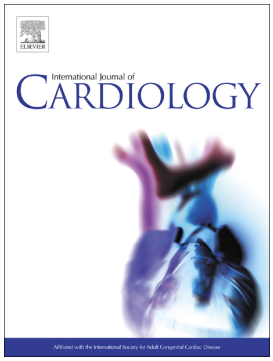

Women-specific predictors of cardiovascular disease risk - new paradigms

Silvia Maffei, Letizia Guiducci, Lucia Cugusi, Christian Cadeddu, Martino Deidda, Sabina Gallina, Susanna Sciomer, Amalia Gastaldelli, Juan-Carlos Kaski, Working Group on Gender difference in cardiovascular disease of the Italian Society of Cardiology

PII: S0167-5273(18)34923-4
DOI: https://doi.org/10.1016/j.ijcard.2019.02.005
Reference: IJCA 27434

To appear in: *International Journal of Cardiology*

Received date: 23 October 2018
Revised date: 19 December 2018
Accepted date: 4 February 2019

Please cite this article as: S. Maffei, L. Guiducci, L. Cugusi, et al., Women-specific predictors of cardiovascular disease risk - new paradigms, International Journal of Cardiology, https://doi.org/10.1016/j.ijcard.2019.02.005

Women-specific Predictors of Cardiovascular Disease Risk - New Paradigms

Silvia Maffei MD[1], Letizia Guiducci PhD[2], Lucia Cugusi PhD[3], Christian Cadeddu MD, PhD[3], Martino Deidda MD, PhD[3], Sabina Gallina MD, FESC, FACC[4], Susanna Sciomer MD[5], Amalia Gastaldelli PhD[6], and Juan-Carlos Kaski DSc, MD, FRCP, FESC, FACC, FAHA[7], on behalf of the Working Group on "Gender difference in cardiovascular disease" of the Italian Society of Cardiology.

1.Department of Gynecological and Cardiovascular Endocrinology, CNR-Tuscany Region, G. Monasterio Foundation, Pisa Italy. Electronic address: silvia.maffei@ftgm.it
2.Biochemistry and Molecular Biology Laboratory, Clinical Physiology Institute, CNR, Pisa
3.Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy
4.Department of Neuroscience, Imaging and Clinical Science University "G. D'Annunzio", Chieti-Pescara, Italy.
5.Department of "Scienze cardiovascolari, respiratory, nefrologiche, anestesiologiche e geriatriche" Sapienza, University of Rome, Roma, Italy
6.Cardiometabolic Risk Unit, Clinical Physiology Institute, CNR, Pisa
7.Molecular and Clinical Sciences Research Institute, St. George's, University of London, London, United Kingdom

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.

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***). 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).

Figure 1

Women-specific risk factors for Cardiovascular Disease

Polycystic Ovary Syndrome PCOS is one of the most common disorders occurring in the childbearing 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. More than 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 30–50% 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).

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).

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 (33, 23). Hormonal deficiency leads to abnormalities in different organs and systems, including the central nervous

system, endothelium, bones and liver. During menopause, lipids shift toward 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 peri-menopause (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, 50, 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).

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.

Figure 2

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).

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. More than 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 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, 74, 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).

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 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).

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, 100, 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, 103, 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).

Small for gestational age pregnancies

Low weight for the gestational age (i.e. birth weight less than 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).

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).

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. 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.

References

1Wenger NK. Coronary heart disease in women: evolving knowledge is dramatically changing clinical care. In: JulianDJ, Wenger NK, Eds. Women and Heart Disease, Martin Dunitz, London, 1997;21-38

2 Rossouw JE. Hormones, genetic factors, and gender differences in cardiovascular disease. Cardiovasc Res 2002; 53:550-557

3 Hasdai D, Porter A, Rosangren A, et al. Effect of gender on outcomes of acute coronary syndromes. Am J Cardiol 2003;91:1466-1469.

4 Roeters van Lennep JE, Westerveld HT, Erkelens DW et al Risk factors for coronary heart disease: implications of gender. Cardiovasc Res 2002;53:538-549.

