

Preeclampsia (marker of chronic kidney disease): from genesis to future risks

Pré-eclâmpsia (indicador de doença renal crônica): da gênese aos riscos futuros

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ABSTRACT

Preeclampsia (PE) is a pregnancy-specific disease which, in addition to other hypertensive disorders, is an important cause of maternal and perinatal morbidity and mortality. With an incidence ranging from 3 to 14% of all pregnancies worldwide, the disease can present in different clinical forms. PE and cardiovascular diseases (CVD) have similar pathophysiological mechanisms, such as endothelial dysfunction, metabolic changes and oxidative stress, and they also share some risk factors such as obesity, kidney disease and diabetes. Although the exact relationship between PE and cardiovascular risk has not been fully elucidated, PE-triggered metabolic stress may cause vascular injury, thus contributing to the development of CVD and/or chronic kidney disease (CKD) in the future. This risk appears to be increased especially in women with a history of recurrent, severe PE and eclampsia. The investigation of a history of PE may assist in assessing the future risk of CVD and CKD, their prevention and early diagnosis.

Keywords: Preeclampsia. Cardiovascular Diseases. Renal Insufficiency, Chronic. Hypertension. Proteinuria.

RESUMO

A pré-eclâmpsia (PE) é uma doença específica da gestação que, somada às demais desordens hipertensivas, constitui importante causa de morbimortalidade materna e perinatal. Tem incidência estimada de 3 a 14% entre todas as gestações e pode manifestar-se de diferentes formas clínicas. A PE e a doença cardiovascular (DCV) possuem mecanismos fisiopatológicos semelhantes, como disfunção endotelial, alteração metabólica e estresse oxidativo, assim como também compartilham alguns fatores de risco como obesidade, doença renal e diabetes. A exata relação entre PE e risco cardiovascular ainda não está totalmente elucidada, talvez o estresse metabólico desencadeado na PE provoque a lesão vascular que contribui para o desenvolvimento da DCV e/ou da doença renal crônica (DRC) futuramente. Esse risco parece ser ainda maior em mulheres com história de PE recorrente, severa e eclâmpsia. A investigação do antecedente de PE pode auxiliar na avaliação do risco futuro de DCV e DRC, na prevenção e no diagnóstico precoce.

Palavras-chave: Pré-eclâmpsia. Doenças Cardiovasculares. Insuficiência Renal Crônica. Hipertensão. Proteinúria.

INTRODUCTION

Preeclampsia (PE) is estimated to occur in 3-14% of all gestations.¹ It is a multisystem disease of unknown cause,² unique to pregnancy, which represents one of the main complications of the pregnancy/ puerperal period, either in its pure form or superimposed on pre-existing systemic arterial hypertension (hereafter referred

to as arterial hypertension, AH), being an important cause of maternal and perinatal morbidity and mortality worldwide.^{3,4}

AH during pregnancy may have different clinical manifestations: PE, defined as AH ($\geq 140/90$ mmHg) associated with proteinuria (≥ 300 mg/24h or $\geq 1+$ random sample dipstick test), with onset after 20 weeks of gestation, persisting up to 12 weeks after delivery; chronic arterial

hypertension (CAH), defined as increased pressure levels before 20 weeks of gestation; PE superimposed on HAC, when a patient with CAH develops proteinuria; eclampsia, when PE is complicated by not otherwise-explained seizures and; transient gestational hypertension, defined as AH without proteinuria, with normalization of the blood pressure up to 12 weeks after delivery (persistence after this period is diagnostic of CAH).⁵ Recent studies have shown that PE may be associated not only with a future risk of CAH, but also with the development of cardiovascular disease (CVD).^{6,7}

Sibai *et al.* reported a higher rate of CAH, ten years after delivery in women with a history of eclampsia and PE, than in those with uneventful pregnancies.⁸ Already in 1961, some authors had reported AH persistence in PE-affected women.⁹

It is noteworthy that PE and CVD share similar pathophysiological mechanisms, namely: endothelial dysfunction, metabolic alteration and oxidative stress, also having common risk factors, such as obesity, smoking, advanced age, renal disease and diabetes, among others.^{7,10} Although the precise relationship between PE and CVD has not been fully elucidated, PE-induced metabolic stress might produce vascular injury, the latter contributing to the development of CVD¹¹ and chronic kidney disease (CKD).

