7th Annual Vivian W. Pinn Symposium Meeting Summary: Menopause and Optimizing Midlife Health of Women

Event Date: May 16, 2023
Summary Date: July 20, 2023

Table of Contents

Introduction and Welcome

(VideoCast timestamp 0:00 - 15:49)

Sarah Temkin, M.D. (ORWH) formally opened the 7th Annual Vivian W. Pinn Symposium as a forum for experts to communicate about and collaborate on topics of importance for the advancement of women's health. She introduced Janine Austin Clayton, M.D., FARVO, Director of the Office of Research on Women's Health (ORWH). Dr. Clayton introduced menopause as an inflection point during a woman's life. Midlife is an important life stage that presents challenges and opportunities for women. Following the menopausal transition, women face a greater risk for the onset of chronic disease, another important and relevant women's health research topic.

In fiscal year (FY) 2021, Congress requested NIH evaluate efforts related to women's health research and several focused topics including chronic debilitating conditions, resulting in the "Advancing NIH Research on the Health of Women: A 2021 Conference" hosted by ORWH. A recent ORWH publication outlines the development of an NIH framework for chronic conditions in women, and ORWH sponsored the forthcoming National Academies of Sciences, Engineering, and Medicine *Framework for the Consideration of Chronic Debilitating Conditions in Women* report. Dr. Clayton noted available related funding opportunities, Understanding Chronic Conditions Understudied Among Women (R01 and R21).

Specific to NIH efforts in menopause, Dr. Clayton highlighted a National Institute on Aging (NIA)-funded menopause tool, My Menoplan, and provided an update on the development of a research, condition, and disease categorization code to track menopause research. She noted ORWH's quarterly publication, *Women's Health in Focus at NIH,* and the issue that spotlighted menopause and the Specialized Centers of Research Excellence on Sex Differences (SCORE) sites conducting menopause research. Dr. Clayton closed with a challenge for the audience to consider how they might align menopause research efforts to provide individualized care for women at every reproductive stage and improve the health of all women.

Opening Keynote: Menopausal Hormone Therapy: 30 Years of Lessons from the Women's Health Initiative

(VideoCast timestamp 15:49 - 59:35)

JoAnn Manson, M.D., M.P.H., Dr.P.H., MACP (Harvard T.H. Chan School of Public Health and Harvard Medical School)

Dr. Manson noted that 2023 marks the 30th anniversary of the start of study recruitment for the Women's Health Initiative (WHI). Prior to the WHI, menopausal hormone therapy (MHT) was believed to be appropriate and beneficial for all women; and as such, the WHI was designed to assess the benefit-risk profile of MHT when used for chronic disease prevention among postmenopausal women. Following the early stopping of the trials due to adverse events, opinion in the medical community rapidly shifted toward the belief that MHT was bad for all women. Understanding the right candidates and timing for MHT is far more complex, without a one-size fits all answer.

Dr. Manson emphasized that the primary objective of the WHI was to evaluate the utility of MHT in prevention of cardiovascular disease, not to evaluate the role of MHT for menopausal symptom management. Until the recent approval of a neurokinin 3 receptor (NK3R) antagonist, there has been only one non-hormonal medication approved by the Food and Drug Administration (FDA) to treat vasomotor symptoms (VMS), the most common menopausal symptoms. As described in a publication by Drs. Manson and Andrew Kaunitz, Menopause Management—Getting Clinical Care Back on Track, MHT is the most effective current treatment for VMS with significant reductions in the number of hot flashes per day demonstrated in clinical trials. Given limited therapeutic options and the large number of women (75% of peri- and early postmenopausal patients) with menopausal symptoms, patient preferences should be considered in the decision-making process for treating menopausal symptoms. Dr. Manson added that the limited number of clinicians with the training and expertise to adequately assess and counsel candidates for MHT adds to the challenge patients face when accessing personalized recommendations and care.

The WHI trials were two separate parallel primary prevention trials depending on whether a patient had a uterus: 16,608 women with a uterus received 0.625 mg/d conjugated equine estrogen (CEE) and 2.5 mg/d medroxyprogesterone acetate (MPA) and 10,739 women who had women had had a uterus received CEE alone. These doses and formulations were typical for the time the study was active; however, these are not typically how MHT is prescribed today. In 2002, the WHI results for the CEE+MPA arm were published, demonstrating an increased risk with MHT of a diagnosis of breast cancer, coronary heart disease, stroke, and pulmonary embolism, which demonstrated that the risks outweighed the benefits. In 2004, the CEE-only arm was closed early because of an identified increased risk of stroke. In 2013, a detailed follow-up of both trials was published. The overall risks and benefits of both arms are shown in the adjacent figure. Many of the initial adverse events associated with MHT did not persist over time. Most surprisingly, the long-term follow-up data showed the risk of breast cancer increased, and continued to increase, in patients who received CEE+MPA and decreased significantly in patients who had a history of hysterectomy and received CEE alone. For each of the adverse events described in the WHI, the relative risks were similar for women in different age groups, but because younger women are overall healthier, much lower absolute risks were observed in younger women and those closest to the menopausal transition.

Major Endpoints	Intervention		Post-Intervention	
	CEE+MPA	CEE Alone	CEE+MPA	CEE Alone
CHD	0	0	0	0
Breast cancer	↑	↓	↑	↓
Stroke	↑	↑	0	0
PE	↑	0	0	0
Colorectal cancer	↓	0	0	0
Endometrial cancer	0	NA	↓	NA
Hip fracture	↓	↓	0	0
All-cause mortality	0	0	0	0
Global index	↑	0	0	0

One of the key differences between the WHI and observational studies that preceded the trial is the age of initiation of therapy. The WHI enrolled patients ages 50 to 79, and the average age of participants was 63—more than 12 years on average since the onset of menopause. The timing or

critical window hypothesis theorizes that the benefits and risks of MHT vary depending on the amount of time a woman has been in menopause at the time of initiation of treatment. In healthy coronary vessels, for example, estrogen induces nitric oxide synthase (NOS), vasodilation, and an anti-inflammatory effect that may decrease plaque production and subsequent cardiovascular disease. In atherosclerotic vessels, however, estrogen can induce a paradoxical pro-inflammatory response, which can lead to stenosis, or even occlusion, suggesting that estrogen's favorable effects in early menopause may not apply later in menopause, or to a woman with underlying atherosclerosis.

The Early Versus Late Intervention Trial (ELITE) was a smaller trial of 643 healthy, recently postmenopausal women and women 10 or more years from menopause, designed specifically to test the timing hypothesis. Patients were randomized to receive oral micronized 17β-estradiol 1 mg/d (+ vaginal micronized progesterone gel x 12 days/month in women with a uterus), or placebo, and the endpoint was change in carotid intima-media thickness (CIMT), a surrogate endpoint for cardiovascular disease. While estradiol reduced the rate of CIMT in younger women, it had no effect on the older women. Another trial, the Kronos Early Estrogen Prevention Study (KEEPS), randomized healthy, recently postmenopausal women patients to estrogen or placebo, however, did not support the timing hypothesis as CIMT was similar in the intervention and placebo arms.

