

## Selección de Resúmenes de Menopausia

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### **Comparative Risk of Fracture for Bariatric Procedures in Patients With Obesity: A Systematic Review and Bayesian Network Meta-Analysis**

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**Objective:** Bariatric surgery (malabsorptive [i.e., biliopancreatic diversion, BPD], restrictive [i.e., sleeve gastrectomy, SG; adjustable gastric banding, AGB] and mixed [i.e., gastric bypass, GB] procedures) has been reported to be associated with an increased risk of fracture; however, which procedure poses the greatest risk of fracture is still controversial. The aim of the current meta-analysis was to investigate the degree of fracture risk after different bariatric procedures. **Material and methods:** Electronic databases, including Medline/PubMed, EMBASE and Cochrane library, were systematically searched from inception to July 11, 2019 with no language restrictions to retrieve randomized controlled trials (RCTs) or cohort studies evaluating the impact of any kind of bariatric surgery on postoperative fractures in patients with obesity. Pairwise meta-analysis and Bayesian network meta-analysis were performed to pool the outcome estimates of interest, including fracture incidence and fracture risk. The values of the surface under the cumulative ranking (SUCRA) probability for fracture risk were calculated and sorted according to the different surgical procedures. **Results:** A total of twelve studies published between 2010 and 2019, comprising 159,916 participants with obesity were identified for the analysis. The incidence of fracture increased from 3% (95% confidence interval [CI] 2 - 4%) in patients with non-surgical intervention (drug treatment, alteration in life style and diet control) to 5% (95% CI 4 - 7%) in those who had undergone bariatric surgery (pooled relative risk [RR] = 1.41 95% CI: 1.22 - 1.63). Network meta-analysis revealed that based on the SUCRA ranking of the different surgical procedures, the malabsorptive procedure had the highest possibility of increased fracture risk in patients with obesity (74.75%), followed by the mixed procedures (73.85%), nonsurgical intervention (43.55%) and the restrictive procedure (7.85%); for different surgery types. The BPD group had the highest possibility of increased fracture risk (99.49%), followed by the GB (74.92%), nonsurgical intervention (44.49%), AGB (26.64%) and SG (4.45%) groups. **Conclusions:** Significant differences exist among different bariatric surgeries impacting on fracture risk. The malabsorptive and mixed procedures, but not the restrictive procedure, increase the postoperative risk of fracture. Considering the weight-reduction effects and fracture risk, the sleeve gastrectomy procedure may be the best choice for patients with obesity, especially those who are susceptible to osteoporosis.

**Menopause. [published online ahead of print, 2020 Jan 20].**

### **Lights on MsFLASH: a review of contributions**

Reed SD, LaCroix AZ, Anderson GL, et al.

**Objective:** The Menopause Strategies: Finding Lasting Answers for Symptoms and Health clinical trials network was funded by the National Institutes of Health to find new ways to alleviate the most common, bothersome menopausal symptoms by designing and conducting multiple concurrent clinical intervention studies, accommodating a wide scope of populations and intervention strategies. **Methods:** Trials were conducted in Boston, Indianapolis, Minneapolis, Oakland, Philadelphia, and Seattle, with the Data Coordinating Center in Seattle, and were designed with standardized eligibility criteria and endpoints. Primary outcomes focused on vasomotor symptoms, sleep quality and insomnia symptoms, and vaginal symptoms. Secondary outcomes included quality of life, sexual function, and mood. **Results:** We completed five randomized clinical trials and three ancillary studies, testing nine interventions in over 1,300 women and collecting nearly 16,000 bio-specimens. Escitalopram, venlafaxine hydrochloride extended release, and low-dose estradiol diminished hot flashes by approximately 50% as compared with a 30% decrease by placebo. No benefits on vasomotor symptoms were observed with yoga or exercise compared with usual activity, nor with omega-3 supplementation compared with placebo. Cognitive behavioral therapy for insomnia reduced self-reported insomnia symptoms and improved overall sleep quality compared with menopause education control. We did not find significant benefit from a vaginal estradiol tablet or a vaginal moisturizer compared with placebo tablet and gel in diminishing the severity of vaginal symptoms. **Conclusions:** The MsFLASH trials contributed substantially to our understanding of bothersome menopausal symptom treatment. It is important that clinicians counseling women about available treatment options consider all therapies-both nonhormonal and hormonal.

