide updated evidence-based recommendations for the treatment of postmenopausal osteoporosis.
Target population: Postmenopausal patients with primary osteoporosis. Methods: This guideline was developed using an a priori protocol in conjunction with a writing team consisting of two specialists in obstetrics and gynecology appointed by the ACOG Committee on Clinical Practice Guidelines-Gynecology and one external subject matter expert. ACOG medical librarians completed a comprehensive literature search for primary literature within Cochrane Library, Cochrane Collaboration Registry of Controlled Trials, EMBASE, PubMed, and MEDLINE. Studies that moved forward to the full-text screening stage were assessed by two authors from the writing team based on standardized inclusion and exclusion criteria. Included studies underwent quality assessment, and a modified GRADE (Grading of Recommendations Assessment, Development, and Evaluation) evidence-to-decision framework was applied to interpret and translate the evidence into recommendation statements. Recommendations: This Clinical Practice Guideline includes updated recommendations on who should receive osteoporosis pharmacotherapy, the benefits and risks of available pharmacotherapy options, treatment monitoring and follow-up, and the role of calcium and vitamin D in the management of postmenopausal osteoporosis. Recommendations are classified by strength and evidence quality. Ungraded Good Practice Points are included to provide guidance when a formal recommendation could not be made because of inadequate or nonexistent evidence.

Mortality in COVID-19 among women on hormone replacement therapy: a retrospective cohort study
Hajira Dambha-Miller 1, William Hinton 2, Christopher R Wilcox 1, Mark Joy 2, Michael Feher 2, et al.
Background: Limited recent observational data have suggested that there may be a protective effect of oestrogen on the severity of COVID-19 disease. Our aim was to investigate the association between hormone replacement therapy (HRT) or combined oral contraceptive pill (COC) use and the likelihood of death in women with COVID-19. Methods: We undertook a retrospective cohort study using routinely collected computerized medical records from the Oxford-Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) primary care database. We identified a cohort of 1,863,478 women over 18 years of age from 465 general practices in England. Mixed-effects logistic regression models were used to quantify the association between HRT or COCP use and all-cause mortality among women diagnosed with confirmed or suspected COVID-19 in unadjusted and adjusted models.
Results: There were 5,451 COVID-19 cases within the cohort. HRT was associated with a reduction in all-cause mortality in COVID-19 (adjusted OR 0.22, 95% CI 0.05 to 0.94). There were no reported events for all-cause mortality in women prescribed COCPs. This prevented further examination of the impact of COCP. Conclusions: We found that HRT prescription within 6 months of a recorded diagnosis of COVID-19 infection was associated with a reduction in all-cause mortality. Further work is needed in larger cohorts to examine the association of COCP in COVID-19, and to further investigate the hypothesis that oestrogens may contribute a protective effect against COVID-19 severity.


Time Trends in Unilateral and Bilateral Oophorectomy in a Geographically Defined American Population
Zachary Erickson 1, Walter A Rocca, Carin Y Smith, Liliana Gazzuola Rocca, Elizabeth A Stewart, et al.
Objective: To evaluate trends in the incidence of premenopausal unilateral and bilateral oophorectomy between 1950 and 2018. Methods: The Rochester Epidemiology Project medical records-linkage system was used to identify all women aged 18-49 years who were residents of Olmsted County, Minnesota, and underwent unilateral or bilateral oophorectomy before spontaneous menopause between January 1, 1950, and December 31, 2018. Population denominators were derived from the U.S. Decennial Censuses for the years 1950-2010, and intercensal year population denominators were linearly interpolated. For 2011-2018, the annual population denominators were obtained from the U.S. Census projections. Where appropriate, overall incidence rates were age-adjusted to the total U.S. female population from the 2010 Census. Results: There were 5,154 oophorectomies in Olmsted County across the 69-year period between 1950 and 2018, and 2.9% showed malignant disease on pathology. A total of 2,092 (40.6%) women underwent unilateral oophorectomy, and 3,062 (59.4%) women underwent bilateral oophorectomy. More than half (n=1,750, 57.2%) of the bilateral oophorectomies occurred between 1990 and 2009. Until 1975-1979, the incidence of unilateral oophorectomy was mostly higher than bilateral oophorectomy. From 1980-1984 until 2000-2004, the incidence of bilateral oophorectomy more than doubled and the incidence of unilateral oophorectomy declined. After 2005, both procedures declined and converged to a similar incidence in 2015-2018. The decline in premenopausal bilateral oophorectomy over the past 14 years (2005-2018) was most pronounced for women who underwent oophorectomy concurrently with hysterectomy or did not have any ovarian indication. Conclusion: The incidence rates of unilateral and bilateral oophorectomy have varied greatly across the 69-year period of this study. In the past 14 years, the incidence of premenopausal unilateral and bilateral oophorectomy has decreased. These trends reflect the effects of the initial 2005-2006 publications and the subsequent expanding body of evidence against the practice of oophorectomy for noncancer indications.