Women-specific predictors of cardiovascular disease risk - new paradigms

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ABSTRACT

Cardiovascular disease (CVD) remains a leading cause of morbidity and mortality in women in spite of the overall reduction in age-adjusted CVD mortality in the past few years. Although traditional risk factors for CVD are predictors of increased risk in both men and women, risk factors that are unique to women and related to their reproductive history have recently been considered to be important. The development of CVD in women may correlate with specific events taking place throughout a woman's obstetric and gynaecological history. Gynaecological conditions such as polycystic ovary syndrome, premature ovarian failure, surgical and spontaneous menopause, and conditions related to pregnancy, i.e. gestational diabetes, preeclampsia, intrauterine growth restriction, miscarriages, and preterm birth, may affect the onset, clinical features, and prognosis of CVD later in women's lives. These pathological conditions that develop during the fertile period of life or peri-menopause have been suggested to be early markers of future CVD; their presence presents a unique opportunity for the early identification of women who may be at an increased risk of CVD. The assessment of CV risk in women should not just focus on conventional risk factors but also on different aspects of the gynaecological history to allow specific preventive and therapeutic strategies to be established.
This paper reviews the various pathological conditions occurring in women during their fertile period of life and peri-menopause, which have been identified to potentially increase CVD risk.

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1. Introduction

Cardiovascular disease (CVD) is the leading cause of death in women in Europe; its incidence is much higher than any other cause of death, including breast cancer [1]. CVD and osteoporosis represent the two main pathologic conditions affecting postmenopausal women [2].

CVD prevalence in women after age 75 exceeds that reported for men. In addition, short- to medium-term mortality after acute myocardial infarction (AMI) is higher in women than in men [3] and the impact of classical CV risk factors is also likely to differ in men and women [4]. Recent studies have highlighted the need for a new, sex-tailored approach when evaluating predisposing factors and mechanisms leading to CVD in women, as there are differences in the pathogenesis and pathophysiology of CVD in men and women [5].

Several knowledge gaps have been identified regarding the pathogenesis and pathophysiological mechanisms of CVD in women, and there is a lack of availability of suitable diagnostic, prognostic, and therapeutic strategies in women. These gaps in knowledge are mainly derived from the fact that most of the studies dealing with these variables have been conducted with predominantly male subjects. Moreover, the erroneous perception among many physicians and the public in general that the risk of developing CVD is lower in women than in men has important negative clinical, social, and financial consequences [6,7]. Lack of awareness of their high CVD risk and the importance of both conventional and newer sex-specific risk factors is likely to be the worst "enemy" of a woman's health [8].

The importance of risk factors uniquely related to women's gynaecological history has only been realised recently [9] (Table 1).

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Table 1
Women-specific risk factors for Cardiovascular Disease.

- Polycystic ovaries (PCOS)
- Premature ovarian failure (POF)
- Menopause
- Surgical menopause
- Complications of pregnancy
  Gestational diabetes mellitus
  Preeclampsia
  Preterm birth
  Small for gestational age pregnancies (SGA)
  Miscarriage

Gynaecological conditions such as polycystic ovary syndrome (PCOS), premature ovarian failure (POF), surgical and natural menopause and obstetric conditions, such as complications of pregnancy, i.e. gestational diabetes (GD), preeclampsia, intrauterine growth restriction (IUGR), miscarriage, and preterm birth (PTB), may affect the onset, clinical features, and prognosis of CVD later in life. Data in recent years have suggested that these relatively frequent conditions taking place during the fertile years and around menopause represent early markers of future CVD and provide a unique opportunity for healthcare professionals to attempt early identification of women who may be at risk of developing CVD [8].

