

Preeclampsia and cardiovascular disease: interconnected paths that enable detection of the subclinical stages of obstetric and cardiovascular diseases

Gloria Valdés

Department of Nephrology, Facultad de Medicina, Pontificia Universidad Católica, Santiago, Chile

Abstract: The potent and now longstanding evidence of the association between placentation-related disorders and cardiovascular disease should be translated into clinical practice in order to introduce a preventive approach to future obstetric and cardiovascular diseases. The purpose of this review is to integrate cardiovascular risk/disease and obstetric complications, which are linked by endothelial dysfunction, as windows of opportunity for improving women's health. Questionnaires adaptable to local practices are proposed to incorporate cardiovascular and obstetrical indexes into two stages of a woman's lifetime.

Keywords: pregnancy, preeclampsia, placentation-related disorders, cardiovascular disease, cardiovascular stress test, prevention, endothelial dysfunction, women's health

Plain language summary

This review concentrates the evidence accumulated since the mid-1990s showing that women who suffer hypertensive pregnancies or have premature and/or low-weight babies are at an increased risk of presenting later in life with hypertension and cardiovascular events, such as coronary artery disease, stroke, obstruction of the carotid and lower limb arteries, cardiac failure, and thromboembolism. I intend to reinforce the need for obstetricians to recognize this association to ensure that cardiovascular risks (CVRs) are identified after a complicated pregnancy, to introduce early prevention of cardiovascular disease. It should also stimulate cardiologists to incorporate the outcomes of previous pregnancies when gauging the risk of women consulting for symptoms of myocardial ischemia or infarction. This summary focuses on making women aware that a hypertensive pregnancy is not a one-in-a-lifetime event, but a marker of future gestational complications and cardiovascular events after they lose the protection of estrogen. Though much more research is needed, the triad of women, their obstetricians/gynecologists, and cardiologists can do much to improve health in women and their offspring, who tend to have increased CVR when exposed to an unfavorable intrauterine environment.

Introduction

Since the first associations of preeclampsia with cardiovascular disease (CVD) in the mid-1990s and the start of the 21st century, numerous publications have corroborated this finding and added associations with other placentation-related disorders, including recurrent abortions, intrauterine growth retardation, preterm labor, abruptio placentae, and stillbirths.¹⁻¹⁶ The risk of CVD increases according to the clinical severity of the maternal and fetal manifestations, as demonstrated by a prospective registry follow-up of 506,350 women in Norway in whom the presentation of major coronary

Correspondence: Gloria Valdés
Departamento de Nefrología, Facultad de Medicina, Pontificia Universidad Católica, Diagonal Paraguay 362, Santiago 8330024, Chile
Tel +56 2 2354 3229
Email gvaldes@med.puc.cl

events increased 2.1-fold with previous preeclampsia, while adding intrauterine growth retardation or preterm birth augmented this risk to 3.3- and 5.4-fold risk, respectively.¹⁶ Coronary calcification, a precedent of coronary artery disease, is increased three decades after a preeclamptic pregnancy.¹⁷ Women submitted to angiography for suspected coronary lesions who had previous hypertensive pregnancies presented earlier with clinical manifestations and an increased number of stenotic arteries compared to women with normotensive pregnancies.¹⁸

Systematic reviews and meta-analyses represent potent tools for integrating information and contribute to its rational application and are especially relevant to this issue. In the last decade, four such papers have addressed and proven the association of preeclampsia with CVD with remarkable consistency (Table 1).^{19–22} However, CVR screening has not been incorporated into the preconception or early pregnancy clinical and laboratory evaluations to permit the correction of modifiable factors in order to reduce the risk of gestational hypertension. The short-term and medium-term follow-up of women with hypertension in pregnancy is only performed by a few post-preeclampsia clinics.^{23,24}

Moreover, no retrospective evaluation of the obstetric history is routinely obtained in women presenting with symptoms of CVD several decades after the reproductive period, though the American Heart and Stroke Associations have stressed the remote risk of a complication of pregnancy.^{25,26} This is especially important for improving the screening for ischemic heart disease, the leading cause of death in

women, which remains underdiagnosed and undermanaged for a number of reasons. The main confounding factors are the surreptitious clinical presentation of coronary artery disease in females, the maintenance of the current biochemical and electrocardiographic criteria applied to men, the lesser frequency of coronary arterial lesions, and the presence of microvascular dysfunction, which in the absence of obstructive lesions presents major adverse outcomes in 30% of patients during follow-up.^{27–29}

