MENOPAUSE 101 COURSE

Menopause 101: Overview

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Menopause is a universal experience for midlife women. The average age for menopause is 51 years, although the normal age range for this transition spans over a decade. With the overall increase in life expectancy, the number of women past the age of menopause is increasing. By the year 2060, it is projected that close to 90 million women will be in the postmenopausal age range in the US. As such, it is expected that many women will spend more than 40% of their lives in menopause. Menopause is characterized by the cessation of fertility potential and important changes in hormone levels, which lead to multiple health changes, either directly or indirectly. The diagnosis of menopause is typically made clinically, and hormone testing is not required, and may in fact be unreliable during the menopause transition. The years following the final menstrual period are characterized by changes in multiple organ systems resulting in various symptoms, which can be very bothersome for some women, and significant unique long-term health risks, particularly with respect to body fat distribution, metabolic and bone health, and the risk of coronary artery disease. Given the large number of women in the postmenopausal age range in the US, and the unique health care needs of these women, there is a pressing need for education of both patients and their providers, regarding the potential symptoms of menopause, and management of these symptoms and mitigation of health risks associated with menopause. Vasomotor symptoms are the most common symptom of menopause and occur in up to three fourths of the women at some point during the menopause transition. These can be severe and disruptive to life, in about one-third of the patients who experience them. Despite that, current evidence suggests that majority of these women are not treated. Not only do untreated vasomotor symptoms contribute to impaired quality of life, they are thought to have long term health effects, including an increase in risk for cardiovascular disease and potentially osteoporosis. Even though hormone therapy is very effective for management of vasomotor symptoms and other symptoms of menopause, there has been hesitation in using it, both among the patients and providers. This is essentially based on results of the Women's Health Initiative study, that brought out concerns regarding increased cardiovascular and breast cancer risk with hormone therapy use. However, subgroup analyses of those data and newer evidence suggest that hormone therapy use is essentially safe in recently postmenopausal women. Moreover, hormone therapy use in recently postmenopausal women may, in fact, lead to multiple health benefits, including a reduced risk of diabetes, osteoporosis, all-cause mortality, and potentially reduction in the risk of coronary artery disease. In addition to hormone therapy, there are other effective prescription medications available for patients who are not candidates for hormone therapy use for any reason, although they are less efficacious than hormone therapy.

Vasomotor Symptoms 101: Hormone Therapy and Alternatives

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The most common complaint associated with menopause is that of vasomotor symptoms (VMS), affecting about 80% of menopausal women. Data from the Penn Ovarian Aging study and The Study of Women's Health Across the Nation have shown that VMS are bothersome to about 10-15% of women and never completely resolve in about 9%. Management of VMS is a shared decision based on symptom severity, personal preference, medical history and risk assessment, and treatment objectives. Treatment options may include lifestyle changes, non-FDA approved treatments including CBT, compounded hormones, and botanicals; off label use of FDA approved medications such as SSRI/SNRIs, gabapentin, oxybutynin, combined oral contraceptives, and clonidine; and FDA approved medications such as an SSRI and hormone therapy. There are risks and benefits to each of these. In addition, a number of promising and innovative therapies are being studied but are not yet approved or to market. The use of hormone therapy in menopause has been shown to be effective in the treatment of VMS in multiple studies including Utian W et al, *Fert Steril* 2001. It's use in women who have their uterus requires hormonal protection to prevent endometrial neoplasia. There are a number of medications which effectively protect the endometrium, both on and off label. The initiation and continued use of hormone therapy in menopause requires ongoing vigilance, with continued shared decision making and evaluation of risk/benefit. Discussion, medical history evaluation, as well as use of cardiovascular risk assessment tools may be useful. The route of delivery of hormone therapy may mitigate some risk as in the use of transdermal versus oral hormone therapy. Case studies are useful in decision making learning.

Genitourinary Syndrome of Menopause 101: How To Diagnose and Treat

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For an estimated 60-75% of menopausal women, genital comfort and sexual quality of life can be compromised by the signs and symptoms that accompany Genitourinary Syndrome of Menopause (GSM). GSM is a chronic progressive condition that results from depletion of estrogen in the genitourinary tissues. Signs of GSM include: dryness, pallor and loss of elasticity of the vagina, introital stenosis, atrophy of the clitoris, labia, prepuce, urethra. Vaginal dryness, burning, irritation, dysuria and dyspareunia are bothersome symptoms associated with GSM. The goal of GSM treatment is to restore comfort, maintain genitourinary and sexual function. First line GSM therapies include: use of over-the-counter vaginal lubricants which can temporarily reduce friction during sexual activity and long-acting vaginal moisturizers which can be inserted several times weekly to add long lasting moisture to the vagina. In conjunction, women may benefit from the use of vaginal dilators, which are useful to gradually increase or maintain vaginal vault size. Many women also require therapy to address shortened, painful muscles of the pelvic floor, that can preclude comfortable intercourse. In this case, women are referred for a course of pelvic floor muscle physical therapy. For symptomatic women who do not respond to first line interventions, local low-dose vaginal estrogen therapy (ET) in the form of creams, inserts, tablets, and rings have been approved for the treatment of vulvovaginal atrophy associated with GSM. These work by enhancing thickness and elasticity of genital tissue and improving vaginal blood flow. A 2016 Cochrane review reported that the efficacy of each of these formulations was similar and found no increased risk of endometrial hyperplasia with any of the local therapies. Additional evidence of the safety and efficacy associated with local estrogen therapy for GSM was suggested by a 2018 analysis. No statistical difference was found in risk for cardiovascular outcomes (including: MI, CVA, DVT, PE) or invasive cancers (including colorectal, breast, ovarian and endometrial). Despite being safe and effective options which reverse the underlying physiology of GSM, local vaginal estrogen therapies continue to be an underutilized treatment options for women who are suffering with GSM. There are additional non-estrogen alternatives approved for treatment of GSM/dyspareunia symptoms. Ospemifene, an oral selective estrogen-receptor modulator (SERM) with agonistic vaginal effects, is approved to treat moderate to severe dyspareunia associated with menopause. A dehydroepiandrosterone vaginal insert (prasterone) used daily has been approved for the same indication. Personal preference and reimbursement issues are factors in shared decision making with a woman when initiating therapy for GSM. Laser technology is an emerging technology for treatment of GSM and dyspareunia. Lasers appear to induce wound healing, stimulate collagen and elastin and restore vaginal pH. The results of a recent multicenter, randomized, trial of vaginal laser therapy vs estrogen cream for the treatment of GSM suggested that laser therapy and estrogen therapy produced similar effects in terms of patient global impression of improvement; female sexual function scores; incidence of adverse effects and in sustained efficacy at 6 months. While promising, larger, blinded, long-term, randomized, sham-controlled studies are needed to evaluate the safety and efficacy of this procedure. Cancer therapy can lead to GSM and sexual dysfunction in the millions of women survivors of cancer. Laser therapy, off-label use of local low-dose vaginal estrogen or on-label intravaginal prasterone (which has no contraindications for use with breast cancer survivors) have been proposed as potential treatment options, with decisions made in conjunction with consultation with a woman's oncologist. In summary, postmenopausal women who suffer with distressing symptoms of GSM can benefit greatly from an informed discussion of the physiologic basis of their symptoms, shared decision making regarding efficacy and safety of behavioral, nonhormonal, hormonal and laser therapy treatment options.

Bone Health 101: Diagnosis and Treatment of Osteoporosis

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Osteoporosis is a costly, major public health problem. In the US, 10 million individuals have osteoporosis and another 44 million have low bone mass placing them at risk for fractures, which can be devastating, life altering events. Roughly one in two women aged 50 years or older will suffer an osteoporotic fracture in her lifetime. Fractures are responsible for a substantial clinical burden, which for the individual includes changes to overall health and quality of life, impairments in mobility as well as social and physical functioning, and an increased risk of mortality, especially following hip and vertebral fractures. There is an increased risk of additional fractures, which is highest in the first 1–2 years following the prevalent fracture but persists for many years and can compound morbidity. Despite the significance of osteoporotic fractures, their magnitude and importance are underestimated, and osteoporosis itself remains underdiagnosed and undertreated. A comprehensive approach to diagnosing osteoporosis includes a detailed assessment of fracture risk, personal and family history, physical examination, and as appropriate, bone mineral density (BMD) assessment, vertebral fracture imaging to detect prevalent fractures, and focused studies to evaluate for secondary causes of bone fragility. While osteoporosis has classically been defined by BMD with a T-score of $\leq$-2.5 at the lumbar spine, total hip, femoral neck or 1/3 radius, BMD is not the sole determinant of fracture risk or need for treatment. Indeed, current guidelines have expanded the clinical diagnosis of osteoporosis to include not only BMD criteria, but also the following categories: low-trauma fracture of the hip or spine regardless of BMD; low trauma fracture of the proximal humerus, pelvis or distal radius in people with low bone mass (T-score between -1 and -2.5); and low bone mass (T-score between -1 and -2.5) with a 10-year-hip fracture risk $\geq$3% or a 10-year major osteoporosis-related fracture risk $\geq$20% based on the US adapted FRAX model (or TBS adjusted FRAX risks where available). Nonpharmacologic interventions to preserve bone strength are recommended as part of a treatment plan. These include adequate intake of calcium, vitamin D and protein; regular weight-bearing, muscle strengthening, and balance exercises; cessation of tobacco use and reduction of excessive alcohol intake; and falls risk assessment and prevention. Current medications build bone and/or decrease bone breakdown and dramatically reduce incident fractures. All osteoporosis agents effectively treat but do not cure the disease. Osteoporosis is therefore a chronic disease which requires long-term management if fractures are to be avoided. Even if improved or normal BMD is achieved, osteoporosis and elevated risk for fracture are still present. Current FDA-approved medications for prevention and/or treatment of osteoporosis include the antiresorptive agents: estrogen, estrogen/progestin, estrogen/bazedoxifene, estrogen agonist/antagonist (raloxifene), bisphosphonates (alendronate, ibandronate, risedronate, zoledronate), and the RANK-ligand inhibitor denosumab; and the osteoanabolic agents: teriparatide, abaloparatide, and romosozumab. Therapeutic agents should be assessed based on fracture efficacy, site(s) of fracture prevention (ie, spine, hip, and/or nonvertebral), onset of effect, magnitude of effect, duration of use parameters, and the balance of benefits and risks of therapy. Treatment should be considered in women with a hip or vertebral fracture; a fracture of the proximal humerus, pelvis or distal forearm in the setting of low bone

mass; T-score ≤-2.5 at the femoral neck, total hip, lumbar spine, or 1/3-radius; and/or low bone mass and FRAX or TBS-adjusted FRAX score above the recommended treatment threshold. The ideal initial medication is one best able to sufficiently reduce risk while accommodating a patient's needs and preferences. Most current guidelines provide guidance on the management of osteoporosis according to baseline fracture risk; patients should be risk-stratified before starting therapy. For those at very high risk, in need of skeletal rescue, starting with an anabolic agent is preferred as there is evidence that BMD and fracture outcomes are significantly influenced by the order in which medications are given.

