Selección de Resúmenes de Menopausia

Semana del 5 al 12 de Junio de 2018

María Soledad Vallejo. Clínica Quilín. Universidad de Chile

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A 17β-Estradiol-Progesterone Oral Capsule for Vasomotor Symptoms in Postmenopausal Women: A Randomized Controlled Trial.

Lobo RA, Archer DF, Kagan R, Kaunitz AM, Constantine GD, Pickar JH, Graham S, Bernick B, Mirkin S.

OBJECTIVE: To evaluate efficacy, endometrial safety, and overall safety of a single-capsule 17β-estradiol-progesterone for treating menopausal moderate-to-severe vasomotor symptoms. METHODS: REPLENISH was a phase 3, 12-month, randomized, double-blind, placebo-controlled, multicenter trial. Women (aged 40-65 years) with vasomotor symptoms and a uterus were randomized to daily estradiol (mg)-progesterone (mg) (1/100, 0.5/100, 0.5/50, or 0.25/50), and women in the vasomotor symptoms substudy (women with moderate-to-severe hot flushes [seven or greater per day or 50 or greater per week]) to those estradiol-progesterone doses or placebo. The primary safety endpoint was endometrial hyperplasia incidence at 12 months in all women (the total population), and the primary efficacy endpoints were frequency and severity changes (from daily diaries) in moderate-to-severe vasomotor symptoms with estradiol-progesterone compared with placebo at weeks 4 and 12 in the vasomotor symptoms substudy. A sample size of 250 women in each active treatment arm with two or less endometrial hyperplasia cases would result in 1% or less annual incidence (upper bound 2.5% or less, one-sided 95% CI). RESULTS: One thousand eight hundred forty-five women were enrolled and randomized from August 2013 to October 2015; 1,835 received medication (safety population); 1,255 were eligible for the endometrial safety population; 726 comprised the vasomotor symptoms substudy; their mean age and body mass index were 55 years and 27, respectively; one third were African American. No endometrial hyperplasia was found. Frequency and severity of vasomotor symptoms significantly decreased from baseline with 1 mg estradiol and 100 mg progesterone and 0.5 mg estradiol and 100 mg progesterone compared with placebo at week 4 (frequency: by 40.6 and 35.1 points [1 mg and 100 mg and 0.5 mg and 100 mg, respectively] vs 26.4 points [placebo]; severity: by 0.48 and 0.51 vs 0.34 points) and week 12 (by 55.1 and 53.7 vs 40.2; severity: by 1.12 and 0.90 vs 0.56); 0.5 mg estradiol and 50 mg progesterone improved (P<.05) frequency and severity at week 12, and 0.25 mg estradiol and 50 mg progesterone frequency but not severity at weeks 4 and 12. CONCLUSION: No endometrial hyperplasia was observed while single-capsule estradiol-progesterone provided clinically meaningfully improvements in moderate-to-severe vasomotor symptoms. This estradiol-progesterone formulation may represent a new option, using naturally occurring hormones, for the estimated millions of women using nonregulatory-approved, compounded hormone therapy.

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Fracture incidence and secular trends between 1989 and 2013 in a population based cohort: The Rotterdam Study.

Trajanoska K, Schoufour JD, de Jonge EAL, Kieboom BCT, Mulder M, Stricker BH, Voortman T, et al.

