MENOPAUSE 101 COURSE

Hormone Treatment for Vasomotor Symptoms

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This presentation focuses on the key basics of hormone therapy (HT) prescribing for menopause symptom management. Clinicians typically receive little or no education on menopause management in their training, and HT prescribing rates remain low. Women are undertreated for their symptoms which are known to have significant negative effects on quality of life and are associated with a substantial economic burden in terms of increased health care costs and reduced work productivity. Now, more than ever before, it is possible to individualize the use of HT for women with bothersome menopause symptoms who have a preference to use HT and who are without contraindications to its use. Timing of initiation is important, and there is increasing understanding that both age and time since menopause impact the risk to benefit ratio. In general, the benefits of HT outweigh the risks in women who are under the age of 60 years or within 10 years of menopause onset. There are many HT options available to women, including different formulations, routes of administration and doses that are government approved such that therapy can truly be tailored to a woman's individual needs. It is advisable to use government approved options rather than custom compounded hormone therapy (which is not government approved) given concerns about purity, potency, efficacy and safety of non-approved, non-regulated hormones. This presentation will review the various systemic HT options as well as local vaginal therapies. It will also review when a progestogen is needed. Importantly, it will provide practical and evidence-based information on when and how to prescribe HT in women with chronic medical conditions (eg, hypertension, diabetes, rheumatologic disease), particularly given that 4 in 5 50 year old women have at least one chronic medical condition, and half have two or more chronic conditions.

Nonhormone Treatment for Vasomotor Symptoms

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Vasomotor symptoms (VMS), including hot flashes and night sweats, are the most common symptoms of menopause, affecting up to 80% of midlife women and often persisting for 7 to 10 years or longer. Although hormone therapy remains the most effective treatment, many women are not candidates due to contraindications or personal preference. As a result, nonhormone therapies are increasingly important in clinical practice. This abstract summarizes the full range of nonhormone treatment options for VMS based on the 2023 NAMS position statement. Among prescription therapies, selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), gabapentin, oxybutynin, and the neurokinin B antagonist fezolinetant are supported by Level I evidence and are recommended. These agents vary in mechanism, tolerability, and side effect profiles, and should be selected based on individual patient characteristics. Weight loss and stellate ganglion block are also recommended (Levels II–III), with weight loss particularly beneficial earlier in the menopause transition. Mind-body therapies such as cognitive-behavioral therapy (CBT) and clinical hypnosis are supported by Level I evidence and are effective in reducing the perceived burden and interference of VMS. Other nonpharmacologic approaches that are not recommended due to limited or inconsistent evidence or evidence of no effect will also be discussed. Clinicians will be well informed about the full spectrum of nonhormone options, including those that are not recommended, to support evidence-based, individualized care and to avoid underuse of effective therapies or misuse of ineffective ones.

Management of Perimenopause Symptoms

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The perimenopause is while having a definition is anything but definite in its management. We describe it as the transitional period leading to menopause. I often say to my patients that the only certainty about perimenopause is its uncertainty. It is characterized by significant fluctuations in hormones and as a result menstrual cycles have marked changes as well. We will review STRAW—the stages of reproductive aging which points out that both the early and late menopause transition stages and the first year following the final menstrual period are under the umbrella term perimenopause. Given these unpredictable changes women can and do experience a wide range of symptoms due to fluctuation of hormonal levels. The learning objectives of this presentation are to reformulate the narrative of what reproductive aging is, understand the timing and chronology of the menopause transition and common symptoms, and understand the association of these stages to future likelihood of health and disease so as to personalize patient care.

Management of Genitourinary Syndrome of Menopause

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Over 50% of women experience genitourinary syndrome of menopause (GSM), which can have a significant negative impact on quality of life. GSM encompasses vaginal dryness, vulvovaginal irritation, dyspareunia, dysuria and urinary urgency, among other symptoms. In this presentation we will discuss the presentation and evaluation of GSM, as well as how to distinguish this from other conditions that occur after menopause. Treatment for GSM can range from simple changes to personal care habits, to nonhormone, over-the-counter interventions, to prescription therapies. This talk will review the range of treatment options for different presentations of GSM.

Management of Primary Ovarian Insufficiency, Premature, and Early Menopause

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The vast majority of women will experience menopause at the average age of 52 years, with a normal age range of 46 to 55. Women who experience menopause prior to age 45 (~ 5%) are considered to have an early menopause; those with menopause prior to age 40 (~1%), have premature menopause. In some reports, the prevalence of premature and early menopause may be increasing. The most important initial management step is to recognize that the menstrual cycle is a vital sign, and the possibility that new onset of secondary amenorrhea for $\geq$ 3 months or new cycle irregularity for $\geq$ 6 months may represent early or premature menopause. If untreated, premature menopause is associated with increased risks of cardiovascular disease, osteoporosis, and cognitive decline. Initial evaluation of secondary amenorrhea includes a pregnancy test, and measurement of prolactin, thyroid stimulating hormone (TSH), and follicle stimulating hormone (FSH). If the FSH is elevated, repeat in 4 weeks along with an estradiol level to confirm the diagnosis of early or premature menopause. Usual menopause symptoms such as hot flashes, mood swings, and sleep disturbances may or may not be present or recognized as such. If the diagnosis of premature menopause is confirmed, possible etiologies should be sought but often are not identified. Diagnostic tests include a chromosomal evaluation (Turner Syndrome mosaics), genetic testing for Fragile X premutation carrier status, diagnosis of autoimmune disorders both general and endocrine-associated (measure TSH and anti-adrenal antibodies as anti-ovarian antibodies are unreliable), and infectious etiologies (mumps, TB, and HIV). Making the diagnosis is just the first step of a comprehensive management strategy that needs to be exquisitely sensitive to address a spectrum of concerns. Effective treatment includes psychological counseling for the premature and unanticipated loss of fertility, symptom management if present, and hormone replacement therapy (HRT) until the anticipated age of natural menopause whether or not symptoms are present with the intent of preventing long term estrogen deficiency disorders. In the absence of randomized, placebo-controlled trials to support specific hormone therapy preparations, doses, or duration of therapy over others, clinical practice guidelines recommend that clinicians prescribe HRT promptly—oral or transdermal estrogen therapies per patient preference and usual safety criteria but at higher doses than usually prescribed for women experiencing natural menopause at the usual age. If the patient has a uterus, concurrent progestogen therapy for uterine protection is indicated. If the patient desires conception, prompt referral to a fertility specialist is recommended along with determination of ovarian reserve including antimullerian hormone level and ultrasound determination of antral follicle count. Micronized progesterone appears to be a better choice for endometrial protection than a synthetic progestogen for women who desire to conceive. If the patient is not interested in pregnancy, oral contraceptives can be prescribed for contraception, symptom control, and bone protection. Data with clinical outcomes are sparse with either approach. Longitudinal observational studies of women rendered postmenopausal with bilateral surgical oophorectomy suggest that hormone replacement therapy should be initiated promptly after diagnosis, administered at doses higher than those utilized for women experiencing menopause at the anticipated natural age and continued at least until the average age of natural menopause. Primary ovarian insufficiency differs from natural menopause in that ovulation and menstrual cycles can transiently return in approximately 10 % of women. It is not possible at this time to predict who will experience a transient resumption of ovarian activity, so clinical management must take into account the patient's desires for pregnancy (or not), should she resume ovulation and menstruation. Depending on the specific cause of POI, if identified, family genetic counseling may be indicated along with management of associated conditions.

Management of Sexual Dysfunction at Menopause

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Sexual function is a major concern for menopausal women; 50 to 70% of perimenopausal and postmenopausal women experience sexual dysfunction. Menopause impacts multiple domains of sexual function, including sexual interest, arousal, orgasm, and sexual pain. These may be associated with changes in systemic estrogen or testosterone levels as well as local effects of genitourinary syndrome of menopause, characterized by vaginal dryness and dyspareunia. In addition, other contributing factors include vasomotor symptoms, mood changes, sleep disruption, and urinary tract symptoms, which may interact with sexual function, body image, sexual self-concept, and relationships. Multifactorial sexual function issues may be complex to manage and often require a multimodal, stepwise approach. This discussion will provide an overview of the pharmacologic treatment of sexual dysfunction associated with menopause. Topics discussed will include: 1) decreased or absent sexual interest (libido) and/or arousal – pharmacologic management with systemic nonhormonal and hormonal medications and indications, contraindications, efficacy, adverse effects, and dosing; 2) dyspareunia associated with menopause – nonpharmacologic and pharmacologic management and indications for use of vaginal dilators and pelvic floor physical therapy.

Overview of Cognitive Behavioral Therapy for Vasomotor Symptoms, Insomnia, Anxiety, and Depression

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Introduction—Cognitive behavioral therapy (CBT) is an evidenced-based non-pharmacological treatment that has been used to treat depression, anxiety, phobias, and posttraumatic stress disorder. CBT has been adapted to treat menopause symptoms. Broadly, it is defined as a range of approaches and strategies, including behavioral therapy (taking action to mitigate problems or symptoms), cognitive therapy (modifying cognitive distortions to help manage symptoms), behavioral activation (implementing

strategies to move towards a goal), exposure therapy (coping with feared stimuli), and problem-solving. The National Institute for Health and Care Excellence and The Menopause Society recommend CBT to treat vasomotor symptoms (VMS), (ie, hot flashes and night sweats), menopausal depression, and menopause-related insomnia. **Vasomotor symptoms**—Nonhormonal factors that increase bothersome VMS include higher levels of perceived stress, depressed mood, anxiety, negative beliefs about menopause and ageing, social anxiety about having hot flashes in public, and perceptions of one's ability to cope and control VMS. Several randomized clinical trials tested a theoretical model to treat problematic VMS with inadequate sleep, stress and anxiety. This model includes assessing and treating factors that trigger hot flashes, that heighten attention to body sensations, and cognitive and behavior reactions to menopause symptoms. CBT treatment approaches to teach women how to modify negative cognitive and behavioral reactions and increase their perceived ability to control VMS have also been found to reduce stress and anxiety, while improving menopause-related insomnia. **Menopause-related insomnia**—Is defined as insomnia symptoms related to menopause. Night sweats, thoughts about sleep interference, anxiety, depressed mood, alcohol consumption, obsessive thinking, urinary symptoms, chronic pain, and other medical disorders common in midlife interfere with quality of sleep for peri- and postmenopausal women. Studies have found that traditional CBT for insomnia (CBT-I) and sleep restriction therapy (SRT) improve sleep quality over sleep hygiene education alone. CBT-I had higher improvement with sleep maintenance compared to SRT. The CBT-I practitioner assesses and treats precipitating factors (biological, psychological, or social) and maladaptive coping behaviors that interfere with adequate sleep. CBT-I treatment also includes relaxation strategies, education about sleep hygiene, strategies to cope with pain and to decrease nighttime bathroom visits. **Perimenopausal depression**—Is defined as experiencing classic symptoms of depression, not necessarily major depression, along with problematic menopause symptoms and challenges related to demographic, health-related and psychosocial factors. Postmenopausal women can experience the same challenges. Peri- and postmenopausal depression is a multifaceted and complex area. As health care practitioners, it is important to assess demographic, health-related, and psychosocial factors that can contribute to problematic menopause symptoms and changes in mood and/or increased anxiety. Demographic, health-related and psychosocial factors to inquire about are listed below. Please note, the list is not exhaustive. Demographics: financial, insurance, or employment problems. Health-related: problems with sleep, VMS, cardiovascular disease, diabetes, chronic pain, urinary symptoms, obesity, major depression, bipolar disorder, high anxiety, distress about changes in sexual functioning, changes in memory, nulliparity, current use of antidepressants, and excessive alcohol use. Psychosocial factors: loss of a partner or child, other major stressful events, low social support, lack of close friends, empty nesting, the impact of cultural attitudes towards menopause and ageing. **Summary and future research**—Though studies have shown that traditional CBT can help mitigate depression, models that have treated VMS and menopause-related insomnia can also mitigate depression during the peri- and postmenopausal years. Understanding and treating the health and psychosocial-related factors common in midlife can also help peri- and postmenopausal women manage mood and anxiety. There are many opportunities for additional CBT research studies.