Sexual Health 101: The Basics of Diagnosis and Treatment of Sexual Dysfunction

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Sexual problems are common in women. Despite their frequency and impact, female sexual dysfunctions (FSD)s are substantially undetected in clinical settings and often undertreated even when recognized. FSDs are chronic sexual conditions in the domains of pain and the three phases of the sexual response cycle: desire, arousal, and orgasm. Normal variations in sexual function are distinguished from FSDs by their persistence for a minimum of 6 months, occurrence with at least 75% of sexual experiences, and their association with personal distress. FSD may be lifelong or acquired and situational or generalized. Distress is experienced as bother, frustration, anger, grief, guilt, incompetence, loss, sadness, worry, or hopelessness. Personal distress can be related to the woman's own sexual problem or the potential impact on her partner and their relationship. The PRESIDE study involving 31,581 United States women aged 18-102 years found that 44% reported any sexual problem (desire, arousal, orgasm). Distressing sexual problems were reported by 12% (10% low desire; 5.5% low arousal; 4.7% orgasm difficulties) and were more common in women aged 45-64 years (14.8%) than in younger (10.8%) or older (8.9%) women. In survey data regarding symptoms related to vulvovaginal atrophy (VVA), also known as genitourinary syndrome of menopause (GSM), the prevalence of symptomatic VVA is consistently about 50%. The etiology of FSD is often multifactorial and includes biological, psychological, interpersonal, and sociocultural risk factors and contributors. The most frequently reported factors are depression, poor self-assessed health, anxiety, low educational level, partner sexual problems, sexual abuse, marital difficulties, stress, antidepressants, poor health, cancer, urinary incontinence, and chronic diseases such as diabetes, neurological diseases, and pain. A biopsychosocial assessment is vital for identifying potentially modifiable factors and guiding multi-faceted interventions. Screening is best initiated by a universalizing and normalizing ubiquity statement followed by an open-ended inquiry. All phases of the sexual response cycle and sexual pain should be evaluated. Self-administered questionnaires include the Decreased Sexual Desire Screener; the Sexual Distress Scale-Revised; and the Female Sexual Function Index (FSFI), a well validated instrument that assesses six domains and has an established cut-off score of 26.55 for FSD. Assessment of vaginal and vulvar pain should include an examination to identify potential causes or contributing factors, including infectious, inflammatory, neoplastic, neurologic, traumatic, iatrogenic, and hormonal factors. A pelvic exam including a vulvovaginal exam is important for women complaining of pelvic pain. Laboratory tests such as thyroid function and prolactin may be indicated based on the clinical presentation. A baseline total testosterone and SHBG should be obtained with subsequent monitoring if testosterone is prescribed. The clinician may initiate an array of interventions. Empathic delineation may be therapeutic and help the woman to start solving the problem. Providing education may entail explaining the sexual side effects of a medication, changes in sexual function related to menopause and/or aging, and the importance of foreplay/non-penetrative sexual activities. Clinicians may recommend personal lubricants, moisturizers, and/or vibrators and prescribe low dose local hormone therapy and ospemifene for dyspareunia related to GSM. Pharmacotherapy includes the use of flibanserin and bremelanotide for generalized, acquired HSDD in premenopausal women and off label, evidenced-based transdermal testosterone in postmenopausal women with HSDD. Assessing the patient's ability to talk to their partner(s) about sexual function and experiences and coaching about better communication are important and effective interventions. Sexual health problems often require a multidisciplinary treatment team. FSDs that are predominantly due to psychological, interpersonal, or sociocultural factors are best treated by a mental health provider. Non-pharmacologic treatments include use FDA cleared devices such as laser and the integration of sex therapy and/or pelvic floor physical therapy.

Mood and Cognition 101: What's Normal and What's Not?

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The perimenopause and early postmenopausal years are a particularly vulnerable time for women marked by drastic fluctuations in sex hormones. In addition to the physical changes and associated symptoms, this transition is often accompanied by the occurrence of significant life stressors and changes in personal, family, and professional responsibilities. Together these factors may lead to an increased risk for the poor mental health as well as changes in cognitive function. A growing body of literature has suggested that, for some women, the perimenopause and the early postmenopausal years are associated with an increased risk of experiencing symptoms of depression and the development of an episode of major depressive disorder. Further, studies have highlighted that there is an increased risk for depression following hysterectomy, with or without oophorectomy. A history of primary ovarian insufficiency is also associated with an increased risk of depression. In addition, cognitive symptoms, such as worsening memory and slower cognitive speed, are often reported among newly menopausal women, as demonstrated in prospective, longitudinal studies. First line treatment options for depressive symptoms include antidepressant medications, cognitive behavioural therapy, and other behaviour-based psychotherapies. For women experiencing a new onset of depression, both side effects (eg, sexual dysfunction, weight changes) and drug-drug interactions specific to this population should be considered. Some evidence exists that estrogen containing hormone therapies have antidepressant effects when administered to perimenopausal women with depression, with or without concomitant vasomotor symptoms. However, it has not been shown to be effective in treating depressive disorders in postmenopausal women, suggesting a possible window of opportunity. For women with cognitive complaints, lifestyle modifications are recommended to decrease the risk of cognitive decline. These include increasing aerobic exercise and including vegetables in the diet more often, as well as limiting the potential influence of hypertension, diabetes, and atherosclerotic disease. Menopausal hormone therapy has not been shown to significantly improve measures of cognitive function over several years of use. An approach to assessment and initial treatment for mood changes and cognitive complaints will be discussed.

PRE-MEETING SYMPOSIUM

2020 AHA Statement on Menopause and CVD Risk

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Cardiovascular disease (CVD) is the leading cause of death in women, yet only 56% of women are aware of this fact. Women develop coronary heart disease (CHD) several years later than men, with a notable increase in CHD risk during midlife, a period coinciding with the menopause transition (MT). This observation led to the hypothesis that the MT contributes to the increase in CVD risk. In 2020, the AHA published the first scientific statement discussing the contemporary literature on menopause and CVD risk with the intent of increasing awareness of the significant adverse cardiometabolic health-related changes accompanying midlife and the MT. This presentation will provide an overview of important data presented in the recent AHA statement on menopause and CVD as outlined in this abstract. Reproductive aging includes 7 stages, yet not all women experience each of these 7 stages. Moreover, the duration of each of these stages varies between women, and each stage is characterized by variable changes in the menstruation pattern, hormonal levels, and menopause-related symptomatology, underscoring the complexity of studying the MT and its potential for health-related sequelae. Several MT characteristics beyond the dynamic hormonal alterations are linked to CVD risk. These include age at menopause, type of menopause, menopause stages, and menopause-related symptoms. Earlier age at menopause and iatrogenically induced menopause during the premenopausal period are both associated with higher CVD risk. The perimenopause stage begins with the onset of intermenstrual cycle irregularities or other menopause-related symptoms is identified as a stage of vulnerability accompanied by significant adverse alterations in several cardiometabolic and vascular health parameters strongly linked to higher CVD risk. Further, menopause-related symptoms including vasomotor symptoms, sleep disturbance and depression have all been associated with greater CVD risk. By following women over the MT, researchers have been able to disentangle chronological and ovarian aging with respect to CVD risk. Researchers have documented adverse alterations in body composition, lipids and lipoproteins, and measures of vascular health that are more driven by the MT independent of chronological aging. The reported findings underline the significance of the MT as a time of accelerating CVD risk, thereby emphasizing the importance of monitoring women's health during midlife. The AHA operationalizes cardiovascular health (referred to as Life's Simple 7) as ideal, intermediate, or poor according to 7 core health indicators: body mass index (BMI), physical activity, smoking, diet, cholesterol, blood pressure, and fasting glucose. Data characterizing the current status of Life's Simple 7 in women transitioning through menopause are limited and indicating poor cardiovascular health status in these women. Very limited data suggest that a multidimensional lifestyle intervention can prevent weight gain while reducing triglycerides, blood pressure, and blood glucose, insulin, and subclinical carotid atherosclerosis, among women undergoing the MT. The menopause hormone therapy (MHT) is an effective option to treat menopause symptomatology. Whether MHT could also reduce CVD risk associated with the MT has been a research question for many decades. The current literature supports a critical role for the time of initiation of MHT use relative to menopause, with initiation at <60 years of age or within 10 years of menopause appearing to be associated with reduced CVD risk. To better assist health practitioners and to reduce the burden of CVD while improving quality of life in women transition through menopause, future studies should make a conscious effort to include or to focus on women who are undergoing the MT. Research assessing MHT use, including potential contrasts by form, route, and duration of administration, on cardiometabolic effects in women traversing menopause is critically needed.