2. Women-specific risk factors for cardiovascular disease

2.1. Polycystic ovary syndrome

PCOS is one of the most common disorders occurring in the child-bearing years. It is a complex syndrome consisting of enlarged and micro-polycystic ovaries and clinical features characterised by both endocrinological and metabolic alterations involving both the hypothalamic-hypophysis-ovary-adrenal axis and adipose tissue. The syndrome is associated with psychosocial, reproductive, and metabolic abnormalities [10]. The most prevalent clinical features are menstrual irregularities, i.e. oligomenorrhea, amenorrhea, metrorrhagia, and infertility. PCOS is also characterised by hyperandrogenism (60% of cases) with hirsutism, acne, alopecia, and obesity (50% of cases). Some phenotypes of PCOS are characterised by the presence of insulin resistance (IR) with compensatory hyperinsulinaemia. Increased insulin circulating levels contribute further to the development of hyperandrogenism, inducing a vicious cycle that promotes disease progression [11].

In women affected by PCOS, IR and hyperandrogenism are associated with glucose intolerance and type 2 diabetes mellitus (T2DM). Legro et al. reported that the risk of T2DM in these patients is 5-fold higher than that in controls of the same age and weight [12]. PCOS is an independent risk factor for diabetes and also for hypertension, dyslipidaemia, obesity, and metabolic syndrome [13].

Pro-atherogenic dyslipidaemia, characterised by increased total cholesterol, low-density lipoprotein, and triglycerides with low levels of high-density lipoprotein, is present in PCOS together with abnormalities in fibrinolysis, hyperfibrinogenaemia, and arterial hypertension. >70% of women with PCOS have dyslipidaemia and 40% have metabolic syndrome [14,15].

In patients with PCOS, the presence of visceral obesity influences the production of pro-inflammatory cytokines, which in turn contribute to the development of subclinical inflammation and increase free radical production [16]. Collectively, all of these CV risk factors contribute in a synergistic way to the activation of the endothelium with increased intima-media carotid thickness [17] and the development of preclinical atherosclerosis in young women [13].

Furthermore, a high body mass index (BMI) in women with PCOS increased CVD risk 2-fold. However, PCOS is an independent risk factor for coronary heart disease (CHD) and stroke and may exert a causal effect on CVD [18].

In addition, PCOS is a common cause of infertility and spontaneous abortion which are predictive of future CVD. The percentage of women with PCOS who have miscarriages varies between 30 and 50% compared with 10–15% of healthy women [19]. All these pathological features promote coronary artery disease (CAD), stroke and CV mortality in women with PCOS in the peri-menopausal years [20]. Mazibrada et al. showed an association between proinflammatory markers i.e. hs-CRP and fibrinogen and anthropometric and lipid parameters in adolescent women with PCOS. These inflammatory markers might be useful to monitor normal-weight adolescent women with PCOS to prevent unfavorable changes in body mass and lipid profile [21].

2.2. Premature ovarian failure

POF, which affects 1% of women in the general population, is defined as loss of ovarian function before 40 years of age [22]. POF leads to early menopause and is associated with increased CVD events in predominantly white populations [23]. It has been reported that the earlier the time of onset of menopause, the greater the risk of poor CVD clinical outcomes [24].

POF has been shown to be associated with psychological distress, infertility, osteoporosis, autoimmune disorders, ischaemic heart disease (IHD), and increased risk for all-cause mortality [25]. The decrease in oestrogen levels associated with POF can lead to atherosclerosis, hypercholesterolaemia, and heart failure [26]. Identification of women with a history of early menopause offers a window of opportunity to implement interventions that may improve overall CV health during the postmenopausal years [27]. In the "Early Menopause Predicts Future Coronary Heart Disease and Stroke: The Multi-Ethnic Study of Atherosclerosis (MESA)" [23], women with a history of early menopause ($n = 693$) had worse CHD and impaired stroke-free survival. Both CHD-free and stroke-free survival were significantly lower in women with early menopause than in those women who went through menopause at a normal age. The risk for CHD and stroke also remained statistically significant after model adjustment for age and race/ethnicity, confirming that early menopause is independently and positively associated with an increased risk of stroke and CAD independent even of traditional CVD risk factors [23].

Other studies in Japan [28] and the Framingham cohort [29] have reported a 2-fold increased risk of stroke in women with menopause at ages <42 years as compared with women without early menopause. In the Framingham study, this increased risk persisted even when the sample was restricted to women who never smoked [30]. These data have been confirmed by a meta-analysis showing that women who experienced premature or early-onset menopause had a greater risk of CHD, CVD mortality and all-cause mortality [31].

