# Selección de Resúmenes de Menopausia

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J Drugs Dermatol. 2018 Nov 1;17(11):1186 - 1189.

## A Double-Blind Randomized Pilot Study Evaluating the Safety and Efficacy of Topical MEP in the Facial Appearance Improvement of Estrogen Deficient Females

Draelos ZD.

Facial skin aging is accelerated in postmenopausal females due to decreased collagen, reduced hydration, and loss of skin elasticity constituting the characteristics of estrogen deficient skin (EDS). The presence of estrogen receptors on dermal fibroblasts and epidermal keratinocytes confirms the role of estrogen in skin health. This research examined the efficacy and tolerability of topical methyl estradiolpropanoate (MEP) as an anti-aging cosmeceutical with estrogen like cutaneous effects in postmenopausal women who had never taken hormone replacement therapy (HRT). MEP was applied to the face twice daily for 14 weeks but was metabolized in the skin to an inactive compound avoiding estrogen side effects, as demonstrated by the safety study. The efficacy study investigator noted MEP induced statistically significant improvement from baseline at week 14 in dryness ($P<0.001$), laxity ($P=0.001$), atrophy ($P=0.003$), and dullness ($P<0.001$) as compared to vehicle. Four of nine subjects in the biopsy sub study demonstrated an increase in fibroblasts estrogen receptor staining. The novel concept of a safe and efficacious soft estrogen facial cosmeceutical may provide appearance benefits for postmenopausal women.

Curr Probl Cancer. 2018 Aug 4. pii: S0147-0272(18)30079-5. [Epub ahead of print]

## Causal effect of obesity on gynecologic malignancies.

Griffiths C, Jimenez E, Chalas E.

INTRODUCTION: Gynecologic malignancies are estimated to affect 110,070 women and will be the cause of death in approximately 32,120 in 2018. Endometrial cancer is among the most prevalent with 63,320 estimated new cases and approximately 11,350 deaths, followed by ovarian cancer with an estimate of 22,000 new cases and 14,000 deaths annually. Obesity is one of the most modifiable risk factors. Providers should engage in a multifaceted approach to patient education and healthcare to decrease the projected cases of obesity-related cancers. BACKGROUND: The literature demonstrates a significant link between obesity and the development of certain malignancies such as endometrial, pancreatic, and renal cancer. Specific mechanisms found to play a role in the development of these malignancies include alterations of the metabolic pathway attributed to lipid accumulation as well as a chronic inflammatory process. Obesity also predisposes patients to other medical comorbidities as well as a poorer prognosis once a diagnosis of cancer is established. Factors contributing to poorer prognosis include challenges with treatment planning, specifically pertaining to inappropriate chemotherapy dosing and delivery of radiation therapy. Surgical approach and perioperative management are similarly challenging in obese patients and are associated with increased risk of complications. CONCLUSION: Obesity is a modifiable factor which is associated with an increased risk of cancer and poorer outcomes. Providers should educate patients on all health hazards of obesity, including increased risk of cancer, and encourage them to participate in a structured weight loss plan.

Neurobiol Aging. 2018 Oct 5;74:213-224. doi: 10.1016/j.neurobiolaging.2018.09.029. [Epub ahead of print]

## Neuroendocrine aging precedes perimenopause and is regulated by DNA methylation.

Bacon ER, Mishra A, Wang Y, Desai MK, Yin F, Brinton RD.

Perimenopause marks initiation of female reproductive senescence. Age of onset is only 47% heritable suggesting that additional factors other than inheritance regulate this endocrine aging transition. To elucidate these factors, we characterized transcriptional and epigenomic changes across endocrine aging using a rat model that recapitulates characteristics of the human perimenopause. RNA-seq analysis revealed that hypothalamic aging precedes onset of perimenopause. In the hypothalamus, global DNA methylation declined with both age and reproductive senescence.