CVD Symptoms and Novel Risk Factors for CVD in Women

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Cardiovascular disease is the leading cause of death among women, and accounts for 1 in every 4 female deaths in the United States. Women and men exhibit clear differences in the risk factors, clinical presentation, and outcomes of cardiovascular disease (CVD). Among the most prominent sex-specific risk factors for women are those related to pregnancy commonly referred to as adverse pregnancy outcomes (APOs) and hormonal changes in women such as menopause transition and premature or early menopause. APOs include hypertensive disorders of pregnancy (HDP), such as gestational hypertension and preeclampsia, low birth weight, gestational diabetes. Sondergaard, et al, in a large multiethnic cohort of women from the Women's Health Initiative demonstrated that HDP and low birth weight independently predict future CVD in women after adjustment for established risk factors and other APOs. It remains unknown whether women with

APOs have a pre-existing subclinical vascular condition that is simply unmasked during pregnancy that increases their CVD risk, or whether APOs result in de novo vascular endothelial damage that results in subsequent CVD. In a cohort of women with evidence of ischemia and no obstructive coronary disease, we found that women with APOs had abnormally low microvascular coronary flow reserve up to 30 years after the index pregnancy, raising the hypothesis that the APOs may be related to dysfunction of the microvasculature. Further, the menopause transition has been consistently described as a time of accelerated CVD risk in women, due to alterations in endogenous sex hormones and adverse changes in body fat distribution, lipids, and vascular health. Women with premature (before age 40) or early menopause (age 40 to 45 years) have substantially increased risk of CVD. Early loss of oestrogen is thought to impair vascular function and increase the expression of inflammatory markers. In addition, there are significant difference in the clinical presentation of CVD; the VIRGO (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients) study demonstrated that women with ST elevation myocardial infarction were more likely than men to present without chest pain (odds ratio, 1.51; 95% confidence interval, 1.03–2.22). Women were also more likely to present with ≥3 associated symptoms than men (91.9% vs. 54.8%, $p<0.001$) which included epigastric symptoms, palpitations, and pain or discomfort in the jaw, neck, arms, or between the shoulder blades. Increase in acute myocardial infarction mortality rates in women are potentially modifiable through improved education on women specific risk factors and clinical presentation and guideline-driven care in women to reduce provider bias.

Lipids and Blood Pressure and Menopause, OH MY! Where to Start, What to Recommend

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Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality for women in the United States and worldwide. There has been no American College of Cardiology (ACC)/American Heart Association guideline update specifically for the prevention of CVD in women since 2011. Since then, the body of sex-specific data has grown, in addition to updated hypertension, cholesterol, diabetes, atrial fibrillation, and primary prevention guidelines. The ACC CVD in Women Committee undertook a review of the recent guidelines and major studies to summarize recommendations pertinent to women. In this update, co-author Dr. Margo Minissian addresses special topics, particularly the risk factors and treatments that have led to some controversies and confusion. Specifically, sex-related risk factors hypertension and hyperlipidemia.

Medical Management of Obesity

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The most recent CDC epidemiologic data shows that 42.4% of adults in the United States age 20 and greater are considered obese as defined by BMI or body mass index of 30 or greater and nearly 10% are considered morbidly obese, as defined by a BMI of 40 or greater. Obesity is associated with numerous medical conditions including but not limited to cardiovascular disease, end stage renal disease, diabetes, breast and colon cancer, cirrhotic liver disease, infertility, depression resulting in significant individual morbidity, and cost to the healthcare system. Given the pathophysiology of obesity which includes dysregulation of satiety hormones and therefore appetite, obesity has been recognized as a disease by the American Medical Association in 2013. Despite this designation and the fact that anti-obesity therapies exist, healthcare professionals infrequently counsel patients nor prescribe medications for weight loss. In fact, Veteran's Health Administration showed that only 0.2% of over 2 million patients who met NIH criteria for consideration of a weight loss medication filled a prescription for one of these agents and similar data exist in regards to bariatric or weight loss surgery. Multiple barriers are cited in the medical literature for this disconnect including healthcare professional attitudes and bias towards obese individuals, lack of comfort or familiarity with treatment options, as well as a lack of faith in their efficacy. This presentation will provide an overview of the available treatment strategies for overweight and obesity to include behavioral modification, pharmacal therapy, and surgical therapies for weight loss.

Cardiodiabetology: How Do We Optimize CVD Risk?

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Diabetes is a highly prevalent condition, affecting more than 450 million people worldwide. Of these, type 2 diabetes (T2D) constitutes 90-95% of cases. The etiology and pathophysiology of T2D involve the progressive decline in pancreatic beta-cell function and insulin secretion, often related to insulin resistance. In addition to microvascular complications, elevated risks of macrovascular outcomes (coronary heart disease, stroke, heart failure, peripheral vascular disease, and other forms of cardiovascular disease [CVD]) are well documented. The prevalence of atherosclerotic CVD is 2-3 times higher in patients with, compared to those without, T2D and the relative risks may be particularly high in women. Goals of T2D management include not only achieving glycemic targets such as a HbA1c below 6.5% or 7.0% (with individualization according to comorbidities, risks of hypoglycemia, and personal preferences of the patient) and reducing microvascular risks but also reducing CVD risk. In recent years, new classes of glucose-lowering drugs have become available and have been tested for CVD outcomes reduction, with promising findings. Although lifestyle modifications (diet and physical activity) and initial pharmacologic management with metformin remain the "standard of care," many patients with established CVD (as well as other selected patients at high CVD risk) will benefit from the addition of a glucose-lowering medication with demonstrated CVD benefit. Such medications include specific agents from the glucagon-like peptide-1 (GLP-1) receptor agonist or sodium–glucose cotransporter type 2 (SGLT2) inhibitor classes. For T2D patients with a history of heart failure with reduced ejection fraction or chronic kidney disease, SGLT2 inhibitors are recommended due to their documented benefits for these purposes. For patients with obesity and weight-loss prioritization, a GLP-1 receptor agonist would have advantages, given greater average weight loss with these agents. Another factor that guides the choice of agent is patient preference regarding route of administration and frequency, but either class should facilitate achieving glycemic targets. Frequent follow-up of patients for reassessment and monitoring of glycemic control and CVD risk factors, as well as behavioral/lifestyle counselling, will be essential for optimal management.

Ischemia with No Obstructive Coronary Artery Disease

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Patients with chest pain who have evidence of myocardial ischemia on stress testing usually undergo coronary angiography to evaluate for obstructive coronary artery lesions. However, a large proportion of patients suspected of having ischemic heart disease are found to have no obstructive coronary artery disease (INOCA), a finding that is more prevalent in women. Cardiovascular disease risk factors such as hypertension, diabetes, smoking, inflammation, etc. contribute to INOCA, which is a diagnosis that is associated with major adverse cardiovascular events, such as myocardial infarction and heart failure. Coronary vascular dysfunction is implicated as a major pathophysiologic mechanism contributing to adverse events in INOCA. This includes dysfunction in the larger epicardial vessels as well as coronary microvascular dysfunction. Invasive coronary function testing can help diagnose abnormal coronary vascular reactivity and impairment in microcirculatory flow. Women may be more susceptible to coronary endothelial dysfunction due to mechanistic factors such as inflammation, autonomic dysfunction, and neuro-endocrine disruption, as well as mental stress susceptibility. Therapies that target cardiac risk factors, atherosclerosis, and angina are used to manage INOCA, although it remains underdiagnosed and undertreated.

PLENARY SYMPOSIUM #1

KNDy Neurons and Female Hormone Regulation of Hot Flashes and Sleep Disturbance

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Hormone fluctuations experienced during menopause are associated with both vasomotor symptoms and also sleep disturbances. My lab investigates the neurons, circuits and signaling molecules in the brain that are involved in menopausal hot flushes and sleep disturbances. At the heart of our work lies a population of estrogen-sensing kisspeptin neurons that are functionally and anatomically conserved in mammalian females, from rodents to humans. These neurons are part of the reproductive hypothalamic-pituitary axis, and are coined for the signature expression of genes that encode: kisspeptin, neurokinin B and dynorphin (KNDy). KNDy neurons are robustly activated under low estrogen conditions, such as menopause, and play a critical role in fertility via input to GnRH neurons of the reproductive axis. We are interested in the elaborate pattern of axonal projections from KNDy neurons, which extend to many postsynaptic targets aside from GnRH. KNDy projections suggest that they may disseminate estrogen status beyond the reproductive axis. Using the power of mouse genetics and modern tools in neuroscience, we can artificially manipulate KNDy neurons to understand their functional significance. Based on both the expression of neurokinin B and also projections to the preoptic area of the hypothalamus, it was proposed that KNDy neurons may be involved in menopausal vasomotor hot flushes. To test this hypothesis, we used a combination of optogenetic and chemogenetic techniques to artificially activate KNDy neurons in mice. Acute stimulation of KNDy neurons was sufficient to evoke a flush (rise in skin temperature and drop in core temperature). KNDy-evoked flushes were robustly diminished by the infusing a pharmacological blockade against neurokinin B into the preoptic area. This work was the first to demonstrate a role for KNDy neurons outside of their canonical role in the neuroendocrine reproductive axis. Because KNDy neurons project broadly throughout the hypothalamus and beyond, we believe that they have to potential to mediate a broad range of behavioral and physiological outcomes in response to fluctuations in estrogen and progesterone. We are currently working to determine whether KNDy neurons play a role in the dynamic regulation of skin temperature that occurs when transitioning from a wake to sleep state and whether this transition is influenced by steroid hormone status.

Stress and HPA–Axis Dysregulation in Hot Flashes and Menopausal Sleep Disturbance

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Sleep disturbances and hot flashes are common symptoms of the menopausal transition and have a major impact on quality of life, mood, productivity, and physical health, particularly in women who suffer severe and persistent symptoms. An underlying factor that can exacerbate sleep problems and hot flashes is stress. Indeed, abnormalities in the stress response systems are hypothesized to reflect an underlying biological mechanism for the development of insomnia, and chronic stressful life events predict poorer sleep quality in midlife women. Also, stress can act as a trigger for hot flashes in midlife women. To investigate these relationships further, we and others have used experimental stress paradigms to determine effects of stress on night-time sleep and autonomic nervous system functioning as well as cortisol levels and hot flashes in perimenopausal women. Findings show that anticipation of stress before sleep, compared with a control night, increased pre-sleep salivary cortisol levels, perceived tension, and heart rate, and lowered

vagal activity in perimenopausal women with and without insomnia. Stress anticipation effects on vagal activity extended into the first few hours of sleep, and even longer for women with insomnia, suggesting a greater sensitivity to stress in this group. Anticipation of stress did not increase the frequency of physiological hot flashes during the night, however, during an acute experimental psychosocial stress procedure in the morning, one third of women experienced a hot flash. Findings about physiological HPA-axis and cardiovascular reactivity to acute experimental stress in midlife women with insomnia are ambiguous, with some indicating blunted cardiovascular responses, and others showing no difference compared with controls. Further study is needed, considering factors like menopausal stage, history of chronic stress, and comorbid symptoms like depression, to establish whether insomnia that develops in the context of menopause is characterized by altered stress reactivity either as a pre-existing factor or as a consequence of insomnia, which could potentially be an important factor in the etiology of the disorder. Clinical trials that have investigated efficacy of relaxation techniques for alleviating menopausal symptoms have produced mixed findings, however, a recent study showed that a combined program of relaxation and stress management reduced stress, and improved sleep and psychological symptoms in a group of peri- and postmenopausal women. Further, clinical trials of cognitive behavioral therapy for insomnia in midlife women have shown consistent improvements in sleep and hot flash related interference. These findings show non-pharmacological therapies tailored for midlife women are effective for the management of menopausal-related sleep disturbances.