Long-term outcomes for the subgroup of women ages 50 to 59 enrolled in the WHI have not indicated an increased risk for most health outcomes including all-cause mortality and global index (a composite score of adverse events) for those women who received MHT. In fact, after over 18 years of follow-up, pooling the two WHI trials, the group of younger patients had a significant reduction in all-cause mortality for those who had been assigned MHT. For the 530 women ages 50-59 who enrolled in the WHI following hysterectomy, who received CEE alone, there was a significant reduction in all-cause mortality. Lower doses and alternate (e.g., transdermal) formulations have also been evaluated with safety suggested. Dr. Manson raised the concern that in the absence of available evidence-based clinical care for those seeking treatment for menopausal symptoms, women may turn to custom compounds and other unregulated therapies for which safety is unknown.

Dr. Manson concluded that current evidence does not support the use of MHT for the prevention of cardiovascular disease (CVD), or other chronic diseases, due to the increased risks of adverse events. MHT maintains an important clinical role for many patients in managing menopausal symptoms. The best candidates for systemic MHT are recently menopausal and symptomatic women in generally good health with low absolute risks for whom quality of life benefits are potentially greater. Additional studies of different MHT formulations, doses, methods of delivery, and non-hormonal options are needed.

Understanding the Menopausal Transition

The Menopause Transition: Definitions, Health Implications, Future Directions

(VideoCast timestamp 59:40 - 1:22:34)
Gail Greendale, M.D. (David Geffen School of Medicine at University of California, Los Angeles)

Dr. Greendale shared an overview and insights from the Study of Women's Health Across the Nation (SWAN), a multicenter, multi-ethnic, community-based longitudinal study, intended to characterize the biological symptomatic and psychosocial changes that occur during the menopause transition. The study enrolled 3,302 women at seven clinical sites with deliberate inclusion of diverse women from Black, Hispanic, Chinese, Japanese, and White communities. Menopause is often thought of as a binary category: premenopausal or postmenopausal. The advent of menopausal transition (MT) thinking in the 1980s introduced more nuanced definitions of menopause. The final menstrual period (FMP) time framework represents one of the larger shifts in how the categorization of menopause has been refined. FMP time is defined as "time 0" and must be backdated after the woman has had her FMP. Defining the MT using FMP time is important because other methods are not strong indicators of the time to the onset of menopause. In fact, 69% of women measured by menstrually-defined MT stages as in "early perimenopause" are within 12 months of their FMP.

The FMP framework is useful for understanding bone loss in the post-menopause. The trajectory of lumbar spine bone mineral density (BMD) by FMP time reveals a striking acceleration in the rate of bone loss between one year prior and two years after the FMP, supporting the concept that the MT marks an inflection point in the health of women. Annual rates of BMD loss by FMP time can be used to capture mean annual BMD slopes by FMP time interval and show the bone loss sites. The accelerated changes in biology during the MT are not isolated to BMD alone but can be measured in other health indicators, including an acceleration of accumulation of fat mass following the FMP. This research creates a translational opportunity.

Stopping MT-related BMD loss is important for three reasons: (1) more bone is better than less bone, independent of starting levels; (2) more MT-related BMD loss predicts greater fracture risk; and (3) higher MT-related bone turnover leads to greater fracture risk, independent of BMD loss. To prevent MT-related bone loss, the onset of accelerated bone loss must be identified; however, the decline in bone strength starts during a clinically occult time frame one to two years prior to the FMP. Although understanding when women start to lose bone is complex, some signals precede the onset of MT-related BMD loss. The years leading up to the FMP provide a window of opportunity and studies have examined possible signals of MT-related BMD loss. N-terminal telopeptides of type I collagen (NTX) and anti-Müllerian hormone (AMH) are two markers that can be utilized to predict the onset and rate of MT-related BMD loss. Work remains to ensure these markers are suitable for clinical prediction. If demonstrated as predictive biomarkers for boss loss, preventive interventions could be initiated before BMD loss begins, allowing patients to start their postmenopausal years with higher, absolute BMD. Preventive agents would remove negative consequences of rapid BMD loss and high bone turnover independently related to postmenopausal fracture risk, apart from absolute BMD.

It's Hot in Here! Understanding the Basic Biology of the Menopause Transition

(VideoCast timestamp 1:22:34 - 1:39:50)
Genevieve Neal-Perry, M.D., Ph.D. (University of North Carolina School of Medicine at Chapel Hill)

Dr. Neal-Perry began by explaining that the basic physiologic processes of the MT involve the ovarian, pituitary, and hypothalamic axes. Although thinking about the basic physiology of menopause tends to focus on the ovary and loss of ovarian hormonal function, events in the neuroendocrine axis also contribute to the development of symptoms. In addition to increasing levels of follicle-stimulating hormone (FSH), there are changes in how gonadotropin-releasing hormone (GnRH) neurons respond to estrogen. Several modifiers can change the experience of menopause, including autoimmune disorders, smoking, chemotherapy or radiation, environmental exposures, pelvic surgery, or the removal of one or both ovaries, and genetic defects.

VMS are one of the cardinal symptoms of the MT. Up to 75% of women will report hot flashes, which can last anywhere from six months to over seven years. Moderate to severe hot flashes occur 7-8 times per day, or 50-60 times per week, and cause distress and disruption to quality of life. Genetic polymorphisms (e.g., 17-beta hydroxysteroid, CYP1A1 polymorphisms) affect hormone metabolism and hormone function, influencing the experience and severity of hot flashes.

The "black box" behind hot flashes is a neuro-derived phenomenon and estrogen therapy can reduce hot flashes; however, the onset of hot flashes in perimenopause is more complex than can be explained by the loss of estrogen alone. Using SWAN data, the MT has been shown to be a dynamic reproductive phase with wide hormonal fluctuations and dysregulation occurring at the level of the hypothalamic-pituitary axis.

