Selección de Resúmenes de Menopausia

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Ovarian cancer population screening and mortality after long-term follow-up in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial

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Background: Ovarian cancer continues to have a poor prognosis with the majority of women diagnosed with advanced disease. Therefore, we undertook the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) to determine if population screening can reduce deaths due to the disease. We report on ovarian cancer mortality after long-term follow-up in UKCTOCS. Methods: In this randomised controlled trial, postmenopausal women aged 50-74 years were recruited from 13 centres in National Health Service trusts in England, Wales, and Northern Ireland. Exclusion criteria were bilateral oophorectomy, previous ovarian or active non-ovarian malignancy, or increased familial ovarian cancer risk. The trial management system confirmed eligibility and randomly allocated participants in blocks of 32 using computer generated random numbers to annual multimodal screening (MMS), annual transvaginal ultrasound screening (USS), or no screening, in a 1:1:2 ratio. Follow-up was through national registries. The primary outcome was death due to ovarian or tubal cancer (WHO 2014 criteria) by June 30, 2020. Analyses were by intention to screen, comparing MMS and USS separately with no screening using the versatile test. Investigators and participants were aware of screening type, whereas the outcomes review committee were masked to randomisation group. This study is registered with ISRCTN, 22488978, and ClinicalTrials.gov, NCT00058032. Findings: Between April 17, 2001, and Sept 29, 2005, of 1 243 282 women invited, 202 638 were recruited and randomly assigned, and 202 562 were included in the analysis: 50 625 (25·0%) in the MMS group, 50 623 (25·0%) in the USS group, and 101 314 (50·0%) in the no screening group. At a median follow-up of 16·3 years (IQR 15·1-17·3), 2055 women were diagnosed with tubal or ovarian cancer: 522 (1·0%) of 50 625 in the MMS group, 517 (1·0%) of 50 623 in the USS group, and 1016 (1·0%) of 101 314 in the no screening group. Compared with no screening, there was a 47·2% (95% CI 19·7 to 81·1) increase in stage I and 24·5% (-41·8 to -2·0) decrease in stage IV disease incidence in the MMS group. Overall the incidence of stage I or II disease was 39·2% (95% CI 16·1 to 66·9) higher in the MMS group than in the no screening group, whereas the incidence of stage III or IV disease was 10·2% (-21·3 to 2·4) lower. 1206 women died of the disease: 296 (0·6%) of 50 625 in the MMS group, 291 (0·6%) of 50 623 in the USS group, and 619 (0·6%) of 101 314 in the no screening group. No significant reduction in ovarian and tubal cancer deaths was observed in the MMS (p=0·58) or USS (p=0·36) groups compared with the no screening group. Interpretation: The reduction in stage III or IV disease incidence in the MMS group was not sufficient to translate into lives saved, illustrating the importance of specifying cancer mortality as the primary outcome in screening trials. Given that screening did not significantly reduce ovarian and tubal cancer deaths, general population screening cannot be recommended.

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Senolytics and Senomorphics: natural and synthetic therapeutics in the treatment of aging and chronic diseases

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Cellular senescence is a heterogeneous process guided by genetic, epigenetic and environmental factors, characterizing many types of somatic cells. It has been suggested as an aging hallmark that is believed to contribute to aging and chronic diseases. Senescent cells (SC) exhibit a specific senescence-associated secretory phenotype (SASP), mainly characterized by the production of proinflammatory and matrix-degrading molecules. When SC accumulate, a chronic, systemic, low-grade inflammation, known as inflammaging, is induced. In turn, this chronic immune system activation results in reduced SC clearance thus establishing a vicious circle that fuels inflammaging. SC accumulation represents a causal factor for various age-related pathologies. Targeting of several aging hallmarks has been suggested as a strategy to ameliorate healthspan and possibly lifespan. Consequently, SC and SASP are viewed as potential therapeutic targets either through the selective killing of SC or the selective SASP blockage, through natural or synthetic compounds. These compounds are members of a family of agents called senotherapeutics divided into senolytics and senomorphics. Few of them are already in clinical trials, possibly representing a future treatment of age-

related pathologies including diseases such as atherosclerosis, osteoarthritis, osteoporosis, cancer, diabetes, neurodegenerative diseases such as Alzheimer's disease, cardiovascular diseases, hepatic steatosis, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis and age-related macular degeneration. In this review, we present the already identified senolytics and senomorphics focusing on their redox-sensitive properties. We describe the studies that revealed their effects on cellular senescence and enabled their nomination as novel anti-aging agents. We refer to the senolytics that are already in clinical trials and we present various adverse effects exhibited by senotherapeutics so far. Finally, we discuss aspects of the senotherapeutics that need improvement and we suggest the design of future senotherapeutics to target specific redox-regulated signaling pathways implicated either in the regulation of SASP or in the elimination of SC.