Downstream Effects of Menopause-related Sleep Interruption on Mood State and Metabolism

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Sleep interruption is highly prevalent in women across and after the menopause transition, affecting half of women in midlife. Menopausal sleep disturbance is characterized by repeated middle-of-the-night interruption with brief awakenings as well as sleep fragmentation with multiple sleep stage transitions and cortical arousal, which together translate to diminished sleep consolidation and less refreshing sleep. Nighttime hot flashes (or night sweats) are the primary cause of this sleep interruption. However, other mechanisms also disrupt sleep in some midlife women — including changes in gonadal steroids, the wake-promoting neuropeptide orexin, sleep apnea, periodic limb movement, stress, depression, anxiety, and environmental stimuli. While shortening of total sleep hours is known to adversely affect health outcomes, the impact on health of the menopause-pattern of interrupted sleep occurring within a normal total sleep duration is less well understood. Accumulating experimental data in humans show that menopause-pattern sleep interruption has adversely consequences on metabolic health, daytime wellbeing, and mental health. Each of these adverse effects represents a common health problem that is strongly linked with menopause. Metabolic changes involving reduction in use of fats as a nutrient may lead to body fat gain that is common as women traverse menopause. This specific type of disrupted sleep reduced sleep quality and increases daytime sleepiness, which may affect neurocognitive function. Disruption of mental health includes diminution of positive affect, heightening of negative affect, and increases in depressive symptoms. Demonstration that disrupted sleep adversely affects metabolic and neuropsychological wellbeing provides evidence that sleep is causally linked with these health changes. While the mechanisms through which these effects may occur are not fully understood, changes in cortisol suggest that perturbation of the hypothalamic-pituitary-adrenal axis may contribute to adverse health consequences of menopause-pattern sleep interruption. Other explanatory pathways are under active investigation. Taken together, this accumulating evidence highlights the central role of menopause-related sleep disruption as a highly modifiable target for health interventions in the pathway to improve the health of aging women. Our findings underscore the clinical importance of treating sleep interruption in midlife women even when they meet the recommended guidelines for sleep duration.

PLENARY SYMPOSIUM #2

Breast Cancer Risk Assessment for Women's Health Clinicians

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Breast cancer is the most common cancer in US women with more than 250,000 new cases each year and more than 40,000 deaths. In the US 12% of women or nearly 1 in 8 will develop breast cancer and breast cancer prevention is a public health imperative. Lifestyle, including diet, exercise, and obesity, contribute to breast cancer risk. In the US there is a substantially higher incidence, 90 cases per 100,000, compared to other countries where the incidence is under 20 cases per 100,000. Data suggests that 30% of breast cancer cases, or over 70,000 cases per year in the US could be prevented with lifestyle modification. Efforts to improve identification of women at elevated risk, including those who carry a hereditary cancer mutation and those who are considered to be at very high risk (lifetime estimated risk above 20%) due to other modifiable and non-modifiable factors is critical. Public health efforts have been directed at ensuring women get an annual mammogram, a critical tool in the fight against breast cancer because early detection and size of tumor at diagnosis correlates with survival, but it is a screening strategy, not a prevention strategy. To reduce breast cancer incidence, we must identify individuals at elevated risk so risk reducing strategies can be implemented, including lifestyle interventions, genetic consultation and testing, and enhanced screening and chemoprevention. We are currently failing to identify the vast majority of women at substantially increased risk for breast cancer. It's estimated that only 10% of women who carry a hereditary cancer mutation have been identified in large part because clinical care delivery models do not support or facilitate identification of women who meet NCCN guidelines for genetic testing. An estimated 1 in 4 women seen for routine visits who meet NCCN guidelines for genetic testing are being missed. Education about the importance of family history assessment to identify individuals at risk of carrying hereditary cancer mutations and referral for testing is a critical part of breast cancer prevention. A larger cohort of women at elevated risk, who are also being missed, are those who have established modifiable (lifestyle) and non-modifiable risk factors. The statistic "1 in 8" represents the risk of a woman developing breast cancer in the general population. For a woman that statistic is meaningless as her risk may be substantially higher or lower due to her own individual risk factors. There are available and validated breast cancer risk assessment tools that estimate a woman's 5-year, 10-year and lifetime risk of breast cancer. These models take into consideration established risk factors for breast cancer including family history, genetics, prior breast biopsies including high risk pathology, weight, exercise, diet, alcohol intake, reproductive factors (parity, age at menarche, menopause, first live birth), breast density, and hormone use. The model calculated risk estimates can be used to inform recommendations for risk reducing approaches and enhanced screening. Unfortunately, these risk assessment tools are rarely utilized outside of high-risk breast clinics and women at high risk remain unidentified. Although a breast exam is part of the standard well woman exam, model calculated breast cancer risk assessment is not standard, and there are no guidelines to support risk assessment as part of an annual preventative visit. Yet risk assessment data is telling. When risk assessment tools are applied to women between 40 and 60, approximately 25% will be identified as "high risk" (lifetime risk over 20%). The result is the majority of high-risk women remain undetected, and the opportunity to educate them about lifestyle for risk reduction, enhanced screening, genetic testing, and chemoprevention when appropriate is missed. Breast cancer risk is a concern of all women, and a breast cancer prevention a priority for all clinicians caring for women. Increased genetic testing and identification of mutation carriers, and more widespread use of risk assessment tools to identify women at very elevated risk provides an opportunity to actually prevent breast cancer.

Chemoprevention and Lifestyle for Risk Reduction: Women's Health Clinicians Have a Role

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Breast cancer remains the most common cancer in women and for certain women, preventive medication can greatly decrease risk and is vastly underutilized. Family history assessment is an essential first line tool for evaluating risk and appropriate patients should be referred for genetic testing. It is estimated that only ~5-10% of those carrying genetic mutations associated with hereditary risk have been identified. Carriers particularly predisposed to estrogen receptor positive disease (ie, BRCA2, CHEK2 and ATM) may be more strongly motivated toward risk reduction and there are nuanced management issues regarding risk-reducing medications in both BRCA1 and BRCA2 carriers given recommended early surgical menopause. Other high-risk women include those that have received therapeutic thoracic radiation to the chest between the ages of 10 and 30, women with benign atypical lesions (atypical hyperplasia and lobular carcinoma in situ), women with extreme breast density and women with an estimated lifetime risk of 20% or greater as defined by models that are largely dependent on family history. Guidelines for preventive medication from the United States Preventive Services Task Force (USPSTF) and the American Society of Clinical Oncology (ASCO) recommend using short term risk estimation to assess whether the benefits of preventive medications likely outweigh the risks in the absence of contraindications. Four medications are recommended for preventive purposes: tamoxifen, raloxifene, exemestane and anastrozole. Recently, the option of low-dose tamoxifen has gained appeal in women with intraepithelial neoplasia and personalized genomic risk estimation using the polygenic risk score has also recently been shown to influence uptake of chemoprevention. Women's health clinicians should be expert in managing side effects of these medications to promote and maintain optimum quality of life and improve medication compliance. High risk women intolerant of the vasomotor symptoms of menopause or unable to tolerate those associated with medication should understand the data regarding menopausal hormone use and limited studies of estrogen in combination with bazedoxifene. Promotion of lifestyle modification is important for all women for breast cancer risk reduction and overall health; the strongest breast cancer risk data exists for obesity and excessive alcohol use. Obesity, unhealthy dietary patterns, and physical inactivity, which disproportionately affect minority populations, have been shown to have a major impact on outcomes across the breast cancer continuum. There is a great need in women's health to partner with patients in optimizing health and promoting breast cancer prevention. References: Medication Use to Reduce Risk of Breast Cancer – US Preventive Services Task Force Recommendation Statement. *JAMA*, 2019;322(9):857-867. Visvanathan K, Fabian C, Bantug E et al. Use of Endocrine Therapy for Breast Cancer Risk Reduction; ASCO Clinical Practice Guideline Update. *J Clin Oncol*, 37:3152-3165. DeCensi A, Puntoni M, Guerrieri-Gonzaga A et al. Randomized Placebo Controlled Trial of Low-Dose Tamoxifen to Prevent Local and Contralateral Recurrence in Breast Intraepithelial Neoplasia. *J Clin Oncol*, 37:1-9. Bandera E, Alfano C, Qin B et al. Harnessing Nutrition and Physical Activity for Breast Cancer Prevention and Control to Reduce Racial/Ethnic Cancer Health Disparities. Asco.org/edbook. 2021.

