# Selección de Resúmenes de Menopausia

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## Serum estradiol level according to dose and formulation of oral estrogens in postmenopausal women

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This study was performed to evaluate serum estradiol level in postmenopausal women using oral menopausal hormone therapy (MHT) with different doses and formulations of estrogens. A total of 344 postmenopausal women who received oral MHT was included in this cross-sectional study. Serum estradiol level was compared according to formulation (estradiol hemihydrate [EH] or valerate [EV], conjugated estrogen [CE]) and dose (estradiol 1 or 2 mg, CE 0.45 or 0.625 mg) of the estrogens. Mean age and years since menopause were 56.9 and 7.9 years, respectively. Mean duration of MHT was 27.4 months. Since serum estradiol levels were not significantly different at either dose, EH and EV at the same dose were combined for comparisons: estradiol 1 mg and 2 mg. The serum estradiol level with estradiol 2 mg (107.6 pg/mL) was significantly higher by 60% than with estradiol 1 mg (65.8 pg/mL) or CE 0.45 mg (60.1 pg/mL), and it was also significantly higher than with CE 0.625 mg (76.8 pg/mL). Our findings suggest that serum estradiol level is not directly proportional to estrogen dose. In terms of serum concentration, CE 0.45 mg is equivalent to estradiol 1 mg.

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## Effect of risk-reducing salpingo-oophorectomy on quality of life in Korean BRCA mutation carriers

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Background: This study aimed to compare the quality of life (QOL), psychosocial status, sexual function, and menopausal symptoms between the risk-reducing salpingo-oophorectomy (RRSO) and non-RRSO groups comprising BRCA mutation carriers and to evaluate the effect of timing of RRSO on those aspects. Methods: This cross-sectional study recruited BRCA mutation carriers aged ≥35 years between September 2015 and September 2016. Demographic data of carriers were collected. Outcomes were measured using the questionnaires addressing QOL, anxiety, depression, optimism, sexual function, and menopausal symptoms. Results: Of 52 participants, 30 (57.7%) underwent RRSO, whereas 22 (42.3%) did not. In the RRSO group, 16 (53.3%) and 14 (46.7%) women underwent RRSO before and after menopause, respectively. The mean age in the RRSO group was higher than that in the non-RRSO group (49.8 vs. 42.1 years, respectively, p = 0.002). The scores for QOL, anxiety, depression, optimism, sexual function, and menopausal symptoms were similar between both groups. In the multivariate analysis, RRSO uptake was associated with worse physical QOL (coefficient, -5.350; 95% confidence interval, -10.593 to -0.108). With respect to the timing of RRSO, only the mental QOL was significantly lower in the postmenopausal RRSO group than in the premenopausal RRSO group (39.2 vs. 43.7, respectively, p = 0.043). Conclusion: We could not find any difference in mental QOL, psychosocial status, sexual function, and menopausal symptoms between the RRSO and non-RRSO groups. RRSO uptake only affected worse physical QOL. These results will help physicians counsel BRCA mutation carriers about the effect of RRSO on QOL.

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## Bone Mineral Density in Different Menopause Stages is Associated with Follicle Stimulating Hormone Levels in Healthy Women

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Although estradiol (E2) has been believed to be the most critical factor in the menopause-associated decrease in bone mineral density (BMD), the role of increasing follicle stimulating hormone (FSH) during menopause is relatively unclear. We determined the extent to which hip and lumbar spine BMD differ among the stages of menopause in healthy women, and whether BMD is associated with FSH and E2 levels. A cross-sectional study of 141 healthy women classified as premenopausal (Pre; 38 ± 6 yrs; mean ± SD, n = 30), early perimenopausal (EPeri; 50 ± 3yrs, n = 31), late perimenopausal (LPeri; 50 ± 4yrs, n = 30), early postmenopausal (EPost; 55 ± 3yrs, n = 24), or late postmenopausal (LPost; 62 ± 4 yrs,

n = 26), was conducted. Spine/hip BMD and sex hormones were measured using dual-energy X-ray absorptiometry and enzymatic/colorimetric methods, respectively. Compared to EPeri, spine BMD was lower ($p < 0.05$) in LPeri, EPost, and LPost and hip BMD was lower ($p < 0.05$) in EPost and LPost. BMD was inversely associated with FSH (spine: $r = -0.341$; hip: $r = -0.271$, $p < 0.05$) and directly associated with E2 (spine: $r = 0.274$; hip: $r = 0.256$, $p < 0.05$). The menopause-related loss of spine and hip BMD is associated not only with low E2 but also higher FSH. Future studies are essential to delineating the mechanisms by which FSH regulates bone health in aging women.

