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ESC REPORT

Cardiovascular health after menopause transition, pregnancy disorders, and other gynaecologic conditions: a consensus document from European cardiologists, gynaecologists, and endocrinologists

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Women undergo important changes in sex hormones throughout their lifetime that can impact cardiovascular disease risk. Whereas the traditional cardiovascular risk factors dominate in older age, there are several female-specific risk factors and inflammatory risk variables that influence a woman's risk at younger and middle age. Hypertensive pregnancy disorders and gestational diabetes are associated with a higher risk in younger women. Menopause transition has an additional adverse effect to ageing that may demand specific attention to ensure optimal cardiovascular risk profile and quality of life. In this position paper, we provide an update of gynaecological and obstetric conditions that interact with cardiovascular risk in women. Practice points for clinical use are given according to the latest standards from various related disciplines (*Figure 1*).

Keywords Coronary artery disease • Ischaemic heart disease • Menopausal hormone therapy • Female-specific risk factors • Hypertensive pregnancy disorders • Menopause • Transgender • Sexual health women

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Abbreviations

ACOG, American College of Obstetricians and Gynaecologists
ADA, American Diabetes Association
AF, atrial fibrillation
BP, blood pressure
CAC, coronary artery calcium
CAD, coronary artery disease
CEE, conjugated equine oestrogens
CI, confidence interval
CIMT, carotid intima media thickness
CVD, cardiovascular disease
CT, computed tomography
ELITE, Early vs. Late Intervention trial With Estradiol
ESC, European Society of Cardiology
ESHRE, European Society of Human Reproduction and Embryology
HPD, hypertensive pregnancy disorders
HR, hazard ratio
HRT, hormone replacement therapy
IHD, ischaemic heart disease
MI, myocardial infarction
MINOCA, myocardial infarction with no obstructive coronary artery
MHT, menopausal hormone therapy
MPA, medroxyprogesterone acetate
NETA, norethisterone acetate
OCP, oral contraceptive pills
OGTT, oral glucose tolerance test
PCOS, polycystic ovarian syndrome
POC, progestin-only contraceptives
POI, premature ovarian insufficiency
PPCM, peripartum cardiomyopathy
PVD, peripheral vascular disease
RRSO, risk-reducing salpingo-oophorectomy
SCAD, spontaneous coronary artery dissection
TTS, Takotsubo syndrome
VTE, venous thromboembolism
WHI, Women's Health Initiative

Preamble

This consensus document provides a summary of the views of an expert panel organized by the Task Force on Gender of the European Society of Cardiology (ESC) and an ad hoc multidisciplinary ESC working group on Women's Health in Menopause. It is compiled in collaboration with experts from the International, European, British and Dutch Menopause Societies. Formal approval was provided by the ESC Clinical Practice Guidelines Committee. The writing task force members provide declaration of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. This document provides guidance to the clinical community on diagnostic approach and the management of cardiovascular health during menopause transition, after pregnancy disorders, and other gynaecologic conditions based on existing evidence and the best available current practice.

Introduction

Menopause is an important stage in women's lives, affecting many physical and social changes. The mean onset of menopause is 51 years, but there is substantial inter-individual variation, ranging between 40 and 60 years.[1] Oestrogens regulate vascular reactivity, blood pressure (BP), endothelial function and cardiac remodelling.[2–4] Alterations in oestrogen levels also affect the immune system, which is closely connected to vascular function and ageing.[5,6] After menopause, traditional cardiovascular risk factors are adversely affected particularly hypertension.[7–10]

Since the first ESC consensus paper on the management of cardiovascular risk in perimenopausal women was published in 2007, we have greater understanding on the role of female-specific risk factors for cardiovascular disease (CVD).[11] Our current knowledge of the typical patterns of ischaemic heart disease (IHD) in younger and middle-aged women helps to better diagnose and treat symptomatic women within this age group.[12–15] In addition, the growing number of fertile women with stable and unstable IHD requires specific knowledge and attention from both the cardiology and gynaecology communities.

Although sex-specific risk variables related to hormonal and reproductive status are associated with CVD risk, the justified weighting of these variables remains to be elucidated. When considering all age groups together, they do not seem to alter 10-year risk estimation.[16,17] However, when focusing on younger patients (<55 years), assessment of female-specific risk variables may help to identify women at premature higher risk.[18] The strongest predictors are hypertensive disorders of pregnancy (HPD) and low birth weight, with a two-fold higher IHD risk, which is mediated by hypertension.[19–21]

Epidemiology of cardiovascular disease in women

Ischaemic heart disease is the most important cause of CVD mortality in women worldwide. The regions with the highest age-standardized prevalence of IHD are Eastern Europe, North Africa and Middle East, and Central Europe, while a lower risk of CVD is noted in Chinese and South Americans.[22–25] Most recent European data show that IHD and stroke account for 82% of disability-adjusted life years due to CVD in ESC member countries.[26] Although there are small declines in the age-standardized incidence and prevalence rates of IHD and stroke over the last 27 years, rates for peripheral vascular disease (PVD) and atrial fibrillation (AF) remain stable. As most IHD data are still largely derived from men, the true IHD incidence in women may be underestimated.[15] Risk calculations are mostly based on mortality and not total IHD rates for which women tend to have higher rates of non-fatal events.[27] In addition, women have a lower income and socio-economic status compared to men, which contributes to a lower health status in general.[28]

Although classic type 1 myocardial infarction (MI) occur three times more commonly in men than in (elderly) women, the number of women under 65 years with MI is gradually increasing.[29,30] Especially, the number of type II MIs with no obstructive coronary arteries (MINOCAs) and spontaneous coronary artery dissections