PLENARY SYMPOSIUM #3

Adapting Menopause Care to Telehealth and Virtual Medicine

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Due to the pandemic and social distancing, telehealth is being adopted by many menopause practitioners who were not previously utilizing it. As a result, patients with climacteric complaints are often managed via a computer screen rather than in-office, face-to-face visits. Although a negative event prompted our adoption of telehealth and virtual medicine, it has reaped benefits for clinicians and patients, including easier access to professional health services by the patient. According to data provided to the CDC (https://www.cdc.gov/mmwr/volumes/69/wr/mm6943a3.htm) telemedicine, defined as the delivery of healthcare services by professionals using various technologies rather than in-person encounters, has significantly increased since the COVID 19 pandemic. Telehealth visits from 4 large national providers were reviewed for the last week of March, 2020, vs March, 2021, and increased by 159%. The reasons for this dramatic utilization of virtual visits are obvious; remote encounters mitigate the need for leaving home and travel; incur fewer costs and; avoid direct physical contact between provider and patient. Through electronic means clinicians can, in many scenarios, diagnose, treat, and provide preventive interventions without a hands-on physical exam and the need to space patients visits in order to avoid contact in the waiting area or have patients wait outside. Most clinicians, having now utilized telemedicine, can more clearly note the benefits of virtual health services, which encompass Internet and web applications, phones, wearable activity trackers, interactive voice response systems, and virtual reality sets. Despite our recent acknowledgment of these modalities, several earlier precursors allowed distant transmission of information without individuals being physically together. The first remote system that alerted individuals to eminent harm were smoke signals, first utilized in 200BC. A more advanced smoke system was created in 150BC by Polybius, with a specific pattern of smoke designated for each letter of the alphabet. In 1876 Bell invented the telephone, an invention which continues to be one of the major ways patients and clinicians communicate. The radio was introduced in 1895 and the television in 1926. In 1939, Atanasoff and colleagues invented the computer, which was the predecessor to the Internet, an indispensable part of the healthcare record and medical communication today. By the 1950s, there were some instances of hospital-based telemedicine utilization and in the 1960s closed-circuit television link was established, with its first use for psychiatric consultation. Also, during the 1960s telemedicine began to emerge mainly in urban communities and was useful for medical emergencies. An example is the partnership in 1967 between Jackson Memorial Hospital and a fire department, who transmitted electrocardiographic rhythms over the radio in rescue situations. The benefits of telehealth and virtual medicine are continually emerging with many directed in their use specifically for low-risk menopausal women who are up to date with mammogram and cervical cancer screenings. Consultation for management of menopause symptoms and vaginal atrophy can often be done in this manner. Discussions regarding bone health, weight management, bladder issues, other pelvic floor concerns and of course follow up can be done this way. Telephone based cognitive behavioral therapy, recommended Internet-delivered tools such as applied relaxation techniques, and wearable activity sensors are among the virtual interventions utilized in midlife and older woman's healthcare. Obstacles to virtual clinical practice and care should be addressed with patients including limited access to the Internet, smartphones, tablets, or computers; lack of familiarity with technology; and lack of privacy to discuss personal health matters, such as sexual issues. Telehealth encounters may not be appropriate for some women based on the level of acuity or necessity to conduct an in-person physical examination or diagnostic testing. Telehealth and virtual medicine, which is generally well-accepted by clinicians and patients, is here to stay. Over time, more and more interventions for menopausal women will emerge using a virtual platform for the delivery of patient care.

Collateral Damage of COVID-19 in Women and Methods to Manage

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The COVID-19 pandemic has profound and wide reaching psychosocial ramifications. We have learned from past pandemics that the elevated stress levels experienced during a pandemic may result in increased incidences of depression, anxiety, and symptoms of posttraumatic stress disorder. The Household Pulse survey reveals that our current COVID-19 pandemic follows the pattern or previous pandemics, with approximately 47% of women reporting symptoms of anxiety and/or depression compared to 38% of men in December of 2020, an increase from an overall adult baseline of 10.8% in 2019. In addition, rates of suicide ideation, attempts, and self-harm have increased compared to pre-pandemic rates. The weight of the pandemic is not experienced equally throughout the population, with a greater toll on women and disadvantaged and marginalized people. Intimate partner violence has been reported at increased rates in many countries, including the US. Risk factors for intimate partner violence that have increased in the pandemic include social isolation, fear of dying, loss of loved ones, and difficulties in accessing services. Healthcare providers need to be aware of the context in which patients are experiencing the pandemic including indicators of vulnerability, they must support the therapeutic relationship, and appropriately screen and monitor for COVID-19 associated stressors, secondary adversities, and psychosocial effects. Healthcare providers and systems should strive to provide trauma-informed care utilizing the principles of safety, choice, collaboration, trustworthiness and empowerment. Validated screening tools may be used in addition to therapeutic communication skills for psychosocial assessment and monitoring. Healthcare providers should be prepared to normalize help-seeking behavior, provide appropriate psychoeducation, provide resources for immediate mental health needs and/or community or online mental health and social services. The stress and trauma of the pandemic are impacting women, resulting in increased psychosocial issues. Healthcare providers are important to identify and support women in these difficult times.

PLENARY SYMPOSIUM #4

Osteoporosis Screening in Women in Their 50's: FRAX and Beyond

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Osteoporosis, defined as bone mineral density (BMD) T-score ≤ -2.5 by dual-energy x-ray absorptiometry (DXA) or fragility fracture, is common among postmenopausal women and increases the risk of future fracture. For postmenopausal women younger than age 65 years, the United States Preventive Services Task Force (USPSTF) recommends evaluation of clinical risk factor: smoking, parental hip fracture, excess alcohol, low body weight. If any of these risk factors are present, then the clinician should use a formal clinical risk assessment tool to determine which women should receive a BMD test. There are five formal clinical risk assessment tools recommended by the USPSTF: Fracture Risk Assessment Tool (FRAX), Simple Calculated Osteoporosis Risk Estimation (SCORE), Osteoporosis Risk Assessment Instrument (ORAI), Osteoporosis Index of Risk (OSIRIS), and Osteoporosis Self-Assessment Tool (OST). The only national U.S. studies that have evaluated these tools for prediction of BMD T-score in the osteoporotic range (≤-2.5) or for prediction of fracture are based on the Women's Health Initiative. The studies have compared OST, SCORE, and FRAX in young postmenopausal women. For identifying postmenopausal women with BMD T-score ≤ -2.5, which is the goal of osteoporosis screening (i.e. to identify candidates for pharmacologic therapy), OST and SCORE work better than FRAX, and OST is simplest (formula based on age and body weight). Tools with more risk factors do not have better discrimination (AUC) to identify T-score ≤ -2.5 than tools with fewer risk factors. Change in BMD (baseline to 3 years) in young postmenopausal women (not taking osteoporosis medication) does not add meaningfully to distinguish between women who do, and women who do not, experience subsequent fracture. There are public health consequences of the cost and resources required to perform BMD scans that may not provide meaningfully important information for clinical decision-making regarding fracture prediction. Instead, resources should be devoted to increasing the underuse of baseline BMD testing among older women aged between 65 and 85 years, one-quarter of whom do not receive an initial BMD test. In summary, "Need a baseline" is not a strong rationale for ordering BMD testing in younger postmenopausal women. For young postmenopausal women, use the USPSTF screening strategy (assessing clinical risk factors, and then using one of the five recommended formal clinical risk assessment tools to decide who should receive BMD testing. Keep in mind the BMD measurement error and its implications. The risk-benefit tradeoffs of osteoporosis drug therapy in healthy postmenopausal women less than 65 years-old are unclear.

Osteoporosis in Special Populations

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Osteoporosis is most commonly diagnosed in the context of postmenopausal declines in estrogen with resultant bone loss and skeletal fragility. However, the pathophysiology and evolution of low bone density is often more complex and can occur at many different time points in a woman's lifecycle. To understand the origins of osteoporosis in special populations, it is helpful to first consider the natural history of bone. Women acquire bone in the first two to three decades of life. That is, bone formation rates surpass that of bone resorption, resulting in a net gain of bone density. In the next phase of bone metabolism, skeletal remodeling is in steady state, or balanced formation and resorption, with overall maintenance of bone density. At the time of the perimenopause, a period of rapid bone loss can occur at a rate as high as 1-2% per year, subsequently followed by a period of slower decline thereafter. With this in mind, one can appreciate how a single deleterious health event or accumulation of health challenges in one's lifetime and cycle of bone metabolism could have lasting skeletal effects leading up to the menopause and beyond. Note that these insults may be short or long-term with different impacts on overall bone strength. There are a number of ways to think about categories of conditions that cause "secondary" osteoporosis, or bone disease arising from factors beyond declines in estrogen. At the beginning of the curve are those states that impact "peak" bone density. Any hindrances to healthy skeletal formation in early life will contribute lower-than-expected peak bone density that may underpin frank osteoporosis in the perimenopausal period. Such conditions that may impair bone formation include malnutrition or eating disorders, immobility, chronic childhood illnesses and genetic predisposition (maternal or paternal osteoporosis, osteogenesis imperfecta, hypophosphatasia). Similarly, insults to the skeleton following the period of bone acquisition, many times carried forward from childhood or young adulthood, will additionally compromise bone strength. In general, these deterrents to bone wellness can be thought of in three different categories. The first is patient-related. Lifestyle choices such as smoking, excessive alcohol intake, dietary restriction, lack of exercise and even chronic psychological stress all contribute to adverse skeletal remodeling. The second is iatrogenic or mediation-related. Chronic steroid use (>3-months), aromatase inhibition or tamoxifen in the premenopausal woman, anti-convulsants and cytotoxic drugs can have additional deleterious effects on bone. Finally, and most broadly, there are a number of chronic diseases that play prominently in the development and worsening of osteoporosis over time. These include, but are not limited to, chronic kidney, lung or liver disease, type 1 and type 2 diabetes, and many systemic inflammatory diseases such as rheumatoid arthritis, sarcoidosis and inflammatory bowel disease. With respect to illness arising from autoimmunity or organ transplantation, these are often treated with steroids, leading to additional skeletal compromise. By the time a woman reaches menopause with its own associated risk of bone loss, it is possible that she will have amassed one or several challenges to maintaining optimal bone strength. It is thus important to approach each patient from a specialized lens that does not merely label her osteoporotic based on a DXA scan. Instead, there should be vigorous consideration and work-up of the often-multifactorial components of her health history

that have contributed to her diagnosis. It is with this thoughtful assessment of the etiology of a woman's skeletal fragility that treatment decisions though lifestyle modifications, management of underlying illnesses and pharmacotherapy should be motivated to reduce fracture risk.