SEXUAL HEALTH 101 COURSE

A Primer for Office-Based Assessment and Diagnosis of Female Sexual Problems

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Female sexual health is an essential yet often overlooked aspect of overall well-being, particularly during midlife and menopause. Despite the high prevalence of sexual concerns in women, many clinicians lack formal training in sexual health assessment and feel unprepared to address these issues in women. Common barriers include time constraints, discomfort with the topic, limited clinical resources, and uncertainty about diagnostic frameworks. This presentation offers a practical, evidence-based approach to the office-based evaluation and diagnosis of female sexual problems, empowering clinicians to engage in these important conversations confidently and competently. Drawing from current literature and clinical guidelines, including those from the International Society for the Study of Women's Sexual Health (ISSWSH) and The Menopause Society (TMS), the session presents a biopsychosocial model of sexual health that acknowledges the interplay of hormonal, psychological, relational, and sociocultural factors. A stepwise, patient-centered approach to history-taking is demonstrated using cases and validated tools. The framework emphasizes integration of sexual health into routine care, allowing clinicians to efficiently assess and identify the most common subtypes of female sexual dysfunction: hypoactive sexual desire disorder, sexual arousal disorder, genitopelvic pain/penetration disorder, and orgasmic disorder. Participants will learn strategies to normalize sexual health discussions, reduce stigma, and tailor evaluations to the unique needs of each patient. The session highlights communication techniques, trauma-informed care principles, and the importance of inclusivity—addressing disparities in care and emphasizing cultural competence. By the end of the presentation, clinicians will have the knowledge to initiate dialogue regarding sexual concerns, differentiate contributing factors, and develop management plans. This session aims to enhance awareness, build skills, and promote a proactive approach to female sexual health, supporting the delivery of comprehensive and equitable care focused on the individual. **References**: 1. Kingsberg SA, Clayton AH, Portman D, et al. The International Society for the Study of Women's Sexual Health Process of Care for the Identification of Sexual Concerns and Problems in Women. *Mayo Clin Proc*. 2018;93(4):515-534. doi:10.1016/j.mayocp.2018.02.013 2. Parish SJ, Hahn SR, Goldstein SW, Giraldi A, Kingsberg SA, Larkin L, Minkin MJ, Brown V, Christiansen K, Hartzell-Cushanick R, Kelly-Jones A, Rulle J, Sadovsky R, Faubion SS. The International Society for the Study of Women's Sexual Health Process of Care for the Identification of Sexual Concerns and Problems in Women. Mayo Clinic Proceedings. 2019;94(5): 842-=856. https://doi.org/10.1016/j.mayocp.2019.01.009 3. Clayton AH, Goldstein I, Kim NN, Althof SE, Faubion SS, Faught BM, Parish SJ, Simon JA, Vignozzi L, Christiansen K, Davis SR, Freedman MA, Kingsberg SA, Kirana PS, Larkin L, McCabe M, Sadovsky R. The International Society for the Study of Women's Sexual Health Process of Care for Management of Hypoactive Sexual Desire Disorder in Women. Mayo Clin Proc. 2018 Apr;93(4):467-487. doi: 10.1016/j.mayocp.2017.11.002. Epub 2018 Mar 12. PMID: 29545008. 4. The 2022 Hormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. The 2022 hormone therapy position statement of The North American Menopause Society. Menopause. 2022 Jul 1;29(7):767-794. doi: 10.1097/GME.0000000000002028. PMID: 35797481. 5. Shifren JL, Monz BU, Russo PA, Segreti A, Johannes CB. Sexual problems and distress in United States women: Prevalence and correlates. *Obstet Gynecol*. 2008;112(5):970-978. doi:10.1097/AOG.0b013e3181898cdb

Psychotherapy for the Treatment of Female Sexual Dysfunctions

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Practical, patient-centered psychotherapy approaches can be used as primary or adjunctive treatments for women experiencing sexual dysfunctions. Evidence-based cognitive behavioral approaches will be described for the treatment of hypoactive sexual desire disorder, female arousal disorders, female orgasmic disorders, and genito-pelvic pain/penetration disorders. Cognitive-behavioral therapy (CBT) addresses maladaptive beliefs, negative cognitive schemas, and avoidance behaviors that undermine sexual well-being. Specific CBT interventions include modified sensate focus exercises, directed masturbation techniques for orgasmic difficulties, and mindfulness-based strategies for enhancing interoceptive awareness and reducing performance anxiety. These techniques can be tailored to the specific clinical presentation, whether diminished desire, difficulties with arousal or orgasm, or pain-related sexual avoidance.

Nonhormone Pharmacologic Treatments for Female Sexual Dysfunction

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Approved and emerging pharmacotherapy plays a substantial role in the management of hypoactive sexual desire disorder (HSDD), female sexual arousal disorder (FSAD), and combined female sexual dysfunctions (FSDs). Centrally active substances affecting serotonergic, dopaminergic, and melatonergic pathways have been studied and are available treatments for HSDD. Flibanserin is a centrally acting, oral daily medication, government approved for the treatment of generalized, acquired HSDD in premenopausal women in the US and for premenopausal and postmenopausal women ≤ 60 years of age in Canada. Flibanserin decreases serotonin levels and increases dopamine and norepinephrine levels and is believed to enhance excitatory and diminish inhibitory responses to sexual cues. It is administered as a 100-mg tablet once daily at bedtime. Flibanserin's efficacy, safety, indications, and treatment considerations will be reviewed. Changes in the US flibanserin label include modification of the boxed warning regarding alcohol use and the risk of hypotension and elimination of the Risk Evaluation and Mitigation Strategy for prescribing clinicians and pharmacists. Specific populations to be addressed include postmenopausal women outside of Canada, women with depression on and off anti-depressant medications, and breast cancer survivors. Bremelanotide is the second centrally acting US FDA-approved medication for generalized acquired HSDD in premenopausal women. It is a cyclic heptapeptide analog of the endogenous neuropeptide α-melanocyte-stimulating hormone with high affinity for the melanocortin-4 receptor that acts by modulating dopaminergic neurotransmitter pathways involved in sexual desire and arousal. It is self-administered as needed via a subcutaneous, single-use autoinjector prefilled with 1.75 mg/0.3 ml delivered with a 29-gauge nonvisible needle over 5 seconds, approximately 45 minutes prior to anticipated sexual activity. Bremelanotide's efficacy, safety, indications, adverse effects, and administration guidelines will be appraised. Both flibanserin and bremelanotide demonstrated modest efficacy. Data are not available regarding the impact of duration and frequency of use on neuroplasticity and HSDD remission, resolution, and relapse rates following discontinuation. The combination or comparison of these agents has not been evaluated. Two psychotropic medications are used as evidenced-based off-label therapies and are under investigation in combination with hormonal and other agents. Bupropion, which enhances dopamine and norepinephrine, was found in a randomized, double-blind, placebo-controlled trial (at 300-400 mg/d) to improve sexual desire in women with HSDD, but enrollment was insufficient to reach statistical significance. In women with antidepressant-induced sexual dysfunction, the addition of sustained-release bupropion (300 mg/day) improved sexual desire. Thus, bupropion may be used as an alternative evidenced-based off label treatment strategy or as an add-on antidote in antidepressant-induced FSD. Buspirone, which reduces serotonin inhibition, was found in one small placebo-controlled trial to improve sexual function in depressed women with SSRI-induced sexual dysfunction at a dose of 20-60 mg/d. Small studies demonstrated benefits with PDE5 inhibitors for arousal problems in women with spinal cord injury and antidepressant-associated dysfunction. Topical sildenafil cream is in development for treatment of FSAD and may be particularly useful for women with genital-focused arousal difficulties. Efficacy results from a phase 2b clinical trial showed that topical sildenafil cream improved sexual function in women with FSAD, particularly in a subset of participants who did not have orgasmic dysfunction or who also had concomitant decreased desire, increasing sexual arousal sensation, desire, and orgasm, and reducing sexual distress. Office-based counseling, sex therapy including CBT and mindfulness-based approaches, psychotherapy, and pharmacotherapy all play a role in treating FSD. Combination therapy with pharmacologic and psychological/behavioral therapies has been demonstrated to be effective, but more research is needed. Achieving the optimal balance among available biopsychosocial interventions for FSD continues to be an ongoing clinical challenge.

Androgens for Treating Hypoactive Sexual Desire Disorder in Postmenopausal Women

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Prevalence studies of female sexual dysfunction (FSD) have largely focused on sexually active or partnered women, and notably on low desire with associated distress. Our recent community-based study (The Australian Women's Midlife Years (AMY) study) collected data from an unselected, nationally representative sample of over 5550 women, aged 40-69 years, whose menopausal status could be determined by the STRAW+10 criteria, agnostic to partner status, partner preference and sexual activity. Our data revealed that in the order of 50% of midlife women have low sexual wellbeing: one in 4 have a sexual dysfunction and, of note, another one in 4 have sexually-related distress without an identified sexual difficulty (ie, no dysfunction). Approximately 25% of Australian women aged 40-69 years have low sexual desire, and an estimated half of these have low sexual desire that causes them distress (hypoactive sexual desire dysfunction; HSDD). Whiles it is often said testosterone blood levels decline in the perimenopause and menopause, studies have not shown this to be the case. The AMY Study will provide contemporary data for the associations between age and menopausal stage testosterone blood levels in women. There is evidence to support the use of testosterone therapy for postmenopausal women experiencing HSDD, although the efficacy is generally low to moderate. However, prescribing of testosterone therapy is somewhat chaotic in many countries. Critically, there is no definable "female androgen deficiency "condition and presently no blood test will identify the women with HSDD most likely to benefit from a trial of testosterone; a low blood testosterone alone is not an indication for treatment, and a "normal" blood level is not a reason to deny treatment Barriers to treatment include the lack of regulator approved products in most countries and the ongoing fear that testosterone therapy is unsafe. Conversely, some women are receiving inappropriately excessive doses of male formulations or an array of compounded therapies, as well as testosterone pellets, that have no pharmacokinetic or safety data. In many instances dosing is a best guess.

How to Manage Sexual Dysfunction Due to Genitourinary Syndrome of Menopause

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Genitourinary syndrome of menopause (GSM) has a profound negative impact on sexual function including vaginal dryness and pain with external or internal sexual play or touch. The symptoms can begin early in the perimenopause transition phase and typically worsen over time. Symptoms include vaginal dryness, dyspareunia, increased urinary tract infections (UTIs), vulvovaginal irritation, increased risk of vaginal infections and other vaginitis conditions. These symptoms lead to interruptions in sexual relationships and there is significant distress associated with marital/relationship discord due to sexual pain and reduced arousal, resulting in reduced desire and even avoidance of any intimate touch. Barriers include lack of awareness of the patient regarding normal changes in (peri)menopause, fear regarding safety of local vaginal hormones, and often times underdiagnosis and undervaluing of treatment by clinicians. GSM is defined as the changes to the vulvovaginal and urethral tissues due to a reduction in sex steroid hormones (particularly estradiol and testosterone). Physical changes associated with GSM include labial atrophy, reduced moisture, introital stenosis, clitoral atrophy, vaginal/vestibular surface friability and pallor, with potential for petechiae, ulcerations, and tears as well as urethral caruncles, prolapse, or polyps. These changes can be improved and even reversed with topical vaginal hormones in varied forms and modes of administration. There are a variety of FDA approved local hormone medications (estradiol tablet/cream/ring/insert, DHEA) as well as adjunctive nonhormonal vaginal moisturizers and lubricants to optimize this important quality of life measure. The only FDA approved option for treatment of local androgen deficiency in the vulvovaginal tissues is with DHEA (prasterone), and all forms of topical testosterone would require compounding which is not FDA approved and therefore more difficult to ensure safety and consistency. The local hormone options have been shown to be safe to use for most patients and there are very few contraindications. These will be expanded upon in this lecture. Systemic menopausal hormone therapy is not sufficient treatment for GSM and both systemic and local hormone therapy can be used simultaneously, safely. Patients and their partners benefit greatly from adequate treatment of sexual dysfunction due to GSM.

Sexual Function in Cancer Patients: Causes and Treatments

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Cancer and its treatment affect female sexual function (SF) through biological, psychological, and social mechanisms. Loss of SF in the context of cancer is associated with decrements in physical and mental health, wellbeing, and relationship quality. Many women with cancer are menopausal at time of cancer diagnosis and many others experience iatrogenic menopause as a result of cancer treatment. Menopause itself can have deleterious effects on female SF. Abrupt onset or exacerbation of menopause symptoms resulting from antiestrogen therapies, ionizing radiation involving the ovaries, oophorectomy, and symptoms associated with these interventions commonly result in sexual dysfunction and related distress. Loss of SF in women with cancer is predominantly physiologic and iatrogenic in origin with secondary psychosocial sequelae, rather than psychological or behavioral in origin. Women with a history of sexual or relational dysfunction before a cancer diagnosis and those with a prior history of sexual abuse or assault are more likely to develop SF problems or exacerbation in the cancer context. Dyspareunia with vaginal dryness, loss of libido, and difficulty with sexual arousal and orgasm are highly prevalent conditions among women with cancer. Although attention to sexual sequelae of cancer treatment among women is improving and evidence-based tools are available to assess for and address female SF function concerns in the cancer context, these conditions are still under-diagnosed in routine cancer care. Evidence supports that women with cancer, including unpartnered and older women, value their SF, regard it as an appropriate topic for discussion in the oncology context, and wish to be informed about sexual sequelae as part of decision-making about cancer treatment. Most women with SF concerns during cancer treatment endorse a desire for medical attention to these concerns. Diagnosis and treatment of female SF problems benefit from a holistic biopsychosocial evaluation, including partner status and other potentially contributing partner factors including partner health, relationship quality and interpersonal communication. As many as 1/3 of women presenting with SF concerns in the context of cancer have a history of sexual assault or trauma, and the most prevalent cancer types women survive directly affect the female sexual organs. For these reasons, a trauma-informed approach is warranted and likely benefits all women. Proactive education about sexual sequelae of cancer treatment likely helps to mitigate these outcomes and is correlated with earlier referral to care. For dyspareunia associated with vulvovaginal atrophy, restoration of vaginal moisture and lubrication can be achieved with nonhormone and local hormone methods. Lubricants, especially silicone and oil-based (not compatible with condoms), can help reduce pain due to friction during vaginal intercourse. A patient-centered approach should prioritize patient preferences and consider cancer type, including hormone receptor status, and stage. Behavioral interventions, including elimination of genital soaps and other irritants, avoidance of pads, improvement in urinary and bowel habits and switching from daily systemic, to episodic or local antihistamines for regular users may also be beneficial. Vaginismus commonly develops in women with dyspareunia and can be effectively addressed with anatomical education, self-dilation, and pelvic floor physical therapy. Low libido and arousal difficulties are often multi-factorial in etiology and may improve with resolution of dyspareunia. Other interventions, including adjustments to medications known to cause low libido and arousal difficulty, evidence-based psychological therapies such as mindfulness and sensate focus therapy, education about self-stimulation and partnered techniques, and interventions to promote other chronic disease and pain management, sleep, physical activity, body image and stress reduction may also be beneficial and confer other important health benefits. Evaluation and treatment for SF concerns in the context of cancer should be informed by a thorough and recent gynecologic examination. Imaging should be considered for new onset deep dyspareunia to evaluate for a neoplasm. Cancer treatment may increase a woman's susceptibility to sexually transmitted infections; prevention, testing and counseling should be offered as appropriate.

