MENOPAUSE 101 COURSE

Menopause Basics

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The menopause transition is a natural physiologic event that results from normal aging of the ovarian follicles. The definition and staging of menopause are important concepts as menopause needs to be understood not as a discrete event but rather most often as a gradual hormonal transition marked by declining follicular activity. This normal physiologic transition has been elegantly classified in the Stages of Reproductive Aging Workshop (STRAW, 2011) which has become the gold standard for the categorization of the reproductive phases. STRAW recognizes a reproductive continuum of 7 stages: three of these stages occur during the reproductive years (early, peak, late) and 2 occur within the menopause transition (early, late), just prior to the final menstrual period (FMP). Early and late postmenopause comprise the last 2 stages. Each stage of the STRAW system correlates to specific menstrual, endocrine and symptom characteristics. However, there are limitations to these criteria as not all women will progress predictably from one stage to the next, and STRAW cannot be used to classify reproductive aging in women who have undergone induced menopause or do not have regular menstrual bleeding. Important definitions and terms relevant to the menopause transition are: ● *Early menopause:* FMP before age 45 y ● *Late menopause:* FMP after age 54 y ● *Natural menopause*: Permanent cessation of menses because of loss of follicular activity ● *Induced menopause*: Surgical or iatrogenic loss of ovarian function ● *Perimenopause*: Stage in menopause transition characterized by irregular menstrual cycles (early perimenopause) or 2-12 months of amenorrhea (late perimenopause) ● *Postmenopause*: Defined as 12 months of amenorrhea ● *Premature menopause:* FMP before age 40 y ● *Premenopause*: Reproductive stage between menarche and onset of perimenopause ● *Primary ovarian insufficiency*: Menopause occurring at age <40 y (NAMS, 2020). Menopause will have a global impact on public health due to the sheer number of women affected. The average age of postmenopause in the US is approximately 52 years and in the US alone there are currently more than 64 million women aged 50 or older. By the year 2025, the number of postmenopausal women globally is expected to rise to 1.1 billion. Due to increasing life expectancy, many women will spend up to 40% of their lives in the postmenopause (NAMS, 2020). This will have a far-ranging impact on health and quality of life, as up to 85% of women will experience symptomatology related to this transition. Physiologically, the menopause transition is characterized by variability in both hormone secretion and ovulation. These features can lead to relatively wide swings in levels of estradiol culminating in the eventual withdrawal of estrogen from receptors in brain, bone, cardiac, urinary and vaginal tissues which will have a far-ranging impact on menopausal symptomatology over many years. These symptoms may include vasomotor and urogenital symptoms, alterations in weight, changes in sexual functioning, changes in mood and cognition and alterations in sleep as well as bone loss and cardiovascular issues. As these symptoms greatly impact daily functioning and quality of life, it is important to have clinicians knowledgeable in the clinical care of midlife women. By considering women's concerns, values, and preferences, menopause practitioners have the potential to enhance women's overall health and quality of life, both at midlife and beyond.

Ins and Outs of Hormone Therapy

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Menopausal hormone therapy (HT) is the most effective treatment for vasomotor symptoms (VMS). Although HT has other beneficial effects, including fracture risk reduction, the principal indication for systemic HT is bothersome VMS that adversely affect quality of life. Estrogen combined with a progestogen is provided for endometrial protection to women with a uterus, while estrogen alone is preferred for women without a uterus. Contraindications to HT use include breast cancer, endometrial cancer, and cardiovascular disease, including heart disease, venous thrombotic events, and stroke. The Women's Health Initiative (WHI) randomized, placebo-controlled clinical trials provide information on HT risks and benefits in approximately 27,000 menopausal women aged 50-79 years, with a mean age of 63 years. Women with a uterus received conjugated estrogens (CE) with medroxyprogesterone acetate, while women without a uterus received CE alone. The balance of risks and benefits was quite favorable for women receiving estrogen alone and for those under age 60 years or within 10 years of menopause, the years during which most women experience bothersome VMS. There was no significant increased risk of heart disease, and a slight increased risk of stroke, a rare event in this age group. Venous thrombotic events increased. Although estrogen-progestogen therapy increased breast cancer risk slightly after 4-5 years of use, there was no increased risk with short-term use of estrogen-progestogen or with use of estrogen-alone. HT initiated more than 10 years beyond menopause or in women over age 60 years was associated with greater risk. Many HT formulations are available and WHI studied only one HT formulation. Different and lower dose oral estrogens, transdermal estradiol, and different progestogens may be associated with reduced risks. Combination estrogen-progestogen products and transdermal formulations are available in a wide variety of doses allowing women to identify a convenient, preferred regimen. Non-oral estradiol administration is advised for women at higher cardiovascular risk due to the absence of first pass hepatic effect on coagulation factors. Transdermal estradiol does not increase venous thromboembolic events in observational studies. Very low doses of estrogen placed directly in the vagina effectively treat the genitourinary syndrome of menopause (GSM), including vaginal dryness, dyspareunia, and recurrent urinary tract infections. Many formulations are available, including vaginal creams, tablets, an insert, and a ring. These very low dose estrogen formulations are minimally absorbed and are not associated with systemic risks in observational studies. Long term use and use in women with contraindications to systemic HT, including women with breast cancer and cardiovascular disease, is generally acceptable. Concomitant use of a progestogen is not needed with low dose vaginal estrogen therapy. Early menopause is associated with increased risk of fracture, dementia, and cardiovascular disease in observational studies. Therefore, women experiencing early menopause, without contraindications to HT should be encouraged to use HT until the typical age of natural menopause, approximately age 51 years. For healthy women with bothersome VMS, the benefits of HT typically outweigh risks, especially for women under 60 years of age or within 10 years of the onset of menopause. The decision to use HT, including dose, formulation, and duration of use should made between a woman and her health care provider with shared decision making involving ongoing discussions of symptoms, risks, and benefits.

Midlife Weight Gain

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Weight gain is a common complaint among midlife women and more than two-thirds of midlife women in the US have overweight/obesity. Aging-related metabolic changes promote weight gain in both sexes-the basal metabolic rate falls due to loss of muscle mass and reduced activity in the brown adipose tissue. Other factors contributing to midlife weight gain include genetics, poor nutrition, and physical inactivity. Sleep disturbance and mood disorders, whether menopause-related or otherwise, can interfere with adoption of healthy lifestyle measures, promoting weight gain. The loss of ovarian hormones due to menopause, particularly estrogen, leads to altered body composition, with reduction in lean body mass, and an increase in visceral fat mass. Aging and menopause-related alterations in the gut microbiome also promote midlife weight gain. Obesity in midlife women is associated with worse vasomotor symptoms, increase in the risk of cardiometabolic conditions including type 2 diabetes, hypertension, dyslipidemia, and coronary artery disease. Obesity also increases the risk of female cancers, including breast and endometrial cancer. Obesity is associated with mood disorders and female sexual dysfunction, adding to the already significant burden of these conditions in midlife women. Given the high prevalence and serious consequences of obesity in midlife women, weight management in this population is crucial. The most important intervention is calorie restriction, with the dietary composition not playing a primary role in successful weight loss. However, specific diets like the Mediterranean diet have shown other benefits like reduction in cardiovascular risk. Intermittent fasting has been shown to be beneficial for weight loss, but data specific to midlife women are lacking. While physical activity is less effective than dietary interventions for weight loss initially, it plays a crucial role in weight maintenance and has multiple cardiometabolic effects, including lowering of blood glucose, blood pressure and insulin resistance. Behavioral modification with the goal of sustained adoption of a healthy lifestyle is an essential component of any successful weight management strategy. Medications for weight loss can be considered in clinically appropriate situations, for patients meeting the prescription thresholds. However, common issues with their use include high cost, interaction with other medications, side effects, development of tolerance and potential for long-term toxicity. Bariatric surgery is also a consideration in women with weight-related co-morbidities and those meeting the recommended weight thresholds for surgical interventions. Hormone therapy use for management of bothersome menopause symptoms can indirectly help weight management strategies by reducing the burden of menopause symptoms and facilitating the adoption of a healthier lifestyle. Even in patients who are not candidates for hormone therapy or who do not wish to use it, diligent attention should be paid to management of menopause symptoms with nonhormone strategies. Management of sleep disturbance and mood disorders is particularly crucial given their adverse impact on midlife women's weight. While hormone therapy should not be used for weight management in midlife women, when used for management of bothersome menopause symptoms, it improves body composition by redistributing the visceral fat to the lower body fat depots. Given the rise in life expectancy, women spend more than one-third of their lives in menopause. A focus on weight management with the goal of reduction in risk of obesity-related morbidities is crucial for women in this phase of their lives.