PLENARY SYMPOSIUM #5

An Update of How to Evaluate the Uterus

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As you read this, if you are a gynecologist, you will likely be responsible for performing such an evaluation. If you will NOT be performing it, you should at least have an EXPECTATION of what the healthcare provider you refer to can and should be doing. If menopause is defined as the final menstrual period, a woman never knows that the bleed she just had will be the last one ever. In addition, erratic ovarian function in the late perimenopause can result in laboratory determinations of FSH and estradiol that are in a menopausal range, however that is only a snapshot of ovarian function, or lack thereof, on that day. Subsequent spontaneous bleeding with reversal of seemingly menopausal range labs is not uncommon. That is why a clinical definition of menopause has often been one year of no menses due to a depletion of ovarian follicles. In addition, guidelines from societies, such as ACOG, say that any woman over 40 with abnormal uterine bleeding needs an endometrial evaluation to exclude hyperplasia or carcinoma, but also any structural reason for bleeding such as polyps or myomas, versus non-structural causes associated with bleeding which are mainly anovulation in women with ovarian function or atrophy in truly menopausal patients with no ovarian function. Thus the need to evaluate women for any AUB regardless of whether they are truly menopausal or late perimenopausal will be necessary. However, the timing of such an evaluation will be critical if the woman is undergoing any cycling (still making estradiol or on sequential HT) versus non-cycling (menopausal or on continuous combined HT). In order to better understand this last statement one needs to understand endometrial physiology. The endometrium consists of a basalis and a functionalis. Estrogen stimulates the functionalis to proliferate. After ovulation the production of progesterone (or in sequential HT the addition of a progestogen) causes this estrogen primed functionalis to be converted to a secretory phase and then is shed as a menses. Thus estrogen causes the endometrium to thicken when viewed with transvaginal ultrasound (TV U/S). However, in those patients who are cycling, endometrial thickness measurements by TV U/S will be extremely time sensitive and need to be performed as soon as possible after the bleeding cycle ends. Several decades ago blind endometrial biopsies, originally developed for endometrial dating as part of an infertility work up, quickly became the standard of care for evaluating patients with abnormal uterine bleeding. This was based on very little scientific data. However, recently improved understanding about the limitations of blind endometrial sampling has called this into question as a reliable method of evaluation when such blind biopsies are negative for hyperplasia or cancer. TV U/S employs transducers of higher frequency in closer proximity to the pelvic structures and yields a degree of image magnification that can be considered "sonomicroscopy." There is abundant information about the reliability of a thin distinct endometrial echo (not "stripe") on TV U/S to exclude significant pathology in patients with abnormal uterine bleeding. (However, a thick endometrial echo in non-bleeding patient should not automatically be assumed to be pathologic or in need of further invasive evaluation). In addition, not all uteri lend themselves to a meaningful TV U/S examination. The axial uterus, coexisting fibroids, adenomyosis, previous surgery all can result in an inability to adequately visualize an endometrial echo on TV U/S. In such cases, the installation of saline known as saline infusion sonohysterography, or SIS, will allow better visualization of the endometrial cavity. Structural abnormalities will require further tissue evaluation whereas the lack of any structural abnormality indicates anovulation in patients still producing estradiol or atrophy in truly menopausal patients. Finally, new disposable hysteroscopes that can be easily adapted to an office setting may allow for "point of care" diagnosis in our patients with abnormal uterine bleeding.

Medical Management of Menopausal Bleeding

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Abnormal uterine bleeding (AUB) is a common presenting problem for women throughout their reproductive lifespan and into perimenopause. AUB is defined as bleeding that is abnormal in quantity, duration, or schedule. Given the breadth of the definition, it is imperative to have a systematic approach to ensure accurate diagnosis and treatment. The International Federation of Gynecology and Obstetrics (FIGO) created a classification system in 2007, which was further revised in 2011, to classify specific causes of AUB into discrete categories that include structural and non-structural causes, commonly referred to as PALM-COEIN (polyp, adenomyosis, leiomyoma, malignancy and hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic and not yet classified). One of the challenging aspects in evaluating and managing AUB in the perimenopausal period is distinguishing anovulatory bleeding from other pathology. As ovarian reserve declines in the early to mid-40s, FSH levels rise, and inhibin B levels fall, leading to early follicular recruitment and shorter menstrual cycle intervals. As the menopause transition continues, FSH and LH levels are consistently elevated, leading to disordered follicular growth, impaired follicle rupture, resulting in ovarian cyst formation and anovulatory or oligo-ovulatory bleeding patterns. Despite this background of expected ovulatory dysfunction in the perimenopausal period, it is still important to approach AUB systematically to exclude concurrent issues that may influence the management strategy. The evaluation begins with a thorough history and focused physical examination. Appropriate laboratory and imaging studies should be ordered, and typically include a complete blood count, TSH, HCG and transvaginal ultrasound. If there is suspicion for a bleeding disorder, as suggested by history, then a more thorough evaluation for coagulopathy is indicated. In accordance with the American College of Obstetricians and Gynecologists, endometrial sampling is indicated in women over the age of 45 with AUB, and in women under age 45 with other risk factors for endometrial intraepithelial neoplasia. Treatment should be directed at the source of bleeding and can include expectant, medical and surgical management when appropriate. As previously outlined, ovulatory dysfunction is the predominant cause of AUB during perimenopause, and hormonal treatments are the mainstays of improving the regularity of the bleeding pattern. Medical approaches including combined oral contraceptives, progestin only oral contraceptives, and the levonorgestrel intrauterine releasing system are commonly used. In contrast, postmenopausal bleeding (PMB) is defined as any unexpected vaginal bleeding that occurs after the final menstrual period. For women on hormone therapy, PMB refers to any bleeding that occurs outside of the expected cyclic bleeding in response to hormone withdrawal. The most common cause of PMB is atrophy; however endometrial cancer must also be considered. Over 90% of patients with endometrial cancer will present with PMB, and approximately 14% of patients with PMB will have endometrial cancer. Given these statistics, it is imperative that any patient presenting with PMB undergo a prompt evaluation for causes of bleeding to exclude underlying malignancy. Evaluation includes a detailed personal and family history, review of medications and supplements, and physical examination. Low risk patients presenting with their initial bleeding episode, can be screened with transvaginal ultrasonography or endometrial biopsy. Patients with recurrent bleeding, or who have multiple risk factors for endometrial cancer, should have endometrial sampling. If malignancy is diagnosed, prompt referral to a gynecologic oncologist is warranted. If atrophy is diagnosed, expectant management or localized estrogen therapy may be considered. Breakthrough bleeding (BTB) is a common complaint for patients receiving postmenopausal hormone therapy and is most common during the first 6 months of treatment. Managing BTB can be difficult, but strategies include changing from continuous to cyclic therapy or increasing the dose of progestin.

PLENARY SYMPOSIUM #6

Sexually Transmitted Infections (STI) in Midlife Women

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STIs are a concern for midlife women who are not in long-term, mutually monogamous relationships and may not be as knowledgeable about STI risks or steps to minimize them. Rates of STIs such as chlamydia and HIV are increasing in older American women and men, but absolute number remains quite low. The most important predictor of STIs in older persons is the number of sexual partners in the past year, especially if 2 or more. Recommended treatments are contained in the 2021 CDC STI Treatment Guidelines.[1] *Chlamydia and gonorrhea (GC):* USPSTF recommends annual routine screening for chlamydia and GC in sexually active women ≤24 years and targeted screening in older women at increased risk. Vaginal swab is preferred sample source. *Treatment of chlamydia*: doxycycline 100 mg orally twice a day for 7 days; alternatives azithromycin 1 gram PO or levofloxacin 500 mg PO once a day for 7 days. *Treatment of GC*: ceftriaxone 500 mg IM; if not available, oral cefixime 800 mg PO as a single dose as alternative. If chlamydial infection has not been excluded, co-treat for chlamydia with doxycycline. *Test of cure* is not necessary after treatment in most cases but rescreen in 3 months to detect reinfection. Treat partners with patient-delivered partner therapy in order of preference: 1) provide patient with drugs intended for partners, 2) prescribe extra doses in the index patients' name, or 3) write prescriptions in partners' name. *Genital herpes*: USPSTF recommends against routine serologic screening for genital HSV infection in asymptomatic adults. Women who have had multiple sexual partners may benefit from serologic screening for HSV- 2 but only if they plan to protect themselves if seronegative (with use of condoms) or partners if seropositive (with daily antiviral drug suppressive therapy). *Hepatitis B*: Routine hepatitis B serology screening of the general population or targeted screening based on sexual behaviors, not recommended. Midlife women with multiple sexual partners (or who have other risk factors, such as needle-sharing) who have not been vaccinated should be advised to do so. *Hepatitis C:* USPSTF recommends one-time routine screening for hepatitis C virus (HCV) infection in adults 18-79 years without prior ascertainment of hepatitis C risk. *HIV:* About 16% of people infected with HIV don't know they are infected, yet are responsible for 40% of transmission of HIV in US. CDC and USPSTF recommend adults aged 15-65 years receive 1-time HIV screening, regardless of risk factors. All who seek evaluation and treatment for STIs should be screened for HIV infection. *Human papillomavirus (HPV):* CDC recommends routine immunization between 9-26 years. FDA approved use of Gardasil-9 in 2018 for females and males between 27-45 years. CDC Advisory Committee on Immunization Practice recommends immunization is permitted, but not routinely recommended, for this age group, based on opt-in shared decision making. *Syphilis:* USPSTF recommends screening for syphilis infection for those at increased risk for infection, including being HIV positive, history of incarceration or commercial sex work, and residing in an area with high syphilis rates. Many labs have switched to reverse sequence algorithm using automated treponemal immunoassays. Patients diagnosed with syphilis should be screened for HIV infection. *Vaginal trichomoniasis.* Low-risk women should not be routinely screened but periodic screening for those who are HIV positive or those in high prevalence settings. Trichomoniasis is treated with metronidazole 500 mg twice a day for 7 days, or alternatively, with tinidazole, 2-gram single dose given PO. *Bacterial vaginosis:* CDC recommends treatment with metronidazole 500 mg orally twice a day for 7 days, metronidazole 0.75% vaginal gel once daily for 5 days, clindamycin 2% vaginal

cream at bedtime for 7 days. Oral tinidazole (2 grams once daily for 2 days or 1 gram once daily for 5 days) and clindamycin orally or by vaginal ovules used as alternative regimen. No studies support the addition of any available lactobacillus formulations or probiotic as an adjunctive therapy in women with BV. BV recurs in up to 30% of cases of and twice-weekly suppression metronidazole vaginal gel can be considered. 1. Workowski KA, Bachmann LH, Chan PA, et. al. CDC Sexually Transmitted Infections Treatment Guidelines, *2021 MMWR Recomm Rep* July 23 2021; 70 (4); 1-187.

