Menopause and Its Cardiometabolic Consequences: Current Perspectives

This special issue of Current Vascular Pharmacology (CVP) is dedicated to the menopause. CVP provides current knowledge with regard to the treatment of vascular disease, bridging the gap between ongoing research and clinical practice. This special issue consists of updated, comprehensive and clinically-oriented reviews on the association between menopause, either occurring at a normal age or prematurely, and cardiovascular (CV) disease (CVD). Menopausal hormone therapy (MHT) is also considered.

Tsiligiannis et al. [1] refer to premature ovarian insufficiency (POI, defined as age of menopause <40 years) and its long-term health consequences (such as CV, bone, psychological, neurological and fertility), as well as the ability to reverse any changes with MHT. The authors identify areas where research is needed to ensure optimal management of these patients. Perimenopause and its CV consequences are covered by Stevenson et al. [2]. The authors consider changes in CVD risk, such as dyslipidaemia, deranged glucose homeostasis, arterial hypertension and body fat redistribution, that occur as the result of the loss of ovarian function during perimenopause [2]. The pathophysiology of this cluster of metabolic abnormalities, the so called metabolic syndrome (MetS), in the postmenopausal period, is analysed by Mumusoglu and Yildiz [3]. The authors address the issue whether menopause (either early or at an expected age) has an independent effect on the risk of MetS as a whole or its individual components. They also refer to MetS-associated risks, such as type 2 diabetes mellitus (T2DM) and CVD, during menopause. The former risk is analysed by Paschou et al. [4]. The authors consider the risk factors leading to T2DM in women with T2DM, as well as to the optimal management of T2DM during menopause [4].

MHT constitutes the cornerstone of treatment of symptoms related to oestrogen deficiency (mainly vasomotor ones) [5, 6]. After the publication of the Women’s Health Initiative and the ensuing scepticism regarding MHT [7], evidence during the last decade has restored our knowledge on this topic. In this context, Anagnostis et al. [8] present epidemiological data on the association between menopause and CVD risk and the effect of MHT on this risk. The authors also comment on the distinct effect in terms of oestrogen dose, route of administration, combination with progestogen, as well as the type of progestogen used. Optimal guidance with respect to MHT regimen, on an individualized basis, taking risks and benefits into consideration, is provided. In cases in which MHT is contra-indicated, a non-hormonal therapeutic strategy for the management of vasomotor symptomatology is suggested by international guidelines [5, 6]. Mareti et al. [9] refer to this alternative, widely prescribed regimen, which includes selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, gabapentin, pregabalin, clonidine and phytoestrogens. The authors comment on the risks and benefits of this therapeutic strategy.

Particular interest is paid to some not so well-described issues, such as CVD risk associated with polycystic ovary syndrome (PCOS) [10], as well as and non-alcoholic fatty liver disease (NAFLD) during menopause [11]. Lambrinoudaki et al. [10] refer to CVD risk in postmenopausal women with a history of PCOS. It is well-known that PCOS is associated with increased prevalence of traditional CVD risk factors and predisposition to develop T2DM [12]. However, it has not been established whether a history of PCOS during a woman’s reproductive life (also taking the difficulty of its definition in the postmenopausal population into account) independently increases CVD risk during menopause. The authors discuss epidemiological evidence from studies referring both to clinical and subclinical CVD in this population [10].

NAFLD has been recognized as an epidemic that is independently associated with increased risk of CVD [13]. Venetsanaki et al. [11] report epidemiological data on the prevalence of NAFLD in postmenopausal women, as well as on the risk and underlying pathogenetic mechanisms for the development of non-alcoholic steatohepatitis (NASH). The authors specifically refer to the effect of menopause per se on the development of both NAFLD and NASH, and their long-term health consequences, such as T2DM and CVD. The authors also consider the evidence concerning the effect of MHT on NAFLD [11].

Muscogiuri et al. [14] refer to the CV risks and benefits of calcium and vitamin D supplementation, which are widely prescribed for the treatment of osteoporosis. The authors provide experimental data, referring to the molecular mechanisms underlying these effects. They also consider evidence from observational and interventional studies regarding the effect of vitamin D and calcium supplementation on CVD risk factors and events.
When a woman enters menopause, she is faced with a plethora of metabolic derangements associated with oestrogen loss. More specifically, she adopts a more atherogenic lipid profile characterized by an increase in total cholesterol, low-density lipoprotein cholesterol, triglycerides and apolipoprotein B concentrations, as well as a decrease in high-density lipoprotein cholesterol concentrations, during menopausal transition [15, 16]. She is also characterized by increased visceral adiposity contributing to insulin resistance and risk of MetS [17, 18]. With regard to arterial hypertension, conflicting data exist [18, 19], but, on a pathogenetic basis, it has been shown that the decline in oestrogen promotes the production of vasoconstrictors (e.g. endothelin and angiotensinogen) and greater sympathetic activity [20].

It remains to be established whether transition to menopause is associated with a higher risk of CVD events or if this is a consequence of the ageing process. Current data are insufficient to support an independent association between transition to menopause and increased risk of CVD events. Robust evidence is also lacking with respect to PCOS-associated CVD risk after menopause. Even though some meta-analyses support such a risk, this is lower than what could be estimated by the accumulation of CVD risk factors during the reproductive years [10, 12]. Contributory factors to this phenomenon could be the heterogeneity of PCOS definition in postmenopausal women, studies with small sample sizes and the amelioration of menstrual pattern with ageing [10, 12]. Therefore, we need longitudinal high-quality prospective studies to establish an independent association between menopause per se and CVD risk, by comparing well-defined pre- and post-menopausal women of the same age. This should also be the case for PCOS women after menopause.

The association of transition to menopause and increased CVD risk seems to be more evident for POI and early menopause. Two meta-analyses have shown that POI is associated with increased risk of CVD events, mainly coronary heart disease (CHD), mortality [pooled relative risk (RR) 1.48; 95% confidence interval (CI) 1.02-2.16 [21] and hazard ratio: 1.61 (95% CI 1.22-2.12) [22]. This has also been shown for women who enter menopause at an age <45 years [RR for fatal and non-fatal CHD 1.50 (95% CI 1.28-1.76) and for total CVD 1.19 (95% CI 1.08-1.31). However, no increased risk has been shown for stroke [23]. With regard to other cardiometabolic consequences, a recent meta-analysis showed an association with higher risk of T2DM both for early menopause and POI [odds ratio1.53 (95% CI 1.03-2.27) and 1.12 (95% CI 1.01-1.20), respectively] [24].

It is conceivable that MHT mitigates the cardiometabolic consequences of menopause, especially for early menopause and POI. Amelioration of the lipid profile and glucose homeostasis has been shown in many studies, with some differences depending on the dose and route of oestrogen administration, as well as the type and dose of progestogen used [5, 6]. Future comparative studies should assess CVD risk reduction with different MHT regimens, especially for women with a diagnosis of early menopause and/or POI.

REFERENCES


Panagiotis Anagnostis
(Guest Editor)
Unit of Reproductive Endocrinology,
1st Department of Obstetrics and Gynecology,
Aristotle University of Thessaloniki,
Thessaloniki,
Greece
E-mail: anagnwstis.pan@yahoo.gr

Dimitrios G. Goulis
(Guest Editor)
Unit of Reproductive Endocrinology,
1st Department of Obstetrics and Gynecology,
Aristotle University of Thessaloniki,
Thessaloniki,
Greece
E-mail: dimitrios.goulis@gmail.com