



## Selección de Resúmenes de Menopausia

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### **Menopausal hormone therapy and risk of dementia: health insurance database in South Korea-based retrospective cohort study**

Jin-Sung Yuk 1, Jin San Lee 2, Joong Hyun Park 3

**Introduction:** Menopausal hormone therapy (MHT) is used to alleviate the symptoms associated with menopause, despite the lack of recommendations for MHT in preventing dementia. Recent nationwide studies have explored the association between MHT and dementia risk, but the findings remain limited. This study aims to investigate the association between MHT and the incidence of Alzheimer's disease (AD) and non-AD dementia using national population data from Korea. **Methods:** We conducted a retrospective study using data from the National Health Insurance Service in Korea between January 1, 2002, and December 31, 2019. Women over 40 years were eligible for this study and classified into the MHT or non-MHT groups. The MHT group consisted of women who used Tibolone (TIB), combined estrogen plus progestin by the manufacturer (CEPM), estrogen, combined estrogen plus progestin by a physician (CEPP), and transdermal estrogen during menopause. We compared the risk of dementia between the MHT and non-MHT groups. **Results:** The study included 1,399,256 patients, of whom 387,477 were in the MHT group, and 1,011,779 were in the non-MHT group. The median duration of MHT was 23 months (range: 10-55 months). After adjusting for available confounders, we found that different types of MHT had varying effects on the occurrence of dementia. TIB (HR 1.041, 95% confidence interval (CI) 1.01-1.072) and oral estrogen alone (HR 1.081, 95% CI 1.03-1.134) were associated with a higher risk of AD dementia. In contrast, there was no difference in the risk of AD dementia by CEPM (HR 0.975, 95% CI 0.93-1.019), CEPP (HR 1.131, 95% CI 0.997-1.283), and transdermal estrogen (HR 0.989, 95% CI 0.757-1.292) use. The use of TIB, CEPM, and oral estrogen alone increased the risk of non-AD dementia (HR 1.335, 95% CI 1.303-1.368; HR 1.25, 95% CI 1.21-1.292; and HR 1.128, 95% CI 1.079-1.179; respectively), but there was no risk of non-AD dementia in the other MHT groups (CEPP and topical estrogen). **Conclusion:** Our findings indicate that MHT has varying effects on the incidence of AD and non-AD dementia. Specifically, TIB, CEPM, and oral estrogen alone increase the risk of non-AD dementia, while transdermal estrogen is not associated with dementia risk. It is essential to consider the type of MHT used when assessing the risk of dementia in women.

**Semin Cancer Biol. 2023 Sep 20;S1044-579X(23)00125-6. doi: 10.1016/j.semcancer.2023.09.003.**

### **Excess body weight and postmenopausal breast cancer: Emerging molecular mechanisms and perspectives**

Daniela Nahmias-Blank 1, Ofra Maimon, Amichay Meirovitz, Kim Sheva, Tamar Peretz-Yablonsk, Michael Elkin. Postmenopausal, obese women have a significantly higher risk of developing estrogen receptor-positive (ER+) breast tumors, that are resistant to therapies and are associated with higher recurrence and death rates. The global prevalence of overweight/obese women has reached alarming proportions and with postmenopausal ER+ breast carcinoma (BC) having the highest incidence among the three obesity-related cancers in females (i.e., breast, endometrial and ovarian), this is of significant concern. Elucidation of the precise molecular mechanisms underlying the pro-cancerous action of obesity in ER+BC is therefore critical for disease prevention and novel treatment initiatives. Interestingly, accumulating data has shown opposing relationships between obesity and cancer in either pre- or post-menopausal women. Excess body weight is associated with an increased risk of breast cancer in postmenopausal women and a decreased risk in pre-menopausal women. Moreover, excess adiposity during early life appears to be protective against postmenopausal breast cancer, including both ER+ and ER negative BC subtypes. Overall, estrogen-dependent mechanisms have been implicated as the main driving force in obesity-related breast tumorigenesis. In the present review we discuss the epidemiologic and mechanistic aspects of association between obesity and breast tumors after menopause, mainly in the context of hormone dependency. Molecular and cellular events underlying this association present as potential avenues for both therapeutic intervention as well as the prevention of BC-promoting processes linked to excess adiposity, which is proving to be vital in an increasingly obese global population.