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Postmenopausal hyperandrogenism

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Postmenopausal hyperandrogenism is a state of relative or absolute androgen excess originating from the adrenal glands and/or ovaries clinically manifested by the presence of terminal hair in androgen-dependent areas of the body, and other manifestations of hyperandrogenism such as acne and alopecia or the development of virilization. In such circumstances, physicians must exclude the possibility of rare but serious androgen-producing tumors of the adrenal glands or ovaries. Worsening of undiagnosed hyperandrogenic disorders such as polycystic ovary syndrome, congenital adrenal hyperplasia, ovarian hyperthecosis, Cushing syndrome and iatrogenic hyperandrogenism should be considered for differential diagnosis. Elevated serum testosterone not only causes virilizing effects, but also will lead to hypercholesterolemia, insulin resistance, hypertension and cardiac disease. An ovarian androgen-secreting tumor, which is diagnosed in 1-3 of 1000 patients presenting with hirsutism, comprises less than 0.5% of all ovarian tumors. Adrenal tumors, including non-malignant adenomas and malignant carcinomas, are less common than ovarian tumors but cause postmenopausal virilization. Measurement of serum testosterone, sex hormone-binding globulin, dehydroepiandrosterone sulfate, androstenedione and inhibin B is necessary in postmenopausal women with the complaints and signs of hyperandrogenism. Some tests to discard Cushing syndrome should also be done. After an etiological source of androgen hypersecretion has been suspected, we recommend performing magnetic resonance imaging of the adrenal glands or ovaries. Medical management with gonadotropin-releasing hormone agonist/analogues or antagonists has been reported for women who are either unfit for surgery or in whom the source of elevated testosterone is unidentified.

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Effects of thyroid-stimulating hormone suppression after thyroidectomy for thyroid cancer on bone mineral density in postmenopausal women: a systematic review and meta-analysis

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Objectives: We assessed thyroid-stimulating hormone (TSH) suppression effects on bone mineral density (BMD) in postmenopausal women who underwent thyroidectomy. Data sources: PubMed, EMBASE, Cochrane Library, Web of Science and SCOPUS were searched from inception to 24 February 2021. Study selection: Case-control studies were included. Data extraction and synthesis: Two authors independently reviewed the studies, extracted the data and performed meta-analysis of eligible studies. Research design and methods: Studies evaluating BMD in postmenopausal women with thyroid cancer who had thyroidectomy and levothyroxine therapy were included. Differences in BMD were presented as standardised mean differences (SMDs). Meta-analyses were conducted using a random-effects model. Results: Analysis of 16 case-control studies (426 patients and 701 controls without thyroid cancer) showed that stringent TSH suppression (TSH <0.10 mIU/L) after thyroidectomy had deleterious effects on the BMD of the lumbar spine in postmenopausal women compared with controls (SMD -0.55; 95% CI -0.99 to -0.10; I2=75.8%). There was no significant difference in patients with moderate TSH suppression (TSH 0.10-0.49 mIU/L). TSH suppression in postmenopausal women was not significantly associated with lower femoral neck BMD. Subgroup analysis of the lumbar spine showed that the association between stringent TSH suppression and lower BMD was consistent among studies with >10 years of follow-up (SMD -0.32; 95% CI -0.50 to -0.14). Subgroup analysis of the femoral neck showed that total thyroidectomy was related to detrimental effects on the BMD of the femoral neck (SMD -0.60; 95% CI -0.89 to -0.31; I2=90.4%), but near-total thyroidectomy was not (SMD 0.00; 95% CI -0.30 to 0.30; I2=55.6%).

Conclusions: Stringent TSH suppression had deleterious effects on the BMD of the lumbar spine after thyroidectomy in postmenopausal women. Further studies are needed to determine whether stringent TSH suppression after thyroidectomy increases the fracture risk.