SYSTEMIC ENDOTHELIAL DYSFUNCTION

Although the complex pathophysiology of PE has not been fully elucidated, available studies suggest that maternal immunologically mediated endothelial damage might lead to generalized vasospasm and coagulation activation. The “maternal tolerance” which normally exists during gestation seems to be lost in PE. Imbalance between trophoblast HLA and natural killer cells then triggers a sequence of pathophysiological alterations that clinically manifest as PE.^{12,13}

PE apparently develops in two phases: first there are inadequate implantation and placentation, which induce poor uterine and placental perfusion, with consequent tissue hypoxia and oxidative stress and release of some antiangiogenic factors in the maternal circulation which, in turn, lead to systemic inflammation. In the second phase, these factors lead to generalized endothelial dysfunction, which is responsible for the hypertensive syndrome.¹⁴

The placenta produces antiangiogenic proteins, such as soluble endoglin (sEng) and the soluble vascular endothelial growth factor receptor-1 (sFlt-1), which induce endothelial dysfunction, by inhibiting

pro-angiogenic factors, such as placenta growth factor (PlGF) and vascular endothelial growth factor (VEGF).¹⁵⁻¹⁸ There is evidence of elevated sFlt-1 in PE and eclampsia, but not in gestational hypertensive disease not complicated by proteinuria.¹⁹ Some authors have demonstrated that administration of exogenous VEGF to humans may lead to regression of the AH and proteinuria,²⁰ and that the administration of sFlt-1 and anti-VEGF antibodies to rats can produce PE-like alterations.^{21,22}

REPERCUSSION OF THE PROTEINURIA

The kidneys are among the main organs affected by PE, as can be inferred from the importance of proteinuria in the definition of the disease.²³ The level of proteinuria is directly related to poorer maternal and perinatal prognosis, and higher risk of complications, such as eclampsia and the HELLP syndrome.^{24,25} Proteinuria can be usually detected, on average, three to four weeks before aggravation of the clinical picture, allowing early treatment to be instituted.²⁶

Microalbuminuria, a marker of renal endothelial injury resulting from local or systemic vascular damage, is associated with higher cardiovascular risk, chiefly in hypertensives and diabetics. The detection of microalbuminuria after a PE-complicated gestation is attributed to previously undiagnosed renal disease which did not fully resolve, or to the presence of risk factors which are common to PE and nephropathies.²⁷ There is increased risk of persistent microalbuminuria or proteinuria after PE, and this may be the main cause of kidney disease progression in PE, similarly to what happens with type 1 diabetes mellitus patients. Laboratory monitoring of women who had PE-complicated gestations is thus an important way to prevent CVD and CKD.²⁸

Kidney impairment in PE is closely associated with podocytopathy.²⁹ As happens with vascular endothelium, VEGF is important for the maintenance of global podocyte and glomerular function.^{30,31} The injured podocyte loses its interdigitations, which triggers a process of dedifferentiation, with inadequate adherence to the glomerular basement membrane (GBM) and consequent elimination of this cell in the urine. The denuded GBM favors the development of synchiae and glomerulosclerosis, clinically manifested as proteinuria,³² with functional and morphological kidney impairment.^{33,34} Focal segmental sclerosis, sometimes progressive, may also be found in PE, leading to chronic renal failure.^{35,36}

Podocyturia may be detected in healthy persons as well as in those with CKD, although at significantly lower amounts than in those with acute glomerulopathies.³⁷ Assessment of podocyturia and its correlation with other renal parameters could help with the diagnosis and definition of prognosis of the glomerulopathies, thus contributing to risk reduction.