**Menopause. 2023 Oct 1;30(10):1002-1005. doi: 10.1097/GME.0000000000002234. Epub 2023 Aug 8.**

## **Needs assessment of menopause education in United States obstetrics and gynecology residency training programs**

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**Objective:** This study aimed to assess the variance in menopause education, educational resources, and the needs of obstetrics and gynecology (ObGyn) residency programs by conducting a national survey of program directors (PDs).

**Methods:** In 2022, an institutional review board-approved Web-based Qualtrics survey was designed and distributed electronically to 145 US ObGyn residency PDs. The survey consists of 15 questions. The main outcomes are reported using descriptive statistics. **Results:** The survey was completed by 99 of 145 PDs (68.3%). Almost all participants (92.9%) strongly agreed that residents nationwide should have access to a standardized menopause curriculum that could be utilized in their programs. Only 31.3% reported having a menopause curriculum in their residency program. Of the programs with a menopause curriculum, 96.8% reported using lectures, 77.4% reported assigned readings, and 74.2% had either dedicated menopause clinics or other clinics with a high volume of menopausal patients. Of all programs surveyed, only 29.3% reported that trainees had dedicated time assigned to a menopause clinic. A total of 83 of 99 PDs agreed or strongly agreed that their programs needed more menopause educational resources, and most (89.7%) stated they were likely or very likely to use self-paced menopause modules that include performance feedback if available. **Conclusions:** Data from the needs assessment questionnaire revealed that menopause education and resources vary residency programs, with the majority lacking a dedicated menopause curriculum. Most PDs expressed a desire for more educational resources and standardized training materials, and preferred to access an online national menopause curriculum.

**Womens Health (Lond). 2023 Jan-Dec;19:17455057231199051. doi: 10.1177/17455057231199051.**

## **Higher perceived stress during the COVID-19 pandemic increased menstrual dysregulation and menopause symptoms**

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**Background:** The increased stress the world experienced with the coronavirus disease (COVID-19) pandemic affected mental health, disproportionately affecting females. However, how perceived stress in the first year affected menstrual and menopausal symptoms has not yet been investigated. **Objectives:** This study evaluates the effect that the first year of the COVID-19 pandemic had on female reproductive and mental health. **Methods:** Residents in British Columbia, Canada, were surveyed online as part of the COVID-19 Rapid Evidence Study of a Provincial Population-Based Cohort for Gender and Sex. A subgroup of participants (n = 4171), who were assigned female sex at birth (age 25-69 years) and were surveyed within the first 6-12 months of the pandemic (August 2020-February 2021), prior to the widespread rollout of vaccines, was retrospectively asked if they noticed changes in their menstrual or menopausal symptoms, and completing validated measures of stress, depression and anxiety. **Design:** This is a population-based online retrospective survey. **Results:** We found that 27.8% reported menstrual cycle disturbances and 6.7% reported increased menopause symptoms. Those who scored higher on perceived stress, depression and anxiety scales were more likely to report reproductive cycle disturbances. Free-text responses revealed that reasons for disturbances were perceived to be related to the pandemic. **Conclusion:** The COVID-19 pandemic has highlighted the need to research female-specific health issues, such as menstruation. Our data indicate that in the first year of the pandemic, almost one-third of the menstruating population reported disturbances in their cycle, which was related to perceived stress, depression and anxiety scores.

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## **Meibography and tear function alterations in premature ovarian failure**

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**Purpose:** Premature ovarian failure (POF) is the deterioration of normal ovarian function before the age of 40. In the presence of chemotherapy, radiation, genetic factors, autoimmune conditions, hypoandrogenemia, hypoestrogenemia and increased gonadotropin hormones, dry eye with early menopause findings may be encountered. The goal of our study is to compare the tear film alterations and meibomian gland status of patients diagnosed with POF at the time of diagnosis with healthy volunteers. **Methods:** In our study, 90 patients with POF and 60 control patients were evaluated. Complete ophthalmologic examinations of the patients, ocular surface disease index (OSDI) score, Oxford score for corneal and conjunctival involvement, Schirmer 1 and 2 tests, noninvasive tear break-up time (BUT), lower lid