5 www.iss.it/site/mortalita'

6 Mosca L, Mochari H, Christian et al. A National study of women's awareness, preventive action, and barriers to cardiovascular health. Circulation 2006;113:525-534

7 van der Weijden T, van Steenkiste B, Stoffers HE et al. Primary prevention of cardiovascular diseases in general practice: mismatch between cardiovascular risk and patients' risk perceptions. Med Decis Making 2007;27:754-761

8 Sciomer S et al Gender differences in Cardiology: is it time for new guidelines? Journal of Cardiovascular Medicine 2018, in press)

9 Collins P, Webb CM, de Villiers TJ, Stevenson JC, Panay N, Baber RJ Cardiovascular risk assessment in women - an update. Climacteric. 2016;19:329-336

10 Moran LJ, Norman RJ, Teede HJ. Metabolic risk in PCOS: phenotype and adiposity impact. Trends Endocrinol Metab.2015;26:136-143

11 Diamanti-Kandarakis E, Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. Endocr Rev. 2012;33:981-1030

12 Legro RS, Kunselman AR, Dodson WC Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. J Clin Endocrinol Metab. 1999;84:165-169

13 de Groot PC, Dekkers OM, Romijn JA, Dieben SW, Helmerhorst FM. PCOS, coronary heart disease, stroke and the influence of obesity: a systematic review and meta-analysis. Hum Reprod Update. 2011;17:495-500.

14 Wild RA, Carmina E, Diamanti-Kandarakis E et al Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society. J Clin Endocrinol Metab. 2010;95:2038-2049

15 Glintborg D, Rubin KH, Nybo M, Abrahamsen B, Andersen M. Cardiovascular disease in a nationwide population of Danish women with polycystic ovary syndrome. Cardiovasc Diabetol. 2018 8;17:37.

16 Repaci A, Gambineri A, Pasquali R The role of low-grade inflammation in the polycystic ovary syndrome. Mol Cell Endocrinol. 2011;335:30-41

17 Talbott EO, Guzick DS, Sutton-Tyrrell K et al. Evidence for association between polycystic ovary syndrome and premature carotid atherosclerosis in middle-aged women. Arterioscler Thromb Vasc Biol. 2000;20:2414-2421.

18 Alexander CJ, Tangchitnob EP, Lepor NE Polycystic ovary syndrome: a major unrecognized cardiovascular risk factor in women. Rev Obstet Gynecol. 2009;2:232-239

19 Usadi RS, Legro RS. Reproductive impact of polycystic ovary syndrome. Curr Opin Endocrinol Diabetes Obes. 2012 ;19:505-511

20 Jovanovic VP, Carmina E, Lobo RA. Not all women diagnosed with PCOS share the same cardiovascular risk profiles. Fertil Steril. 2010;94:826-832.

21Mažibrada I, Djukić T, Perović S, Plješa-Ercegovac M, Plavšić L, Bojanin D, Bjekić-Macut J, Simić PD, Simić T, Savić-Radojević A, Mastorakos G, Macut D The association of hs-CRP and fibrinogen with anthropometric and lipid parameters in non-obese adolescent girls with polycystic ovary syndrome. J Pediatr Endocrinol Metab. 2018; 27;31:1213-1220.

22 Sassarini J, Lumsden MA, Critchley HO Sex hormone replacement in ovarian failure - new treatment concepts.Best Pract Res Clin Endocrinol Metab. 2015;29:105-114

23 Wellons M, Ouyang P, Schreiner PJ, Herrington DM, Vaidya D. Early Menopause Predicts Future Coronary Heart Disease and Stroke: The Multi-Ethnic Study of Atherosclerosis (MESA) Menopause. 2012;19:1081–1087

24 Podfigurna-Stopa A, Czyzyk A, Grymowicz M, Smolarczyk R, Katulski K, Czajkowski K, Meczekalski B. Premature ovarian insufficiency: the context of long-term effects. J Endocrinol Invest. 2016 ;39:983-990

25 Gibson-Helm M,Teede H,Vincent A. Symptoms, health behavior and understanding of menopause therapy in women with premature menopause. Climacteric. 2014;17:666-673

26 Katarzyna Jankowska. Premature ovarian failure. Menopause Rev 2017;16: 51-56

27 Appiah D, Schreiner PJ, Demerath EW, Loehr LR, Chang PP, Folsom AR. Association of Age at Menopause With Incident Heart Failure: A Prospective Cohort Study and Meta-Analysis J Am Heart Assoc. 2016 ;5:1-10

28 Gong D, Sun J, Zhou Y, Zou C, Fan Y. Early age at natural menopause and risk of cardiovascular and all-cause mortality: a meta-analysis of prospective observational studies. Int J Cardiol. 2016;203:115–119

29 Jacobsen B, Heuch I, Kvale G. Age at natural menopause and stroke mortality: cohort study with 3561 stroke deaths during 37-year follow-up. Stroke. 2004;35:1548–1551.

