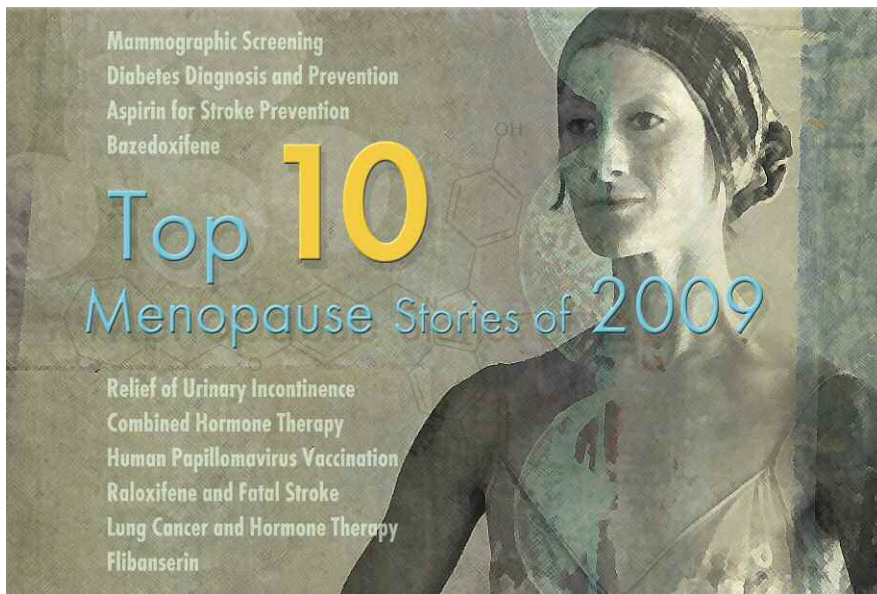


Top Ten Menopause Stories of 2009

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The themes of this year's "Top Ten" reflect evolving strategies for challenging medical issues facing adult women: prevention of chronic disorders of aging, relief of menopausal symptoms, early detection of disease and further refinement of risks versus benefits for therapeutic and diagnostic measures.

Mammographic Screening Recommendations: Taking another Look

In an October article in *JAMA*, Esserman et al challenged readers to consider the apparent paradox that mammographic screening might "increase the burden of low-risk cancers without significantly reducing the burden of

more aggressively growing cancers," questioning the current guidelines for breast cancer detection.¹ Along similar lines, a Massachusetts study presented at the American Society of Clinical Oncologists' 2009 Breast Cancer Symposium reported that over 12 years, 75% of breast cancer deaths occurred in women who did not receive regular screening mammograms; 25% occurred in women who did.² The authors of an updated Cochrane Review estimate that screening leads to a 15% reduction in cancer mortality (translating to an absolute risk reduction of 0.05%) but to a 30% overdiagnosis and overtreatment of breast cancers (an absolute risk increase of 0.5%).³ "This means that for every 2000 women invited for screening throughout 10 years, one will have her life prolonged.

In addition, 10 healthy women, who would not have been diagnosed if there had not been screening, will be diagnosed as breast cancer patients and will be treated unnecessarily. Furthermore, more than 200 women will experience important psychological distress for many months because of false positive findings."³ In the media storm that followed the October 2009 *JAMA* report, representatives of the American Cancer Society confirmed their recommendations for screening women annually starting at age 40.⁴ A few weeks later, the US Preventive Services Task Force (USPSTF), in an update of their 2002 statement, recommended screening women between the ages of 50 and 74 every 2 years.⁵ No recommendation was made for screening women 75 years and older. The Task Force did not recommend routine screening for women 40 to 49 years, but instead recommended individualizing the decision according to the patient's context and values.