Clinical Management of Female Sexual Problems Using Lubricants, Moisturizers, and Devices

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Introduction—Providing comprehensive care for women with menopausal concerns includes having a familiarity with the efficacy and potential dangers associated with a variety of current commercial products that target the menopausal population. Nonhormonal water, oil, and silicone-based lubricants are products designed to enhance genital and anal comfort and can be applied before and during intimacy for women and their partners. Moisturizers are products designed to attract moisture to target tissues in order to provide comfort for a prolonged period. They are used episodically, independent of the timing of intimacy. Several studies have shown evidence-based support for hyaluronic acid (HLA) based moisturizers because of the superior efficacy and tolerability when compared to other moisturizers. Select studies show similar efficacy between HLA products and local estrogen therapy when used to treat VVA/GSM. Specific characteristics that should be considered when evaluating products to recommend include: mechanism of action, osmolality, potential allergens. An emerging area of consideration for clinicians who are evaluating hygiene products for women, is the effect of a product on the vaginal and vulvar microbiome. Products that are shown to cause biome disruption can inadvertently contribute to irritation and infection. An important distinction can be made among products that provide information about their effect on the microbiome and those that do not. Products that support and enhance the vaginal microbiome are also available in the form of oral and vaginal pre- and probiotics. Specific data regarding the ability of a product to colonize the vagina is essential when considering recommendations to patients. Two products, Clairvee and VS-01 provide colonization data from their clinical studies. A new study further supports the use of the expanding Milli vaginal dilating device designed for alleviating dyspareunia and enhancing pleasure for women challenged by pelvic floor dysfunction and VVA/GSM. Survey results support the time efficiency of use (10-20 minutes 4-5x/ week) and superior patient compliance when compared to traditional static vaginal dilators. More products that address vaginal pain include the OhNut device for collision dyspareunia and the Intimate Rose vibrating muscle release wand for home pelvic floor muscle relaxation. An area of product development that is in its infancy is the use of unique compounds to alleviate sexual and vulvar pain, a major concern among postmenopausal women. Two commercially available products include: biomimetic peptides and cannabinoids, supported by animal model data. Although most commercial products are available without a prescription, many menopausal women look to their trusted providers to suggest products that are reputable and effective.

OPENING SYMPOSIUM: PERIMENOPAUSE

Perimenopause Definitions, Epidemiology, and Hormone Overview

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Approximately 6,000 women experience menopause each day in the US, or about 1.3 million women per year. Menopause occurs at the average age of 51 years because of the progressive attrition of ovarian follicles, a process that begins in utero and progresses throughout reproductive life. The rate of atresia can be increased by environmental factors, smoking, oncology treatments (chemotherapy and radiation therapy), disorders of metabolism such as galactosemia, infectious agents such as mumps and HIV, and genetic and autoimmune disorders. By definition, perimenopause is the phase of reproductive aging characterized by the onset of menstrual cycle changes and extends for 1 year after the final menstrual period. The Stages of Reproductive Aging Workshop (STRAW) initially established this definition in 2002, to standardize subject criteria for participation in clinical research, but also to promote standard definitions to utilize in patient care. In 2012, STRAW +10 updated the clinical criteria. In addition to menstrual cycle changes of > 7 or more days difference of cycle length in the early menopause transition (median age of 47 years), in the late transition (median age 49 years), episodes of 2 months or more of amenorrhea or skipped menstrual cycles are characteristic. Additionally, vasomotor symptoms (VMS) most commonly start during the late perimenopausal transition and in the early postmenopause, but for some, VMS can begin earlier. A number of prospective longitudinal studies of women coursing through the menopause transition provide the evidence upon which the STRAW criteria were based. These studies include the Study of Women's Health Across the Nation (SWAN), which has been the largest, longest, and included the most ethnically diverse participants. Other studies include the Massachusetts Women's Health Study, the Penn Ovarian Aging Study, the Seattle Midlife Women's Health Study, and the Melbourne Women's Midlife Health Project. New data suggest that some symptoms of the perimenopause can start during the late reproductive stage when menstrual cycles are still regular—women complain of "not feeling like myself." During perimenopause, ovarian steroid hormones (estrogen and progesterone) eventually dramatically decline as does ovarian inhibin while follicle stimulating hormone (FSH) levels reciprocally increase. Estradiol, the predominant estrogen during reproductive life, declines overall while estrone becomes the dominant estrogen after menopause. Testosterone levels decline with age but do not show an abrupt drop during menopause. The menopausal transition, however, can be marked by wide fluctuations and at times markedly elevated levels of estradiol with lower progesterone secretion during ovulatory cycles. Consequences of elevated estrogen levels include heavier bleeding, endometrial hyperplasia, and growth of uterine fibroids. Because of the unpredictability of hormone levels during the menopause transition, measurement of hormone levels is discouraged. Pregnancy can occur during ovulatory cycles, so contraception remains an important priority. Clinically, vasomotor symptoms (VMS), mood swings, and sleep disorders predominate. Black women often experience an earlier onset of VMS during the menopause transition and a longer duration of symptoms; non-Hispanic White women are intermittent, and Asian women have the fewest VMS. Symptoms of the Genitourinary Syndrome of Menopause can begin as do libido concerns. Finally, the menopause transition is characterized by deleterious metabolic changes—bone loss, visceral adipose tissue (including the heart and liver) increases, lean mass decreases, and the metabolic syndrome and its components increase. As awareness grows, measures to adopt preventive strategies for enduring health are encouraged.

When Does Perimenopause Actually Begin?

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In 2001, The Stages of Reproductive Aging Workshop (STRAW) created a framework to define the stages of the menopause transition—the first ever. It was an attempt to allow consistency from study to study for research in this area. The same group of menopause experts reconvened 10 years later to further refine this framework and named it STRAW+10.[1] In this model, entry to the menopause transition or perimenopause begins when a menstrual cycle parameter is met, a greater than 7-day change in consecutive cycle lengths—2 times in 10 cycles to be precise. But is this consistent with women's* lived experience? Is this when women first notice changes associated with perimenopause, the menopause transition? Findings from the 2020 Women Living Better survey would suggest not.[2] This survey of women aged 35-55 demonstrated that for some women sleep disruption, moodiness, brain fog, and more begin with only subtle changes to their menstrual cycles and flow during what STRAW designates the Late Reproductive Stage (LRS). The recently published Australian Midlife Study[3] supports these observations. For some women, the menopause transition is uneventful but for others it is prolonged, symptomatic, and distressing. Both women and clinicians stand to benefit from a more complete appreciation of when perimenopause begins, and how it is manifest. This knowledge can also give clinicians an opportunity to provide anticipatory guidance to patients of a certain age about what may be in their future. Data will be presented about what women expect with respect to the timing of menopause. Additionally, what they can experience such as "not feeling like myself" along with fatigue, low libido, irritability, and vasomotor symptoms while they are still menstruating fairly regularly will be reviewed. We will consider whether it's time for a frameshift with respect to the beginning of perimenopause to align with patient experience. Improved alignment would allow clinicians to: Prepare women as they enter the late reproductive years to recognize the variety of menopause related symptoms that they might encounter Set expectations for women about the dynamic nature of perimenopause Validate women's experiences with symptoms when they begin before noticeable menstrual cycle changes This is doable now. And as we continue to study the physiology of the menopause transition with its multiple manifestations we will get better at supporting our patients even if we can't pinpoint a precise beginning of perimenopause. And we can encourage menopause researchers to identify and evaluate treatments for women who are suffering during these sometimes-difficult years. What's in a name and more about defining menopause.[4] *People with ovaries **References:** 1. Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, Sherman S, Sluss PM, de Villiers TJ; STRAW + 10 Collaborative Group. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. *J Clin Endocrinol Metab*. 2012 Apr;97(4):1159-68. 2. Coslov N, Richardson MK, Woods NF. Symptom experience during the late reproductive stage and the menopausal transition: observations from the Women Living Better survey. *Menopause*. 2021 Jul 26;28(9):1012-1025. 3. Islam, Rakibul M, et al. Prevalence and severity of symptoms across the menopause transition: cross-sectional findings from the Australian Women's Midlife Years (AMY) Study. *The Lancet Diabetes & Endocrinology*, www.thelancet.com/diabetes-endocrinology Published online July 25, 2025. 4. Ambikairajah A, Walsh E, Cherbuin N. A review of menopause nomenclature. *Reprod Health*. 2022 Jan 31;19(1):29.

Floodgates and Frustration: Evidence-Based Approaches to Abnormal Uterine Bleeding in Perimenopause

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Abnormal uterine bleeding (AUB) is among the most disruptive and commonly reported symptoms in the menopause transition yet is often overlooked or misattributed to hormonal fluctuations alone. In this presentation, we will review prospective epidemiologic data, including findings from SWAN and the Melbourne Women's Midlife Health Project, on bleeding patterns across the menopause transition, including how to recognize when bleeding is likely to be physiologic versus pathologic. Using a PALM-COEIN framework, we will discuss structural and hormonal causes of AUB in perimenopause. We will also address diagnostic and management challenges in complex populations, including individuals with IUDs and prior endometrial ablation. Finally, we will review evidence-based strategies for managing bleeding once pathology has been excluded.

Vasomotor Symptoms, Sleep, and Mood

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With the increasing attention paid to menopause over the past decade, clinicians, researchers, and patients have been struggling to strike a delicate balance. On one hand, there exists a legitimate concern regarding the potential over-medicalization of a natural process experienced by all women. At the same time, they are seeking evidence of ways to prevent or early detect symptoms or medical conditions commonly associated with this period in life that could warrant timely intervention to improve quality of life and increase the chances of better health – eg, cardiovascular, bone, sexual, and brain health. As a result, more focus has been directed towards the transitional phase leading up to menopause – the perimenopause or menopause transition – a complex period that involves a progressive depletion of ovarian follicles and intense – at times, chaotic – hormonal fluctuations. These hormonal changes are responsible for the occurrence of menstrual cycle irregularities and have been linked to the emergence of vasomotor symptoms (VMS), ie, hot flashes and night sweats, considered the most frequent and bothersome symptoms of this period in life. Notably, vasomotor symptoms, when persistent, have also been associated with cardiovascular disease risk factors, including hypertension, insulin resistance, and poorer lipid profiles, as well as an increased risk of myocardial infarction, stroke, and CVD mortality later in life. For decades, VMS were thought to occur mainly due to changes in the hypothalamic thermoregulatory system's ability to regulate body temperature while responding to fluctuating levels of estrogen. More recently, it has been recognized that hypothalamic kisspeptin/neurokinin B/dynorphin (KNDy) neurons may significantly contribute to the generation of flushes and the regulation of body temperature, thereby opening a new pathway for the development of effective, nonhormonal interventions. However, the efficacy of neurokinin-targeted therapies in managing VMS during perimenopause has yet to be established. Menopause-associated sleep disturbances are characterized by sleep disruption, with frequent nighttime awakenings and more frequent periods of wakefulness after sleep onset (WASO), leading to non-restorative sleep. Such disturbances may be linked to hormonal changes, VMS, psychosocial factors, and other conditions like obstructive sleep apnea and restless legs syndrome. Interestingly, sleep problems can also occur independently of VMS, likely due to the effects of estrogen and progesterone on the central nervous system. The menopause transition is also a period of vulnerability for mood and anxiety symptoms. Cohort studies have identified a history of depression as a strong risk factor for major depressive disorder during perimenopause. However, new onset may also occur, especially in women who are more sensitive to hormone fluctuations. Overall, treatment guidelines suggest that first-line treatments for menopause-associated depression are the same ones recommended across the lifespan – ie, cognitive behavioural therapies (CBT) and pharmacological interventions – eg, use of SSRIs, SNRIS – have the best evidence for the management of depression. There have been, however, a few studies exploring the effectiveness of hormone interventions. The use of transdermal estradiol has been shown to improve depressive symptoms in peri but not postmenopausal women, again corroborating the notion of a critical window for estrogen-based therapies. The antidepressant effects of estrogen seem to be independent of the presence and/or improvement of VMS. Although estrogen-based therapies are not approved for or considered first-line treatments for mood symptoms, clinicians and patients can benefit from their antidepressant properties when used for other menopause-related symptoms (VMS, sexual dysfunction) or in

combination with antidepressants, due to their augmenting effects. Meanwhile, conventional antidepressants and neurokinin-targeted therapies may assist in managing VMS and sleep disturbances during menopause and contribute to a better quality of life. These are promising times for menopause care, with an expanding range of therapeutic options that can be tailored to meet our patients' needs.

Personalized Treatment Options for Common and Uncommon Symptoms

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As the list of symptoms attributed to perimenopause proliferates—from burning mouth and tinnitus to frozen shoulders and gastrointestinal disturbances—menopause clinicians face significant challenges. These symptoms can impact patients' quality of life and lead to misdiagnosis or ineffective, suboptimal treatments. This presentation will review current evidence for purported symptoms and address the complexities clinicians encounter in assessing these symptoms. It will discuss evidence-based, individualized strategies for evaluating and managing both common and uncommon symptoms reported by patients during perimenopause. Emphasis will be placed on enhancing patient education and shared decision-making.

Addressing Contraceptive Needs of Perimenopausal Women

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Nonsmoking perimenopausal women without cardiovascular risk factors – obesity, lipid disorders, hypertension, coronary heart disease, diabetes, migraines with aura – can safely use currently marketed combination (estrogen-progestin) contraceptives: pills, patches, or rings. The cardiovascular risk factors detailed above become more prevalent as women age. When such risk factors are present, hormonal regimens with an estrogen dose lower than that used in combination hormonal contraceptives, but with a dose of progestin sufficient to suppress ovulation, are appropriate. The combination oral contraceptive with the lowest dose of estrogen combines 10 mcg of ethinyl estradiol (EE) with 1 mg of the progestin norethindrone acetate. A number of other currently marketed combination oral contraceptives also contain 1 mg of norethindrone acetate, a dose sufficient to prevent ovulation. A formulation (packaged with 28 hormonally active tablets) which combines 5 mcg of EE with 1 mg of norethindrone acetate is labeled for treatment of menopausal symptoms and available as a generic. This formulation should provide effective contraception for perimenopausal women. Most perimenopausal women using this menopausal formulation off-label for contraception will become amenorrheic over time. Another hormonal strategy for providing contraception to perimenopausal women combines the high intrauterine progestin levels associated with use of levonorgestrel-releasing intrauterine devices (LNG IUDs) with menopausal doses of estrogen. If transdermal (rather than oral) estradiol is employed, this strategy can safely be used by women with the cardiovascular risk factors detailed above. The combination of a levonorgestrel IUD with transdermal estradiol (patch, spray, gel, ring) represents a strategy that can be used in low-risk women as well as those with cardiovascular risk factors. Clinicians, however, should be aware that regardless of age, use of estrogen and/or progestin-containing medications are considered contraindicated in women with a history of venous thromboembolism, myocardial infarction, stroke, or breast cancer. Use of combination oral contraceptives, depot medroxyprogesterone acetate, and LNG IUDs is associated with a reduced risk of endometrial cancer. Combination oral contraceptive use also reduces risk of ovarian cancer; this protection extends for at least 35 years after use, meaning that perimenopausal oral contraceptive users experience protection during their 50s and 60s, times of peak incidence for ovarian cancer. While the best conducted studies indicate that oral contraceptive use does not impact risk of breast cancer in reproductive aged women, some studies have suggested a small elevation in risk. The Centers for Disease Control recommends that, in the absence of contraindications, women who require contraception can continue to use hormonal contraception until menopause or age 50-55 years. Although widely employed, checking follicle- stimulating-hormone levels to assess the menopausal status of women using hormonal contraception is not be dependable.