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Effects of anthropometric parameters on bone mineral density in women: from perimenopause to old age

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Aim: To analyze the influence of body components on bone mineral density (BMD) in women from perimenopause to old age. Material and methods: A total of 117 women were allocated into three groups according to the reproductive stage (STRAW): perimenopausal (PEM, N = 28, mean age 44.8 ± 3.6), early postmenopausal (EPM, N = 36, mean age 51.4 ± 2.8) and late postmenopausal (LPM, N = 53; mean age 64.0 ± 1.7). Total body mass, body mass index (BMI), lean mass (LM), fat mass (FM), fat percentage (FP) and BMD at the lumbar spine (lBMD) and femoral neck (fBMD) were assessed. Results: BMI, FM, LM and BMD values decreased from PEM to LPM. The total effect of FM on fBMD and lBMD was of 42% and 8% for PEM, 28% and 33% for EMP and 9% and 1% for LPM respectively. Additionally, the total effect of LM on fBMD and lBMD was 48% and 3% for PEM, 54% and 53% for EMP and 9% and 11% for LPM women respectively. Conclusion: BMI, LM, and FM decreased with aging. All these components had great influence on both fBMD and lBMD in EMP women. Conversely, in PEM these parameters only had influence on femoral BMD, but not on lumbar spine. These data suggests that LM is the most important component in BMD for women older than 50 years old, particularly in the hip.

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Safety assessment of compounded non-FDA-approved hormonal therapy versus FDA-approved hormonal therapy in treating postmenopausal women

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Objective: To assess the safety and serum estradiol (E2) and total testosterone (T) concentrations in postmenopausal women treated with Pellet Hormonal Therapy (PHT) and Food and Drug Administration approved Hormonal Therapy (FHT). Methods: A total of 539 postmenopausal women were identified, including 384 on PHT and 155 on FHT. Data extracted from medical records include demographics, indication for hormone therapy, treatment duration, side effects, serum E2 and T levels, and frequency of laboratory follow-up. Results: The incidence of overall side effects was significantly higher in PHT compared with FHT (221 [57.6%] vs 23 [14.8%], P < 0.00001, odds ratio [95% CI] =8.0[4.5-14.2]). When examining women with an intact uterus prior to hormone therapy initiation, 55.3% (136/246) on PHT vs 15.2% (12/79) on FHT had at least one episode of abnormal uterine bleeding (P < 0.0001, odds ratio [95% CI] = 7.9[3.6-17.0]). Furthermore, a significantly higher proportion of women on PHT (20.3% [50/246]), compared with 6.3% (5/79) on FHT, had a hysterectomy (P = 0.036, odds ratio [95% CI] = 3.2[1.1-9.3]). Both mean (SD, Min-Max) peak E2 (pg/mL) and peak T (ng/dL) are significantly higher in the PHT group than those in the FHT group (E2: 237.70 [168.55, 10-1,111] vs 93.45 [130.77, 5.5-465.8], T: 194.04 [84.94, 4.3-599] vs 15.59 [19.52, 0.2-70], P < 0.00001). Of those on PHT, four women had E2 level > 1,000 pg/mL and nine women with T level > 400 ng/dL. Conclusion: Women on PHT had a significantly higher incidence of side effects than FHT as well as a significantly higher supraphysiological level of peak E2 and T during the treatment.

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A core outcome set for genitourinary symptoms associated with menopause: the COMMA (Core Outcomes in Menopause) global initiative

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Objective: Genitourinary symptoms, such as vaginal dryness and pain with sex, are commonly experienced by postmenopausal women. Comparing treatments for these genitourinary symptoms are restricted by the use of different outcome measures in clinical trials and the omission of outcomes, which may be relevant to women. The aim of this project was to develop a Core Outcome Set (COS) to be reported in clinical trials of treatments for genitourinary symptoms associated with menopause. Methods: We performed a systematic review of randomized controlled trials of treatments for genitourinary symptoms associated with menopause and extracted their outcomes. This list was refined and entered into a two-round modified Delphi survey, which was open to clinicians, researchers, and postmenopausal women from November 2019 to March 2020. Outcomes were scored on a nine-point scale from "not important" to "critically important." The final COS was determined following two international consensus meetings. Results: A total of 26 unique outcomes were included in the Delphi process, which was completed by 227 participants of whom 58% were postmenopausal women, 34% clinicians, and 8% researchers. Predefined thresholds were applied to the Delphi scores to categorize outcomes by importance, which informed the e consensus meetings, attended by 43 participants from 21 countries. The final COS includes eight outcomes: (1) pain with sex, (2) vulvovaginal dryness, (3) vulvovaginal discomfort or irritation, (4) discomfort or pain when urinating, (5) change in most bothersome symptom, (6) distress, bother or interference of genitourinary symptoms, (7) satisfaction with treatment, (8) side effects of treatment. Conclusion: These eight core outcomes reflect the joint priorities of postmenopausal women, clinicians, and researchers internationally. Standardized collection and reporting of these outcomes in clinical trials will facilitate the comparison of different treatments for genitourinary symptoms, advance clinical practice, and ultimately improve outcomes for symptomatic women.