**Curr Neuropharmacol. 2020 Jan 23[Online ahead of print]**

## **The Critical Period for Neuroprotection by Estrogen Replacement Therapy and the Potential Underlying Mechanisms**

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17 $\beta$ -Estradiol (estradiol or E2) is a steroid hormone that has been broadly applied as a neuroprotective therapeutic for a variety of neurodegenerative and cerebrovascular disorders such as ischemic stroke, Alzheimer's disease, and Parkinson's disease. Several laboratory and clinical studies have reported that estrogen replacement therapy (ERT) had no effect against these diseases in elderly postmenopausal women, and at worst, increased their risk of onset and mortality. This review focuses on the growing body of data from in vitro and animal models characterizing the potential underlying mechanisms and signaling pathways that govern successful neuroprotection by ERT, including the roles of E2 receptors in mediating neuroprotection, E2 genomic regulation of apoptosis-related pathways, membrane-bound receptor-mediated non-genomic signaling pathways, and the antioxidant mechanisms of E2. Also discussed is current evidence for a critical period of effective treatment with estrogen following natural or surgical menopause and the outcomes of E2 administration within the advantageous time period. The known mechanisms governing the duration of the critical period include depletion of E2 receptors, the switch to a ketogenic metabolic profile by neuronal mitochondria, and a decrease in acetylcholine that accompanies E2 deficiency. Also summarized are the major clinical trials and observational studies concerning postmenopausal hormone therapy (HT), to compare their outcomes with respect to neurological disease and discuss their relevance to the critical period hypothesis. Finally, potential controversies and future directions for this field are discussed throughout the review.

**Breast Cancer (Auckl)14, 1178223419898458, 2020 Jan 10 eCollection 2020**

## **Linkage Between Obesity Leptin and Breast Cancer**

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Many cancers might be influenced by obesity, including breast cancer, the leading cause of cancer death among women. Obesity is a complex state associated with multiple physiological and molecular changes capable of modulating the behavior of breast tumor cells and the surrounding microenvironment. This review discussed the inverse association between obesity and breast cancer among premenopausal breast cancer females and the positive association among postmenopausal. Four mechanisms may link obesity and breast cancer including leptin and leptin receptor expression, adipose chronic inflammation, sex hormone alternation, and insulin and insulinlike growth factor 1 (IGF-1) signaling. Leptin has been involved in breast cancer initiation, development, and progression through signaling transduction network. Leptin functions are strengthened through cross talk with multiple oncogenes, cytokines, and growth factors. Adipose chronic inflammation promotes cancer growth and angiogenesis and modifies the immune responses. A pro-inflammatory microenvironment at tumor site promotes cytokines and pro-inflammatory mediators adjacent to the tumor. Leptin stimulates pro-inflammatory cytokines and promotes T-helper 1 responses. Obesity is common of chronic inflammation. In obese patients, white adipose tissue (WAT) will promote pro-inflammatory mediators that will encourage tumor growth and WAT inflammation. Sex hormone alternation of estrogens is associated with increased risk for hormone-sensitive breast cancers. Estrogens cause tumorigenesis by its effect on signaling pathways that lead to DNA damage, stimulation angiogenesis, mutagenesis, and cell proliferation. In postmenopausal females, and due to termination of ovarian function, estrogens were produced extra gonadally, mainly in peripheral adipose tissues where adrenal-produced androgen precursors are converted to estrogens. Active estradiol leads to breast cancer development by binding to ER $\alpha$ , which is modified by receptor's interaction of various signal transduction pathways. Hyperinsulinemia and IGF-1 activate the MAPK and PI3K pathways, leading to cancer-promoting effects. Cross talk between insulin/IGF and estrogen signaling pathways promotes hormone-sensitive breast cancer development. Hyperinsulinemia is a risk factor for breast cancer that explains the obesity-breast cancer association. Controlling IGF-1 level and targeting IGF-1 receptors among different breast cancer subtypes may be useful for breast cancer treatment. This review discussed several leptin signaling pathways, highlighting the potential advantage of targeting leptin as a potential target of the novel therapeutic strategies for breast cancer treatment.