It has also been demonstrated that cardiac autonomic function is impaired in patients with POF even in the absence of overt cardiac involvement and symptoms. Cardiac autonomic dysfunction may, therefore, be involved in the etiopathogenesis of CVD in women with POF [32].

2.3. Menopause

Menopause is a well-known CVD risk factor. Since the protective effect of endogenous oestrogens is lost. Women develop CVD later in comparison to men, mainly after menopause. The age of onset of menopause appears to influence the development of CVD and/or CVD risk factors. Early menopause leads to a higher incidence of CVD than later onset menopause [23,33]. Hormonal deficiency leads to abnormalities in different organs and systems, including the central nervous system, endothelium, bones and liver. During menopause, lipids shift towards a "proatherogenic" profile with an increase in circulating total cholesterol, LDL-cholesterol and triglycerides and a decrease in HDL-cholesterol [34,35]. Moreover, menopause promotes a change in body fat distribution, increasing visceral adiposity [36,37] and reduced insulin sensitivity with a risk of developing diabetes [38] and advancing the

development of metabolic syndrome. Menopause is an independent CVD risk factor [39]. Post-menopausal women are exposed to increased oxygen free radical production, which results in a pro-inflammatory state that favours blood hypercoagulability, atherogenesis, endothelial dysfunction, stroke [40] and hypertension [41,42]. The increase in peripheral resistance due to the vascular effects of oestrogen deficiency favours an increase in blood pressure [43,44] as well as the administration of oestradiol at physiological doses, improves blood pressure readings, confirming the importance of oestrogen deficiency in the pathogenesis of hypertension in the post-menopause

[43]. The contribution of oestrogen to the control of blood pressure during the fertile years involves several mechanisms. Oestradiol improves vascular compliance by inducing the synthesis of nitric oxide (NO) via NO-synthase and the release of NO at the endothelial level [44]. Oestrogen also inhibits the mechanisms of vascular smooth muscle (VSM) contraction including reduced expression and permeability of voltage-gated Ca^{2+} channels $[Ca^{2+}]i$, reduced protein kinase C activity and inhibited Rho-kinase expression/activity [45]. Oestrogen deficiency during menopause reduces vascular compliance and studies have shown a decrease in endothelium-mediated dilatation in perimenopause [42]. Moreover, oestradiol directly modulates blood pressure affecting renin concentration and circulating natriuretic peptides levels [46]. Other expressions of oestrogen deficiency are post-menopausal vasomotor symptoms (hot flashes and night sweats). The severity of vasomotor symptoms is associated with decreased vascular response to endothelium-mediated dilatation, suggesting a decline in endothelial function and reduced vascular compliance [47]. Moreover, a higher frequency of hot flashes has been correlated with increased awake and sleep systolic blood pressure, independent of the menopausal status [43], and an increased risk of developing coronary events over a period of 14 years, even after taking the effects of age, menopause status, lifestyle and other chronic disease risk factors into account [48]. Therefore, the treatment of hot flashes may contribute to improving women's CV health since the presence of hot flashes appears to be an independent CV risk factor [43].

In addition, cardio-metabolic risk during menopause may be affected by a decrease in sex hormone binding globulin (SHBG) and an increase in androgen levels (particularly free testosterone) [49–51]. Other sex hormones may modify the vascular actions of oestrogen or have direct effects on the vasculature. The relationship between circulating levels of free E2, free testosterone and SHBG may be more predictive of changes in carotid intimal thickening than the levels of any of these hormones alone [51].

Environmental factors, i.e. work-related stress, and psychological factors, such as anxiety and depression, often seen in women during menopause, appear to be important CV risk factors [52,53]. According to the National Health and Nutrition Examination Survey I study, women with depression had a higher relative risk (RR) of developing CAD than women without depression [54].