The debate over mammographic screening on the eve of healthcare reform leads us to review the basis for established guidelines for screening and our approach to managing abnormal findings. Additional priorities include determining which early, small cancers will (or won't) progress so treatment can be reserved for women harboring the most aggressive tumors,¹ identifying younger women at highest risk for breast cancer so appropriate screening is employed,⁶ ensuring that underserved women receive breast cancer screening and utilizing

available preventive strategies for women at risk.⁷ Long-term adverse effects of ionizing radiation from annual screenings are generally considered small. While the discourse is certain to continue, what should you recommend to your patients? The most conservative stance is to follow the recommendation of the American Cancer Society: annual mammograms for women age 40 years and older.⁴ In any case, anticipate further debate and analysis before the mammogram screening issue is resolved.

Emerging Trends in Diabetes Diagnosis and Prevention

An International Expert Committee, with members appointed by the American Diabetes Association, the European Association for the Study of Diabetes, and the International Diabetes Federation, published a report of their recommendation to consider the use of the hemoglobin A1C assay for the diagnosis of diabetes.⁸ They specify a number of advantages over blood glucose determinations: A1C assays are well standardized, provide an index of overall glycemic exposure, and correlate well with the risk for long-term complications. There is no need for fasting or timed samples, and the A1C is currently used to guide management and adjust therapy. What levels would be used as a cutoff? The Committee proposes that the diagnosis of diabetes consists of an A1C level $\geq 6.5\%$.

Individuals with A1C levels $\geq 6\%$ but $< 6.5\%$ are probably at the highest risk for progression to diabetes. Some experts refer to this as “prediabetes,” currently defined as a fasting glucose of 100 to 125 mg/dL (impaired fasting glucose), a 2-hour postprandial level of 140 to 199 mg/dL (impaired glucose tolerance) or a diagnosis of the metabolic syndrome.⁹ Lifestyle modification constitutes the cornerstone of prevention.^{9,10} Specific therapies to lower

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blood glucose in select high-risk individuals and aggressive treatment of lipids and blood pressure to reduce associated cardiovascular risks are also recommended.

The 10-year follow-up of the Diabetes Prevention Program Outcomes Study confirms that the cumulative incidence of diabetes remained lowest in the lifestyle group (weight loss 5-10%; 150 minutes/week of moderate activity). Prevention or delay of diabetes with lifestyle intervention or metformin persists for at least 10 years.¹¹

The US spends more than \$200 billion per year on diabetes and pre-diabetes. While 20-million Americans suffer from diabetes now, that number is expected to double by 2025. As the experts debate the absolute best criteria for diagnosis (the ADA should weigh in this year), making the diagnosis is what counts. Testing should begin at age 45 and should be repeated at least at 3-year intervals.¹² Test earlier and more often in high-risk individuals—adults of any age who are overweight or obese, those with non-white ancestry, and those with a positive family history of diabetes, cardiovascular disease, sedentary lifestyle, hypertension and dyslipidemia (high triglycerides and low high-density lipoprotein [HDL] cholesterol). In women, look for a history of gestational diabetes, delivery of a baby weighing more than 9 pounds, and polycystic ovary syndrome—all markers of added risk.

An Aspirin a Day (for Select Women) Keeps Stroke Away

Five years ago, the Women's Health Study provided the first report that low-dose aspirin (100 mg on alternate days) was effective at reducing stroke, particularly ischemic stroke, in women ≥ 45 years of age.¹³ Overall, strokes were reduced by 17%; ischemic strokes were reduced by 24%. No increase in hemorrhagic stroke was seen with aspirin. The downside was a significant 40% increase in gastrointestinal (GI) bleeding requiring transfusion, the risk of which increases with age. In response to the Women's Health Study and a meta-analysis of additional controlled trials,¹⁴ the USPSTF now recommends the use of aspirin for women ages 55 to 79 years when the potential benefit of a reduction in ischemic stroke outweighs the potential harm of an increase in GI hemorrhage.¹⁵ Risk factors for ischemic stroke include age, high blood pressure, diabetes, smoking, history of cardiovascular disease, atrial fibrillation and left ventricular hypertrophy. To calculate risk, use the Stroke Risk Estimation Tool, derived from the Framingham Heart Study, available at: <http://www.westernstroke.org/PersonalStrokeRisk1.xls>. Risk factors for GI bleeding include a history of gastrointestinal ulcers (2- to 3-fold increase in bleeding) and use of non-steroidal antiinflammatory drugs (NSAIDs; 4-fold increase). Uncontrolled hypertension and use of anticoagulants also increase the risk for serious bleeding.