30 Muka T,Oliver-Williams C, Kunutsor S, Laven JS, Fauser BC, Chowdhury R, Kavousi M, Franco OH. Association of Age at Onset of Menopause and Time Since Onset of Menopause With Cardiovascular Outcomes, Intermediate Vascular Traits, and All-Cause Mortality: A Systematic Review and Meta-analysis. JAMA Cardiol. 2016;1:767-776

31 Atsma F, Bartelink ML, Grobbee DE et al. Postmenopausal status and early menopause as independent risk factors for cardiovascular disease: a meta-analysis. Menopause. 2006;13:265-279.

32 Yorgun H, Gürses KM, Canpolat U, Yapıcı Z, Bozdağ G, Kaya EB, Aytemir K, Oto A, Kabakçı G, Tokgözoğlu L. Evaluation of cardiac autonomic function by various indices in patients with primary prematureovarian failure. Clin Res Cardiol. 2012;101:753-759

33 Shuster LT, Rhodes DJ, Gostout BS et al. Premature menopause or early menopause: long-term health consequences. Maturitas. 2010;65:161-166

34 Matthews KA, Crawford SL, Chae CU et al. Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or to the menopausal transition? J Am Coll Cardiol. 2009;54:2366-2373

35 Bittner V. Lipoprotein abnormalities related to women's health. Am J Cardiol. 2002;90:77i-84i

36 Kolovou GD, Kolovou V, Kostakou PM, Mavrogeni S. Body mass index, lipid metabolism and estrogens: their impact on coronary heart disease. Curr Med Chem. 2014;21:3455-65.

37 Polotsky HN, Polotsky AJ. Metabolic implications of menopause. Semin Reprod Med. 2010;28:426-434

38 Mascarenhas-Melo F, Marado D, Palavra F et al. Diabetes abrogates sex differences and aggravates cardiometabolic risk in postmenopausal women. Cardiovasc Diabetol. 2013;9:12-61

39 Sciomer S, De Carlo C, Moscucci F, Maffei S. Age at menopause: A fundamental data of interest to acquire in female patients' anamnesis. Int J Cardiol. 2016;215:358-9.

40 Vassalle C, Mercuri A, Maffei S Oxidative status and cardiovascular risk in women: Keeping pink at heart. World J Cardiol. 2009;1:26-30

41 Staessen JA, Celis H, Fagard R.The epidemiology of the association between hypertension and menopause. J Hum Hypertens. 1998 ;12:587-592

42 Mercuro G, Longu G, Zoncu S et al. Impaired forearm blood flow and vasodilator reserve in healthy postmenopausal women. Am Heart J.1999;137:692-697

43 Gerber LM, Sievert LL, Warren K et al. Hot flashes are associated with increased ambulatory systolic blood pressure. Menopause. 2007;14:308-315

44 Khalil RA Estrogen, vascular estrogen receptor and hormone therapy in postmenopausal vascular disease. Biochem Pharmacol. 2013;86:1627-1642

45 Reslan OM, Khalil RA.Vascular effects of estrogenic menopausal hormone therapy. Rev Recent Clin Trials. 2012;7:47-70

46 Maffei S, Del Ry S, Prontera C et al. Increase in circulating levels of cardiac natriuretic peptides after hormone replacement therapy in postmenopausal women. Clin Sci (Lond). 2001;101:447-453

47 Bechlioulis A, Kalantaridou SN, Naka KK at al. Endothelial function, but not carotid intima-media thickness, is affected early in menopause and is associated with severity of hot flushes. J Clin Endocrinol Metab. 2010;95:1199-1206

48 Herber-Gast GC, Pop VJ, Samsioe GN, et al. Vasomotor menopausal symptoms are associated with increased risk of coronary heart disease.Menopause. 2011;18:146-151

49 Chen BH, Song Y et al Age, body mass, usage of exogenous estrogen, and lifestyle factors in relation to circulating sex hormone-binding globulin concentrations in postmenopausal women. Clin Chem. 2014;60:174-185

50 Maturana MA, Breda V, Francisco Lhullier F et al. Relationship between endogenous testosterone and cardiovascular risk in early postmenopausal women. Metabolism 2008;57:961-965

