REVIEW

Update in Women's Health

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INTRODUCTION

The aim of this clinical update is summarize articles and guidelines published in the last year that are scientifically rigorous and have the potential to impact women's health clinical practice.

Methods. We used two independent search strategies to identify potentially relevant articles published between March 1, 2008 and February 28, 2009. We reviewed journal indices from the New England Journal of Medicine, Journal of the American Medical Association, Annals of Internal Medicine, Archives of Internal Medicine, Journal of General Internal Medicine, British Medical Journal, Lancet, Circulation, Diabetes and Obstetrics and Gynecology. We also reviewed Journal Watch, Journal Watch Women's Health, and the ACP Journal Club and the Cochrane database of systematic reviews. Second, we did a MEDLINE search using the medical subject heading, "sex factors." All three authors, reviewed all article titles, abstracts and when indicated, full text publications. We focused on articles relevant to general internists and excluded articles focusing on obstetric medicine. We also identified new and or updated women's health guidelines that were released during the same time period. Using a process of individual ratings and discussion, we reached consensus about the most important articles.

RESULTS

We identified 122 articles with potential relevance to women's health; 34 articles were selected for presentation as part of the clinical update and 14 for detailed discussion in this paper.

CARDIOVASCULAR DISEASE

Ridker P, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein (CRP). NEJM 2008: 359; 2195–2207.

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What is already known. When national guidelines (ATP III) for cholesterol lowering were applied to the NHANES population, 58% of women over 60 and men over 50 qualified for statin treatment. However, only 24% of those eligible in NHANES reported current statin use.[1] Inflammation has also been linked to CHD risk. High sensitivity CRP, blood pressure as well as CHD and stroke events decrease with a DASH-style diet.[2]

What does this study add?. This double-blind, placebo controlled, multi-center international clinical trial, JUPITER, provided rosuvastatin treatment to individuals with a high sensitivity CRP values ≥2 mg/L and LDL cholesterols >130. This industry-sponsored trial demonstrated significant benefit after an average 1.9 years treatment with the primary endpoint of non-fatal myocardial infarction or stroke, admission for angioplasty or unstable angina, or confirmed cardiovascular death. Over a 5-year period, 25 patients like the ones in this trial would need treatment to prevent one event. Subgroup analysis by gender, race and age documented benefit for all sub-groups. There were no increased rates of myopathy, rhabdomylosis or intracranial bleeding during follow up. While more treatment participants were newly diagnosed by their physicians with diabetes, there were no significant differences in glucose or glycosuria levels. Further study is required to know whether similar results would be achieved with other statins.

How should I change my clinical practice?. Since statins have become available for hyperlipidemia treatment, prescribing indications have steadily expanded. If the JUPITER criteria were applied to the general population, an additional 19% of the population could benefit from statin treatment. If these findings are confirmed in other studies, the indications for statin use may further expand beyond current ATP III guidelines to include most middle age Americans.

DIABETES

Fox CS, et al. Lifetime risk of cardiovascular disease among individuals with and without diabetes stratified by obesity status in the Framingham Heart Study. Diabetes Care 2008: 31; 1582–1584.

Charlton J, et al. Explaining the decline in early mortality in men and women with Type 2 Diabetes: a population-based cohort study. Diabetes Care 2008: 31; 1761–1766.

What is already known. Women with diabetes have not experienced the decrease in all-cause and cardiovascular

mortality documented in diabetic men over the last several decades.[3] For diabetics with known cardiovascular disease the risk of dying is also greater for women (hazard ratio 2.2 for women, 1.7 for men).[4] Diabetic women also receive less aspirin and statins than diabetic men.[5,6]

What do these studies add?. Over 30 years, in the original Framingham cohort, the risk of developing CVD was 67% in women with diabetes compared to 38% in women without diabetes. In the Framingham offspring cohort, CVD rates were lower: 48% of women with diabetes and 26% of women without diabetes developed CVD. Furthermore, among diabetic women in the original cohort, over thirty years, CVD would occur in 79% of the obese diabetic women compared with 55% of the normal-weight women

A retrospective exploration of mortality within two years of the diagnosis of type 2 diabetes from 1996–2006 was completed from The United Kingdom General Practice Research Database.[7] Overall incidence of diabetes increased. In women the relative decline of mortality within two years of diabetes diagnosis was 26% compared with a 47% decrease among men. Also noted were gender differences in medications at time of diabetes diagnosis- more men than women were on renin-angiotensin system drugs, and statins. More women than men were taking metformin.