PLENARY SYMPOSIUM #1

Hormones and Brain Health/Cognition

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Cognitive complaints are common in midlife women and worsen with advancing menopause stage. Validating these complaints, reliable evidence from longitudinal studies shows small but measurable declines in one cognitive domain, verbal memory, as women transition from the pre- to perimenopause. Less reliable changes are observed in processing speed and attention/working memory. Oophorectomy in premenopausal women also induces declines in verbal memory that improve with estrogen treatment. While such evidence raised the possibility that hormone therapy might also enhance memory in naturally menopausal women, randomized clinical trials reliably produced no evidence of improved memory with hormone therapy in early postmenopausal women. There are two notable gaps in the literature. First is the absence of large-scale clinical trials of hormone therapy on cognition in perimenopausal women. Second is the absence of large-scale clinical trials on cognition in women with bothersome vasomotor symptoms (VMS). VMS may be an important modifier of the effect of hormone therapy on cognition. When measured objectively using ambulatory skin conductance monitors, VMS are associated with declines in memory, alterations in neural circuits critical for memory functions, and even Alzheimer's disease biomarkers. Although definitive evidence is not available, findings from a randomized, controlled trial of non-hormonal intervention for VMS (stellate ganglion blockade) provided initial proof of concept that effective treatment of VMS may also confer benefits to memory. Nighttime VMS disturb sleep, which in turn can also affect cognitive function. Notably, however, the association between VMS and memory persists even when accounting for objectively measured sleep disturbance. Broadly, the evidence to date suggests that hormone therapy does not provide cognitive benefit in naturally postmenopausal women, but use of hormone therapy for its primary indication – treatment of VMS – may confer cognitive benefits. Importantly, the evidence also suggests that effective non-hormonal treatments for VMS may also confer cognitive benefit. When counseling patients about the off-label use of hormone therapy for dementia prevention, it is important to consider reliable findings from four recent, large-scale epidemiological studies showing a small (9-22%), but significant increased risk of Alzheimer's disease among women using hormone therapy. This association was evident regardless of timing of initiation, formulation, or duration of use. One study translated this risk into an absolute risk of 9 to 18 excess diagnoses of Alzheimer's disease per 10,000 person-years. By conventional standards, this magnitude of risk is considered "rare" (<10/10,000) to "uncommon" (<100/10,000). By comparison, the black box warning on hormone therapy about dementia risk came from the Women's Health Initiative Memory Study (WHIMS) finding 23 extra cases of dementia/10,000 person years. Overall, clinical trials support the conclusion of the 2022 Hormone Therapy Position Statement that hormone therapy is not recommended at any age to prevent or treat a decline in cognitive function or dementia. The exception is in women with premature menopause, where use of estrogen therapy until the typical age of menopause may help to maintain cognitive function and potentially prevent Alzheimer's disease. Continuing research is also needed to determine if hormone therapy and non-hormonal therapies might improve memory and lower dementia risk in women with bothersome VMS.

Gut-Brain Connection and Mental Health

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Trillions of microbes living in your gut play an essential role in your health. Remarkably, crosstalk between your gut microbes and your body influences your brain and your behaviour. Microbes include viruses, fungi, parasites, protozoa, and bacteria – at this time, most research has studied gut bacteria and how this group of microbes influences mental health. Curiosity by the public in this fast-moving area of research is fueled by media attention related to recent advances in our understanding of how your microbiome impacts the brain and behaviour. Importantly, a potential role for the microbiome and microbe-brain signaling pathways in mental health over the life span has emerged. Biomarker discovery in psychiatry lags behind other chronic medical conditions, such as cancer and cardiovascular disease due to the reliance on subjective symptoms in clinical diagnosis. Broadly across the psychiatric community, there is little recognition of the importance of peripheral biological factors in depression, or how individual differences in these factors contribute to clinical heterogeneity in depression. Hence, we have limited understanding of the biological mechanisms underlying clinical heterogeneity which directly limits our choice of molecular targets to optimize treatment. Deciphering the gut-microbiome-brain connection in psychiatry may be an avenue to fill this gap. An individual's current mood state, their biology, their exposure to early and proximal stressors, and their lifestyle is represented in their microbiome. Therefore, a clear advantage to integrating the microbiome into the generation of a clinically relevant biosignature is that on its own, it provides a holistic combined outcome measure that is driven by host, environmental, lifestyle, and life history factors. This presentation will provide an overview of preclinical and clinical evidence demonstrates that microbiota-brain signaling is important to mood. Our preclinical findings demonstrate a mechanistic role for microbiota-immune signaling in brain function and behavior at several levels including microbiome, gut, metabolite, immune, and brain. Recognizing the important contribution of both the microbiome and the host our recent work examines how the microbiome and how microbe-host (metabolite-immune) signaling pathways that contribute to inter-individual differences in clinical presentation in depression. The complex nature of microbe-host dialogue along the gut-brain axis and the implications for mental health outcomes will be discussed in the context of women's health.

Trauma Exposure and Its Importance to Women's Health During The Menopause Transition

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Trauma exposure is prevalent among women. Estimates indicate that up to a quarter of women in the United States experience childhood maltreatment and that 60-70% will experience one or more traumatic events in adulthood. For women, sexual and interpersonal trauma are particularly prevalent. The experience of psychosocial trauma has long been understood to be important to mental health, increasing the risk for most adverse mental health conditions. However, an increasing body also underscores the important implications that a trauma history has for physical health, including during the menopause transition, a pivotal time of marked biological change for women. Specifically, our studies, including the Study of Women's Health Across the Nation and the MsHeart/MsBrain studies, have underscored that women with a history of childhood maltreatment show more vasomotor symptoms and poorer sleep over the menopause transition, even when these symptoms are objectively measured. Our studies implementing vascular, neuroimaging, and clinical event ascertainment further reveal women with a childhood and/or adult trauma history have greater subclinical atherosclerosis, more cerebral small vessel disease, and greater risk of clinical cardiovascular disease events in late midlife and early old age. Newer data also indicate that childhood maltreatment and adult trauma are linked to accelerated epigenetic aging in midlife women. Finally, our data point to the key role that derangements in sleep and nocturnal physiology play to the impact of trauma on women's midlife health. Collectively, these studies underscore the importance of trauma to the occurrence of menopausal symptoms, to cardiovascular health, and to women's brain health at midlife and beyond. Future directions and implications for clinical care will be discussed.

Hormone Sensitivity, Mood, and Anxiety

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The menopause transition is associated with important changes in ovarian hormone production. While rises in progesterone become less frequent with increasing frequency of anovulation, estradiol production becomes more variable, with periods of both hyper- and hypo-estrogenism. Mounting research suggests that exposure to rapid shifts in perimenopausal estradiol may trigger depressive symptoms in a subset of individuals exhibiting affective sensitivity to ovarian hormone fluctuation. However, observational studies suggest that there may be important individual differences in the direction of this affective sensitivity, with some experiencing dysphoric mood following estradiol withdrawal, others following a rise in estradiol, and still others exhibiting sensitivity to estradiol shifts in either direction. Though the existence of these sensitivity profiles is consistent with observed individual differences in affective sensitivity across other reproductive transitions, such as the menstrual cycle and peripartum period, experimental research is needed to confirm. Consistent with the observed role of estradiol fluctuation in triggering depressive mood in some, stabilization of estradiol levels through the administration of estrogen therapy has been shown to effectively treat perimenopausal depressive symptoms and may also have prophylactic mental health benefits. Recent meta-analytic evidence suggests that transdermal estradiol may be of particular benefit over oral formulations; estradiol administration in the perimenopause may also have greater benefits than administration in postmenopausal individuals. Though some research suggests that risk for clinically significant anxiety may also increase in the menopause transition in those with pre-existing anxiety, and that transdermal estradiol may be of benefit, additional research is warranted. Research developing and validating methods for estimating the strength and direction of an individual's sensitivity to estradiol may improve the early identification of those at risk of perimenopausal mental illness and help clarify the neurological mechanisms by which estradiol exerts its psychological effects. Such research may also help identify those individuals who stand to benefit most from the prophylactic administration of estradiol. Longitudinal research investigating relationships between perimenstrual, perinatal, and perimenopausal mood disorders may also improve our understanding of both the causes and consequences of affective sensitivity to ovarian hormones across the female lifespan.

Depression During the Perimenopause: Clinical, Endocrine, and Cellular Characteristics

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Epidemiologic studies report an increased risk of depression in women during the perimenopause compared with the premenopause. The appearance of mood disorders during the perimenopause (ie, PMD) suggests that hormonal events accompanying this stage of life might underlie the affective dysregulation that occurs in some women. We have investigated the role of reproductive hormones in the development of PMD using both in vivo and in vitro study designs. First, we conducted a prospective, longitudinal study of healthy asymptomatic women who were followed every 6-8 months during and after their transition through the menopause. Outcome measures included structured diagnostic interviews (SCID) to confirm depressive episodes, hot flushes, and circulating hormone levels. Eighty-eight asymptomatic premenopausal women were monitored for an average of 6.1 years (range: 2-13 years) until 6-12 months after their final menstrual period (FMP). We identified 29 episodes of depression in 22 women. Twenty of these episodes occurred within the 24 months surrounding the FMP. Approximately 70% of women experiencing depression during the study did so for the first time in their lives. Women with and without PMD did not differ in average levels of E2 and FSH. However, we did identify differences in the rates of change for both E2 and FSH levels, which were higher in women with PMD (ie, steeper slopes of the serial measures) compared to those who remained asymptomatic ($p=0.04$ and $p=0.004$, E2 and FSH, respectively). These differences in the patterns of hormone secretion emerged before the onset of depressive episodes, suggesting that a steeper E2 withdrawal prior to the onset of depression may be a key factor in PMD vulnerability. Second, to more directly address the role of E2 withdrawal in PMD, we conducted a placebo-controlled study examining the effects of acute withdrawal of E2 therapy on mood in women with past history of PMD. We found that blinded E2 withdrawal induced depressive symptoms in women with past PMD, but not in those without such a history; ie, women with a past PMD who were crossed over from transdermal estradiol (TE) to placebo experienced a significant increase in depression symptom severity (CES-D and HDRS $p<0.001$). In contrast, women with past PMD who were continued on TE and all control women remained asymptomatic. The emergence of E2 withdrawal-induced mood symptoms only in women with past PMD suggests that ostensibly normal changes in ovarian E2 secretion can trigger an abnormal behavioral state in these susceptible women. Third, we investigated whether the E2 withdrawal signal in PMD is mediated by ER alpha or beta (or both) in a clinical study in which we evaluated the ability of a selective ER beta agonist (LY500307) to mitigate E2 withdrawal-induced mood symptoms in women with past PMD. We employed a double-blind, placebo-controlled E2 withdrawal design in 46 asymptomatic postmenopausal women with past PMD. Our findings suggest that LY500307 alone does not have the same beneficial effects on PMD as TE. Women with a past PMD who were crossed over from TE to placebo experienced an increase in depression symptom severity (CES-D and HDRS $p<0.001$), similar to our findings in the original E2 withdrawal study. LY500307 appeared to attenuate the symptom recurrence in these women after E2 withdrawal compared with TE but not significantly better than placebo. Finally, we investigate possible cellular substrates underlying the differential susceptibility to E2 withdrawal using in vitro cellular models via lymphoblastoid cell lines (LCLs) obtained from women with past PMD and controls whose sensitivity to (or absence of) E2 withdrawal-induced depressive symptoms was confirmed in the clinical study. We observed significant differences in the transcriptomes of PMD compared with control LCLs. Our findings implicate new molecular targets and several gene networks that could cause or be altered as consequence of PMD. These include pro-inflammatory genes (ie, *CXCL10*) and networks hyperactivated in PMD, particularly after E2-withdrawal, and *CYP7B1*, coding a steroid enzyme that metabolizes pregnenolone and DHEA, which was consistently upregulated in PMD regardless of E2 exposure/withdrawal.