meibomian drop out grades with noncontact meibography, and meibomian gland distortion and shortening scores were compared between the two groups. Results: The mean age was  $29.49 \pm 2.92$  years in the patient group and  $29.37 \pm 2.85$  years in the control group ( $p=0.830$ ). OSDI scores were statistically significant higher in the patient group ( $32.11 \pm 18.88$ ) compared to the control group ( $12.93 \pm 14.92$ ) ( $p<0.001$ ). On Oxford scoring, there was a significant increase in the patient group ( $p<0.001$ ). There was no significant difference between the groups in terms of Schirmer 1 and 2 tests ( $p=0.195$ ,  $p=0.117$ ). NUBIT was significantly lower in the patient group ( $11.93 \pm 4.59$ ) compared to the control group ( $18.72 \pm 5.38$ ) ( $Pp<0.001$ ). While there was no difference between the groups in terms of lower lid meiboscores or meibomian gland length ( $p>0.005$ ), there was a significant deterioration in the patient group in the distortion grading showing the morphological evaluation of the meibomian glands ( $p=0.037$ ). In the ROC analysis, OSDI score (AUC=0.816,  $p<0.0001$ ) and NIBUT (AUC=0.820,  $p<0.0001$ ) parameters showed high specificity and sensitivity for the disease. Discussion: Ocular surface damage and dry eye symptoms are observed more frequently in patients with POF. We believe that hormonal insufficiency may cause deterioration in tear film composition, ocular surface damage with changes in tear homeostasis, and a change in the structure of the meibomian glands, starting with distortion at an early age.

**Bone. 2023 Sep 18;177:116913. doi: 10.1016/j.bone.2023.116913. Online ahead of print.**

## **Osteoporosis and bone fractures in patients with celiac disease: A nationwide cohort study**

Susanne Hansen 1, Peter Schwarz 2, Jüri Rumessen 1, Allan Linneberg 3, Line Lund Kårhus 4

Celiac disease (CD) is an autoimmune disease caused by an abnormal immune response triggered by ingestion of gluten. Treatment of CD is a lifelong gluten-free diet. Both diagnosed and undiagnosed CD has been found to be associated with reduced bone mineral density, which can lead to an increased risk of fractures. We therefore aimed to investigate the association of CD and the risk of fractures and osteoporosis in Denmark in a nationwide registry-based study. We identified all patients with CD (ICD-10 code K90.0) between 2000 and 2018 and included those with at least two contacts with a CD diagnosis. In total, 9397 CD patients and 93,964 randomly selected age- and sex-matched (1:10) references from the general population were identified. The overall hazard ratio (HR) of developing osteoporosis in CD patients compared with matches was 5.39 (95 % confidence interval (CI): 4.89, 5.95), however when excluding events of osteoporosis occurring within 12 months from the date of diagnosis the overall HR was reduced to 3.87 (95 % CI: 3.44, 4.33). The HR for major osteoporotic fractures was 1.37 (95 % CI: 1.25, 1.51) and for any fractures 1.27 (95 % CI: 1.18, 1.36). For osteoporosis, major osteoporotic fractures, and any fracture prior to diagnosis of CD the odds ratios comparing CD patients with matches were 4.32 (95 % CI: 3.64, 4.68), 1.29 (95 % CI: 1.21, 1.37) and 1.34 (95 % CI: 1.27, 1.41), respectively. Thus, this study showed an increased risk of osteoporosis and bone fractures among individuals with CD, both before and after diagnosis of CD. These results underline that the risk of osteoporosis should be considered in the clinical management of patients with CD and that early diagnosis and treatment could be important.

**Diabetes Care. 2023 Oct 1;46(10):1866-1875. doi: 10.2337/dc23-0451.**

## **Effect of Postmenopausal Hormone Therapy on Glucose Regulation in Women with Type 1 or Type 2 Diabetes: A Systematic Review and Meta-analysis**

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Background: Blood glucose regulation in women with diabetes may change during and after menopause, which could be attributed, in part, to decreased estrogen levels. Purpose: To determine the effect of postmenopausal hormone therapy (HT) on HbA1c, fasting glucose, postprandial glucose, and use of glucose-lowering drugs in women with type 1 and women with type 2 diabetes. Data sources: We conducted a systematic search of MEDLINE, Embase, Scopus, the Cochrane Library, and the ClinicalTrials.gov registry to identify randomized controlled trials (RCTs). Study selection: We selected RCTs on the effect of HT containing estrogen therapy in postmenopausal women ( $\geq 12$  months since final menstrual period) with type 1 or type 2 diabetes. Data extraction: Data were extracted for the following outcomes: HbA1c, fasting glucose, postprandial glucose, and use of glucose-lowering medication. Data synthesis: Nineteen RCTs were included (12 parallel-group trials and 7 crossover trials), with a total of 1,412 participants, of whom 4.0% had type 1 diabetes. HT reduced HbA1c (mean difference  $-0.56\%$  [95% CI  $-0.80$ ,  $-0.31$ ],  $-6.08$  mmol/mol [95% CI  $-8.80$ ,  $-3.36$ ]) and fasting glucose (mean difference  $-1.15$  mmol/L [95% CI  $-1.78$ ,  $-0.51$ ]). Limitations: Of included studies, 50% were at high risk of bias. Conclusions: When postmenopausal HT is considered for menopausal