How should I change my clinical practice?. Diabetes remains especially hazardous to women. For diabetic women, and for all women at increased risk for CVD, aggressive CVD risk factor management to treatment goals is essential and often difficult to achieve.[1] Obese diabetic women are at especially high risk for CVD.

OBESITY

Svetkey LP, et al. for the Weight Loss Maintenance Collaborative Research Group. Comparison of strategies for sustaining weight loss the weight loss maintenance randomized controlled trial. JAMA 2008: 299(10):1139–1148.

What is already known. Obesity is associated with increases in: overall mortality, CHD, stroke, deep venous thrombosis, diabetes, hypertension, hyperlipidemia, obstructive sleep apnea, asthma and multiple cancers including breast and colorectal.[8] Clinical trials have facilitated weight loss with group counseling interventions focused on increasing fruit and vegetable consumption, keeping records of food consumption and promoting physical activity.[9]

What does this study add?. After 1032 obese adults successfully completed six months in a weight loss program with at least 4 kg weight loss, they were randomized for thirty months into the following: 1) Three monthly phone contacts alternating with one monthly in person visit; 2) at least weekly participation in an interactive web-site; or 3) "self-motivation"- which provided written materials and follow-up at 12 months. While the initial weight loss was on average 8.5 kg, after 30 months of follow-up most participants regained substantial weight in all three groups.

How should I change my clinical practice?. This study found that maintaining weight loss is difficult. Some studies have shown that physical activity is key for sustained weight reduction.[10]

MENOPAUSE AND HORMONE THERAPY

Duration of Vasomotor Symptoms During Menopause

Politi MC, Shlentz MD, Col NE et al. Revisiting the duration of vasomotor symptoms of menopause: a meta-analysis. JGIM 2009: 23: 1507–13.

What is already known. Some clinical guidelines suggest that the menopausal symptoms last from 6 months to two years.[11,12] Hormone therapy is the most effective therapy for menopausal symptoms. Guidelines recommend using the "lowest dose for the shortest duration" [13,14] because of the known risks and benefits of hormone therapy. However, data are limited regarding the natural duration of menopause because many studies only follow women up to two years after menopause.[15,16]

What does this study add?. This rigorous meta-analysis included ten studies with over 35,000 participants. The authors used a clear definition of vasomotor symptoms.

Overall, vasomotor symptoms increased in the two years before the final menstrual period, peaked one year after the final menstrual period and did not return to baseline levels until 8 years after the final menstrual period. About half of women had continued symptoms during the four years after the final menstrual period and 10% continued to have symptoms up to 12 years after the final menstrual period. The prevalence of *bothersome* symptoms peaked about 1 year after the final menstrual period and decreased 3–7 years after the final menstrual period.

Recently published evidence based guidelines for the use of hormone therapy (HT) focus on the use of HT for symptomatic relief. Highlights of the guidelines include putting the absolute level of risk with HT use in perspective, acknowledging that there are no data to support any particular route of administration, and advising greater caution in prescribing HT to women over the age of 60, since the risk of CHD associated with HT is greater in older than in younger women [17]

How should I change my clinical practice?. We should counsel women that menopausal symptoms generally last about 4 years. Women who are considering hormone therapy for symptomatic treatment should consider the risks and benefits of hormone therapy within the context of the longer duration of use, although it is not known exactly what duration of use is safe.

OSTEOPOROSIS

Vitamin D Deficiency and Hip Fracture

Cauley JA, LaCroix AZ, Wu L et al. Serum 25-Hydroxyvitamin D concentrations and risk for hip fracture. Ann Intern Med 2008: 149: 242–250.

What is already known about this topic?. Vitamin D deficiency is common in older adults, homebound individuals and women admitted with hip fracture. However a recent AHRQ evidence report on vitamin D and bone health found that the association between Vitamin D and fracture risk was inconsistent.[18] This study was designed to answer the following question: "What is the association between Vitamin D level and fracture?" Additional questions include "When should Vitamin D levels be checked?" and "When and how should Vitamin D supplementation be given?"

