



## Selección de Resúmenes de Menopausia

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### Ovarian tissue cryopreservation and transplantation to delay menopause: facts and fiction

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Ovarian tissue cryopreservation and transplantation (OTCT) is increasingly being used in young cancer patients for fertility restoration and prevention of premature ovarian insufficiency (POI) and has recently been advocated as a method to delay menopause. This is accomplished by cryopreserving ovarian tissue that is excised laparoscopically in thin pieces at a young age. Cryopreserved tissue will be transplanted at menopause, when ovarian function is no longer present. Transplantation may need to be repeated several times to achieve long-term restoration of ovarian function. However, it is unknown whether ovarian grafts result in a normal steroid pulsatile secretion, similar to that present during reproductive years. In addition, it is not known whether the need to restore ovarian activity appears earlier in women who undergo OTCT to delay menopause, although indirect data suggest that this is likely to be true. Until today, no cohort or comparative studies evaluating OTCT as a potential alternative to hormone replacement therapy (HRT) have been published and, thus, there is no evidence to suggest that OTCT is superior to HRT in terms of both efficacy and safety. Given the availability of alternative, established treatments for managing menopausal symptoms, as well as the multiple unanswered questions regarding the method, it is imperative that, before OTCT is regarded as a mainstream technique for management of menopausal symptoms, further evaluation and clinical investigation are undertaken.

**Age Ageing. 2020 Nov 6;afaa237.doi: 10.1093/ageing/afaa237. Online ahead of print.**

### Does vascular endothelial dysfunction play a role in physical frailty and sarcopenia? A systematic review

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Background: Frailty is strongly associated with adverse cardiovascular outcomes; however, the underlying pathophysiological processes are largely unknown. Vascular endothelial dysfunction (VED) is the earliest stage of cardiovascular disease (CVD) progression and predicts long-term CVD outcomes. Both these conditions share an elevated inflammatory state as a common pathological factor. Objective: Systematic literature review was conducted to examine the evidence supporting an association between VED and physical frailty and/or sarcopenia, in electronic databases including Scopus, Ovid Medline, CINAHL, ScienceDirect, ProQuest Health & Medicine and Embase from January 1980 to August 2019. Results: A total of 18 studies met the inclusion criteria. VED is independently associated with increased frailty phenotypes and measures of sarcopenia. Several markers of VED, including higher levels of asymmetric dimethylarginine, abnormal ankle brachial index, pulse wave velocity, pulse pressure and lower levels of flow-mediated dilatation, peripheral blood flow and endothelial progenitor cell counts, have been associated with frailty/sarcopenia measurements. Some studies demonstrated the effect of inflammation on the association. Conclusions: Recent studies, although limited, showed that VED could be one of the underlying mechanisms of frailty. It is entirely possible that inflammation-related pathological changes in the vascular endothelium are involved in the early causative mechanisms in physical frailty. The exact mechanism(s) underlying this association are still unclear and will need to be evaluated. The outcomes of these future research studies could potentially inform early preventative strategies for physical frailty and sarcopenia.

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### Cardiovascular Changes in Menopause

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Menopause is associated with changes consistent with cardiovascular aging. The effects on cardiac disease is multifaceted affecting endothelial function, coronary artery physiology and metabolic dysfunction leading to structural changes in the coronary anatomy. A systematic review of literature from 1986 to 2019 was conducted using PubMed and Google Scholar. The search was directed to retrieve papers that addressed the changes in cardiovascular physiology

in menopause and the current therapies available to treat cardiovascular manifestations of menopause. The metabolic and clinical factors secondary to menopause such as dyslipidemia, insulin resistance, fat redistribution and systemic hypertension contribute to the accelerated risk for cardiovascular aging and disease. Atherosclerosis appears to be the end result of the interaction between cardiovascular risk factors and their accentuation during the perimenopausal period. Additionally, complex interactions between oxidative stress and levels of L-arginine and ADMA may also influence endothelial dysfunction in menopause. The increased cardiovascular risk in menopause stems from the exaggerated effects of changing physiology on the cardiovascular system affecting peripheral, cardiac and cerebrovascular beds. The differential effects of menopause on cardiovascular disease at the subclinical, biochemical and molecular levels form the highlights of this review.