Genome-wide epigentic analysis revealed changes in DNA methylation in genes required for hormone signaling, glutamate signaling, and melatonin and circadian pathways. Specific epignetic changes in these signaling pathways provide insight into the origin of perimenopause-associated neurological symptoms such as insomnia. Treatment with 5-aza-2'-deoxycytidine, a DNA-methyltransferase-1 inhibitor, accelerated transition to reproductive senescence/ whereas supplementation with methionine, a S-adenosylmethionine precursor, delayed onset of perimenopause and endocrine aging. Collectively, these data provide evidence for a critical period of female neuroendocrine aging in brain that precedes ovarian failure and that DNA methylation regulates the transition duration of perimenopause to menopause.

**Menopause. 2018 Nov 26. doi: 10.1097/GME.0000000000001271. [Epub ahead of print]**

## Oral 17β-estradiol/progesterone (TX-001HR) and quality of life in postmenopausal women with vasomotor symptoms.

Simon JA, Kaunitz AM, Kroll R, Graham S, Bernick B, Mirkin S.

OBJECTIVE: The aim of the study was to describe the effects of TX-001HR (17β-estradiol [E2] and natural progesterone [P4] in a single oral capsule) on menopause-specific quality of life in women with moderate to severe vasomotor symptoms (VMS). METHODS: The REPLENISH study (NCT01942668) was a phase 3, randomized, double-blind, placebo-controlled, multicenter trial which evaluated four E2/P4 doses in postmenopausal women with VMS and a uterus. Women with moderate to severe hot flushes (≥7/d or ≥50/wk) were included in a VMS substudy. Participants self-administered the Menopause-Specific Quality of Life (MENQOL) questionnaire. Baseline changes in MENQOL overall and domains were determined as well as correlations between changes in MENQOL scores and VMS frequency or severity. RESULTS: In the VMS substudy, women treated with E2/P4 had significantly greater improvements from baseline in their MENQOL overall score at week 12, and months 6 and 12, compared with placebo (all, $P<0.05$, except the lowest E2/P4 dose at months 6 and 12). Improvements from baseline for the MENQOL vasomotor domain score were significantly greater with TX-001HR doses versus placebo at all time points (all, $P<0.01$). Changes in MENQOL vasomotor scores moderately correlated with changes in VMS frequency ($r=0.56$, $P<0.0001$) and severity ($r=0.55$, $P<0.0001$). CONCLUSION: In the REPLENISH trial, women with moderate to severe VMS treated with most E2/P4 doses reported significant improvements in quality of life from baseline to 12 weeks compared with placebo, which were maintained up to 12 months. TX-001HR, if approved, may provide the first oral hormone therapy formulation in a single capsule containing E2 and P4 for the treatment of VMS in postmenopausal women with a uterus.

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## Estrogen Improves Insulin Sensitivity and Suppresses Gluconeogenesis via the Transcription Factor Foxo1.

Yan H, Yang W, Zhou F, Li X, Pan Q, Shen Z, Han G, Newell-Fugate A, Tian Y, Majeti R, Liu W, Xu Y, et al.

Premenopausal women exhibit enhanced insulin sensitivity and reduced incidence of type 2 diabetes mellitus (T2D) compared with age-matched men, but this advantage disappears after menopause with disrupted glucose homeostasis, in part owing to a reduction in circulating 17β-estradiol (E2). Fasting hyperglycemia is a hallmark of T2D derived largely from dysregulation of hepatic glucose production (HGP), in which Foxo1 plays a central role in the regulation of gluconeogenesis. Here, we investigated the action of E2 on glucose homeostasis in male and ovariectomized (OVX) female control and liver-specific Foxo1 knockout (L-F1KO) mice, and sought to understand the mechanism by which E2 regulates gluconeogenesis via an interaction with hepatic Foxo1. In both male and OVX female control mice, subcutaneous E2 implant improved insulin sensitivity and suppressed gluconeogenesis; however, these effects of E2 were abolished in L-F1KO mice of both sexes. Using mouse primary hepatocytes, E2 suppressed HGP and gluconeogenesis in hepatocytes from control mice but failed in hepatocytes from L-F1KO mice, suggesting that Foxo1 is required for E2 action on the suppression of gluconeogenesis. We further demonstrated that E2 suppresses hepatic gluconeogenesis through activation of ERα-PI3K-Akt-Foxo1 signaling, which can be independent of insulin receptor substrates 1 and 2 (Irs1 and Irs2), revealing an important mechanism for E2 in the regulation of glucose homeostasis. These results may help explain why premenopausal women have lower incidence in T2D than age-matched men and suggest targeting ERα can be a potential approach to modulate glucose metabolism and prevent diabetes mellitus.