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Evaluation of systemic estrogen for preventing urinary tract infections in postmenopausal women

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Importance: Current guidelines for postmenopausal recurrent urinary tract infection (rUTI) prevention recommend the use of vaginal topical estrogen products but not systemic estrogens. Studies show that vaginal estrogen decreases the risk of rUTI, but evidence against use of systemic estrogen is less convincing. Objective: We performed a comprehensive literature review to evaluate the effect of systemic estrogen on UTI occurrence among postmenopausal women. Evidence review: MEDLINE (PubMed), EMBASE, and CINAHL were searched for manuscripts published in English between January 1990 and July 2020. The search terms were "urinary tract infection" and "estrogen." Inclusion criteria were studies of postmenopausal women who received systemic estrogen therapy (any regimen) that reported UTI frequency during any follow-up period. Case studies, commentaries, and reviews were excluded. A priori specifications of seven study criteria were set representing the ideal study for assessing efficacy of systemic estrogen for rUTI prevention and were used to evaluate each included study. Findings: Searches identified 281 results, and after deduplication and review, 8 studies met inclusion criteria: 4 randomized controlled trials, 1 secondary analysis of a randomized controlled trial, 1 prospective cohort study, 1 case-control study, and 1 cross-sectional study. Of the eight included studies, only two enrolled postmenopausal women with a rUTI diagnosis, four had sufficient sample size to detect a clinically meaningful difference between systemic estrogen versus placebo, two used dosage regimens anticipated to achieve a therapeutic effect, and three assessed UTI rates for an adequate duration of 6 months or more (the standard minimum duration of time needed to make a diagnosis of rUTI). Overall, none of the studies met all predefined criteria for the ideal study to assess the efficacy of systemic estrogen for rUTI prevention. Conclusions and relevance: UTIs will continue to be a significant cause of morbidity and hospitalizations in postmenopausal women unless more research is done to better understand the role of estrogen on UTI rates. The evidence arguing use (or abandonment) of systemic estrogen for the prevention of rUTI is based on few studies with substantial methodologic limitations; there is significant room for improvement.

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What Happens After Menopause? (WHAM): A prospective controlled study of cardiovascular and metabolic risk 12 months after premenopausal risk-reducing bilateral salpingo-oophorectomy

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Objective: To prospectively measure cardiometabolic risk 12 months after premenopausal risk-reducing bilateral salpingo-oophorectomy (RRBSO) compared to a similar age comparison group, and the effects of Hormone Therapy (HT) on cardiometabolic risk. Methods: Prospective observational study of 95 premenopausal women planning RRBSO and 99 comparisons who retained their ovaries. At baseline and 12 months, blood pressure (BP), Body Mass Index (BMI), waist and hip circumference, fasting total, HDL and LDL cholesterol, triglycerides, high-sensitivity C-reactive protein, glucose and insulin were measured and HOMA-IR was calculated. Chi-square tests, t-tests and adjusted logistic regression models were used to compare groups. Results: Baseline cardiometabolic phenotypes were similar between groups but more RRBSO participants were overweight/obese with higher waist/hip ratios. By 12 months, BP and cardiometabolic phenotypes were largely unchanged. Paired t-tests showed statistically significant increases in BMI ($p = 0.037$) and weight ($p = 0.042$) and larger increases in waist circumference ($p < 0.001$) and waist-hip ratio ($p = 0.009$) after RRBSO vs comparisons. However, these were not significant when adjusted for baseline values. After RRBSO 60% initiated Hormone Therapy (HT). Paired t-tests demonstrated that non-HT users had a significantly greater mean increase in waist circumference of 4.3 cm (95% CI 2.0-6.5) compared to 1.3 cm in HT users (95% CI -0.2-2.7, $p < 0.001$), which remained significant when adjusted for baseline values ($p = 0.02$). At 12 months, mean waist circumference was 2.94 cm greater in non-HT users compared to HT users. Conclusions: Cardiometabolic risk markers are largely unchanged 12 months after RRBSO. Hormone Therapy after RRBSO may prevent against an increase in waist circumference.