This review represents a call to action to translate epidemiological, clinical, and molecular biology research into patient care, stressing the recent appeal of Arabin and Baschat.¹⁴ The future diffusion of preventive programs will benefit mothers who failed an early stress test, as well as the offspring exposed to an unfavorable intrauterine environment, thus perpetuating the cycle generated by an unfavorable pregnancy and CVD.^{30,31}

Pathophysiology

Apart from epidemiological studies that support the association of placentation-derived disorders (hereafter represented by preeclampsia) with CVD, many pathophysiological conditions are common to both: arterial hypertension, obesity, insulin resistance, diabetes, hyperlipidemia, oxidative stress, inflammation (autoimmune or infectious), snoring, familial premature CVD and CVD-related genotypes.^{11,32–34} Additional common features are the mild to moderate preventive effect of aspirin in pregnancy and coronary artery disease late in life and the atherosclerotic plaques and atherosclerosis.^{35–38}

Table 1 Systematic reviews and meta-analyses assessing the remote cardiovascular risks of women who presented with preeclampsia.

Reference	Studies (n)	PE cases (n)	Control cases (n)	Hypertension, RR (95% CI)	CVD, RR (95% CI)	Ischemic heart disease, RR (95% CI)	Stroke, RR (95% CI)	Other risks, RR (95% CI)
Bellamy et al, 2007 ¹⁹	25	198,252	>3 million	3.70 (2.7–5.05)		Fatal and nonfatal: 2.16 (1.86–2.52)	1.81 (1.45–2.27)	Thromboembolism: 1.79 (1.37–2.33)
McDonald et al, 2008 ²⁰	15	116,175	2 million		2.48 (1.22–5.9)		2.03 (1.95–2.67)	Cardiovascular death: 2.29 (1.73–3.04)
Brown, 2013 ²¹	43	Stroke: 62,235 CVD: 87,250 Hypertension: 40,584	>1 million 1.9 million 779,135	3.13 (2.51–3.89)	2.28 (1.87–2.39)		1.77 (1.43–2.21)	
Wu et al, 2017 ²²	22	>250,000	>4 million			2.50 (1.43–4.37)	1.81 (1.29–2.55)	Heart failure: 4.19 (2.09–8.38) Cardiovascular death: 2.21 (1.83–2.66)

Note: Empty spaces represent unreported data.

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; PE, preeclampsia; RR, relative risk.

In contrast, deficient endometrial preconditioning in adolescence, increased placental mass in multiple pregnancies, and smoking, which benefits from the reduction of sFLT1, differ between preeclampsia and CVD.^{39,40}

Healthy endothelial cells throughout life protect from atherosclerosis and its clinical cardiovascular complications through nitric oxide and related vasoactive factors by modulating blood flow and preventing platelet aggregation, fibrosis, proliferation of vascular smooth muscle, monocyte infiltration, and lipid accumulation.⁴¹ During the reproductive stage, endothelial function is primordial in the uteroplacental and systemic adaptations of pregnancy. In the presence of a responsive endothelium, the remodeling of the spiral arteries is primed by the extravillous trophoblast approaching and transforming its nearby spiral artery before invading its wall, subsequently replacing its muscle layer to finally lodge in its luminal border.^{42,43} On the other hand, defective maternal endothelial function has been posited to impair the paracrine response of the spiral arteries to nitric oxide generated by the extravillous trophoblast, impairing their remodeling into saccular vessels that provide appropriate placental perfusion.⁴⁴ Shallow remodeling causes placental ischemia and increased deportation of placental debris into the maternal circulation, which accentuates the endothelial dysfunction secondary to preexisting CVR and the imbalance between vasoconstrictive and vasodilatory factors.^{45,46} Glitches in the processes of adaptation, added to the expanded maternal blood volume and challenges to cardiac function, expose a failure in the systemic and local adaptations of pregnancy, presenting decades later as CVD.⁴⁹ The predictive capacity of future cardiovascular resilience or susceptibility has the advantage of being comprised of the relatively long duration of pregnancy, the extended area of maternal and placental endothelium (syncytiotrophoblast), and the gestational “excursions into the metabolic syndrome”.⁵ However, the validity of this prolonged “stress test”, and the “windows of opportunities” it provides, is not currently heeded.