J Womens Health (Larchmt). 2018 Nov 28. doi: 10.1089/jwh.2018.6956. [Epub ahead of print]

## Increased Incidence of Endometrial Cancer Following the Women's Health Initiative: An Assessment of Risk Factors.

Constantine GD, Kessler G, Graham S, Goldstein SR.

BACKGROUND: The Surveillance, Epidemiology, and End Result (SEER) database shows a variable increase in endometrial cancer incidence over time. The objective of this review was to examine published endometrial cancer rates and potential etiologies. METHODS: Endometrial cancer incidence was obtained from the SEER Program database from 1975 through 2014, and a test for trend in incidence was calculated. Changes in risk factors thought to be associated with endometrial cancer, including age, obesity, diabetes, diet and exercise, reproductive factors, and medications (hormone therapy [HT] including Food and Drug Administration [FDA]-approved and non-FDA-approved [compounded] estrogens and progestogens, tamoxifen, and hormonal contraceptives) were found through PubMed searches. Temporal trends of risk factors were compared with endometrial cancer trends from SEER. RESULTS: Although endometrial cancer rates were constant from 1992 to 2002 (women 50-74 years of age), they increased 2.5% annually with a 10% increase from 2006 to 2012 (trend test 0.82). Use of approved prescription estrogen-progestogen combination products decreased after the publication of the Women's Health Initiative (WHI) data, whereas other risk factors either remained constant or decreased during the same time; however, compounded bioidentical HT (CBHT) use increased coincident with the endometrial cancer increase. CONCLUSION: Endometrial cancer rate increases after the first publication of WHI data in 2002 may be associated with the decreased use of approved estrogen-progestogen therapy, the increase in CBHT use, and the prevalence of obesity and diabetes; potential relationships require further evaluation.

Calcif Tissue Int. 2018 Nov 27. doi: 10.1007/s00223-018-0498-x. [Epub ahead of print]

## Fracture Risk in Women with Dysglycaemia: Assessing Effects of Baseline and Time-Varying Risk Factors.

de Abreu LLF, Holloway-Kew KL, Mohebbi M, Sajjad MA, Kotowicz MA, Pasco JA.

Although individuals with diabetes appear to have a higher fracture risk compared to those without diabetes, fracture risk in impaired fasting glucose (IFG) has not been thoroughly explored. This study determined associations between glycaemia status and fracture risk. Women (n = 575, aged 50 + years) enrolled in the Geelong Osteoporosis Study, were followed from baseline (1993-1997), to date of first fracture, death or December 31, 2010, whichever occurred first (median 13.7 years, IQR 7.4-14.8). Hazard ratios (HRs) for any fracture (excluding fingers, toes, skull/face), as well as major osteoporotic fracture (MOF, clinical spine, hip, proximal humerus, wrist), in diabetes (n = 69), IFG (n = 250) and normoglycaemia (n = 256), were calculated using a Cox proportional hazards model. Normoglycaemia was set as the reference category. A Cox proportional hazards model with time-varying covariates was also used to assess change in baseline risk factors at the 10-year follow-up visit (2004-2008). During follow-up (6433 person-years), 162 women sustained any fracture and 104 had a MOF. Unadjusted fracture risk was higher in diabetes (HR 1.64; 95% CI 1.02-2.63) compared to normoglycaemia, but IFG and normoglycaemia had similar risk (HR 1.06; 95% CI 0.76-1.47). Age- and BMD-adjusted any-fracture risk in diabetes compared to normoglycaemia was greater (HR 1.59; 95% CI 0.98-2.58); IFG was similar to normoglycaemia (HR 1.01; 95% CI 0.72-1.41). For MOF, unadjusted and age- and BMD-adjusted fracture risk in IFG was similar to normoglycaemia HR 1.02; 95% CI 0.74-1.40 and HR 0.95; 95% CI 0.69-1.32, respectively, but diabetes was higher compared to normoglycaemia (unadjusted HR 1.64; 95% CI 1.04-2.60; adjusted HR 1.57; 95% CI 0.98-2.51). In the time-varying model, there was no difference between IFG in either the unadjusted or adjusted models, for both any fracture and MOF ($p > 0.05$). For diabetes, there was a significant difference between normoglycaemia in the adjusted model for any fracture ($p = 0.046$), but not for MOF ($p = 0.103$). An increased risk of fracture for women with diabetes was observed after accounting for time-varying risk factors. There was no difference in fracture risk detected for women with IFG.