(SCADs) are more prevalent in younger women.[31–33] It is estimated that up to 30% of MI in women <60 years are caused by a SCAD.[32] In contrast, most women diagnosed with a Takotsubo syndrome (TTS) are post-menopausal and over sixty.[34] Altered sex hormone levels, especially an oestradiol deficiency, have thus far not been identified as a risk factor for TTS[35] Mental stress is more related to IHD caused by coronary vascular dysfunction and MINOCA than to obstructive coronary artery disease (CAD), which underscores important gender differences in coping with stress.[36,37]

Menopause, cardiovascular disease risk factors, and ischaemic heart disease

Obstructive CAD occurs 7–10 years later in women than in men, with women having fewer focal coronary artery stenoses at all ages.[38] Women have a lower plaque burden, fewer vascular calcifications, a more diffuse pattern of atherosclerosis and, more often, soft plaques and erosive lesions compared to men.[39–43] Coronary vasomotor disorders, such as coronary artery spasm and/or coronary microvascular dysfunction represent a major cause of IHD in middle-aged women.[15,44–46] These can be present with or without non-obstructive CAD. In a sub-analysis of the ISCHEMIA trial, women have more frequent angina with less extensive CAD and less severe ischaemia than men.[47] This was also shown in the large CorMICA trial.[48] These findings confirm important sex differences in the complex relationships between angina, atherosclerosis, and ischaemia.[49]

Lower oestrogen levels after menopause are related to altered vascular function, enhanced inflammation, and up-regulation of other hormonal systems such as the renin–angiotensin–aldosterone system, the sympathetic nervous system, and reduced nitric oxide-dependent vasodilation.[8,9,50,51] Healthy endothelium is sensitive to the vasodilator properties of oestrogens, but this reverses when vascular stiffness and atherosclerotic disease develops over time.[52,53] While CVD risk increases with the menopause, this cannot be distinguished from ageing.[54] The Women's Ischemia Syndrome Evaluation study found that the presence of cardiovascular risk factors accounted for comparable CAD lesions among pre- and post-menopausal women.[55] A validated tool to measure CVD risk in middle-aged women is to assess the coronary artery calcium (CAC) score with computed tomography (CT) scanning, having a higher prognostic value than in men.[43] It is recommended to assess the CAC score in symptomatic women and those at intermediate cardiovascular risk.[43,47]

The decline in endothelial function starts in early menopause even before signs of subclinical atherosclerosis are present.[56,57] This mechanism may be involved in the pathophysiology of 'undetermined' chest pain and dyspnoea, which is often labelled as 'stress' or to 'menopausal symptoms'. However, women with 'undetermined' chest pain syndromes have a two-fold increased risk of developing an IHD event in the following 5–7 years.[58,59] The changing hormonal milieu is associated with alterations in body composition. Fat mass increases predominantly in the central and visceral regions, while lean mass decreases after menopause.[60] Visceral adipose tissue secretes inflammatory cytokines such as tumour necrosis factor-α, interleukin-6, and retinol-binding protein-4. The efflux of free fatty acids to the liver generates reactive oxygen species. Chronic inflammation and oxidative stress respectively increase insulin resistance.[61] Animal studies indicate that post-gonadectomy oestrogen decline is associated with an impairment of pancreatic β-cell function.[62] In clinical practice, post-menopausal women have 2–3 times higher prevalence of metabolic syndrome, compared to similar aged premenopausal women.[63]

Menopause transition results in lipid profile changes, with a 10–15% higher LDL-cholesterol and triglyceride levels and slightly lower HDL cholesterol levels.[64] The sharp rise in BP after menopause may be both a direct effect of hormonal changes on the vasculature and metabolic changes with ageing.[65–70] Hypertension is a critically important risk factor that affects women in the early post-menopausal years and is often poorly managed.[10,71,72] Recent data from Canada report a worsening of hypertension awareness and treatment over the past decade, especially in women.[73] In all, 30–50% of women develop hypertension (BP >140/90 mmHg) before the age of 60 and the onset of hypertension can cause a variety of symptoms, such as palpitations, hot flushes, headaches, chest pain, pain between the shoulder blades, tiredness and sleeping disturbances, which are often attributed to menopause.[74–76] Sodium sensitivity increases during menopausal transition, frequently leading to intermittent fluid retention (oedema of the legs, hands, and lower eyelids).[77–80] Physicians should intensify the detection of hypertension in middle-aged women, especially after HPD and pre-eclampsia.[81,82] Systolic BP is the most important arbiter of risk with ageing and results in greater vascular and myocardial stiffness in women than in men,[83–85] an important factor in why heart failure with preserved ejection fraction dominates in older women.[86] Sex differences in heart failure have been recently described, hence our focus on IHD.[87,88]

Immune reactivity increases in women during and after menopause transition.[89,90] Autoimmune rheumatic and endocrine disorders such as rheumatic arthritis, systemic lupus erythematosus, antiphospholipid syndrome, Sjøgren-syndrome, and thyroid disorders are more prevalent in women than in men and are associated with an increased CVD risk.[91–94] Patients with these disorders also have a higher clustering of traditional risk factors.[95] These risk variables should be taken into consideration when assessing individual risk around menopause.

