

KEYNOTE ADDRESS

Menopause, Hormones, Pendulums, and Wheels

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Over 40 years of submersion in one specific area of women's health, namely the menopause, has provided the unique opportunity to live through historical scientific developments and to observe how these discoveries are interpreted or misinterpreted by the media, women, the public in general, and health providers. The manner in which the findings are reported directly influence perception and the swing of the pendulum of opinion. Reflection and further interpretation or misinterpretation of the facts over time drives the wheel of reaction. The outcomes are not always anticipated. Ignorance of the facts, or failure to appreciate the full literature leads to the inevitable vicious cycle, or what I term the constant spinning of the wheel. The purpose of this presentation will be to relate all of the above to the swings and turns regarding menopause and hormonal therapies, emphasizing how opposing views create media interest, controversy drives change, and all of this affects markets. Finally, I speculate on the next swing of the pendulum and turn of the wheel for menopause-related medicine.

PRESIDENTIAL SYMPOSIUM: PLENARY SYMPOSIUM #1

SERMs and the Breast

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Follow-up data from the phase III prevention trials have established a net benefit of the selective estrogen receptor modulator tamoxifen for the reduction of ER-positive breast cancers, particularly in women younger than 50 years, with continued benefit for at least 10 years. The tamoxifen prevention trials showed a 38% (95% CI 28-46; $p < 0.0001$) reduction in breast-cancer incidence. There was no effect for breast cancers negative for estrogen receptor (ER; hazard ratio 1.22 [0.89-1.67]; $p = 0.21$), but ER-positive cancers were decreased by 48% (95% CI 36-58; $p < 0.0001$) in the tamoxifen prevention trials. Age had no apparent effect on beneficial outcomes. Rates of endometrial cancer were increased in all tamoxifen prevention trials (consensus relative risk 2.4 [95% CI 1.5-4.0]; $p = 0.0005$); no increase has been seen so far with raloxifene. Venous thromboembolic events were increased in all tamoxifen studies (relative risk 1.9 [95% CI 1.4-2.6]; $p < 0.0001$) and with raloxifene. The results of the STAR trial have confirmed the risk reduction effects of raloxifene in postmenopausal women, and the effect of raloxifene on DCIS is similar to that of tamoxifen. Further, up to 8 years of raloxifene use for osteoporosis is associated with continued breast cancer risk reduction. Tamoxifen and raloxifene have a similar favorable effect on fracture incidence. They both increase the incidence of venous vascular events, but the influence of tamoxifen on such events appears somewhat greater. The effect of both agents on arterial vascular events appeared to be higher in older women and women with known risk factors for such events. Women who were treated with raloxifene had fewer uterine cancers, gynecologic symptoms, and cataracts compared with women who were treated with tamoxifen. Statistically significant differences in the average mean severity of individual quality-of-life measures between tamoxifen and raloxifene were observed in the STAR trial. An increase in gynecologic symptoms, vasomotor symptoms, leg cramps, and bladder control problems was observed in both groups during treatment, with the difference being significantly greater for the tamoxifen group compared with the raloxifene group ($P < .001$ for all symptoms). In contrast, women in the raloxifene group reported significantly more musculoskeletal problems, dyspareunia, and weight gain ($P < 0.002$ for all symptoms). Despite being statistically significant, these differences were associated with small effect sizes. Similar findings for raloxifene were reported in the raloxifene placebo-controlled trials (i.e., RUTH, CORE, and MORE trials). In the RUTH trial, hot flashes, leg cramps, and peripheral edema were significantly more common in the raloxifene arm compared with placebo ($P < .001$ for all symptoms). Hot flashes ($P < .001$) and leg cramps ($P = .008$), but not peripheral edema, were also more common in the raloxifene arm compared with the placebo in controlled trials. These findings illustrate that potential adverse effects on components of quality of life should be taken into consideration when discussing risk reduction options. Women with a calculated breast cancer risk of $>1.66\%$ in 5 years as determined by the Gail model should be considered as high-risk individuals and potential candidates for SERM therapy. The U.S. Food and Drug Administration approved the use of both tamoxifen and raloxifene to reduce the incidence of breast cancer in women greater than age 35 who are at increased risk of breast cancer. The risks and benefits of using tamoxifen depend upon age and race, as well as on a woman's specific risk factors for breast cancer. In particular, the absolute risks of endometrial cancer, stroke, pulmonary embolism, and deep venous thrombosis associated with tamoxifen use increase with age, as does the protective effect of tamoxifen and raloxifene on fractures. All of the prevention trials used reduced breast cancer incidence, rather than reduced mortality, as the primary end point. To design a prevention trial that has the power to determine a reduction in mortality would require a much longer follow-up and expense. Therefore, it is unlikely that meaningful mortality data will be known from any of the published trials because of the limited power for this end point, the long follow-up time necessary, and the effects of unblinding in certain trials.