PLENARY SYMPOSIUM #2

Body Composition Changes in Menopause

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Weight gain and adverse changes in body composition are common during the menopausal transition. On average, women gain 1.5 pounds per year during midlife, independent of race or baseline body size, with approximately 60-70% of midlife women reporting weight gain during menopause. This period is characterized by a loss of estrogen, redistribution of fat from subcutaneous to visceral depots, and a concurrent decline in lean muscle mass, compounding metabolic and cardiovascular risk. Longitudinal studies such as SWAN (Study of Women's Health Across the Nation) and others have shown that weight gain during menopause cannot be solely attributed to chronological aging. Hormonal changes including declines in estradiol and increases in follicle-stimulating hormone contribute to central fat accumulation, particularly visceral adipose tissue, which is metabolically active and associated with insulin resistance, inflammation, and dyslipidemia. Increases in visceral adipose tissue begin roughly two years before the final menstrual period and continue thereafter, correlating with subclinical atherosclerosis and elevated blood pressure. Overweight and obesity during menopause are associated with **increased frequency, severity, and duration** of vasomotor symptoms such as hot flashes and night sweats, likely due to factors such as impaired thermoregulation, systemic inflammation, and altered estrogen metabolism in adipose tissue. Bone mineral density also declines significantly in the peri- and postmenopausal periods due to estrogen withdrawal, increasing the risk for osteopenia and osteoporosis. These skeletal changes intersect with body composition shifts, as sarcopenic obesity and bone loss often co-occur. While hormone replacement therapy has shown mixed results in mitigating weight gain and central fat accumulation, lifestyle factors such as physical inactivity, poor diet, and poor sleep also contribute to increased adiposity. Sleep disturbances are common in postmenopausal women and have been linked to higher BMI. Behavioral interventions, including dietary education and physical activity, have demonstrated efficacy in reducing or maintaining weight during this transition. Despite the recognition of menopause as a critical window for prevention of adverse body composition changes and subsequent increased cardiovascular risk, research that includes women in the menopausal transition remains limited. Furthermore, it remains unclear to what extent aging, hormonal shifts, or behavioral factors are the predominant drivers of adverse body composition changes. Some evidence suggests that both aging and menopause contribute independently and interactively. In conclusion, menopause is a period of accelerated and clinically significant changes in body composition, characterized by increased visceral fat, decreased lean mass, and bone loss. These shifts have profound implications for long-term health. Comprehensive, longitudinal research is needed to disentangle the relative contributions of biological and behavioral factors and to guide targeted prevention strategies for midlife women.

Managing Menopause Symptoms to Optimize Weight Loss

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Midlife weight gain among women is mostly a result of age-related decline in lean body mass and physical activity. Although the hormone changes of menopause do not directly contribute to midlife weight gain, menopause-related symptoms can be barriers to adoption of healthy lifestyle measures that are necessary for weight loss. Therefore, in addition to calorie restriction and regular physical activity, it is important to address the characteristic symptoms of menopause— vasomotor symptoms (VMS), sleep disturbances, and mood disorders—all of which are known to interfere with weight loss interventions. Hormone therapy, the most effective intervention for treatment of VMS and sleep disturbances in the context of VMS, is generally considered frontline therapy in the absence of a contraindication. However, hormone therapy use by itself is not associated with weight loss. In situations where hormone therapy use is contraindicated, or the patient prefers not to use it, non-hormone interventions can be considered to manage vasomotor symptoms, sleep disturbances, and mood disorders, either occurring individually or in combination. It is imperative to avoid medications that are associated with weight gain, including gabapentin, paroxetine, escitalopram, citalopram, amitriptyline, imipramine, clozapine, and fluoxetine. Weight-neutral medications like venlafaxine, desvenlafaxine, fezolinetant, and oxybutynin, are the preferred agents. Given the close association between sleep disturbance and weight gain, midlife women should be screened for sleep disorders, including obstructive sleep apnea, and appropriate treatment options must be offered. The treatment options for insomnia include a combination of cognitive behavioral therapy and prescription medications, with a focus on choosing weight neutral options. Despite the lack of a direct effect on body weight, hormone therapy use may be associated with a mildly favorable impact on body composition, including reduction in abdominal adiposity. However, the effect on body composition is likely related to the dose and type of hormone therapy formulation and may be of minor clinical significance. In summary, it is important to address menopause symptoms for an optimal response to weight loss interventions in midlife women. The potential treatment options include a varying combination of hormone therapy, non-hormone prescription therapies, and cognitive behavioral therapy.

Nutrient-Stimulated Hormone-Based (NuSH) Therapeutics: Dosing, Outcomes, and Clinical Considerations

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Advances in understanding the hormonal regulation of energy balance have driven the development of targeted obesity treatments, most notably glucagon-like peptide-1 receptor agonists (GLP-1 RAs). Originally developed for type 2 diabetes based on their incretin effect, GLP-1 RAs are now recognized as among the most effective pharmacologic options for obesity. These agents mimic the actions of endogenous GLP-1 to modulate appetite regulation, slow gastric emptying, and influence metabolic processes. They may be used as monotherapy, in combination with other hormone-based agents, or as part of dual or triple receptor agonists. Given their ability to reproduce nutrient-triggered gut hormone signaling, these drugs are collectively referred to as Nutrient-Stimulated Hormone-Based (NuSH) therapeutics. Three NuSH therapeutics are currently approved for the treatment of overweight or obesity, in combination with lifestyle interventions. Liraglutide and semaglutide are single GLP-1 RAs, whereas tirzepatide is a dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) RA. In large phase III trials in adults with overweight or obesity, liraglutide 3.0 mg daily achieved a mean placebo-adjusted weight loss of ~5–6% at 56 weeks, semaglutide 2.4 mg weekly achieved ~12–13% at 68 weeks, and tirzepatide 15 mg weekly achieved ~17–18% at 72 weeks. This relative efficacy is consistent in real-world settings. Beyond weight loss, all three agents provide broad cardiometabolic benefits, including improvements in glycemic control, blood pressure, lipid profile, and inflammatory markers, as well as reductions in major adverse cardiovascular events (MACE) in high-risk patients with and without diabetes. They also improve heart failure symptoms and have demonstrated benefits in metabolic dysfunction–associated steatotic liver disease, obstructive sleep apnea, and chronic kidney disease. Importantly, many of these effects appear partly independent of weight loss. While their clinical benefits are substantial, their use must be balanced against a well-characterized safety profile. Across trials, gastrointestinal adverse events, including nausea, vomiting, diarrhea, and constipation, are the most common adverse events, typically arising during dose escalation and declining with continued treatment. Weight-loss–associated gallstones have been reported, particularly with rapid weight reduction. Transient elevations in pancreatic enzymes occur, though evidence for an increased risk of pancreatitis remains inconclusive. The risk of thyroid C-cell tumors seen in rodents has not been replicated in humans. Rarely, severe gastroparesis, intestinal obstruction, and worsening of diabetic retinopathy have been reported. Reports of suicidal ideation have emerged in post-marketing surveillance; however, controlled observational studies and meta-analyses consistently show no causal association and very low absolute event rates. Given their potent efficacy, broad cardiometabolic benefits, and distinct safety considerations, optimal use of NuSH therapeutics requires understanding their mechanisms, dosing, benefits, and risk mitigation. This presentation will provide an evidence-based review of these topics and address common misconceptions to support safe and effective use.

PLENARY SYMPOSIUM #3

Perimenopause and Bone Health

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Menopause-related estrogen deficiency results in an interval of relatively rapid bone loss that begins a few years before the final menstrual period (FMP) and lasts for a few years after FMP in almost all women. On average, women lose 9-12% of their bone mineral density (BMD), almost one T-score unit, about half of the total bone loss that occurs between menopause and age 80. This bone loss is accompanied by substantial deterioration in bone structure and increasing risk of fracture. These changes can be prevented with either estrogen or intermittent low-dose bisphosphonate therapy, and both forms of treatment significantly reduce fracture risk as long as therapy is administered. BMD during perimenopause is the strongest predictor of the probability of developing osteoporosis and should be considered in women with risk factors for low BMD (thinness, previous fracture, family history of osteoporosis). Available approaches for preventing perimenopausal and postmenopausal bone loss will be reviewed including a strategy for life-long maintenance of BMD. **Key Points:** Risk factors for osteoporosis should be considered at the onset of perimenopause. General measures (nutrition, exercise) are important but are not capable of preventing perimenopausal bone loss. Estrogen doses required to prevent bone loss in early menopause are larger than those required for maintaining BMD in older women Skeletal benefits of estrogen are quickly lost when therapy is discontinued. Low dose, short-term bisphosphonate therapy preserves BMD when estrogen is stopped. For women who cannot take estrogen or following the discontinuation of estrogen, intermittent bisphosphonate therapy can maintain BMD for the remainder of the patient's life. It is much easier, more effective and less expensive to prevent the development of osteoporosis than it is to restore bone health after osteoporosis has developed. **Conclusions:** Transmenopausal bone loss is a major contributor to the development of postmenopausal osteoporosis. Assessment of bone health should occur routinely in perimenopausal women. Intervention to prevent perimenopausal and postmenopausal bone loss should be considered at least in women at high risk for developing osteoporosis. A strong case can be made for therapy, including oral or transdermal estrogen, to prevent bone loss in women who come to menopause with low bone mass, even in those without vasomotor symptoms. Hopefully this recommendation will be incorporated into the next update of the MHT guidance.

Which Treatment Option for Which Patient?

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Osteoporosis or osteopenia (low bone mineral density) impacts more than half of United States (US) adults, who are 65 years or older. Women are particularly impacted, and both menopause and aging are risk factors for bone loss and fracture. Osteoporotic fractures cause significant morbidity and mortality; with the greatest morbidity and mortality being associated with hip fractures. According to the US Centers for Disease Control and Prevention, each year, more than 300,000 older adults nationwide sustain a hip fracture requiring hospitalization. Notably, the first-year post-hip fracture is associated with 25% risk of death and 33% risk of disability that prevents independent living. Prescription anti-osteoporosis medications, which include antiresorptive and anabolic agents, have been available since 1995. These medications both reduce the risk of fracture and mortality (i.e. they are associated with increased survival). There is, however, overwhelming underusage of these therapies; based on claims data, approximately 10% of patients who have sustained hip fracture are taking anti-osteoporosis medication post hip fracture. Concerns related to medication associated side effects contribute to the undertreatment of patients with osteoporosis, osteopenia, and/or fragility fractures. It is crucial that providers and patients understand the benefits and risks associated with taking (and not taking) anti-osteoporosis medications. Additionally, it is important to understand the different therapeutic options that exist.

PLENARY SYMPOSIUM #4

Progestogens: Impact on Sleep, Vasomotor Symptoms, and Breast Cancer

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This presentation will focus on the impact of different progestogens and their impact on sleep, vasomotor symptoms, and breast cancer. For women with an intact uterus receiving estrogen a progestogen is given in concert. Does the kind of agent we use have different profiles in these three areas? Why focus on these areas? Insomnia affects 30-60% of midlife women and is commonly associated with heightened risk for prevalence of depression. When it is associated with vasomotor symptoms: we see poorer sleep efficiency and a negative impact on QoL Progestogens are known to have off target effects on the breast. This presentation will seek to review the literature on the differences between agents. In addition, synthetic progestins versus micronized progesterone in menopause management will be looked at to assess impact as an additional tool for reduction of vasomotor symptoms. The presentation will seek to balance risk and assess therapeutic benefits of each agent. **References:** 1. Management of Menopausal Symptoms: A Review. Crandall CJ, Mehta JM, Manson JE. *JAMA*.2023;329(5): 405-420. doi:10.1001/jama.2022.24140. 2. Hormone Therapy for Postmenopausal Women. Pinkerton JV. *The New England Journal of Medicine*. 2020;382(5):446-455. doi:10.1056/NEJMcp1714787. 3. Progesterone vs. Synthetic Progestins and the Risk of Breast Cancer: A Systematic Review and Meta-Analysis. Asi N, Mohammed K, Haydour Q, et al. *Systematic Reviews*. 2016;5(1):121. doi:10.1186/s13643-016-0294-5. 4. Menopausal Hormone Therapy Formulation and Breast Cancer Risk. Abenhaim HA, Suissa S, Azoulay L, et al. *Obstetrics and Gynecology*. 2022;139(6):1103-1110. doi:10.1097/AOG.0000000000004723. 5. Risk of Breast Cancer by Type of Menopausal Hormone Therapy: A Case-Control Study Among Post-Menopausal Women in France. Cordina-Duverger E, Truong T, Anger A, et al. *PloS One*. 2013;8(11):e78016. doi:10.1371/journal.pone.0078016

Progesterone and Progestins: When, How Much, and What if it Goes Wrong?

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Progesterone (P) is a steroid hormone that interacts with its cognate receptor, a member of the steroid hormone receptor superfamily, to affect an array of tissue specific actions. Progesterone receptors and the various progestin compounds, including native progesterone, interact with other receptors in the superfamily including estrogen, glucocorticoid, mineralocorticoid and androgen receptors. In specific tissues, co activators and co repressors will induce tissue specific effects. There is possibly a membrane progesterone receptor, that mediates rapid effects of the hormone as well. The best-known role of progesterone/progestogens in menopausal medicine is the transformation of the endometrium into its secretory phase, downregulation of estrogen receptor, and reduction of mitosis. In this respect P 'opposes' estrogen action and prevents endometrial hyperplasia or cancer when exogenous estrogen(s) are given. However, the specific type of progestin, and the frequency and duration of its use are also critical determinants of its effectiveness in preventing hyperplasia. FDA mandated safety studies for most progestins are based on studies of relatively short duration (ie, 52 weeks). Yet hormone therapy is often used for many years. Clinicians should be aware of the relative scarcity of systematically collected long term safety data but overall can rest assured that observational studies have not provided any worrisome signals with long term E+P use. Since many women will have their worst menopausal symptoms before their final menses, it is recommended that hormone therapy, if it is to be used, not be delayed until a woman has gone for an entire year without menses. However, when hormones are given exogenously to a woman whose ovaries are still intermittently making estrogen and progesterone, breakthrough bleeding (BTB) can occur and can be troublesome to manage. Evaluation and management strategies for BTB in premenopausal women will be discussed. Progesterone/progestin intolerance can also pose problems in clinical practice. Although natural progesterone is favored as a first line agent, some patients experience side effects that limit its use. Alternative methods for delivering P can be tried, and bazedoxifene-containing hormone therapy provides a progestin free way to provide symptom relief with estrogen while protecting the endometrium.