Midlife Sexuality

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Although sexual health can be considered a vital sign for overall health, lack of training, tools, time, and limited treatment options impede healthcare professionals (HCPs) from providing women with necessary medical counseling, support, and/or care for their sexual health needs and concerns. Midlife Sexuality will provide an overview of female sexual dysfunctions including hypoactive sexual desire disorder (HSDD), Female Sexual Arousal Disorder (FSAD), Female Orgasmic Disorder (FOD) and pain with sexual activity, particularly pain due to genitourinary syndrome of menopause (GSM). In addition, it will provide a model to identify sexual problems in women and provide basic management strategies, taking into account the biological, psychological, sociocultural, and interpersonal factors that may contribute to sexual dysfunction

Menopause, Mood, and Sleep

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Depression is a highly prevalent, burdensome condition that affects more than 300 million worldwide. Women are more affected by depression than men, and such increased risk is likely multi-factorial including cultural and behavioural aspects, exposure to hormonal changes and gender-related determinants of health, just to name a few. Epidemiologic

and clinical data have shown that some women may have an increased vulnerability for depression at certain reproductive stages or *windows* in their lifespan. For them, depression (new onset, recurrence), may be linked to *windows of vulnerability*, during which an increased sensitivity to hormonal changes contributes to mood symptoms and influences clinical presentation; this seems to the case, for example, for women experiencing dysphoria or irritability during luteal phases of their menstrual cycles, or depressive symptoms postpartum or during the menopausal transition. Depressive symptoms during the menopause transition are often associated with psychosocial impairment and poorer quality of life. Major depressive episodes are less common than depressive symptoms, but still occur more often during midlife years than during premenopausal or postmenopausal years. That are moderating factors for depression that seem to represent a *continuum of risk* throughout the lifespan. Poor psycho-social conditions and health-related factors are known contributors to depression and are relevant to midlife depression as well; however, a previous depressive episode remains the strongest predictor for MDD during midlife years. There are also timing or context-related factors (i.e., *window-related* factors) that mediate the occurrence of menopause-related depression. They include a heightened sensitivity to hormone variations, the occurrence/severity of sleep problems and/or vasomotor symptoms, the exacerbation of chronic medical conditions and the occurrence of stressful life events close to the menopause transition. A better understanding and proper recognition of continuum-related and window-related factors may be critical for prevention, early detection, and prompt management of midlife depression. Some women also report poor sleep during and following the menopause transition. Cross-sectional and longitudinal studies suggest that 30 to 40 % of midlife women endorse poor or disrupted sleep, including sleep fragmentation and reduced sleep efficiency. Women experiencing depression and vasomotor symptoms also report poorer sleep quality, despite the lack of objective measures of sleep disruption. Aging and health-related conditions (e.g., obesity) are also confounding factors, associated with shorter total sleep time, poor sleep efficiency, and greater sleep fragmentation. Clinicians should consider various therapeutic options while tailoring treatments for symptomatic midlife women. Antidepressants and behavioral interventions (e.g., cognitive-behavioural therapies) remain the first-line treatment for depression across the life span, including midlife years. Antidepressants should be prioritized for those who with multiple depressive episodes in the past, those reporting severe symptoms or significant functional impairment, and for patients with suicidal ideation. For recurrent episodes, a satisfactory response to an antidepressant in the past should be considered. For first episodes, treatment-naïve patients, or for those with a partial or no response to antidepressants in the past, existing evidence support the efficacy and tolerability of various SSRIs and SNRIs, including fluoxetine, sertraline, venlafaxine, citalopram, escitalopram, duloxetine, desvenlafaxine, and vortioxetine. Tolerability, safety (i.e., drug-drug interactions) and potential benefits for other menopause-related symptoms (VMS, pain, disrupted sleep) are often part of the decision-making process. Behavior-based interventions have shown to be effective not only for depression but also for the alleviation of other menopause-related concerns such as sleep problems and VMS. For those who are eligible to receive estrogen-based therapies, it is reasonable to consider a brief trial to assess the benefit of estrogen (particularly transdermal estradiol) for the improvement of VMS and concurrent depressive symptoms.

Bone Health

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Osteoporosis is a common problem among postmenopausal women, being present in 19.6% of American women aged 50 years and older in 2017-2018. The prevalence increases with advancing age. In the 2010 NHANES survey, the proportion of US women ages 50 and 59 estimated to have osteoporosis was 6.8% while that proportion was 12.3% in women aged 60-69. As a result, all menopause practitioners should be familiar with approaches to the diagnosis, assessment, and treatment of the disorder. This session will focus on recommendations in the 2021 NAMS Osteoporosis Position Statement for the evaluation and management of osteoporosis. Osteoporosis is a combination of low bone mass and abnormal bone structure due to bone loss beginning around the time of menopause. Decrease in bone density is particularly fast in the 5-10 years around the menopause transition due to loss of the protective effect of estrogen. During that rapid bone loss, the delicate structure (microarchitecture) of the skeleton is damaged, weakening the bone and predisposing to a fracture (a "bone attack"). Important risk factors for postmenopausal osteoporosis include older age, thinness, family history of osteoporosis, personal history of fracture, smoking and many diseases and medications that adversely affect the skeleton. Falls and recent fractures are additional risk factors for fracture. Screening for osteoporosis involves evaluation of all postmenopausal women who experience a fracture, accurate height measurement at regular clinic visits and targeted bone density testing. NAMS recommends DXA testing in postmenopausal women with risk factors for low bone density where knowing the result will influence clinical management including ● history of fracture since menopause ● known medical causes of bone loss or fracture ● one or more of these risk factors → body weight less than 127 lb (57.7 kg) or BMI less than 21 kg/m2 → history of hip fracture in a parent → current smoker ● age 65 years and older General measures such as good nutrition, regular physical activity and avoiding harmful habits are important measures to minimize bone loss, but these measures do not prevent the bone loss associated with menopause, do not restore bone loss that has already happened and are not adequate for the treatment of women with osteoporosis. Estrogen therapy can prevent bone loss at the time of menopause and should be considered in women in early menopause who are at high risk for osteoporosis (being thin, family history of osteoporosis or fractures, T-score <-1.5), especially if they have hot flashes that could also be benefited by estrogen. Bone density usually remains stable as long as estrogen is taken, but bone loss happens quickly when estrogen is stopped. Other osteoporosis drugs (bisphosphonates) may then be used for a few years to prevent the rapid loss that occurs if estrogen is discontinued. For women who cannot take estrogen, bisphosphonates are approved to prevent the rapid bone loss of early menopause and then, after several years, can be stopped, at least temporarily. The objective of treating women with osteoporosis is to minimize future fracture risk. Clinical evaluation and indications for therapy will be reviewed. The initial therapy will depend on the patient's current fracture risk. Raloxifene is considered in women a few years beyond menopause who no longer have hot flashes, are not yet at high risk for hip fracture and do not have risk factors for venous thrombosis. Anti-remodeling drugs (bisphosphonates and denosumab) are usually chosen for women at high risk of fracture. These treatments improve bone density modestly and reduce fracture risk by as much as 70%. However, these drugs inhibit the activity of osteoblasts (bone-forming cells). They do not rebuild the skeleton nor repair the damaged bone structure. For patients at very high fracture risk, bone-building therapies are recommended as initial treatment, followed by an anti-remodeling drug to maintain the skeletal benefits. Reducing fall risk in older patients is important. Patients with or at risk for osteoporosis can be readily identified. While osteoporosis cannot be cured, it can be prevented in most women with estrogen followed by additional therapy. Managing patients with osteoporosis is a long-term, perhaps life-long endeavor, usually involving treatment with different drugs in various sequences.

Cardiovascular Health

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The menopause transition is an ideal opportunity to assess and treat cardiovascular disease risk. While menopause does not directly cause heart disease, certain cardiovascular risk factors can shift due to the hormonal changes associated with this stage of life. It is estimated that by midlife ninety percent of women have at least one risk factor for cardiovascular disease; therefore, screening women during midlife has substantial implications for prevention. Furthermore, recognizing which cardiovascular disease risk factors are associated with ovarian aging versus chronologic aging is important for the menopause practitioner. The overall goal of Menopause 101 is to educate menopause practitioners on the evidence-based guidelines for the recognition, management, and treatment of cardiovascular disease in midlife women. This presentation will review evidence-based guidelines by the American Heart Association and the United States Preventive Services Taskforce on the use of statins and aspirin in women. Further, it will provide clinicians with tools to help identify women in the menopause transition which is an important opportunity to assess cardiovascular risk and disease prevention.

OPENING SYMPOSIUM

Epidemiology of Vasomotor Symptoms

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A majority of women will experience vasomotor symptoms (VMS) during their menopause transition with a resultant negative impact on quality of life. A smaller percentage of women will have severe symptoms that impact on their ability to function on a daily basis. About 2/3 of women will consult a clinician during their menopause transition to discuss their symptoms and whether or not treatment is appropriate. The chief driver of treatment seeking is VMS. It is estimated the VMS cause significant disruption for women in the work force. Lost wages, physician office visits, and lack of adequate treatment all contribute to the economic costs of VMS. It is estimated that women with VMS have 1.5 million more health care visits per year than those who do not experience this cardinal symptom of menopause. This level of disruption is beginning to attract attention in the UK, where the workforce is dwindling and the costs of losing productivity from midlife women who are nearing the apogee of their careers is substantial, because there is not a large pool of workers available to replace them. Discussions of workplace flexibility, increased work-from-home options, and other concessions have begun. One can only hope that the US will follow suit. VMS begin in the early menopause transition and increase in prevalence across the late transition. They peak in prevalence in the years immediately surrounding the final menstrual period and decline slowly thereafter. Longitudinal data indicate that VMS last for a median duration of 7.5 years. Women whose hot flashes appear early in the transition are more likely to have a longer duration, as are those whose VMS appear at a younger age. Social determinants of health impact significantly on the VMS experience. African-American women have the longest duration of VMS, followed by Hispanic women, White women, Japanese, and Chinese women. Early and persistent VMS are associated with a more adverse psychosocial and health profile. Moreover, early onset and persistent/frequent VMS are associated with increased carotid intimal medial thickness and decreased heart rate variability, indicating that VMS may not be benign clinical entity. A high BMI tends to be protective against VMS later in the transition and beyond. Whether treating VMS reduces later life risk for cardiometabolic disease remains unknown.