SERMs and the Endometrium

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Selective estrogen receptor modulators (SERMs) have the ability to provide mixed functional estrogen receptor (ER) agonist or antagonist activity, depending on the target tissue. Tamoxifen, the first SERM available for clinical use, is regarded as a highly effective agent for the prevention and treatment of breast cancer. However, tamoxifen

exhibits ER agonist activity in the uterus and is associated with an increased risk of endometrial hyperplasia and malignancy. Endometrial safety has been an important consideration in the clinical development of SERMs with improved benefit-risk profiles. Raloxifene, currently approved for the prevention and treatment of postmenopausal osteoporosis and for the prevention of breast cancer, appears to have neutral effects on the uterus. Safety has been shown with raloxifene in combination with vaginal estrogen, but not with systemic estrogen. Promising safety results have been observed with the targeted development of newer and more tissue-specific SERMs, many of which are under investigation for postmenopausal osteoporosis. Of the newer SERMs in development, lasofoxifene has been shown to reduce fracture risk and decrease the incidence of breast cancer, but has been associated with an increased incidence of vaginal bleeding, endometrial thickening, and endometrial polyps. Lasofoxifene and ospemifene have had beneficial effects on the vaginal epithelium. Phase 3 clinical trial data have shown that bazedoxifene is effective in preventing and treating postmenopausal osteoporosis without adverse effects on the endometrium or breast. Phase three trials of bazedoxifene in combination with oral conjugated estrogen (Tissue selective estrogen complex, TSEC) are ongoing. To date, use of the combination TSEC has provided relief of vasomotor symptoms without stimulation of the endometrium. Arzoxifene is currently being evaluated in phase 3 trials for osteoporosis prevention and has been studied for the treatment of uterine malignancies. Further investigation of newer SERMs is warranted to more clearly define the endometrial safety of these agents.

SERMs and Bone

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Prevention of fractures remains the primary use of SERMs besides tamoxifen. Raloxifene decreases bone turnover, increases bone density, and reduces the risk of vertebral fracture. It is approved and widely used for prevention of fractures. However, raloxifene does not reduce the risk of nonvertebral fractures and this fact has been its main drawback for treatment of osteoporosis. Other SERMs have been developed with the aim of finding one that reduces the risk of nonvertebral fractures while retaining the reduction in risk of breast cancer and without increasing the risk of endometrial cancer or other important safety problems. Lasofoxifene is more potent than raloxifene and decreases markers of bone turnover somewhat more than does. The PEARL trial recently demonstrated that lasofoxifene 0.5 mg daily reduced both the risk of vertebral fractures by 42% and nonvertebral fractures by 24%. Besides reducing the risk of breast cancer, it reduced the risk of CHD and stroke. Bazedoxifene decreases bone turnover and increases BMD to a similar degree as raloxifene. A placebo and raloxifene-controlled trial showed that bazedoxifene reduced the risk of vertebral fractures to the same degree (37 to 42%) as raloxifene (42%). Neither treatment reduced the risk of nonvertebral fractures. The effects of bazedoxifene on risks of breast cancer and CVD are not yet known. However, bazedoxifene is intended to be used along with Premarin (conjugated equine estrogen). Preliminary results suggest that the combination has greater effects on BMD than does raloxifene. Effects on fracture risk and other conditions, such as CVD and breast cancer are not yet known. Arzoxifene is another very potent SERM whose major clinical trials have recently completed and results may be available in 2009. If new treatments live up to their preclinical promise, clinicians might soon have several SERMs for use in prevention of vertebral and nonvertebral fractures with additional advantages of reducing the risk of breast cancer and other common conditions.

PLENARY SYMPOSIUM #2

Does Vitamin D Prevent Cancer and Cardiovascular Disease?

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Vitamin D may have roles other than those related to bone health. Many cell types express vitamin D receptors. The relation between vitamin D status and cancer risk has been investigated in a number of epidemiologic studies, while data from interventional studies remain scarce. In terms of cancer sites, the body of evidence is most extensive for colorectal cancer, where those with low levels of vitamin D may have double the risk compared with those with adequate levels. The evidence for breast cancer is also intriguing but prospective studies of 25-hydroxy-vitamin D, the major circulating metabolite of vitamin D, are sparse and somewhat conflicting. In one case-control study, retrospectively reported sun exposure during ages 10-19 was most strongly associated with reduced risk of breast cancer. For prostate cancer, the data on circulating 25-hydroxy-vitamin D have been equivocal, suggesting no association or a weak inverse association. Most of the epidemiologic studies to date have examined vitamin D status in relation to risk of cancer, but emerging evidence suggests that vitamin D may be an important factor for cancer progression and mortality, independently of any effects on incidence. Further study is needed to establish the precise role of vitamin D on carcinogenesis, especially in terms of when in the lifespan and on what stages of carcinogenesis vitamin D is relevant, the precise intakes and levels required, the magnitude of the associations, and which cancer sites are most affected. In addition, recent studies indicate that deficient vitamin D status may increase risk of both ischemic and non-ischemic cardiovascular diseases independently of established cardiovascular risk factors. The role of vitamin D in potentially regulating many functions in the cardiovascular system is just beginning to be unraveled. Among the potentially relevant mechanisms for cardiovascular diseases, vitamin D may influence blood pressure through the renin-angiotensin system, parathyroid hormone (PTH) levels, myocardial function, inflammation, and vascular calcification. Both cancer risk and cardiovascular disease risk appear especially elevated at 25-hydroxy-vitamin D levels below 10 or 15 ng/mL, and optimal levels may be at least 30 ng/mL. Among individuals who are not receiving substantial exposure to sun, intakes of 1,000 to

2,000 IU per day may be needed to achieve levels of at least 30 ng/mL. Further study, including properly designed randomized control trials, is required to further establish the role of vitamin D on neoplastic and cardiovascular diseases.

Nutrients from Foods vs. Supplements: Does it Matter?