51 Karim R, Hodis HN, Stanczyk FZ, Lobo RA, Mack WJ. Relationship between serum levels of sex hormones and progression of subclinical atherosclerosis in postmenopausal women. J Clin Endocrinol Metab. 2008;93:131-138

52 Green SM, Key BL, McCabe RE Cognitive-behavioral, behavioral, and mindfulness-based therapies for menopausal depression: a review. Maturitas 2015;80:37-47

53 Möller-Leimkühler AM Gender differences in cardiovascular disease and comorbid depression. Dialogues Clin Neurosci. 2007;9:71-83

54 Ferketich AK, Schwartzbaum JA, Frid DJ, Moeschberger ML. Depression as an antecedent to heart disease among women and men in the NHANES I study. National Health and Nutrition Examination Survey. Arch Intern Med. 2000. ; 160 : 1261– 1268

55 Yoshida T, Takahashi K, Yamatani H,Takata K, Kurachi H. Impact of surgical menopause on lipid and bone metabolism Climacteric.2011;14:445-452.

56 Ley SH, Li Y, Tobias DK, Manson JE, Rosner B, Hu FB, Rexrode KM . Duration of Reproductive Life Span, Age at Menarche, and Age at Menopause Are Associated With Risk of Cardiovascular Disease in Women. J Am Heart Assoc.2017 2;6-11

57 Rocca WA, Gazzuola-Rocca L, Smith CY, Grossardt BR, Faubion SS, Shuster LT, Kirkland JL, Stewart EA, Miller VM. AcceleratedAccumulation of Multimorbidity After Bilateral Oophorectomy: A Population-Based Cohort Study. Mayo Clin Proc. 2016;91:1577-158

58 Tawfik SH, Mahmoud FB, Saad MI, Shehata M, et al. Similar and Additive Effects of Ovariectomy and Diabetes on Insulin Resistance and Lipid Metabolism. Biochemistry Research International 2015;2015:1-8

59 Mercuro G, Podda A, Pitzalis L, Zoncu S, Mascia M, Melis GB, Rosano GM Evidence of a role of endogenous estrogen in the modulation of autonomic nervous system. Am J Cardiol 2000 85:787–789

60 Cohen A, Pieper CF, Brown AJ, Bastian LA. Number of children and risk of metabolic syndrome in women. J Womens Health (Larchmt). 2006;15:763-73.

61 Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. Diabetes Care. 2002;25:1862-1868

62 Catov JM, Newman AB, Sutton-Tyrrell K, Harris TB, Tylavsky F, Visser M, et al. Parity and cardiovascular disease risk among older women: how do pregnancy complications mediate the association? Ann Epidemiol. 2008;18:873-879.

63 Wenger NK Recognizing pregnancy-associated cardiovascular risk factors. Am Cardiol 2014;113:406-409

64 Clifton VL, Stark MJ, Osei-Kumah A et al. Review: The feto-placental unit, pregnancy pathology and impact on long term maternal health. Placenta. 2012;33:S37-S41

65 Lauenborg J, Mathiesen E, Hansen T, Glumer C, Jorgensen T, Borch-Johnsen K, et al. The prevalence of the metabolic syndrome in a danish population of women with previous gestational diabetes mellitus is three-fold higher than in the general population. J Clin Endocrinol Metab. 2005;90:4004-10.

66 Di Cianni G, Lencioni C, Volpe L, Ghio A, Cuccuru I, Pellegrini G, et al. C-reactive protein and metabolic syndrome in women with previous gestational diabetes. Diabetes Metab Res Rev. 2007;23:135-140

67 Carr DB, Utzschneider KM, Hull RL, Tong J, Wallace TM, Kodama K, et al. Gestational diabetes mellitus increases the risk of cardiovascular disease in women with a family history of type 2 diabetes. Diabetes Care. 2006;29:2078-83.

68 Goueslard K, Cottenet J, Mariet AS, Giroud M, Cottin Y, Petit JM, et al. Early cardiovascular events in women with a history of gestational diabetes mellitus. Cardiovasc Diabetol. 2016;15:15.