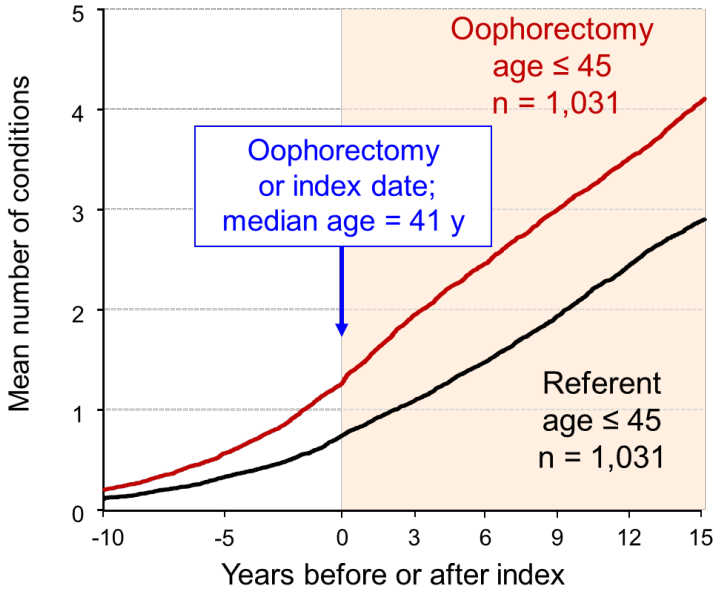
Seminal work performed by Naomi Rance, M.D., Ph.D. (University of Arizona, Tucson), investigated the origin of hot flashes by examining the infundibular nucleus within the brain. The density of kisspeptin, neurokinin B (NKB), and dynorphin (KNDy) neurons in this region of the brain change during the MT. In the absence of estradiol feedback, KNDy neurons become hypertrophied and hyperactive and stimulate each other using NKB. NKB, through the stimulation of KNDy and other neurons, stimulate thermoregulation areas in the brain that trigger the sensation of hot flashes. Using a thermocline device with hot and cold areas, mice injected with NKB agonists will gravitate toward the cooler areas compared to animals injected with vehicle. Similarly, in premenopausal women, injection of NKB agonists induces hot flashes, heart rate increases, and anxiety. Dr. Neal-Perry highlighted the neurokinin 3 (NK3) receptor antagonist that modulates NKB activity was recently approved by FDA to treat hot flashes. Finally, Dr. Neal-Perry discussed an ancillary WHI study that demonstrated an association between intolerable hot flashes with polymorphisms of the tachykinin receptor-3, the receptor which responds to NKB. What remains unknown is whether the neurons responsible for thermoregulation also influence the metabolic dysfunction and sleep dysregulation associated with the menopausal transition.

The Accumulation of Morbidity After Menopause

Premature or Early Menopause and Accelerated Accumulation of Multi-Morbidity

(VideoCast timestamp 1:39:48 - 2:03:08)
Walter Rocca, M.D., M.P.H (Mayo Clinic College of Medicine and Science)

Dr. Rocca centered his presentation on clinical research evidence collected within the Mayo Clinic's Cohort Study of Oophorectomy and Aging-2 (MOA-2). This unique cohort consists of two groups of women who underwent bilateral oophorectomy, either between ages 46 and 49 (n=1653), or at age 45 or younger (n=1031), each accrued with a referent cohort who have been followed for at least 14 years. Bilateral oophorectomy remains the most common cause of premature or early menopause and provides a unique clinical scenario in which to study the effects of menopause on aging. Within the research from this cohort, the development of 18 HHS-defined chronic conditions were used as individual outcome measures as well as in combination as a composite measure of multimorbidity. Hazard rations were adjusted for baseline characteristics using inverse probability weights for the conditions, education, race, BMI, smoking, age, and calendar year.
Investigators found that early iatrogenic menopause was associated with mental health conditions, including depression and anxiety; cardiovascular conditions including hyperlipidemia, diabetes, arrythmia, and coronary artery disease; and other somatic conditions such as arthritis, cancer, asthma, chronic obstructive pulmonary disease (COPD), and osteoporosis. Women who underwent bilateral oophorectomy at age 45 years or younger had a significantly increased risk (HR=1.22, 95% CI 1.14-1.31, p<0.001) of accumulating chronic conditions compared to the referent population. Within the sub-group of women who had a bilateral oophorectomy at or before age 45 and had zero conditions at baseline significant acceleration in morbidity (HR=1.24, 95% CI 1.12-1.37, p<0.001) over time was seen compared to the general population. This trend for acceleration of morbidity was similar regardless of the indication for surgery. In women aged 45 or younger, who were treated with estrogen following oophorectomy, an increase in morbidity was not observed. This evidence suggests that bilateral oophorectomy causes accelerated mortality, rather than solely acting as a marker of aging.



Dr. Rocca discussed additional evidence suggesting oophorectomy and the associated loss of estrogen accelerates aging. By measuring cellular DNA methylation, investigators have demonstrated an acceleration of biological compared with chronological age following menopause. Epigenetic aging is associated with earlier age of menopause, oophorectomy, length of time since menopause, and is inversely associated with the use of menopausal hormone therapy. In multiple animal models, ovariectomy is associated with adverse health outcomes, including vascular and neurologic outcomes, as well as reductions in lifespan. In mice, ovarian transplantation from young mice into older mice has been demonstrated to be associated with longer lifespan.

Studying women who have undergone a bilateral oophorectomy provides a unique natural experiment to understand the aging process. In aggregate, data support an acceleration of aging processes at the cellular, organ, and tissue level in the setting of the premature loss of estrogen that manifest at the clinical level as multi-morbidity and/or frailty. Modifiable factors that influence health after oophorectomy include estrogen replacement therapy and behavioral, genetic, and environmental factors. However, oophorectomy should only be performed when there is a clear indication and estrogen replacement therapy should be considered following the procedure to offset the associated potential harmful health effects.

To E or Not to E: Metabolic Actions of Estrogens

(VideoCast timestamp 2:03:02 - 2:23:57)
Wendy Kohrt, Ph.D. (University of Colorado Anschutz Medical Campus)