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Nutritional factors play an important role in the health of postmenopausal women. Generous consumption of plant foods high in vitamin, minerals, fiber and other bioactive compounds is consistently associated with reduced risk of cancer and cardiovascular disease, the two most common causes of morbidity and mortality in postmenopausal women. Whether obtaining some of these important compounds from dietary supplements can either replace or augment that obtained from food is of considerable interest to patients and clinicians alike, albeit not without controversy. Many types of dietary supplements are available ranging from standard multivitamin to single ingredient supplements and specialty supplements containing botanicals. Use of supplements may be particularly high among women who have already been diagnosed with cancer or cardiovascular disease. A recent report from the Women's Health Initiative noted that among over 160,000 postmenopausal women use of multivitamins neither increased nor decreased risk of several common cancers, cardiovascular disease and mortality. The results were consistent across most subgroups in this population, including those with less than ideal diets. One reason for this lack of association in the WHI study may be that plants foods contain many more healthful compounds than can possible be packaged into a pill. Current evidence suggests that postmenopausal women should rely on whole, intact foods for maximum reduction in diet-related disease risk reduction.

PLENARY SYMPOSIUM #3

Osteoporosis and Fracture Risk Assessment

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Technology has advanced the field of bone health over the past two decades. Since osteoporosis is a "silent disease" until a fracture occurs, bone mass measurement has provided to ability to quantitate bone mineral density (BMD). However, research has demonstrated that individuals have different fracture risk at the same level of measured bone mass. For any bone mineral density level, short-term fracture risk is higher for older than for younger postmenopausal women. Fracture risk is highest in osteoporotic women, but most fractures occur in osteopenic women because so many more women have BMD in that category. All osteopenic women are not alike. For example, a 65-year-old woman many years post-menopause with an osteopenic T-score has gotten to that level through bone loss — so there is a loss of microarchitecture as well as lower bone mass. Her short-term fracture risk is higher than that of a 50-year-old woman with the same osteopenic T-score. However, her short-term fracture risk is lower than that of a 65-year-old woman with osteoporotic T-score. Age is a major factor in assessing future fracture risk. To address the limitations of the WHO diagnosis of osteoporosis established in 1994 and to include key risk factors for fracture, a new WHO fracture risk assessment tool called "FRAX" was released in 2008. This tool incorporates key risk factors along with hip BMD to provide a 10-year probability of hip and major osteoporotic fractures. At the present time, FRAX can be accessed on the website: <http://www.shef.ac.uk/FRAX/or> just put "FRAX" in your internet search. In the near future, software will be added to the DXA machines to incorporate FRAX. New National Osteoporosis Foundation guidelines were also released in 2008 that incorporate FRAX and provide information on whom to test, on whom to treat, and therapeutic options. NOF Clinician's Guide gives recommendations for pharmacologic treatment are based in part on algorithms that incorporate the costs and health consequences of clinical osteoporotic fractures. As with any technology or tools, there are limitations and individual patient's clinical circumstances need to be taken into account.

Update on Current and Future Osteoporosis Treatments

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Osteoporosis is a painless loss of bone that affects all women and men in the process of aging, leading to skeletal fragility and an increased risk of fracture. Contemporary bone densitometry techniques quantify the amount of bone present at different skeletal sites and provide a good estimate of long term fracture risk, particularly when combined with other important risk factors such as age and history of previous fracture as in the FRAX model developed under the auspices of the World Health Organization. Currently, all osteoporosis prevention and treatment agents target the bone density portion of the fracture risk equation, predicated on the understanding that the prevention of bone loss—or the stimulation of bone formation—will lead to a material reduction in the risk of fracture. Most current treatment agents act primarily by limiting bone breakdown; calcium, estrogen, calcitonin, the bisphosphonates and the SERMs (EAs) are therefore described as "antiresorptive" or "anticatabolic" agents. Through so-called coupling, a treatment-induced decrease in bone resorption is followed by a decrease in bone formation, thus restricting the net increase in bone density. The limited bone density response to antiresorptive therapy has nevertheless been associated with surprisingly large reductions in fracture risk—reductions far out of proportion to the modest changes in bone density. This clinical observation provides prima facie evidence that the antiresorptive agents improve bone "quality," not just bone density. However, the exact microarchitectural basis for that quality improvement remains unclear, and there is no diagnostic test yet available to assess the change. Although a number of novel antiresorptive agents are under clinical development—particularly SERMs, a monoclonal antibody to RANKL and a cathepsin K inhibitor—it is not yet obvious that such agents will have fracture protection superior

to that achievable with existing agents. The inherent limitation of antiresorptive therapy has spurred interest in regimens that permit a sustained increase in bone formation. At this time, such anabolic therapy involves the daily, subcutaneous injection of PTH. A truncated form of PTH—teriparatide—is the only PTH preparation approved for use in the United States, although the full-length PTH molecule has also been approved outside of the United States. There is great research interest in the development of alternative routes of PTH administration, as well as the stimulation of endogenous PTH release through the use of so-called calcilytic agents. Other potential anabolic agents include various analogs of PTH and PTHrP, as well as agents—such as an anti-sclerostin antibody—that target steps in the Wnt signaling pathway. The availability of a safe, effective anabolic approach could significantly change our clinical approach to osteoporosis, particularly if coupled with a refined assessment of bone quality to identify patients at high risk of fracture. Rather than emphasizing long-term bone-specific preventive therapy, it might be possible to shift to intensive, relatively short-term anabolic therapy to prevent fractures in that high-risk population.