69 Shah BR, Retnakaran R, Booth GL. Increased risk of cardiovascular disease in young women following gestational diabetes mellitus. Diabetes Care. 2008;31:1668-1669

70 Retnakaran R, Shah BR. Mild glucose intolerance in pregnancy and risk of cardiovascular disease: a population-based cohort study. CMAJ. 2009;181:371–376

71 Freire CM, Barbosa FB, de Almeida MC et al. Previous gestational diabetes is independently associated with increased carotid intima media thickness, similarly to metabolic syndrome a case control study. Cardiovasc Diabetol. 2012;31;11-59

72 Guzmán-Gutiérrez E, Abarzúa F, Belmar C et al. Functional link between adenosine and insulin: a hypothesis for fetoplacental vascular endothelial dysfunction in gestational diabetes. Curr Vasc Pharmacol. 2011;9:750-762.

73 Roca-Rodríguez MM, López-Tinoco C, Murri M et al. Postpartum development of endothelial dysfunction anoxidative stress markers in women with previous gestational diabetes mellitus. J Endocrinol Invest. 2014;37:503-509

74 Rao R, Sen S, Han B, et al Gestational diabetes, preeclampsia and cytokine release: similarities and differences in endothelial cell function. Adv Exp Med Biol. 2014;814:69-75

75 Heitritter SM, Solomon CG, Mitchell GF et al. Subclinical inflammation and vascular dysfunction in women with previous gestational diabetes mellitus. J Clin Endocrinol Metab 2005, 90:3983–3988

76 Zajdenverg L, Rodacki M, Polo Faria J et al. Precocious markers of cardiovascular risk and vascular damage in apparently healthy women with previous gestational diabetes . Diabetol Metab Syndr 2014;6:63

77 Shostrom DCV, Sun Y, Oleson JJ, Snetselaar LG, Bao W. History of Gestational Diabetes Mellitus in Relation to Cardiovascular Disease and Cardiovascular Risk Factors in US Women. Front Endocrinol (Lausanne). 2017;8:1-6

78 Gillon TE, Pels A,von Dadelszen P et al. Hypertensive disorders of pregnancy: a systematic review of international clinical practice guidelines. PLoS One.2014;9:1-20

79 Marín R, Gorostidi M, Portal CG et al. Long-term prognosis of hypertension in pregnancy. Hypertens Pregnancy. 2000;19:199-209

80 Magnussen EB, Vatten LJ, Smith GD et al. Hypertensive disorders in pregnancy and subsequently measured cardiovascular risk factors. Obstet Gynecol. 2009;114:961-970

81 Fraser A, Nelson SM, Macdonald-Wallis C Associations of pregnancy complications with calculated cardiovascular disease risk and cardiovascular risk factors in middle age: the Avon Longitudinal Study of Parents and Children. Circulation. 2012;125:1367-1380

82 McDonald SD, Malinowski A, Zhou Q et al. Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. Am Heart J. 2008;156:918-930

83 Bokslag A, Teunissen PW, Franssen C , van Kesteren F, Kamp O , Ganzevoort W, Paulus WJ , de Groot CJM. Effect of early-onset preeclampsia on cardiovascular risk in the fifth decade of life .: Am J Obstet Gynecol.2017;216:523-527

84 Yinon Y, Kingdom JC, Odutayo A et al Vascularm dysfunction in women with a history of preeclampsia and intrauterine growth restriction: insights into future vascular risk. Circulation. 2010;122:1846-1853

85 Al-Nasiry S, Fajta MM et al. Am J Obstet Gynecol. Cardiovascular and thrombogenic risk of decidual vasculopathy in preeclampsia. 2014; 545:1-6

86 Staff AC, Johnsen GM, Dechend R et al Preeclampsia and uteroplacental acute atherosis: immune and inflammatory factors J Reprod Immunol. 2014;101-102:120-126

87 Charlton F, Tooher J, Rye KA Cardiovascular risk, lipids and pregnancy: preeclampsia and the risk of later life cardiovascular disease. Heart Lung Circ.2014;23:203-212

88 Banerjee M, Cruickshank JK Pregnancy as the prodrome to vascular dysfunction and cardiovascular risk. Nat Clin Pract Cardiovasc Med. 2006;3:596-603.

89 Kabiru W, Raynor BD. Obstetric outcomes associated with increase in BMI category during pregnancy. Am J Obstet Gynecol. 2004;191:928-32.

90 Abhari FR, Ghanbari Andarieh M, Farokhfar A, Ahmady S. Estimating rate of insulin resistance in patients with preeclampsia using HOMA-IR index and comparison with non-preeclampsia pregnant women.Biomed Res Int. 2014;2014:1-9.