symptoms in women with type 2 diabetes, HT is expected to have a neutral-to-beneficial impact on glucose regulation. Evidence for the effect of postmenopausal HT in women with type 1 diabetes was limited.

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### **Different effects of menopausal hormone therapy on non-alcoholic fatty liver disease based on the route of estrogen administration**

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The effects of menopausal hormone therapy (MHT) on non-alcoholic fatty liver disease (NAFLD) were compared based on the route of estrogen administration. The study included 368 postmenopausal women who received MHT for 12 months. Patients were divided into transdermal (n = 75) and oral (n = 293) groups based on the estrogen route. Changes in the prevalence of NAFLD were compared between the two groups before and after 12 months of MHT. In addition, differences in the progression of NAFLD after MHT based on the dose of estrogen and type of progestogen were evaluated in the oral group. After MHT, the prevalence of NAFLD decreased from 24 to 17.3% in the transdermal group but increased from 25.3 to 29.4% in the oral group. Little or no change was found in clinical characteristics and laboratory tests in the transdermal group during MHT. However, serum levels of total cholesterol and low-density lipoprotein cholesterol decreased and triglycerides and high-density lipoprotein cholesterol increased significantly in the oral group. Furthermore, changes in the prevalence of NAFLD were not significantly different based on the dose of estrogen or type of progestogen. Our findings indicate that transdermal estrogen can be beneficial in terms of NAFLD progression.

**JAMA Netw Open. 2023 Sep 5;6(9):e2334545. doi: 10.1001/jamanetworkopen.2023.34545.**

### **Premenstrual Disorders, Timing of Menopause, and Severity of Vasomotor Symptoms**

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Importance: Although premenstrual disorders (PMDs) end at menopause, it is unclear whether they are associated with the timing and symptom severity of menopause. Objective: To prospectively examine whether women with PMDs have increased risks of early menopause and menopause-related vasomotor symptoms (VMS). Design, setting, and participants: This population-based cohort study was nested in the Nurses' Health Study II (data collected from questionnaire sent between June 1991 and June 2017). Analysis of menopause timing included participants who did not have natural or surgical menopause before study entry, while the analysis of VMS was restricted to women who provided information on VMS. Data were analyzed from August 2022 to March 2023. Exposures: PMDs were identified by self-reported diagnosis and confirmed with symptom questionnaires from 1991 to 2005. Participants were age-matched to women without PMD diagnoses and confirmed absence of or minimal premenstrual symptoms. Main outcomes and measures: During follow-up through 2017, timing of natural menopause was assessed biennially, and VMS were assessed in 2009, 2013, and 2017. The association of PMDs with early menopause was assessed by Cox proportional hazards models and with VMS by logistic regression models. Results: Of 1220 included women with PMDs, the median (IQR) age was 40.7 (37.3-43.8) years; of 2415 included women without PMDs, the median (IQR) age was 41.7 (38.3-44.8) years. The median (IQR) follow-up in this study was 20.3 (17.8-22.2) years. Early natural menopause (menopause before age 45 years) was reported by 17 women with PMDs (7.1 per 1000 person-years) and 12 women without PMDs (2.7 per 1000 person-years; adjusted hazard ratio, 2.67; 95% CI, 1.27-5.59). In addition, 795 women with PMDs (68.3%) and 1313 women without PMDs (55.3%) reported moderate or severe VMS (adjusted odds ratio, 1.68; 95% CI, 1.32-2.14). There was no observed association between PMDs and mild VMS (adjusted odds ratio, 0.99; 95% CI, 0.76-1.28). Conclusions and relevance: In this cohort study of US women, PMDs were associated with increased risks of early menopause and moderate or severe VMS. PMDs may be indicative of underlying physiology linked to early menopause and VMS, suggesting a phenotype observable during the reproductive years that may allow clinicians to target women at risk of earlier menopause and subsequent health risks later in the life course.