Practice points

- Menopause is associated with central adiposity, insulin resistance, and a pro-atherogenic lipid profile
- Assess lipid levels and BP during menopause transition according to prevention guidelines[23]
- Regular control/self- measurement of BP is needed in women after HPD/pre-eclampsia
- Inflammatory co-morbidities increase CVD risk in women around menopause

Healthy lifestyle in menopause

The loss of oestrogen has been associated with reduced energy expenditure.[96] Lower oestrogen levels are associated with feeding behaviours and meal size, promoting hyperphagia and obesity.[60,97,98] Obesity is also associated with depression, which enhances food intake and sleep deprivation and reduces physical activity.[99] Effective management of vasomotor symptoms with menopausal hormone therapy (MHT) may reverse this.[100–102] Regular physical exercise has a beneficial effect on vasomotor symptoms and quality of life.[103–105] Although oestrogen therapy is not approved to treat perimenopausal depression, there is evidence that it has antidepressant effects and increases well-being in perimenopausal women.[106]

Improvement of quality of life enhances the ability to work. Women suffering from severe menopausal symptoms have an eight-fold increased risk of working disability, leading to lower productivity, more absenteeism, earlier termination of workforce participation, and a rise in employer and healthcare community costs.[107,108]

Practice points

- Adherence to a healthy lifestyle and diet with regular exercise are important factors in the optimal management of menopausal health[23]
- Menopausal complaints may interfere with working ability and need attention of employers and businesses

Vasomotor symptoms and cardiovascular disease risk

Women with severe menopausal symptoms have an unfavourable cardiometabolic profile and overactivity of the sympathetic nervous system compared to asymptomatic women.[109–115] Autonomic dysfunction enhances heart rate variability, which may result in symptoms of dyspnoea on exercise.[50] Increased sympathetic activity with disabling vasomotor symptoms is more often present in women after HPD.[116,117] In the Women's Health Initiative (WHI) observational study, women with severe symptoms of hot flushes and night sweats had a 48% higher risk of incident diabetes at follow-up.[118] They also have evidence of impaired endothelial function and increased subclinical atherosclerosis compared to women without vasomotor symptoms.[119–121]

Practice points

- Menopausal vasomotor symptoms can be associated with an unfavourable cardiovascular risk profile
- Autonomic dysfunction enhances heart rate variability after menopause.

Use of menopausal hormone therapy since Women's Health Initiative

Preliminary findings from the WHI reported a significant increase in IHD events with a combined MHT regimen of conjugated equine oestrogens (CEE) and medroxyprogesterone acetate (MPA) compared with placebo, but this was non-significant in the long-term follow-up.[122–124] In contrast, MHT with CEE alone resulted in a non-significant decrease in coronary events compared with placebo, especially in those initiating treatment below 60 years of age.[124,125] In a meta-analysis of 23 randomized clinical trials (RCTs) women initiating MHT treatment below 60 years of age or within 10 years of onset of menopause showed a significant reduction (>30%) of MI or cardiac deaths.[126] In the Danish national registry wherein almost 700 000 women were included, about a quarter of whom were current or past MHT users.[127] Overall, MI risk was not influenced by MHT use, but continuous combined oestrogen–progestogen appeared to increase the risk while a transdermal and vaginal oestrogen reduced the risk. The oestrogen used was almost universally oestradiol and vaginal oestrogen is 80% weaker than transdermal oestrogen. No differences in risk were seen between different progestogens, namely norethisterone acetate (NETA), MPA, or norgestrel. Further RCT data came from the Danish Osteoporosis Prevention Study (DOPS), which included over 1000 women in early post-menopause, randomised to oral MHT, oral oestradiol with or without NETA addition, or to no treatment.[128] Menopausal hormone use was associated with a significant reduction in a composite endpoint of MI, death or admission to hospital with heart failure compared with placebo [hazard ratio (HR) 0.48; 95% confidence interval (CI) 0.26–0.87].

A more recent meta-analysis of RCTs and data from a Finnish register confirm that initiating MHT (oral/transdermal) within 10 years of the onset of menopause significantly reduces MI and death around 50%, whereas discontinuation of MHT resulted in a transient increase in coronary death.[129–131] Thus, many studies following the initial WHI reports largely support a preventive effect of MHT on CVD. Recent MHT studies such as the Kronos Early Estrogen Prevention Study (KEEPS) and the Early vs. Late Intervention Trial with Estradiol (ELITE) have focused on recruiting mainly younger women (<6 years since menopause) using more favourable MHT regimens with surrogate cardiovascular endpoints.[132,133] The ELITE trial demonstrated less progression in carotid intima media thickness (CIMT) in younger women randomized to MHT compared to older women who were more than 10 years post-menopause ($P = 0.007$ for the interaction).[133] Possible mechanisms mediating the CVD benefit of MHT, especially transdermal, include increase in insulin sensitivity, improvement of the lipid profile and body composition, decrease in BP in case of drospirenone-containing regimens, and finally, a direct vasodilatory and anti-inflammatory effect.[51,134,135]

Breast cancer remains the main concern of MHT use. A recent meta-analysis of disparate studies with different entry criteria that included over 108 000 women diagnosed with breast cancer concluded that any MHT use would result in up to a two-fold increase in breast cancer risk.[136] This study was dominated by the Million Women Study (MWS) data, a study widely criticized on a number of methodological issues.[137,138] Few data were included from studies of

Table 1 Benefits and risks of menopausal hormone therapy (MHT) for women with age at menopause >45 years and of hormone replacement therapy (HRT) for women with early menopause (<45 years) and women with premature ovarian insufficiency (POI, <40 years)