Vasomotor Symptoms Physiology: It's Hot!

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Vasomotor symptoms (VMS) are a cardinal symptom of the menopausal transition and menopause. They are characterized as a sudden onset of intense heat that is accompanied by sweating and flushing of primarily the upper body. VMS are experienced by up to 80% of menopausal and perimenopausal individuals and more than 40% of those affected characterize them as moderate to severe as well as disruptive to daily life activities. Although VMS peak around the final menstrual period, the median and average duration of frequent VMS is 7.4 and 4.5 years, respectively, and the duration of any VMS is up to 10 years after the final menstrual period. Bothersome VMS are a

common reason for which menopausal and perimenopausal U.S. women seek medical treatment. Approximately one in four women report daily VMS and an average of 4-5 hit flashes per day. Night sweats are typically described as more bothersome and life disruptive than daytime symptoms. In addition to adverse effects on quality of life, VMS are independently associated with multiple risk factor known to adversely affect cardiovascular and bone health. Individuals whose VMS begin at an earlier age tend to have a longer duration of symptoms. For example, about 50% of individuals whose VMS precede entry into the menopausal transition experience VMS for 10 years or longer after their final menstrual period. There are also disparities in the duration and severity of VMS. Individuals who identify as Black or African American are more likely to have persistent and bothersome VMS compared with other racial/ethnic groups; approximately 40% will report persistence of 10 years or longer beyond the final menstrual period. In contrast, when compared to non-Asians, individuals who identify as Asian may report a shorter duration and fewer VMS. VMS reporting also varies across different countries and cultures, with the highest reporting in the United States and Europe and the lowest in Asian countries. Socioeconomic and physical demographic findings may also affect the duration and severity of VMS. The duration of VMS may be longer in individuals with a lower educational level, greater perceived stress, more depressive symptoms, and anxiety at the time of the first report of VMS. Whereas a higher body mass index (BMI) at the time of the early menopause is associated with more VMS, a higher BMI at the time of the late menopause is associated with fewer vasomotor symptoms. Additionally, Individuals with estrogen receptor polymorphisms and selected single nucleotide polymorphisms of genes code for estrogen metabolizing enzymes may have more severe and persistent VMS. The physiological manifestation of VMS reflects the interplay of central and peripheral systems important in thermoregulation and heat dissipation and their response to hypogonadism and changing gonadal steroid levels during menopausal transition. Although menopausal hormone therapy is a highly effective treatment for VMS, some affected individuals cannot or chose not to use hormone therapy to manage bothersome symptoms. Non-hormonal regimens such as SSRI, SNRIs, gabapentin, and clonidine offer variable benefits and side effects. The development of highly effective non-hormonal therapy has been limited by a clear understanding of how reduced estrogen receptor signalling triggers VMS. Recent human and non-human studies suggest VMS are caused by aberrant activation of the tachykinin system. This new understanding of the biology of VMS may offer new opportunities for the development of novel non-hormonal therapeutic options.

Thermoregulatory Disturbance: Implications for Sleep, Alertness, and Mental Health

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The primary symptom of menopause, vasomotor symptoms (VMS) represent the clinical manifestation of the underlying thermoregulatory disturbance of menopause. While VMS may present in isolation, they are closely linked with other core symptoms of the menopause transition that also adversely impact wellbeing — including disruption of sleep, attention, and mood state. The connection between VMS and these other neuropsychological symptoms reflects the potential for indirect pathways (ie, from VMS to sleep to mood) but can also reflect parallel processes stemming directly from hormonal and/or neural mechanisms. Nonetheless, the common co-occurrence of VMS with these symptoms has implications for strategic approaches that can be implemented to improve treatment for women who are currently experiencing VMS in combination with one or more of these neuropsychological symptoms. This presentation will characterize the nature of abnormalities in sleep, attention, and mood that are closely linked with VMS, as well as the dynamic changes in female reproductive hormones and neural processes that may be driving the presentation of this highly overlapping array of neuropsychological symptoms. The talk will describe our efforts to dissect out these relationships and mechanistic pathways with the goal of informing women's understanding of their symptom experience and empowering clinicians caring for menopause-age women with strategies to optimize symptom relief and improvement of well-being.

Vasomotor Symptoms: Implications for Physical Health

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Vasomotor symptoms (VMS) are the "classic" menopause symptom, experienced by upwards of 70% of women at some point during the menopause transition. For a sizable minority of women, VMS are frequent or severe. It has long been understood that VMS have important implications for women's mental health, quality of life, and overall functioning during the menopause transition. However, newer research has underscored the potential importance of VMS to physical health. A major link emerging is between VMS and cardiovascular disease (CVD) risk in women. CVD is the leading cause of death in women. Although clinical CVD does not typically manifest until women's later years, the hallmarks of CVD are laid down earlier in life. In fact, midlife and the menopause transition are particularly important times of accelerating vascular risk in women. Evidence linking VMS and CVD risk comes from large epidemiologic cohort studies as well as clinical studies using physiologic assessments of VMS. This research shows that women with more frequent VMS have poorer CVD risk factor profiles including elevated blood pressure or hypertension, insulin resistance or diabetes, and dyslipidemia. Further, this research indicates that women with a greater burden of VMS have elevated subclinical CVD, including endothelial dysfunction and carotid atherosclerosis. Further, studies using physiologic measures of VMS and neuroimaging indicate that women with more VMS during sleep have greater white matter hyperintensities in the brain, a marker of brain small vessel disease. Moreover, more frequent or persistent VMS have also been linked to elevated risk for clinical CVD events such as myocardial infarction and stroke as women age. Associations between VMS and CVD indicators typically persist controlling for CVD risk factor profiles as well as endogenous estradiol concentrations. Although the underlying physiologic mechanisms that may link VMS to CVD risk have not been fully identified, research has considered potential autonomic nervous system, hypothalamic pituitary adrenal axis, and inflammatory mechanisms. Finally, whether VMS are causally linked to CVD and whether treating VMS may improve cardiovascular health is not yet known. However, this accumulating body of research does suggest that frequent or persistent VMS may point to midlife women at increased CVD risk. Thus, women with a high burden of VMS may particularly benefit from targeted CVD risk reduction efforts as they age.

Vasomotor Symptoms: What's New, What Works? Pharmacologic Treatment Options

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It is estimated that 25% of women will seek pharmacologic therapies for menopausal vasomotor symptoms (VMS), and consider using either hormonal or nonhormonal medications, in the form of pills, patches, mists, or gels. An evidence-based individualized approach to management is essential. A "card sort" method can assist the patient and the clinician in the prioritization of symptom management and will be demonstrated. Once VMS are determined to be a high treatment priority, the choice of a pharmacologic agent should be based on the remaining constellation of bothersome symptoms and the medical history of the patient before you. This presentation reviews the efficacy of hormonal and nonhormonal therapies, as well as their cost, with a demonstration of clinical decision trees for safe, effective, FDA approved, cost effective therapies for patients desiring pharmacologic treatments. In addition, new nonhormonal therapies that are not yet approved by the FDA deserve mention. Their development is founded on our understanding of VMS physiology controlled by the Kisspeptin, Neurokinin B, Dynorphin (KNDy) neuron complex in the hypothalamus of the brain, located directly adjacent to the thermoregulatory center. Evidence supporting potential future use of neurokinin B (NKB) antagonists comes from published results of RCTs for three distinct NKB antagonists. Two, fezolinetant and elinzanetant, remain in development and one, pavinetant, is no longer being pursued as a VMS treatment due to untoward hepatic effects. The findings from NKB antagonist trials for VMS are limited to less-definitive phase 2a and 2b studies, but all 3 NKB antagonists have demonstrated efficacy relative to placebo. Fezolinetant is a selective NKB receptor-3 antagonist and elinzanetant is a dual NKB receptor-3 and receptor-1 antagonist. Both show benefit over placebo within 2 weeks of use. The magnitude of the effect appears promising, with a statistically significant additional reduction of 2.5 to 4.0 VMS events per day over and above the reduction of VMS seen with placebo. Large, definitive phase 3 trials are completed for fezolinetant and are ongoing for elinzanetant. Results of these trials are not yet published. Initial evidence points to good safety and tolerability profiles. When given in higher doses than those used in the VMS Phase 2 trials, NKB receptor-3 antagonists appear to suppress LH, estradiol, and progesterone in premenopausal women, but this has not been studied in perimenopausal or postmenopausal women; higher doses appear to suppress LH but not estradiol in postmenopausal women with VMS. Potentially advantageous and detrimental effects on other physiologic processes have yet to be fully investigated in large populations. **References** ● Depypere H, Timmerman D, Donders G, et al. Treatment of menopausal vasomotor symptoms with fezolinetant, a neurokinin 3 receptor antagonist: a phase 2a trial. *J Clin Endocrinol Metab* 2019;104:5893-5905. ● Fraser GL, Lederman S, Waldbaum A, et al. A phase 2b, randomized, placebo-controlled, double-blind, dose-ranging study of the neurokinin 3 receptor antagonist fezolinetant for vasomotor symptoms associated with menopause. *Menopause* 2020;27:382-392. ● Fraser GL, Ramael S, Hoveyda HR, Gheyle L, Combalbert J. The NK3 receptor antagonist ESN364 suppresses sex hormones in men and women. *J Clin Endocrinol Metab* 2016:101:417-426. ● Prague JK, Roberts RE, Comninos AN, et al. Neurokinin 3 receptor antagonism as a novel treatment for menopausal hot flushes: a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet* 2017;389:1809-1820. ● Trower M, Anderson RA, Ballantyne E, Joffe H, Kerr M, Pawsey S. Effects of NT-814, a dual neurokinin 1 and 3 receptor antagonist, on vasomotor symptoms in postmenopausal women: a placebo-controlled, randomized trial. *Menopause* 2020;27:498-505.