PLENARY SYMPOSIUM #4

Innovations in Urogynecology and Reconstructive Pelvic Surgery

Marie Fidela R. Paraiso, MD. Dept. Ob/Gyn, Cleveland Clinic, Cleveland, OH
This lecture summarizes current and future innovations in Female Pelvic Medicine and Reconstructive Surgery. Challenges in the treatment of pelvic organ prolapse, urinary incontinence, and voiding disorders are discussed. Ideal solutions for these conditions are proposed. Summarized topics include 1) graft implantation for the treatment of pelvic organ prolapse and the recent FDA notification regarding associated complications, 2) minimally invasive surgery including robotic-assisted and single-port laparoscopic surgery for urinary incontinence and pelvic organ prolapse, 3) stem cell injection for stress urinary incontinence and pelvic organ prolapse, 4) tissue engineering for the urinary tract and applications in pelvic floor disorders, 5) neuromodulation for voiding disorders, and 6) preventive, diagnostic, and educational initiatives on the horizon.

Robotic Surgery: The Future is Upon Us

Rosanne M. Kho, MD. Dept. of Ob/Gyn, Mayo Clinic, Phoenix, AZ
The use of robotics in gynecologic procedures was approved by the FDA in 2006. Since then, it has been widely applied in all aspects of gynecology – benign, urogynecology and gynecologic oncology. Features unique to the robotic system include 3D visualization, downsizing of movements, articulated instruments providing 7 degrees of freedom and abolition of hand tremor. A review of the literature regarding the surgical outcomes and limitations to the approach will be conducted. Multiple surgical video segments will also be presented.

PLENARY SYMPOSIUM #5

Quantifying Breast Cancer Risk

Karla Kerlikowske, MD. Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, CA

Risk factors for breast cancer are in one of four groups: 1) family history/genetic, 2) reproductive/hormonal, 3) proliferative benign breast disease and 4) breast density. The challenge has been to combine these risk factors into risk prediction models that accurately and precisely identify women at increased risk of breast cancer. Investigators at the National Cancer Institute developed a model of a woman's risk for breast cancer (the Gail model) that incorporated her reproductive history and the number of first-degree relatives with breast cancer. This remains the most widely used tool for estimating a woman's future risk for breast cancer. A web-based calculator is available for women and their physicians to use: <http://www.cancer.gov/bcrisktool/>. The model estimates a women's risk of developing invasive breast cancer in the next five years as well as her lifetime risk for invasive breast cancer. The Gail model significantly underestimates breast cancer risk for patients with family histories suggestive of hereditary breast cancer because it does not incorporate 2nd or 3rd degree relatives' cancer history and does not account for age of diagnosis of relatives, bilateral breast cancer, or ovarian cancer. Models that may be more appropriate for patients with strong family histories include BRCApro, the Claus model, and the Tyrer-Cuzick model. More recently investigators recognized that breast density is a strong risk factor for breast cancer and have incorporated it into new models. Breast density is probably the single most important factor in terms of population attributable risk. About 30-40% of women have high breast density, which exceeds the frequency of most recognized risk factors such as family history of breast cancer that occurs in 10% of women. The addition of breast density has provided a significant improvement to risk prediction estimates, reflected by a corresponding increase in the discriminatory accuracy of results. Models that include a breast density measure will be described and how well they discriminate women with and without breast cancer compared to other risk models.

Methods to Reduce Risk

Rowan T. Chlebowski, MD, PhD. Medicine, LAbioMed, Torrance, CA

For breast cancer risk reduction both tamoxifen and raloxifene have federal drug administration approved indications based on randomized clinical trial evidence. Tamoxifen for use in women over 35 years of age and raloxifene for postmenopausal women. Both reduce invasive breast cancer to a similar degree and both have similar effects on fractures and differences in side effects will be discussed. The Women's Health Initiative has conducted full scale randomized clinical trials evaluating menopausal hormone therapy, calcium and vitamin D supplementation and dietary modification with

breast cancer as primary or secondary endpoint. Use of estrogen plus progestin was associated with increased breast cancer incidence which rapidly dissipated once hormones were discontinued and change in combined menopausal hormone therapy use has been associated with decrease breast cancer incidence. In contrast, estrogen alone use in women with prior hysterectomy demonstrated a trend for fewer breast cancers. Observational studies identify an association between lifestyle choices and breast cancer incidence perhaps especially for body weight and physical activity. Prophylactic surgery (bilateral mastectomy and/or oophorectomy) is effective but are reserved for women at highest risk. Ongoing trials with next generation selective estrogen receptor modulators (lasofoxifene, arzoxifene) and aromatase inhibitors (anastrozole, exemestane) may increase breast cancer for breast cancer risk reduction in the near future.

2009/NAMS WYETH WULF H. UTIAN ENDOWED LECTURE

The Science of Sexuality Through and Beyond Menopause

Julia R. Heiman, PhD. Kinsey Institute for Research in Sex, Gender and Reproduction, Bloomington, IN

The value of studying the entire range of a woman's lifecycle has become an increasing area of health focus given the privilege of longer survival in the developed world. Sexuality, its changes and its connection to other areas of life functioning, personal welfare and social meaning remains a useful area to explore through and after menopause. Assumptions about aging, menopause, sexuality and women have long been held with limited data to support or refute misconceptions and myths where they exist. The most common problems are poor measurement and misuse of sampling to draw too broad conclusions. These areas are improving but far from resolved or unconflicted. There remains a hunger, both intellectual and economic, for reputable data. The present talk will present selected areas of measurement of sexual response, the importance of self report and physiological data, and key findings from studies of individuals and couples which bear mention and careful interpretation. The tendency to overstate or under account for the role of sexuality and its changes over a woman's lifetime remains a consistent issue that needs attention if we are to deal with advancing age and its dilemmas in a humane and intelligent fashion.