Benefits for stroke prevention exceed GI harm for women age 55 to 59 years with a 10-year stroke risk $\geq 3\%$, who are not taking NSAIDs, do not have upper GI pain and do not have a history of GI ulcer.¹⁵ At that age and level of risk, 5.1 strokes would be prevented and four episodes of GI bleeding would occur per 1,000 women us-

ing aspirin for 10 years. As the 10-year stroke risk increases, so does a woman's net benefit from taking aspirin. For women ages 60 to 69 years, the minimum 10-year stroke risk is $\geq 8\%$ in order for benefit (13.6 strokes prevented) to exceed GI risk (12 episodes of bleeding). For women ages 70 to 79, the minimum 10-year stroke risk increases to $\geq 11\%$ in order for benefit (18.7 strokes prevented) to exceed risk (18 GI bleeds). The USPSTF does not recommend the use of aspirin for primary stroke prevention in women younger than 55 years, and makes no recommendation for women over age 80. The optimum dose of aspirin is not known, but a dosage of approximately 75 mg/d seems as effective as higher doses.¹⁵

Given the ease of this online tool, the USPSTF recommends that stroke risk assessment be repeated as part of your patient's cardiovascular risk evaluation every 5 years. If your patient meets criteria and is willing, recommend aspirin for stroke prevention. Readily available formulations include one baby aspirin (81 mg) every day or one regular aspirin (325 mg) every other day.

Tissue-Selective Estrogen Complex: A Pathway for Estrogen without Progestogens

Bazedoxifene (BZA), a new selective estrogen-receptor modulator (SERM), reduces bone loss in women with low bone density¹⁶ and reduces vertebral fractures in women with osteoporosis.^{17,18} When BZA 20 mg is combined with conjugated estrogen (CE) 0.625 mg or 0.45 mg in recently postmenopausal women, the tissue-selective estrogen complex relieves vasomotor^{19,20} and vaginal symptoms,^{19,21} and improves sleep and quality of life.²² BZA/CE combinations decreased bone turnover and bone loss in postmenopausal women at increased risk for osteoporosis.²³ During 2 years of

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follow up, rates of breast tenderness,¹⁹ vaginal bleeding²⁴ and endometrial hyperplasia²⁵ were comparable to placebo therapy. Anticipated metabolic changes reflecting the oral estrogen component include declines in total and low-density lipoprotein cholesterol, augmentation of HDL and triglycerides, and a reduction in homocysteine levels.¹⁹ With the BZA/CE combo there were no significant changes in glucose metabolism or C-reactive protein, and only minor alterations of coagulation factors.¹⁹

In theory, this combination could preserve the benefits of postmenopausal estrogen therapy without incurring some potential risks. Women would have an alternative option to provide endometrial protection during estrogen therapy, without bleeding or added progestogen. Of possible concern, both classes of agents individually increase the risk of venous thromboembolic events (VTE). While the initial safety findings and surrogate endpoint measures are reassuring, we await the results of larger, longer trials to learn what effect this combination will have on key clinical endpoints: heart disease, stroke, VTE, breast cancer and cognition. (Note: BZA has not been tested

with other estrogen formulations. Given the complexity of ligand-estrogen-receptor-gene interactions, careful evaluation of other combinations would be necessary to delineate clinical outcomes.²⁶ The concomitant use of raloxifene with systemic estrogens has not been established and is not recommended.)²⁷