Benefits	Risks
• MHT is the most effective treatment for menopausal symptoms.[100,102,103]	• Oestrogen-alone MHT increases the risk of endometrial cancer.[100,102,103]
• Systemic and topical (vaginal) MHT is effective for the genitourinary syndrome of menopause (GSM).[102,103,142]	• Oral, but not transdermal, MHT increases the risk of VTE.[100,141]
• MHT prevents postmenopausal bone loss.[101,128]	• The risk of stroke with MHT is slightly elevated, with less risk of transdermal preparations compared to oral therapy.[100–102,141]
• MHT may aid in the management of low mood that results from menopause.[102,106]	• MHT, especially when containing progestogens, may be associated with an increased risk of breast cancer. This depends on the type of progestogen and seems to dissipate when MHT is discontinued.[136–140]
• MHT may decrease CVD and all-cause mortality in women <60 years of age and within 10 years of menopause.	• MHT use over the age of 65 may cause deterioration in cognitive function.[101]
• Early initiation of MHT after menopause has the greatest benefit for cardiovascular health.[100,102,103]	• MHT is not recommended in women at high cardiovascular risk and after a previous CVD event.[100–102]
• In women with POI, the use of HRT until the average age of menopause is recommended for menopausal symptoms, CVD, osteoporosis, and cognitive decline.[143–146]	
• Short-term (up to 4 years) HRT in women after risk-reducing salpingo—oophorectomy (RRSO) does not increase the risk of breast cancer and reduces the long-term effects of early menopause.[147,148]	

modern MHT regimens with non-androgenic progestogens such as dydrogesterone and micronized progesterone.[136] The French E3N cohort study was not included, but showed a lower breast cancer risk in users of micronized progesterone and dydrogesterone.[139,140]

Modern MHT regimens contain lower doses of systemic and vaginal oestrogens.[101] Oral, but not transdermal, MHT increases the risk of venous thromboembolism (VTE).[141] Current evidence is summarized in *Table 1*.

Practice points

- MHT is indicated to alleviate menopausal symptoms
- MHT may be of potential prophylactic benefit in depression
- Doses and types of MHT regimens, and age at initiation are crucial for its safety
- Before starting MHT, assessment of cardiovascular risk factors should be performed
- Consider measuring CAC with CT when there is uncertainty on individual cardiovascular risk
- MHT is not recommended in women at high cardiovascular risk and after a CVD event
- Initiation of MHT is generally not advised in asymptomatic women

Premature ovarian insufficiency

Women with premature ovarian insufficiency (POI), defined as the loss of ovarian function before the age of 40, have a shorter life expectancy than women with a late menopause due to CVD and osteoporosis.[149–151] A meta-analysis showed an increased risk of CVD for women with POI, early menopause (age 40–44 years), and relatively early menopause (age 45–49 years).[152] Each year of early menopause was associated with a 3% increased risk of CVD.

Data regarding risk of stroke in early menopause and POI are conflicting.[143,150,153,154] A recent meta-analysis demonstrated an increased risk of stroke in both POI and early menopause, but not in women with relatively early menopause.[152] Adverse effects of POI and early menopause have been shown on lipid profile, body composition, systolic BP, insulin sensitivity, risk of metabolic syndrome, endothelial function, and inflammatory markers.[155–162] Women with an early menopause have a 12% higher risk of developing diabetes compared to women who experienced menopause at a later age.[163,164]

Although in non-human primate studies premature atherosclerosis was found in animal models of POI, this was not replicated in human studies on subclinical atherosclerosis as assessed by CIMT and CAC.[52,157,165] The lack of endogenous hormones after menopause and an underlying genetic predisposition to abnormal DNA repair may result in an accelerated general ageing phenotype, contributing to both early age at menopause and increased risk of CVD.[166] Genetically impaired DNA repair also contributes to higher risk for cancer and cardiac damage of cancer therapy and to a higher risk for peripartum cardiomyopathy (PPCM).[167,168]

Management of premature ovarian insufficiency

Prospective randomized data are lacking on the effect of hormone replacement therapy (HRT) as it is termed in women with POI, although most available evidence suggests a beneficial effect on CVD.[144,145,169,170] In women with POI, HRT is recommended until at least the average age of menopause.[146] This is supported by a recent meta-analysis which showed that the largest reduction in CVD incidence was in women with POI or early menopause who used HRT for at least 10 years.[152] Early initiation of HRT had the greatest reduction in CVD, highlighting the importance of timely diagnosis and treatment. Although combined oral contraceptive and HRT are both treatment options in women with POI, the use of HRT has a superior effect metabolically and on bone density.[171] The risks and benefits of HRT in women with POI and early menopause are different from those using MHT in peri- and post-menopause, and accurate individual counselling is therefore vital.

Practice points

- Early menopause is associated with higher risk of diabetes and CVD
- Women with POI and early menopause (<45 years) should have an assessment of their cardiovascular risk factors
- Women with POI are recommended to take HRT until the average age of menopause.[146]
- In women with early menopause, HRT should be considered on an individual basis
- A genetic predisposition to POI may also increase risk for cancer

Pregnancy-related disorders and cardiovascular disease risk

Recurrent pregnancy loss

Recurrent miscarriage or recurrent pregnancy loss, the preferred term by the European Society of Human Reproduction and Embryology (ESHRE), includes all pregnancy losses from the time of conception until 24 weeks of gestation.[172] Women with a history of two or more pregnancy losses, consecutive or not, appear to have an increased risk of IHD.[173,174] Cardiovascular disease and recurrent pregnancy loss share common risk factors such as smoking, obesity, and alcohol intake.[175,176] Moreover, endothelial dysfunction may be the underlying link between recurrent pregnancy loss, pre-eclampsia, intrauterine growth restriction, and future cardiovascular events.[177] Most studies have not found any relationship between recurrent pregnancy loss and stroke. However, data from Danish registers have shown that women from families with manifest atherosclerotic disease may be predisposed to pregnancy losses which may induce a greater risk of IHD and stroke.[178] Adjustment for antiphospholipid antibodies did not affect the estimates. A detailed family history for CVD and pregnancy history should therefore be an integral part of cardiovascular risk assessment in women.