91 Rao R, Sen S, Han B et al Gestational diabetes, preeclampsia and cytokine release: similarities and differences in endothelial cell function.Adv Exp Med Biol. 2014;814:69-75

92 Skjaerven R, Wilcox AJ, Klungsoyr K, Irgens LM, Vikse BE, Vatten LJ, et al. Cardiovascular mortality after pre-eclampsia in one child mothers: prospective, population based cohort study. Bmj. 2012;345:e7677.

93 Craici IM, Wagner SJ, Hayman SR, Garovic VD. Pre-eclamptic pregnancies: an opportunity to identify women at risk for future Cardiovascular disease. Women's Health 2008;4:133-135

94 Roberge S, Odibo AO, Bujold E. Aspirin for the Prevention of Preeclampsia and Intrauterine Growth Restriction. Clin Lab Med. 2016; 36:319-329.

95 Mercuro G, Bassareo PP, Flore G, Fanos V, Dentamaro I, Scicchitano P, Laforgia N, Ciccone MM. Prematurity and low weight at birth as new conditions predisposing to an increased cardiovascular risk. Eur J Prev Cardiol. 2013;20:357-367.

96 Robbins CL,Hutchings Y, Dietz PM ,Kuklina EV, Callaghan WM. Hystory of preterm birth and subsequent cardiovascular disease: a systematic review Am J Obstet Gynecol. 2014;210:285–297

97 Minissian MB, Kilpatrick S, Eastwood JA, Robbins WA, Accortt EE, Wei J, Shufelt CL, Doering LV, Merz CNB Association of Spontaneous Preterm Delivery and Future Maternal Cardiovascular Disease Circulation. 2018; 20;137:865-871

98 Kessous R, Shoham-Vardi I, Pariente G. An association between preterm delivery and long-term maternal cardiovascular morbidity Am J Obstet Gynecol. 2013;209:368.e1-8

99 Romero R, Espinoza J, Kusanovic JP, Gotsch F, Hassan S, Erez O, Chaiworapongsa T, Mazor M. The preterm parturition syndrome. BJOG. 2006;113:17–42.

100 Siddiqui N, Hladunewich M. Understanding the link between the placenta and future cardiovascular disease. Trends Cardiovasc Med. 2011;21:188–193.

101 Romero R, Kusanovic JP, Chaiworapongsa T, Hassan SS. Placental bed disorders in preterm labor, preterm PROM, spontaneous abortion and abruptio placentae. Best Pract Res Clin Obstet Gynaecol. 2011;25:313–327.

102 Catov JM, Lewis CE, Lee M, Wellons MF, Gunderson EP. Preterm birth and future maternal blood pressure, inflammation, and intimal-medial thickness: the CARDIA study. Hypertension. 2013;61:641–646.

103 Hastie CE, Smith GC, Mackay DF, Pell JP. Association between preterm delivery and subsequent C-reactive protein: a retrospective cohort study. Am J Obstet Gynecol. 2011;556.e1–4.

104 Perng W, Stuart J, Rifas-Shiman SL, Rich-Edwards JW, Stuebe A, Oken E. Preterm birth and long-term maternal cardiovascular health. Ann Epidemiol. 2015;25:40–45.

105 Kaaja RJ, Greer IA. Manifestations of chronic disease during pregnancy. JAMA. 2005;294:2751–2757.

106 Williams D. Pregnancy: a stress test for life. Curr Opin Obstet Gynecol.2003;15:465–471.

107 Wu P, Gulati M, Kwok CS, Wong CW, Narain A, O'Brien S, Chew-Graham CA, Verma G, Kadam UT, Mamas MA. Preterm Delivery and Future Risk of Maternal Cardiovascular Disease: A Systematic Review and Meta-Analysis. J Am Heart Assoc. 2018;7:1-46

108 Harskamp RE, Zeeman GG. Preeclampsia: at risk for remote cardiovascular disease. Am J Med Sci. 2007;334:291–295

109 Bonamy AK, Parikh NI, Cnattingius S et al. Birth Characteristics and Subsequent Risks of Maternal Cardiovascular Disease: Effects of Gestational Age and Fetal Growth Circulation 2011;124:2839-2846

110 King TF, Bergin DA, Kent EM et al. Endothelial progenitor cells in mothers of low-birthweight infants: a link between defective placental vascularization and increased cardiovascular risk? J Clin Endocrinol Metab. 2013;98:E33-39

111 Melchiorre K, Sutherland GR, Liberati M et al. Maternal cardiovascular impairment in pregnancies complicated by severe fetal growth restriction. Hypertension. 2012;60:437-443