PLENARY SYMPOSIUM #6

National Trends in HIT and Physician Funding Under ARRA

William Zelman, DO, PowerMed Corporation, Portland, ME

The Health information technology (HIT) provisions of the Recovery Act are found primarily in Title XIII, Division A, Health Information Technology, and in Title IV of Division B, Medicare and Medicaid Health Information Technology. These titles together are cited as the Health Information Technology for Economic and Clinical Health Act or the HITECH Act. The provisions of Title IV deal directly with the enormous EHR incentives available to physicians in the form of increased medicare and medicaid payments. There are two central requirements for physicians to qualify, requiring only a few critical words to convey; "Meaningful use of a certified EHR". While definitions of "meaningful use" and "certified EHR" are in evolution and not likely to be finally defined until late 2009 (at the earliest), several important conclusions can be made now. This presentation will focus the most current status of those definitions, and the most likely scenarios that will unfold for physicians under this program.

Patients Use of the Social Web: The Demand for Patient-Centered Medical Informatics

Jeana Frost, PhD. PatientsLikeMe Inc., Cambridge, MA

Increasingly, patients interested in improving quality of life and health outcomes are going online not only to research health questions, but to solidify knowledge, share expertise and organize individual level experience to create data sets of patient-reported outcomes. In this talk, I take as a case example one platform for patient interaction and data-driven inquiry, PatientsLikeMe. Citing behaviors on and evidence from the website, I will discuss how the social web and patient participation presents new possibilities for the patient-provider relationship and medical research. PatientsLikeMe joins the functionality of an online community with a platform for sharing medical information. Patient members record structured data about their symptoms, treatments, tests and health status. This information is reflected back to community members in coherent graphical displays as individual-level health profiles and community-level reports on symptoms, treatments and outcomes. These data displays are the focal points for discussion in a public forum, within a specific patient's profile, or in private-messaging between patients. Health profiles, community-level reports, and user discussions are dynamically linked to introduce data into the conversation and signal the health status, history, and credibility of the author. And, each profile is synthesized in a provider visit sheet for members to print out and bring to clinical consults. Launched in March 2006, the site has over 40,000 members. There are over 36,000 patient members across 6 larger communities and 6 rarer conditions: ALS, multiple sclerosis, Parkinson's disease, HIV, mood conditions, fibromyalgia, and several rare disorders related to neurological conditions. We are currently building an epilepsy community. In this talk, I will present illustrative cases of use of the website with particular emphasis on how our members who are going through menopause employ the tool. I will also present findings from a member survey that both indicates the primary benefits of participation and suggests how participation supports and improves - contrary to some concerns - the relationship between the patient and the provider. I propose that as the burden on providers mount, patients who are online,

engaged in learning about their health, self-monitoring symptoms, and understanding how to manage treatments are a powerful resources for one another and to inform medical research and are better equipped to talk to providers and elicit good care.

PLENARY SYMPOSIUM #7

Autoimmune Thyroiditis

Jorge H. Mestman, MD. Dept. of Ob/Gyn, University of Southern California, Los Angeles, CA

Thyroiditis include many common disorders, the most common is Chronic Thyroiditis (CT) or hashimoto's thyroiditis. May start at any age, the incidence peaks at 30-50 yrs age. Is more frequent in women than men with a ratio of 8-9:1. It is an autoimmune phenomenon: lymphocytic infiltration, Germinal centers and fibrosis are the typical cytopathologic features. The diagnosis is based on family history of thyroid diseases, presence of a small goiter (in 10% of patients the gland is atrophic), about 2 times normal size, firm and rubbery to palpation and positive TPO antibodies. Ultrasonography shows a typical hypoechogenic gland. Most patients are euthyroid at the time of diagnosis, with a significant propensity to become hypothyroid with age progression. Occasionally hyperthyroidism may developed. CT affects 8-15% of women in the childbearing age. Pregnancy by itself, may trigger the development of hypothyroidism early after conception. If untreated, maternal and fetal complications are significant. Postpartum thyroiditis (PPT) occurred in about 40-50% of women with chronic thyroiditis; it is characterized by 3 stages, hyperthyroidism in the first 3 months postpartum followed by hypothyroidism between 3 and 8 months followed by euthyroidism, in most women; however 5% of them remained hypothyroid. Not every patient develop the 3 phases of PPT Permanent hypothyroidism occurred in 50% of women 5 years after the episode of PPT. PPT may also occur following a spontaneous or therapeutic abortion in women with CT. The incidence of miscarriages and preterm delivery is significantly increased in women with CT even if they remain euthyroid. Preliminary studies suggest treatment with levothyroxine in euthyroid chronic thyroiditis women for prevention of both potential complications. Screening of a selective population at risk for autoimmune thyroiditis is recommended before or soon after conception. Positive serum TPO Antibodies will detect women with CT and serum TSH values will assess thyroid function. The incidence of subclinical hypothyroidism in the first trimester of pregnancy is ~ 4%. Women with CT are at higher risk of developing other autoimmune diseases such as Type 1 Diabetes mellitus, SLE, RA, Celiac Disease, Pernicious anemia. Other types of thyroiditis are uncommon, among them painful or painless thyroiditis, a self limited clinical picture with spontaneous recovery of thyroid function.