**J Pediatr Adolesc Gynecol. 2020 Jan 20[Online ahead of print] PMID: 31972296 DOI: 10.1016/j.jpjag. 2020.01.003**

## **Bones and Birth Control in Adolescent Girls**

Neville H Golden <sup>1</sup>

Peak bone mass acquisition during adolescence is an important determinant of adult bone health. Knowledge about the effects of different contraceptives on peak bone mass acquisition could influence choice of method recommended. This review summarizes normal bone acquisition during adolescence, discusses methods of assessing bone health in this age

group, and reviews the effects of different contraceptive options on bone health, both in adults and in adolescents. Based on the evidence, LARC does not appear to affect peak bone mass acquisition or future fracture risk and remains the first line contraceptive choice for adolescents. Oral contraceptives with doses of ethinyl estradiol > 30µg should be used in preference to lower dose preparations, and the adverse effects of DMPA on bone health are reversible on discontinuation of the medication. Concerns about bone health should not prevent use of DMPA in an adolescent who prefers this method.

**Arterioscler Thromb Vasc Biol. 2020 Jan 23[Online ahead of print]. ATVBAHA119313622**

## **Arterial Stiffness Accelerates Within 1 Year of the Final Menstrual Period: The SWAN Heart Study**

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**Objective:** Menopause may augment age-dependent increases in arterial stiffness, with black women having greater progression in midlife compared with white women. We sought to determine whether and when women experience changes in arterial stiffness relative to the final menstrual period (FMP) and whether these changes differ between black and white midlife women. **Approach and Results:** We evaluated 339 participants from the SWAN Heart Ancillary study (Study of Women's Health Across the Nation). Women had  $\leq 2$  carotid-femoral pulse-wave velocity (cfPWV) exams over a mean  $\pm$ SD of 2.3  $\pm$  0.5 years of follow-up. Annual percentage changes in cfPWV were estimated in 3 time segments relative to FMP and compared using piecewise linear mixed-effects models. At baseline, women were 51.1  $\pm$  2.8 years of age and 36% black. Annual percentage change (95% CI) in cfPWV varied by time segments: 0.9% (-0.6% to 2.3%) for >1 year before FMP, 7.5% (4.1%-11.1%) within 1 year of FMP, and -1.0% (-2.8% to 0.8%) for >1 year after FMP. Annual percentage change in cfPWV within 1 year of FMP was significantly greater than the other 2 time segments;  $P < 0.05$  for both comparisons. Adjusting for concurrent cardiovascular disease risk factors explained part of the change estimates but did not eliminate the difference. Black women had greater increase in cfPWV compared with white women in the first segment;  $P$  for interaction, 0.04. **Conclusions:** The interval within 1 year of FMP is a critical period for women when vascular functional alterations occur. These findings underscore the importance of more intensive lifestyle modifications in women transitioning through menopause.

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## **Vitamin D Deficiency 2.0: An Update on the Current Status Worldwide**

Karin Amrein, Mario Scherkl, Magdalena Hoffmann, Stefan Neuwersch-Sommeregger, Markus Köstenberger, Adelina Tmava Berisha, Gennaro Martucci, Stefan Pilz, Oliver Malle.

Vitamin D testing and the use of vitamin D supplements have increased substantially in recent years. Currently, the role of vitamin D supplementation, and the optimal vitamin D dose and status, is a subject of debate, because large interventional studies have been unable to show a clear benefit (in mostly vitamin D replete populations). This may be attributed to limitations in trial design, as most studies did not meet the basic requirements of a nutrient intervention study, including vitamin D-replete populations, too small sample sizes, and inconsistent intervention methods regarding dose and metabolites. Vitamin D deficiency (serum 25-hydroxyvitamin D [25(OH)D] < 50 nmol/L or 20 ng/ml) is associated with unfavorable skeletal outcomes, including fractures and bone loss. A 25(OH)D level of >50 nmol/L or 20 ng/ml is, therefore, the primary treatment goal, although some data suggest a benefit for a higher threshold. Severe vitamin D deficiency with a 25(OH)D concentration below <30 nmol/L (or 12 ng/ml) dramatically increases the risk of excess mortality, infections, and many other diseases, and should be avoided whenever possible. The data on a benefit for mortality and prevention of infections, at least in severely deficient individuals, appear convincing. Vitamin D is clearly not a panacea, and is most likely efficient only in deficiency. Given its rare side effects and its relatively wide safety margin, it may be an important, inexpensive, and safe adjuvant therapy for many diseases, but future large and well-designed studies should evaluate this further. A worldwide public health intervention that includes vitamin D supplementation in certain risk groups, and systematic vitamin D food fortification to avoid severe vitamin D deficiency, would appear to be important. In this narrative review, the current international literature on vitamin D deficiency, its relevance, and therapeutic options is discussed.