Relief of Urinary Incontinence: Another Benefit of Weight Loss

While 40% of postmenopausal women report leakage of urine, fewer than half of women who consider their incontinence a problem seek help.²⁸ Incontinence has adverse effects on quality of life and increases the risk of falls, fractures and nursing home admissions.²⁹ In clinical trials, pelvic floor muscle training plus bladder training improves urinary incontinence, as do anticholinergic drugs.³⁰ Now, there is another confirmed nonsurgical treatment for urinary incontinence in overweight and obese women: weight loss.²⁹ In a 6-month, randomized controlled trial, the Program to Reduce Incontinence by Diet and Exercise (PRIDE), 338 women with a mean body mass index of 36 ± 6 , a mean age of 53 ± 11 years and, on average, 24 incontinence episodes per week were assigned to behavioral weight-reduction intervention with diet and exercise (similar to that employed in the Diabetes Prevention Program) or a structured education program. Women in the intervention arm achieved weight loss of 8% (7.8 kg) and experienced a 47% reduction in the mean weekly number of incontinence episodes (predominantly stress incontinence, but urge incontinence improved as well). The women in the control group (structured education) had a 1.5% (1.5 kg) weight loss and significantly reduced incontinence episodes by 28%.

Weight loss has been on the list of treatments for incontinence in the past, but the bulk of the studies that support

that recommendation reflect weight loss induced by bariatric surgery. The PRIDE trial confirms a few prior reports that modest weight loss through diet and exercise leads to significant improvement in incontinence. In addition to the anticipated benefits to glucose metabolism, lipid regulation, blood pressure modulation, cardiovascular risk modification and, most recently, Alzheimer's disease prevention,³¹ behavioral weight-reduction intervention should be de rigueur for your overweight/obese patients with incontinence. The PRIDE trial results also remind us of the importance of proactively inquiring about urinary leakage, considering that many women are reluctant to bring the concern to your attention.

Combined Hormone Therapy and the Breast: Is Timing Everything?

Early reports from the WHI suggested that the increase in breast cancer in women participating in the combined therapy arm was limited primarily to women with a history of hormone therapy (HT) use prior to enrollment. Women naïve to HT could anticipate taking combined therapy for up to 5 years without concerns of increased breast cancer.³² Subsequent reports, however, suggest that women who start HT within 3 to 5 years of menopause might be at greater risk than those starting HT following a longer "gap" in time, even with short duration of use.³³⁻³⁵ What happens when women stop therapy? By 2.4 years of follow up, most risks (and benefits) receded.³⁶ In the most recent report, the incidence of breast cancer in adherent women declined within the first year after HT was discontinued, unrelated to changes in frequency of mammography.³⁷ As with the initial report describing breast cancer characteristics in women in the combined therapy arm,³⁸ breast cancers that occurred in women who had used HT

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were somewhat larger, abnormal mammograms requiring additional views were more common, and breast biopsies were required more frequently in the 2 to 3 years after stopping therapy.³⁷

The potential for increasing breast cancer risk with combined HT remains a nagging concern for many women and their clinicians, even when the overall absolute increased risk is very small (3 cases per year per 1,000 women not taking HT, compared to 4 cases per year per 1,000 women on HT). The most recent analyses suggest that increased breast cancer risk may be of greater concern for women taking HT for a short time if they start at the time of menopause, consistent with Key and Pike's hypothesis suggesting an increased risk in women with later natural menopause (ie, longer continuous duration of hormone exposure).³⁹ That the risk of breast cancer declines shortly after HT is discontinued in women who took their hormones faithfully comes as reassuring news. We are reminded, however, that commitment to HT even for a few years is also a commitment to possible additional

breast surveillance in the years to follow. Additional mammographic views following annual screening mammography, and breast biopsies to evaluate ambiguous findings, should be considered when women are initially counseled about combined HT for postmenopausal symptom relief.