Rheumatoid Arthritis

Nancy E. Lane, MD. Aging Center, Medicine and Rheumatology, University of California at Davis Medical Center, Sacramento, CA

Rheumatoid arthritis (RA) is a disease that affects women in early adulthood and then in their seventh decade. Women are affected nearly 8 times as often as men. While we do not yet know the etiopathogenesis of RA, it has become clear that it is a combination of genetic predisposition and environmental exposure, and together this leads to immune dysregulation and the clinical disease. The presentation of RA is classic for inflammatory arthritis, often with bilateral small and medium sized joints with swelling and pain. The inflammatory arthritis, results from proliferation of the synovium, synovitis, which produces proteins that alter bone remodeling with reduction in bone formation and increased bone resorption and destruction of articular cartilage. Treatment is directed to reduction of the inflammation and pain and maintenance of physical function. Today, the treatment of RA often involves the use of biologic agents (anti-TNF agents, anti-B cell agents, inhibitors of T cell costimulation, and inhibition of IL-6 activity, etc.). These biologic agents, when added to standard DMARD therapy with methotrexate and plaquenil have significantly reduced systemic inflammation, the signs and symptoms of the disease, maintained or improved physical function, and there is some indication they have improved life expectancy. The use of these biologic agents during pregnancy will be reviewed.

Systemic Lupus Erythematosus (SLE) and Menopause

Bevra H. Hahn, MD. UCLA Medical Specialty Suites, Los Angeles, CA

SLE is a symptom complex associated with autoantibodies. A person with any 4 of the following is classified as SLE with 96% specificity and 80% sensitivity: polyarthritis, malar rash, photosensitive rash, discoid lupus, oral ulcers, serositis, cytopenias, nephritis, CNS disease (seizures, psychosis), ANA, or other autoantibodies (anti-cardiolipin, anti-Sm, anti-DNA). Nephritis is the most important determinant of survival, which is 90-95% over 10 years. African-Americans and Texas Hispanics have worse outcomes than Caucasians. Evidence that estrogen drives this disease includes a 9:1 female-to-male ratio, HRT increasing risk for mild flares, and increased risk for developing SLE with early menarche, oral contraceptive or HRT therapies. However, early menopause also increases risk. Estrogens are "permissive" but other characteristics of femaleness are also important in predisposing to disease. Menopause is not associated with decrease in disease activity; more importantly over time disease tends to be less active with fewer flares. However, patients with onset of disease before age 50 (80% of patients) and after age 50 (20%) are somewhat different. Younger patients are more likely to have nephritis, malar/discoid rash, anti-DNA, and highly active disease. Older patients are more likely to have arthritis, serositis, cardiopulmonary involvement, CNS disease, and organ damage. Treatment involves the following phases: 1) suppression of active disease; 2) maintenance of improvement and prevention of flares; 3) prevention of damage. Initial treatment depends on disease severity. If not life-threatening, SLE can be treated with antimalarials (hydroxychloroquine is most common), NSAIDs, analgesics, and topical glucocorticoids

and/or tacrolimus. If life-threatening, treatment should be high dose glucocorticoids (i.v. pulses give earlier responses), hydroxychloroquine (helps prevent damage), and usually another immunosuppressive. Both mycophenolate mofetil (MMF) and cyclophosphamide are in wide use as these immunosuppressives; African Americans are less likely to improve on cyclophosphamide than Caucasians. MMF is more widely used in the US than cyclophosphamide because it is as effective as cyclophosphamide and generally safer; long term data are available for cyclophosphamide but not for MMF. Azathioprine is also acceptable. Maintenance of improvement usually involves tapering prednisone and the 2nd immunosuppressive and discontinuing if possible, maintaining the antimalarial. Patients with clotting related to anti-phospholipid are anticoagulated for long terms. Preventing damage involves prevention/early treatment of infection, minimizing bone loss, and preventing the accelerated atherosclerosis which is a frequent cause of death in SLE (risk of MI or stroke is increased approximately 5-fold). Vaccinations are safe in SLE; early treatment of suspected infection is advised. Most authorities recommend that patients treated with glucocorticoids receive calcium and Vit D supplementation (1500 mg Ca, Vit D to 25OHD serum levels of 40) and a bisphosphonate, if not contraindicated. Alendronate is more effective than calcitriol or Ca alone in maintaining bone mass. Prastera (DHEA) at 200 mg daily doses helps maintain mass and decrease SLE activity. Raloxifene is also useful, but data suggest bisphosphonates are the most effective intervention. For prevention of atherosclerosis, which may be signaled by the presence of HDL that are normal in quantity but defective in anti-oxidant capacity, control of hypertension, hyperglycemia, weight and hyperlipidemia are recommended. A recent trial of a statin in SLE patients did not show reversal of coronary calcification or beneficial effects on disease activity compared to placebo. However, we currently recommend that treatment of hyperlipidemia follow the NCEP guidelines for its treatment in patients with diabetes, as SLE is probably confers a similar risk. It is likely that control of disease activity lowers risk for atherosclerosis; however high cumulative doses of glucocorticoid predispose to it. Thus, treatment involves suppression of disease with as minimal immunosuppression as possible, and careful interventions to minimize the damage that is a major cause of death in SLE.