What does this study add?. This study addressed the question of whether serum (25) OH D concentration is associated with hip fracture in community dwelling older women. It was a nested case-control study within the Women's Health Initiative Observational Study. None of the participants had a prior history of hip fracture nor were on estrogen or other bone resportive therapies. A total of 400 cases and 400 controls were followed for 7.1 years. Mean 25-(OH) vitamin D levels were lower in cases than in controls. Women with vitamin D levels in the lowest quartile had an increased risk of fracture compared with women in the highest quartile (OR 1.71; 95% C. I. 1.05, 2.79). There was a significant trend across quartiles of 25-(OH) vitamin D (p=0.016), suggesting a dose-response effect. The association was not affected by age, geographic location, number of falls, frailty or renal function.

How should I change my clinical practice?. Low serum 25-(OH) vitamin D levels can help identify women at high risk for hip fracture. Perhaps we should consider vitamin D levels in our decision making about anti-resportive therapies. This study answers the question of whether or not vitamin D level is a risk factor for fracture, but does not answer the other important questions of whom we should test for vitamin D deficiency and or how we should treat vitamin D deficiency or insufficiency.

Low-Trauma Fracture and Mortality

Bliuc D, Nguyen ND, Milch, VD, Nguyen TV, Eisman, JA, Center JR. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. JAMA 2009: 301 (5): 513–521.

What is already known about this topic?. As the population ages, osteoporotic fractures are increasing,[19] with concomitant increases in morality among individuals with hip or vertebral fractures.[20,21] However, it is less clear whether other fractures are also associated with increased mortality. The goals of this study were: 1) to assess mortality risk following an osteoporotic fracture; 2) to determine whether the degree of trauma and subsequent fracture affect this mortality risk.

What does this study add?. This prospective cohort study from the Dubbo Osteoporosis Epidemiology Study included all individuals who had any fracture between 1989 and 2007. Age and gender-specific standardized mortality ratios are compared with the overall Dubbo population for major (pelvis, distal femur, proximal tibia, proximal humerus, three or more simultaneous ribs) and minor (all other) osteoporotic fractures. Age adjusted standardized mortality ratios in women increased after a hip fracture (SMR 2.43; 95% C.I. 2.02, 2.93), after a vertebral fracture (SMR 1.82; 95% C.I. 1.52, 2.17), and after a major fracture (SMR 1.65; 95% C.I 1.31, 2.08). In addition, after a minor fracture, the age adjusted SMR was also increased (1.42; 95% C.I.1.19, 1.70). Increased mortality risk persisted for 5 years for all fractures and up to 10 years for hip fractures. In addition, a subsequent fracture was associated with an increased risk of mortality in women (HR 1.53; 95% CI 1.15, 2.04).

How should I change my clinical practice?. Although hip and other major fractures have been associated with an increase in mortality, the increased mortality following minor fractures is important new information. Any fracture is associated with an increased 5–10-year mortality risk. In addition, a subsequent fracture is associated with an increased mortality risk for 5 more years. We should pay more attention to non-hip, non-vertebral fractures.

One potential tool clinicians can use to calculate the 10-year probability of fractures is the FRAX tool, developed by the World Health Organization. It has been suggested that treatment is beneficial when there is a 10-year risk of hip fracture of ≥3% or a 10-year risk of a major osteoporosis related fracture that is ≥20% based on the US adapted WHO algorithm.[22]

SEXUAL HEALTH

Sildenafil and Sexual Side Effects from Serotonin Reuptake Inhibitors

Numberg HG, Hensley PL, Heiman JR, et al. Sildenafil treatment of women with anti-depressant-associated sexual dysfunction: a randomized controlled trial. JAMA 2008: 300 (4): 395–404.

What is already known about this topic?. Sexual side effects of serotonin reuptake inhibitors (SRIs), particularly delayed orgasm, can affect 30–70% of women and men.[23] Although sildenafil is FDA approved for treating sexual dysfunction in men [24–26], it is not FDA approved in women. Trials of sildenafil for sexual arousal disorder in women have not show any benefit.[27] However, case reports[28], open-label studies[29] and subgroup analyses[30,31] have suggested sildenafil's efficacy for specific groups of women with sexual dysfunction.