Endothelial dysfunction is characterized by flow-mediated vasodilation and has been found to precede preeclampsia, persisting up to 3 years postpartum.⁴⁷ Of four studies with a longer follow-up, one including 47% of subjects with severe preeclampsia found persistence of endothelial dysfunction after 10–20 years.⁴⁸ Another study with a mean follow-up of 6 years detected decreased flow-mediated vasodilation, microalbuminuria, increased uric acid, and a 32% prevalence of chronic hypertension in previous preeclamptics compared to no hypertension in control subjects.⁴⁹ The remaining two had biochemical indexes indicative of vascular activation

5–11 years after the index pregnancy.^{50,51} The value of biochemical markers of endothelial dysfunction was validated by a review and meta-analysis of 65 studies that tested vascular dysfunction by an array of images and/or biochemical markers in 3,356 cases of pregnancy-induced hypertension and 5,346 controls, as women with prior hypertensive pregnancies had vascular functional and structural abnormalities that derive from endothelial dysfunction.⁵² Though the endothelial dysfunction is usually considered a remnant of the injury provoked by the factors deported by the placenta to the maternal circulation, the fact that endothelial dysfunction is present after pregnancy in women with recurrent abortions supports its causal role because they were exposed intermittently to minimal placental factors.⁴⁴ This postulate is reinforced by the presence of preconceptional CVRs linked to endothelial dysfunction in women presenting with a hypertensive pregnancy or preeclampsia (familial, pre- and gestational diabetes mellitus, familial premature myocardial infarction, overweight, obesity, elevated blood pressure, leukocyte count, and elevated triglycerides).^{53–56}

Endothelial dysfunction became central to preeclampsia when Roberts et al⁵⁷ and Redman et al⁵⁸ presented the novel concept that preeclampsia is a two-stage syndrome that begins with defective spiral artery remodeling leading to placental underperfusion and the clinical syndrome provoked by endothelial injury due to cytotoxic, inflammatory, oxidative, and immunological cytotoxic factors. Later, an intermediate stage was added to include placental ischemia/reperfusion and probable mechanic damage of the blood jet entering the intervillous space.^{59,60} Finally, a recent study has attributed a determinant role of decidualization, stretching the concept of a multistage syndrome to five phases while substantiating the potential effect of deficient endometrial preconditioning in teenage pregnancy.^{39,61}

Therefore, I propose integrating the pathophysiology and preconceptional and postgestational management to emphasize a clinical continuum that provides several stages for screening and preventing complications of subsequent pregnancies, as well as CVR and CVD (Figure 1). Thus, introducing CV prevention during the reproductive phase will translate current evidence into routine obstetric practice.

Conclusion

As the evidence derived from retrospective and prospective epidemiological registries, partial pathophysiological insight, clinical studies, systematic reviews, and meta-analyses substantiating the association of preeclampsia and CVD has achieved level 1, the time is ripe for implementing a safe, integral obstetric, and cardiological approach.⁶⁶ The fact that

the subjects of these studies are derived from different ethnic and geographic backgrounds indicates that the association is not limited to confined groups.

From a practical standpoint, questionnaires and basic laboratory screenings have to be developed and consensuated among the leading scientific societies in the field, to be applied in centers of excellence as well as underdeveloped nations.

The Global Pregnancy Collaboration (CoLab) provides a very solid starting point for clinical registries and biobanks that would contribute to elucidate the missing links of the association of gestational diseases and CVDs.⁶⁷ Based on this and our clinical research experience, I have drafted questionnaires for obstetric and cardiology attentions that may be adapted to local clinical practices (Tables 2 and 3). These questionnaires