2.4. Surgical menopause

Surgical menopause has been shown to be associated with premature death, CVD, osteoporosis, cognitive impairment and dementia, parkinsonism, negative effects on psychological well-being and sexual dysfunction [55,56]. Women undergoing bilateral oophorectomy before age 46 showed an increased risk of depression, hyperlipidaemia, cardiac arrhythmias, CAD, arthritis, asthma, chronic obstructive pulmonary disease and osteoporosis. This significant increase in morbidity risk was present even after adjustment for other conditions and several other possible confounders such as ethnicity, education, BMI, smoking, age and calendar year. Of importance, several of these associations were reduced in women who received oestrogen therapy [57].

A meta-analysis by Atsma et al. [31] showed that bilateral oophorectomy is an independent risk factor for CV disease with a RR of 4.55, while early menopause was associated with a RR of 1.25 [31]. In the

presence of comorbidities, i.e. DM, surgical menopause may have a synergistic effect on aging and well-being. Women with diabetes who have had oophorectomy have IR, an atherogenic lipid profile, hyperinsulinaemia, higher leptin and lower adiponectin concentrations which my increase their predisposition to CVD [58].

The effect of sex hormones on cardiac autonomic function has been evaluated in several studies. Mercuro et al. reported that oophorectomy causes an imbalance of the autonomic nervous control of the CV system characterised by a decrease in cardiac vagal modulation and an increase in sympathetic activity [59]. Both early and surgical menopause should be considered to represent markers of future CVD and may provide a unique opportunity for the early identification of women who are at increased risk of developing CVD (Figs. 1 and 2).

3. Complications of pregnancy

Pregnancy contributes to weight gain and metabolic syndrome. Normal pregnancy is associated with a shift of the coagulation and fibrinolytic systems towards hypercoagulability. Although these changes are ultimately designed to minimize the risk of blood loss during delivery, they increase the risk of thrombosis 3- to 4-fold in pregnant women. Moreover, multiparity is also independently associated with higher rates of metabolic syndrome [60]. Women with a history of five or more births have a higher (2.27 times) prevalence of CVD [61]. Nulliparous women have a lower prevalence of CVD than women who have given birth (18.0% vs. 30.2%), and after adjustment for socio-demographic and lifestyle variables, including age, race, education, income, marital status, and smoking status, parous women with no complicated births had a 1.95-fold (95% confidence interval [CI] 1.03–3.7) higher CVD prevalence than nulliparous women [62].

Pregnancy poses a "metabolic stress test" to women. Failing such a test may predict future CVD. Pregnancy can, therefore, be considered to be an opportunity to identify, at an early stage, women who may be at increased risk for CVD and who might benefit from early preventative measures [63]. Recent studies have shown that some pregnancy complications such as gestational diabetes mellitus (GDM), gestosis and miscarriage, as well as conditions affecting the foetus, such as premature gestational age and small for gestational age (SGA) represent real risk factors for the development of the mother's future CVD [8,64].

3.1. Gestational diabetes mellitus

GDM significantly increases the risk for subsequent glucose intolerance, T2DM (from 2.6% to over 70%) [60] and metabolic syndrome. Metabolic syndrome is more prevalent in women with a history of GDM than in healthy controls [65]. Abdominal obesity, lower HDL concentrations, elevated LDL-cholesterol and triglyceride levels, as well as elevated C-reactive protein, are often present in women with GDM and significantly enhance their risk of developing CVD [66]. Women with GDM have a higher prevalence of CAD and/or stroke, which occur at a younger age and are independent of T2DM [67]. Moreover, a recent study showed that GDM is associated with angina pectoris, MI and hypertension (seven years postpartum follow up), regardless of the development of DM [68].

The prevalence of GDM in the Italian female population is approximately 5%. A study [69] involving 81,262 women without, and 8191 with GDM, with a mean age of 31 years and followed up for 11.5 years, showed that the risk of CVD in women with GDM was 1.71. After adjusting for T2DM, this ratio decreased to 1.13, proving that young women with GDM actually have an increased risk of CVD and this increase is mainly related to the subsequent development of T2DM. >70% of women with GDM develop T2DM within 5 years of pregnancy [70]. Therefore, early monitoring of women with previous GDM in relation to the increased risk of developing DM is crucial.