Levonorgestrel IUS for Endometrial Protection: Benefits, Side Effects, and Risks

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In our upcoming Cochrane review on hormone therapy in postmenopausal women and risk of endometrial hyperplasia (2025), we included 72 trials - only 3 had levonorgestrel intrauterine system (LNG-IUS) as the intervention. Two further trials were excluded from our review. A 2015 metanalysis of these five trials reported no events of endometrial hyperplasia in any of the participants. These trials were small, of short duration, and published over 20 years ago. Yet menopause societies worldwide recommend LNG-IUS for endometrial protection in combined MHT regimes. In New Zealand, LNG-IUS is approved, licensed, and regulated for endometrial protection during estrogen therapy use. In symptomatic perimenopausal women with abnormal uterine bleeding, it makes sense to prescribe LNG-IUS to reduce menstrual blood loss. This is based on our Cochrane network metanalysis (2023) where LNG-IUS was found to be the best medical treatment for heavy menstrual bleeding. Thus, we can extrapolate and assume that it also provides endometrial protection from estrogen therapy in menopause. Moreover, in this clinical situation, it is likely more effective to use a progestogen like LNG rather than micronized progesterone. A benefit of LNG-IUS over systemic administration is that a lower dose can be used and systemic progestogenic side effects may be reduced. Studies comparing different MHT regimes show more spotting, more amenorrhea, and less discontinuation compared to systemic progestogen. LNG-IUS provides continuous progestogen which may reduce the risk of endometrial hyperplasia compared to sequential regimes. It also provides highly effective long-acting reversible contraception during perimenopause. A drawback is the insertion procedure. For the outcome of breast cancer, there are no trials comparing users of LNG-IUS to non-users. Although several metanalyses have been published with titles suggesting that LNG-IUS is associated with an increased risk of breast cancer, the included studies are limited by low quality design (cohort and case-control), small sample sizes, and confounding (unable to control for MHT or estrogen use). I found only one cohort study of a prospective design that included women > 50 years old; this study found no association between LNG-IUS and breast cancer. Given the limited and outdated evidence base, further high-quality research is urgently needed to clarify the role of LNG-IUS in endometrial protection during estrogen therapy, particularly in relation to long-term outcomes such as breast cancer risk.

PLENARY SYMPOSIUM #5

Evaluation of Vulvar Disorders in Midlife Patients

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Although clinicians may examine the vulva and vagina of patients daily, they often do not actually “see” the vulva until a woman presents with symptoms. However, in order to diagnose skin diseases, an appreciation of normal findings is crucial. An under-recognition of common normal findings such as erythema of the labia majora, pallor of the labia minora and modified mucous membranes, and age-appropriate shrinkage of the labia minora following menopause leads to overdiagnosis of skin diseases such as lichen sclerosus and contact dermatitis. The morphology of dermatoses is often atypical when occurring in skin folds such as the vulva and perianal skin. The histologic appearance on biopsy can be more nonspecific in these areas as well. Hints such as the area of involvement on the vulva and extension into the vagina can help to provide clues to the clinician. In addition, most patients present with more than one factor producing discomfort. Postmenopausal women often experience estrogen deficiency and urinary incontinence as complications in the management of vulvar dermatoses, as does secondary vulvar Candidiasis in older women with diabetes A full evaluation to proactively identify and address all aspects producing discomfort at each visit and when symptoms flare is important, and results are gratifying.

Vulvar Dermatoses

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Vulvar skin conditions are common. One in six patients will have vulvar irritation or pain during their lives – many of these symptoms are exacerbated by menopause. Embarrassed to talk to providers about vulvar itching or burning, patients will aggressively clean or coat their vulvas with home remedies before presenting to our clinics. Patients often have more than one condition when they present to vulvar specialty clinics, muddying the waters. After this presentation, you will approach patients with vulvar dermatoses with more confidence. From lichen sclerosus to psoriasis, we will review common diagnostic and management pearls.

New Approaches to Vulvodynia

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This presentation explores recent advancements in the understanding and management of vulvodynia. Emphasizing the need for individualized, multidisciplinary care, this approach integrates insights from research published between January 2023 and September 2025. **Pathophysiology & Diagnosis—**Emerging data highlight neuroinflammation, central sensitization, immune dysregulation, and pelvic floor hypertonicity as key contributors. Diagnostic improvements include pelvic floor assessments and the use of vulvar photography for documentation. A detailed algorithm for vulvodynia is presented to guide clinical care. **Vulvar Care Measures—**Simple strategies—such as using shower heads for rinsing, avoiding soap, applying cool gel packs, and selecting appropriate vaginal lubricants—support symptom management. **Multidisciplinary Management—**A model vulva clinic includes gynecologists, dermatologists, pelvic floor specialists, physical therapists, sex counselors, psychologists, and others. Treatment approaches encompass: **Topical Therapies:** Lidocaine is effective for short-term relief; benzocaine is discouraged due to sensitization risks. Compounded therapies using amitriptyline, baclofen, ketamine, gabapentin, and diazepam suppositories offer targeted relief. **Hormonal Therapies:** Estradiol, estriol, testosterone, and prasterone (DHEA) are explored. Vaginal estrogen may benefit breast cancer survivors. **Oral Medications:** Tricyclic antidepressants (e.g., amitriptyline), SNRIs (venlafaxine, duloxetine), and anticonvulsants (gabapentin, pregabalin) provide systemic options. Low-dose naltrexone and cannabis are discussed, though more data are needed. **Injections:** Local anesthetics, steroid combinations, nerve blocks (pudendal, genitofemoral, ilioinguinal), and vestibular hyaluronic acid injections show promise. **Neuromodulation & Interventional Approaches:** Techniques include TENS, spinal cord stimulation, sacral neuromodulation, impar ganglion block, and botulinum toxin injections. **Psychosocial Support:** One-on-one sexual counseling and cognitive behavioral therapy have shown emotional benefit and symptom improvement. **Emerging Treatments—**New agents—maresin-1, resiniferatoxin, and ketotifen fumarate—are under investigation. **Future Directions—**A lack of randomized controlled trials and FDA-approved therapies remains. The importance of patient advocacy, research collaboration, and quality-of-life assessments is emphasized. Educational resources are available via the International Society for the Study of Vulvovaginal Disease (ISSVD) and the National Vulvodynia Association. This evolving field demands nuanced, collaborative care to improve outcomes for women suffering from vulvodynia.

PLENARY SYMPOSIUM #6

Cardiovascular Disease in Midlife Women: Epidemiology, Awareness, and What the Future Holds

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Cardiovascular disease (CVD) is the leading cause of death in women. While the prevalence of CVD is roughly similar in men and women, women tend to develop coronary heart disease about 10 years later in life than men, unless they have diabetes. However, CVD incidence and mortality rates rise sharply in women during midlife, around age 55, coinciding with the menopause transition. This makes menopause a critical window for intervention and preventative screening to reduce the risk of death from CVD. It’s also important to note that the impact of some traditional CVD risk factors, like diabetes and smoking, appears to be greater in women than in men. Additionally, women face unique and emerging risk factors, including early or premature menopause, adverse pregnancy outcomes like gestational diabetes and preeclampsia, autoimmune diseases, depression, and certain cancer treatments. Despite the leading cause of death status, awareness of CVD as a primary threat in women remains suboptimal, particularly regarding sex-specific risk factors. Studies show that many women are unaware of these unique risks and how they contribute to their overall CVD burden. This lack of awareness can lead to delayed diagnosis, undertreatment, and worse outcomes for women. Furthermore, women are less likely to receive preventative guidance and treatment, including medication like statins, compared to men with similar risk profiles. There is an urgent need to improve cardiovascular workforce competencies in the menopause transition with the focus on improving cardiometabolic health. There are several cardiovascular risk factors that worsen during this menopause transition, and cardiovascular clinicians need to have a heightened sense of urgency in identifying and optimizing these risk factors. Improving cardiovascular health in midlife women requires a multi-pronged approach: **Increased Awareness & Education:** Public health campaigns and targeted educational materials are needed to raise awareness about CVD in women, including the importance of early detection and management of traditional and unique risk factors. **Targeted Screening & Risk Assessment:** Guidelines should incorporate female-specific risk factors and emphasize a personalized approach to screening and risk assessment, including a detailed reproductive history. **Enhanced Diagnosis & Treatment:** Addressing diagnostic delays and disparities in treatment is crucial. This includes increased physician awareness of women’s unique symptoms and ensuring equitable access to care and preventative therapies. **Further Research & Funding:** Dedicated research is needed to better understand the nuances of CVD in women, including how to incorporate novel risk factors into risk assessments and develop sex-specific guidelines for diagnosis, treatment, and prevention. Addressing these issues can lead to a future where women receive equitable cardiovascular care and prevention, improving outcomes and reducing the burden of CVD in midlife women.

Primary Prevention of Cardiovascular Disease in Women: Blood Pressure, Lipids, and Diabetes

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Cardiovascular disease (CVD) remains a leading cause of death of morbidity and mortality in women. It is estimated that up to 90% of atherosclerotic CVD (ASCVD) are due to modifiable risk factors. Therefore, primary prevention efforts for the identification and treatment of risk factors are paramount. There are disparities conferred by traditional risk factors such that diabetes, hypertension, and obesity confer greater relative risk in women compared to men. In addition, women have unique sex-specific contributions to CVD risk factors related to PCOS, adverse pregnancy outcomes, and early menopause. Lipids: Multiple lines of evidence have confirmed low density lipoprotein cholesterol (LDL-C) is causally related to ASCVD pathogenesis; as such across all professional society guidelines, LDL-C is the primary target for ASCVD prevention with lower LDL-C for longer periods of time conferring the greatest ASCVD risk reduction. Lipoprotein (a) [Lp(a)], which is strongly genetically determined, confers increased

CVD risk independent of LDL-C and should be measured at least once in a lifetime as part of risk assessment. New guidelines recommended even lower LDL-C levels with target thresholds based on one's global risk. While statins remain 1st line therapy, many non-statin therapies are now available and provide the same risk reduction per mmol/L of LDL-C reduction as statins. LDL-C and LP(a) confer similar CVD risk in women as in men. Delays in lipid treatment in women of reproductive age affect their long-term CVD risk. Furthermore, LDL-C and Lp(a) levels increase with the menopause transition. Women benefit from statins and other lipid lowering therapies similar to men but are undertreated. A high HDL-C is not necessarily protective and should never be a reason not to treat a patient who would qualify for lipid lowering treatment for their LDL-C & apoB related risk. Blood pressure (BP): Hypertension is the leading modifiable risk factor for the development of CVD and a major contributor to mortality worldwide. The rate of BP increases in women across the lifespan—particularly after midlife—is steeper, eventually surpassing that of men by the sixth decade of life. Systolic BP and hypertension confer greater relative hazard of myocardial infarction in women than in men. Furthermore, cardiovascular risk increases at a lower BP level in females than in males. Females have a larger increase in sympathetic nervous activity with age and obesity than males. Treatment of hypertension reduce the risks of CVD in women. Healthy lifestyle and nonpharmacologic interventions are effective in reducing BP in women. Furthermore, clinical trial data have shown similar efficacy of antihypertensive treatment for reducing adverse cardiovascular outcomes for both women and men. Diabetes: Diabetes confers a greater relative risk of CVD in women compared to men. Women tend to develop type 2 diabetes (T2D) at higher BMI and with more comorbidities at time of diabetes diagnosis, which may explain their worse outcomes. Significant changes in body fat composition and relative hyperandrogenism at the menopause transition have the potential to lead to worsening insulin resistance, impaired glucose tolerance and T2D risk. Healthy lifestyle changes including weight management are cornerstone for diabetes prevention. In patients with T2D, pharmacological treatment with SGTL2 inhibitors and GLP-1 receptor agonists reduce cardiovascular events similarly in women as in men.

Microvascular Disease in Women: Small Vessels, Big Impact

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Patients with chest pain who are suspected of having myocardial ischemia usually undergo coronary angiography to evaluate for obstructive epicardial coronary atherosclerosis. However, a large proportion of patients with angina or ischemia have no obstructive coronary arteries (ANOCA/INOCA), a condition that is more prevalent in women, and is largely attributed to coronary microvascular dysfunction (CMD) or coronary vasospasm. Cardiovascular disease risk factors such as hypertension, diabetes, estrogen loss, and inflammation contribute to CMD, which can occur due to structural or functional problems in the resistance microcirculatory vessels. CMD is defined by low coronary flow reserve or abnormal microvascular reactivity, and it is a diagnosis that is associated with major adverse cardiovascular events, such as myocardial infarction and heart failure. In addition, ANOCA/INOCA are associated with reduced functional capacity and lower health-related quality of life. Invasive coronary function testing can diagnose abnormal coronary vascular reactivity and impairment in microcirculatory flow (<2.5). 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 ANOCA/INOCA and CMD, although it remains underdiagnosed and undertreated.

PLENARY SYMPOSIUM #7

Dense Breasts: What Do We Do, With Whom, When, How Often, and Why?

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Screening for breast cancer with mammography has been proven in randomized controlled trials and observational studies to decrease mortality rates among women 40-75 years old by 15-40%. However, the effectiveness of mammography is limited in patients with dense breasts, lowering sensitivity from 84% to 25-50%. Increased tumor size, later stage, worsened prognosis and increased risk of breast cancer are associated with increased breast density. As of September 10, 2024, mammography facilities must provide all patients with information about their breast density. Those with increased breast density are notified that dense tissue makes it harder to find breast cancer on a mammogram and also raises the risk of developing breast cancer. Digital Breast Tomosynthesis (DBT) has been shown to increase breast cancer detection by 2-3 additional breast cancers per 1,000 women screened when compared to digital mammography. However, DBT is no longer considered supplemental in the USA since most sites have DBT available for screening. In 2010 (EVA Trial) it was proven that MRI is the most sensitive exam with the highest cancer detection rate compared to mammography and mammography with ultrasound. MRI with an abbreviated protocol (AbMRI) of 10 min length was studied in a multisite randomized prospective trial (EA1141) comparing DBT to abbreviated MRI in women with dense breasts and no other risk factor. AbMRI detected 15.2 cancers per 1,000 women screened compared to DBT alone which detected 6.2 cancers per 1000 women screened. The DENSE Trial done in the Netherlands was a randomized controlled multicentered trial that studied women with extremely dense breasts with MRI after a negative mammogram demonstrating a cancer detection rate of 16.5 per 1,000 women screened and a very low interval cancer rate of 0.8 per 1,000 women screened compared to mammography alone with 5 interval cancers per 1,000 women screened. Another vascular based exam that has similar outcome measures to MRI is Contrast Enhanced Mammography (CEM). There is a recent study published in 2025 (SCEMAM TRIAL) which screened high risk women, that were eligible for screening MRI, with CEM and DBT. This trial had an increase in cancer detection rate of 10.0 per 1000 women screened with CEM compared to DBT alone. Because of the data in recent large studies the 2025 NCCN guidelines recommend supplemental screening MRI in women with extremely dense breasts and no other risk factor and consider supplemental screening with MRI in those women with heterogeneously dense breast tissue.