Preterm delivery

Preterm delivery, defined as delivery before 37 weeks of gestation, affects about 10% of pregnancies in the US.[179] Lower rates are found in Europe, around 5–6%.[180] About 30–35% of preterm deliveries are medically indicated, most frequently due to pre-eclampsia and foetal growth restriction.[181] In the Nurses' Health Study II, preterm delivery was found to be independently predictive of CVD.[182] Women with a history of preterm delivery appear to have a two-fold increased risk of CVD in later life.[183] No specific follow-up for these women is recommended, except to optimize modifiable cardiovascular risk factors.[184] Small-for-gestational age newborns also increase maternal CVD risk.[185]

Hypertensive pregnancy disorders

HPD affect 5–10% of pregnancies worldwide. These include pre-existing (chronic) hypertension, diagnosed before pregnancy or before 20 weeks of gestation, and gestational hypertension developing after 20 weeks of pregnancy. Pre-eclampsia is now defined as persistent hypertension that develops after 20 weeks of pregnancy or during the post-partum period, associated with proteinuria and/or other maternal organ dysfunction.[186] Pre-existing hypertension is associated with increased risk of developing pre-eclampsia which may complicate up to 25% of cases. Pre-eclampsia is associated with a 4-fold increase in heart failure and hypertension and a 2-fold increased risk in IHD, stroke, and cardiovascular deaths.[21,187] This finding is now endorsed by the 2018 American College of Cardiology/American Heart Association cholesterol guidelines using a history of pre-eclampsia to justify statin prescription in asymptomatic middle-aged women with an intermediate 10-year risk.[188] Hypertensive complications in pregnancy are also a major risk factor for PPCM.[189,190] The risk of developing pre-eclampsia can be substantially reduced by a low dose of aspirin, 100 mg up to 150 mg/day in high-risk women, initiated from week 12 and continued to weeks 36–37 of gestation.[191,192]

Thirty percent of previously pre-eclamptic women have signs of CAC around the age of 50 years compared with 18% in a reference group.[193] Women with a history of HPD have increased risk of arterial stiffness and greater incidence of IHD, heart failure, aortic stenosis, and mitral regurgitation[20] and a three-fold higher risk for vascular dementia later in life.[194] Cardiovascular risk after HPD is largely, but not entirely, mediated by development of chronic hypertension.[195] The severity, parity, and recurrence of these HPD increases the risk of subsequent cardiovascular events.[196]

Although women after HPD are recognized as a higher risk population in the 2018 ESC arterial hypertension guidelines, there is still a need to establish systematic follow-up recommendations aimed at timely detection and control of all major risk factors.[23,197–199] Regular BP control is needed at least in the first post-partum months and use of eHealth technology with self-monitoring of BP with feedback to the primary care physician should be encouraged.[184]

Gestational diabetes mellitus

Gestational diabetes mellitus (GDM), defined as the first development of glucose intolerance during pregnancy, occurs in about 7% of pregnancies.[200] Although the carbohydrate intolerance of GDM frequently resolves after delivery, an estimated 10% of women with GDM will have diabetes mellitus soon after delivery with another at least 20% being affected by impaired glucose metabolism at post-partum screening. In the remaining women, 20–60% will develop type 2 diabetes mellitus later in life, often within 5–10 years after the index pregnancy.[201] Gestational diabetes is associated with a two-fold risk of future CVD events, with the risk being apparent within ten years after pregnancy.[202] There is also growing evidence that HPD are associated with increased risk of developing type 2 diabetes beyond sustained hypertension.[196] It is recommended that all women with GDM have a screening oral glucose tolerance test (OGTT) test at 4–12 weeks post-partum. The American Diabetes Association (ADA) and American College of Obstetricians and Gynaecologists (ACOG) recommend repeat testing every 1–3 years for women who had GDM and normal post-partum test results.[200,203]

Pregnancy in women at increased risk for IHD

Due to an increasing maternal age of pregnancy, a greater number of women are at risk for stable or unstable IHD during pregnancy.[192,204–206] In a large US cohort of 1.6 million pregnancies, HPD were associated with 1.4- to 7.6-fold higher risk of MI, heart failure, and stroke.[207] Mortality data have been reported as high as 5–10% in elderly cohorts.[208,209] In the European registry of pregnancy and cardiac disease (ROPAC), women with IHD accounted for about 4% of 5739 included pregnancies.[210] Although these women were typically older and more often multiparous, no mortality was observed and in only 4%, heart failure was reported. Recent findings in a UK cohort of 79 women with pre-existing IHD reported only 6.6% adverse cardiac events without any maternal deaths.[211] However, the rates of adverse obstetric and neonatal events were increased, with an occurrence rate of pre-eclampsia in 14%, preterm delivery in 25%, and small-for-gestational age in 25%. Foetal risk may therefore be higher than maternal risk in women with known IHD. In women with a prior SCAD, a new pregnancy seems to be well tolerated without evidence of an increased risk of SCAD recurrence.[212]

Practice points

- Pregnancy history should be an integral part of cardiovascular risk assessment
- Women after HPD, especially after pre-eclampsia/HELLP, are at increased risk of developing premature hypertension and CVD.
- Women with GDM should have a screening OGTT test at 4–12 weeks post-partum, and this test should be repeated every 1–3 years.[200,203]
- Consider secondary prevention guidelines in women after HPD and GDM
- Consider self-monitoring of BP at follow-up in women after HPD