112 Barker DJ, Osmond C, Golding J, Kuh D,Wadsworth ME. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. BMJ. 1989;298:564–567

113 Andersson SW, Lapidus L, Niklasson A, Hallberg L, Bengtsson C, Hulthen L. Blood pressure and hypertension in middle-aged women in relation to weight and length at birth: a follow-up study. J Hypertens. 2000; 18:1753–1761

114 Palmsten K, Buka SL, Michels KB. Maternal pregnancy-related hypertension and risk for hypertension in offspring later in life. Obstet Gynecol. 2010;116:858-864

115 Davis GK, Newsome AD, Ojeda NB, Alexander BT. Effects of Intrauterine Growth Restriction and Female Sex on Future Blood Pressure and Cardiovascular Disease. Curr Hypertens Rep 2017;19:1-15

116 Smith GC, Pell JP, Walsh D. Spontaneous loss of early pregnancy and risk of ischaemic heart disease in later life: retrospective cohort study. BMJ. 2003;326:423-424

117 Kessous R, Shoham-Vardi I, Pariente G et al Recurrent pregnancy loss: a risk factor for long-term maternal atherosclerotic morbidity? Am J Obstet Gynecol. 2014;211:414.e1-11

118 Parker DR, Lu B, Sands-Lincoln M. Risk of cardiovascular disease among postmenopausal women with prior pregnancy loss: the women's health initiative. Ann Fam Med. 2014;12:302-309

119 Oliver-Williams CT, Heydon EE, Smith GC et al. Miscarriageand future maternal cardiovascular disease: a systematic review and meta-analysis. Heart. 2013;99:1636-1644

120 Ranthe MF, Andersen EA, Wohlfahrt J et al.Pregnancy loss and later risk of atherosclerotic disease. Circulation. 2013;127:1775-1782.

Tables and Figures:

Table 1
Women-specific risk factors for Cardiovascular Disease

Figure legends:

Figure 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.

Figure 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.

Table 1

- 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

Highlights

- 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 important. The development of CVD in women may correlate with specific events taking place throughout a woman's obstetric and gynaecological history.
- 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.
- Menopause, GDM, preeclampsia, and SGA, in addition to the other risk factors described in this manuscript, are associated with the development of CVD later in life.
- These events should be considered to represent sex-specific risk factors and considered by health practitioners and used for CVD risk calculation and CVD prevention programs in women.
- The evaluation of women's specific CV risk factors is of importance to establish early, sex-targeted preventative and therapeutic strategies.

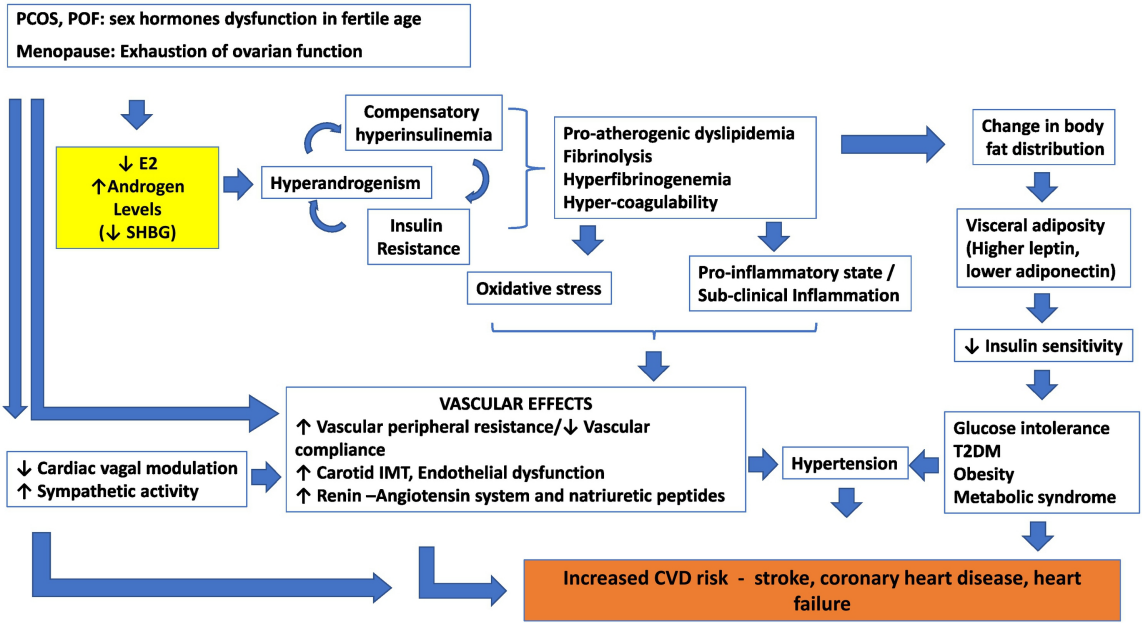
PCOS, POF: sex hormones dysfunction in fertile age
Menopause: Exhaustion of ovarian function
↓ E2
↑Androgen
Levels
(↓ SHBG)
Hyperandrogenism
Compensatory
hyperinsulinemia
Insulin
Resistance
Pro-atherogenic dyslipidemia
Fibrinolysis
Hyperfibrinogenemia
Hyper-coagulability
Oxidative stress
Pro-inflammatory state /
Sub-clinical Inflammation
Change in body
fat distribution
Visceral adiposity
(Higher leptin,
lower adiponectin)
↓ Insulin sensitivity
Glucose intolerance
T2DM
Obesity
Metabolic syndrome
VASCULAR EFFECTS
↑ Vascular peripheral resistance/↓ Vascular
compliance
↑ Carotid IMT, Endothelial dysfunction
↑ Renin –Angiotensin system and natriuretic peptides
↓ Cardiac vagal modulation
↑ Sympathetic activity
Hypertension
Increased CVD risk - stroke, coronary heart disease, heart
failure