Behavioral Treatment Options

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Several behavioral treatment options have been studied for their effects on vasomotor symptoms. These options include cognitive behavioral therapy, clinical hypnosis, mindfulness-based stress reduction, relaxation training, paced respiration, exercise, and yoga. Some of these modalities require specialized therapists and most require a high degree of motivation, time, and/or effort from symptomatic women. Knowing which therapies are likely to be the most effective can help alleviate frustration for both symptomatic women and their health care providers as they search for various vasomotor symptom treatment options. The purpose of this presentation is to review the evidence base for these behavioral treatment options to better guide treatment decision making in clinical practice. Methods, findings, strengths, and limitations of published research studies will be discussed. Based on the number and quality of research studies done to date, an overall rating of the level of evidence will be presented. Health care providers can use these ratings to guide treatment decision making. Conclusions are as follows. Level 1 evidence shows cognitive behavioral therapy and clinical hypnosis are efficacious in reducing vasomotor symptoms. Level II evidence shows mindfulness-based stress reduction and to a lesser extent relaxation training have some evidence of efficacy and may be reasonable for women to try. However, additional large-scale, randomized controlled trials with diverse participants are needed to establish Level 1

evidence for mindfulness-based stress reduction and relaxation training. In contrast, there is Level 1 evidence showing that paced respiration, exercise, and yoga are not likely to be efficacious in treating vasomotor symptoms, and therefore, should not be recommended.

PLENARY SYMPOSIUM #1

Female-Specific Risk Factors for Cardiovascular Disease

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Cardiovascular disease (CVD) is the leading cause of death of women in the United States and worldwide. Unfortunately, heart disease mortality rates have recently been increasing among young women <65 years, highlighting the critical importance of assessment of CV risk and implementation of appropriate preventive therapies. Even among traditional CVD risk factors, there can be disparity by sex. For example, smoking and diabetes confer relatively greater risks of CVD in women compared to men. Autoimmune diseases, which affect approximately 8% of the population, are more prevalent in women (~80%). Rheumatoid arthritis and systemic lupus erythematosus are associated with increased CVD risk beyond traditional CV risk factors and associated with increased prevalence of premature atherosclerosis. In addition to the disparity conferred by traditional risk factors and the excess female burden of autoimmune disease, women also experience unique risk factors throughout their lifetime related to pregnancy, hormones, and menopause that men do not experience. There is a U-shaped relationship between age at menarche with risk of coronary heart disease and stroke, with both early (<11 years) and late (≥17 years) menarche age being associated with future CVD risk. Polycystic ovary syndrome (PCOS) is the most common endocrine abnormality among women of reproductive age, affecting 5-13% of women. Women with PCOS have increased risk of cardiometabolic complications such as type 2 diabetes (T2D), increased prevalence of subclinical atherosclerosis, and increased future risk of CVD, compared to BMI-matched controls without PCOS. Spontaneous pregnancy loss, lack of breastfeeding, and grand multi-parity have also all been linked to elevated CV risks. Notably adverse pregnancy outcomes, such as gestational diabetes (GDM), small for gestational age infant, preterm delivery, and hypertensive disorders of pregnancy have all been associated with increased CV risk, even more than a decade out from index pregnancy. Gestational diabetes, which affects 1 in 10 pregnancies, is associated with an 8-fold increased risk of developing T2D and a 2-fold increased risk of future CVD. A history of GDM is associated with subclinical and clinical CVD even among women who do not develop interim T2D. Preeclampsia affects 5-8% of pregnancies, with higher rates experienced by Black women. Having a history of pregnancy with preeclampsia is associated with a 4-fold increased risk of heart failure and a 2-fold increased risk of subsequent CVD. Two out of three women who experienced pre-eclampsia will ultimately die of CVD, making this an important "red flag" for maternal CV risk. Additionally, early onset menopause before the age of 45 is associated with increased risk of future CVD. There has been increasing recognition of the impact of these female-specific factors for CVD risk. Current American Heart Association/American College of Cardiology guidelines considers a history of adverse pregnancy outcomes, early menopause, and/or autoimmune disease as "risk-enhancing" factors that would favor initiation of statin therapy for prevention among women who would be otherwise considered to be borderline or intermediate risk. A coronary artery calcium score could be considered for women over the age of 45 if additional CV risk assessment is needed to guide shared decision making about preventive therapies. Nevertheless, few clinicians outside of OB/Gyn routinely ask their female patients about their reproductive history, leading to missed opportunities for screening and preventive efforts. In sum, there are unique risk factors in women across their lifespan. Obtaining a reproductive history is important for early prevention and treatment of CVD. It is imperative that we use appropriate guideline-directed CV prevention therapy in women.

Menopause Approach in Women With Cardiovascular Disease

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Menopausal hormone therapy (HT) was widely used in the past, but with the publication of seminal primary and secondary prevention trials which reported an excess cardiovascular (CV) risk with combined estrogen-progestin, HT use declined significantly. However, over the past 20 years, much has been learned about the relationship between menopause timing, HT route of administration, and cardiovascular disease risk. While no medical societies recommend HT for prevention of cardiovascular disease, HT is recommended for the use in appropriate patients with bothersome menopausal symptoms by 5 leading medical societies. My talk will focus on caring for symptomatic menopausal women with CVD risk.

Estrogen Loss at an Early Age: Looking Back Before Moving Forward

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The cardiovascular consequences of estrogen loss after menopause have been well studied, resulting in the knowledge that the menopause transition is associated with adverse changes to cardiovascular risk factors. In 2020, the American Heart Association Scientific Statement recognized that the menopause transition is a window of opportunity for cardiovascular disease (CVD) prevention. The impact of estrogen deficiency in younger women however lacks as much attention. Premature estrogen loss in women undergoing surgical oophorectomy or natural menopause before the age of 40 years has been associated with an increased risk of CVD and CVD mortality. Early menopause (<45 years), resulting either from surgical removal of the ovaries, chemotherapy agents, or spontaneously, also increases the risk for CVD. More recently late menarche and infertility have been identified to be a female-specific risk factor that adversely affects a woman's cardiovascular risk. Consideration of reversible states of hypoestrogenemia in young women (i.e., functional hypothalamic amenorrhea) which can result in prolonged estrogen deficiency over months to years, and the cardiovascular consequences should be further evaluated. Utilizing the menstrual cycle as a reproductive vital sign will provide insight into hormonal imbalance and incorporating female-specific risk factors over a woman's lifespan is an important component of a comprehensive CVD risk assessment in midlife women.

PLENARY SYMPOSIUM #2

2022 NAMS Hormone Therapy Position Statement: Translating Guidelines to Practice

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This statement was organized and developed by The North American Menopause Society (NAMS) to update and expand the 2017 NAMS Hormone Therapy Position Statement. Hormone therapy remains the most effective treatment for vasomotor symptoms (VMS) and genitourinary syndrome of menopause (GSM) and has been shown to prevent bone loss and fracture. The risks of hormone therapy differ for women, depending on type, dose, duration of use, route of administration, timing of initiation, and whether a progestogen is needed. Treatment should be individualized using the best available evidence to maximize benefits and minimize risks, with periodic reevaluation. For women aged younger than 60 years or within 10 years of menopause onset and without contraindications, the benefit-risk ratio appears favorable for treatment of bothersome VMS and the prevention of bone loss and reduction of fracture. Longer duration may be more favorable for estrogen alone than for estrogen combined with a progestogen. For women who initiate hormone therapy more than 10 or 20 years from menopause onset or when aged 60 years or older, the benefit-risk ratio appears less favorable than for younger women because of greater absolute risks of coronary heart disease, stroke, venous thromboembolism, and dementia. For GSM symptoms not relieved with nonhormone therapies, low-dose vaginal estrogen therapy or other government-approved therapies (eg, vaginal DHEA or oral ospemifene) are recommended. Hormone therapy formulation, dose, regimen, route of administration, and the timing of initiation of therapy likely produce different effects, although these have yet to be evaluated in head-to-head randomized controlled trials. Benefits may include relief of bothersome VMS, prevention of bone loss for women at high risk and reduction of fracture, treatment of GSM, and improved sleep, well-being, and quality of life. Absolute attributable risks for women in the 50- to 59-year-old age group or within 10 years of menopause onset are low, whereas the risks of initiation of hormone therapy for women aged 60 years and older or who are further than 10 years from menopause onset appear greater, particularly for those aged 70 years and older or more than 20 years from menopause onset, with more research needed on potential risks of longer durations of use. Women with premature ovarian insufficiency and premature or early menopause have higher risks of bone loss, heart disease, and cognitive or affective disorders associated with estrogen deficiency. In observational studies, these risks appear to be mitigated if estrogen therapy is given until the average age of menopause, at which time treatment decisions should be reevaluated. In limited observational studies, women who are BRCA-positive and have undergone risk-reducing bilateral oophorectomy appear to receive similar benefits from receiving hormone therapy until the average age of menopause, with minimal to no increased risk of breast cancer. There is a paucity of randomized clinical trial data about the risks of extended duration of hormone therapy in women aged older than 60 or 65 years, although observational studies suggest a potential increased rare risk of breast cancer with increased duration of hormone therapy. It remains an individual decision in select, well-counseled women aged older than 60 or 65 years to continue therapy. There are no data to support routine discontinuation in women aged 65 years. For select survivors of breast and endometrial cancer, short-term observational data show that use of low-dose vaginal ET for those who fail nonhormone therapy for treatment of GSM appears safe and greatly improves quality of life for many. The use of systemic hormone therapy needs careful consideration for survivors of estrogen-sensitive cancers and should only be used for compelling reasons in collaboration with a woman's oncologist after failure of nonhormone therapies. Additional research is needed on the thrombotic risk of oral versus transdermal therapies (including different formulations, doses, and durations of therapy).