What does this study add?. This 8-week, 7-site, randomized, double-blind, placebo-controlled trial included 98 sexually active premenopausal women whose major depression was remitted by serotonin uptake inhibitors, but who were also experiencing sexual dysfunction. These women were randomized to sildenafil, 50–100 mg before sex, versus placebo. The primary outcome of the study was based on the 7-point, anchored, clinician-rated Clinical Global Impression scale, adapted for sexual function.[32] Multiple other measurements of desire, arousal, and orgasm were examined. For the primary outcome, both the sildenafil and placebo groups reported an improvement in sexual function, with a

larger mean improvement in sildenafil users. In the intent to treat analysis, the mean difference between groups on this 7-point scale was 0.8 (p=0.001). A more conservative analysis assumed that women who did not return for the final visit at 8 weeks returned to baseline sexual function, and these results showed a mean difference between groups of 0.6 (p= 0.03). Most secondary outcomes were not statistically significant; however those that measured orgasm tended to demonstrate statistical significance. Side effects of sildenafil included headache, visual disturbances, dyspepsia, flushing, and nasal congestion.

How should I change my clinical practice?. The clinical significance of a mean change of 0.8 on a 7-point sexual satisfaction scale is unclear, and sildenafil is not without side effects. Sildenafil is also not FDA approved or covered by most insurance companies for women. So, in practical terms, it is not likely that sildenafil use will substantially increase for women with SRI-associated sexual side effects. However, this study reminds us of the importance of taking a sexual history before and after initiation of SRIs.

URINARY INCONTINENCE

Weight-Reduction and Urinary Incontinence

Subak LL et al. Weight loss to treat urinary incontinence in overweight and obese women. NEJM 2009: 360 (5): 481–490.

What is already known about this topic?. Observational studies have suggested that obesity is a strong risk factor for urinary incontinence.[33–36] For obese women, weight loss, including that from bariatric surgery [37–39] may have a beneficial effect on urinary incontinence [37–41], particularly for stress urinary incontinence.

What does this study add?. This two-site, 6-month, randomized clinical trial enrolled 338 overweight and obese women with at least 10 urinary incontinence episodes per week. 226 women who received diet, exercise, and behavior modification lost an average of 7.8 kg; 112 women who received a structured education program lost an average of 1.5 kg (p<0.001). Incontinent episodes decreased from 24/week (in both groups) to 13/week in the weightloss group (47% reduction versus 28% in the control group, p=0.01). Stress incontinence was reduced more than urge incontinence in the intervention group.

How should I change my clinical practice?. In overweight and obese women, moderate weight reduction has multiple benefits, including the potential for decreasing incontinent episodes, particularly stress incontinence episodes. The intervention was modeled after weight-reduction programs used in large diabetes trials, and it required 1-hour weekly meetings for 6 months. Although the 8% weight loss observed in the intervention group may be difficult to replicate over 6 months in practice, weight reduction is generally without side effects and has other health benefits. This study provides evidence for yet another benefit of a rigorous weight-reduction program.

Behavioral and Drug Therapy for Urge Urinary Incontinence

Burgio KL et al. Behavioral therapy to enable women with urge incontinence to discontinue drug treatment. Annals of Internal Medicine 2008; 149 (3): 161–169.

What is already known about this topic?. For women with urge-predominant urinary incontinence, antimuscarinic medications and behavioral treatments are both considered safe and effective first-line treatments.[42–44] Many women, however, discontinue these medications. Furthermore, few studies have examined the effectiveness of either therapy alone compared to combination therapy.[45–47]

What does this study add?. This randomized clinical trial of 307 women with urge-predominant incontinence studied 10 weeks of tolterodine alone versus 10 weeks of tolterodine plus behavioral training, examining outcomes at 8 months. The primary outcome was the proportion of women at 8 months who were not taking medications AND had achieved a 70% or greater reduction in the frequency of incontinence episodes. In both groups, this proportion was 41%, and therefore not statistically significant. At 10 weeks, there was a modest, nonsignificant improvement in the frequency of incontinence in the combination group. Combination therapy had a statistically significant benefit for patient satisfaction, perceived improvement, and reduction of other bladder symptoms.

How should I change my clinical practice?. Although combination therapy for urge incontinence improved several secondary outcomes of this study, it did not augment drug therapy in improving urge incontinence at 8 months, nor did it enhance the ability to discontinue medications at 8 months. In clinical practice, therefore, behavioral treatments may have beneficial effects on satisfaction and other secondary outcomes; but many women with urge incontinence will require long-term medication for maintenance.