PLENARY SYMPOSIUM #7

How to Win at Losing: Hair Loss in Midlife Women

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Hair loss in middle aged females is common. Normal hair cycle includes anagen (growth phase) lasting 2-4 years with individual variation. This is followed by catagen (transitional phase) lasting 2-3 weeks, and finally telogen (resting) during which time the terminal hair detaches from the papilla and sheds (3 months) until re-entering anagen. Common causes for hair loss include non-scarring alopecia – androgenetic alopecia and telogen effluvium; and scarring alopecias – frontal fibrosing alopecia and central centrifugal cicatricial alopecia. Androgenetic alopecia was the traditional term to describe progressive loss of terminal hairs on the frontal and/or vertex scalp in both sexes. This was considered an androgen-dependent hereditary trait, hence the terminology. More recently, female pattern hair loss is preferred, since this distinguishes the differing clinical features between sexes, and reflects the lack of evidence to support a hormonal etiology. Although hormonal and genetic predisposition may be relevant, the mechanism through which these factors play a role is unclear since most patients do not have abnormal serum androgens. Women typically report progressive ponytail thinning, increased scalp visibility, and easy sunburn. These features are noted over months to years, and although insidious, patients may describe episodes of increased hair loss prior to noting their female pattern hair loss. Usually there is preservation of the frontal hairline, with diffuse central thinning and accentuation of the part-line with a "Christmas tree" appearance. Treatment includes daily application of topical 5% minoxidil and may take at least 3 months before noticing benefit. Finasteride is a 5-reductase inhibitor FDA approved for male hair loss. As an off-label indication, it may be effective in females, although higher doses are required. Additional treatments include drospirenone containing OCP, and spironolactone. Newer therapies like platelet rich plasma have emerged as treatment options. Telogen effluvium is a relatively common non-scarring alopecia due to temporary alteration in the hair cycle. This cycle shift results in fewer anagen hairs, with increased shedding as proportionally more hairs enter telogen. This causes a diffuse reduction in hair density with increased loss noted on the brush or in the shower. Triggers include serious illness, major surgery, childbirth, rapid weight loss, or severe stress. In most cases it is self-limited, with loss beginning 2-3 months after the inciting event and reversing once resolved. Less than 50% of the normal hair density is lost, and progression to balding does not occur. Less common causes of hair loss include scarring disorders such as frontal fibrosing alopecia. This is most common in women 55-65 years, although 15% are in younger females. It is characterized by a bandlike alopecia along the frontal hairline, noted as anterior recession. There may be associated eyebrow loss, and involvement of vellus hairs produces characteristic facial papules. Pathogenesis is not well understood, although immune dysregulation, genetic, hormonal, and environmental factors are implicated. It is considered a subtype of lichen planopilaris, with permanent hair loss due to damage of the follicular bulge from the inflammatory process. The condition is increasingly common and the association with sunscreen use has been extensively debated. The first reported case was in 1994, which paralleled the introduction of sunscreens such as oxybenzone and avobenzone. Many experts therefore prefer physical sunscreens such as zinc oxide. Treatment is challenging and includes topical and intralesional corticosteroids, as well as systemic therapies and rarely, immunosuppressive therapy. CCCA is another scarring alopecia presenting with centrifugal spread of hair loss beginning on the crown. Most patients with this disorder are African American females. Previous terms included hot comb alopecia, follicular degeneration syndrome, chemically induced alopecia. Clinical signs of inflammation such as papules, pustules, erythema, and scale may or may not be present; and pain, itching, tenderness is variable with some patients asymptomatic. Again, permanent hair loss may result, and early diagnosis is important. Biopsies are frequently needed to distinguish these varying causes of alopecia, and referral is recommended.

Menopause and the Voice

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It is common for women to notice vocal changes around the time of menopause, which may include deepening of the voice, a more raspy or hoarse sound quality, and the quicker onset of vocal fatigue. While the majority of menopausal women are not distressed by these changes, for elite voice professionals even small changes can drastically change the trajectory of a career. Although endocrine signaling was not discovered until 1849, the relationship between voice and hormones was appreciated as early as 400 B.C. when Aristotle described the effect of castration on the songbird. During the Medieval Period it was common practice to castrate young male choristers prior to puberty to maintain their vocal range. For centuries, opera divas, recognizing the cyclic changes in their vocal quality, refused to perform while in the second half of their menstrual cycle. The intuitive understanding of the relationship between voice and hormones became scientifically cemented when Jean Abitbol, an otorhinolaryngologist, and his wife, gynecologist Beatrice Abitbol, compared tissue smear samples from both the cervix and the vocal folds every day during the menstrual cycle and found that they were indistinguishable. Further study has elucidated the mechanism for hormonally-induced vocal changes. During the follicular phase of the menstrual cycle, the increased amounts of estrogen and markedly lower levels of progesterone cause vocal fold edema and increased blood flow to the laryngeal structures. Polysaccharides in the vocal folds break down and bind water more readily, furthering fluid accumulation in the vocal folds. In the luteal phase, increased levels of progesterone promote sloughing of the laryngeal epithelium and also make the glandular secretions more viscous, leading to a decrease in vibratory efficiency. The relative androgenic state of menopause causes thickening of the vocal cords, remodeling of surrounding tissues, and dehydration of the larynx resulting in a reduction in vocal range and a loss of high frequencies. Vocal changes during menopause can be due to other causes as well. Inflammation, infection neoplastic lesions of the larynx, GERD, drugs, and adrenal and thyroid disorders are just some of the conditions that can lead to altered vocal quality. Certain steroids (danazol, testosterone, tibolone) are known to cause vocal changes which may be permanent, even after withdrawal of the drug. The perceived pitch of the voice is called the fundamental frequency, the "f0". An f0 difference of more than 1% can be detected by experienced listeners (e.g. opera, theater, and concert audiences). Controlling for age-related changes the difference in f0 between menopausal women without hormone therapy and those on hormone therapy was found to be 7.4%. For singers, voice actors, and professional presenters, voice changes of this magnitude can be career-ending. Unfortunately, there are relatively few studies providing specifics on therapeutic options. For Premenstrual Voice Syndrome, which usually starts 4 - 7 days prior to menses, the use of combined oral contraceptives has been successful in improving most acoustic measures. For Menopause Voice Syndrome, estrogen therapy has been shown to reverse most of the observed voice changes and results in improvement in 73% of affected women at one year of therapy. It is imperative that an experienced otorhinolaryngologist follow these patients to ensure that the expected improvements in vocal quality are occurring. As an adjunct or for those patients who are not candidates for hormone therapy, vocal exercises or voice therapy by a professional instructor is recommended. Do all menopausal women need hormone or vocal therapy for their voice changes? Not at all, since the vast majority of these women maintain overall good vocal quality. For those who are employed in voice-intensive professions, however, even small vocal changes can have profound occupational consequences, thus restorative therapy should be considered.

PLENARY SYMPOSIUM #8

Female Sexual Function in the Context of Aging and Complex Medical Conditions

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Sexual function is a key component of personhood, relationships, well-being, and health across the life course.[1] Most partnered people are sexually active through the 9th decade of life and the vast majority of older people regard sexual function as important to their health, even if they are not partnered or sexually active. Most older people feel sexual function and problems are appropriate for discussion with a physician, but only a minority report having had these conversations[1] – including people with health conditions, like breast or gynecologic cancer, and taking medications, like anti-hormone therapies, that directly affect their sexual function.[2] The most common sexual function concerns among older women are associated with changes in the sex hormonal milieu that comes with menopause and changes in male partner sexual function, especially erectile function.[3,4] Common problems include vulvovaginal dryness which commonly co-occurs with dyspareunia, decreased libido and arousal, and diminished genital sensation causing difficulty with orgasm.[5] These problems commonly co-occur and, although distressing to women,[1,6] are also commonly overlooked in medical practice, even in gynecology and primary care visits.[7] Aside from menopausal hormonal therapies, few other FDA-approved treatments for female sexual dysfunction have been tested for safety and effectiveness among older women.[3] Further, the preponderance of research on female sexual dysfunction treatments targets efficacy outcomes,[4] excluding people with medical comorbidities, which are highly prevalent among older women. Far less is known about sexual function in the context of aging and illness about people with female anatomy but who identify with other gender groups. With nearly two decades of support from the National Institute on Aging, both the National Social Life, Health and Aging Project and the Study of Midlife Women Across the Nation provide publicly-available, longitudinal data to study sexual activity and relationships in the context of aging and women's health.[8,9] References: [1]Lindau ST, Shumm LP, Laumann EO, Levinson W, O'Muircheartaigh CA, Waite LJ. A study of sexuality and health among older adults in the United States. *New England Journal of Medicine*. 2007 Aug 23;357(8):762-74. PMID: 17715410. [2]Sobecki JN, Curlin FA, Rasinski KA, Lindau ST. What We Don't Talk about When We Don't Talk about Sex: Results of a National Survey of U.S. Obstetrician/Gynecologists. *The Journal of Sexual Medicine*. PMID: 22443146 [3]Lindau ST, Fruin K. Sexuality, Sexual Function, and the Aging Woman. In: Halter JB, Ouslander JG, Studenski S, High KP, Asthana S, Supiano MA, Ritchie C. eds. *Hazzard's Geriatric Medicine and Gerontology*, 7e. McGraw Hill; Accessed August 12, 2021. https://accessmedicine-mhmedical-com.proxy.uchicago.edu/content.aspx?bookid=1923§ionid=144520960 [4]The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society. *Menopause*. 2020 Sep;27(9):976-992. PMID: 32852449 [5]Gandhi J, Chen A, Dagur G, Suh Y, Smith N, Cali B, Khan SA. Genitourinary syndrome of menopause: an overview of clinical manifestations, pathophysiology, etiology, evaluation, and management. *American Journal of Obstetrics and Gynecology*. 2016 Dec;215(6):704-711. PMID: 27472999. [6]Shifren JL, Monz BU, Russo PA, Segreti A, Johannes CB. Sexual problems and distress

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When and How to Use Androgens