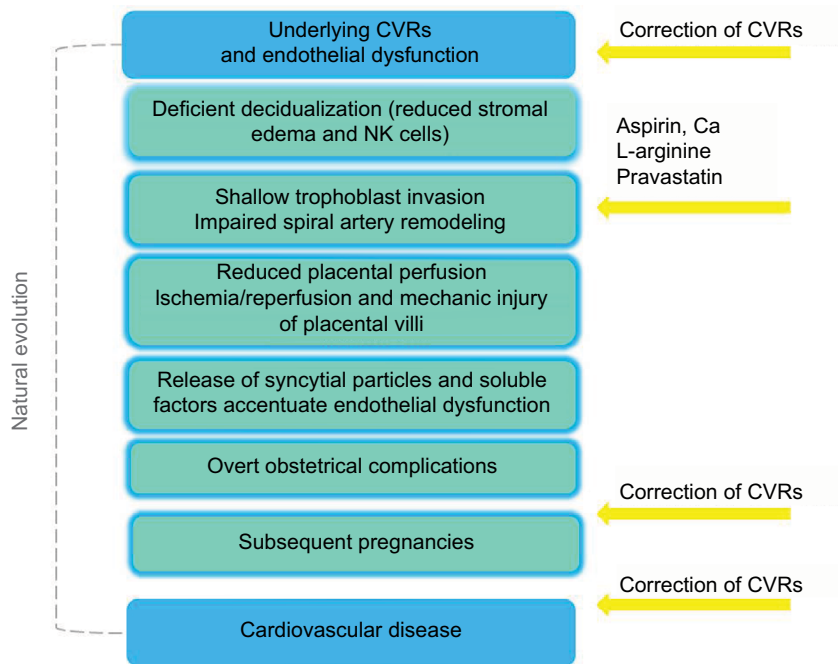


Figure 1 Diagram depicting the stages of preeclampsia integrated to subsequent pregnancies and cardiovascular risk and disease in order to install preventive measures and impact women’s health.

Notes: The natural evolution of CVRs to disease is purposefully depicted in gray, as an active preventive strategy should reduce the spontaneous transition. The different gestational stages are framed in blue to highlight the fact that underlying maternal factors enhance impaired vascular remodeling and its alterations. Yellow arrows point to the four windows that permit preventive interventions. In women with a high risk of severe preeclampsia, the addition of L-arginine to the early use of low dose aspirin and calcium supplementation in women with low intake has proven safe and effective, whereas pravastatin is emerging as a potential intervention.⁶²⁻⁶⁵ This flowchart complements the one recently proposed by Arabin and Baschat regarding the different levels of clinical care that should be provided at the different stages.¹⁴

Abbreviations: CVR, cardiovascular risk; NK, natural killer.

Table 2 Questionnaire to evaluate of cardiovascular risks in pregnant women

Personal risks			
Nutritional status	Weight	Height	BMI
Smoking	Yes	No	Age at initiation/suspension
Snoring	Yes	No	
Hypertension	Yes	No	Age at initiation treatment
Hyperlipidemia Type Last value(s)	Yes	No	Age at diagnosis/treatment Col/triglycerides/HDL
Diabetes	Yes	No	
Family history			
	Father	Mother	Siblings
Cause of death (age)			
Hypertension	Yes/no	Yes/no	Yes/no
Diabetes	Yes/no	Yes/no	Yes/no
Coronary artery disease (years)	Yes/no	Yes/no	Yes/no
Stroke (years)	Yes/no	Yes/no	Yes/no
Preeclampsia in mother or sisters who underwent pregnancies	Yes/no	Yes/no	Yes/no

Abbreviations: BMI, body mass index; col, cholesterol; HDL, high-density lipoprotein.

Table 3 Questionnaire to evaluate obstetric and gynecological history in women with suspected coronary artery disease

Total pregnancies, n			
Spontaneous abortions, n	Yes/no		
Hypertensive pregnancy	Yes/no	Which pregnancy(ies)	Trimester or week of pregnancy
Preeclampsia	Yes/no	Which pregnancy(ies)	Trimester or week of pregnancy
Preterm birth <37 weeks	Yes/no	Which pregnancy(ies)	Week of pregnancy
Newborn weight <2500 g	Yes/no	Which pregnancy(ies)	
Gestational diabetes	Yes/no	Which pregnancy(ies)	
Hospitalizations during pregnancy, n	Yes/no	Which pregnancy(ies)	Cause
Other complications: eclampsia, HELLP, stillbirths, abruption, placenta previa, intrahepatic cholestasis	Which pregnancy(ies)		
Current age(s) of offspring, years			
Sex of offspring, M/F			
Age at menopause, years			
Hormonal replacement	Yes/no	Duration of replacement	

Abbreviations: F, female; HELLP: hemolysis, elevated liver enzymes, low platelets; M, male.

should make a proviso for aspects missed in past studies, such as the need to include women with impeccable pregnancies in the control group (no preterm delivery or intrauterine growth restriction in normotensive pregnancies, spontaneous abortions), the characterization of the different types of pregnancy hypertension, the parity of the index pregnancy, and the precise use and timing of hormonal replacement, data that have not been considered in studies including women over 60 years of age.^{12,13,68} The weight of the evidence is such that waiting for prospective controlled cohort studies, full understanding of the molecular pathways involved in this association, identification of the most cost-effective markers, and an evaluation of the effect of CVR modification on pregnancy constitute an ethical conundrum.

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Disclosure

The author reports no conflicts of interest in this work.

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