**Climacteric. 2020 Nov 2;1-7.doi: 10.1080/13697137.2020.1834530. Online ahead of print.**

### **Neurokinin 3 receptor antagonists - prime time?**

J K Prague

Vasomotor symptoms (hot flushes, flashes, night sweats) occur in the majority of menopausal women, and are reported as being of the highest symptom priority as they often persist over many years and can be highly disruptive. Hormone therapy is the most effective available treatment but is not without risk if taken long term, and is sometimes contraindicated; for example, in women with a personal or family history of breast cancer, which is the most common female cancer worldwide. Other treatment alternatives are not as efficacious, can cause side effects, and/or are not widely available. A new, effective, targeted treatment could therefore benefit millions of women worldwide. This became possible to investigate after accumulated evidence from both animal and human models implicated heightened signaling of a hypothalamic neuropeptide together with its receptor (neurokinin B/NK3R) in the etiology of sex-steroid-deficient vasomotor symptoms. Four clinical trials of three chemically distinct oral NK3R antagonists for the treatment of menopausal flushes have since completed and published, which consistently demonstrate efficacy and tolerability of these agents. These suggest great promise to change practice in the future if ongoing further larger-scale studies of longer duration confirm the same; as, estrogen exposure will no longer be required to effectively and safely treat vasomotor symptoms.

**Am J Physiol Endocrinol Metab. 2020 Nov 2.doi: 10.1152/ajpendo.00211.2020. Online ahead of print.**

### **Estetrol prevents western diet-induced obesity and atheroma independently of hepatic estrogen receptor (ER) $\alpha$**

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Estetrol (E4), a natural estrogen synthesized by the human fetal liver, is currently evaluated in phase III clinical studies as a new menopause hormone therapy. Indeed, E4 significantly improves vasomotor and genito-urinary menopausal symptoms and prevents bone demineralization. Compared to other estrogens, E4 was found to have limited effects on coagulation factors in the liver of women allowing to expect less thrombotic events. To fully delineate its clinical potential, the aim of this study was to assess the effect of E4 on metabolic disorders. Here, we studied the pathophysiological consequences of a western diet (42% kcal fat, 0.2% cholesterol) in ovariectomized female mice under chronic E4 treatment. We showed that E4 reduces body weight gain and improves glucose tolerance in both C57Bl/6 and LDLR<sup>-/-</sup> mice. To evaluate the role of hepatic ER $\alpha$  in the preventive effect of E4 against obesity and associated disorders such as atherosclerosis and steatosis, mice harbouring a hepatocyte-specific ER $\alpha$  deletion (LERKO) were crossed with LDLR<sup>-/-</sup> mice. Our results demonstrated that, whereas liver ER $\alpha$  is dispensable for the E4 beneficial actions on obesity and atheroma, it is necessary to prevent steatosis in mice. Overall, these findings suggest that E4 could prevent metabolic, hepatic and vascular disorders occurring at menopause, extending the potential medical interest of this natural estrogen as a new hormonal treatment.

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### **Pre-Menopausal Breast Fat Density Might Predict MACE During 10 Years of Follow-Up: The BRECARD Study**

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Objectives: This study sought to determine whether the breast gland adipose tissue is associated with different rates of major adverse cardiac events (MACEs) in pre-menopausal women. Background: To our knowledge, no study

investigated the impact of breast adipose tissue infiltration on MACEs in pre-menopausal women. Methods: Prospective multicenter cohort study conducted on pre-menopausal women >40 years of age without cardiovascular disease and breast cancer at enrollment. The study started in January 2000 and ended in January 2009, and the end of the follow-up for the evaluation of MACEs was in January 2019. Participants underwent mammography to evaluate breast density and were divided into 4 groups according to their breast density. The primary endpoint was the probability of a MACE at 10 years of follow-up in patients staged for different breast deposition/adipose tissue deposition. Results: The propensity score matching divided the baseline population of 16,763 pre-menopausal women, leaving 3,272 women according to the category of breast density from A to D. These women were assigned to 4 groups of the study according to baseline breast density. At 10 years of follow-up, we had 160 MACEs in group 1, 62 MACEs in group 2, 27 MACEs in group 3, and 16 MACEs in group 4. MACEs were predicted by the initial diagnosis of lowest breast density (hazard ratio: 3.483; 95% confidence interval: 1.476-8.257). Further randomized clinical trials are needed to translate the results of the present study into clinical practice. The loss of ex vivo breast density models to study the cellular/molecular pathways implied in MACE is another study limitation. Conclusions: Among pre-menopausal women, a higher evidence of adipose tissue at the level of breast gland (lowest breast density, category A) versus higher breast density shows higher rates of MACEs. Therefore, the screening mammography could be proposed in overweight women to stage breast density and to predict MACEs.