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## Thyroid autoimmunity is associated with higher risk of premature ovarian insufficiency-a nationwide Health Insurance Research Database study

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Study question: Is thyroid autoimmunity associated with a higher risk of low ovarian reserve and POI? Summary answer: Thyroid autoimmunity significantly increases the risk of POI in women. What is known already: POI is closely related with autoimmune disease, and according to some studies, thyroid autoimmunity (TAI) may account for diminished ovarian reserve. However, no large-scale cohort study has demonstrated the association between TAI and POI. Study design, size, duration: A longitudinal population-based retrospective cohort study on the National Health Insurance Research Database (NHIRD) was designed. Since 1 March 1995, the National Health Insurance (NHI) programme in Taiwan has included 99.9% of the 23 million population of Taiwan. Patients between 1 January 2000 and 31 December 2012 were eligible for recruitment, and 21 325 subjects were analysed in our study. Participants/materials, setting, methods: Two cohorts, Hashimoto's and Grave's disease, were composed of patients with autoimmune thyroid disease between 20 and 40 years of age. The comparison cohorts consisted of patients in the NHIRD without autoimmune thyroid disease matched by age at a ratio of 1:4 in subject numbers. Main results and the role of chance: The Hashimoto's disease (HD) cohort, Grave's disease (GD) cohort and two comparison cohorts were followed up until a diagnosis of amenorrhoea, menopausal syndrome, other ovarian failure or infertility due to ovarian failure had been made. Compared statistically with the non-HD cohort, patients with HD exhibited an 89% higher risk of amenorrhoea (95% CI =1.36-2.61). The HD patients exhibited a 2.40-fold higher risk of infertility due to ovarian failure than the non-HD subjects (hazard ratio (HR)=2.40, 95% confidence interval (CI)=1.02-5.68). In comparison with the non-GD cohort, patients with GD exhibited a 68% higher risk of amenorrhoea (95% CI = 1.43-1.98) after adjustment. According to the Kaplan-Meier analysis, the cumulative incidence of amenorrhoea and menopausal syndrome was significantly higher in the TAI groups than in the control groups. Limitations, reasons for caution: This is a retrospective study using ICD-9 disease code analysis to determine the statistical association between two diseases. Wider implications of the findings: Given that autoimmune thyroid disease is highly associated with early diminished ovarian reserve or even premature ovarian failure or POI, the options for infertility treatment may be re-directed to more efficient methods in infertile patients diagnosed with the disease. If the ovarian reserve is normal at the time of diagnosis of thyroid autoimmune disease, close follow-up of ovarian reserve may be highly recommended.

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## Association between body mass index and fragility fracture in postmenopausal women: a cross-sectional study using Korean National Health and Nutrition Examination Survey 2008-2009 (KNHANES IV)

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Background: The present study examined the relationship between body mass index (BMI) and the risk for fragility fractures in postmenopausal Korean women. Methods: Among subjects who participated in the 4th Korea National Health and Nutrition Examination Survey (2008-2009), 2114 women ≥ 40 years of age were included. BMI was based on standards set by the Korean Society for the Study of Obesity, as follows: < 18.5 kg/m2, underweight; 18.5 ≤ to < 25 kg/m2, normal weight; and ≥ 25 kg/m2, obese. Subjects were also divided into three groups according to the location of fragility fracture: spine, hip, or wrist. Results: The mean (± SD) rate of fragility fracture was significantly different among the three groups: 5.9 ± 2.9% (underweight), 1.1 ± 0.3% (normal weight), and 3.0 ± 0.7% (obese) ($p = 0.001$). After correcting for age, family history, and treatment history of osteoporosis and rheumatoid arthritis, smoking and drinking status, and level of exercise, multivariable regression analysis revealed that the odds ratio for fragility fracture in the underweight group was 5.48 [95% confidence interval (CI) 1.80-16.73] and 3.33 (95% CI 1.61-6.87) in the obese group. After subdividing fragility fractures into vertebral and non-vertebral, the odds ratio for vertebral fracture in the underweight group was 5.49 (95% CI 1.31-23.09) times higher than that in the normal weight group; in the obese group,

the non-vertebral fracture odds ratio was 3.87 (95% CI 1.45-10.33) times higher. Analysis of non-vertebral fractures in the obese group revealed an odds ratio for fracture 22.05 (95% CI 1.33-365.31) times higher for hip fracture and 3.85 (95% CI 1.35-10.93) times higher for wrist fracture. Conclusions: Obesity and underweight increased the risk for fragility fractures in postmenopausal Korean women.