Figure 1

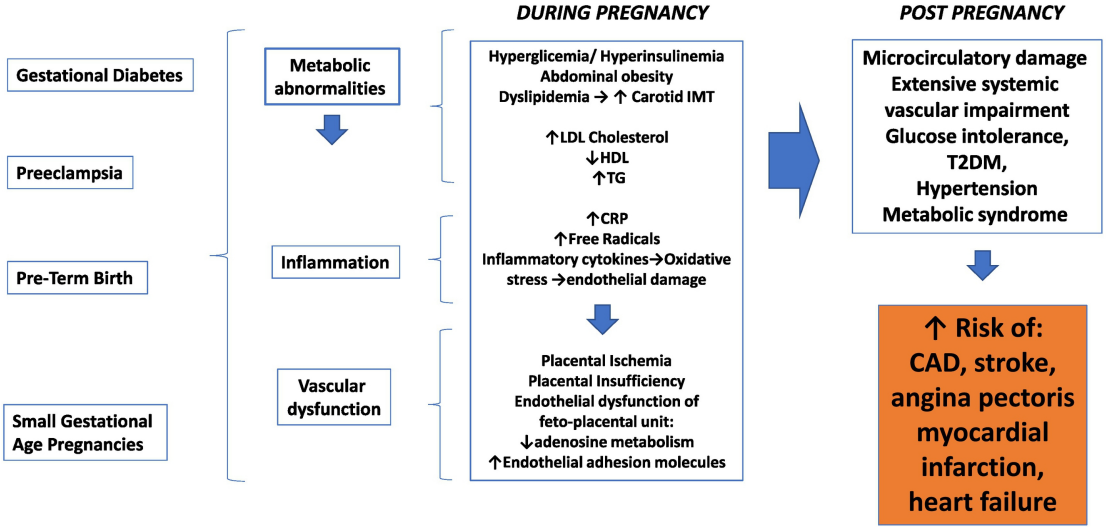
DURING PREGNANCY
POST PREGNANCY
Gestational Diabetes
Preeclampsia
Pre-Term Birth
Small Gestational Age Pregnancies
Metabolic abnormalities
Inflammation
Vascular dysfunction
Hyperglicemia/ Hyperinsulinemia
Abdominal obesity
Dyslipidemia → ↑ Carotid IMT
↑LDL Cholesterol
↓HDL
↑TG
↑CRP
↑Free Radicals
Inflammatory cytokines→Oxidative stress →endothelial damage
Placental Ischemia
Placental Insufficiency
Endothelial dysfunction of feto-placental unit:
↓adenosine metabolism
↑Endothelial adhesion molecules
Microcirculatory damage
Extensive systemic vascular impairment
Glucose intolerance, T2DM,
Hypertension
Metabolic syndrome
↑ Risk of:
CAD, stroke, angina pectoris myocardial infarction, heart failure

Figure 2