It has been hypothesised that the risk of CVD in women increases linearly with the degree of hyperglycaemia. A study of 169 women
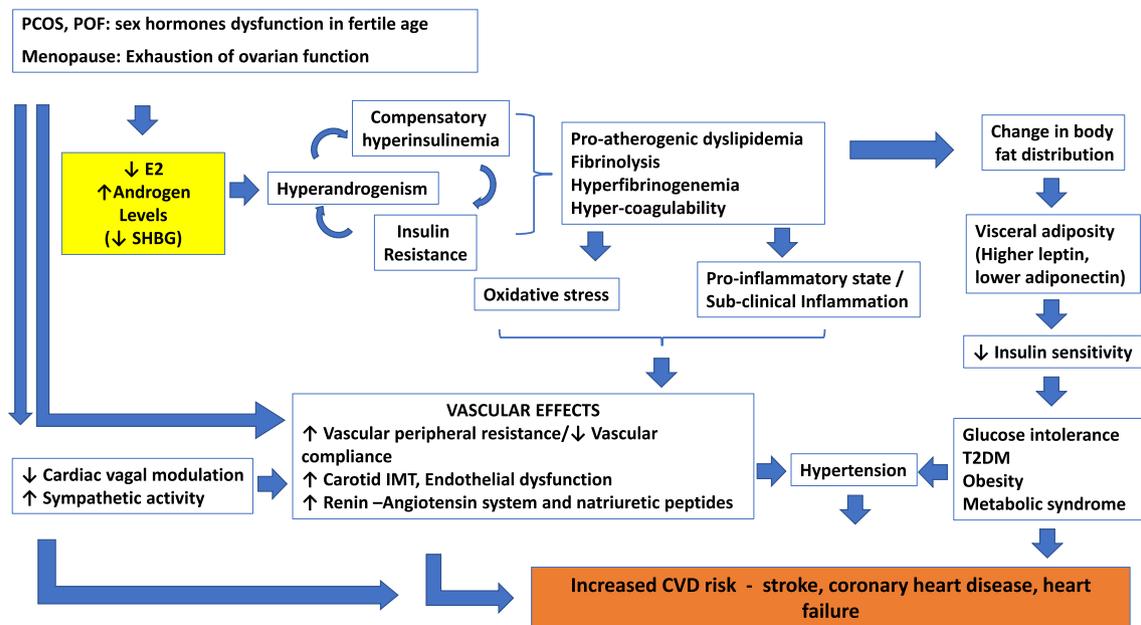
Fig. 1. Polycystic Ovary Syndrome (PCOS) and Premature Ovarian Failure (POF) and Menopause: Common pathological mechanisms of Cardiovascular Disease (CVD) risk Abbreviations: Oestradiol, E2. Sex Hormones Binding Protein, SHBG. Type 2 Diabetes Mellitus, T2DM. Intima-Media Thickness, IMT.

showed that GDM is positively and independently associated with increased carotid intima-media thickness, compared to that in control subjects [71].

Endothelial dysfunction of the foeto-placental unit underlies CV damage in GDM and is associated with a more extensive systemic vascular impairment caused by the reduced metabolism of adenosine and by hyperinsulinaemia [72]. Furthermore, women with GDM appear to have altered levels of catalase, free radicals, inflammatory cytokines and increased expression of endothelial adhesion molecules. All of these positively correlate with glucose intolerance and promote subclinical inflammation and oxidative stress resulting in vascular dysfunction [73–75]. Moreover, microcirculatory damage was shown to increase 3.3 times in women with previous GDM compared with healthy controls [76]. Consensus exists that GDM and blood pressure disorders are factors associated with CVD risk [77].

3.2. Preeclampsia

In gestational women, preeclampsia is defined as systolic blood pressure of at least 140 mmHg and/or diastolic blood pressure of at least 90 mmHg, confirmed by at least two repeat blood pressure recordings. The incidence of hypertensive disorders in pregnancy ranges between 6 and 8% [78]. Proteinuria is present from the 20th week of gestation in women known to be normotensive before pregnancy.

According to more restrictive statistics, the incidence of most serious forms of preeclampsia is 3–5%. Marin et al. reported a 5-fold increased risk in a 14-year follow-up in early gestational preeclampsia (before the 30th week) and chronic pre-existing hypertension [79].