Hormone Therapy in Chronic Medical Conditions and Comorbidities

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Menopause symptoms are common in midlife women, and include but are not limited to vasomotor symptoms, sleep disturbance, and sexual problems, which can negatively impact quality of life. Menopause hormone therapy (HT) is the most effective treatment for the vasomotor symptoms of menopause and can be used to prevent osteoporosis, but many women go untreated. The evidence supports that for healthy women early in menopause, less than age 60 or within 10 years from their final menstrual period, that the benefits of HT typically outweigh the risks if no absolute contraindications exist. Since 80% of women over the age of 55 years have at least one chronic medical condition, decision making about initiation of HT can be more complex and requires a discussion of risk benefit balance. Outlining the state of the science for women with common chronic conditions, such as dyslipidemia, hypertension, diabetes, prior venous thromboembolism, and obesity, and how it relates to HT can be beneficial to guide clinical decision making.

Exploring the type and formulation of HT that may be most appropriate in each of these scenarios can also be helpful in informing an approach to treatment of menopause symptoms in midlife women.

Hormone Therapy for the Aging Transgender Woman

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An estimated 71% percent of transgender women use or intend to use gender affirming hormone therapy (GAHT) during their gender journeys. In a retrospective review of patients presenting to a large gender clinic, approximately 23% of patients started GAHT at age 40 or over, with 12% beginning GAHT after age 50. Given the use of GAHT in transgender women in mid-life and beyond, special considerations need be given to the impact of GAHT on mental, cardiovascular, and breast health. Multiple studies demonstrate GAHT improves psychologic outcomes and overall wellbeing in transgender persons, including older transgender women. A secondary analysis of data collected from the National Transgender Discrimination Study examined quality of life outcomes in transgender women over age 60 and found those who recently initiated GAHT reported statistically significant higher quality of life scores than their age matched peers who had not initiated GAHT. In a study examining perspectives of GAHT necessity and safety, transgender women ≥ 50 years old reported that hormone therapy was highly necessary and had low concerns about safety of GAHT. Currently there is no evidence to support the termination of GAHT in transgender patients based on age alone. Expert opinion supports shared decision making in aging transgender women using estradiol, adjusting dosing or routes of administration based on co-existing medical conditions, patient expectations, and quality of life. In most aging populations, there is concern about increased cardiovascular risk. There is a growing body of evidence regarding cardiovascular outcomes in transgender patients, though more research specific to transgender populations is needed to strengthen recommendations. In transgender patients using GAHT who have cardiovascular risk factors, literature supports transdermal estradiol as the preferred route, with studies in both cisgender women and transgender women suggesting transdermal estradiol is likely the least thrombogenic. Contemporary studies of transgender women using GAHT suggest an increase venous thromboembolism risk compared to cisgender men and cisgender women, though the absolute risk in transgender women is likely lower than previously reported. Replacement of ethinyl estradiol with 17b estradiol in gender affirming hormone regimens over the last 20 years has contributed to the improved safety profile. Multivariable analyses of cross-sectional self-reported data and retrospective cohort studies demonstrate that transgender women experience myocardial infarction at approximately two-times higher rates than cisgender women but have no statistically significant increased risk compared to cisgender men. Similar trends are suggested with ischemic stroke. The 2021 Scientific Statement from the American Heart Association proposes that the increased cardiovascular risk seen in transgender women is multifactorial, with experienced discrimination and stigma, as well as psychologic, behavioral, and clinical risk factors, contributing to overall risk. Thus, risk needs to be mitigated through behavioral changes, addressing modifiable personal risk factors, and addressing systemic issues that impact health outcomes. Current data on breast cancer risk in transgender women is limited by small sample size, lack of control of GAHT use and duration, and short follow up intervals. Cohort studies of transgender women on GAHT demonstrate mixed outcomes, with some studies suggesting breast cancer rates similar to cisgender men, and others reporting breast cancer rates higher than cisgender men, but lower than ciswomen. Due to lack of definitive data regarding risk, recommendations for breast cancer screening vary among organizations, with differences in recommended frequency (annual or biennial) and starting age (40 or 50 years old). Length of time on GAHT, personal history, and family history should be taken into consideration when choosing a screening approach.

PLENARY SYMPOSIUM #3

Psychedelics in Clinical Practice—From Stigma to Science

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Psychedelics have a long history of usage, both therapeutic and recreational, dating back over 1,000 years in indigenous societies. However, "psychedelics" is a very broad, and potentially inaccurate categorization, grouping together in one sub-class both plant-based psychedelics synthetic drugs discovered in the 20th century. In Western Cultures, the discovery of LSD in the 1940s sparked clinical interest, and a wave of research into psychedelics in the 1950s and 60s ensued. This largely ended in the 1970s, with probation taking hold in the United States, Canada and other countries. However, beginning in the 1990s and into the 2000s, a second wave of research employing the use of psychedelics began to take hold, with scientists studying their application in treating conditions such as Post-Traumatic Stress Injury, Major Depressive Disorder and Alcohol Use Disorder. The results of these studies spurred renewed interest among scientists in these and other fields. In particular, clinician scientists have been drawn to incorporating psilocybin into their programs of research by the potential for learning how we can increase the potential impact of existing treatments for patients who do not currently benefit, through a synergistic effect. In addition to mental health disorders, researchers are using psychedelic drugs in areas as diverse as existential distress at end-of-life, disordered eating, and sexual health. Publication and coverage of these emerging findings have created a strong interest among patients and families, particularly those for whom there is a paucity of current effective treatments. This presentation will summarize some of the most promising recent findings in psychedelics and human health, as well as provide insight into developments on the horizon. Finally, the presentation will provide a review of the key ethical, regulatory, scientific, and societal questions emerging for decision makers, including clinicians, regulators, patients and citizens.

PLENARY SYMPOSIUM #4

Lasers and Technology in Genitourinary Syndrome of Menopause

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While local hormone therapies are considered the gold standard treatment for genitourinary syndrome of menopause (GSM), newer energy-based devices have been used as alternatives to local treatment for patients with refractory symptoms or those who desire non-hormonal therapy. ● By participating in this activity, attendees should be able to ● List differences between laser and radiofrequency devices ● Outline short-term outcomes of CO2 and Erbium laser therapy for GSM based on prospective cohort and randomized controlled trials ● Cite reported adverse events from energy-based therapies for GSM ● Describe potential role of laser therapy for drug-delivery References: Alshiek J, Garcia B, Minassian V, Iglesia CB, Clark A, Sokol ER, Murphy M, Malik SA, Tran A, Shobeiri SA. Vaginal Energy-Based Devices. Female Pelvic Med Reconstr Surg. 2020 May;26(5):287-298. doi: 10.1097/SPV.0000000000000872. PMID: 32324684. Romero-Otero J, Lauterbach R, Aversa A, Serefoglu EC, García-Gómez B, Parnhan A, Skrodzka M, Krychman M, Reisman Y, Corona G, Lowenstein L. Radiofrequency-Based Devices for Female Genito-Urinary Indications: Position Statements From the European Society of Sexual Medicine. J Sex Med. 2020 Mar;17(3):393-399. doi: 10.1016/j.jsxm.2019.12.015. PMID: 32129169. Salvatore S, Nappi RE, Zerbinati N, et al. A 12-week treatment with fractional CO2 laser for vulvovaginal atrophy: a pilot study. *Climacteric* 2014;17(4):363–369. Sokol ER, Karram MM. An assessment of the safety and efficacy of a fractional CO2 laser system for the treatment of vulvovaginal atrophy. *Menopause* 2016;23(10):1102–1107. Cruz VL, Steiner ML, Pompei LM, et al. Randomized, double-blind, placebo-controlled clinical trial for evaluating the efficacy of fractional CO2 laser compared with topical estriol in the treatment of vaginal atrophy in postmenopausal women. *Menopause* 2018;25(1):21–28. Paraiso MFR, Ferrando CA, Sokol ER, Rardin CR, Matthews CA, Karram MM, Iglesia CB. A randomized clinical trial comparing vaginal laser therapy to vaginal estrogen therapy in women with genitourinary syndrome of menopause: The VeLVET Trial. Menopause. 2020 Jan;27(1):50-56. doi: 10.1097/GME.0000000000001416. PMID: 31574047. Li FG, Maheux-Lacroix S, Deans R, Nesbitt-Hawes E, Budden A, Nguyen K, Lim CY, Song S, McCormack L, Lyons SD, Segelov E, Abbott JA. Effect of Fractional Carbon Dioxide Laser vs Sham Treatment on Symptom Severity in Women With Postmenopausal Vaginal Symptoms: A Randomized Clinical Trial. JAMA. 2021 Oct 12;326(14):1381-1389. doi: 10.1001/jama.2021.14892. PMID: 34636862; PMCID: PMC8511979.