Fracture incidence needs to be evaluated over time to assess the impact of the enlarging population burden of fractures (due to increase in lifespan) and the efficacy of fracture prevention strategies. Therefore, we aimed to evaluate the association of femoral neck bone mineral density (FN-BMD) measured using dual-energy X-ray absorptiometry (DXA) at baseline with fracture risk over a long follow-up time period. Incident non-vertebral fractures were assessed in 14,613 individuals participating in the Rotterdam Study with up to 20 years of follow-up. During a mean follow-up of 10.7 ± 6.2 years, 2971 (20.3%) participants had at least one incident non-vertebral fracture. The risk for any non-vertebral fracture was 1.37 (95% Confidence Interval (CI): 1.25-1.49) and 1.42 (95%CI: 1.35-1.50) for men and women, respectively. The majority (79% in men and 75% in women) of all fractures occurred among participants a normal or osteopenic T-score. The incidence rates per 1000 person-years for the most common fractures were 5.3 [95%CI: 5.0-5.7] for hip, 4.9 [95%CI: 4.6-5.3] for wrist and 2.3 [95%CI: 2.0-2.5] for humerus. To examine the predictive ability of BMD through follow-up time we determined fracture hazard ratios (HR) per standard deviation decrease in femoral neck BMD across five year bins. No differences were observed, with a HR of 2.5 (95%CI: 2.0-3.1) after the first 5 years, and of 1.9 (95%CI: 1.1-3.3) after 20 years. To assess secular trends in fracture incidence at all skeletal sites we compared participants at an age of 70-80 years across two time

periods: 1989-2001 (n = 2481, 60% women) and 2001-2013 (n = 2936, 58% women) and found no statistically significant difference ($p < 0.05$) between fracture incidence rates (i.e., incidence of non-vertebral fractures of 26.4 per 1000 PY [95%CI: 24.4-28.5]) between 1989 and 2001, and of 25.4 per 1000 PY [95%CI: 23.0-28.0] between 2001 and 2013. In conclusion, BMD is still predictive of future fracture over a long period of time. While no secular changes in fractures rates seem to be observed after a decade, the majority of fractures still occur above the osteoporosis threshold, emphasizing the need to improve the screening of osteopenic patients.

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Cholesterol profile in women with premature menopause after risk reducing salpingo-oophorectomy.

Teixeira N2, Mourits MJ, Oosterwijk JC, Fakkert IE, Absalom AR, Bakker SJ, van der Meer P, de Bock GH.

This cross-sectional study aimed to investigate the effect of premenopausal risk reducing salpingo-oophorectomy (RRSO) on the cholesterol profile of women at increased ovarian cancer risk and to assess possible effects of age at and time since RRSO. We included 207 women who underwent RRSO before menopausal age (52 years) attending the family cancer clinic of an academic hospital and 828 age-matched women from a general population cohort (PREVEND). Participants filled out a questionnaire on socio-demographic characteristics, lifestyle and medical history, had anthropometric measurements and provided blood samples for assessment of serum levels of total cholesterol, HDL-cholesterol and non-HDL-cholesterol. The correlation between RRSO and cholesterol profile was assessed with logistic regression. Furthermore, subgroup analyses were performed to explore a possible effect of age at and time since RRSO. At a median time of 5.9 years (range 2.3-25.2) after surgery, RRSO was associated with low (< 60 mg/dl) HDL-cholesterol (OR 9.74, 95% CI 5.19-18.26) and high (≥ 160 mg/dl) non-HDL-cholesterol (OR 1.85, 95% CI 1.21-2.82) when adjusting for body mass index, hormone therapy, participation on sports and previous chemotherapy. The observed association was not dependent on age or time since RRSO. The RRSO group had less smokers (19.3 vs. 25.8%) and more participation on sports (45.4 vs. 22.0%). Our results suggest that RRSO is associated with a more atherogenic cholesterol profile, despite a lower prevalence of smoking and higher prevalence of participation on sports as compared to controls. This observation can be useful for physicians involved in the counselling and follow-up of women having RRSO.

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Evaluating the Evidence Behind Treating Osteoporosis in the Oldest Adults.

Wolverton D, Elliott DP.