Furthermore, women with preeclampsia have a 11.6 times higher risk of developing arterial hypertension than healthy women [80]. Among pregnancy complications, preeclampsia seems to be the best
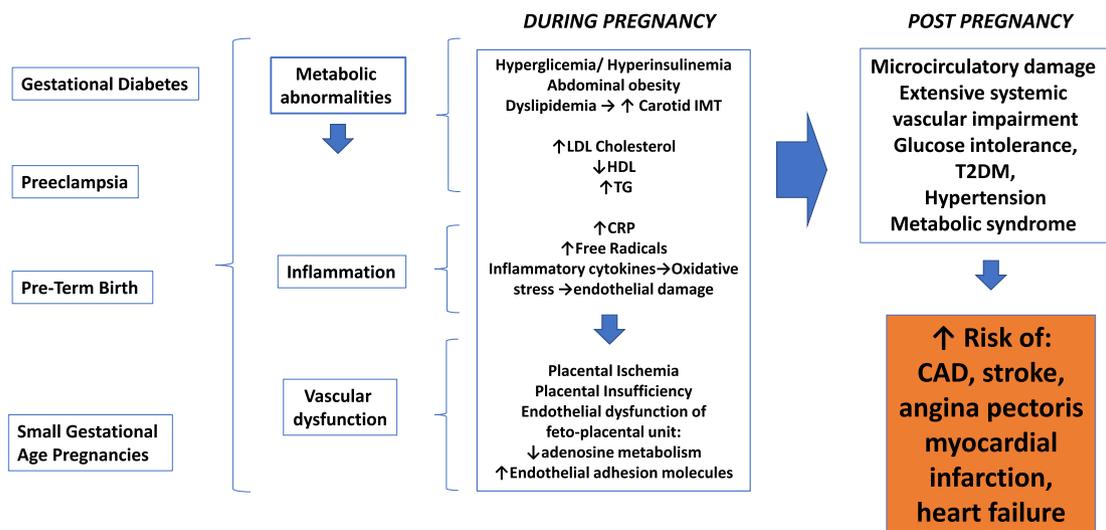

Fig. 2. Pregnancy Complications: peculiar risk factors of future Cardiovascular Disease Abbreviations: Intima-Media Thickness, IMT. Low-Density Lipoprotein, LDL. High-Density Lipoprotein, HDL. Triglycerides, TG. C-reactive Protein, CRP. Type 2 Diabetes Mellitus, T2DM. Coronary Artery Disease, CAD.

predictor of later CVD because it correlates with a greater number of CV risk factors [81]. In McDonald's meta-analysis [82], the average risk of developing heart disease in women with preeclampsia was 2.2 compared with that in controls and risk increases with the severity of preeclampsia. The timing of onset of preeclampsia is also of importance. Women with early-onset preeclampsia have a hiher incidence of major CV risk factors in the fifth decade of life compared with healthy controls [83]. Yinon et al. compared women with physiological pregnancies, late and early preeclampsia and IUGR and demonstrated that those with early preeclampsia and IUGR showed impaired brachial endothelium-mediated dilatation. [84]. Moreover, an imbalance towards the production of placental vasoconstrictive and procoagulant molecules is seen in preeclampsia compared with physiological pregnancies. [83]. The involvement of the utero-placental vascular unit subsequently enhances and worsens the clinical scenario of preeclampsia, increasing peripheral vascular resistance, systemic arterial pressure and platelet aggregation, and decreasing utero-placental flow [85].

Systemic subclinical inflammation in preeclampsia [86], also contributes to endothelial damage by promoting oxidative stress wich in turn can predispose women to CVD after pregnancy [87]. The Avon Longitudinal Study of Parents and Children, evaluated 3416 women 18 years after pregnancy and concluded that the risk of CV increased by 30% in women who have had disorders such as gestational hypertension, preeclampsia, GDM and SGA [81].