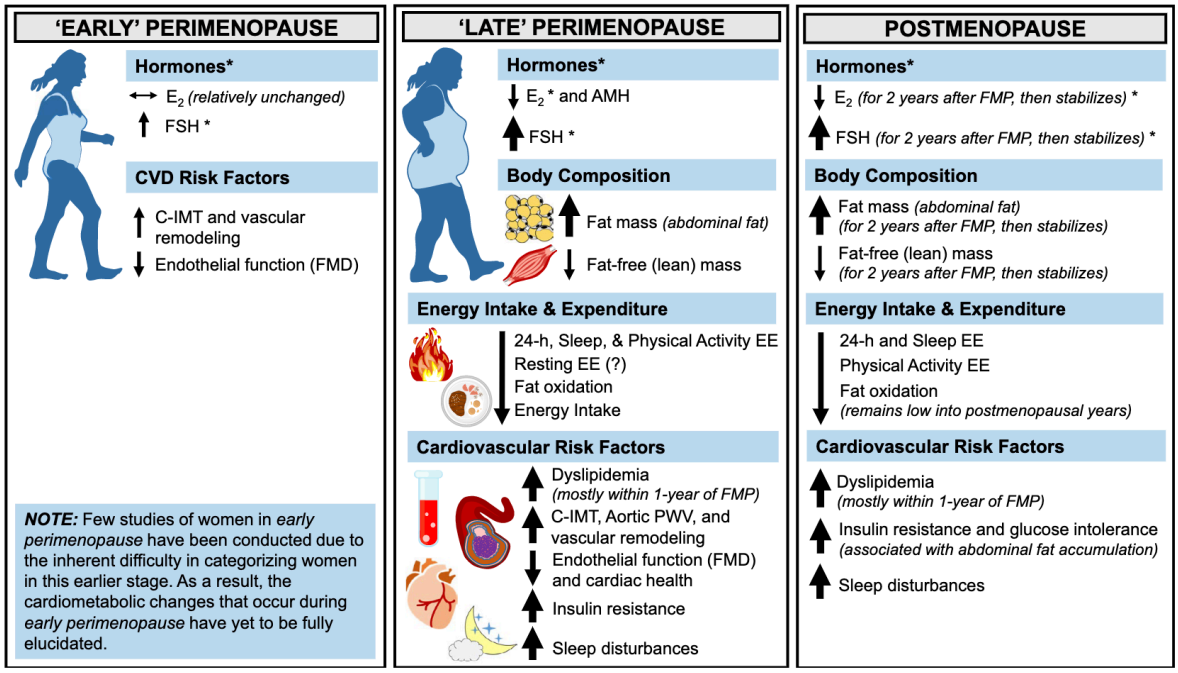
Dr. Kohrt shared research from the University of Colorado's Specialized Center of Research Excellence on Sex Differences (UC-SCORE) site, which focused on the bioenergetic and metabolic consequences of the loss of gonadal function. Studying loss of gonadal function is particularly important for women's health as menopause occurs during midlife. Loss of endocrine function impacts other systems, modifying factors that influence subsequent disease risk. Accelerated bone loss that accompanies menopause is one example discussed earlier in this symposium, but other impacts include altered hormonal function in the brain or skeletal muscle, and increased risk for dementia or sarcopenia. The regulation of systems, including those that control energy balance, are also affected by the loss of ovarian function that accompanies menopause. Subsequent fat gain, alterations in fat distribution, and composition of adipose tissue can affect risk of other disorders (e.g., cardiovascular disease and diabetes). Because steroid hormones exert a potent effect on spontaneous physical activity, a decrease in activity that occurs with loss of gonadal function potentially exacerbates other factors that influence health after menopause.

In preclinical ovariectomy models, both mice and rats have accelerated rates of weight gain compared to mice and rats with intact ovaries, even when caloric intake is controlled. Additionally, following ovariectomy, animals have decreased locomotor activity (measured by wheel running). Following ovariectomy, this decline in activity recovered in animals given add-back estradiol, but not in animals without hormone replacement therapy. Estrogen replacement following ovariectomy prevents gains in weight and adiposity and shows decreases in resting metabolic rate and insulin resistance that are seen in mice that do not receive replacement therapy. Treadmill exercises may provide similar protective effects to estrogen in animal models of menopause.

In the human system, the effects of menopause are difficult to isolate from the effects of aging due to the long timeline of the MT. A temporary pharmacologic model of menopause can be mimicked using GnRH analogs, with or without estrogen add-back therapy. GnRH induces hormonal changes leading to loss of bone and lean mass and increased visceral fat deposits—effects that are prevented by estrogen replacement. Similarly, research has demonstrated that estrogen can prevent GnRH-induced declines in physical activity as measured by accelerometer, and resting energy expenditures measured with a room calorimeter. Another recent study conducted at the UC-SCORE, induced loss of

ovarian function with GnRH agonists in peri-menopausal women and randomized participants to an endurance exercise intervention. Endurance exercise did not modify decreases in lean body mass; however, this intervention did prevent the acceleration of the accumulation of fat mass, including truncal fat mass, and the decrease in energy expenditure induced by loss of gonadal function.

In summary, consistent evidence supports the critical role of estrogen in regulating energy balance. The loss of estrogens, or estrogen signaling, promotes fat gain through multiple system-level mechanisms, including decreased resting metabolic rate, decreased physical activity, and increased energy intake. Additional research is required to better understand the molecular signaling mechanisms by which the loss of estrogen during the MT induces these metabolic changes.



Special Populations

Menopause and the High-Risk Patient

(VideoCast timestamp 2:51:30 - 3:12:35)
Barbara S. Norquist, M.D. (University of Washington School of Medicine)

Dr. Norquist began by defining the patients at highest risk for the development of ovarian cancer as including patients with inherited *BRCA1* or *BRCA2* mutations, mutations of other homologous recombination genes, and gene mutations leading to Lynch syndrome. Large prospective studies have not shown a benefit to screening for ovarian cancer in reducing mortality from this lethal disease. Efforts to reduce morbidity and mortality have focused on prevention through surgical removal of at-risk organs, the fallopian tubes and ovaries. Risk-reducing salpingo-oophorectomy (RRSO) is currently recommended for cancer prevention at ages 35 to 40 for patients with

pathogenic *BRCA1* mutations who have a 4% risk of ovarian cancer by age 40, and 40% lifetime risk, and between ages 40 and 50 for patients who are carriers of *BRCA2* and other mutations associated with risk of ovarian cancer. Despite the negative health effects of surgical menopause for patients at high inherited risk for ovarian cancer, RRSO both reduces cancer risk and all-cause mortality. Unfortunately, risk-reducing surgery often occurs after the recommended ages. Multiple factors contribute to surgical delays, but for some, anxiety around menopause influences RRSO timing.

Few organizations provide specific guidelines regarding MHT for menopausal patients after an RRSO. A primary concern for using MHT among *BRCA1, BRCA2,* and other mutation carriers who have undergone risk-reducing surgery is their underlying increased risk of developing breast cancer. Although MHT increases risk of recurrence for patients with a history of breast cancer, clinical trials have been underpowered to examine subgroups of breast cancer patients with hormone receptor-negative cancers. Many patients for whom RRSO is indicated also undergo prophylactic mastectomy, influencing subsequent MHT-associated risk of breast cancer. Studies to date have been too small to differentiate whether certain formulations of MHT are associated with differential risks in high-risk patients. Extrapolating from WHI data presented earlier by Dr. Manson suggesting estrogen-alone MHT lowers breast cancer risk, some patients opt for hysterectomy along with RRSO. Following hysterectomy estrogen-alone MHT can be prescribed allowing patients to avoid the risks associated with progesterone therapy.

Accumulating research is examining the effects of RRSO and subsequent treatment for menopausal symptoms on quality of life. Preliminary data from the What Happens After Menopause? (WHAM) study has demonstrated that MHT reduces (but doesn't eliminate) VMS and improves health-related quality of life following surgical menopause. Yet, in many clinical scenarios, patients with inherited genetic mutations such as *BRCA1* and *BRCA2* have difficulty accessing prescribers due to fears among the medical community or risks associated with MHT.