Because during gestation there is a physiological increase in the glomerular filtration rate (GFR) and reduction of serum creatinine, even mild elevations of the latter can indicate renal function deficit. Severe PE can lead to deterioration of kidney function, chiefly in women with previous CKD and GFR below 40 mL/min/1.73m² (< 0.67 mL/s/m²).³⁸

A retrospective study of 29 pregnant women with CKD showed that 65.5% of the kidney injuries were only diagnosed during pregnancy, with 75% of the patients undergoing their first dialysis during pregnancy. At the end of the follow-up period, over 68% of the patients who needed dialysis remained on this therapeutic modality, and two received kidney transplants.³⁹ Another study of 52 patients who got pregnant after renal transplantation, detected CAH in 63.5%, and renal dysfunction in 44.2%, PE being the main cause.⁴⁰ These results point to the impact of pregnancy on women with CKD, and to the importance of early diagnosis.

The discussion above underlines the importance of a combined nephrologic/obstetric follow-up of CKD patients who want to get pregnant, even before conception occurs, in an attempt to prevent complications. CKD, which is common and under-reported, has high mortality, chiefly due to CVD, the latter being preventable and treatable if diagnosed early.⁴¹

CARDIOVASCULAR RISK

PE can lead to permanent metabolic and vascular damage.⁴² The importance of endothelial dysfunction lies not only in its contribution to the PE pathogenesis, but also in its relationship with the increased risk of subsequent CVD.⁴³

A systematic review and metanalysis,⁴⁴ shown in Table 1, revealed an increased relative risk (RR) of CVD after PE, but no increased risk of cancer. CVD is now among the main causes of death worldwide, and screening women with a history of PE may be a preventive measure to reduce morbidity and mortality in the long run. A study⁴⁵ of rats with sFlt-1-induced PE did not show persistent hypertension after delivery; although other variables were not analyzed in the study, PE may also be an exacerbation of a condition

antedating the pregnancy. Nevertheless, more investigation is necessary before it can be decided whether PE is an isolated risk factor for CVD or it is associated with other pre-existing genetic, environmental and socioeconomic factors.⁴²

PE is associated with the metabolic syndrome, according to a study⁴⁶ investigating insulin resistance and angiogenesis dysfunction, which showed that one year after delivery there was a persistent increase in serum glucose and sFlt-1, a finding that may indicate that, even without any clinical manifestation, the systemic vascular disease was already installed.

It is noteworthy that increased rates of CVD and type 2 DM are found after gestational hypertension, chiefly with severe PE with pregnancy termination before 37 weeks of gestation.^{47,48} Furthermore, CVD and PE share some confounding risk factors, such as obesity, the metabolic syndrome and AH.⁴⁹ Therefore, whereas CVD may be a risk factor for PE,⁵⁰ the latter may be a risk factor for CVD.⁵¹

Gestational diabetes is known to be a risk factors for type 2 DM and, apparently, PE is a risk factor for CFAH, metabolic impairment, endothelial alterations, stroke, acute myocardial infarction, diabetes and CKD, including situations in which a renal biopsy is necessary.⁵²

Persons born to pregnancies complicated by PE or gestational hypertension may also have some future cardiovascular impairment.⁵³ An increased risk of hemorrhagic and ischemic stroke after the ages of 60-70 years was reported,⁵⁴ chiefly among those with a history of severe PE, probably due to cerebral vascular dysfunction brought about by development failure during intrauterine life.⁵⁵ It must be highlighted that PE and intrauterine growth impairment seem to share the same pathogenesis, both being associated with a higher prevalence of CVD.⁴²

Table 1

SYSTEMATIC REVIEW AND META-ANALYSIS OF RISK OF CARDIOVASCULAR DISEASE AFTER PREECLAMPSIA

	RR (95% CI)	Time (years)
Chronic arterial hypertension	3.70 (2.70 – 5.05)	14.10
Stroke	1.81 (1.45 – 2.27)	10.40
Acute coronary disease	2.16 (1.86 – 2.52)	11.70
Venous thromboembolism	1.79 (1.37 – 2.33)	4.70
Mortality	1.49 (1.05 – 2.14)	14.50
Cancer	0.96 (0.73 – 1.27)	17.00

RR: relative risk; CI: confidence interval.