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Estrogens and androgens are human hormones, not as often misinterpreted, female and male hormones, respectively. Yet, our medical and regulatory focus in menopause has been on estrogen therapy both its efficacy and for the last 20 years, its safety. Despite this, androgens including testosterone are highly prevalent in women across the lifespan. In fact, androgens are present in women in much greater concentrations than estrogens. Testosterone, the primary androgen focus of this lecture, is present in women with concentrations nearly 10-fold greater than estradiol. Our misunderstanding of this fact is largely related to subjugation of women's sexual health and pleasure, inadequate medical and postgraduate training, including the misappreciation of the units used in measuring these two chemical entities (estradiol and testosterone). A misplaced and inordinately high regulatory barrier to FDA approval for testosterone in women compared to men, has unfortunately made testosterone unavailable to most women except when used off-label. In contrast, there are more than 25 different testosterone therapies that are FDA-approved for men, including a variety of dosage forms (nasal, subcutaneous, intramuscular, transdermal, trans-scrotal, subcutaneous implants, etc.). The absence of FDA approved testosterone products for women has forced practitioners to use either compounded testosterone treatments which come without: regulatory oversight, a package insert, warnings and precautions, etc., and suffer all the vagaries of compounding generally; or the use of FDA approved male products that can be scaled down to an appropriate female dose with their inherent risks of overuse and the downstream overdosage leading to acne, hirsutism, balding, clitoromegaly, and frank virilization. In recent years, the international scientific and medical communities, and the endocrinological, menopause, and sexual medicine-focused societies representing them have formalized our understanding of and use of testosterone in postmenopausal women. Much of the data utilized in these efforts come from historically failed regulatory efforts representing billions of dollars in wasted research investment. Utilizing these regulatory data and other resources, efforts lead by The International Menopause Society (IMS) (Global Consensus Position Statement on the Use of Testosterone Therapy for Women*; J Clin Endocrinol Metab.* 2019 Oct; 104(10): 4660–4666, and The International Society for the Study of Women's Sexual Health (ISSWSH) (International Society for the Study of Women's Sexual Health Clinical Practice Guideline for the Use of Systemic Testosterone for Hypoactive Sexual Desire Disorder in Women. *J Sex Med*. 2021 May;18(5):849-867, have resulted in consensus documents toward an evidence-based approach to the diagnosis and treatment of androgen insufficiency in postmenopausal women. According to those documents, testosterone treatment in postmenopausal women should be used primarily, if not exclusively, for amelioration of hypoactive sexual desire disorder (HSDD) which has been codified in the mental health literature as female sexual interest and arousal disorder (FSIAD). HSDD is a disorder characterized by low or absent sexual desire, sexual interest, or receptivity to sexual activity accompanied by personal or interpersonal distress. Here, the focus will be an explanation of the IMS and ISSWSH consensus guidelines as the current standard of care for our menopausal patients. These practical international guidelines utilize total testosterone by GC/MS or similar sensitive methods to measure testosterone deficiency, and to assess the adequacy of testosterone replacement while avoiding testosterone excess. Two preparations of testosterone are recommended for use in women. They are 1% hydroalcoholic testosterone in resealable tubes (Testim®, and multiple available generics) but not in sachets ("ketchup packets"), and Androfeme1®, a 1% testosterone cream, and the only regulatory approved (Australia) testosterone product for menopausal women. In addition to the use of these agents for the treatment of HSDD in postmenopausal women, the importance of topical local testosterone in the care of the postmenopausal women with vulvar vestibular pain, and focused penetration related dyspareunia will be reviewed.

PLENARY SYMPOSIUM #9

Physiology of Hormonal Migraines and Migraine at Menopause

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Women are disproportionately affected by migraine. One in four women experience a migraine attack at some point in their reproductive life cycles. After menarche, women shoot past men in migraine prevalence. These sex differences continue even after menopause, albeit to a lesser extent. Estradiol fluctuations are thought to play a role in migraine, as evidenced by increasing migraine attack prevalence prior to menstruation, after childbirth, and during the menopausal transition (MT) and perimenopausal periods. Pure menstrual migraine and menstrually-related migraine are in the International Criteria of Headache Disorders, Volume 3 (ICHD-3) appendix, whereas estrogen-withdrawal headache and headache attributed to exogenous hormones (headache attributed to long-term use of non-headache medication) are in the main ICHD-3 index. During the menstrual cycle itself, estradiol levels have a precipitous drop just prior to menstruation, and drop to a lesser extent after ovulation. This would explain greater migraine incidence prior to menstruation as opposed to a modest increase around ovulation. Estradiol levels falling dramatically at birth also can explain some of the post-pregnancy increase in migraine frequency. Estradiol can cross the blood brain barrier, and also can be synthesized in the brain. Estradiol can increase cortical and neuronal excitability, including in the brainstem and trigeminal nucleus caudalis, structures involved in pain. Estradiol can affect various neurotransmitters, including serotonin, glutamate, Gamma Aminobutyric Acid (GABA), and calcitonin gene-related peptide (CGRP), all implicated in pain signaling in migraine. Estradiol can work by both genomic and non-genomic pathways. In the MT and perimenopausal periods, the orderly pattern of estrogen and progesterone fluctuation disappears and fluctuations in sex hormones undoubtedly leads to an increase in migraine incidence. Migraine prevalence ranges from 10-29% in the menopausal period (menopausal transition, perimenopause, and early menopause). Between 8-13% of women develop new onset migraine during MT. In women at a headache clinic who were perimenopausal, 81.9% of patients reported new or worsening headache during the perimenopausal period. After menopause, migraine incidence and prevalence drops considerably, thought to be due to stability of estradiol levels. Interestingly, women who experience pure menstrual migraine and menstrually-related migraine often have better prognoses post-menopause. Alternatively, surgical menopause (with or without oophorectomy) has been shown to worsen migraine, thought to be due to abrupt hormonal fluctuations.

Treatment Options for Midlife Migraines

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Migraines are a common medical condition, affecting as many as 38 million people in the US. One out of every five households includes a person with migraine; it is the third most common cause of missed days of work. Women are three times as likely to have migraines as men; part of this may be explained by hormonal fluctuation that women experience although there are likely differences in brain pain expression in women compared to men. Migraines often present in puberty and then may worsen during the menopause transition. Despite the high frequency of the condition, there are no specific evidenced guidelines for treating migraines in midlife other than standard of care. This presentation will review medication and complementary and alternative options, focusing on best practice, unifying therapies, and shared decision making. A review of migraine pathophysiology will be followed by discussion of newer targeted biologics and the lecture will conclude with cased-based examples.

PLENARY SYMPOSIUM #10

How to Advise of the Risks and Benefits of Hormone Therapy During Menopause

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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. Hormone therapy (HT) is the most effective treatment for the vasomotor symptoms of menopause and has a role in the prevention of osteoporosis, but many women go untreated. Various myths persist about the risk profile of HT. Since the Women's Health Initiative (WHI) trial results in 2002, it has become clear that the risks of HT are low for healthy women within ten years from menopause or less than age 60. Taken together, the benefits are likely to outweigh the risks in view of HT's efficacy for symptom management. Discussing the risks and benefits of HT by system (cardiovascular, brain, breast, bone, etc.) will empower healthcare practitioners to council their patients appropriately and provide an individualized and informed approach to HT prescribing.

Vasomotor Symptom Management: What's on the Horizon?

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Vasomotor symptoms are prevalent, experienced by about 75% of women in the menopause transition. Further, symptoms last a mean of 7-10 years, longer in women whose symptoms begin in perimenopause. There are associations of vasomotor symptoms with not only poorer quality of life, sleep problems and negative mood, but also with lower bone density and subclinical cardiovascular disease. Several therapies, both hormone and nonhormone, are under investigation for vasomotor symptom management. Some of these are approved for other indications and others are novel compounds that are not yet government approved. Oxybutynin is an antimuscarinic, anticholinergic agent used for management of overactive bladder symptoms and hyperhydrosis which also has been found to reduce vasomotor symptom frequency and severity. Although there are concerns regarding dementia risk with longer-term use, short term use may provide symptom relief for women with significant or bothersome vasomotor symptoms. Neurokinin 3 receptor antagonists are in phase 3 clinical trials for treatment of vasomotor symptoms and represent a promising nonhormone therapy for women who are unable or unwilling to use hormone therapy. These agents appear to rapidly reduce hot flash frequency and severity. The effects of NK3 inhibitors on weight, cardiovascular, bone, brain or sexual health remain unknown, and long-term safety and efficacy have yet to be established. Estetrol (E4) is a naturally occurring estrogen with selective action in tissues and is produced by the fetal liver. Initial studies show reduced vasomotor symptom frequency and severity as well as improvements in the vaginal maturation index. E4 has recently been approved in the US and Canada for use as a contraceptive and is under investigation for vasomotor symptom management. These promising therapies have the potential to provide women with a greater number of options for vasomotor symptom management.

NAMS/PFIZER WULF H UTIAN ENDOWED LECTURE

Promises and Challenges of Gene Editing in the Age of CRISPR

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We have developed advanced tools to manipulate the written word, digital information, and computer code. But, until recently, we have had few tools for easy manipulation of DNA — the programming language of all living things. In this talk, I will explore the scientific frontiers in DNA manipulation using a new tool called CRISPR that is transforming biomedical science. I will explain how CRISPR is used to precisely modify genomes, including human genomes, and what are the broader implications of this new capability. This includes the ability to address pressing global problems, including food security through engineered plants, battling infectious diseases like malaria, and designing new cellular therapies for cancer. I will also present an example of genome editing in action from our lab's research at the New York Genome Center and NYU. In our work, we take advantage of the easy programmability of CRISPR to target not just one or two genes but all of the approximately 20,000 genes in the human genome. In this manner, we can efficiently "hunt" for genes responsible for SARS-CoV-2 (COVID-19) infection and, using this information, engineer new therapeutic strategies. For more about Dr. Sanjana's research, please visit: http://sanjanalab.org.

NAMS/KENNETH W KLEINMAN ENDOWED LECTURE

Death, Dying, and Dignity: The Art of End-of-Life Care

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All of us are born and all of us die. Most of us will not die suddenly, we will die of chronic, progressive, life limiting illnesses. Most hospitalized patients suffer from these illnesses: cancer, heart disease, COPD, and dementia. Unfortunately, care for patients who are approaching the end of life is often scattered, ineffective, and distressing to patients, providers, and family members, despite the best intentions of all involved. For the past 40 years we have attempted to improve care at end of life by encouraging open and honest communication between patients and providers and the use of advance care directives to allow people to choose quality of life instead of aggressive life-prolonging care. Despite the increase in education surrounding ethics, death and dying, and despite the increased availability of hospice and palliative care services, many, if not most people with life limiting illnesses still spend the end of life going in and out of emergency departments, hospitals, ICUs and nursing homes getting care that does not improve their quality of life and often does not improve their length of life. What if the frame we have used to consider end of life is wrong? What if, instead of looking at death as something extrinsic to life, something with causes that can continually fought back, we saw it as intrinsic, something that is built in to being human. Instead of seeing end of life care as a matter of "choice" and "communication," this talk will ask what it would be like to view end of life as part of the continuum of care, and ask what the best medical care is for those whose illnesses are no longer responding to disease specific therapies. As Atul Gawande put it "what should medicine do when it can't save your life?"