Evidence from the past two decades has suggested that most ovarian cancers originate in the fallopian tubes. This has led to interest in salpingectomy rather than RRSO to reduce subsequent risk of ovarian cancer. The benefit of this cancer prevention strategy is the retention of hormonal function to the natural age of menopause. The Women choosIng Surgical Prevention (WISP) trial accrued premenopausal patients with high-risk genetic mutations to interval salpingectomy and delayed oophorectomy or RRSO. Outcome measures include sexual function and menopausal symptoms. The results of this study will add to results of a similar study performed in the Netherlands, TUBectomy With Delayed Oophorectomy in High Risk Women to Assess the Safety of Prevention (TUBA-WISP-II), that demonstrated that quality of life and sexual function remained higher with salpingectomy. Study data has not yet matured to understand the effects of salpingectomy with delayed oophorectomy on cancer outcomes.

Dr. Norquist summarized that because ovarian cancer screening is ineffective, salpingo-oophorectomy is a life-saving intervention, but one that results in surgical menopause. Even with MHT, quality of life and sexual function are not the same after RRSO. More data is needed regarding the optimal formulations, doses, and durations of therapy to mitigate these side effects.

Menopause in Women with HIV: Emerging Knowledge & Special Considerations

(VideoCast timestamp 3:12:48 - 3:30:56)
Sara Looby, Ph.D., ANP-BC, FAAN (Harvard Medical School)

Dr. Looby opened her presentation by noting the critical importance of considering social determinants of health, psychological health, and comorbid conditions when approaching patient care in general and highlighted specific considerations for treating menopause in women with HIV. Using patient narratives, Dr. Looby illustrated the difficulty some women perceive in disentangling their menopause symptoms from HIV symptoms, noting this can cause psychological distress among mid-life women with HIV. Trauma-informed, culturally appropriate patient and provider education are key to addressing menopause in women with HIV.

Women with HIV experience an earlier onset of menopause compared to women without HIV . Behavioral, lifestyle, and clinical factors (e.g., substance use disorder, history of low weight, and certain medications) as well as HIV-specific factors (e.g., immune health and adherence to antiretroviral therapy or medicines) can all influence the cessation of menses. The interplay between HIV and aging also influences the development of aging-associated comorbid conditions following menopause.

The symptoms of menopause often overlap with symptoms of HIV, leading to difficulty distinguishing them as menopausal. However, existing research confirms that the prevalence and severity of menopausal symptoms including depressive symptoms and anxiety, hot flashes that negatively impact quality of life, and urogenital symptoms, are higher among women with HIV. Despite these differences, few studies have prospectively evaluated menopausal hormone therapy in women with HIV.

Many pre-menopausal women with HIV have conditions like cardiovascular disease, bone loss, and increased fracture risk, frailty, cognitive impairment, and depression. These conditions are independently associated with aging and menopause, and they add to the effects of estrogen loss during the menopause transition. For women with HIV, reduced ovarian reserve may be associated with subclinical cardiovascular disease and increased markers of immune activation, such as soluble CD14 (sCD14). Research shows an association between hot flash frequency and higher levels of sCD14, which is a distinct biomarker of inflammation that has been associated with cardiovascular disease and other conditions in women with HIV.

Dr. Looby presented an analysis associating time since the onset of hot flashes with increased intramyocardial steatosis and decreased diastolic function. Additionally, women with HIV are at increased likelihood for osteopenia and osteoporosis due to HIV-related factors and have a higher prevalence of these indices during the menopause transition.

Social Determinants of Health

Social Determinants of Disparities in Menopause and Midlife Health: Considerations for Future Research

(VideoCast timestamp 3:30:56 - 3:51:16)
Siobán D. Harlow, Ph.D. (University of Michigan School of Public Health)

Dr. Harlow began by discussing the importance of socio-historical context in understanding health outcomes measured in the Study of Women's Health Across the Nation (SWAN) study. The women who were enrolled into the study were born between 1944 and 1954 and were raised in an environment that included laws sanctioning racial discrimination and segregation in housing, education, employment, and health care. Although structural racism was not directly measured within the study, differences in socioeconomic status, life stressors, and access to medical care were assessed. These differences led to persistent inequities for Black participants in the study, who were less likely to have a college degree and be employed, more likely to report financial strain, less likely to be married, and more likely to have children compared to White participants. As measured by the 10-item Everyday Discrimination Scale, Black participants were more likely to have experienced discrimination than White women. Additional exposures (smoking, diabetes, exposure to perfluorooctane sulfonic acid (PFOS) and other industrial chemicals) beyond life stressors associated with early menopause were also more frequently amongst Black participants. And indeed, Hispanic and Black participants in the SWAN study reached their FMP at an age earlier than women from other racial and ethnic groups, suggesting accelerated ovarian aging.

Black women reported more hot flashes during all stages of menopause compared to White women; those hot flashes were more frequent and bothersome, and experienced for an average of 3.5 years longer than White women. Chronic discrimination (more commonly experienced by Black women) was associated with increased rates of vasomotor symptoms. Sleep disturbances during the MT were also more common among Black participants in the SWAN study. Notably, Black women entered the MT with higher cardiometabolic health burden. But despite an increased severity of menopausal symptoms, Black women were half as likely than White women to use MHT.

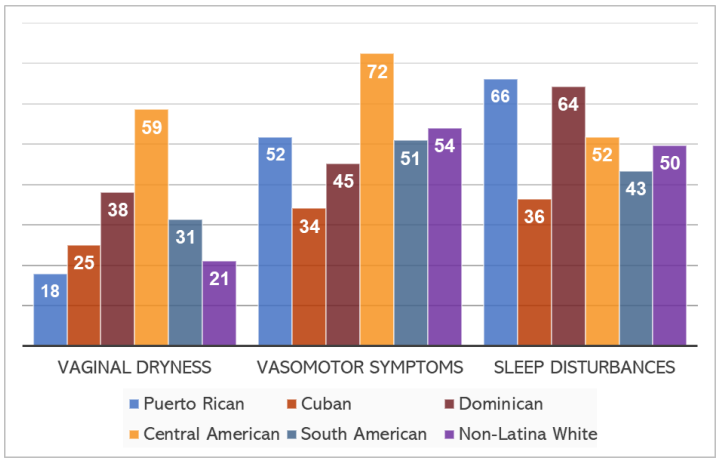
Overall, SWAN documented disparities in the timing of reproductive aging, the experience of menopausal symptoms, and the timing and burden of cardiometabolic disease for Black participants. Dr. Harlow highlighted three critical gaps in scientific knowledge about menopause that remain. First, updates to the 2011 STRAW+10 criteria to incorporate AMH as a critical marker of menopause and validated questionnaires to reliably identify the onset of early and late MT are needed. Second, more research is needed to understand the etiology, categorization, and treatment of hot flashes. Third, there is a need for an improved understanding and treatment of bleeding changes during the MT. Three quarters of the women enrolled in SWAN reported three or more episodes of prolonged bleeding and one in three reported three or more episodes of very heavy bleeding. Abnormal bleeding is associated with fatigue, but additional research is needed to understand how heavy bleeding in menopause influences risks of anemia, cognitive fog, poor sleep, and other menopausal symptoms.