Hormonal dysregulation and cardiovascular disease risk

Polycystic ovarian syndrome and cardiovascular disease risk

Polycystic ovarian syndrome (PCOS) affects 6–16% of women with marked ethnic variation.[213] Central to the disorder are dysovulation, hyperandrogenism, and metabolic disturbances, particularly insulin resistance. Diagnosis is most commonly based on the Rotterdam criteria, requiring 2 out of 3 of oligo-or anovulation, clinical or biochemical evidence of hyperandrogenism, and polycystic ovary(-ies) on ultrasound.[214] PCOS has been associated with many risk factors for CVD including impaired glucose tolerance, dyslipidaemia, hypertension, metabolic syndrome, type 2 diabetes and raised inflammatory markers.[215–219] Young women with PCOS have evidence of endothelial dysfunction and subclinical atherosclerosis, as assessed by CIMT and CAC scores.[220–223] Although most women are diagnosed in their 20s and 30s, long-term follow-up studies are limited. The natural progression of cardiovascular risk factors has been hampered by confounders like obesity and the heterogeneous criteria and various phenotypes of the disorder. Several cardiovascular risk factors associated with PCOS seem to ameliorate over time.[224] In a meta-analysis performed for the development of the ESHRE/American Society for Reproductive Medicine guidelines on PCOS, and restricted to only higher quality studies, no increased risk of MI, stroke or CAD was found in women with PCOS compared to controls.[225–227] Another meta-analysis confirmed that the risk of CVD was increased in women of reproductive age, but not in peri- or post-menopausal women.[228] This may be related to timely modification of cardiovascular risk factors, a cardio-protective effect from a delayed menopause, or other unknown (genetic) factors.[229–232]

It is recommended that all women with PCOS should have an assessment of BP and OGTT, and a fasting lipid profile.[227,233] Dietary and lifestyle education is recommended and as women with PCOS have increased risk of diabetes and HPD, they should be offered screening for GDM in pregnancy.

Other chronic gynaecological conditions associated with cardiovascular disease risk

There is considerable overlap between gynaecologic conditions and chronic disease, particularly CVD. In addition to the gynae-endocrine disorders (e.g. PCOS, POI, hypogonado-trophic hypogonadism), endometriosis, uterine fibroids, and hysterectomy <50 years with ovarian conservation have all been associated with increased CVD risk.[234–237] Endometriosis is associated with enhanced inflammation, oxidative stress, and an adverse lipid profile.[238] Although causal relationships have not been proven, the gynaecological and reproductive history may provide important insights into potential long-term health risks in women for which a more systems-wide approach may be beneficial.

Practice points

- Several chronic gynaecologic conditions may be associated with an adverse CVD risk
- Women with PCOS should have a cardiovascular risk assessment with measurement of BP, OGTT, fasting lipid profiles, and screening for GDM in pregnancy.[233]
- Dietary and lifestyle modifications should be extra emphasized in women with PCOS

Contraception in women at high cardiovascular disease risk

Combined oral contraceptive pills (OCP) carry an increased risk for venous thrombosis, MI, and stroke, which is significantly enhanced by cigarette smoking.[239,240] OCPs containing high-dose ethinyl oestradiol have been associated with increased BP. This is due to increased production of angiotensinogen/angiotensin II and related to OCP formulation/dose. In the Danish Cohort Study, use of combined OCPs containing 20 µg of ethinyl oestradiol increased the relative risk of both thrombotic stroke and MI by 1.60 (95% CI 1.37–1.86) and 1.40 (95% CI 1.07–1.81), respectively, in comparison to non-OCP users.[241] Thus, OCP's containing ethinyl oestradiol should be avoided in women with a history of VTE, stroke, CVD, or any other PVD. The ACOG has developed guidelines for use of OCP in women at elevated cardiovascular risk.[242] In healthy women below 35 years with pre-existing hypertension, OCP can be used. If BP remains stable after a few months, OCP may be continued.[243] Use of OCP is contraindicated in women older than 35 years who smoke, have severe dyslipidaemia, or obesity.[244] Progestin-only contraceptives (POCs) are not associated with increased vascular risk (arterial or venous), although evidence suggests that MPA use may be associated with a slightly increased risk.[241,245] In women at CVD risk, POC administered by oral, sub-cutaneous, or intra-uterine routes can be prescribed.[246,247]

Practice points

- Combined OCP should be avoided in women with a history of VTE, stroke, CVD, or any other PVD
- Use of OCP is contraindicated in 35 plus women who smoke and in women with severe dyslipidaemia or obesity
- POCs, administered by oral, sub-cutaneous, or intra-uterine routes can be prescribed in women at elevated cardiovascular risk

Women with heart disease and abnormal uterine bleeding

With the rise in the number of premenopausal women in need of any kind of anticoagulant therapy and/or (dual) antiplatelet therapy including the growing number of young women with congenital heart disease, established IHD and AF, the prevalence of abnormal uterine bleeding is increasing.[248] The levonorgestrel-releasing intra uterine system can be an effective and safe option in these women, both as a contraceptive and for treating heavy menstrual bleeding.[247]

Practice point

- Abnormal uterine bleeding should be monitored in young women in need of anticoagulant and/or antiplatelet therapy, in collaboration with a GP or gynaecologist

Cardiovascular disease risk in women with BRCA 1/2 mutations and after breast cancer

Breast cancer affects an estimated 2.1 million women worldwide each year.[249] Early detection and improved treatment have increased survival rates; however, breast cancer remains the most common female cancer in Europe.[250,251] The majority of hereditary breast cancers occur due to mutations in the BRCA 1 and 2 genes, which are also associated with ovarian cancer. Due to the lack of effective screening methods, a risk-reducing salpingo-oophorectomy (RRSO) is recommended at age 35–40 years in $BRCA_1$ and age 40–45 years in $BRCA_2$ mutation carriers.[252] Women with $BRCA_{1/2}$ mutations may be at increased risk for CVD by iatrogenic early menopause and a potentially elevated CVD risk as a result of abnormal ability of DNA repair.[253–255] Moreover, BRCA1 is now considered as an important gatekeeper of cardiac function and survival after ischaemia and oxidative stress, making mutation carriers more susceptible for the occurrence of heart failure after an MI.[167] Thus far, data on risk of BRCA ½ mutation carriers for cardiotoxicity after chemotherapy are conflicting.[256–258]