OBJECTIVE: To review clinical trial data supporting the use of drugs to treat osteoporosis in the oldest adults, 74 years of age and older. DATA SOURCES: The PubMed database (September 1969-June 2017) was searched utilizing the following Medical Subject Headings terms: osteoporosis, postmenopausal, aged, 80 and over, and fractures, bone, in combination with diphosphonates, denosumab, parathyroid hormone, raloxifene, and calcitonin. STUDY SELECTION/DATA EXTRACTION: An initial search revealed 119 results, of which 18 clinical trials were included. Studies were selected that featured a randomized controlled design, fractures reported as a key outcome, and included subjects within the desired age range. DATA SYNTHESIS: Osteoporosis is common among older adults, and with an increasingly aging population, it will be imperative to know how to best manage this condition. Sparse clinical evidence exists for the impact of osteoporosis treatments in the given age range, and no clinical trials have exclusively looked at this age group as the primary target. CONCLUSION: Studies that included participants in this age group were found for alendronate, risedronate, zoledronic acid, denosumab, teriparatide, and abaloparatide. Efficacy appears to be maintained with advancing age for alendronate, zoledronic acid, denosumab, and teriparatide as demonstrated by post hoc analyses of pivotal trials. Alendronate has only demonstrated benefit in patients with previous vertebral fractures because of the study design of the trial. Abaloparatide showed improvement with treatment in the overall population, but age-specific analyses have not been published at this time.

Front Public Health. 2018 May 23;6:141. doi: 10.3389/fpubh.2018.00141. eCollection 2018. **Open Access**.

Steroid Hormones and Their Action in Women's Brains: The Importance of Hormonal Balance.

Del Río JP, Alliende MI, Molina N, Serrano FG, Molina S, Vigil P.

Sex hormones significantly impact women's lives. Throughout the different stages of life, from menarche to menopause and all stages in between, women experience dramatic fluctuations in the levels of progesterone and estradiol, among other hormones. These fluctuations affect the body as a whole, including the central nervous system (CNS). In the CNS, sex hormones act via steroid receptors. They also have an effect on different neurotransmitters such as GABA, serotonin, dopamine, and glutamate. Additionally, studies show that sex hormones and their metabolites influence brain areas that regulate mood, behavior, and cognitive abilities. This review emphasizes the benefits a proper hormonal balance during the different stages of life has in the CNS. To achieve this goal, it is essential that hormone levels are evaluated considering a woman's age and ovulatory status, so that a correct diagnosis and treatment can be made. Knowledge of steroid hormone activity in the brain will give women and health providers an important tool for improving their health and well-being.

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Higher Levels of Serum 25-Hydroxyvitamin D Are Related to Improved Glucose Homeostasis in Women with Postmenopausal Osteoporosis.

Ávila-Rubio V, García-Fontana B, Novo-Rodríguez C, Cantero-Hinojosa J, Reyes-García R, Muñoz-Torres M.

BACKGROUND: Postmenopausal osteoporosis (PMO) is associated with other comorbidities such as impaired glucose homeostasis and cardiovascular disease. Vitamin D insufficiency is highly prevalent and may be a common link between these disorders. However, the relationship between circulating 25-hydroxyvitamin D [25(OH)D] and insulin resistance in women with PMO has not been well evaluated. The aim of this study was to assess the relationship between circulating levels of 25(OH)D and parameters of glucose homeostasis in a cohort of women with PMO to establish a serum concentration threshold of 25(OH)D for improved glycemic parameters. MATERIALS AND METHODS: This cross-sectional study included 40 women with PMO. We measured 25(OH)D serum levels and glucose homeostasis parameters (glucose and insulin levels, insulin sensitivity, and β-secretion index HOMA2-%S and HOMA2-%B, respectively). Anthropometric, biochemical, and clinical parameters and bone markers were also evaluated. RESULTS: Circulating levels of 25(OH)D were related to glucose parameters (negatively with HOMA2-%B and insulin levels and positively with HOMA2-%S) in women with PMO, resulting in an indicator of insulin sensitivity independent of age, body mass index, percent body fat, and undercarboxylated osteocalcin. Patients with serum 25(OH)D ≥45 ng/mL showed lower HOMA2-%B values and insulinemia and greater HOMA2-%S. CONCLUSIONS: Our results support the hypothesis that circulating 25(OH)D levels are related to improved glucose homeostasis in women with PMO. However, this relationship was apparent only in the presence of high circulating levels of 25(OH)D.