PLENARY SYMPOSIUM #8

Hot Issues Symposium

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In a time of confusion and conflicting points of view, good clinical judgment is more important than ever — making decisions based upon a foundation of knowledge gained through our journals, but also by our continuing education and our experience, the knowledge gained from every clinical encounter. And most importantly, clinical decisions should be individually modified according to a patient's needs and a clinician's understanding of each individual patient. It is the task of an epidemiologist to derive study conclusions based on study data. It is the obligation of a clinician to make a judgment whether the epidemiologist's conclusions have clinical meaning. For example, an epidemiologist can conclude that estrogen reduces coronary artery calcification and point out that a randomized clinical trial has not proved that such a reduction lowers the risk of coronary heart disease. But it is appropriate for a clinician, knowing the correlation between coronary artery calcification and coronary heart disease, to conclude that estrogen reduction of coronary calcification will translate into less coronary heart disease. Medical judgments require more than absolute evidence from randomized trials; medical judgments frequently do not have the luxury of postponing clinically meaningful decisions until data are conclusive. The purpose of the "Hot Issues" symposium is to address questions with no clear-cut answers, but represent the important issues in clinical decision-making that require medical judgements in order to serve the needs of patients.

PLENARY SYMPOSIUM #9

Learn to Like the Lichens: Lichen Sclerosus, Lichen Simplex Chronicus and Lichen Planus

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Objective: A variety of conditions affecting the vulva are associated with pruritus. Three conditions, lichen sclerosus, lichen simplex chronicus and lichen planus will be discussed. Lichen sclerosus of the vulva is commonly seen by health care providers. It is characterized by a crinkling, white, cigarette paper appearance. Histologic findings consist of a loss of rete ridges and hyperkeratosis. Patients tend to respond well to topical steroids. It is best to utilize an ointment base. Another condition that is often seen is lichen simplex chronicus. Other names that have been utilized for this condition are squamous cell hyperplasia, neurodermatitis, pruritus vulvae, and hyperplastic dystrophy. It is involved with the itch-scratch cycle and has a variety of causes. For early disease, topical steroid ointments may give adequate relief. However, when significant disease associated with scratching is present, a regimen of oral steroids, sedation, antibiotics, and at times, antifungals, may be required. For patients that do not respond adequately, intramuscular steroids may be required. It is important to stop all irritants when treating this patient population. Another condition, lichen planus, is a distinctive inflammatory eruption of the skin and mucous membranes. It is a disorder of altered cell mediated immunity with exogenous antigens targeting the epidermis. Erosive lichen planus is the most common form of lichen planus affecting the vulva. While topical steroids are generally used as the initial treatment, many patients require a variety of other medications to control the disease. A detailed approach to treating these three conditions will be provided.

When Sex Hurts: Evaluation and Management of Dyspareunia

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Introduction: Female sexual pain (dyspareunia) may present in a variety of ways and stems from many causes. Dyspareunia may have substantial impact on a woman's relationships and quality of life. The estimated prevalence of dyspareunia in postmenopausal women is 11-45%. The most common causes of dyspareunia in postmenopausal women are atrophic vulvovaginitis, pelvic floor hypertonus, and vulvar dermatologic conditions. **Atrophic vaginitis** Estimated to occur in 10-40% of postmenopausal women, atrophic vaginitis describes symptomatic vaginal atrophy due to low estrogen levels. This occurs most commonly with menopause and aging, but can result in younger women due to hypothalamic amenorrhea, hyperprolactinemia, lactation, and usage of anti-estrogenic medications. Occasionally usage of extra-low dose contraceptive pills and cancer therapy may cause similar symptoms. During the reproductive years, estrogen plays a major role in maintaining the normal vaginal environment. This includes a thickened, rugated vaginal surface, increased blood flow and lubrication, lactobacillus-dominant flora, and a low (<4.5) pH. With estrogen withdrawal during menopause, significant changes occur in the vagina, resulting in the tissue becoming pale, thin, and less flexible. The physiological changes occurring in vaginal atrophy expose menopausal women to potential dyspareunia in several ways. Vaginal dryness causes increased friction during intercourse. The thin vaginal walls are friable and become prone to mechanical damage and formation of petechiae, ulcerations and tears with sexual activity. With longstanding estrogen deficiency, the vagina may become shorter, narrower, and less elastic. All of these changes increase the likelihood of trauma, infection and pain. Estrogen therapy, both systemic and topical, is the most effective treatment for atrophic vaginitis, but some authors advocate lubricants and moisturizers as first line therapy. Intravaginal estrogen therapy is generally considered safer and can be less concerning to patients. Estradiol creams, tablets, and rings are equally efficacious for the treatment of vaginal atrophy. **Pelvic Floor Hypertonus** Pelvic Floor Hypertonus (also called Levator Ani Spasm), or the chronic spasm of the muscles of the female pelvic floor (levator ani muscles), is becoming increasingly recognized as a cause of chronic pelvic pain and dyspareunia in women. Pelvic floor muscle spasm may occur as a primary event or secondary to other physical or psychological factors (i.e. vaginismus.) This condition may be treated with pelvic floor physical therapy where the therapist employs a variety of techniques, including myofascial release, biofeedback, and electrical stimulation. Sex therapy, cognitive behavior therapy and vaginal dilators may be used in women with vaginismus. Recently, the use of botulinum toxin type A has been shown to be highly effective in achieving relaxation of the pelvic floor muscles and successfully treats associated sexual pain. **Vulvar Dermatologic Conditions** The most common dermatologic disorders in the postmenopausal women causing dyspareunia are lichen sclerosus and erosive lichen planus. Recurrent fissuring of the posterior fourchette (vulvar granuloma fissuratum) may also be considered in this category. Diagnosis is made by physical examination (aided by a colposcope) and vulvar biopsy evaluated by a dermatopathologist.