Un Cambio de Vida: Experiences and Social Determinants of Menopause Among Latinas

(VideoCast timestamp 3:51:27 - 4:11:38)

Yamnia I. Cortés, Ph.D., M.P.H., FNP-BC, FAHA (University of North Carolina School of Nursing at Chapel Hill)

Dr. Cortés introduced the term Hispanic/Latina as describing a heterogeneous group population living in the U.S. who primarily identify their heritage with Spanish-speaking parts of Latin America and the Caribbean. Variations within the Hispanic population in racial identity, nationality, language, socio-historic context, and immigration policies create disparate health outcomes within Latina populations. To date, Latina women have been under accrued in menopause studies yet qualitative research has demonstrated cultural differences in how the MT is viewed. Overall, menopause is viewed positively, MHT negatively, and many Latina women report having little knowledge about menopause.



Although Latina women experience similar symptoms of menopause compared to non-Latina women, menopause occurs at a younger age and VMS have a longer duration compared to White women. Examining disaggregated health outcomes from SWAN reveals wide variations in menopause-related symptoms within Latina subgroups (Puerto Rican, Cuban, Dominican, Central American, and South American). The National Institute on Minority Health and Health Disparities (NIMHD) conceptual framework can be useful for examining the socio-cultural factors that influence menopausal health disparities within specific Latina populations.

Acculturation—the process by which individuals adapt to new living environments and adopt the values, beliefs, and norms of that society—is often used to explain differences in health outcomes between Latinas and other ethnic groups. However, acculturation is inconsistently related to menopause symptoms and outcomes. Linear or unidimensional measures of acculturation may not accurately measure the entirety of the social environment. Furthermore, the current measures of acculturation may focus on individual behaviors without accounting for social and structural variables that influence the menopausal experience. Immigration status, for example, is often used as a proxy for acculturation, but can be better viewed as a social determinant of health, as immigration status affects socioeconomic status, housing, neighborhood safety, and healthcare access. Notably, Latinas have the highest rate of uninsurance in the U.S., resulting in less access to preventive care. Depression was higher among Latina SWAN participants than other populations, and associated with uninsurance, financial hardship, and lower levels of social support. VMS in Latina SWAN participants were associated with the experience of everyday discrimination and sleep discrimination.

Specific cultural factors often limit access to care for menopausal symptoms for Latina women. U.S. health care providers often expect that patients will present symptoms and ask questions, whereas Latina patients often expect the healthcare professional to initiate a conversation. The healthcare workforce, which has limited proficiency in menopause management, may lack time during visits where language barriers may be present. Future research should be focused on how social and community contexts impact the menopause experience and outcomes. This will require recruitment of diverse populations of Latina women, examination of structural factors that influence health, increased access to culturally relevant health education, and dissemination and implementation of best practices.

Patient Advocacy Perspective

Facing Our Risk of Cancer Empowered (FORCE)

(VideoCast timestamp 4:11:38 - 4:26:38)
Susan Friedman, D.V.M (FORCE)

FORCE is a national non-profit organization for people at risk for hereditary cancers. Dr. Friedman provided her personal experience with surgical, early-onset menopause. When she was early in her career and a new mom, she was diagnosed with breast cancer and shortly after with a recurrence. She was diagnosed with a *BRCA2* mutation and at age 35, underwent risk-reducing hysterectomy and oophorectomy, which resulted in menopause. She subsequently experienced severe menopausal symptoms, including loss of libido, joint pain, weight gain, hot flashes, bone loss, and fatigue. Often and repeatedly, her symptoms were dismissed within the healthcare system. Ultimately, despite being told by multiple physicians that her history of breast cancer made her ineligible for MHT, Dr. Friedman found an oncologist willing to prescribe estrogen. For her, this was a decision about her quality of life, and restored her energy and allowed her to return to a functional and full life.

For many women with inherited risk of ovarian cancer, the choice between a potentially life-threatening malignancy and surgical menopause is terrifying. Beginning in 2007, research emerged identifying the fallopian tubes, not the ovaries, as the site of origin for most pelvic cancer. This led to the hypothesis that salpingectomy before menopause with delayed oophorectomy could provide the benefit of cancer prevention without the risks of menopause associated with RRSO. In a FORCE conducted survey in 2011, one-third of high-risk women endorsed interest in participating in a study of premenopausal salpingectomy, knowing they would need an additional surgery post menopause. The ongoing National Cancer Institute (NCI)-supported trial, A Non-Randomized Prospective Clinical Trial Comparing the Non-Inferiority of Salpingectomy to Salpingo-Oophorectomy to Reduce the Risk of Ovarian Cancer Among BRCA1 Carriers (SOROCk), is assessing the safety of this cancer prevention strategy.

Dr. Friedman noted that people at high risk for gynecologic cancer need better options for managing their risk, particularly those patients for whom hormonal therapy is contraindicated. Health care professionals should have honest conversations with patients about menopausal side effects and symptoms. Continued investment in studies like SOROCk and TUBectomy With Delayed

Oophorectomy in High Risk Women to Assess the Safety of Prevention (TUBA-WISP-II) is needed to avoid another generation of high-risk women being forced to make agonizing health care decisions.

Older Women Embracing Life (OWEL)

(VideoCast timestamp 4:26:40 - 4:38:04)
Dorcas Baker, RN, M.A., B.S.N., ACRN (OWEL)

Ms. Baker provided the history of her organization, Older Women Embracing Life (OWEL), pronounced, "Oh well." OWEL is an organized network of older women who provide support for women living with or affected by HIV. Founded in 2004, OWEL's vision is to have a community of women who are living full, productive lives despite the challenges of HIV. The OWEL mission is to plan, develop, and implement programs and projects that affect physical mental, spiritual, and emotional health for members. Members, many whom have been living with HIV for decades, build strong connections with one another as well as other community advocates, HIV service agencies, health care providers, and other key stakeholders. Ms. Baker noted that OWEL members are advocates, educators, mentors, grandmothers, preceptors, caregivers, community board members, research participants, and more. Baker reiterated the importance of including women with lived experience in research, particularly on menopause and HIV. OWEL members have experience with multimorbidity and can provide patient perspectives on conditions like diabetes, CVD, cognitive changes, COPD, chronic kidney disease, frailty, and polypharmacy. Ms. Baker shared that OWEL members embody resilience and adherence.

OWEL embraces community education by participating in multiple activities and talking about sexual health and prevention, among other topics. OWEL is involved locally, regionally, and nationally, including hosting an annual conference called "Legends and Young'uns" for 18 consecutive years. OWEL members are active participants in research studies and advocate for more research to include and examine older populations of women. OWEL participated in the Follow Your Heart Study, The Cognitive Change in Women Study, and one of its members participated in clinical trials for new HIV therapies in 1985 and 1989. OWEL has won numerous awards, including the Henrietta Lacks Memorial Award in 2018 for ongoing participation in the Checkup Study. Ms. Baker closed by emphasizing that people with HIV are living longer, more resilient lives.