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The role of androgens in the treatment of genitourinary syndrome of menopause (GSM): International Society for the Study of Women's Sexual Health (ISSWSH) expert consensus panel review.

Simon JA, Goldstein I, Kim NN, Davis SR, Kellogg-Spadt S, Lowenstein L, Pinkerton JV, Stuenkel CA, Traish AM, Archer DF, Bachmann G, Goldstein AT, Nappi RE, Vignozzi L.

OBJECTIVE: The objective of this consensus document is to broaden the perspective on clinical management of genitourinary syndrome of menopause to include androgens. METHODS: A modified Delphi method was used to reach consensus among the 14 international panelists representing multiple disciplines and societies. RESULTS: Menopause-related genitourinary symptoms affect over 50% of midlife and older women. These symptoms have a marked impact on sexual functioning, daily activities, emotional well-being, body image, and interpersonal relations. Tissues in the genitourinary system are both androgen and estrogen-dependent. The clitoris, vestibule, including minor and major vestibular glands, urethra, anterior vaginal wall, periurethral tissue, and pelvic floor are androgen-responsive. Historically, treatment of postmenopausal genitourinary symptoms involved both androgens and estrogens. This subsequently gave rise to predominantly estrogen-based therapies. More recently, double-blind, placebo-controlled clinical trials have demonstrated that local vaginal dehydroepiandrosterone improves symptoms in postmenopausal women, including moderate to severe dyspareunia. Limited data suggest that systemic testosterone treatment may improve vaginal epithelial health and blood flow. Open-label studies that have used high doses of intravaginal testosterone in the presence of aromatase inhibitor therapy for breast cancer have resulted in supraphysiological serum testosterone levels, and have been reported to lower vaginal pH, improve the vaginal

maturation index, and reduce dyspareunia. CONCLUSIONS: Vaginal dehydroepiandrosterone, hypothesized to enhance local production of both androgen and estrogen, is effective for the management of dyspareunia in menopause. Vaginal testosterone offers potential as a treatment for genitourinary syndrome of menopause, but more studies are needed.

Cureus. 2018 Mar 31;10(3):e2401. doi: 10.7759/cureus.2401.

Transdermal Testosterone in Female Hypoactive Sexual Desire Disorder: A Rapid Qualitative Systematic Review Using Grading of Recommendations Assessment, Development and Evaluation.

Ganesan K1, Habboush Y1, Sultan S2.

Female hypoactive sexual desire disorder (HSDD) is a multifactorial sexual dysfunction disorder characterized by a decrease in sexual desire and personal distress. HSDD occurs in naturally occurring postmenopausal women or secondary to oophorectomy. Multiple studies have assessed the use of transdermal testosterone (TDT) as a management option for patients with HSDD. Our aim is to assess published studies using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework for the quality of evidence regarding testosterone use as a short- and long-term therapy for HSDD. We implemented this qualitative systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. We set a GRADE score of 4 (high evidence) as a cutoff point for the quality measure of published studies assessing the use of TDT in HSDD. The outcomes of interest were the efficacy of TDT on the total number of satisfying sexual activity, number of orgasms, sexual desire and distress level in patients with HSDD. These outcomes were evaluated through Sexual Activity Log (SAL), Profile of Female Sexual Function (PFSF), and Personal Distress Scale (PDS) evaluation tools. Five randomized controlled trials were identified to meet the inclusion criteria. The selected studies were of high evidence based on the GRADE score as two of the studies scored 4 points, the other two studies scored 5 points and one study scored 6 points. All of the high quality selected studies had similar outcomes suggesting high effectiveness for the use of 300 µg/d TDT with or without estrogen for the management of HSDD with minimal side effects. One study showed a trend for higher risk of breast cancer in long-term use (0.37%). The use of 300 µg/d of TDT in surgical and natural menopause is an effective plan to manage HSDD in the short- and long-term. Although side effects are minimal, further prospective research is needed to assess the more severe side effects such as breast cancer in the long-term use of TDT.