Probiotics and the Vaginal Microbiome: Fact or Fiction?

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The community of microbes colonizing the vagina have a profound impact on reproductive and sexual health. Communities dominated by *Lactobacillus* species are associated with lower risk for HIV acquisition, bacterial sexually transmitted infections and persistent HPV infection in premenopausal women. These associations have not been well studied in postmenopausal women. After menopause, approximately half of women lose vaginal colonization with lactobacilli, and approximately half of women have genitourinary discomfort. Currently, the most reliable strategy for promoting vaginal *Lactobacillus* colonization after menopause is treatment with estrogen. However, many providers also recommend probiotics for people with genitourinary symptoms after menopause, and there are several companies that claim such products will improve overall vaginal health. There are few data to support a link between loss of lactobacilli and genitourinary symptoms, or to demonstrate benefits from probiotic therapy in postmenopausal people. This presentation will review what is known about vaginal microbiota in postmenopausal people, their contribution to genitourinary health and whether probiotics are a reasonable strategy to improve genital and sexual wellbeing after menopause.

PLENARY SYMPOSIUM #5

Survivorship in Breast Cancer

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Breast cancer survivors compromise the largest group of cancer survivors. Advances in screening and improvements in multidisciplinary therapeutics have improved disease outcomes significantly over the last several decades with a reduction in breast cancer mortality. Further, there are a growing number of patients with metastatic breast cancer who are maintained on treatment for longer periods of time. As survival outcomes have improved for all stages of breast cancer, many individuals are living with a variety of survivorship issues that impact their physical, emotional, and overall quality of life. Breast cancer is comprised of diverse subtypes of disease that require varying management strategies. Since treatments vary significantly across subtypes, this can also pose additional complexity to survivorship management for both oncology and non-oncology professionals. The multidisciplinary management of survivorship concerns is challenging due to multiple factors including diverse populations of breast cancer

patients with unique survivorship needs, gaps in knowledge in symptom management, and coordination of care within strained healthcare systems. These three areas will be discussed with a focus on the current status of care and emerging solutions. Among the vulnerable populations of breast cancer survivors are younger women. Special concerns including life stage, early menopause, reproductive and fertility concerns. Earlier age of diagnosis can significantly impact coping and adjustment to breast cancer diagnosis as well as the toxicities they experience from treatments. On the other side of the age spectrum, older breast cancer survivors have unique concerns including maintain functional independence and balancing out potential toxicities of cancer therapies with other comorbidities throughout all phases of cancer survivorship from the time of diagnosis to end of life. Patients living with metastatic breast cancer are a growing group of cancer survivors whose survivorship needs have not been focus of many studies to date. Their needs include optimizing symptom management and improving quality of life in the setting of an incurable illness which can still be treated for several years. Additional concerted efforts are needed to ensure that survivorship care is inclusive of all patients. The second key focus area of breast cancer survivorship is optimizing symptom toxicities and developing better management strategies. There are a wide range of side effects experienced by cancer survivors including fatigue, hot flashes, genitourinary syndrome of menopause, weight gain, neuropathy, cognitive issues, and lymphedema. The prevalence and the most common strategies in management will be discussed. The third focus area will be on how survivorship care is delivered. Although we do still have gaps in knowledge, there are many evidence-based strategies that do exist, yet they are not implemented. The dissemination and uptake of survivorship care recommendation is variable in different practice settings and is one of the key challenges of breast survivorship care. Risk stratification of breast cancer survivors is one attempt to help create cost effective follow up care and reduce disparities in survivorship care. How to coordinate care across multiple specialties including close partnership with primary care and women's health experts is the focus of ongoing research. The overarching goal is to continue to advance breast cancer survivorship care by directly addressing how we can improve on the ongoing care of this largest group of cancer survivors.

Nutrition and Prevention of Breast Cancer

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Breast cancer (BC) is the most common cancer in women, excluding skin cancer, both in the United States and worldwide. It is the second most common cause of cancer death among US women. Family history and genetics are well-known BC risk factors, but they only account for 15-20% of BC cases. The World Cancer Research Fund (WCRF)/ American Institute for Cancer Research (AICR) estimates that successful lifestyle changes, including weight management, exercise, optimal nutrition, and avoiding alcohol, could reduce the incidence of BC by 33%. That is nearly 83,400 BC cases each year that could be prevented. In 2018, the WCRF/AICR third expert report updated 10 cancer prevention recommendations, half of these are specific to nutrition and alcohol. The 2020 American Cancer Society (ACS) Diet and Physical Activity Guidelines for Cancer Prevention reflects the high-quality evidence set forth by the WCRF/AICR. Current ACS recommendations highlight the following dietary evidence for BC prevention: ● A plant predominant dietary pattern that is low in animal products and refined carbohydrates reduces BC risk (2015 US Dietary Guidelines Advisory Committee) ● The Mediterranean dietary pattern lowers BC risk (Toledo 2015) ● Consumption of nonstarchy vegetables and/or vegetables rich in carotenoids may reduce the risk for estrogen receptor negative BC (WCRF/AICR 2018) ● Diets higher in calcium, including calcium-rich dairy, may reduce BC risk (WCRF/AICR 2018) ● Alcohol increases the risk of postmenopausal BC and may increase the risk of premenopausal BC (WCRF/ AICR 2018) Although methodologic challenges in dietary research exist, there are hundreds of observational studies suggesting that poor dietary habits increase BC risk and mortality. Emerging evidence suggests that a healthy compared to an unhealthy dietary pattern is associated with reduced BC risk. The 2018 WCRF/AICR CUP shows strong evidence that the Mediterranean type of dietary (MD) pattern decreases the risk of being obese, overweight, and reduces weight gain. It is known that adult weight gain and postmenopausal overweight and obesity drives BC risk. The 2018 WCRF/AICR CUP showed inconsistent evidence as to premenopausal BC prevention and MD research to date with or without alcohol; however, among 8 studies on postmenopausal BC risk there was an observed inverse association. Recently, findings from the Women's Health Initiative Dietary Modification Trial 19.6-year follow-up illuminated the power of a low-fat (20%) diet rich in vegetables, fruits, and whole grains compared to a Western Dietary pattern (>32% fat) on reducing BC mortality, overall mortality, and the risk of estrogen receptor positive / progesterone receptor negative BC. The study included almost 49,000 postmenopausal women. Pharmacologic BC risk reduction trials have never shown a reduction in BC deaths like was seen in this high-quality dietary intervention study. A 2022 systematic review and meta-analysis of prospective studies suggests that high fruit and vegetable consumption is associated with a reduced risk of BC; however, fruit juice consumption was associated with an overall increased breast cancer risk. The WCRF/AICR dose-response meta-analysis showed no consistent evidence milk causes BC. There was an inverse association observed suggesting calcium/calcium-rich dairy may reduce BC risk; however, it was non-significant. In the US, an estimated 12.1 % of female BC cases (n=115,794) and 11.3 % of female BC deaths (n=18,572) were attributable to alcohol consumption. Numerous studies have confirmed, alcohol consumption increases the risk of female BC by about 7%-10% for each 10 grams of alcohol per day. No type or quantity of alcohol beverages is less risky; therefore, there is no safe level of consumption. In addition to family history, healthcare providers must consider and council patients on nonmodifiable personal lifestyle risk factors associated with an increase in BC risk. In line with the evidence informed dietary recommendations set forth by WCRF/AICR and ACS, healthcare providers should encourage patients to eat mostly plant foods, avoid processed meat, limit sugary beverages and highly processed foods, and avoid alcohol for primary breast cancer prevention. Lastly, *"Physician Heal Thyself."* Healthcare providers should serve as effective role models and include this pattern of eating into their own life too!

PLENARY SYMPOSIUM #6

Implications of Sleep Disturbances on Health

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There is mounting evidence from basic to epidemiological studies that sleep and/ or circadian disruption increase the risk for cardiometabolic disease, mood disorders, cognitive disorders, accidents, and negatively affects quality of life. Many biological factors, lifestyle behaviors, societal and work pressures contribute to poor sleep (insufficient sleep duration, fragmented sleep, and/or sleep and circadian rhythm disorders). Sleep disturbances increase with age, and among women, there is a sharp rise in prevalence in midlife. Approximately 25%-75% of menopausal women report sleep problems, characterized by difficulty falling asleep, staying asleep and early morning awakening. The pathobiological mechanisms underlying sleep disturbances in menopause are not fully understood. Hormonal changes and associated vasomotor symptoms are associated with poor subjective sleep quality, and it is commonly thought that vasomotor symptoms cause nighttime awakenings. However, more recent data indicate that awakenings can also precede hot flashes, suggesting that physiological changes may drive hot flashes and sleep interruption in parallel. It remains unclear whether the onset of sleep problems in menopausal women is due to hormonal changes, effects of normal aging on sleep, depression, and/or the onset of sleep disorders, such as insomnia, obstructive sleep apnea, or restless legs syndrome. Symptoms of sleep disturbance should be differentiated from insomnia disorder, which is characterized by difficulty falling and or staying asleep that is accompanied by daytime impairment in functioning for at least 3 months. The prevalence of insomnia is estimated to be approximately 40% during the period of transition to menopause and after menopause. The recognition that the etiology of sleep disturbance is often multifactorial, and that in addition to hot flashes, medical disorders, medications, mood disorders, sleep disorders, and lifestyle factors should be considered. Due to the high prevalence of sleep disorders in this population, recommend screening for insomnia, sleep apnea and restless legs syndrome. In addition to the history, a sleep diary over a 2-week period can provide a more detailed assessment of sleep and wake behavior. When a diagnosis of sleep apnea, restless legs syndrome and periodic leg movements of sleep is suspected, an overnight sleep study (polysomnogram) is a useful diagnostic tool. In addition to the patient's own sleep habits, it is important to inquire about the bed partner's snoring or movements during sleep which in turn can disturb the patient's sleep. Recognizing and appropriately treating sleep disturbances and disorders represent an opportunity for improving mental and physical health and to potentially modify the risk of mood and medical disorders in late life.