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## **Calcium Supplement Use Is Associated With Less Bone Mineral Density Loss, But Does Not Lessen the Risk of Bone Fracture Across the Menopause Transition: Data From the Study of Women's Health Across the Nation**

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Diet is a modifiable factor that is related to bone mass and risk for fractures; however, the use of calcium supplements for bone health is controversial, with little scientific agreement. The purpose of this analysis was to estimate the change in lumbar spine and femoral neck BMD and the risk of bone fracture by the use of calcium supplements among the Study of Women's Health Across the Nation (SWAN) participants. SWAN is a multicenter, multiethnic, community-based longitudinal cohort designed to examine the health of women across the menopause transition (n = 1490; aged 42 to 52 years at baseline in 1996 to 1997 and followed annually until 2006 to 2008). A mixed-effect model for repeated measures was used to estimate annualized BMD change across time between supplement users and nonusers, unadjusted or fully adjusted (age, race, height, weight, menopausal status [pre-, early peri-, late peri-, and postmenopausal], DXA scanner mode, alcohol intake, vitamin D supplement use, smoking, and physical activity) and a log-linear model with repeated measures was used to estimate the relative risk of fracture by calcium supplement use. All models were also stratified by baseline menopausal status. In fully adjusted models, calcium supplement use was associated with less annualized loss of femoral neck BMD (-0.0032 versus -0.0040 g/cm<sup>2</sup>/year; p < .001) and lumbar spine BMD (-0.0046 versus -0.0053 g/cm<sup>2</sup>/year, p = 0.021) in the complete cohort. However, this protective association of calcium supplement use with BMD loss was significant only among premenopausal women (femoral neck: -0.0032 versus -0.0042 g/cm<sup>2</sup>/year; p = 0.002; lumbar spine: -0.0038 versus -0.0050 g/cm<sup>2</sup>/year, p = 0.001); no significant differences in BMD were observed among women who were early perimenopausal by calcium supplement use at baseline. No significant differences in the relative risk of fracture were observed, regardless of baseline menopausal status. The use of calcium supplements was associated with less BMD loss over more than a decade, but was not related to the risk of incident bone fracture across the menopause transition.

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## **Age at Natural Menopause and Development of Chronic Conditions and Multimorbidity: Results From an Australian Prospective Cohort**

Xiaolin Xu <sup>1</sup>, Mark Jones <sup>1</sup>, Gita D Mishra <sup>1</sup>

Study question: Is age at natural menopause (ANM) associated with the development of multiple chronic conditions (multimorbidity) in postmenopausal life? Summary answer: Women with premature menopause experience increased odds of developing individual chronic conditions and multimorbidity. What is known already: ANM is considered as a marker of age-related morbidity and mortality in postmenopausal life. Multimorbidity affects more than 60% of older women and has been recognized as the most common 'chronic condition'. Few studies have examined the association between ANM and the development of multimorbidity. Study design, size, duration: A prospective national cohort study of 11 258 Australian women, aged 45-50 years in 1996. Women were followed from 1996 to 2016. Participants/materials, setting, methods: Information about ANM and 11 chronic conditions (diabetes, hypertension, heart disease, stroke, arthritis, osteoporosis, asthma, chronic obstructive pulmonary disease, depression, anxiety and breast cancer) were estimated approximately every 3 years. Multimorbidity is defined as 2 or more of these 11 conditions. Generalized estimating equations were used to link the categorical ANM with individual chronic conditions and multimorbidity. Main results and the role of chance: Among 5107 women reporting ANM, 2.3% experienced premature menopause (≤40 years) and 55.1% developed multimorbidity. Compared with women who experienced menopause at age 50-51 years, women with premature menopause had twice the odds of experiencing multimorbidity by age 60 (OR = 1.98, 95% CI 1.31 to 2.98) and three times the odds of developing multimorbidity in their 60s (OR = 3.03, 95% CI 1.62 to 5.64). Women with premature menopause also experienced higher incidence of most individual chronic conditions. Limitations, reasons for caution: The main limitation of this study was the use of self-reported data, but with repeated assessments from prospective study design and the validity of most of the chronic conditions from hospital data, the potential for non-differential misclassification is minimized. Wide implications of the findings: To our knowledge, this is the first study to assess the association of premature menopause and development of multimorbidity in a larger national cohort of mid-aged women. Health professionals should consider comprehensive screening and assessment of risk factors for multimorbidity when treating women who experienced premature menopause.