Comorbidities may worsen the clinical scenario of the preeclampsia and share similar placental vascular alterations that synergistically increase the risk of subsequent development of CVD. For example, almost one-third of the cases of GD are complicated by preeclampsia [88]. Moreover, preeclampsia is a risk factor for the development of DM; the probability of developing DM in the post-pregnancy years is 3.8 times greater than that in healthy controls. [80]. Increased pre-pregnancy BMI is a risk factor for preeclampsia [89] and preeclampsia increases the risk for subsequent IR and hypertension in the peri-menopausal years [90].

The association between preeclampsia and future CV disease seems to be due to underlying vascular dysfunction [91,92]. The vascular damage arising during pregnancy lasts into the postpartum years and represents the etiopathological trigger of future CV damage [92]. A meta-analysis confirmed that women with a history of preeclampsia compared with women without such a history, had an increased risk of hypertension, a 2-fold increased risk of IHD, stroke, and deep venous thrombosis, and a 1.5-times higher risk of all-cause mortality, later in life [93].

These women are currently outside the scope of most preventative programs due to their relatively young age but have important modifiable risk factors and may be eligible for preventative therapies at an earlier age. During pregnancy, low-dose aspirin prophylaxis is indicated in patients with preeclampsia, particularly if other risk factors are also present [94].

3.3. Preterm birth

PTB, defined as delivery of an infant before 37 weeks, affects 11% of all pregnancies. It is the leading cause of long-term neurologic disabilities in children and the most common cause of infant death [95]. PTB not only poses risk to the child, but it may also identify women with elevated lifetime risk for CVD [96]. Indeed, women with PTB are more likely to have CV events and increased hospitalization rates [97].

Robbins et al. reported a significant increase in the incidence of AMI, stroke and CAD in these women [98]. Compared with normal term delivery, spontaneous preterm delivery (sPTD) has been associated with a 3-fold increased risk of maternal CVD death later in life. A recent meta-analysis of 14 CVD outcome studies, including nonfatal MI, revascularization, CV death, stroke, thromboembolism, IHD-related hospitalizations, and IHD death in women with sPTD showed that all-cause PTD (medically indicated and sPTD) is associated with a 1.5- to 3-fold

increased risk of CV morbidity and mortality after controlling for CV-related risk factors [97].

Kessous et al., in a population-based study comparing the incidence of CV morbidity in 47,908 women who delivered preterm (<37 weeks' gestation) and those who gave birth at term during the same period, showed that adjusting for confounders such as induction of labour, DM, preeclampsia, and obesity, PTD was associated with increased rates of CV hospitalizations (adjusted hazard ratio, 1.4; 95% CI, 1.2–1.6). They concluded that PTD is an independent risk factor for long-term (>10-year) CV morbidity [98]. The pathogenesis of PTB remains poorly understood; systemic inflammation, infection, and vascular diseases have been proposed [99–101]. The length of gestation has been shown to inversely correlate with IR, high blood pressure and low-grade inflammation in the years after delivery [102–104]. Thus, dysregulation of cardio-metabolic factors may provide a possible explanation for the reported association between PTB and the development of CVD [105,106].

Moreover, in the decade following delivery, women with a history of PTB, but without preeclampsia or SGA births, have been shown to have a higher incidence of an atherogenic lipid profile and carotid arterial wall thickening than control women. This increased risk is greatest in PTB occurring before week 32 and in women with early deliveries due to medical indications such as SGA or preeclampsia.

A recent large meta-analysis that included 5,813,682 women, 338,007 of whom had PTB, demonstrated that PTB was associated with a 1.4- to 2-fold increase in future adverse CV events, CV death, CHD events, CHD death and stroke [107]. Moreover, women with a greater number of recurrent PTBs showed higher risks for CVD and CHD adverse outcomes. Therefore, PTB identifies women at risk for CVD who would not have been detected using traditional risk assessment tools at a time when it may still be possible to change their CV risk trajectory [108].

3.4. Small for gestational age pregnancies

Low weight for the gestational age (i.e. birth weight <1.5 Kg) of the unborn child represents a risk factor for the development of CVD in the mother [109]. A retrospective study conducted in Sweden with almost 1 million women showed an additive effect between pre-term delivery and SGA pregnancies as CVD risk factors, i.e. RR 1.38 for SGA and 3.40 in SGA and PTB pregnancies, respectively [110].