Early Surgical Menopause in BRCA Previvors: Practical Recommendations for Systemic Vaginal Hormone Therapy

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Women with pathogenic variants in *BRCA1* or *BRCA2* face significantly elevated lifetime risks of breast and ovarian cancer. Risk-reducing bilateral salpingo-oophorectomy (RRSO), typically recommended between ages 35 and 45, depending on the type of mutation. This procedure substantially reduces the risk of ovarian cancer, breast cancer (particularly in *BRCA2* carriers), and all-cause mortality. A significant proportion of women with *BRCA1 or BRCA2* mutations undergo RRSO before reaching natural menopause. While the oncologic benefits are clear, this intervention induces premature surgical menopause, which carries significant health consequences including vasomotor symptoms, sexual dysfunction, bone loss, cardiovascular disease, cognitive changes, and diminished quality of life. More than 80% of women report vasomotor symptoms after RRSO, and nearly half report reduced libido. Hormone therapy (HT) is strongly recommended for BRCA mutation carriers without a personal history of breast cancer to mitigate these effects. HT has been shown to improve quality of life, sexual function, and bone health, and to reduce the risks of early osteoporosis, cardiovascular disease, and cognitive decline. Despite valid concerns about breast cancer risk, data from longitudinal and prospective cohort studies support the safety of short-term HT in this population. Retrospective studies have shown no association between HT duration or formulation and increased breast cancer risk. Moreover, the cumulative incidence of breast cancer is lower in those using estrogen-only HT (12%) compared to those using combined estrogen-progestin therapy (22%). Importantly, failure to initiate HT after RRSO before age 45 is associated with increased all-cause mortality. Women who undergo premature surgical menopause and do not use HT have a two-fold increased risk of death compared to those who do. Data support the recommendation that HT be used at least until the average age of menopause (age 50–52), with ongoing risk-benefit reassessment, whereas prolonged use beyond age 50 was associated with decreased survival. When feasible, hysterectomy at the time of RRSO is encouraged to simplify HT to estrogen-only regimens, which have a more favorable safety profile. For women who retain their uterus or are poor surgical candidates, transdermal estrogen combined with micronized progesterone is preferred, though it may confer a modest increase in breast cancer risk particularly among *BRCA2* carriers and should be used with caution. For those unable or unwilling to use systemic HT, or for persistent genitourinary symptoms despite systemic therapy, low-dose vaginal estrogen may be considered. Vaginal estrogen has minimal systemic absorption and has not been associated with an increased risk of breast cancer, even in high-risk populations, making it a reasonable and generally safe option for the management of genitourinary syndrome of menopause. In, well-counseled patients, bilateral salpingectomy may be considered as a temporary measure in lieu of immediate RRSO, although this strategy remains investigational. Overall, HT is a critical component of survivorship care in BRCA mutation carriers undergoing premature surgical menopause. These women should be counseled on the risks of cardiovascular disease, osteoporosis, and increased mortality if HT is not used. A personalized approach integrating genetic risk, surgical history, patient goals, and timing is essential to balance oncologic safety with long-term health and quality-of-life outcomes. Referral to specialized clinics, when available, can support adherence, monitoring, and optimal management.

Cardiovascular and Musculoskeletal Health in Breast Cancer Survivors

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Most individuals treated for breast cancer will experience long-term survival and it is estimated that there are currently about 4.3 million breast cancer survivors in the US. These individuals often face lasting consequences of cancer and its treatment including higher rates of heart disease and adverse musculoskeletal effects. Certain chemotherapy agents and targeted therapies are associated with cardiotoxicity. For example, anthracycline chemotherapy drugs and trastuzumab, a monoclonal antibody targeting human epidermal growth factor receptor 2, increase the risk for cardiomyopathy. Use of the selective estrogen receptor modulator tamoxifen increases risk for thromboembolic events. Treatments that result in a reduction in estrogen production have been associated with worsening of blood pressure, cholesterol, and blood sugar control. The induction of early menopause and other estrogen lowering therapies frequently used to treat breast cancer can also contribute to bone density loss and musculoskeletal symptoms. Strategies to monitor and mitigate these concerns include assessment through history and physical examination, selective testing, addressing co-existing risk factors, enabling healthy behaviors, and appropriately treating emergent conditions. Management of cardiovascular and skeletal consequences of breast cancer treatments often includes a multidisciplinary team that may include oncology, primary care, cardiology, rheumatology, physical medicine and rehabilitation, other exercise programs and more. A variety of resources are available to help patients and providers optimize cardiovascular and musculoskeletal health following a diagnosis of breast cancer.

PLENARY SYMPOSIUM #8

Primary Ovarian Insufficiency/Functional Hypothalamic Amenorrhea

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Premature estrogen loss can significantly impact the cardiovascular health of young women. Endogenous estrogens provide cardiovascular protection during the premenopausal years, however, abrupt hypoestrogenemia in the reproductive period is associated with increased endothelial dysfunction, vascular inflammation, and higher long-term risk of cardiovascular disease risk. Premature ovarian insufficiency (POI) is defined as the loss of ovarian function before age 40, characterized by irregular or absent menses with elevated gonadotropins and low estradiol. Functional hypothalamic amenorrhea (FHA) is a reversible form of secondary amenorrhea with at least three or more months of amenorrhea and results in low estradiol and low gonadotropins, typically triggered by stress, undernutrition, or excessive exercise. Both POI and FHA result in premature estrogen loss, albeit through different mechanisms and durations of time. This presentation reviews the causes and clinical definitions of POI and FHA, highlighting their shared pathophysiology of hypoestrogenemia and distinct underlying etiologies. Epidemiologic evidence linking premature estrogen loss to adverse cardiovascular outcomes is reviewed. For example, surgical menopause at a young age carries an 87% higher CVD risk, while premature natural menopause increases risk by 36%. Recent findings also shows that FHA is linked to reduced endothelial function and increased pro-inflammatory cytokines compared with eumenorrheic and recently menopausal women. These vascular and inflammatory changes may contribute to an elevated lifetime risk of cardiovascular disease, yet this population is understudied, underscoring the need for early recognition and intervention to protect long-term cardiovascular health. Diagnostic considerations, differentiation of FHA from other causes of secondary amenorrhea, and evidence-based management strategies are addressed. Recommendations emphasize physiologic estrogen replacement in women with premature estrogen loss when not contraindicated and highlight the need for heightened clinical awareness to reduce long-term cardiovascular risk.

Trauma-Informed Menopause Care in the VA

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A rapidly growing proportion of U.S. military Veterans are women, and the number of women Veterans enrolled in Veterans Health Administration (VHA) health care has tripled over the past two decades. The median age of women Veterans in VHA care is 49, and almost half are in midlife (46% age 45-64), making midlife and menopause care an important area of focus for VHA research and clinical care. Military service-related exposures (eg, military environmental exposures, military sexual trauma), sociodemographic characteristics (eg, race and ethnicity), social determinants of health (eg, trauma), and clinical correlates prevalent in this population (eg, sleep disorders, chronic pain, depression, anxiety, posttraumatic stress disorder) may influence the timing of menopause, experience of menopause symptoms and related comorbidities, and menopause-related health care engagement among women Veterans. This has been supported by a growing body of evidence suggesting a high burden of menopause symptoms among women Veterans, with associations seen between menopause symptoms and mood symptoms, chronic pain and higher-risk opioid prescribing, intimate partner violence and military sexual trauma, and suicide risk, as well as risk for early menopause associated with military exposures such as Gulf War Illness. The integrated care setting of the VHA provides advantages for optimal evidence-based, comprehensive care to improve health and well-being for women Veterans in midlife and the menopause transition, and several efforts are underway to inform and improve this care. Additionally, as only 30% of eligible women Veterans are enrolled in VHA, and many of those that get VHA care also get care in the private sector, understanding the unique considerations and care needs of this population is important for providers across care settings.

Menopause in Indigenous and Hispanic Populations

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Menopause is a universal experience for women, yet it remains under-addressed in both clinical practice and research, particularly for racially and ethnically diverse populations. Vasomotor symptoms (VMS), including hot flashes, night sweats, and palpitations, affect the majority of midlife women and can persist for years, significantly impacting quality of life. Despite this, most healthcare providers receive little to no training in menopause management, and many women turn to integrative health approaches for relief. This abstract presents a series of community-engaged, culturally responsive interventions developed to address this gap through collaborative research and practice. Three interventions—MENOGAP, Mujeres en Menopausia, and Waning Moon—were co-developed using community-based participatory research (CBPR) principles and the Two-Eyed Seeing framework, which integrates Indigenous and Western ways of knowing. MENOGAP, a group-based intervention combining medical and integrative care, demonstrated statistically significant improvements in menopause-related symptoms, including somatovegetative and psychological domains, and was rated highly for acceptability, feasibility, and appropriateness. Mujeres en Menopausia adapted the MENOGAP model for Hispanic/Latina women, incorporating bilingual delivery, cultural tailoring, and community health worker facilitation. Participants showed increased knowledge of menopause, hormone therapy, and self-care practices, with improved self-efficacy and symptom management. MENOGAP was also adapted to create Waning Moon, which was developed in partnership with an American Indian/Alaska Native (AI/AN) community advisory board to address the needs of midlife AI/AN women. The intervention centers Indigenous knowledge and natural medicine, and emphasizes relational accountability, trust-building, and ethical research practices. Listening sessions and pilot testing revealed strong preferences for culturally grounded care and highlighted systemic barriers to healthcare access. The project also critiques colonial language in research, advocating for respectful terminology and inclusive engagement strategies. Together, these interventions demonstrate the power of collaborative, culturally attuned approaches to menopause care. They offer scalable models for addressing barriers to healthcare access and promoting whole-person health among midlife women across diverse communities. This work underscores the importance of ethical, inclusive, and community-driven research in advancing health access and improving outcomes for women navigating the menopause transition.

PLENARY SYMPOSIUM #9

Starting, Swapping, and Stopping Hormone Therapy

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The mean age of menopause is 51.4 years and 90% of women will experience natural menopause between ages 45 and 56 years. Most women will be postmenopausal for 40% of their lives. 80% of postmenopausal women experience vasomotor symptoms (VMS), with the duration and severity being variable for individual women. During the menopausal transition (MT), approximately 50% to 75% of women begin having VMS. They are most prevalent in the late perimenopause and symptoms peak for approximately 1 year after menopause. Longitudinal data from The Study of Women's Health Across the Nation (SWAN) indicate that hot flashes persist longer than initially thought, with a median duration of 7.4 years. Women who first reported VMS, when they were premenopausal or early perimenopausal, had the longest duration of VMS as opposed to onset in the postmenopause, which has the shortest duration of VMS. VMS are associated with changes in psycho-social and physical well-being which can include sleep disruption, mood changes, difficulty concentrating, impaired short-term memory, reduced quality of life, poor health, and bone loss. VMS are also associated with an increased risk of cardiovascular disease and cognitive changes. Menopausal symptoms that go untreated are also associated with higher health care costs and loss of work productivity. Bone loss and fracture risk can also accelerate during this time of estrogen decline but can be maintained if given hormone therapy (HT). Although HT is the most effective treatment for VMS and can prevent menopausal bone loss and fracture risk, the use of systemic HT has decreased by at least 80% among U.S. women since the initial findings of the Women's Health Initiative (WHI) were published in 2002. This is despite the WHI 18 year cumulative follow up study which reported that HT was not associated with increased risk of all-cause, cardiovascular, or cancer mortality. In addition, guidelines from The Menopause Society and other professional societies endorse the use of HT for symptomatic women without contraindications, less than age 60 years, and within 10 years after the onset of menopause. HT is also recommended for women with early menopause or primary ovarian insufficiency and should be used until at least the average age of menopause. Systemic HT is FDA approved as first line therapy and remains the most effective treatment for the relief of menopausal VMS. HT can also reduce bone loss and fracture risk. The decision to initiate or continue HT involves a careful assessment of the potential benefits and risks, but the majority of symptomatic healthy women will experience a significant quality of life benefit from the use of HT. The benefits of HT usually outweigh the risks for women without contraindications such as breast cancer, endometrial cancer, cardiovascular disease, active liver disease, and undiagnosed vaginal bleeding. Baseline risk of cardiovascular disease and breast cancer, and personalized risk assessment is helpful for an initial therapeutic recommendation. Before initiating therapy, a comprehensive past medical, gynecologic, surgical and family history is advised along with an updated physical exam, pertinent laboratory tests (liver function tests, lipids), and mammogram. Optimal duration of HT varies for individual women. In the absence of contraindications, if on HT, women and clinicians should share in the decision of a preferred dose, formulation, and duration of use, with ongoing yearly reevaluation of the risks and benefits, and education about other alternatives. There is no evidence for a mandatory age of discontinuation for HT in healthy women. The use of custom-compounded HT is not recommended because of lack of regulation, rigorous safety and efficacy testing, batch standardization, and purity measures. It is important to recognize that it has been reported that up to 30–40% of women in their 60s and 10–15% in their 70s report bothersome VMS and women might prefer to stay on long term HT for VMS and for the prevention of osteoporosis.