Identification and Treatment of Sleep Disorders: Behavioral and Pharmacologic

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Good sleep and appropriately timed circadian rhythms promote physical, emotional, and cognitive health for people of all ages and genders. Conversely, sleep-wake disorders have detrimental impacts on these outcomes. Women in perimenopause, menopause, and postmenopause experience increased risk for specific sleep disorders. Treatment of those disorders, tailored to the menopausal transition, improves health, function, and quality of life. This talk will provide a framework for the assessment and treatment of sleep-wake disorders in women during menopause. It will begin with a brief overview of the six categories of sleep-wake disorders: Insomnias, hypersomnias, sleep-related breathing disorders, circadian rhythm sleep-wake disorders, parasomnias, and sleep-related movement disorders. Next, we will review key elements of evaluation for sleep-wake disorders, focusing on the clinical interview and exam, but also addressing the role of polysomnography (sleep studies), actigraphy, and personal health and fitness monitors. The presentation will then summarize evidence regarding the epidemiology, key symptoms, evaluation, and treatment of the major sleep disorder categories. This review will focus on features specific to women during the menopause. Treatment discussions will address behavioral, pharmacologic, and device-based approaches. We will conclude with a brief discussion of when to refer patients for more specialized care.

PLENARY SYMPOSIUM #7

The Gut-Bone Axis: How the Gut Microbiome Communicates With Bone

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In the last 10 years it has become clear that critical communications that take place between the gut microbiome and bone, which are critical for the activity the main bone regulating hormones, estrogen, PTH and glucocorticoids. In addition, gut-bone communications affect postnatal skeletal development and skeletal involution and bone metastases. Alterations in microbiota composition and host responses to the microbiota contribute to pathologic bone loss while changes in microbiota composition that prevent, or reverse, bone loss may be achieved by nutritional supplements with prebiotics and probiotics. One mechanism whereby gut microbe influence bone is through the production of metabolites that diffuse from the gut into the systemic circulation. Short

chain fatty acids (SCFAs) have emerged as key regulatory metabolites produced by the gut microbiota. SCFAs regulate both bone formation and bone resorption. They are key mediators of the bone anabolic activity of PTH and several probiotic strains. A second pivotal mechanism of communications is the migration of intestinal immune cells such as activated by the microbiome to the bone marrow. The homing of immune cells to bone is driven by chemokine gradients activated by bone remodeling or inflammation. Among these cells are Th17 cells, TNF producing T cells and NK cells. Once in the bone marrow, these cells regulate a variety of processes including bone resorption, bone formation, the development of bone metastases or fracture repair. Additional mechanism of communications relevant for the gut-bone axis are activation of the vagal nerve by bacterial particles, direct translocation of bacterial component such as LPS to distant organs, and communications between the gut and the liver, which results in the production of factors such as IGF-1, which then regulate bone.

PLENARY SYMPOSIUM #8

Race-Related Stressors and Risk factors for coronary heart disease in African-American Women at Midlife

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African-American women have strikingly high rates of coronary heart disease (CHD)-related death and disability compared to women of all other racial/ethnic groups. This excess burden has persisted for decades and is on the rise among young to middle-aged women. Further, research suggests that these racial/ethnic disparities in CHD among women are not primarily due to genetic differences, nor are they completely explained by socioeconomic status, traditional CHD risk factors, or access to care. Thus, other factors likely play a role. Several scholars have argued that the disproportionate burden of CHD observed in African-American women may be due in part to social stressors associated with being African-American and female in the United States. The current presentation will present findings from the Study of Women's Health Across the Nation (SWAN) and other cohorts of middle-aged women, documenting linkages between several social stressors patterned by race (including racism and intersectional forms of discrimination) and a range of indices of CHD risk in African-American women. Implications for CHD prevention and intervention will also be discussed.

Disparities in the Menopause Transition

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To reduce disparities in care of menopausal women and to improve culturally responsive menopausal care, increasing awareness and understanding of the unique physical, psychological and social experiences of menopausal women and how the impact of race, ethnicity, and social determinants of health influence expectations, perceptions, and attitudes about menopause is critically important. Experiences of women during the menopause transition may be influenced by the interactions and intersection of many factors: race, ethnicity, and sociodemographics. The Study of Women's Health Across the Nation (SWAN), a longitudinal study of the biological, physical, social and psychological changes in a multi-racial and ethnically diverse cohort of menopausal women, helped advance our limited understanding of racial and ethnic differences in symptoms and characteristics of the menopause transition. SWAN noted distinct differences in symptom prevalence, frequency and duration experienced by African American women compared to other racial or ethnic groups. Other studies suggest race and ethnicity may also influence menopausal women's access to healthcare services and the quality of the experiences when services are accessed. African American women may perceive symptoms differently, be less likely to discuss menopause symptoms with healthcare providers, and healthcare providers recommend menopausal therapy to African American women less often. This presentation will review and highlight available data elucidating contributors to disparities in menopause care.

PLENARY SYMPOSIUM #9

Sex and Cancer

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Due to significant advances in oncology care, the number of female cancer survivors continues to grow significantly each year. Fortunately, the majority of women and girls now diagnosed with cancer will go on to become long-term cancer survivors. However, between 60-80% of these female survivors will also face serious treatment-related sexual dysfunction. Sexual dysfunction due to cancer and cancer treatment, is one of the common and distressing side effects of cancer therapy. All major modalities of cancer treatment (e.g., surgery, chemotherapy, radiotherapy, hormonal therapy) have the potential to negatively impact various aspects of sexual function including desire, arousal, and orgasm. Other aspects of sexual health are also impacted such as sexual satisfaction and perceived body image. That is, sexual dysfunction extends across both physical (e.g., pain, genitourinary symptoms, loss of sensation) and emotional / motivational domains (loss of desire and sexual satisfaction). Girls and adolescents can face disruption of developmental milestones as well as biological challenges such as lack of physical development and premature ovarian failure. It is notable that in contrast to other side effects of treatment, sexual dysfunction does not tend to self-resolve, and it often worsens over time. Survivors who face loss or disruption of sexual function report negative impact on both quality-of-life (QOL) and psychological well-being. For example, sexual dysfunction is associated with anxiety, depression, loss of self-efficacy and self-esteem. Beyond the individual experience, sexual dysfunction can also cause distress and disruption in a relational context. Loss of sexual function can be particularly problematic for women trying to forge or maintain intimate relationships and these changes impact both survivors and partners. In addition, unmanaged sexual dysfunction is also a primary reason why female survivors do not adhere to potentially life-saving adjuvant cancer therapies. Unfortunately, there are populations of women with significant treatment-induced sexual dysfunction who continue to remain largely unacknowledged such as young adult survivors of pediatric cancer, women who are living with advanced disease and healthy women at high risk for cancer who undergo prophylactic procedures such as prophylactic bilateral oophorectomy and bilateral prophylactic mastectomy. There is now a growing consensus that sexual rehabilitation needs to encompass a biopsychosocial approach to maximize the potential for both short and long-term sexual recovery. Yet, despite the prevalence of sexual dysfunction, the majority of all female cancer survivors do not receive adequate information, support, or treatment. Research demonstrates that most oncology providers continue to lack training in this aspect of patient care, are not familiar with validated tools to efficiently identify patients with sexual problems and do not feel knowledgeable about available resources. Both patients and oncology providers report they do not want to make the other uncomfortable, often leading to a stalemate in communication. Although this topic has been taboo in the oncology space for decades, there is evidence that this may be changing. There is now increasing attention to not only developing evidence-based treatment for the physical symptoms that affect sexual function after cancer but also to building interventions that enhance couples-based intimacy, doctor-patient sexual health communication, and patient self-management skills. There are also an increasing number of cancer centers that offer some type of services to address sexual rehabilitation such as specialized counseling, menopause management and referrals to adjunctive providers such as pelvic floor physical therapy, couples counseling and sex therapy as needed.

Mindfulness and the Management of Low Desire and Vulvovaginal Pain in Women

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Rates of sexual dysfunction in women are high, and discrepant sexual desire in couples represents one of the most common causes for seeking sex therapy. For women, the uptake among the FDA and Health Canada approved sexual pharmaceuticals has been modest, and there has been a corresponding increase in people pursuing more holistic treatment approaches that address human "wellness." Mindfulness meditation, defined as present-moment, non-judgmental awareness, has become a popular tool in Western healthcare for a wide range of medical and psychological ailments, from chronic pain to anxiety to tinnitus. Since 2005, the UBC Sexual Health Research Laboratory has been developing and evaluating mindfulness-based interventions for women with low sexual desire, those with vulvovaginal pain, and several other populations across genders, and the empirical findings strongly point to a beneficial effect of mindfulness interventions on sexual function, vulvovaginal pain, mood, relationship satisfaction, and sex-related distress. In this plenary symposium, I will review the science of mindfulness as it has been applied to improving sexual response and decreasing sex-related pain in various samples of women. I will review what is known about potential mechanisms of action, and discuss newer adaptations of this mindful sex program to a digital health tool. Attendees will be encouraged to consider integrating mindful sex skills into their own clinical practices, and personal lives.