Birth weight is inversely related to future maternal CV mortality. There is evidence of a reduced migratory function and number of endothelial progenitor cells in SGA mothers, indicating vascular endothelial damage in these individuals [110].

Similar to preeclampsia, the pathophysiological mechanism underlying SGA pregnancies is triggered by placental vascular damage and involves the systemic vasculature. The effects may persist well beyond 1 year postpartum. SGA pregnancies show a statistically significant reduction in vascular compliance, as assessed by endothelial flow-mediated dilation, compared with controls [84].

Melchiorre et al. demonstrated an increase in total vascular resistance, asymptomatic left ventricular diastolic dysfunction, and abnormal myocardial relaxation indices, as assessed by 12-week postpartum cardiac echo Doppler studies [111], in mothers of SGA infants compared with those in controls. Foetal growth-restricted (FGR) pregnancies were characterised by lower cardiac index and higher total vascular resistance index. Compared with controls, FGR pregnancies were associated with a significantly increased prevalence of asymptomatic left ventricular diastolic dysfunction (28% versus 4%) and widespread impaired myocardial relaxation (59% versus 21%). Cardiac geometry and intrinsic myocardial contractility were preserved in FGR pregnancies. Two-thirds of women with FGR pregnancies showed evidence of poorer diastolic reserve, as demonstrated by impaired myocardial relaxation, and one third had overt diastolic chamber dysfunction despite a normal ejection fraction. SGA pregnancies are characterised by low

cardiac output, increased peripheral vascular resistance and high prevalence of asymptomatic diastolic global dysfunction and reduced cardiac reserve [111]. These data may help explain the increased risk of CVD observed in mothers of children with IUGR.

Barker et al. demonstrated an association between abnormalities occurring during foetal life and mortality in adult life, with an increased prevalence of IHD, further supporting "Barker Hypothesis" that the susceptibility to CVD can in many cases start in utero [112].

Andersson et al. reported that the prevalence of hypertension later in life was increased in low birth weight women compared with normal birth weight women [113].

The prevalence of hypertension at 60 years of age was increased in women who were SGA compared with normal birth weight counterparts, suggesting a very early origin of heightened CV risk [114]. Therefore, girls who were SGA are at risk of early menopause and postmenopausal hypertension as suggested by the "foetal programming" theory [115]. Birth weight and other perinatal factors are not yet considered to represent risk factors potentially leading to adult hypertension [116].

3.5. Miscarriage

Repeated spontaneous miscarriage is associated with the development of CVD and risk factors [116]. Women with a history of repeated miscarriage have an increased risk of CV events, hospital admissions for CVD and are more frequently admitted to a hospital for invasive and non-invasive diagnostic CV procedures compared to control subjects [117]. In a retrospective study involving 7701 women, Parker et al. showed a correlation between increased risk of CAD and poliabortivity, a finding that was independent of blood pressure, BMI, waist to hip ratio and leukocyte count [118]. These associations were also confirmed in a meta-analysis study by Oliver-Williams et al. [119]. A large cohort population study in women with a history of miscarriage and/or foetal death confirmed the increased incidence of MI, cerebral infarction, and renal vascular hypertension compared to that in controls [120].

4. Conclusions

CVD remains the leading cause of morbidity and mortality in postmenopausal women, despite the overall reduction in age-adjusted CVD mortality in recent years. Traditional CV risk factors are equally important in men and women, but recently, evidence has been gathered showing the importance of gynaecologic and obstetric events taking place in women during their reproductive years. Menopause, GDM, preeclampsia, and SGA, in addition to the other risk factors described in this manuscript, are associated with the development of CVD. These events should, therefore, be considered to represent sex-specific risk factors and should be considered by health practitioners and used for CVD risk calculation and CVD prevention programmes in women [121]. The perinatal period is a valuable time for giving medical advice, education and intervention.

The evaluation of women's specific CV risk factors is of importance to establish early, sex-targeted preventative and therapeutic strategies.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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