The Who, When, and What of Menopausal Hormone Therapy

The Science Behind Personalizing Hormone Treatments

(VideoCast timestamp 4:51:31 - 5:14:14)
Virginia Miller, Ph.D., M.B.A (Mayo Clinic College of Medicine and Science)

Dr. Miller described that multiple physiologic forms of estrogen influence various complex functions at the cellular level following receptor binding. The non-genomic effects are typically reversible, while genomic regulatory effects can be long-lasting and alter protein synthesis, metabolism, proliferation, and other cellular functions. Oral CEE, which contains multiple forms of estrogen, are metabolized through the liver after intestinal absorption where they influence inflammatory and

clotting factors. Transdermal estrogens (17β-estradiol) are, however, absorbed directly into the systemic circulation. For those using MHT, both estrogen formulation and delivery method influence outcomes.

The KEEPS study was a multicenter, clinical trial that evaluated the effectiveness of oral CEE, at a lower dose than used in the WHI or transdermal estradiol. Both given with cyclic oral, micronized progesterone for participants with a uterus, compared to placebo, in preventing progression of CIMT. The study enrolled different patients than the WHI (all participants were within three years of FMP and otherwise healthy, as they had been screened for CVD prior to entry). The women who received transdermal estradiol had increased estradiol levels, while those who received CEE did not, but did have increased estrone levels. Despite differences in the circulating estrogen metabolites, both formulations of MHT significantly and comparably reduced menopausal symptoms of hot flashes, night sweats, and insomnia.

Within the KEEPS cohort, variability in the response to MHT was assessed. The presence of increasing numbers of genetic variants of sulfotransferases (SULTs) enzymes increase estrogen metabolism and was associated with earlier onset of menopause. Pharmacogenomic effects, the influence of genetic variant (SNP), on the outcome were also measured within patients enrolled in the KEEPS study. Differences in the SLCO1B1 transporter, which brings estrogen into the cell to begin its journey through the metabolic pathway, influenced serum concentration of estrogen and severity of night sweats. Women with the heterozygous (CT) allele had higher serum estradiol levels and more improvement in their symptoms, including greater decreases in night sweats than those with the homozygous (TT) allele. Also examined within the KEEPS cohort were brain amyloid deposition three years after completion of study interventions. Carriers of apolipoprotein E4 (APOE4) were more likely to have amyloid, a characteristic of Alzheimer's disease (AD), and with the estrogen treatment, the level of amyloid detected in the brain was lower for both estrogen formulations.

Dr. Miller addressed the challenges of using science to personalize MHT moving forward: studies to date have enrolled dissimilar populations making it difficult to generalize across studies; treatment regimens are inconsistent (i.e., type, mode of delivery, dose, duration); measurement of symptoms and outcomes measures have varied; and potential interactions among genetic variations may have influenced results. The goal of delivering the correct MHT formulation at the right dose to the right patient will depend on having a better understanding of the genetic composition of multiple enzymes involved in estrogen metabolism and the receptors. Dr. Miller ended by thanking Dr. Pinn for her contributions to the field of menopause research.

Systemic Hormone Therapy for Symptom Management in Menopausal Women: Balancing Evidence with Clinical Judgement

(VideoCast timestamp 5:14:14 - 5:35:25)
Andrew M. Kaunitz, M.D., FACOG, NCMP (University of Florida College of Medicine at Jacksonville)

Dr. Kaunitz began by discussing the tremendous drop in MHT prescriptions since the publication of the results of WHI in 2002. Concerns about the safety of MHT persist today despite the evidence that accumulated regarding the safety of MHT when prescribed for symptomatic relief to women within 10 years of their FMP. Despite a lack of randomized data comparing the benefits and risks of transdermal and oral estrogen, a large amount of observational data suggests transdermal estrogen does not impact venous thromboembolism (VTE) risk in the same way as oral estrogen. This aligns with the biologic rationale of safety through avoiding first pass metabolism and is particularly important for women with obesity, hypertriglyceridemia, or other risk factors for VTE. Similarly, no randomized trial data have compared the safety of natural progesterone compared to synthetic progestins (such as megoxyprogesterone acetate used in the WHI), but observational data suggest natural progesterone is unassociated with increased breast cancer risk. A recent case-controlled study, for example, evaluated over 43,000 breast cancer cases in the U.K. and found a relative risk (RR) of 1.28 for the development of breast cancer with MHT formulations that used progestin, compared to a RR of 0.99 with progesterone. Dr. Kaunitz suggested that providing scripts for MHT counselling might improve health care professionals' comfort in evidence-based prescribing.

In symptomatic young and/or recently menopausal women, guidance on starting doses of MHT is limited. As a result, many clinicians start with doses lower than recommended which may delay symptom resolution. After prolonged symptom resolution at a stable dose, dosages can be reduced to wean a patient off of MHT to avoid the potential adverse events associated with long-term use. The use of vaginal estrogen to relieve genitourinary syndrome of menopause can help patients lower their systemic doses of MHT if this is a bothersome symptom. For patients at high risk of osteoporosis or fractures with low risk of adverse effects of MHT, continuing MHT might be warranted. The use of intermittent progesterone for endometrial suppression can be considered for patients with progesterone associated dysphoria. For women with a uterus, abnormal bleeding should be assessed, regardless of the progesterone regimen. Regardless of the indication, dose or formulation of MHT, the risks and benefits should be individualized, evidence-based, and discussed with the patient.

Dr. Kaunitz offered potential opportunities to address unanswered questions about systemic MHT. He proposed the following studies to fill our current research gaps:

- A randomized trial comparing VTE risk with oral and transdermal estradiol
- A randomized trial comparing breast cancer risk of estrogen plus synthetic progesterone versus estrogen plus natural progesterone
- A trial of estrogen as breast cancer chemoprophylaxis in patients without a uterus with incidence and mortality endpoints
- A clinical trial of MHT starting soon after menopause and extending at least a decade to understand the potential interaction of MHT and Alzheimer's and other dementias

By supporting this research, the health of women around menopause and midlife can be improved.

Interventions to Promote Healthy Aging

The Key Ingredients for Traversing a Healthy Menopause

(VideoCast timestamp 5:35:25 - 5:57:15)
Andrea Z. LaCroix, Ph.D. (The Herbert Wertheim School of Public Health and Human Longevity Science at University of California, San Diego)

Dr. LaCroix began by discussing the recent elevation of concerns about menopause among women, and referenced a recent *New York Times* editorial article and symposium hosted by Oprah Winfrey. Dialogue concerning MHT has been primarily oriented around the WHI and Dr. LaCroix reemphasized that the WHI was not designed to study the use of MHT for menopausal symptoms but rather for preventing chronic diseases. Following the WHI results, the NIH supported the Menopause Strategies: Finding Lasting Answers for Symptoms and Health (MsFLASH) Trials to focus on identifying hormonal and nonhormonal therapies for menopausal symptoms, and to provide useful information for traversing a healthy menopause. The MsFLASH network of researchers established inclusive common eligibility criteria to target a broader population of women with bothersome menopausal symptoms (hot flashes and sleep disturbances) by including healthy women ages 40–62 years who had 14 or more hot flashes per week. These eligibility criteria were broader and more generalizable than other trials investigating interventions for VMS, as although hot flashes are common, only 2-5% of the population has seven or more hot flashes per day.