PLENARY SYMPOSIUM #10

HPV Vaccination and Public Health: Opportunity and Challenge

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Human papillomavirus (HPV) infection is the most common viral sexually transmitted infection. HPV infections are extremely common, and most young adults are exposed to HPV soon after sexual debut. Although most HPV infections resolve, persistent infection by one or more of the oncogenic HPV types can cause cervical neoplasia. HPV can also cause other anogenital neoplasias and a smaller proportion of oropharyngeal neoplasias. Worldwide, cervical cancer is the second most common cancer in women and the 3rd leading cause of cancer death in women worldwide. Secondary prevention by cytologic screening has been effective in some countries, but the screening policies vary widely. Therefore, the incidence rates of cervical cancer differ strikingly between countries, also within Europe. Due to mass screening, the disease burden has shifted to management of cervical intraepithelial neoplasias (CIN). This also causes compliance problems, short-term and long-term complications and drains health care resources. The development of prophylactic HPV vaccines that target HPV16/18 which account for at least 70% of cervical cancers has been a remarkable success. HPV vaccines are now licensed in more than 100 countries. National and regional immunisation programs aimed at young adolescent girls have been widely implemented, and include catch-up programs in some countries up to the age of 18 years or older. These vaccines can substantially reduce the public health and economic burden of cervical precancer and cancer and other HPV-associated diseases. The vaccines are safe and highly immunogenic. The safety profile of the HPV vaccines has generally been similar to that of the control vaccine. The vaccines have been well tolerated with a good safety profile in women of all ages. No evidence exists for increased risk of vaccine related serious adverse events, new onset chronic diseases, autoimmune diseases, or adverse pregnancy outcomes. International phase III trials among 15-26 year old women have demonstrated that among HPV naive women the vaccines are nearly 100% efficacious against persistent infection and high grade cervical precancer (CIN2/3) caused by the vaccine HPV types. This is extremely reassuring since CIN2/3 is considered a valid surrogate marker of cervical cancer. Thus, primary prevention by vaccination of young adolescents before sexual debut will be the most effective strategy to prevent cervical (and other HPV related) cancer. Not surprisingly the efficacy among those already exposed to HPV is lower. However, it appears that only a small subpopulation of young adults have been infected by more than one vaccine HPV type suggesting that catch-up vaccination may still be beneficial resulting in less HPV

infections and less need for invasive cervical procedures to evaluate atypical Pap smear findings. Regarding catch-up vaccination, public health benefit and overall resources need to be taken into account when making decisions how to implement vaccination programs. An important bonus effect of the vaccines is cross-protection against infection and disease caused by 16/18-related HPV types, specifically HPV31, 33, and 45 which are the next most important HPV types causally attributed to cervical cancer, with an attributable proportion of approximately 12% of cases. Vaccines providing significant degree of cross-protection may therefore increase the overall impact. Clinical trials have also raised several questions and challenges to be addressed to assess the public health impact, and to design the most effective vaccination strategy. These include duration of immune response, vaccination of males, efficacy against other non-cervical HPV-related cancers, postmarketing surveillance, impact of vaccination on screening programs, potential type-replacement after widespread vaccination, and finally feasibility of HPV vaccination in developing countries where the disease burden is enormous. Although the importance of continued tests for Pap or HPV in vaccinated or unvaccinated women must be emphasised, HPV vaccination has the potential to substantially reduce the incidence of cervical cancer and precancer, and the numbers of colposcopy referrals and cervical excision procedures.

Menopause and Women's Environmental Health

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Human reproductive function can be adversely affected by exposure to environmental contaminants. Concerns have been raised about effects of chemical exposures in the workplace, home and ambient environment on women's reproductive health, but the literature on menopause is sparse. Using a lifestage approach, we recognize that reproductive health is a dynamic process with functional status at each stage of life somewhat dependent on function in earlier life. In a similar way, exposure to contaminants that perturb reproductive function earlier in life can also play a role in the timing of menopause. While evidence suggests a relation between endocrine-active compounds and ovarian function, the effect on menopause is equivocal. Exposure to organochlorine compounds such as dichloro-diphenyl-trichloroethane (DDT) and dichloro-diphenyl-dichloroethylene (DDE) and dioxin has been associated with both earlier and later ages at menopause. For example, earlier age at menopause was observed in Italian women exposed to an accidental dioxin emission, as well as with DDT, DDE and other pesticides in data from the Hispanic Health and Nutrition Examination Survey. In contrast, DDT exposure in the Agricultural Health Study was associated with slightly older age at menopause. Studies of polychlorinated biphenols and polybrominated biphenols have been generally negative in their findings regarding changes in age at menopause. These equivocal data may reflect the reliance on cross-sectional data and the inability of many researchers to collect exposure information during relevant timeframes and follow the same individuals over time to evaluate the impact of exposure on menopause. Environmental research that focuses on changes in menopausal symptoms is exceedingly rare in the literature, but one study observed increased symptoms in rural areas compared to more urban areas. Data on other environmental exposures in relation to symptoms is lacking. Given our concerns about the impact of chemical exposures on ovarian function, menopause is a reproductive outcome that merits additional research and attention.