PREVENTIVE MEASURES

Although primary preventive measures for PE are still unavailable, low-dose aspirin (60-100 mg/day) leads to a 10% reduction of the risk of PE, and calcium intake (1-2 g/day) may optimize vascular reactivity, despite the fact that the latter approach seems to be more consistent in populations on calcium-poor diets.⁵⁶ Routine use of these measures is warranted in CAH patients, as there is a higher risk of PE superimposition.⁵⁷

L-arginine supplementation for pre-existing endothelial dysfunction or at the start of pregnancy seems to optimize the obstetric outcome and reduce the risk of CVD, although more studies are necessary to better understand this possible relationship.⁵⁸

In spite of the possible usefulness of antioxidants, such as vitamins C and E for primary prevention of CVD, controlled studies have failed to identify a reduction of PE risk in treated patients. Indeed, adverse outcomes, such as membrane rupture, have been identified with this approach. Therefore, there is no medical justification at present for the use of such medications for the reduction of PE-associated risks.^{59,60} As for vitamin D deficiency, because there is evidence pointing to its possible role as an independent risk factor for PE, it could be preventively used during pregnancy and also in CVD. Nevertheless, further research in this group of patients is warranted.⁶¹

Sleep disorders, frequent during pregnancy, may also interfere with gestation outcomes through a worsening of the systemic inflammatory response, increasing the risk of PE, intrauterine growth retardation and future CVD.⁶² The practice of physical exercises before and during pregnancy may reduce the incidence of PE, through optimization of vascular reactivity.⁶³ On the other hand, smoking has been long known as an important cardiovascular risk factor, increasing the incidence of PE and CVD during gestation.⁶⁴

Control of obesity and of the blood lipid and glucose profiles, before, during and after gestation, may also prevent CVD⁶⁵ and obstetric events.

It is worth emphasizing that persons born to PE-complicated gestations are at higher risk of metabolic dysfunction and CVD, which leads to a vicious cycle through the transmission of genetic factors, besides having a higher risk of developing PE themselves.⁶⁶

The acknowledgement of PE as indicative of CVD may help with the counseling of these patients on

the use of oral contraceptives after pregnancy and of perimenopausal and postmenopausal hormone replacement therapy, with a reduction of the risk of thromboembolism.⁵⁰

Although PE is more frequently found in primigravidas, the precise mechanism of this association remains elusive. Mean blood pressure is lower in the second gestation than in the first one, but this difference disappears after a 2-year interval between the deliveries, indicating that other adaptive conditions, which have no repercussion on the blood pressure, might be involved.⁶⁷

It is noteworthy that increased levels of C-reactive protein (CRP), an indicator of inflammation and cardiovascular risk, were detected in women with a history of eclampsia, 30 years after the delivery. Vascular inflammation, insulin resistance and low levels of high-density lipoprotein (HDL) cholesterol may increase the risk of PE and subsequent CVD⁶⁸ and of prematurity.⁶⁹ Therefore, women with these laboratory alterations should be duly advised and treated at any moment in their lives.

Obesity, chiefly of the central type, is related to lipotoxicity, which may lead to endothelial dysfunction, hampering trophoblast invasion, placental function and fetal growth. It is thus important to monitor the abdominal circumference before conception and during gestation, and advise on weight control after delivery, in order to reduce the risk of CVD.⁷⁰ A cross-sectional study of women who had developed PE found, after 10 years, higher diastolic blood pressure and body mass index, and greater abdominal circumference in comparison with those with normal gestations.⁷¹

CONCLUSION

Although delivery is the only cure for PE at present, its complications may be prevented if diagnosed early. Better maternal and perinatal prognoses clearly depend on adequate screening, monitoring and multidisciplinary follow-up during and even before pregnancy.

Several studies have shown increased risk of CVD and CKD in patients with a history of PE. The cause-effect relationship of this association has not been fully elucidated, but these diseases are known to share the same risk factors, probably related to endothelial dysfunction.

In clinical practice, investigation of a previous history of PE may help with the assessment of the risk of CVD and CKD in the future, their

prevention and early diagnosis. More studies are necessary to better understand this disorder and its repercussions.

Finally, from an eminently nephrologic point of view, the authors of this review consider that physicians (general practitioners, surgeons and specialists in any field) must pay attention to a past history of PE of any patient they care for, managing these persons as any other member of those at risk of CVD: screening for present kidney disease (urinalysis and serum creatinine) and following up, or recommending such approach to their attending physician (obstetrician or gynecologist, for example).

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