Hormone replacement therapy after risk-reducing salpingo-oophorectomy

Women who have an early or premature surgical menopause often have debilitating menopausal symptoms. Studies assessing the safety of HRT in this population are limited. A meta-analysis of 3 cohort studies with 1100 $BRCA_{1/2}$ mutation carriers showed no increased risk of breast cancer with HRT after RRSO (HR 0.98, CI 0.63–1.52).[147] $BRCA_2$ mutation carriers have higher rates of

oestrogen and progesterone-positive tumours and may have a different level of risk with HRT. Short-term (2.8–4.4 years) HRT appears to be safe with no increase in breast cancer risk.[148] Current guidelines of the European Menopause and Andropause Society (EMAS) and International Gynaecologic Cancer Society (IGCS) recommend that $BRCA_{1/2}$ mutation carriers who have had a RRSO should be offered HRT up until the natural age of menopause (51–52 years).[259] As in the general menopause population, oestrogen therapy alone appears to have a different effect compared to combined oestrogen and progestogen therapy.[147] In a prospective analysis of 872 $BRCA_1$ mutation carriers, there was no overall difference in breast cancer risk between HRT users and non-users; however, the estimated 10-year risk of breast cancer differed significantly between women using oestrogen-only and combined oestrogen and progestin replacement therapy (12% vs. 22%; $P = 0.04$).[260]

MHT after breast cancer

Management of menopause symptoms should be individually tailored and carried out in close liaison with the oncologist. Lifestyle alterations and non-hormonal treatment options, such as clonidine, SSRIs, venlafaxine, gabapentin, and pregabalin are recommended first line in these women.[142,261–263] Although these are effective for mild-to-moderate vasomotor symptoms, their use is often limited by side effects.[262] SSRIs such as fluoxetine and paroxetine should be avoided in women on tamoxifen due to inhibition of the CYP2D6 enzyme pathway which may reduce its efficacy. Complementary therapies such as isoflavones, soy, red clover, and black cohosh are not recommended as they may have oestrogenic effects and there is a lack of data regarding safety and efficacy, although some may have SERM-type effects (NICE, NG101).

Data regarding the safety of MHT in breast cancer survivors are limited, as several studies were terminated early due to an increased risk of recurrence in the interim analysis.[264,265] Current UK guidance suggests to reserve MHT for those with refractory symptoms after other non-hormonal treatments have been unsuccessful (NICE NG 101). Other guidelines advise against MHT in oestrogen receptor-positive breast cancer.[142,266]

Practice points

- $BRCA_{1/2}$ gene mutation carriers and women treated for breast cancer have increased risk of CVD. Check for their cardiovascular risk factors.
- Short-term (up to 4 years) HRT in women after RRSO does not increase breast cancer risk and reduces the long-term effects of early/premature menopause.
- If breast cancer risk is low, HRT until natural age of menopause is advised.
- The use of MHT in women after breast cancer should be individualized with expert advice for menopausal treatment

Sexual health, menopause, and cardiovascular disease

Sexual health concerns are common in patients with all types of CVD.[267–270] Approximately 60–90% of patients with chronic heart failure report having sexual problems, but fewer than 15% have had a consultation with their physician in matters related to sex and intimacy.[268] For women, the most frequently reported problems are diminished feelings of sexual arousal and enjoyment, leading to difficulties in experiencing orgasm, pain during intercourse, and, with sexual activity being less pleasurable and satisfactory, to decreased desire for sexual activity.[267] Whereas in men CVD coexists with erectile dysfunction, for which endothelial dysfunction is the common underlying pathophysiological mechanism, a definitive pathophysiological link between sexual problems in women and CVD is less clear.[271–274] However, endothelial dysfunction is unrelated to sexual problems in women with CVD.[275] Sexual problems in women related to low sexual arousal are very common in healthy women.[276,277] Theoretically, if the heart supplies less blood to the vaginal wall, labia, and clitoris during sexual stimulation, this may lead to reduced capacity to become genitally aroused, resulting in orgasm problems, dyspareunia, and decreased sexual desire. In the first large study investigating the impact of somatic and psychological comorbidities on sexual function in women, CVD was specifically related to lubrication difficulties.[278] Psychological concerns about whether it is safe to be sexually active after a cardiac event may lead to avoidance of physical affection and intimacy.[279] Other symptoms of CVD such as chest pain, shortness of breath, and fatigue may interfere with engaging in and enjoyment of sexual activities. Side effects of medication may also disrupt sexual arousal.

In recent years, a limited number of medical treatment options for women with sexual problems have become available. Flibanserin, a serotonin 5-HT-receptor agonist marketed for women with low sexual desire, is associated with considerable risk of syncope and hypotension, and is therefore unsuitable for women with CVD.[280] Bremelanotide, a melanocortin receptor agonist for the treatment of premenopausal women with low sexual desire, was approved in 2019. However, efficacy and safety of the drug in women with CVD are unknown. Although not evidence-based, a recent position statement advises testosterone therapy in post-menopausal women with low sexual desire, supported by measurement of testosterone concentrations in blood to monitor treatment response to prevent overuse.[281] Transdermal testosterone therapy is not associated with increases in BP, blood glucose, or HbA1c levels. However, its safety is not investigated in women at high CVD risk.