Human Papillomavirus Vaccination in Midlife Women: Not Ready for Prime Time...Yet

The quadrivalent human papillomavirus (HPV) vaccine, currently approved for vaccination of girls ages 9 to 26, protects against persistent HPV infection, cervical cancer precursor lesions, vaginal and vulvar cancer precursor lesions, and genital warts caused by HPV types 6, 11, 16 and 18 among females who have not already been infected.⁴⁰ Safety labeling revisions by the FDA now include syncope, sometimes associated with tonic-clonic and other seizure-like activity, following administration. A 15-minute observation period following administration is recommended.⁴¹ Relevant to care of midlife women is the intriguing report from a trial conducted by the National Institute of Cancer, Bogotá, Colombia, involving nearly 4,000 women, describing vaccine efficacy in reducing HPV infections, a precursor to cervical cancer, in women ages 24 to 45 years.⁴² Trial duration was inadequate to detect differences in cervical cancer rates.

As clinicians, we must be sensitive to the sexual practices of our patients. Although one analysis concludes that HPV vaccine use in all women ages 35 to 45 years is not cost-effective,⁴³ you may wish to consider recommending the vaccine for your midlife patients on a case-by-case basis. Maintain your vigilance and screen appropriately, not just for HPV but also for other sexually transmitted diseases, including HIV, as recommended by the CDC.⁴⁴ In the latest ACOG Com-

mittee Opinion, annual pelvic examination and cervical cytology are recommended for women ages 30 to 64 years.⁴⁵ Screening can be decreased to every 2 to 3 years after three normal tests results if the patient has no history of cervical intraepithelial neoplasia (CIN2 or CIN3), is not immunosuppressed, is not-HIV-positive, and was not exposed to diethylstilbestrol in utero. The need to begin screening again should be evaluated at each annual exam.

Raloxifene and Fatal Stroke: Who is at Risk?

The Raloxifene Use for the Heart (RUTH) trial, originally published in July 2006, failed to detect overall cardiovascular benefit or harm with raloxifene therapy in women selected because of high cardiovascular risk,⁴⁶ findings consistent with the Multiple Outcomes of Raloxifene Evaluation (MORE) and Continuing Outcomes Relevant to Evista (CORE) osteoporosis trials,⁴⁷ and the Study of Tamoxifen and Raloxifene (STAR) breast cancer prevention trial.⁴⁸ What differed about RUTH was an increase in fatal strokes for women assigned to raloxifene. Mosca and colleagues attempted to answer the logical next question; namely, can women at increased risk for fatal stroke be identified?⁴⁹ In prespecified subgroup analyses for all strokes and post hoc subgroup analyses for fatal strokes the only hint was the finding that current smokers had a nonsignificant increased risk for all strokes.⁴⁹ In perhaps the final word on the subject, the RUTH investigators utilized the Framingham Stroke Risk Score—which estimates risk for first stroke based on a constellation of risk factors (age, blood pressure, diabetes, history of noncerebrovascular cardiovascular disease, cigarette smoking, atrial fibrillation and left ventricular hypertrophy)⁵⁰—to assess stroke risk in

After a diagnosis of non-small cell lung cancer, women assigned to HT lived a median of 9.4 months; women taking placebo lived 16.1 months.

RUTH participants.⁵¹ The excess risk of fatal stroke (1-2 fatal strokes per 1,000 person-years of treatment with raloxifene) appeared almost entirely (16 out of 17 total cases) among postmenopausal women with a higher baseline stroke risk (Framingham 10-year probability > 10%). Statistical tests for interaction of baseline stroke risk and increased risk for raloxifene-associated stroke were not, however, statistically significant, possibly due to the low number of fatal strokes in RUTH.

How do you translate this to your practice? First of all, women with a history of stroke or transient ischemic attacks are at very high risk for stroke and should not take raloxifene.⁵¹ For other patients with cardiovascular risks who are considering raloxifene therapy, use the online stroke risk estimation tool recently recommended by the U.S. Preventive Services Task Force (<http://www.westernstroke.org/PersonalStrokeRisk1.xls>). If your patient's 10-year stroke risk is ≤ 10%, she is not likely to experience a fatal stroke on raloxifene therapy, but the possibility of a fatal stroke cannot be completely excluded based on the RUTH results. If stroke risk is > 10%, avoid raloxifene therapy.