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## Relationships between intensity, duration, cumulative dose, and timing of smoking with age at menopause: A pooled analysis of individual data from 17 observational studies.

Zhu D, Chung HF, Pandeya N, Dobson AJ, Cade JE, Greenwood DC, Crawford SL, Avis NE, Gold EB, et al.
Cigarette smoking is associated with earlier menopause, but the impact of being a former smoker and any dose-response relationships on the degree of smoking and age at menopause have been less clear. If the toxic impact of cigarette smoking on ovarian function is irreversible, we hypothesized that even former smokers might experience earlier menopause, and variations in intensity, duration, cumulative dose, and age at start/quit of smoking might have varying impacts on the risk of experiencing earlier menopause. METHODS AND FINDINGS: A total of 207,231 and 27,580 postmenopausal women were included in the cross-sectional and prospective analyses, respectively. Overall, 1.9% and 7.3% of women experienced premature and early menopause, respectively. Compared with never smokers, current smokers had around twice the risk of experiencing premature (RRR 2.05; 95% CI 1.73-2.44) ($p < 0.001$) and early menopause (1.80; 1.66-1.95) ($p < 0.001$). The corresponding RRRs in former smokers were attenuated to 1.13 (1.04-1.23; $p = 0.006$) and 1.15 (1.05-1.27; $p = 0.005$). In both current and former smokers, dose-response relationships were observed, i.e., higher intensity, longer duration, higher cumulative dose, earlier age at start smoking, and shorter time since quitting smoking were significantly associated with higher risk of premature and early menopause, as well as earlier menopause at 45-49 years. Duration of smoking was a strong predictor of age at natural menopause. Among current smokers with duration of 15-20 years, the risk was markedly higher for premature (15.58; 11.29-19.86; $p < 0.001$) and early (6.55; 5.04-8.52; $p < 0.001$) menopause. Also, current smokers with 11-15 pack-years had over 4-fold (4.35; 2.78-5.92; $p < 0.001$) and 3-fold (3.01; 2.15-4.21; $p < 0.001$) risk of premature and early menopause, respectively. Smokers who had quit smoking for more than 10 years had similar risk as never smokers (1.04; 0.98-1.10; $p = 0.176$). A limitation of the study is the measurement errors that may have arisen due to recall bias. CONCLUSIONS: The probability of earlier menopause is positively associated with intensity, duration, cumulative dose, and earlier initiation of smoking. Smoking duration is a much stronger predictor of premature and early menopause than others. Our findings highlight the clear benefits for women of early smoking cessation to lower their excess risk of earlier menopause.

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## Impact of micronized progesterone on body weight, body mass index, and glucose metabolism: a systematic review.

Coquoz A, Gruetter C, Stute P.
In women, body weight increases with age. Often menopausal hormone therapy (MHT) is blamed for enhancing this effect. In recent years, the debate on bioidentical MHT including micronized progesterone (MP) has increased. Among others, the question has been raised of whether MHT containing MP has an impact on body weight and glucose metabolism. Based on a systematic literature review on the impact of MHT containing MP on body weight, body mass index (BMI), and glucose metabolism, the following conclusions can be drawn: estrogens combined with MP (1) either do not change or reduce body weight in normal weight postmenopausal women, (2) do not change BMI in normal and overweight postmenopausal women, (3) do not change or improve fasting serum glucose levels in (non-)diabetic postmenopausal women, (4) do not change or improve fasting serum insulin levels in (non-)diabetic postmenopausal women, and (5) do not have an impact on serum glycated hemoglobin in postmenopausal diabetic women. This beneficial effect is probably mostly due to the estrogen MHT component.