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## Alterations in the estrogen receptor profile of cardiovascular tissues during aging

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Estrogen exerts protective effects on the cardiovascular system via three known estrogen receptors: alpha (ERα), beta (ERß), and the G protein-coupled estrogen receptor (GPER). Our laboratory has previously showed the importance of GPER in the beneficial cardiovascular effects of estrogen. Since clinical studies indicate that the protective effects of exogenous estrogen on cardiovascular function are attenuated or reversed 10 years post-menopause, the hypothesis was that GPER expression may be reduced during aging. Vascular reactivity and GPER protein expression were assessed in female mice of varying ages. Physiological parameters, blood pressure, and estrogen receptor transcripts via droplet digital PCR (ddPCR) were assessed in the heart, kidney, and aorta of adult, middle-aged, and aged male and female C57BL/6 mice. Vasodilation to estrogen (E2) and the GPER agonist G-1 were reduced in aging female mice and were accompanied by downregulation of GPER protein. However, ERα and GPER were the predominant receptors in all tissues, whereas ERß was detectable only in the kidney. Female sex was associated with higher mRNA for both ERα and GPER in both the aorta and the heart. Aging impacted receptor transcript in a tissue-dependent manner. ERα transcript decreased in the heart with aging, while GPER expression increased in the heart. These data indicate that aging impacts estrogen receptor expression in the cardiovascular system in a tissue- and sex-specific manner. Understanding the impact of aging on estrogen receptor expression is critical for developing selective hormone therapies that protect from cardiovascular damage.

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## Perfluoroalkyl substances and sex hormones in postmenopausal women: NHANES 2013-2016

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Background: Although an alteration in sex hormones has been linked to perfluoroalkyl substances (PFAS) in premenopausal women and girls, whether such associations exist in postmenopausal women remains uncertain. Objects: To examine the associations between serum PFAS concentrations and sex hormone levels in postmenopausal women. Methods: Data from the National Health and Nutrition Examination Survey (NHANES) 2013-2016 waves were used. A total of 706 postmenopausal women with information on serum PFAS [perfluorohexane sulfonic acid (PFHxS), pefluorodecanoic acid (PFDA); perfluorononanoic acid (PFNA); linear perfluorooctanoate (n-PFOA); linear perfluorooctane sulfonate (n-PFOS); monomethyl branched isomers of PFOS (Sm-PFOS)], sex hormones indicators [e.g., total testosterone (TT), estradiol (E2) and sex hormone binding globulin (SHBG)] as well as selected covariates were included. An indicator of circulating free testosterone (FT), and ratio of TT to E2 (TT/E2) were generated. Multiple linear regression accounting for the primary sampling unit, strata, and environmental sampling weights of PFAS was used for association analyses. Effect modification by obesity and type of menopause was explored via stratified analyses as well as the testing of interaction terms. Principal component analysis (PCA) and Bayesian kernel machine regression (BKMR) were conducted to assess these relationships in a multiple PFAS exposure setting. Results: After adjusting for potential confounders, total perfluorooctanoate (TPFOA: n-PFOA + Sb-PFOA) and total perfluorooctane sulfonate (TPFOS: n-PFOS + Sm-PFOS), and their linear and branched isomers were positively associated with two androgen indicators (i.e., TT and FT). PCA results revealed that the principal component (PC) composed of n-PFOA was positively associated with ln (TT) [β = 0.09, 95% confidential interval (CI): 0.02, 0.16; per ln-ng/mL increase in exposure], and ln (FT) (β = 0.12, 95% CI: 0.05, 0.2) in overweight/obese [body mass index (BMI) ≥ 25 kg/m2] women, but not in those with BMI < 25 kg/m2. Additionally, among overweight/obese women, PFHxS was positively associated with androgens and negatively with ln (SHBG) (β = -0.06, 95% CI: -0.12, -0.01). The PC composed of Sm-PFOS, n-PFOS, and PFHxS was positively associated with ln (TT) levels among overweight/obese women. Results from BKMR also confirmed the findings on n-PFOA and PFHxS.Conclusions: Our study indicates that n-PFOA and PFHxS were positively associated with levels of several androgen indicators in postmenopausal women, particularly among overweight/obese ones. Given the higher risk of cardiometabolic diseases associated with elevated levels of androgens in postmenopausal women, future studies are needed to explore the potential underlying mechanisms.