Lung Cancer and Hormone Therapy: Where There's Smoke, There's Fire

That “all cancers” increased (30 additional cases/10,000 woman/years of use) during the post-intervention phase of the WHI combined HT trial came somewhat as a surprise.⁵² Mortality from all causes was 15% higher in the group assigned to combined therapy, although this difference reached statistical significance only in adherent women. Most deaths were due to cancer (101 deaths in the conjugated equine estrogens (CEE) plus medroxyprogesterone (MPA) group versus 69 in the placebo group). Breast, colorectal, endometrial and ovarian cancer accounted for approximately one-quarter of the cancer deaths in both groups; lung cancers constituted the largest proportion of cancer deaths (33 events in the CEE+MPA group versus 15 in the placebo group).

In a post-hoc analysis of lung cancers diagnosed in the trial during the intervention and post-intervention phases, the annual incidence of lung cancer overall was not significantly increased by HT use (0.16% in the combined therapy arm versus 0.13% among those receiving placebo).⁵³ Deaths from lung cancer, however, were significantly increased (0.11% annually in the combined therapy versus 0.06% in the placebo group), resulting from an almost 2-fold increase in deaths related to non-small-cell lung cancer (0.09% per year on combined therapy versus 0.05% on placebo). After a diagnosis of non-small cell lung cancer, women assigned to HT lived a median of 9.4 months; women taking placebo lived 16.1 months. Four years from diagnosis, mortality was 70% in the combined therapy group and 54% in the placebo group. Lung cancer cases were largely confined to women who smoked (current and past) and were over 60 years

of age. Of smokers who used HT, 3.4% died from non-small cell lung cancer compared with 2.3% of those on placebo, a difference of 1%, or 1 death per 100 smokers using HT.

As the authors advise, these findings should influence the discussion between physicians and women considering HT initiation or continuation, especially for women with a smoking history. More research is needed to help us understand the association between combined HT and lung cancer death. Heightened surveillance of women at risk for lung cancer seems prudent.

Flibanserin Stimulates Sexual Desire in Women

Flibanserin modulates serotonin in the brain, acting as a 5-HT_{1A} receptor agonist and 5-HT₂ receptor antagonist. Initially evaluated and found to be ineffective as an antidepressant, flibanserin was noted to stimulate libido in study subjects. To assess the possible role as an agent of female desire, clinical trials at 360 locations in the US, Canada and Europe were undertaken in over 5,000 premenopausal women, ages 18 to 55 years, with hypoactive sexual desire disorder (HSDD). The trials collectively are known as the Bouquet studies; each is named for a flower: ROSE, VIOLET, DAISY, DAHLIA, ORCHID, SUNFLOWER, and MAGNOLIA. At the November Congress of the European Society for Sexual Medicine, data from pooled North American phase III trial results (DAISY and VIOLET) involving 1,378 premenopausal women demonstrated that flibanserin (100 mg taken once daily at bedtime) significantly increased the number of satisfying sexual events (SSE) in women assigned to flibanserin (from 2.8 SSE at baseline to 4.5 at study end) compared to placebo (2.7 SSE at baseline to 3.7) over the 24-week study period.⁵⁴ Consistent results were also presented from the European

Phase III Trial (ORCHID),⁵⁵ as well as a pooled analysis of all three trials. As measures of sexual desire increased, the distress associated with HSDD decreased. Positive effects were observed after ~4 weeks of therapy. Adverse effects, most prominent during the first 2 weeks of therapy, include dizziness, nausea, fatigue, somnolence and insomnia.⁵⁶ Studies in older women are planned.

Flibanserin might provide the first non-hormonal therapy to improve HSDD in premenopausal women. Whether this agent will aid postmenopausal women as well is uncertain. As we await the findings of trials evaluating long-term safety of transdermal testosterone preparations, the idea of an alternative mechanism for improving sexual interest and satisfaction is timely. As stated by a number of authorities polled, however, we must not lose sight of the complexity of women's sexual response and the need to address multiple variables in the equation. As with any new therapy affecting central neurotransmitters, long-term safety will be important to monitor. ■

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