BREAST HEALTH

Screening Breast Ultrasound and Mammography

Berg WA, et al. for the ACRIN 6666 Investigators. Combined screening with ultrasound and mammography vs. mammography alone in women at elevated risk of breast cancer. JAMA 2008; 299 (18): 2151–2163.

What is already known about this topic?. Mammography in women with dense breasts is associated with increases in both false positive and false negative readings.[48] In some studies, particularly studies of women with dense breasts, the addition of a screening ultrasound has been shown to improve sensitivity.[49–51] The number of cancers detected in the literature from screening breast ultrasounds is still quite small, at less than 200, in over 48,000 exams reported.[49–51]

What does this study add?. This study was designed to examine the diagnostic yield (the proportion of women with positive

screen test results and positive reference standard) when screening ultrasound is added to mammography. It included 2809 women with dense breasts who received both screening mammogram and physician-preformed breast ultrasound at 21 sites. Forty women were diagnosed with breast cancer during the study: 8 cancers were found by both mammography and ultrasound; 12 with ultrasound alone; 12 with mammography alone; and 8 with neither modality. The diagnostic yield was 7.6 per 1000 women screened with mammography alone, and 11.8 per 1000 women screened with combined mammography plus ultrasound. The difference of 4/1000 cancers detected, however, was associated with a substantial increase in false positives. Of the 84 abnormal mammograms that led to biopsy, 77% were not related to cancer; of the 235 abnormal ultrasounds that led to biopsy, 91% were not related to cancer. Per screen, about 5% of all screening mammograms required further study versus about 10% of all screening ultrasounds.

How should I change my clinical practice?. Although the primary outcome of this study (diagnostic yield) improved when ultrasound was added to mammography, it was at a substantial clinical cost. The increased sensitivity of adding ultrasound to mammography was associated with a decrease in specificity from over 95% to about 90%. This resulted in an approximately threefold increase in biopsies to work-up false positive screens. Women at high risk of breast cancer who might be candidates for enhanced screening, as well as their providers, should be aware of the substantial risk of false positive screens that could lead to biopsy.

Menopausal Hormone Therapy, Breast Screening, and Breast Cancer

Chlebowski RT, Anerson G, Pettinger M, et al. Estrogen plus progestin and breast cancer detection by means of mammography and breast biopsy. Archives of Internal Medicine 2008; 168: 370–377.

Chlebowski RT et al. Breast cancer after use of estrogen plus progestin in postmenopausal women. NEJM 2009; 360 (6): 573–587.

What is already known about this topic?. Combined menopausal hormone therapy (HT) increased the risk of breast cancer in the Women's Health Initiative (WHI) study.[52] Observational studies have suggested that HT also increases the false positive rate of screening mammography.[53–55] Prior to these studies, the effects of HT on breast cancer detection in a large randomized controlled trial had not been examined, nor had the time course for these effects been carefully examined. Additionally, the link between the observed decrease in breast cancer incidence and the decrease in HT use [56,57] had not been examined in the WHI population.

What do these studies add?. In the WHI HT trial, the cumulative rates of abnormal mammograms and breast biopsies in women randomized to HT were significantly higher than these rates in women randomized to placebo ($P<0.001$ for both comparisons). Although breast cancers were significantly increased and were diagnosed at higher stages in the HT group, biopsies in the HT group less frequently diagnosed cancer. After stopping HT, its adverse effects on mammograms persisted for at least 12 months. Additionally, by examining trends in breast cancer diagnosis in the WHI setting, where mammography rates and HT use were carefully monitored, investigators could rigorously examine the potential cause-effect relationship between stopping HT and decreasing breast cancer risk.

How should I change my clinical practice?. Women on long-term HT should be counseled not only of the increased risk of breast cancer, but also about the increased risk for false positive mammograms that could lead to breast biopsies. After 5 years, over 10% of HT users would be expected to experience an otherwise avoidable false positive mammogram; and over 4% of HT users are predicted to require an otherwise avoidable breast biopsy. After stopping HT use, breast cancer risk decreases rapidly, as does the risk of abnormal mammography. It may take several years for these risks to return to the baseline risk of a non-HT user.

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