Practice points

- Sexual health and cardiovascular risk in women needs to be further investigated
- Transdermal testosterone therapy cannot be recommended in women with established CVD for lack of data

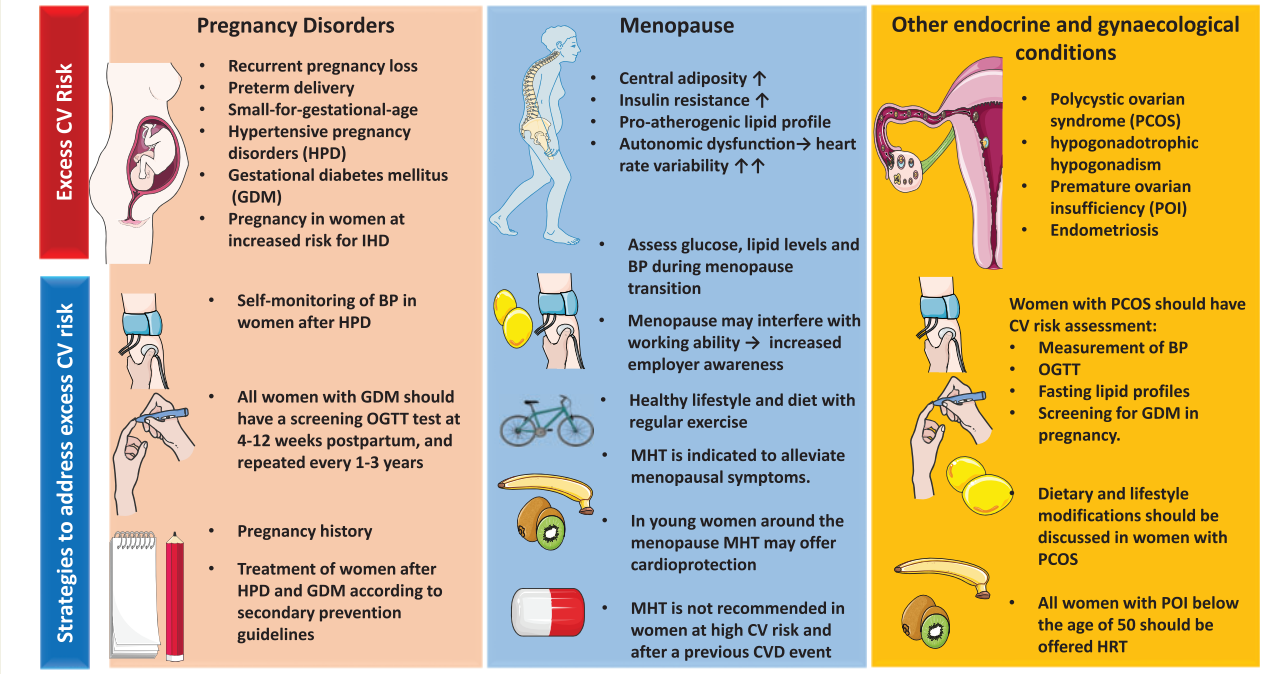

Figure 1 Female-specific risk factors and strategies for prevention. BP, blood pressure; CVD, cardiovascular disease; GDM, gestational diabetes mellitus; HPD, hypertensive pregnancy disorders; IHD, ischaemic heart disease; MHT, menopausal hormone therapy; OGTT, oral glucose tolerance test; PCOS, polycystic ovarian syndrome; POI, premature ovarian insufficiency.

Cardiovascular disease risks for cross-sex therapy in female transgender persons

Currently, the prevalence of transgender persons is 0.6% in adulthood.[282,283] Evidence-based recommendations for cardiovascular risk prevention are lacking, as treatment regimens vary globally.[284,285] Gender-affirming therapy, including sex hormones, enables a life in congruence with a personal gender identity, which significantly improves quality of life. Until recently, only VTE risk has been evaluated in transgender women (meaning persons assigned male at birth) undergoing oestrogen treatment. Other appearances of CVD have only been considered within the range of the cisgender population whose gender identity matches the sex that they were assigned at birth.[286–289] Current evidence in the ageing transgender population suggests that both transgender men and transgender women are more at risk for various manifestations of CVD compared to others.[290–294]

Transfeminine hormone therapy

In the late 1990s, reports showed an increase up to 20-fold in VTE with oral ethinyloestradiol and this led to cessation of the use of this medication in this context.[287] Since then, oestradiol has become the preferred oestrogen for the transfeminine treatment. The hyper-coagulable effect of oestrogen may be one of the mediators of the increased CVD risk in transgender women.[295] Transdermal oestradiol is therefore preferred in transgender females over 40–50 years to avoid the increased risk of a prothrombotic state by oral intake.[296] The VTE risk in transgender women, however, is different compared to cisgender women in whom this risk is mainly present in the first year of use and thereafter reduces over time.[141] In contrast, VTE risk in transgender women increases over time, with a 2-year and 8-year risk of 4.1 (95% CI 1.6–6.7) and 16.7 (95% CI 6.4–27.5) per 1000 person-years, respectively, compared to the reference population of men 3.4 (95% CI 1.1–5.6) and women 13.7 (95% CI 4.1–22.7).[293] Concomitant treatment of transgender women with androgen-lowering agents (e.g. spironolactone or cyproterone acetate) allows for administration of lower doses of exogenous oestrogen.[285,297]

Transgender women receiving hormonal therapy have no increased risk of MI but are at increased risk of stroke (127 per 100 000 person-years) and VTE (320 per 100 000 person-years). This is respectively 80% higher and 355% higher than in cisgender men.[293] In addition, concomitant use of tobacco and other negative lifestyle factors in transgender persons are disproportionally present.[298] Ischaemic stroke appears most pronounced after 6 years of continuous oestrogen use and continues to rise thereafter.

Cessation of cross-sex hormones is not an option for transgender persons. Therefore, they should always be encouraged to reduce modifiable lifestyle risks. The psychosocial benefits of hormone therapy with an improved body image may result in healthier lifestyle choices.

Practice points

- Transgender persons are at increased risk for CVD
- VTE risk in transgender women increases over time.
- Transdermal oestrogens are preferred over oral treatment

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