PLENARY SYMPOSIUM #10

Obesity: Pharmacologic Treatment Options

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Obesity is a chronic treatable disease. It is defined as a disease in which excess body fat has accumulated to a level that may have an adverse effect on health. The treatment of obesity reduces the risk of diabetes, sleep apnea, heart disease and cancer among many other diseases. The risk of obesity can be divided into non-modifiable or inheritance factors such as genetics, epigenetics, and familial/societal impact. Modifiable risk factors include nutrition, physical activity, stress, sleep, and concomitant medications. This presentation will focus on understanding the pillars of obesity treatment and evaluating options for anti-obesity medications (AOM). The obesity treatment pathway starts with lifestyle modifications for patients with lower health risk and is intensified to prescriptive nutritional interventions and pharmacotherapy for patients with BMI >30 or > 27 with an obesity related comorbidity. Weight loss surgery is considered in patients with a BMI >40 or >35 with an obesity related comorbidity. The weight set point and the body's own metabolic adaptation can make long term weight management challenging without the use of additional therapies. The current approved AOMs include phentermine, orlistat, phentermine/topiramate ER, naltrexone SR/bupropion SR, liraglutide and semaglutide. The choice of medication is based on insurance coverage, contraindications and/or risks, potential benefit to other comorbidities such as diabetes and patient preference. Phentermine is a central sympathetic stimulant and should be avoiding in patients with cardiovascular disease, HTN and history of anxiety. The side effects can include palpitations, tachycardia, increased BP, dry mouth, and insomnia. Phentermine/topiramate ER is a combination pill that has similar side effects as phentermine in addition to risk of kidney stones, cognitive impairment due to the addition of topiramate. Orlistat is a lipase inhibitor and reduces fat absorption. Common side effects include greasy, oily stools and less commonly fat-soluble vitamin deficiency. Naltrexone SR/

bupropion SR increases the release of alpha-MSH and decreases feedback inhibition of alpha-MSH release. It can be beneficial in treating patients with binge/emotional eating and side effects include nausea, constipation, headache, dizziness. Lastly, treatment with GLP-1 receptor agonists, including liraglutide and semaglutide, have shown to have the most significant weight loss associated with them. Common side effects including nausea, vomiting and in rare cases pancreatitis. Cost of medication and self-injection can be barriers to this class of medications.

Obesity: Behavioral Treatment Options

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Overweight and obesity affects approximately 74% of adults in the United States. Behavioral weight management programs, which use behavioral skills training to help individuals make changes in their eating and activity habits, remain a first-line and preferred treatment. As defined in the clinical guidelines for the management of overweight and obesity, effective programs are delivered by trained behavioral interventionists, over a minimum of 16 in-person sessions (ideally delivered in a group). These programs should include three key components: a reduced-calorie diet, a physical activity program, and behavior therapy. There are numerous ways of eating (eg, intermittent fasting, low-carbohydrate consumption, vegan diets, meal replacements) that all achieve the same goal of reducing caloric consumption. In terms of physical activity for weight management, 250 minutes of moderate-to-vigorous physical activity is recommended. The behavior therapy components for weight management are based in Self-Regulation Theory and Social Cognitive Theory, and typically focus on effective goal setting; daily self-monitoring of dietary intake, physical activity, and weight; feedback on this self-monitoring; and structured problem solving to overcome barriers identified during the self-monitoring process. In particular, consistent self-weighing and dietary self-monitoring are early and important predictors of who will be successful in behavioral weight management programs. Personalized feedback from the interventionist enhances weight losses, through increasing self-monitoring adherence and likely creating supportive accountability. These evidence-based in-person programs (including publicly-available interventions such as the Diabetes Prevention Program and Look AHEAD intensive lifestyle intervention) consistently produce clinically-significant weight losses of 8-10% of initial weight in adults with obesity. This degree of weight loss leads to reductions in cardiovascular disease, prevention and control of type 2 diabetes, as well as improvements in quality of life, urinary incontinence, and sleep. Unfortunately, access to these in-person programs is often restricted to individuals within driving distance of academic medical centers who can travel weekly to in-person sessions. This limitation likely exacerbates existing health disparities, as populations most at-risk for obesity (e.g., adults living in rural areas, individuals from lower socio-economic groups, shift workers, and those with caregiving responsibilities) may be least able to access evidence-based programs. Newer digital health approaches, which remotely deliver behavioral weight management interventions via the Internet and mobile devices, offer promise for expanding reach of evidence-based treatment. Early Internet-based programs that primarily provided static, text-based didactic lessons were largely not effective for promoting weight loss. However, outcomes improved as interventions added programmatic structure; interactive lessons; daily self-monitoring of dietary intake, physical activity, and weight; tailored feedback messages in response to self-monitoring data, and group sessions via videoconferencing. The use of digital tools for self-monitoring weight, dietary intake, and physical activity (e.g., smart scales which securely transmit weights, and smartphone applications and activity trackers that allow participants to easily track dietary intake and physical activity throughout the day) facilitate self-monitoring behaviors. Despite these improvements, weight losses in digital weight management interventions have lagged behind those seen in the gold-standard in-person programs, with average reductions of 5% of initial weight. Determining how to retain and optimize the "human touch" within digital weight management interventions will likely be a critical piece for enhancing these programs and encouraging health care coverage for these digital programs. In addition, it will be important to determine what supports are necessary in order to effectively imbed evidence-based behavioral weight management programs into primary care including appropriate reimbursement for clinicians.

KEYNOTE ADDRESS

The Impact of Perimenopause and Menopause on Weight Status: Through the Lens of Equity

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Obesity is a chronic disease that affects millions of Americans yearly. The impact of obesity on peri- and postmenopausal women is vast, and this cohort is known to have higher rates of severe obesity when compared with their male counterparts. Unfortunately, the high prevalence of obesity leads to higher levels of morbidity and mortality. There is a concomitant proliferation of obesity-related diseases, including but not limited to Type 2 diabetes, heart disease, obstructive sleep apnea, osteoarthritis, and several cancers. This talk will examine the epidemiology, pathophysiology, clinical assessment, and treatment of peri- and postmenopausal women with obesity. Obesity is a chronic, complex, relapsing multifactorial disease where genetics, development, behavior, and environment play pivotal roles in its development. The menopausal transition is associated with hormonal changes, which increase the propensity for central adiposity and subsequent cardiometabolic disease. We will focus on practical considerations for the clinical management of obesity to improve health outcomes in peri- and postmenopausal women.

NAMS/PFIZER WULF H UTIAN ENDOWED LECTURE

Stress and Its Effect on Cardiovascular Health

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The influence of psychological stress on the etiology and outcomes of coronary heart disease (CHD) has been studied with a number of different approaches. Current knowledge points to a "brain-heart axis" that may be especially important in specific subgroups, like individuals with pre-existing CHD and women. Women, in particular, have a higher prevalence than men of a set of psychosocial factors that have been linked to increased risk of CHD, such as depression and early life adversities. This psychosocial profile may disproportionately increase the risk of CHD among women. Emerging data suggest that young women are uniquely susceptible to the adverse cardiovascular effects psychosocial stress, which can result in earlier onset of CHD and/or more adverse prognosis if the disease is already manifest. Women, especially younger women, have benefited less than their male counterparts from recent declines in the incidence and mortality of CHD. In this presentation we will propose that psychological stress, social adversity and mental health factors play an important role in CHD risk and prognosis among women. The use of acute psychological stress provocation in the laboratory has been useful in clarifying the effects of psychological stress on cardiovascular physiology, immune function, vascular reactivity, myocardial ischemia, neurobiology and cardiovascular outcomes. Among individuals with CHD, dynamic perturbations of physiological and molecular pathways during acute stress have emerged as important in influencing cardiovascular outcomes. This approach has provided new data on sex differences, revealing a female's vulnerability to stress-related pathways related to inflammation and vascular function. These findings could also play a role in sex differences in the pathophysiology of CHD, and help explain the higher propensity to abnormal coronary vasomotion and microvascular disease which have been described in women compared with men.

NAMS/KENNETH W KLEINMAN ENDOWED LECTURE

Barriers Women Face in Academic Medicine: Are We There Yet?

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Women account for six of every ten college students and now over 50% of medical students in both allopathic and osteopathic medical schools. In OB/GYN more than 80% of residents are women yet only about a third of leadership positions in the specialty are held by women. In academic medicine overall, women are underrepresented in senior leadership positions. Women make up 41% of all faculty, however the only rank where there are more women than men is at the instructor level. Women account for only 18% of academic chairs, 18% of deans, and 25% of full professors. During this lecture we will explore some of the barriers women face in academic medicine and offer some potential solutions. Some barriers are present for everyone, and amplified for women and minorities, such as lack of mentors and role models, sense of not belonging, child rearing and aging parents. Others are particular to women (childbearing and menopause) and these critical life events frequently overlap with key periods in an academician's life (finding a job, getting promoted). Finding and supporting effective mentors, creating an inclusive environment where "others" belong and promoting the "not usual suspect" are crucial elements to increasing the numbers of women in leadership in Academic Medicine.