The first three MsFLASH Trials tested the efficacy of the following in reducing VMS: 1) escitalopram; 2) exercise or yoga and Omega-3; and 3) low-dose estradiol with venlafaxine. Low-dose estradiol resulted in two fewer hot flashes per day, while escitalopram and venlafaxine both reduced hot flash frequency comparably by 1.5 fewer per day. Exercise, yoga, and Omega-3 led to no significant changes in daily hot flashes. Reductions in VMS bother paralleled reductions in VMS frequency. The fourth MsFLASH trial evaluated the effect of telephone-based cognitive behavioral therapy on insomnia (CBT-I) and sleep quality. The robust intervention involved education on menopausal and age-related changes in sleep, robust sleep hygiene education, sleep restriction and stimulus control procedures, and cognitive strategies to disrupt sleep-related dysfunctional beliefs and attitudes, while patients in the control group received educational resources by phone. CBT-I improved sleep outcomes more than any other intervention, while medication (venlafaxine, escitalopram, and estradiol) and yoga and exercise provided some improvement. All MSFlash interventions led to modest, similar improvements in menopause-related quality of life as measured by the validated questionnaire, the MenQOL. Dr. LaCroix also mentioned a recent Institute for Clinical and Economic Review (ICER) that established VMS severity as clinically significantly reduced by fezolinetant (the newly FDA-approved drug for VMS).

Dr. LaCroix encouraged attendees to visit the My Menoplan website, which provides information about menopause, symptoms, treatments, a toolbox to create a personalized plan, and more. Finally, Dr. LaCroix acknowledged that mid-life women are a major market for products and services, estimated to be worth $24.4 million in 2023. Women deserve accurate, unbiased information on all available treatments. Current treatments have modest and largely similar effects on vasomotor

symptoms and menopause-related quality of life, and all women should be well informed by their clinicians about their choice in the type of medicine they take.

ORWH Research Agenda: Where We Are and Where We Need to Be

(VideoCast timestamp 5:57:23 - 6:18:37)
Robert A. Wild, M.D., Ph.D., M.P.H. (University of Oklahoma College of Medicine)

Dr. Wild introduced his history with ORWH as an advisor for the office between 1999 and 2003 and a liaison for the WHI. He also served on the WHI review committee and provided input on the study's design, warning about route, preparations, doses, messages to clinicians, and the critical importance of central adjudication of events related to study interventions. The completion of the WHI was a particularly monumental task given the research focus of the trial on women, in the historical context of exclusion of women in clinical research. Gender bias in science persists today complicating the science of how to promote healthy aging amongst women. Women's life expectancies are longer than men's, but women live with more disability. The current paradigm in aging research tends to focus on "successful agers" (i.e., older adults with health statuses like those of younger people without disability or physical illness) rather than on the majority of aging individuals (and in particular women) who live with a disability or chronic illness, but maintain good cognitive function, life satisfaction, and social engagements.

Dr. Wild emphasized understanding aging as a continuum and the confluence of multiple factors is of particular importance to women. The menopause transition is a call to action: it's the phase when chronic disease acquisition accelerates and preventative interventions may be most effective. The rapid changes in disease risk associated with a decline in estrogen during the MT justify a focus on the role of hormones to offset risks. However, focusing too much on hormonal treatments may unduly eclipse other valuable insights on prevention and treatment learned from the WHI.

Many of the medications used in the treatment of menopausal symptoms including statins, bisphosphonates, selective serotonin reuptake inhibitors (SSRIs), and MHT impact other systems beyond the target organ, yet harms related to polypharmacy are often ignored. CVD is the most common cause of death for women, but studies on CVD still often exclude women participants as well as consideration of their unique risks. Recent attention to the relationship between conditions such as pregnancy, polycystic ovary syndrome, and CVD later in life, is encouraging, but gaps in knowledge of women's unique CVD risk persist. Invasive treatment of acute coronary symptoms (ACS) is still underutilized for women in part because the symptoms that women usually present with are considered "atypical." This bias likely contributes to adverse health outcomes. Increasing rates of myocardial infarction and rising rates of comorbidities provide evidence for the need for risk assessment and preventive interventions.

Understanding targets and the role of inflammation in disease development and progression are critical components of risk assessment and prevention. An enhanced understanding of clinical (rates of spontaneous coronary dissection and hypertension) and molecular (steroid and plaque development) sex differences is needed to develop effective preventative interventions.

The role of hormones in the development of neurogenerative diseases is another area that requires additional research. While it is known that estradiol and progesterone pass through the blood-brain barrier and have receptors throughout the brain, their impact on cognition is not well understood. Estradiol regulates multiple facets of metabolism in neurons, and both estradiol and progesterone influence verbal memory, fluency, performance on spatial tasks, and fine motor skills. These and other effects (e.g., psychoactive properties) of endogenous hormones, and how they interact with lifestyle factors and influence aging remain understudied.

Dr. Wild concluded by sharing opportunities to research successful aging in women. More research using novel techniques can help us to understand the hormonal effects on end organs; sex, gender and age-based differences in disease prevention; and the interactions between behaviors such as physical activity and social factors that modify health outcomes.

Concluding Remarks

(VideoCast timestamp 6:25:22 - 6:37:16)
Vivian W. Pinn, M.D., ORWH Founding Director (Retired)

Dr. Pinn, founding director of ORWH (retired) thanked ORWH for holding the symposium in her name. As the co-director of the WHI, menopause and midlife changes for women remain of great interest. The tremendous lessons learned from the study should stay embedded in current conversations about menopause and MHT. The findings of WHI have been monumental and should not be forgotten. More funding will be needed to fully understand the sex and age-based factors that affect the mid-life health of women. It is critical to look beyond a woman's reproductive years to understand the activity and engagement of women during the postmenopausal years. Dr. Pinn expressed her appreciation to ORWH for the new initiatives, research, and opportunities that have been funded to improve the health of women. Dr. Pinn congratulated Dr. Clayton and ORWH for organizing another successful symposium and closed by saying she is thrilled to have her name attached to a wonderful event.

Appendix A. Graphic Identifier Keynote Speech: Follow-Up from WHI

Appendix B. Graphic Identifier Patient Advocacy Perspectives

Appendix C. Graphic Identifier Full Day Synthesis