Nonhormone Pharmacologic Options

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Although hormone therapy is considered the gold standard for treatment of vasomotor symptomatology (VMS) in women traversing the menopause transition, some women may require alternative pharmacologic options due to complex medical comorbidities such as estrogen receptor positive cancers or a history of thrombogenic events or mutations. Symptomatic women may also desire nonhormonal pharmacologic options secondary to personal preference. Thus, clinicians caring for patients in the menopause transition need to be well versed in these options including the pertinent pharmacology and recommended dosages needed to decrease VMS, as well as any potential side effects and relevant safety issues, ensuring that treatment may be individualized to enhance effectiveness. In this presentation we will review the nonhormone pharmacologic agents with the strongest evidence base for reducing vasomotor symptomatology including: gabapentin and oxybutynin; the selective serotonin reuptake inhibitors paroxetine, citalopram, and escitalopram; the serotonin-norepinephrine reuptake inhibitors venlafaxine and desvenlafaxine; the NK3 receptor antagonist fezolinetant and the dual NK1 and NK3 receptor antagonist elinzanetant. FDA-approved nonhormone

pharmacologic options include paroxetine mesylate 7.5 mg and fezolinetant 45 mg, with expected FDA approval for elinzanetant 120 mg in October 2025. Additionally, throughout the presentation relevant clinical caveats will be discussed with the overarching objective of increasing clinician comfort with prescribing nonhormone pharmacologic agents and educating patients on these options--thus promoting shared decision making and patient centered care.

Nonpharmacologic Options

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Vasomotor symptoms (VMS) are highly prevalent and often distressing for midlife women. Although hormone therapy is the most effective treatment, many women seek nonpharmacologic options due to contraindications or personal preference. This abstract summarizes the current evidence for nonhormone, non-drug interventions for VMS. Cognitive-behavioral therapy (CBT) and clinical hypnosis are supported by Level I evidence and have demonstrated efficacy in reducing the perceived burden and interference of VMS. Weight loss and stellate ganglion block are also recommended (Levels II–III), with weight loss particularly beneficial earlier in the menopause transition. Other commonly used approaches—including yoga, exercise, mindfulness, relaxation, acupuncture, and dietary changes—lack sufficient evidence and are not recommended. Despite widespread use, over-the-counter supplements and herbal remedies also fail to meet evidence thresholds. These findings underscore the importance of guiding women toward nonpharmacologic options that are both safe and supported by rigorous research. Clinicians should be prepared to counsel women on the relative benefits, limitations, and accessibility of these therapies, and to help them avoid ineffective or potentially harmful alternatives.

PLENARY SYMPOSIUM #10

Androgens for Muscles, Mood, and More

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Testosterone is a female hormone that is essential for fertility and that exerts physiological effects in multiple non-ovarian tissues. Clinical trials have consistently demonstrated benefits of testosterone therapy on several domains of sexual function for postmenopausal women with low sexual desire causing substantial personal concern. However, there is a wave of enthusiasm to include testosterone as part of standard hormone therapy for perimenopausal and postmenopausal women, with claims that "testosterone deficiency" can contribute to reduced quality of life, tiredness, depression, headaches, cognitive problems, osteoporosis and muscle loss. These claims raise the questions: 1) Do testosterone blood levels change as a consequence of perimenopause and menopause? 2) Is there a clinical state of "testosterone deficiency" in women? and 3) is there any evidence that safe testosterone supplementation significantly improves these symptoms or conditions, or prevents disease? The most recent data on the impact of age and menopausal stage on testosterone blood levels will be shared and will be associations between testosterone and clinical characteristics/symptoms. There is irrefutable evidence that testosterone therapy may improve sexual interest and reduce sexual distress in postmenopausal women with low desire and distress not caused by other factors (HSDD), with efficacy seen in most, but not all women. Non-oral, physiological testosterone replacement is associated with increased likelihoods of weight gain, acne, and body/facial hair growth, but not with adverse effects on indices of cardiometabolic health in women without known cardiovascular disease. Evidence pertaining to the prescribing of testosterone as a treatment for muscles, mood and more, will be reviewed with the aim of equipping health care providers with the knowledge base to support their patients to make informed choices regarding the use of testosterone.

Androgens for Hypoactive Sexual Desire Disorder

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Low libido is a highly prevalent problem for midlife women with many etiologies and a range of effective treatment options. Evidence supports the use of low dose transdermal testosterone (T) in carefully selected menopausal women with hypoactive sexual desire disorder (HSDD), defined as low libido with associated distress. A thorough assessment of a woman's sexual concerns with treatment of underlying causes and contributing factors is required before considering a trial of testosterone. Common causes of low libido for menopausal women include genitourinary syndrome of menopause (GSM), dyspareunia, vasomotor symptoms, urinary incontinence, weight gain with poor body image, anxiety, depression, SSRI use, cancer, relationship conflict, lack of novelty, a partner's sexual problems, fatigue, and stress. The use of T for HSDD should be considered only if the disorder persists after all contributing factors have been addressed. The goal of androgen treatment in menopausal women is to raise the low T levels seen after bilateral oophorectomy or with aging to the upper limit of normal for younger women with intact ovaries. Although substantial increases in sexual desire and frequency are seen with high T doses that result in blood levels in the low male range, the impact of low dose T is relatively subtle, especially compared with the high placebo response seen in most studies of treatments for sexual dysfunction. In a series of large, randomized controlled trials (RCTs) of the transdermal T patch in menopausal women with HSDD, T patches resulted on average in 1 to 1.5 additional satisfying sexual events in a four-week period compared with placebo. The percentage of women reporting a clinically meaningful benefit from treatment was high in placebo-treated women (31%), but significantly greater in women treated with T (52%). In subsequent large RCTs of a similarly dosed T gel for menopausal women with HSDD, T treatment was no more effective than placebo. A low dose of the androgen DHEA administered vaginally is approved for the treatment of dyspareunia due to vulvovaginal atrophy with RCTs demonstrating improved libido compared with placebo. As there is no increase in systemic androgen levels with vaginal DHEA, this is likely due to effective treatment of GSM with desire increasing when sex is no longer painful. DHEA dosed systemically does not treat HSDD. There are no government-approved systemic androgen products for women in the US, although a regulated formulation of 1% T cream is available by prescription in Australia. Testosterone formulations used in the US typically are dose-adjusted products approved for men or compounded products with limited quality control. As T levels in women are approximately 1/10th those of men, women are instructed to apply 1/10th of a 1% T gel tube or packet or 0.5 gm of 1% T compounded cream or gel topically daily to the skin of the calf, thigh, buttocks, or abdomen. Hands should be washed thoroughly after use and skin-to-skin contact with others avoided. Monitoring of blood T levels is advised, given inconsistent dosing and variable absorption of available formulations. The goal is to maintain a blood level within the normal range for reproductive-aged women. Efficacy is assessed by clinical response, as no T blood level can ensure a satisfactory sex life. Women electing androgen therapy for the treatment of HSDD should be informed of potential risks, side effects, and off-label nature of use. Side effects include facial hair, acne, and rarely lowering of the voice, especially with supraphysiologic dosing. Although adverse changes in lipids or liver function are not seen with low dose transdermal T, given abnormalities seen with high dose and oral androgens, confirmation of normal values is advised prior to initiating treatment. There are no long-term safety studies of T in women and androgens are aromatized to estrogens, so those electing testosterone should be informed of potential risks, including breast cancer and cardiovascular disease.

KEYNOTE ADDRESS

Abstract not received by publication date

THE MENOPAUSE SOCIETY/PFIZER WULF H UTIAN ENDOWED LECTURE

Curing the Number One Killer of Men Women and Children: An Update on Bioengineering Personalized Human Hearts

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Heart disease is the leading cause of death globally, killing 1 in 3 individuals and costing the US approximately $252.2 billion in 2020. Because heart disease is progressive, over 64 million people suffer from heart failure (HF) where damage has progressed, and the only "definitive" treatment is a heart transplant. HF is increasing and in the US is projected to exceed 8 million cases by 2030. As an incurable disease, HF drives US annual healthcare costs beyond $70B and when considering secondary costs like renal failure and dialysis, costs soar above $160B. Guidelines Directed Medical Therapies for HF are anticipated to rise to a cost of $16.7B annually by 2034, and yet these do not halt the progression of existing HF, nor do they reduce hospitalizations, or directly improve patients' quality of life. Despite significant advancements in medicine, treatment for HF addresses symptoms rather than providing lasting cures, leaving millions without an effective treatment. Heart transplant occurs in 10-11 patients per day in the US despite more than 3,200 individuals in need each day. Then it fails in 18% of patients within 1 year and 59% within 10 years usually due to rejection or preexisting comorbidities. Organamet Bio, a biotechnology start-up company, is committed to revolutionizing heart failure treatment by developing personalized, bioengineered products that address the root causes of the two most prevalent forms of HF: HF with preserved ejection fraction (HFpEF) or diastolic HF, which affects women to a high degree and HF with reduced ejection fraction (HFrEF) that occurs after heart attack, viral cardiomyopathy or other large injury to the myocardium. The strategy is to halt progression where possible and when not possible, to provide a personalized long-lasting superior therapy for transplant. The 3 approaches include: 1) A novel biopolymer for HFpEF delivered directly into cardiac muscle via injection that restores native healthy cardiac proteins to repair heart cell damage, reduce inflammation and restore relaxation of heart muscle cells. Unlike previous unsuccessful HFpEF treatments, it addresses root cellular causes of HFpEF and offers a one-time injection to reverse pathology instead of attempting and failing to manage it chronically. 2) A bioengineered cardiac patch for HFrEF designed to prevent dilated HF progression by stabilizing the heart, promoting vascularization, and creating an environment for regeneration. Proven effective in preclinical models, the patch serves as a near-term, scalable treatment to address dilated heart failure in >500,000 patients annually before irreversible damage occurs. 3) Your-Heart™: A fully bioengineered, patient-specific heart for transplant in end-stage HF created from a patient's own cells, eliminating rejection risks and the need for lifelong immunosuppressants. Designed to cure end-stage heart failure, Your-Heart™ offers a personalized product not dependent on donor availability. It is a fully vascularized, bioengineered human heart, eliminating rejection risks and reducing dependence on lifelong immunosuppression. While technologies like xenotransplantation, artificial hearts, and 3D bioprinting are also evolving, these remain significantly limited in scope and feasibility. Xenotransplantation relies on genetically modified pig organs. While this approach aims to address organ shortages, it faces high risks of severe immune rejection and disease transmission and remains encumbered by ethical arguments against gene editing. Artificial hearts attempt to replicate human heart function through mechanical devices, but these technologies lack biological integration, are prone to mechanical failure, and cannot provide true regenerative potential. 3D Bioprinting shows potential but remains years away from

producing hearts with complex vascular networks. Even if achieved, recellularization of the new scaffold remains a critical challenge. In contrast, Organamet Bio's technologies will halt the progression of HF, stabilize patients, improve quality of life and potentially cure patients with HF. We developed and scaled a prototype heart during the COVID pandemic, under budget and ahead of schedule. An update on our 3 bioengineered therapies will be shown.

THE MENOPAUSE SOCIETY/KLEINMAN ENDOWED LECTURE

Impact of Alcohol on Health Outcomes

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Alcohol is commonly consumed. In the US, approximately 49% of women over age 18 report alcohol consumption in the last month and 20% of that group report past-month binge drinking. Globally, more than 2.5 million total deaths total, 600,000 for women, are attributable to alcohol annually, primarily from non-communicable diseases and injuries. Alcohol consumption has a wide range of effects both short- and long-term, including on the functioning of the brain, the endocrine system, the liver, the gastrointestinal tract, the cardiovascular system, and immune function, as well as effects on outcomes including pregnancy, injury, cancer, and cardiovascular disease. In the US, the Dietary Guidelines provide recommendations for alcohol consumption: for those who don't drink, to not start drinking, and for women who do drink, not to exceed one drink per day. Further, identified are groups who should not consume alcohol at all, including those who are pregnant, have alcohol use disorder, or with certain medical conditions. There is clear evidence of adverse health effects for consumption above these guidelines. For some outcomes, there are adverse health effects even for low to moderate intakes, including below the guidelines; for other outcomes, alcohol may have no effect or be protective at low to moderate intakes. Alcohol consumption is well-established as a cause of cancers of the oral cavity, larynx, pharynx, esophagus (squamous cell), colorectum, breast, and liver. There is emerging evidence that it may also contribute to increased risk of other cancers including of the stomach, pancreas, bladder, and lung, and to decreased risk of renal cancer for low intake. More than 6% of cancer cases in the US among women are attributable to alcohol consumption, with only cigarette smoking and excess body weight as other potentially modifiable risk factors accounting for more. There is evidence that for even low to moderate alcohol consumption, there is increased risk of cancer, particularly of the breast and the oral cavity. For breast cancer, risk increases linearly with intake; there is no evidence of a threshold below which there is no increased risk. Risk increases 9% for each 10g of alcohol per day. For head and neck cancer, there is also evidence of a linear association, a 10-20% increase in risk for each 10g consumed per day. Reduction or cessation of alcohol consumption has been found to be associated with decreased risk of oral and squamous cell esophageal cancer. Evidence is more limited of decreased risk with reduction/cessation of alcohol consumption for cancers of larynx, breast, and colorectum. For cardiovascular disease, evidence is strong that heavy drinking and binge drinking increased risk of hypertension, stroke, coronary artery disease, and heart failure. Risk of hypertension is increased with alcohol consumption even for intakes below the guidelines (<1 drink/day). For drinking within the guidelines, evidence is less clear for other cardiovascular disease outcomes. There may be no effect or decreased risk of stroke, coronary artery disease and heart failure with low or moderate consumption. However, studies of risk of these outcomes with low to moderate intake may be affected by inclusion in the comparison group of those who are currently non-drinkers but who quit drinking for health reasons, leading to an inflation of the number of events among non-drinkers. There is a need for more research on women in particular regarding health effects of alcohol on cardiovascular outcomes, as well as more research on the impact of change in alcohol consumption on cancer and cardiovascular disease outcomes, of effects of consumption on other outcomes including cognition and lactation, of differences in health effects of consumption depending on age, as well as research regarding the impact of alcohol consumption after a cancer or cardiovascular diagnosis. The recent Surgeon General's report highlighted both the impact of alcohol on cancer and the fact that less than half of Americans know that there is increased cancer risk with alcohol consumption. The overall situation in the US regarding alcohol is similar to understanding of tobacco health effects at the time of the first Surgeon General's report in the 1960's in that there is a general lack of awareness of health effects of alcohol.